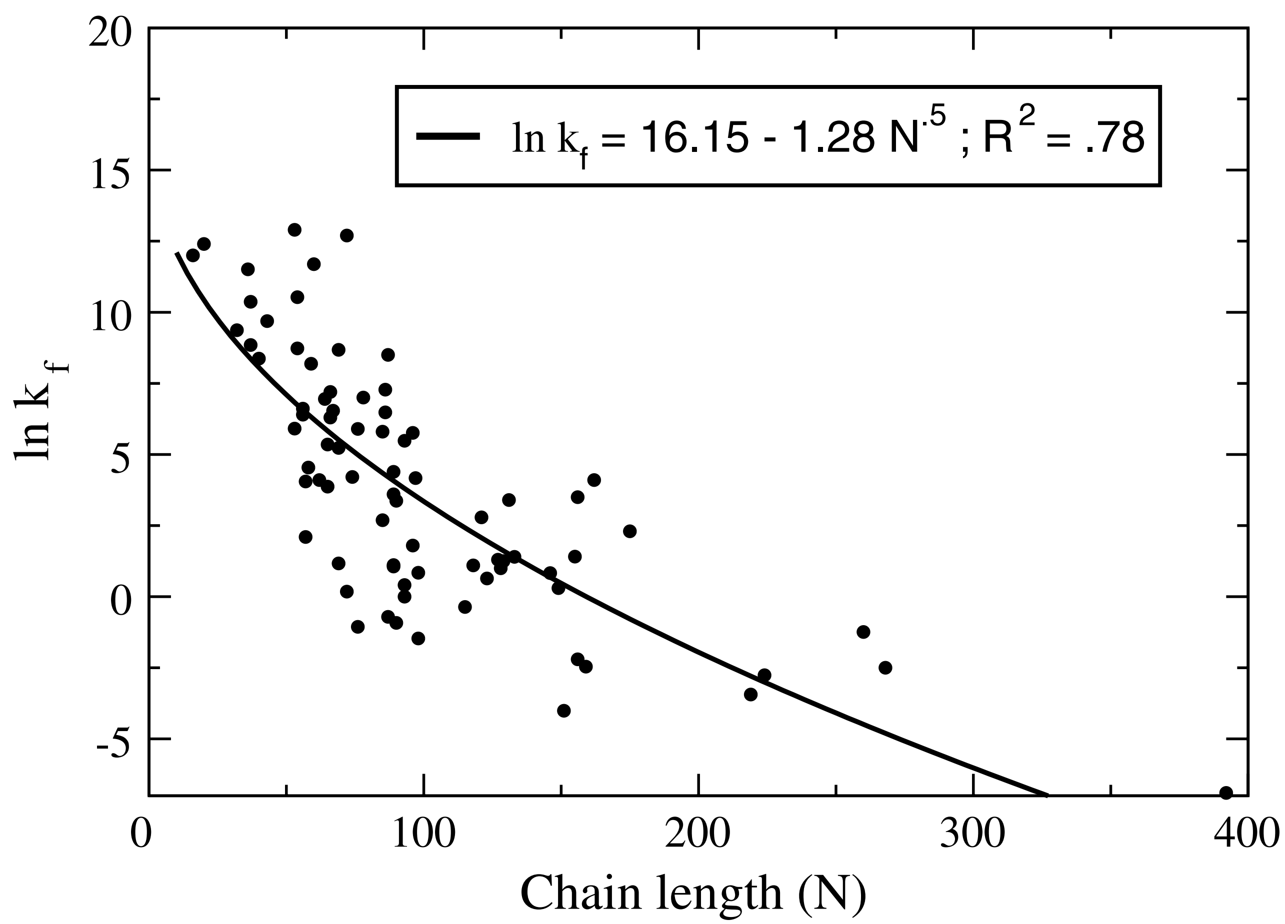
“Slow” relaxation dynamics in bio-molecular processes

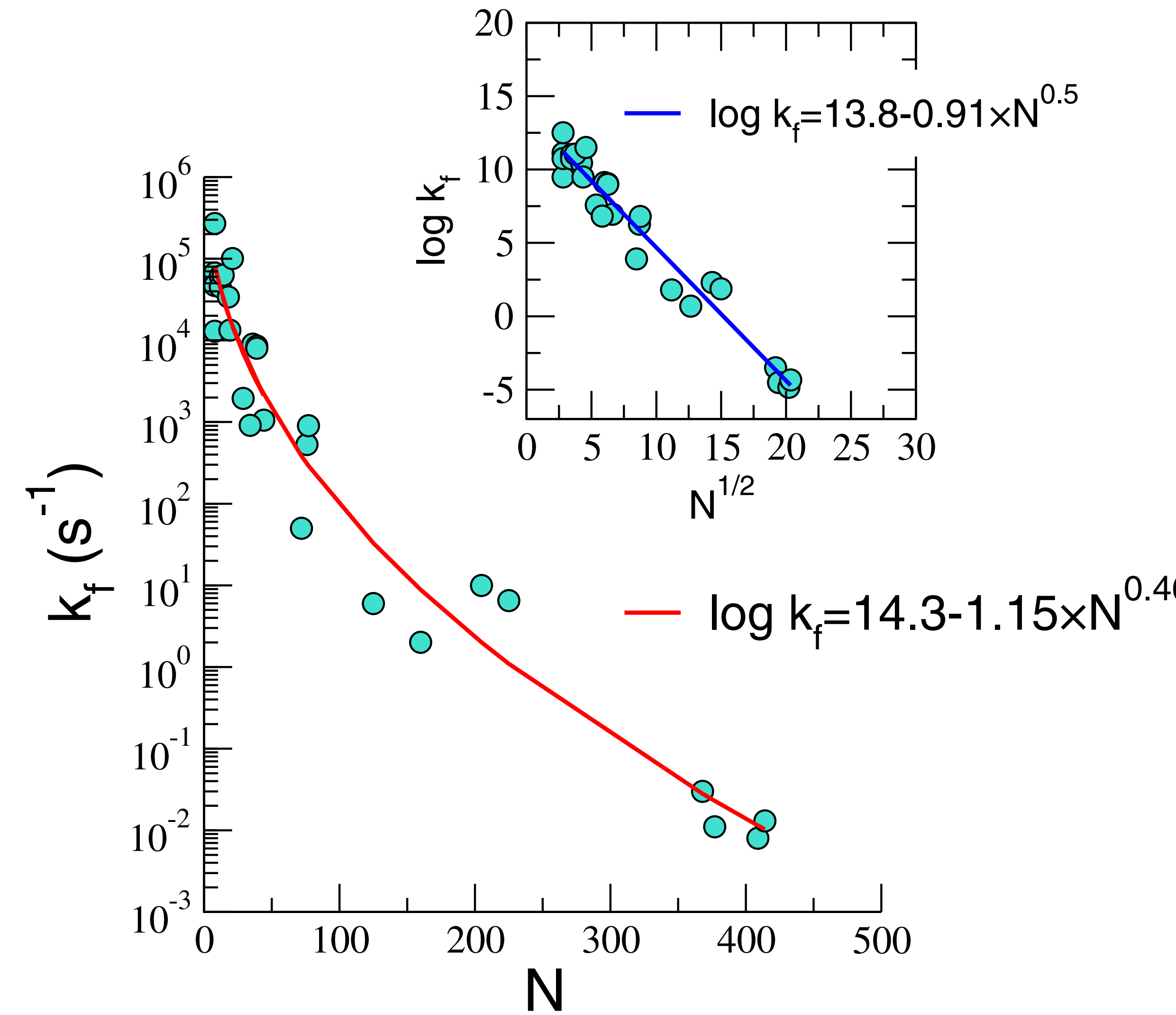
Folding kinetics of biopolymers

Protein folding time



17876–17882 | PNAS | November 1, 2011 | vol. 108 | no. 44

RNA folding time



Biophysical Journal Volume 102 February 2012 L11–L13

$$k_o^{-1} \simeq 0.1 \mu s$$

$$k_f = k_o \exp\left(-\alpha N^{\beta}\right)$$

$$\beta \approx 0.5$$

$$k_o^{-1} \simeq 1.0 \mu s$$

- Some Basics : Rate processes

- Types of disorder in dynamical processes : Quenched vs Dynamic disorder (CO binding to myoglobin)

- Relaxation of single polymer chain (Protein folding under tension, Expanding sausage model)

- Broken ergodicity : Heterogeneity in biomolecular dynamics

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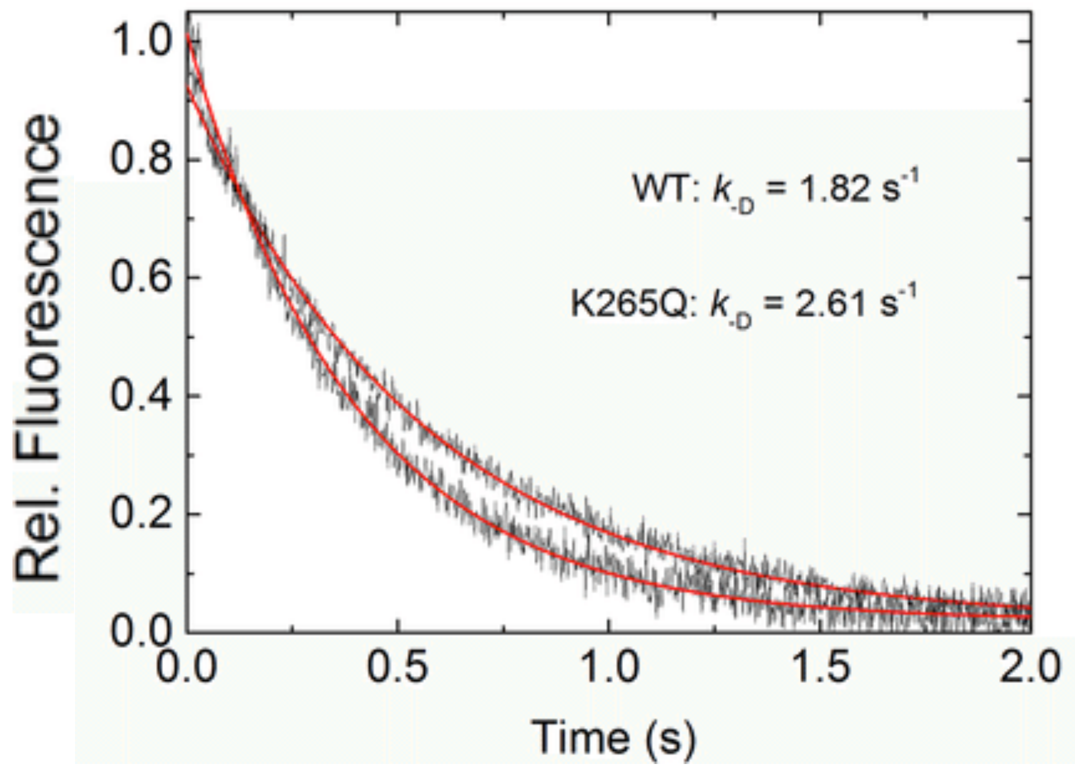
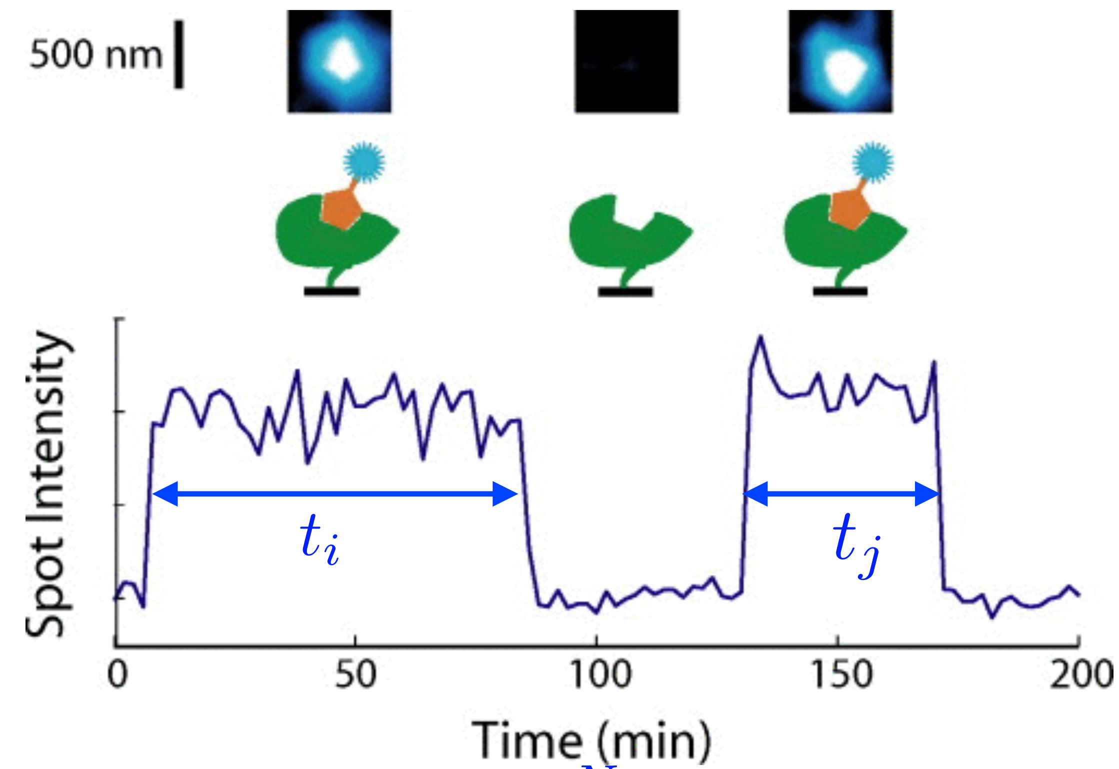
Dissociation kinetics of ADP from myosin



$S(t) \sim e^{-kt}$



$$p(t) = \frac{1}{N}\sum_{i=1}^{N}\delta(t-t_i)$$

$$B \xrightarrow{k} \phi \qquad dP_B(t)/dt = -kP_B(t)$$

$$\rightarrow S(t)(= P_B(t)/P_B(0)) = e^{-kt}$$

Reaction time distribution $\quad p(t) = ke^{-kt}\left(= -\frac{dS(t)}{dt}\right) \qquad S(t) = 1 - \int_0^t d\tau p(\tau)$

$$S(t) - S(t+dt) = p(t)dt$$

# of events that occurred for *dt* following *t*

$$\langle t\rangle = \int_0^\infty tp(t)dt = \int_0^\infty S(t)dt$$

Sequential processes

$$B \xrightarrow{k_1} B' \xrightarrow{k_2} \phi$$

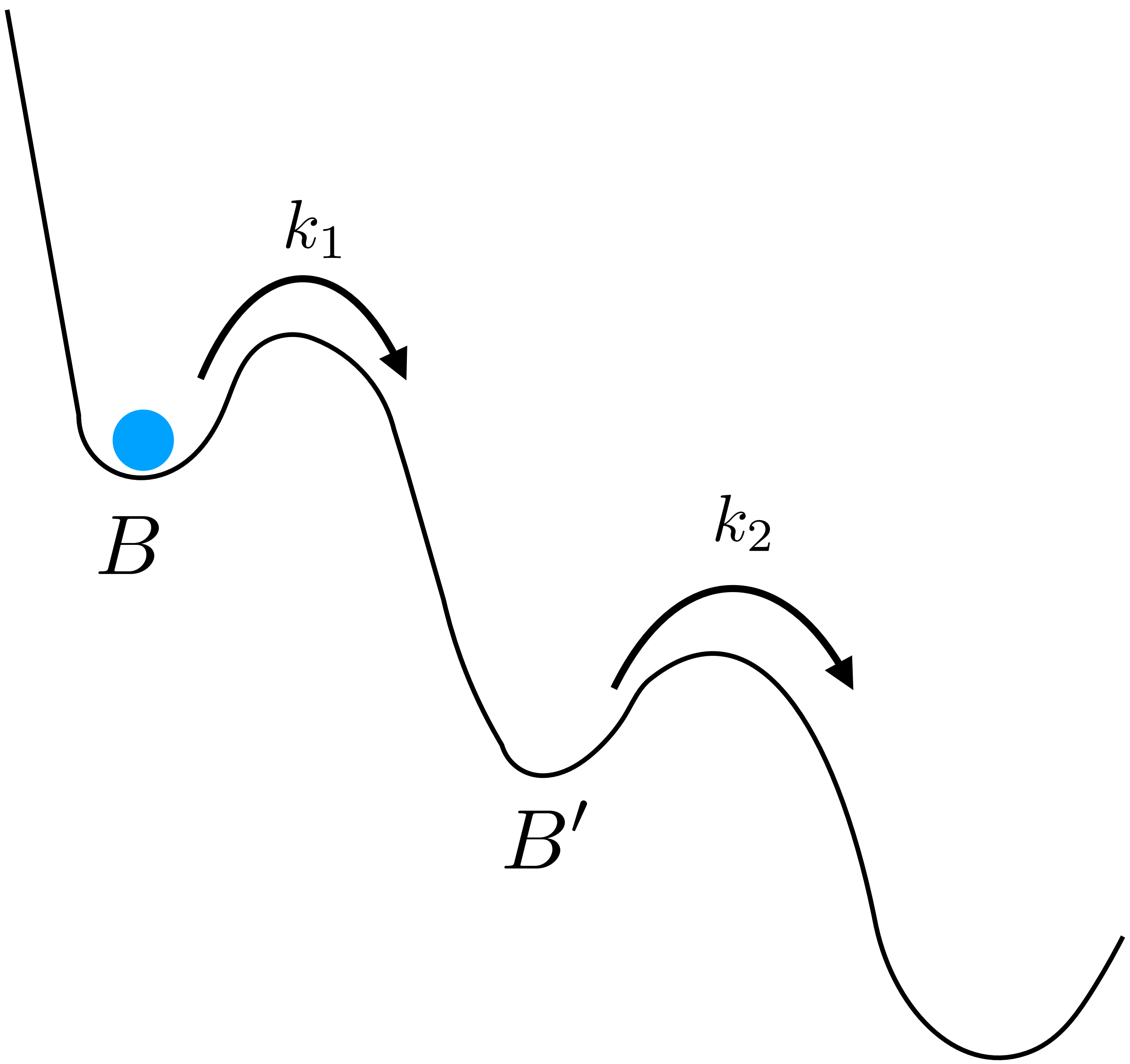
$$p_{k_1}(t) = k_1 e^{-k_1 t}$$

$$p_{k_2}(t) = k_2 e^{-k_2 t}$$

$$p(t) = \int_0^t p_{k_1}(\tau) p_{k_2}(t-\tau) d\tau$$

$$= \frac{k_1 k_2}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t})$$

$$\xrightarrow{k_1 = k_2 = k} k^2 t e^{-kt}$$



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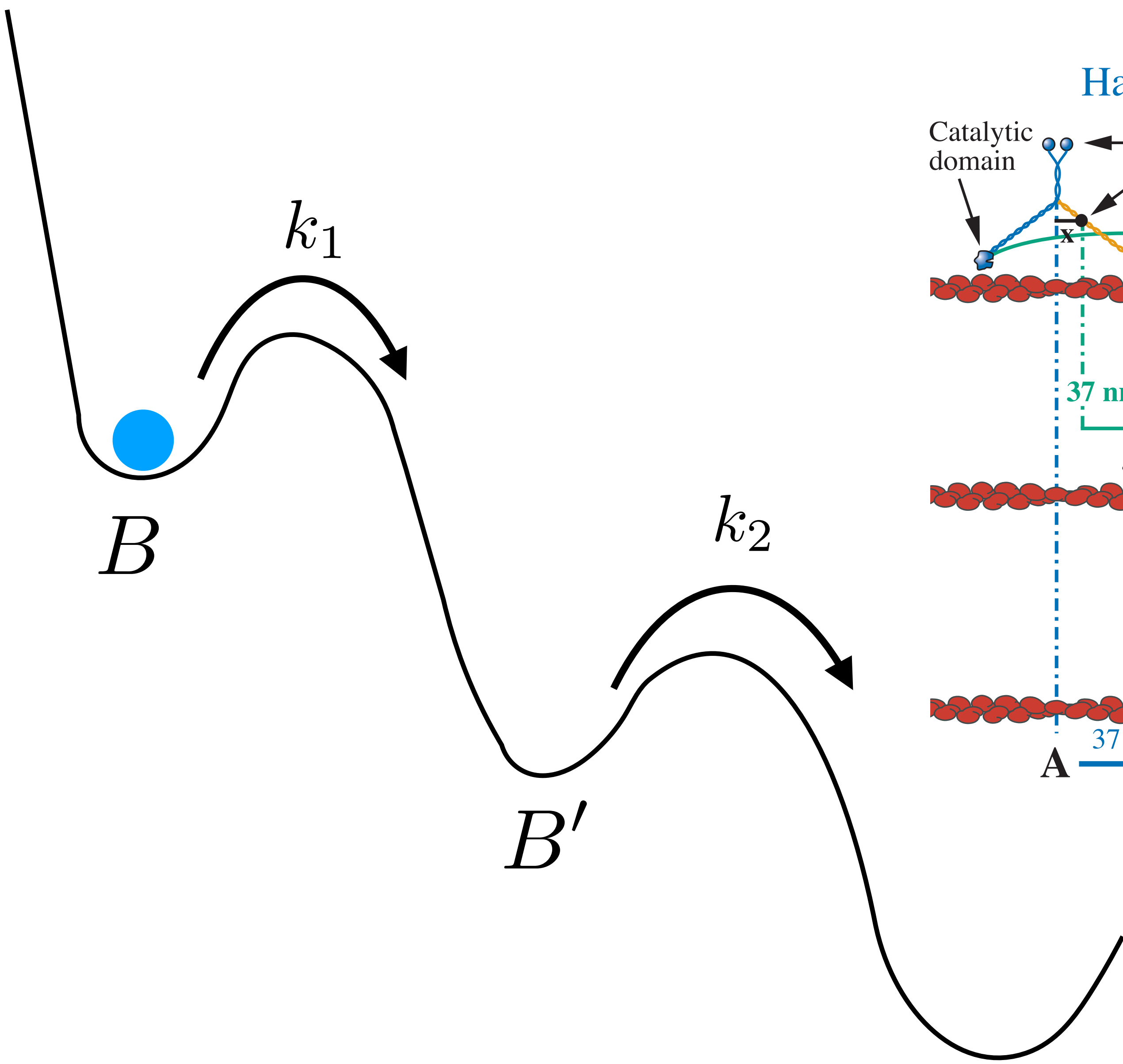

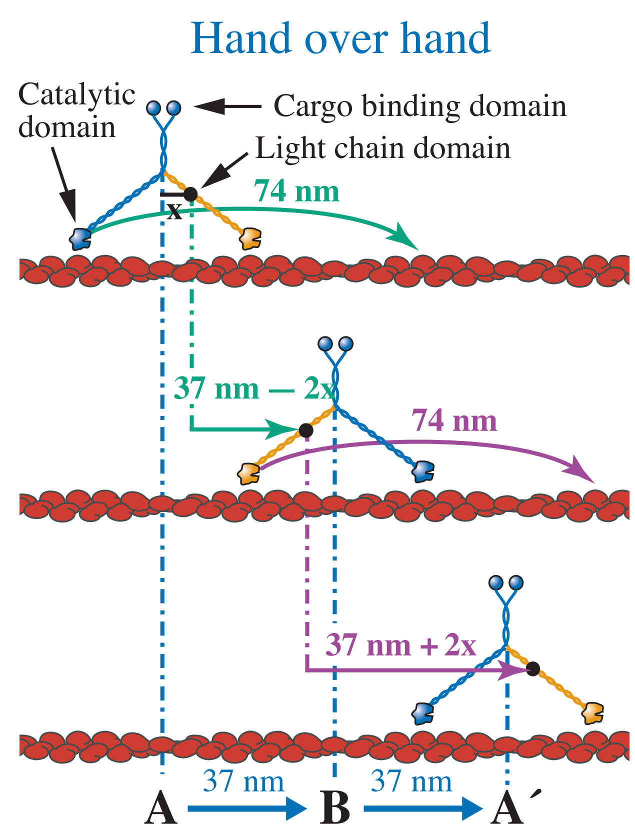

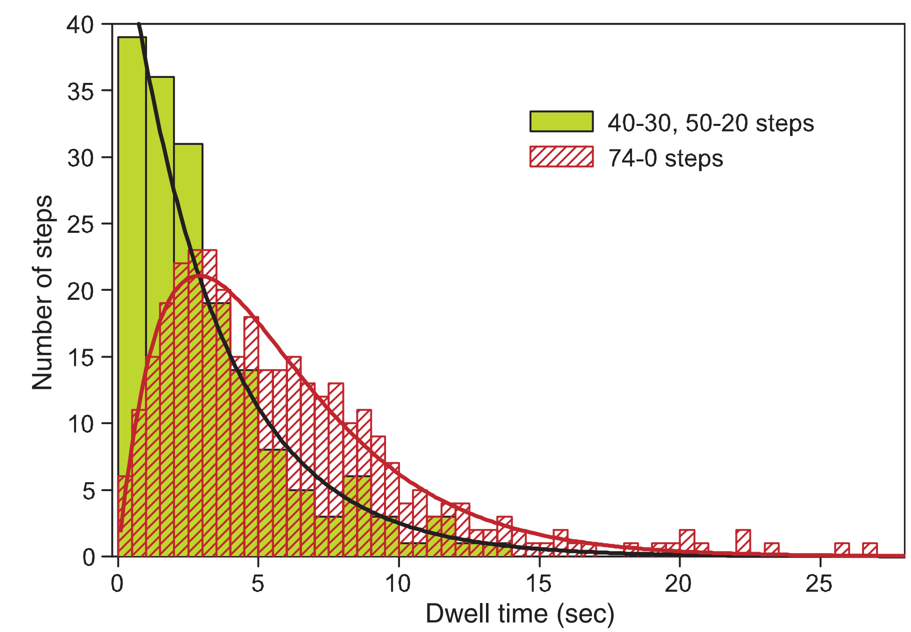

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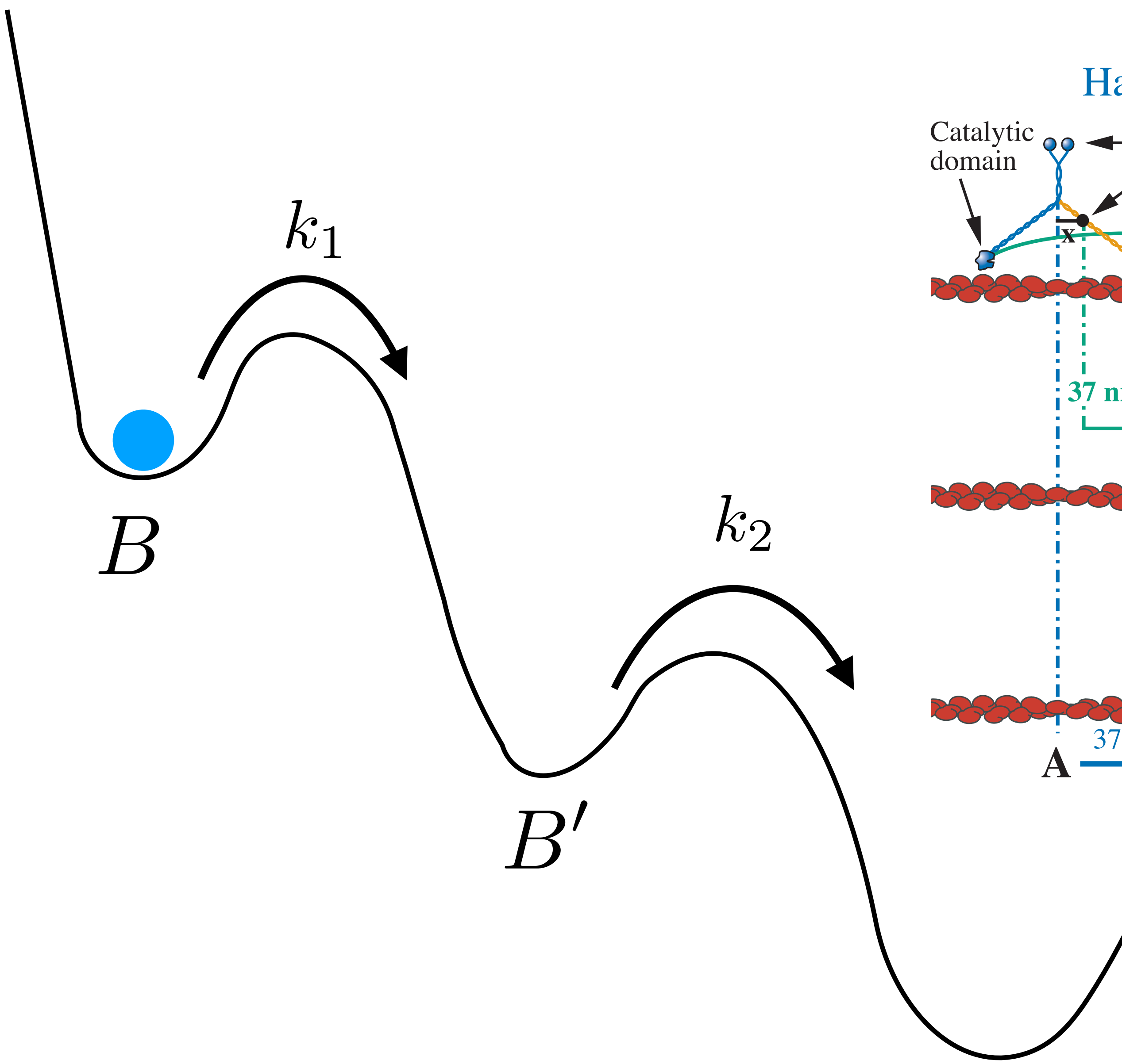
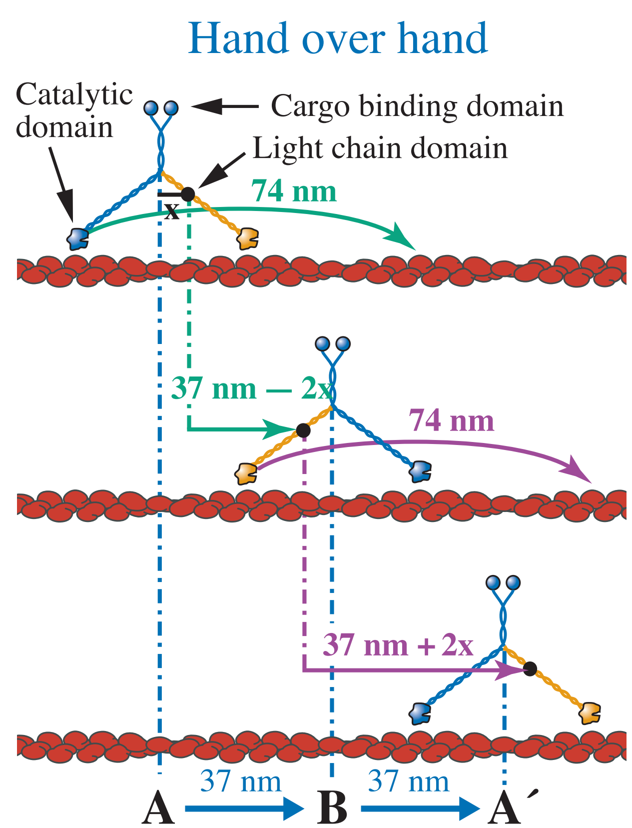
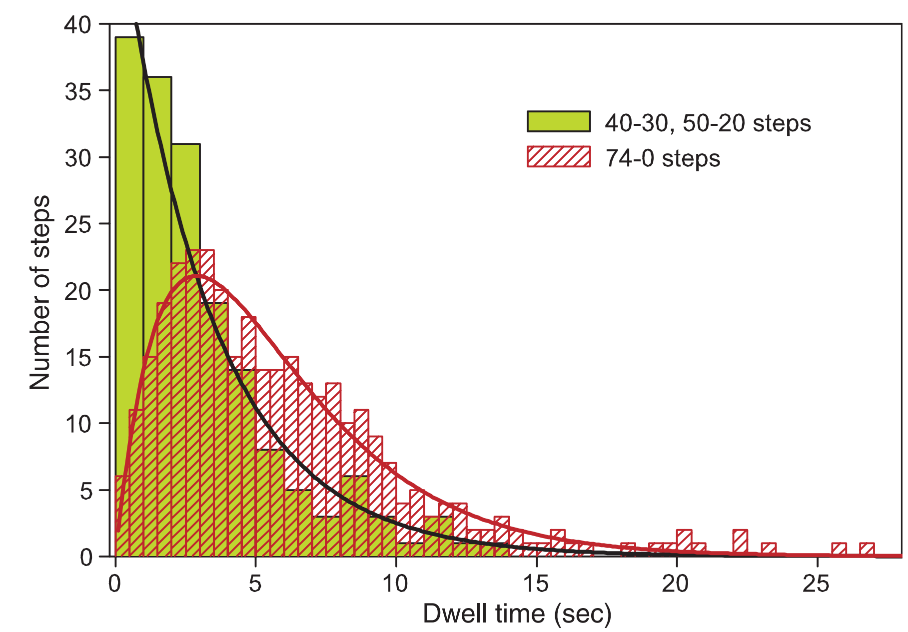




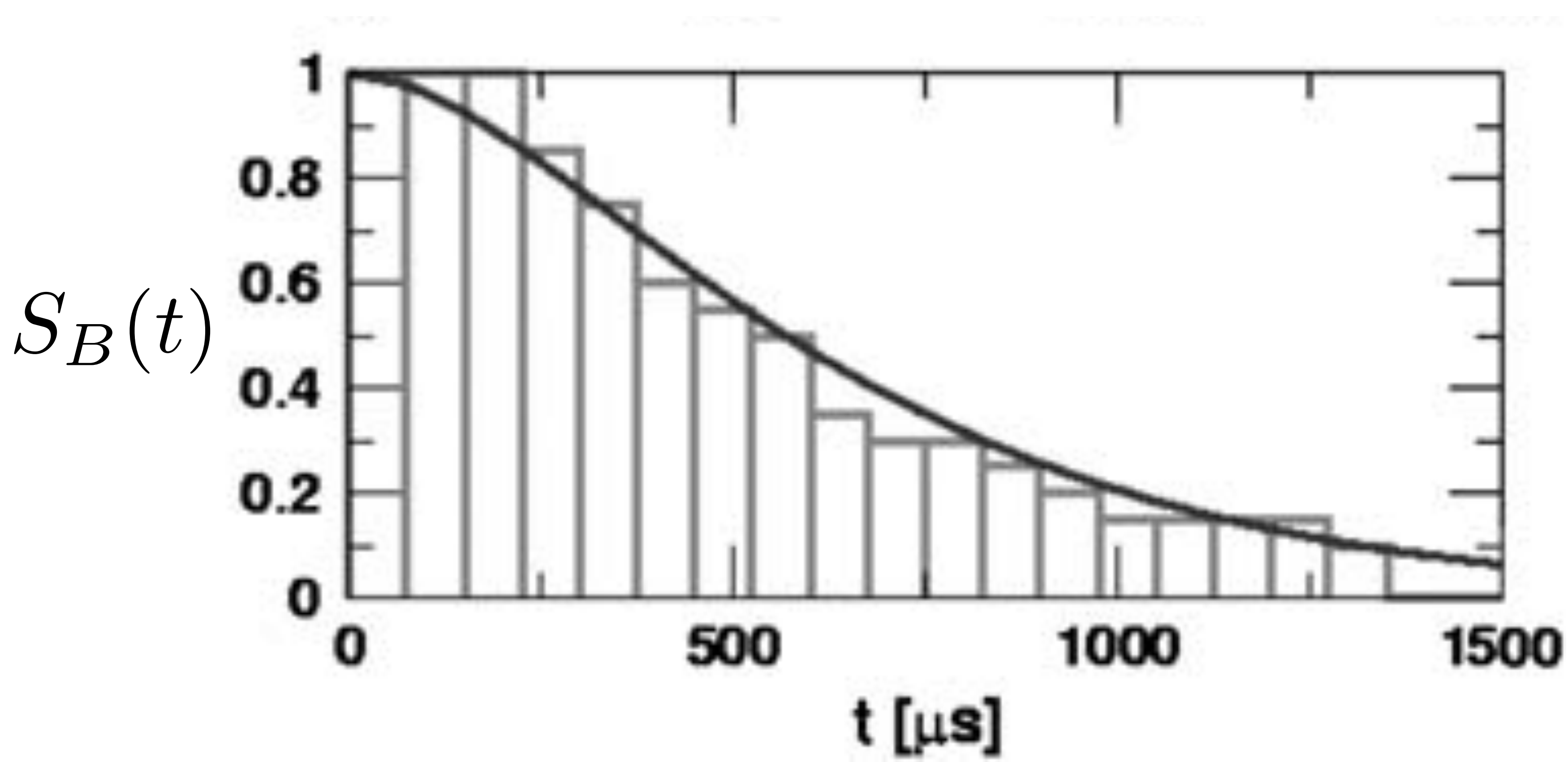


$$p_n(t) = \frac{k^n}{(n-1)!} t^{n-1} e^{-kt}$$

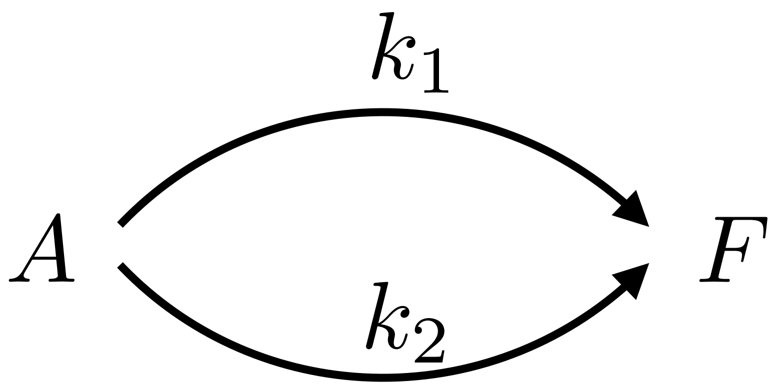
show this !

$$S_B(t) = 1 - \int_0^t d\tau p(\tau) \qquad \left[p(\tau) = \frac{k_1 k_2}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t})\right]$$

$$S_B(t) = \frac{1}{k_2 - k_1}(k_2 e^{-k_1 t} - k_1 e^{-k_2 t})$$



Parallel processes

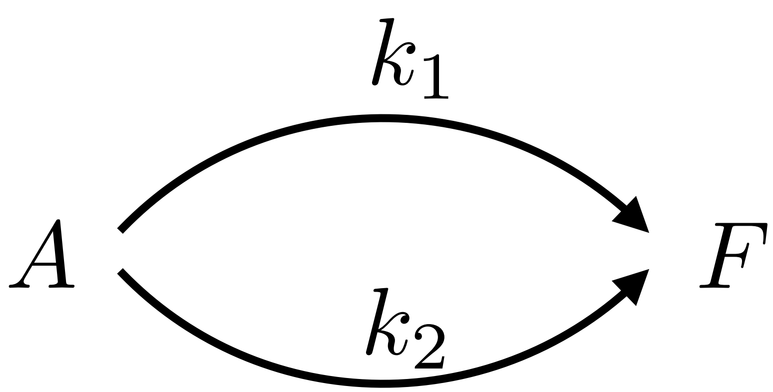


$$\frac{dP_A(t)}{dt} = -k_1 P_A(t) - k_2 P_A(t)$$

$$S_A(t) = e^{-(k_1+k_2)t}$$

$$S_F(t) = 1 - e^{-(k_1+k_2)t}$$

Parallel processes



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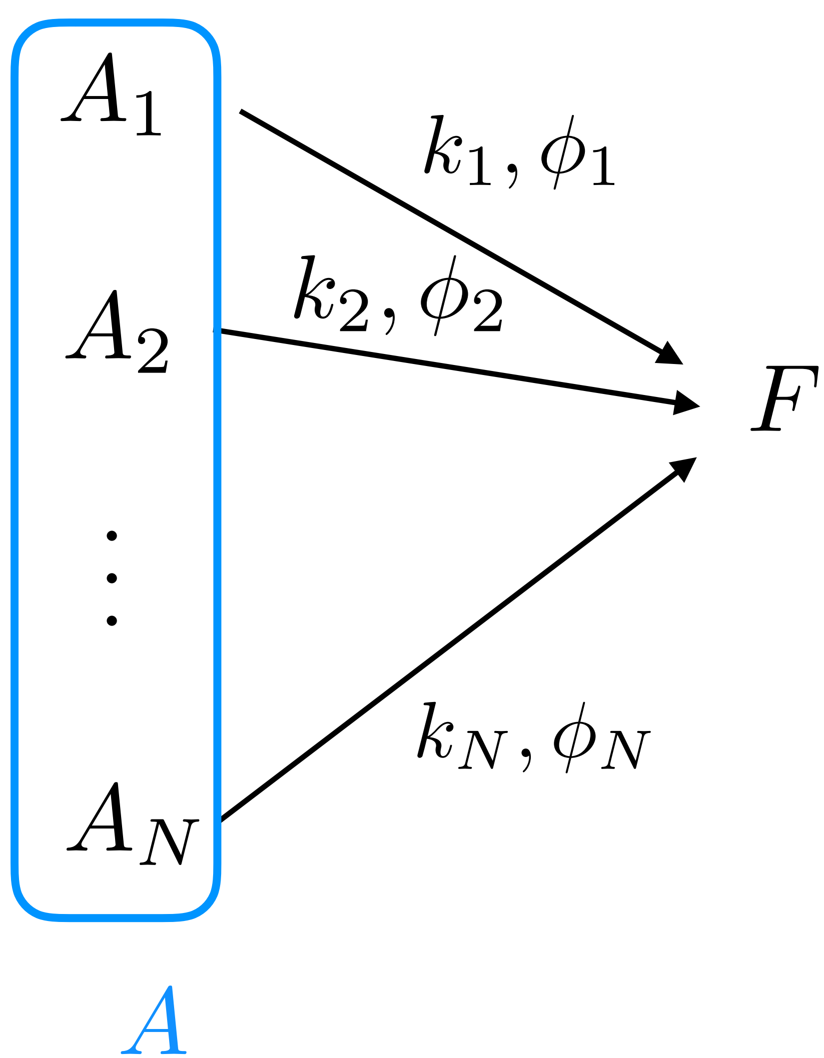


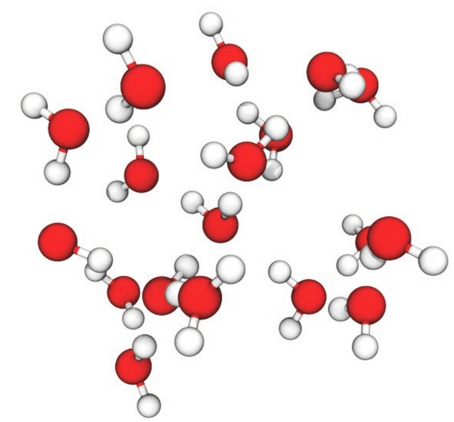
$$S_A(t) = \sum_{i=1}^{N} \phi_i e^{-k_i t} \quad \left(\sum_{i=1}^{N} \phi_i = 1 \right)$$

$$:= \int_0^\infty dk \phi(k) e^{-kt}$$

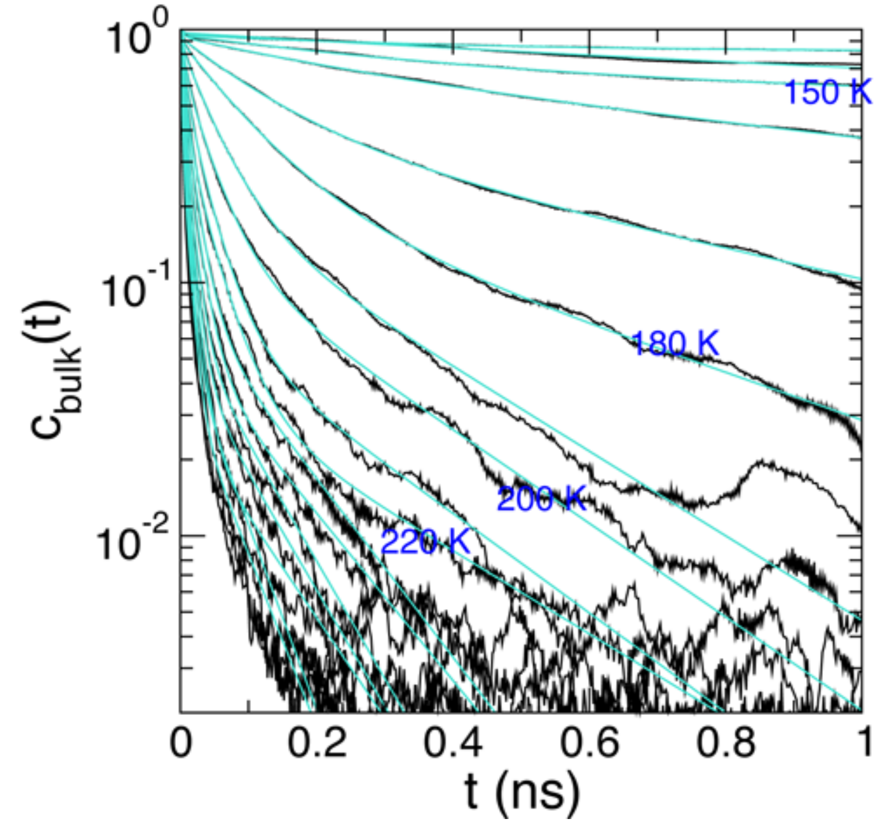
$$
\begin{aligned}
c(t) &= \langle h(0)h(t)\rangle \\
&= \frac{1}{N}\frac{1}{T-t}\int_0^{T-t}\sum_{i=1}^{N} h_i(t'+t)h_i(t')\,\mathrm{d}t' \\
&\approx \phi_1 e^{-t/\tau_1} + \phi_2 e^{-t/\tau_2} + \phi_3 e^{-t/\tau_3}
\end{aligned}
$$

$$
\sum_i^3 \phi_i = 1 \qquad \tau_1 \ll \tau_2 \ll \tau_3
$$

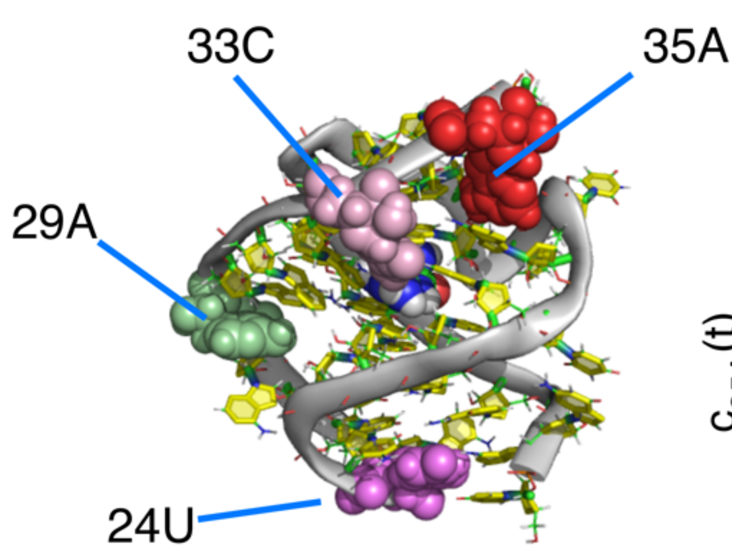
$$
\text{cf. } c(t) \sim \exp\left[-(t/\tau)^{\beta}\right]
$$

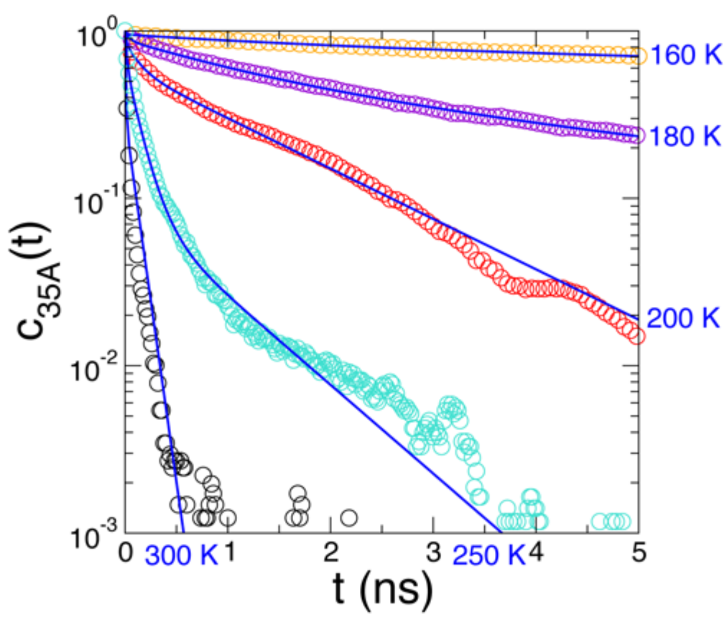


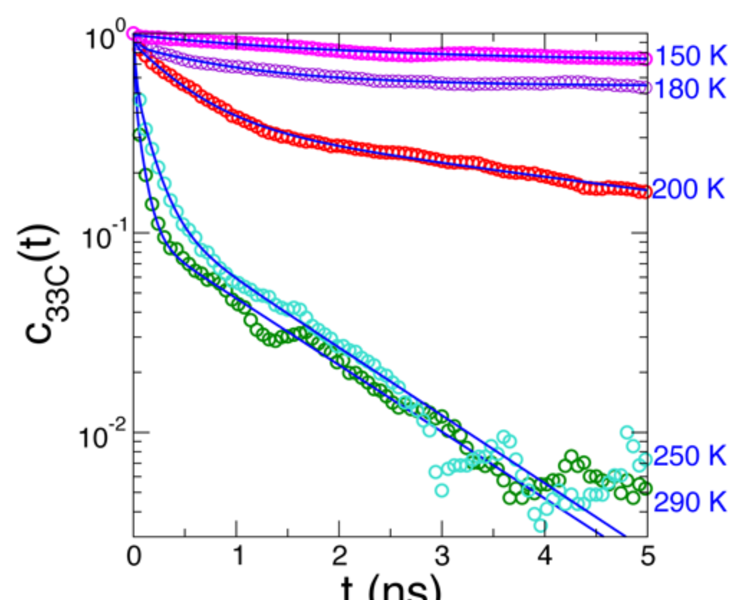
Bulk water H-bond kinetics



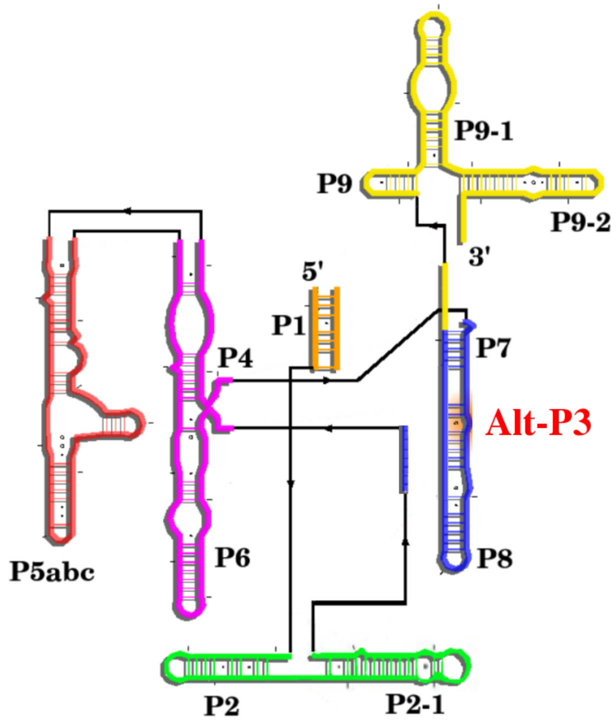
Surface water H-bond kinetics

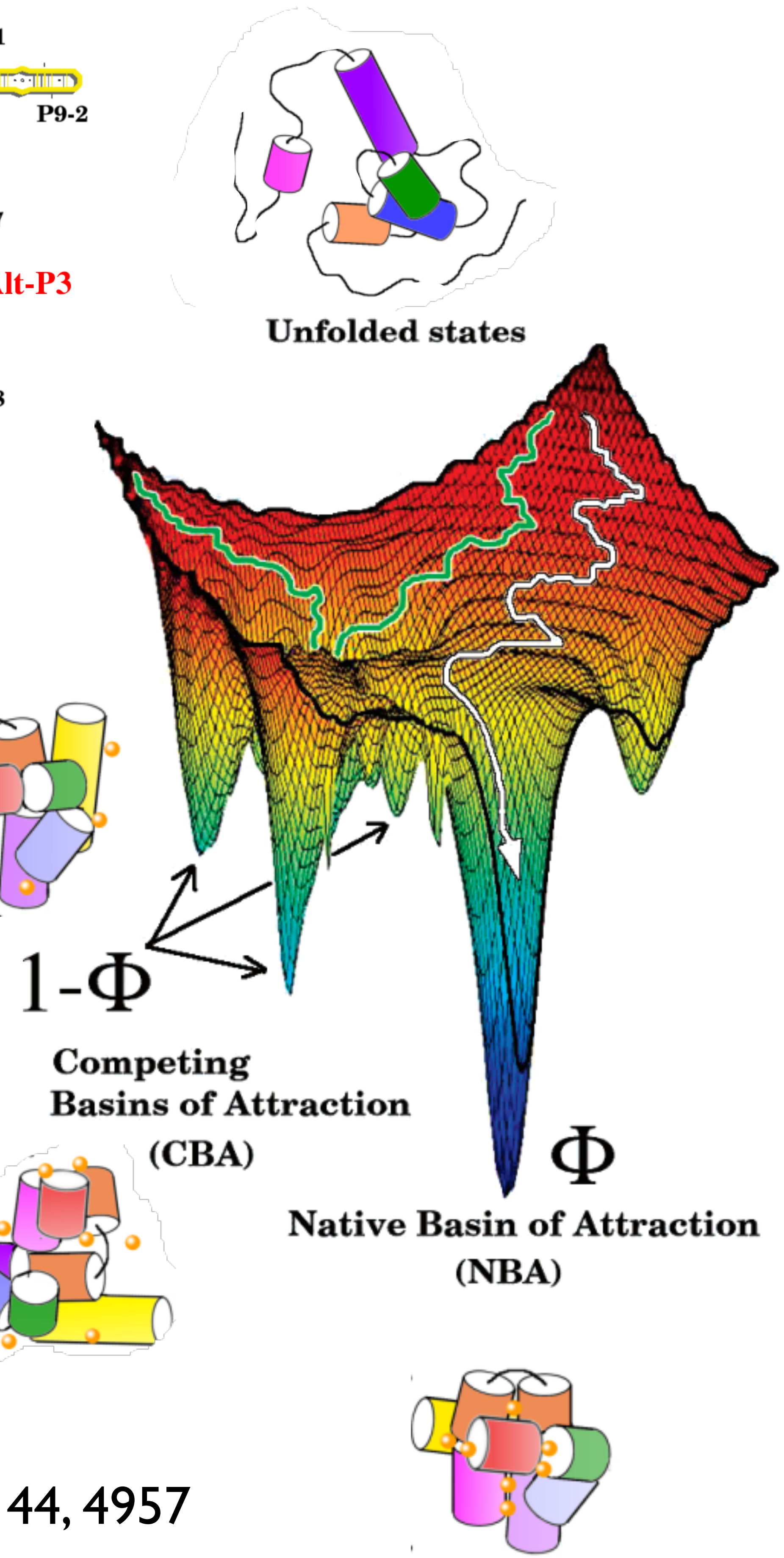


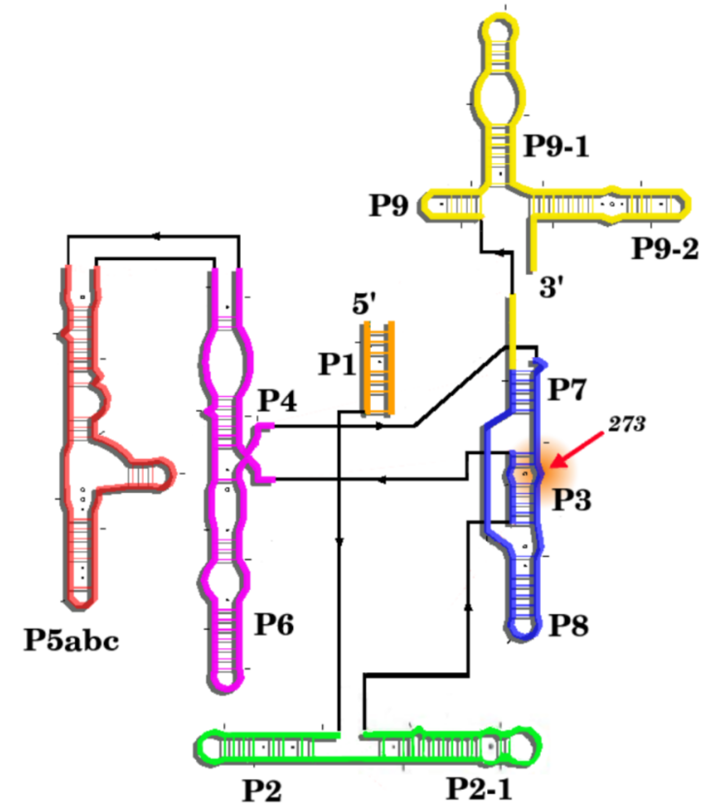




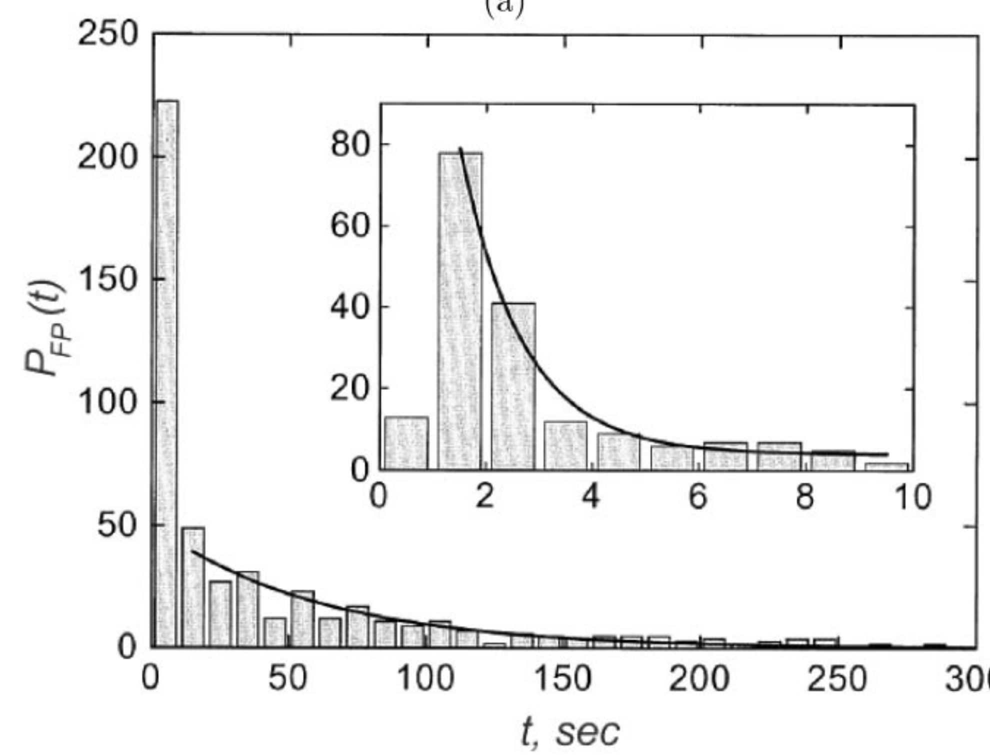
J. Phys. Chem. B. (2014) vol. 118, 7910



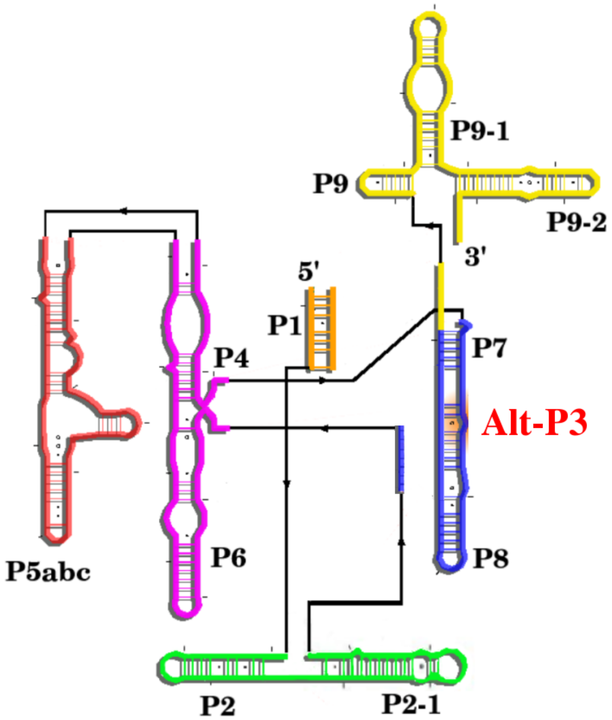


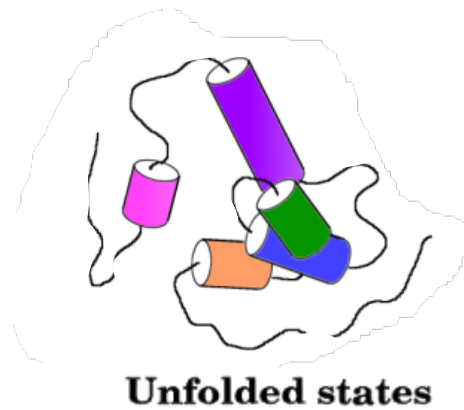


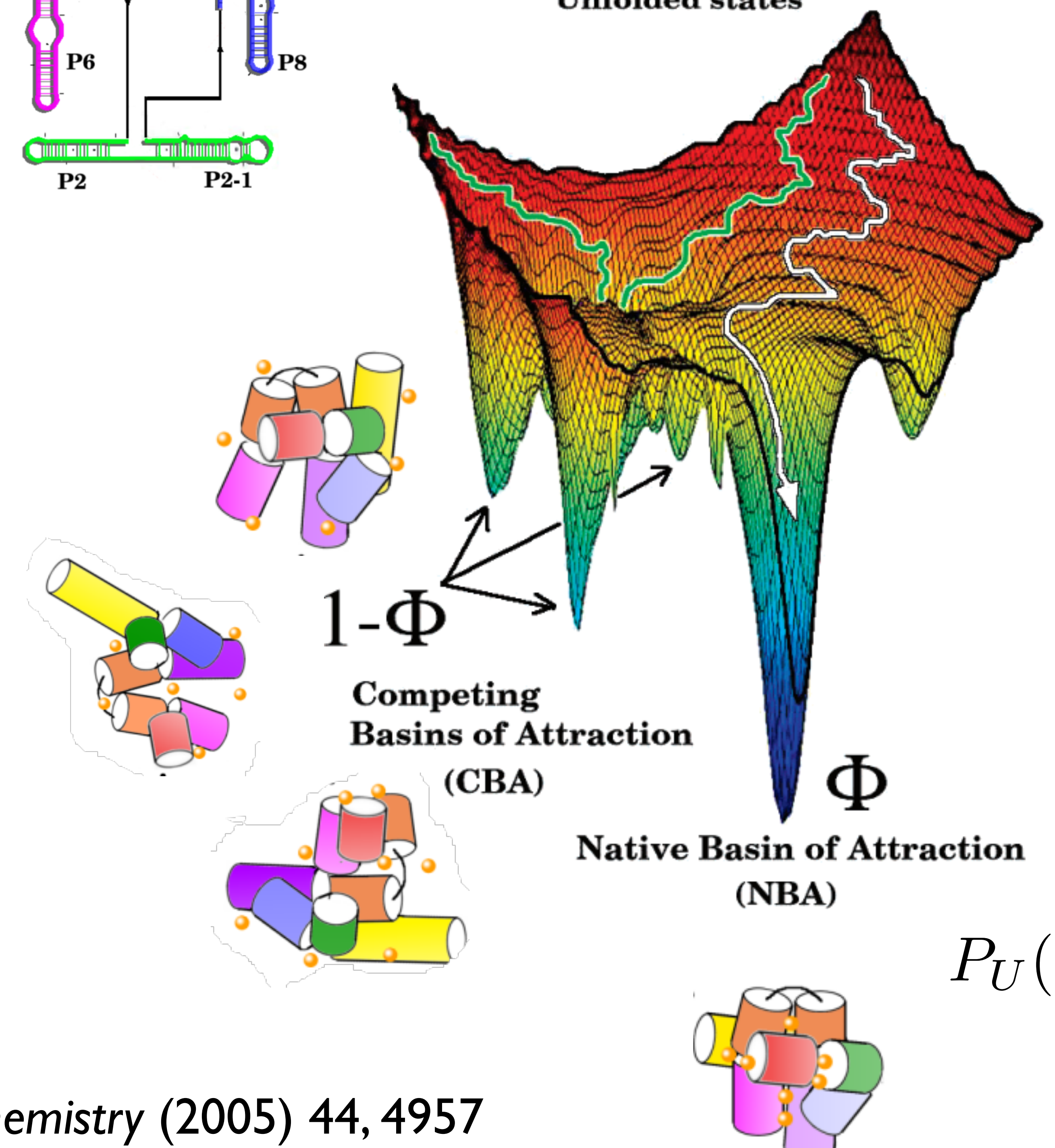
(a)

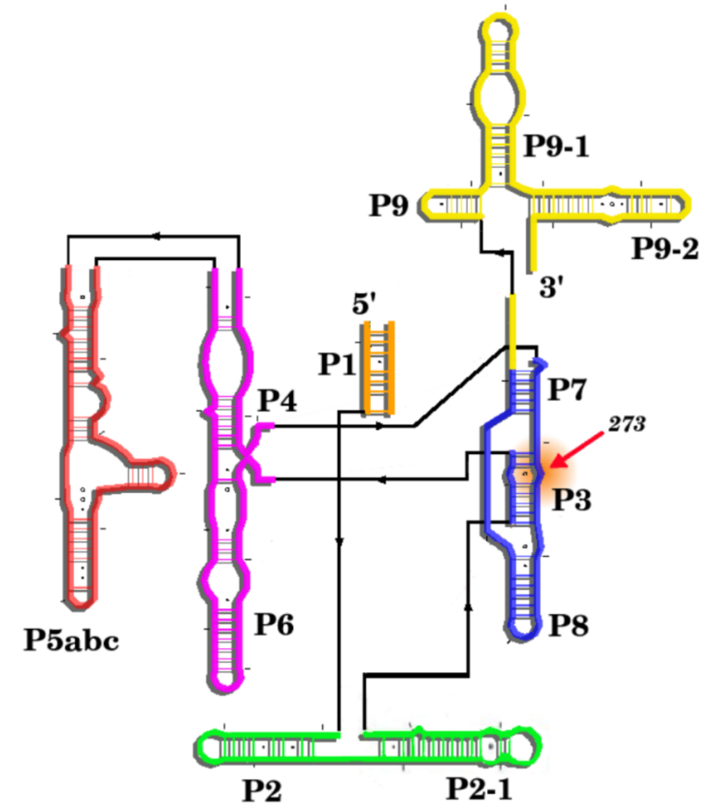


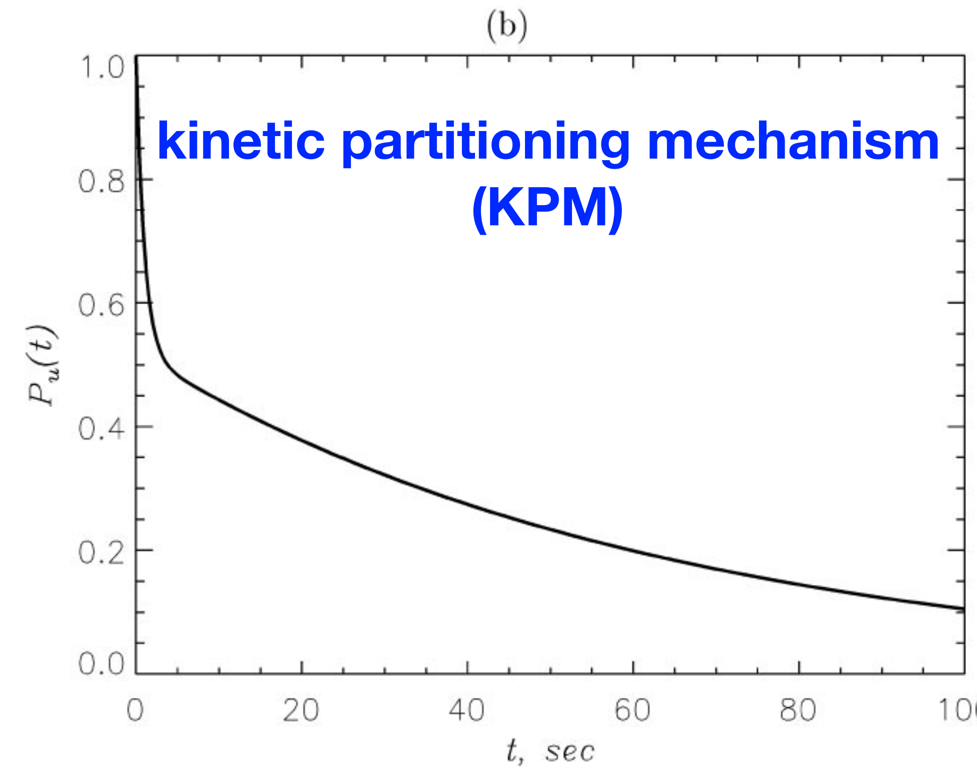
Biochemistry (2005) 44, 4957







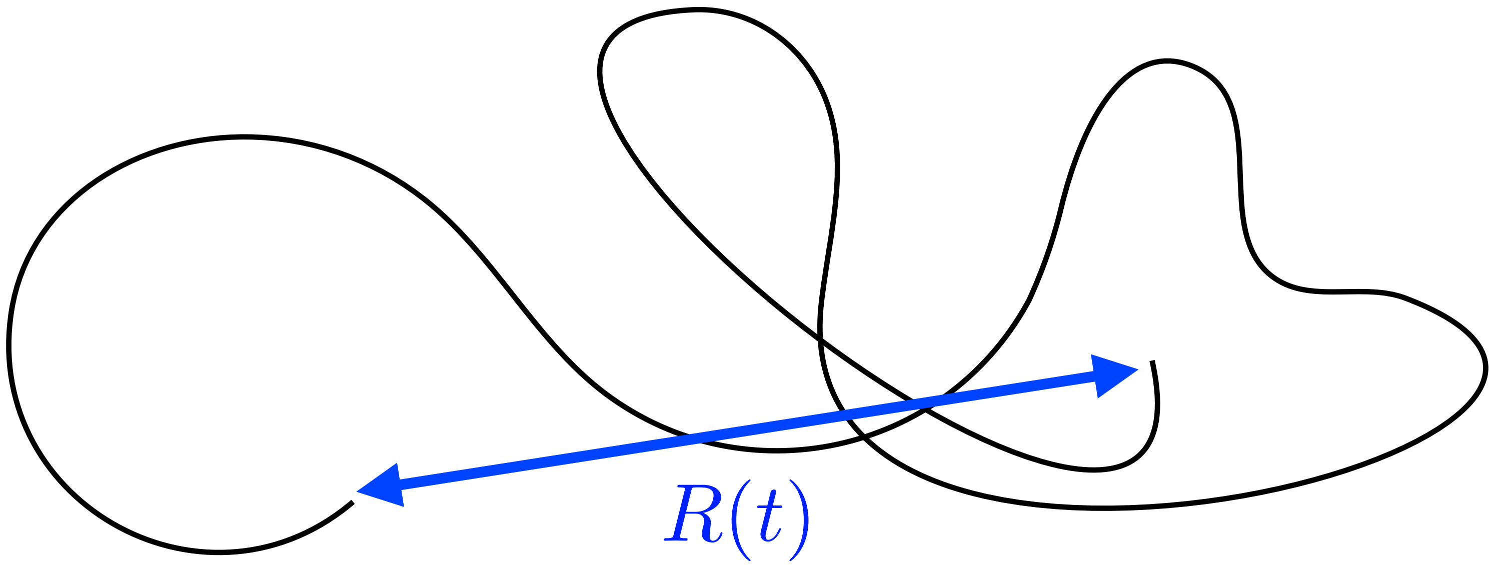




$$P_U(t) = \Phi e^{-t/\tau_{\text{fast}}} + (1-\Phi)e^{-t/\tau_{\text{slow}}}$$

$$\Phi = 0.08$$

Biochemistry (2005) 44, 4957



$$\tau_R = \frac{N^2 a^2}{3\pi^2 D_0}$$

$$\boxed{\langle \vec{R}(t) \cdot \vec{R}(0) \rangle = N a^2 \sum_{n \text{ odd}} \frac{8}{n^2 \pi^2} e^{-n^2 t/\tau_R}}$$

$$\zeta \frac{\partial r(s,t)}{\partial t} = -\frac{\delta U[r(s,t)]}{\delta r_i} + \xi(s,t) \qquad U[r(s,t)] = \frac{3k_BT}{2a^2} \int_0^N \left(\frac{\partial r(s,t)}{\partial s} \right)^2 ds$$

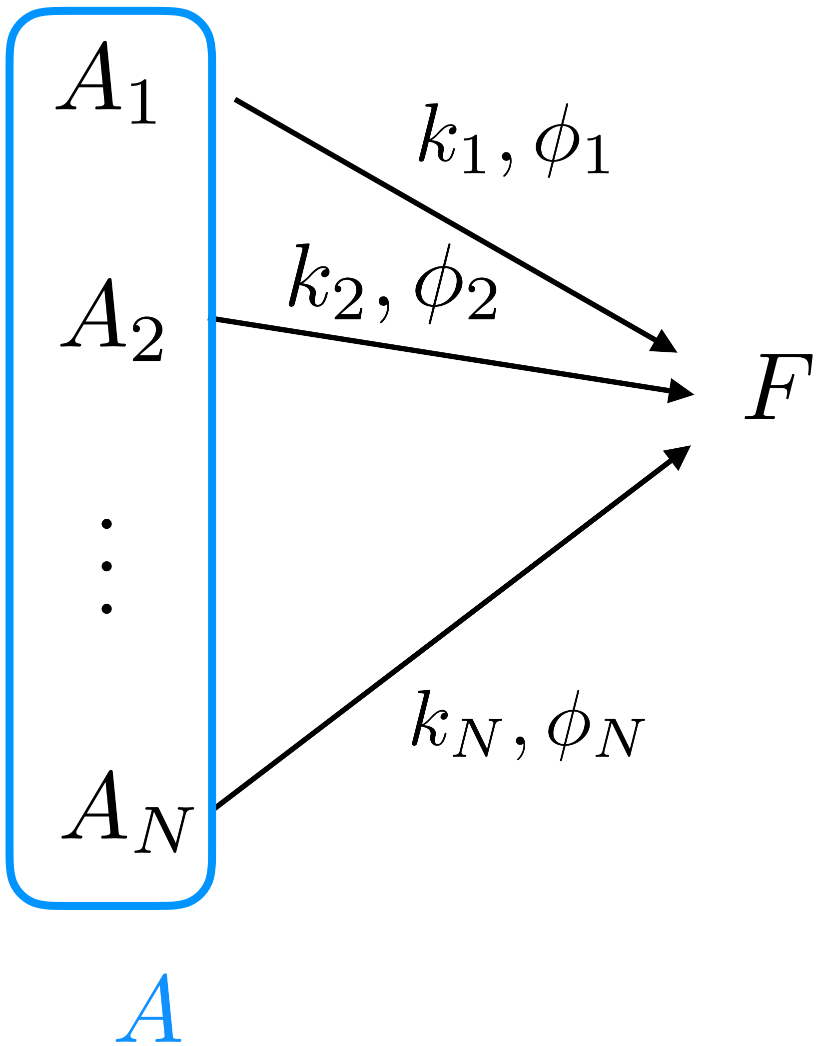
$$= \frac{3k_BT}{a^2} \frac{\partial^2 r(s,t)}{\partial s^2} + \xi(s,t) \longrightarrow 2N\zeta \dot{r}_n(t) = -\frac{6k_BT\pi^2}{Na^2} n^2 r_n(t) + N\xi_n(t)$$

$$r(s,t) = r_0(t) + 2 \sum_{n=1}^{N-1} r_n(t) \cos\left(\frac{n\pi s}{N} \right)$$

see Doi & Edwards
(The Theory of Polymer Dynamics)

$$R(t) = r(N,t) - r(0,t) = 2 \sum_{n=1}^{N-1} r_n(t) \cos(n\pi) - 1)$$

Parallel processes



$$S_A(t) = \sum_{i=1}^{N} \phi_i e^{-k_i t} \quad \left(\sum_{i=1}^{N} \phi_i = 1 \right)$$

$$:= \int_0^\infty dk \phi(k) e^{-kt}$$

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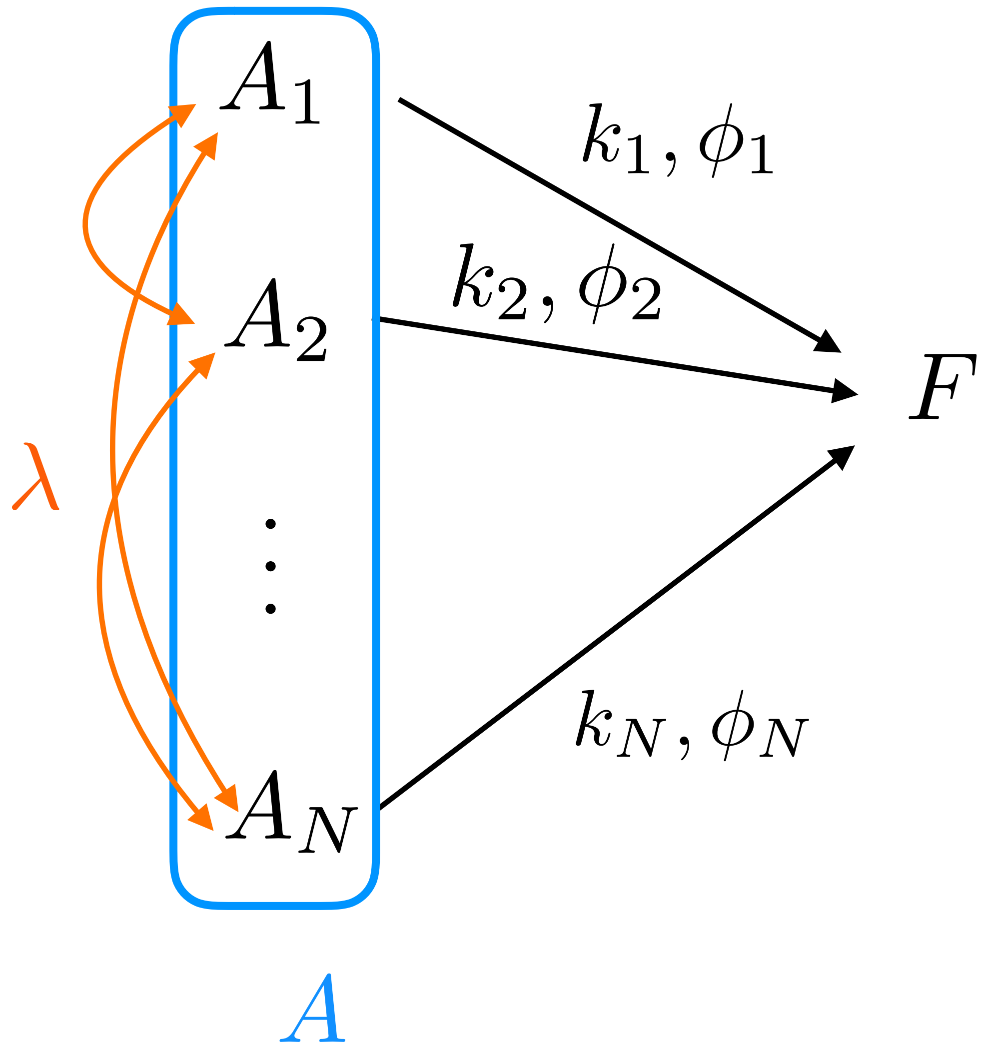

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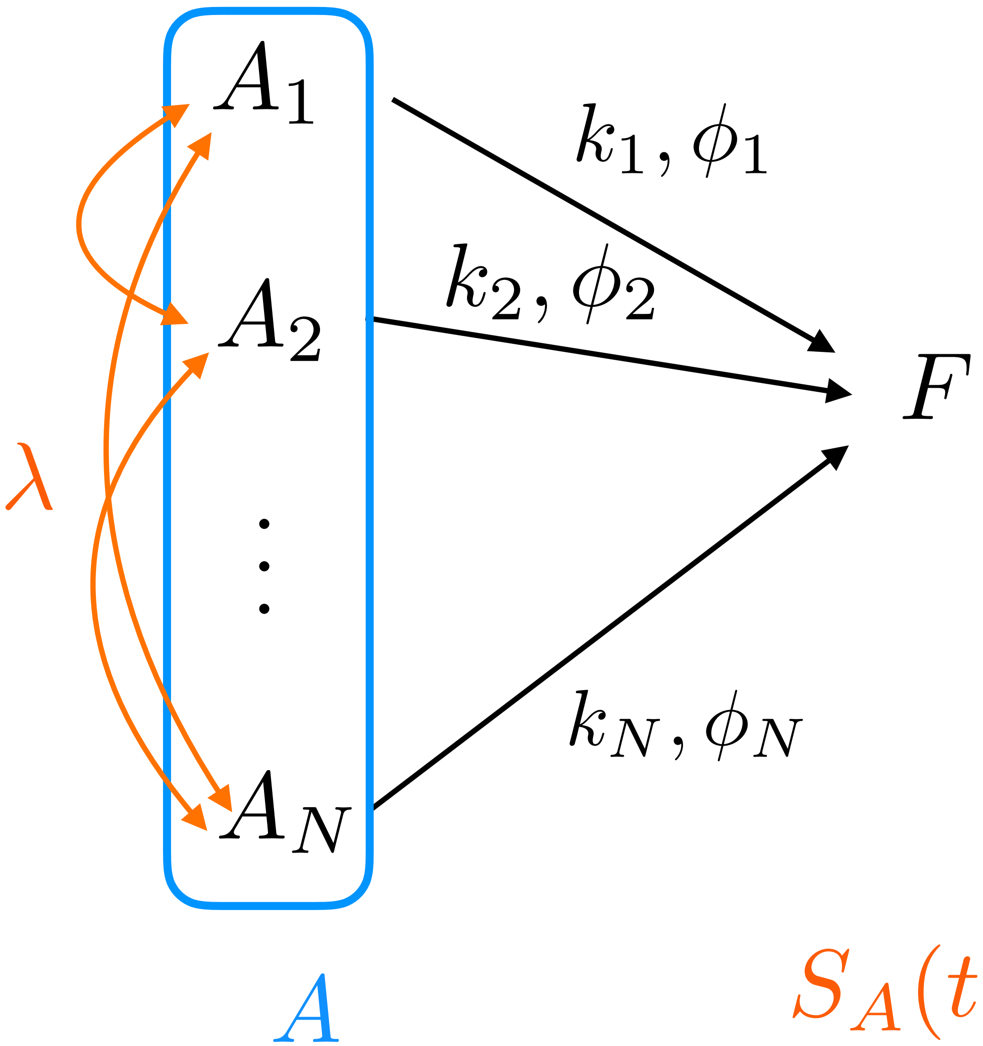

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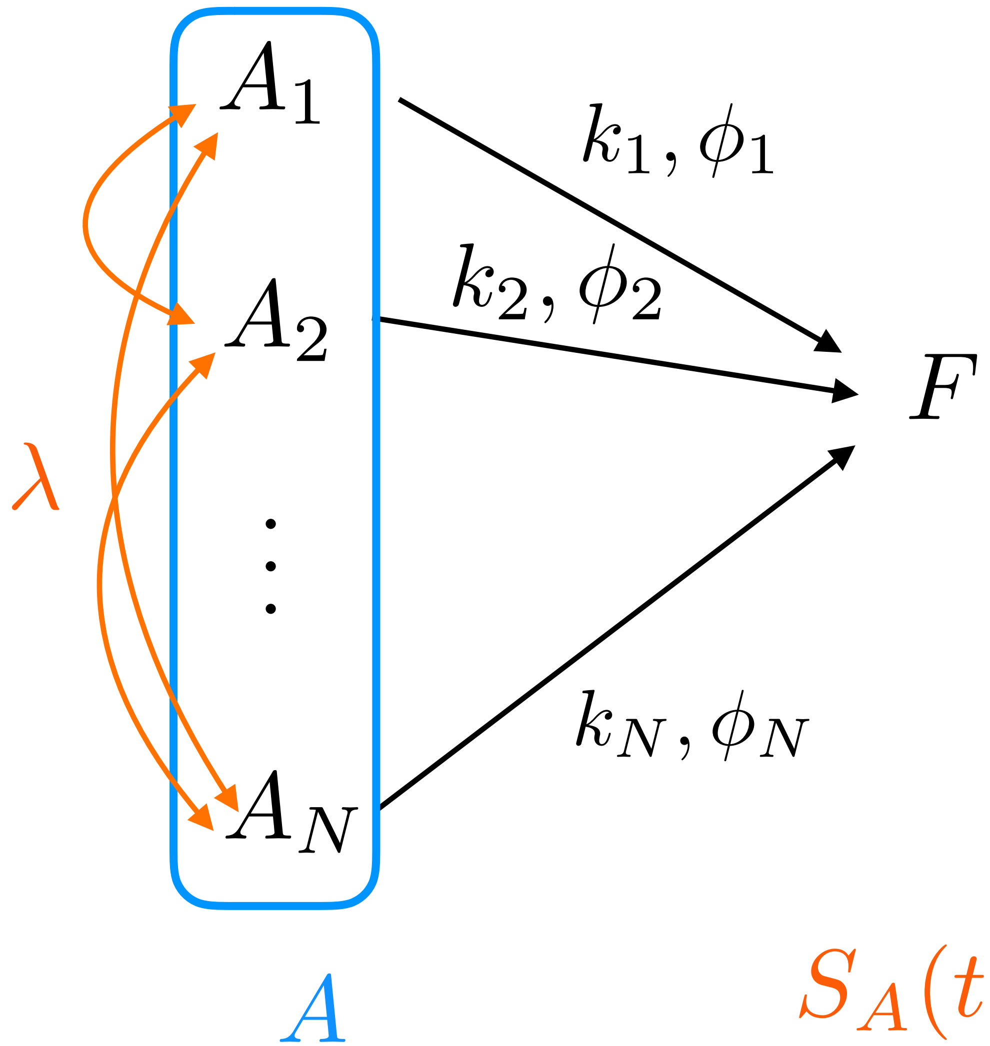
$$S_A(t) \sim e^{-\left(\sum_i k_i\right) \times t}$$

Parallel processes



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$$k/\lambda$$

Deborah number : “The mountains flowed before the lord”

$$De = \frac{\text{time of relaxation}}{\text{time of observation}} = \frac{\tau_{\text{relax}}}{\mathcal{T}_{obs}}$$

De << 1 : fluid-like

De >> 1 : solid-like

Weissenberg number

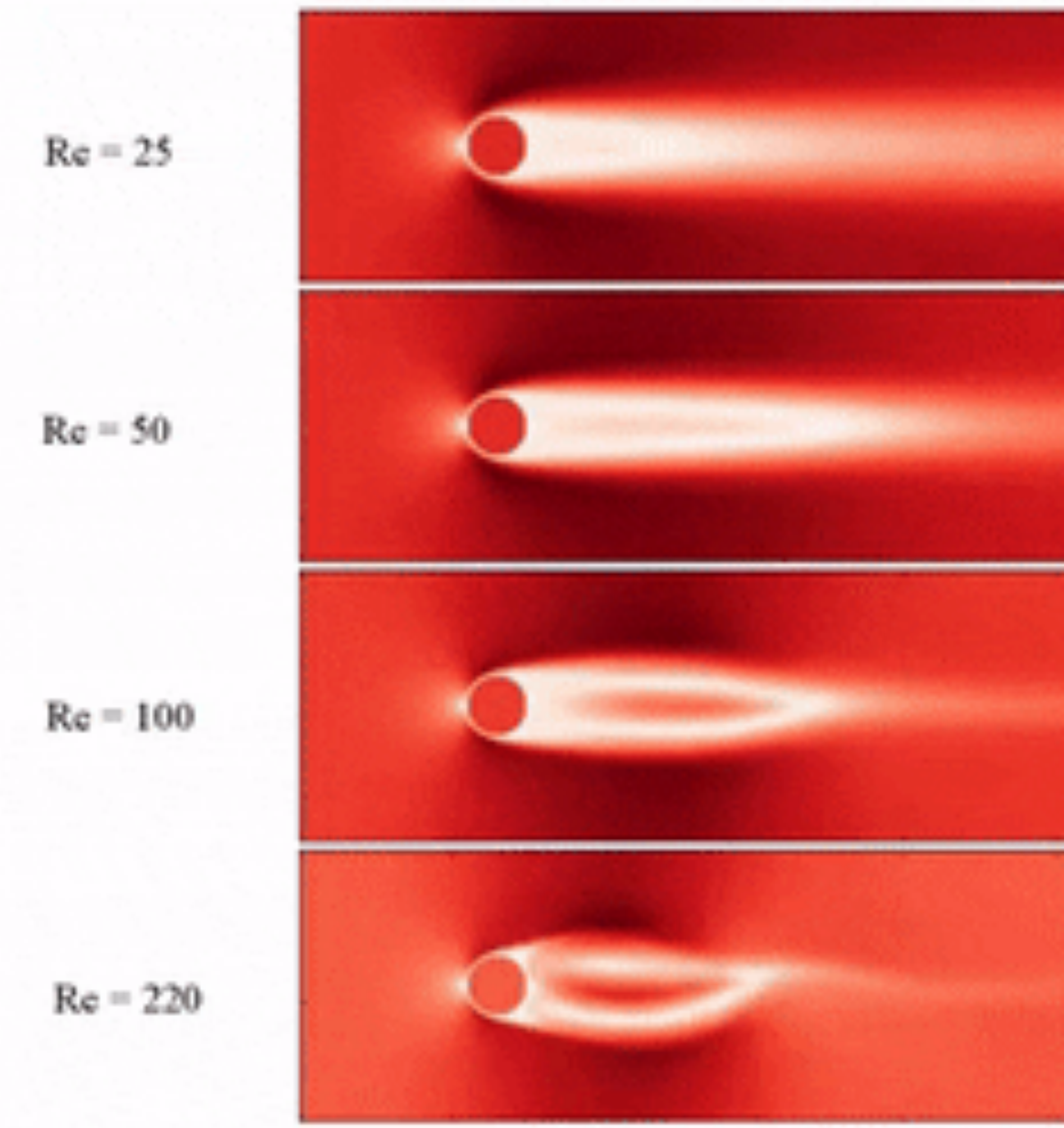
$$\text{Wi} = \frac{\text{elastic forces}}{\text{viscous forces}} \sim \tau_{\text{relax}}\dot{\gamma}$$

Reynolds number

$$\text{Re} = \frac{\text{intertial forces}}{\text{viscous forces}} \propto \frac{\rho u_0 L}{\mu}$$

$$Re = 10^{-5} \text{ (bacteria)}$$

$$L/l_p \qquad t/\tau_R \qquad E/k_B T$$



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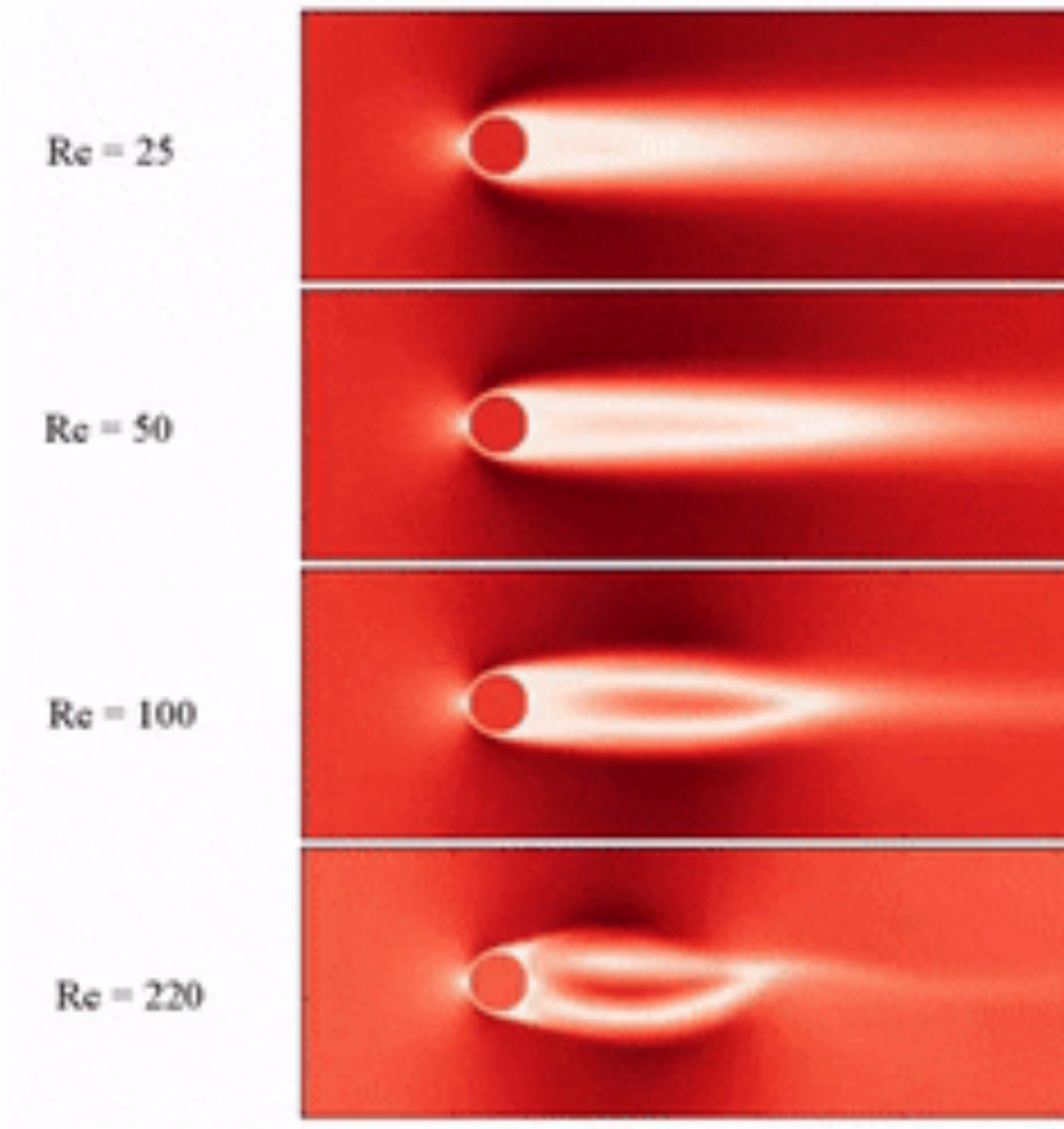

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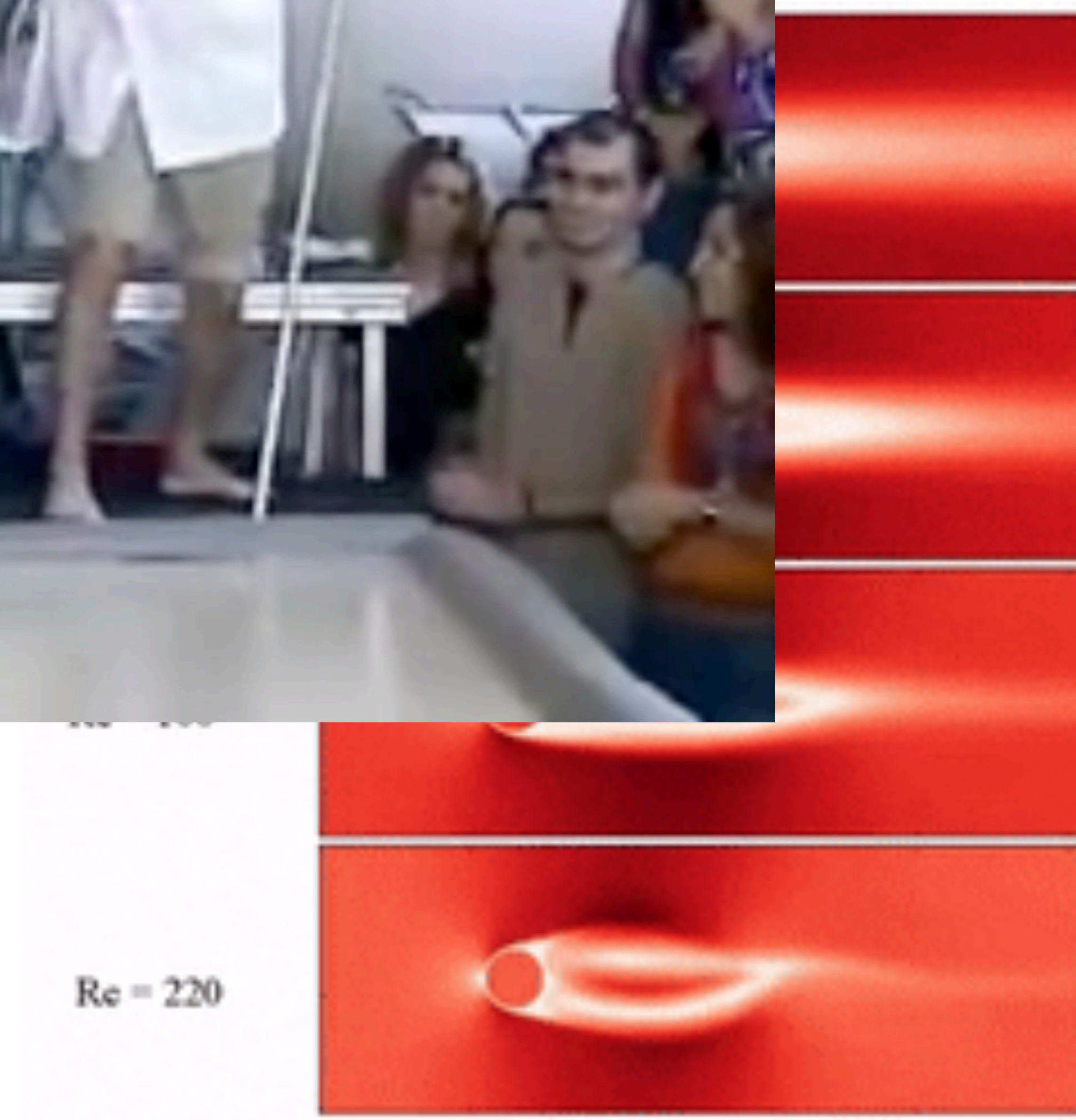

$$Re = 10^{-5} \text{ (bacteria)}$$

$$L/l_p \qquad t/\tau_R \qquad E/k_BT$$

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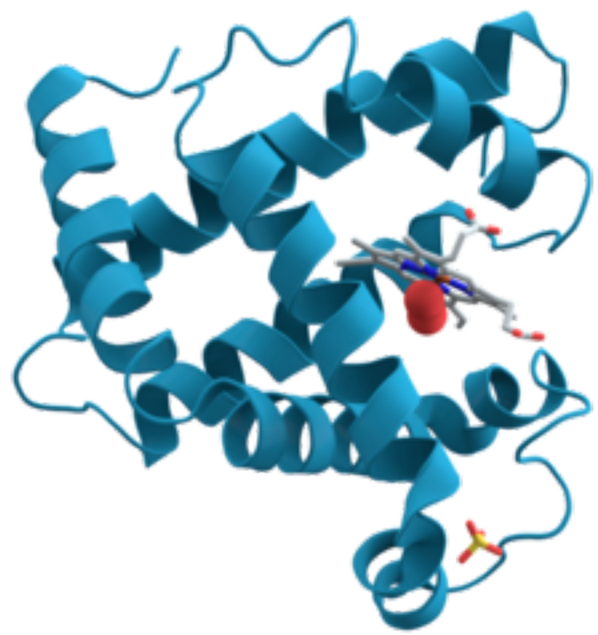
- Polymer relaxation (Protein folding under tension, Expanding sausage model)
- Broken ergodicity : Heterogeneity in biomolecular dynamics

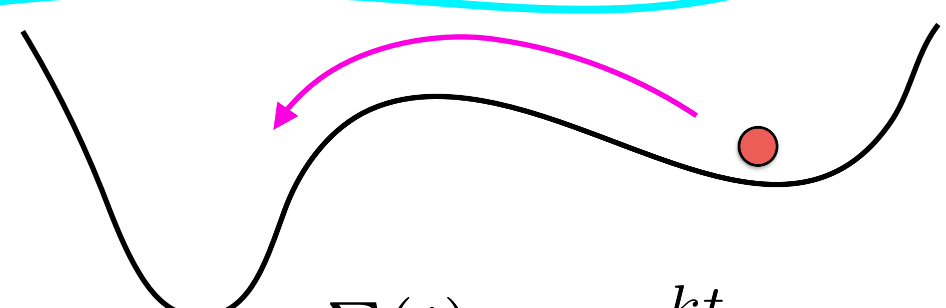
Kinetics from disordered systems:
Binding kinetics of CO to myoglobin in 80s by Frauenfelder & colleagues ….

$k \sim \eta^{-\kappa}$ (solvent viscosity) $\kappa = 0.4 - 0.8$?

D. Beece, L. Eisenstein, H. Frauenfelder, D. Good, M. C. Marden, L. Reinisch, A. H. Reynolds, L. B. Sorensen, and K. T. Yue, Biochemistry 19, 5147 (1980).



cf. $k \sim \frac{\omega_0 \omega_{ts}}{\eta} e^{-\Delta F^{\ddagger}}$

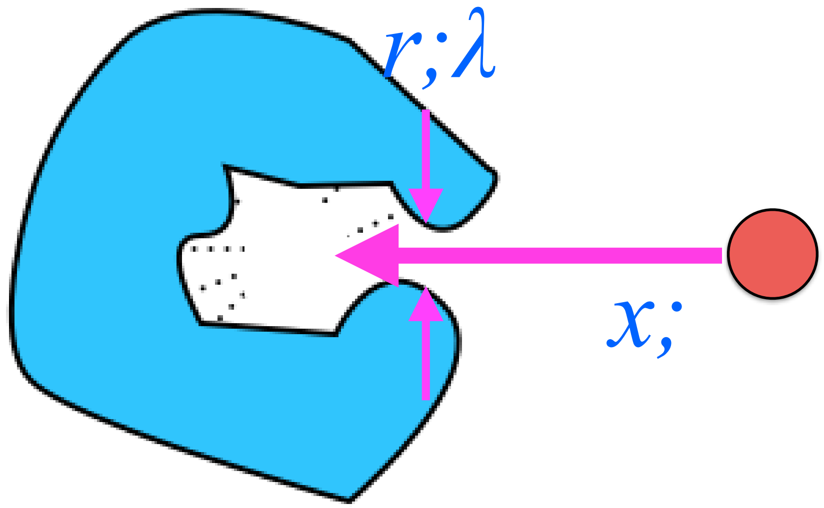


$\Sigma(t) = e^{-kt}$

Dynamical disorder: Passage through a fluctuating bottleneck

Robert Zwanzig
Laboratory of Chemical Physics, Building 2, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda Maryland 20892

J. Chem. Phys. (1992) 97, 3587



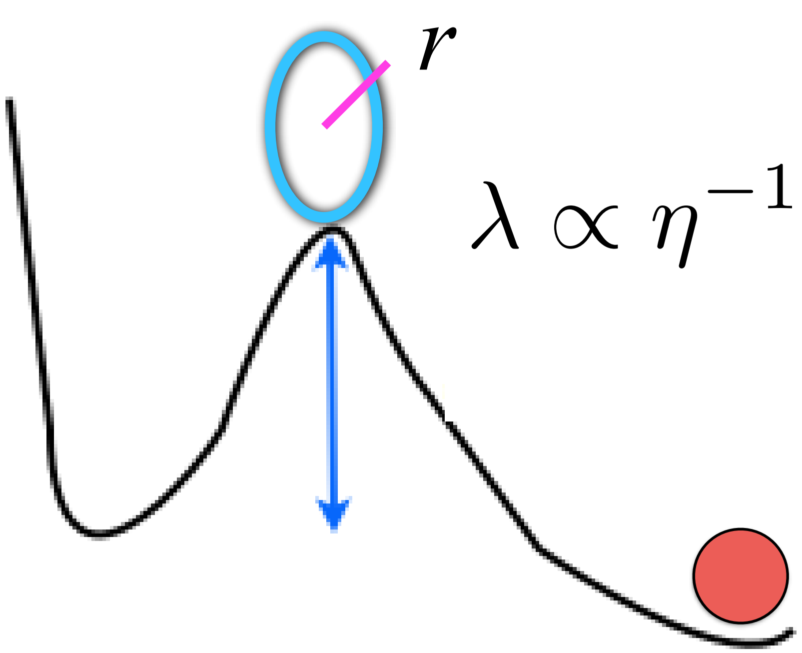
$$\zeta \partial_t x = -\partial_x U_{\text{eff}}(x; r) + F_x(t)$$

$$\partial_t r = -\lambda r + F_r(t)$$

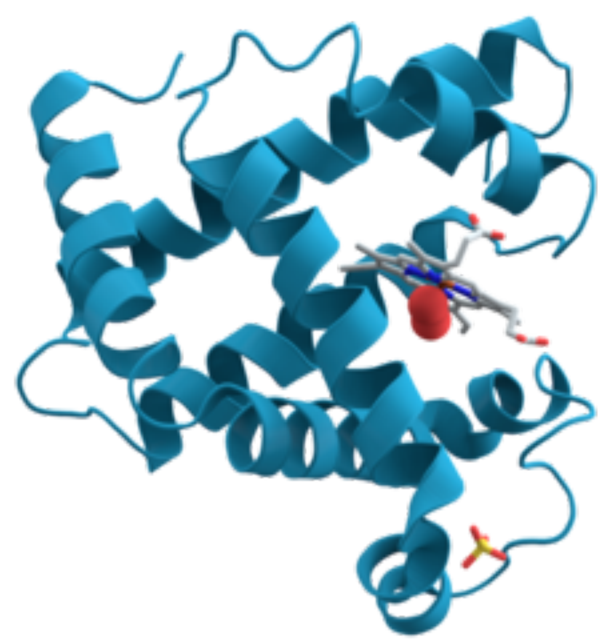
$$\langle F_x(t) F_x(t') \rangle = 2\zeta k_B T \delta(t - t')$$

$$\langle F_r(t) F_r(t') \rangle = 2\lambda\theta\delta(t - t') \qquad \langle r^2 \rangle_{eq} = \theta$$

Binding rate ~ kr^2



$$\lambda \propto \eta^{-1}$$



$$K(r) = kr^2$$

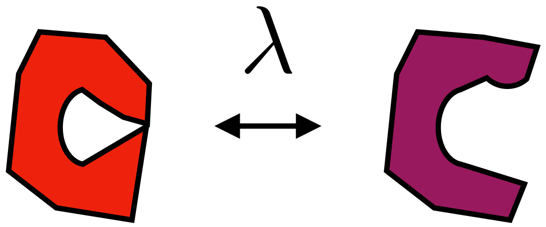
$$\frac{d\Sigma}{dt} = -K(r)\Sigma \qquad \partial_t r = -\lambda r + F_r(t) \qquad \langle r^2 \rangle_{eq} = \theta$$

$\lambda \to \infty$

(annealed disorder)

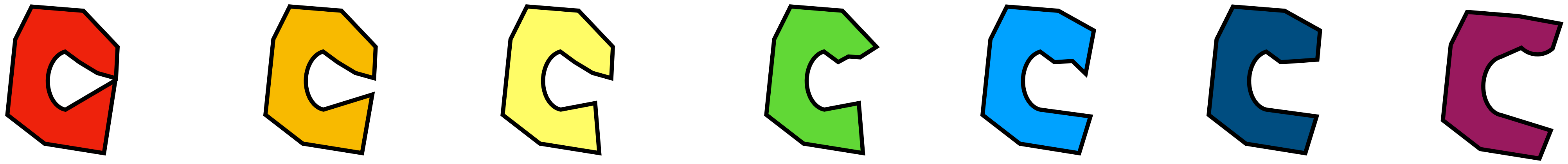
$$kr^2 \to k\theta$$

$$\Sigma(t) = e^{-k\theta t}$$



$\lambda \to 0$

(quenched disorder)



$$\Sigma(t) \sim \int_0^\infty dr e^{-kr^2 t} P(r) \sim \int_0^\infty dr e^{-kr^2 t} e^{-r^2/2\theta}$$

$$\sim (1 + 2k\theta t)^{-1/2}$$

$$\zeta \partial_t x = -\partial_x U_{\text{eff}}(x; r) + F_x(t) \qquad \langle F_x(t) F_x(t') \rangle = 2\zeta k_B T \delta(t - t')$$

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$$\langle r^2 \rangle_{eq} = \theta$$

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$$\boxed{\partial_t \overline{\rho} = D\partial_x(\partial_x + \beta U'(x))\overline{\rho} + \lambda\theta\partial_r(\partial_r + r/\theta)\overline{\rho}}$$

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$$\partial_t \overline{\rho}(x,r,t) = D\frac{\partial}{\partial x}\left(\frac{\partial}{\partial x} + \beta U'(x)\right)\overline{\rho} + \lambda\theta\frac{\partial}{\partial r}\left(\frac{\partial}{\partial r} + \frac{r}{\theta}\right)\overline{\rho} \underline{- k_r r^2 \delta(x - x_{ts})\overline{\rho}(x,r,t)}$$

$$\partial_t \overline{\rho}(x,r,t) = \mathcal{L}_x \overline{\rho}(x,r,t) + \mathcal{L}_r \overline{\rho}(x,r,t) - \mathcal{S}\overline{\rho}(x,r,t) \qquad \mathcal{S}(x,r)\overline{\rho}$$

$$\overline{C}(r,t) = \int dx \overline{\rho}(x,r,t)$$

$$\frac{\partial \overline{C}}{\partial t} = \mathcal{L}_r \overline{C}(r,t) - k_r r^2 \overline{\rho}(x_{\text{ts}}, r, t).$$

$$\overline{\rho}(x_{\text{ts}}, r, t) = \phi_x(x_{\text{ts}})\overline{C}(r,t)$$

$$\phi(x_{\text{ts}}) = \frac{e^{-U_{\text{eff}}(x_{\text{ts}})/k_B T}}{\int dx e^{-U_{\text{eff}}(x)/k_B T}} \approx \sqrt{U''_{\text{eff}}(x_0)/2\pi k_B T}\, e^{-\beta(U_{\text{eff}}(x_{\text{ts}}) - U_{\text{eff}}(x_0))}$$

$$\frac{\partial \overline{C}}{\partial t} = \mathcal{L}_r \overline{C}(r,t) - k r^2 \overline{C}(r,t) \qquad \text{with } \overline{C}(r,0) \sim e^{-r^2/2\theta}$$

$\longrightarrow \Sigma(t) = \int_0^\infty \mathrm{d}r\, \overline{C}(r,t)$ survival probability

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$$\mathcal{L}_r \equiv \lambda\theta \frac{\partial}{\partial r}\left(\frac{\partial}{\partial r} + \frac{r}{\theta}\right)$$

$$\longrightarrow \Sigma(t) = \int_0^\infty \mathrm{d}r\, \overline{C}(r,t) \text{ survival probability}$$

By setting $\overline{C}(r,t) = \exp\left(\nu(t) - \mu(t)r^2\right)$, equation (29) can be solved exactly, leading to

$$\begin{aligned} \nu'(t) &= -2\lambda\theta\mu(t) + \lambda \\ \mu'(t) &= -4\lambda\theta\mu^2(t) + 2\lambda\mu(t) + k. \end{aligned} \tag{30}$$

The solution for $\mu(t)$ is obtained by solving $\frac{4\theta}{\lambda}\int_{1/4\theta}^{\mu(t)-1/4\theta} \frac{\mathrm{d}\alpha}{S^2-16\theta^2\alpha^2} = t$, and this leads to

$$\begin{aligned} \frac{\mu(t)}{\mu(0)} &= \frac{1}{2}\left\{1 + S\frac{(S+1)-(S-1)E}{(S+1)+(S-1)E}\right\} \\ \nu(t) &= -\frac{\lambda t}{2}(S-1) + \log\left(\frac{(S+1)+(S-1)E}{2S}\right)^{-1/2} \end{aligned} \tag{31}$$

with $\mu(0) = 1/2\theta$. The survival probability, which was derived by Zwanzig, is

$$\Sigma(t) = \exp\left(-\frac{\lambda}{2}(S-1)t\right)\left(\frac{(S+1)^2-(S-1)^2E}{4S}\right)^{-1/2} \tag{32}$$

where $S = \left(1 + \frac{4k\theta}{\lambda}\right)^{1/2}$ and $E = \mathrm{e}^{-2\lambda S t}$.

$$\Sigma(t) = \exp\left(-\frac{\lambda}{2}(S-1)t\right)\left(\frac{(S+1)^2 - (S-1)^2 E}{4S}\right)^{-1/2}$$ *show this !*

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where $S = \left(1+\frac{4k\theta}{\lambda}\right)^{1/2}$ and $E = e^{-2\lambda St}$.

$$\boxed{\begin{array}{ll} \lambda \to \infty & \Sigma(t) = e^{-k\theta t} \\ \lambda \to 0 & \Sigma(t) = (1+2k\theta t)^{-1/2} \end{array}}$$

show this !

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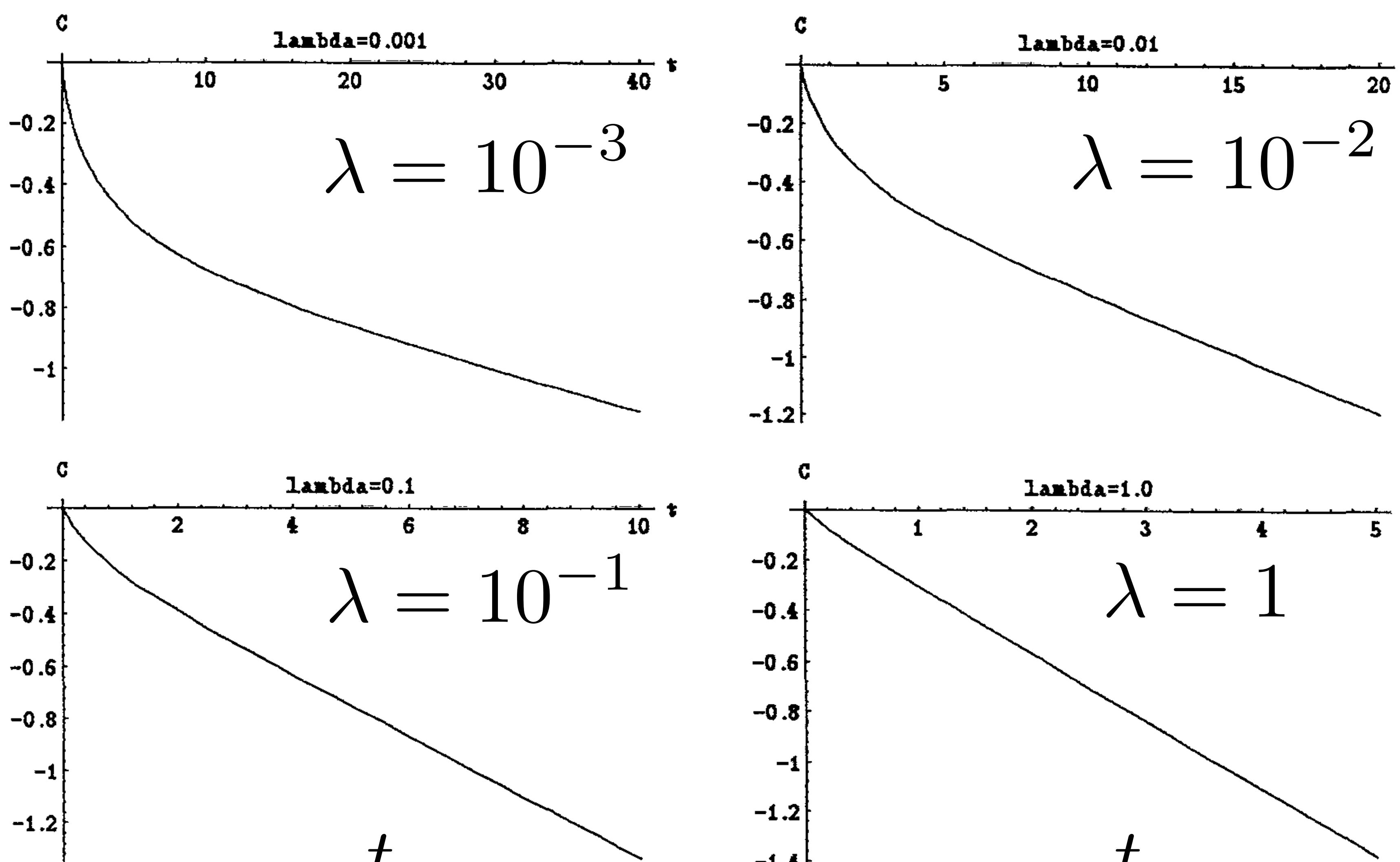
$\log_{10}\Sigma(t)$

$(k\theta = 1)$



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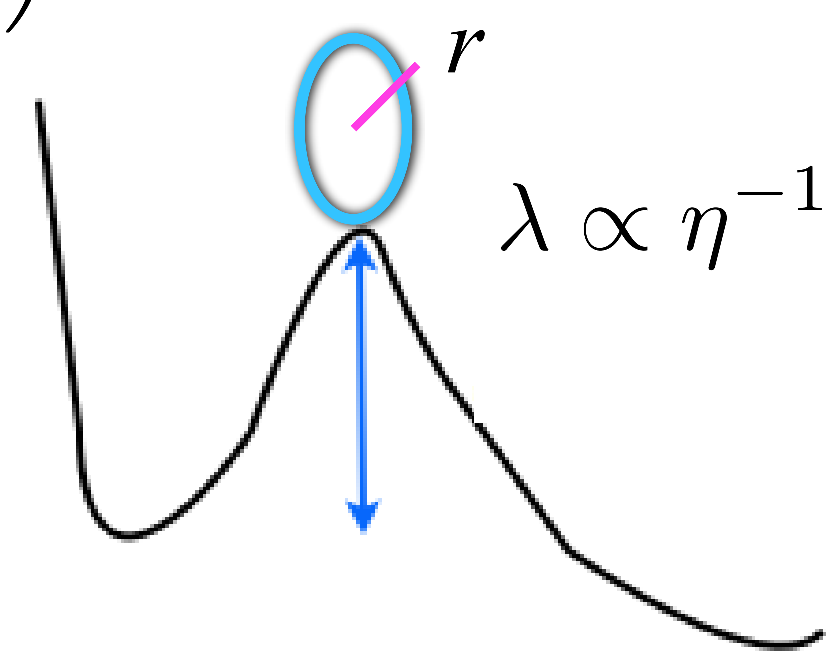
$$= \sum_{n=0}^{\infty} c_n e^{-\mu_n t}$$

$$\mu_n = \frac{\lambda}{2}(S-1) + 2n\lambda S$$

$$\mu_0 = \frac{\lambda}{2}(S-1) = \frac{\lambda}{2}\left(\left(1+\frac{4k\theta}{\lambda}\right)^{1/2} - 1\right)$$

$$\mu_0(\lambda\to\infty) \approx k\theta$$

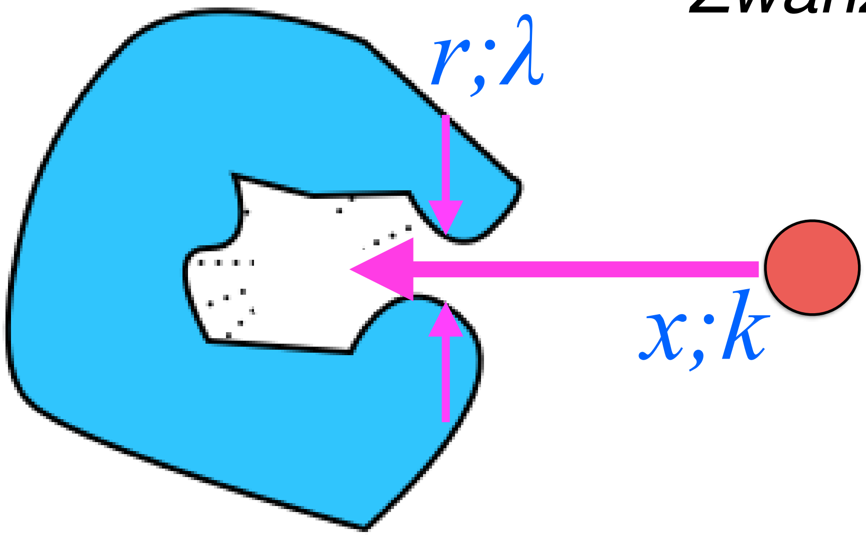
$$\boxed{\mu_0(\lambda\to 0) \approx (k\theta\lambda)^{1/2} \sim \eta^{-1/2}}$$



Fluctuating bottleneck model

- *Zwanzig (1992) JCP 97: 3567.*

k/λ



k vs λ

(i) k << λ : annealed disorder $\Sigma(t) = e^{-k\theta t}$

(ii) k >> λ : quenched disorder $\Sigma(t) = (1+2k\theta t)^{-1/2}$

(iii) k ~ λ : dynamical disorder

$$\Sigma(t) = e^{-\frac{\lambda}{2}(S-1)t}\left[\frac{(S+1)^2-(S-1)^2E}{4S}\right]^{-1/2}$$

$$S = (1+4k\theta/\lambda)^{1/2}$$

$$E(t) = e^{-2\lambda S t}$$

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$$\partial_t r = -\lambda r + F_r(t)$$ Binding rate $\sim kr^2$

$$\langle F_x(t)F_x(t')\rangle = 2\zeta k_B T\delta(t-t') \qquad \langle F_r(t)F_r(t')\rangle = 2\lambda\theta\delta(t-t')$$

$$\frac{\partial\overline{\varphi}(x,r,t)}{\partial t} = [\mathcal{L}_x(x)+\mathcal{L}_r(r)-\mathcal{S}(x,r)]\,\overline{\varphi}(x,r,t)$$

$\int_{-\infty}^{\infty}dx$

$$\partial_t\overline{C}(r,t) = [\mathcal{L}_r(r)-kr^2]\overline{C}(r,t)$$

$$\Sigma(t) = \int_0^\infty dr\overline{C}(r,t)$$

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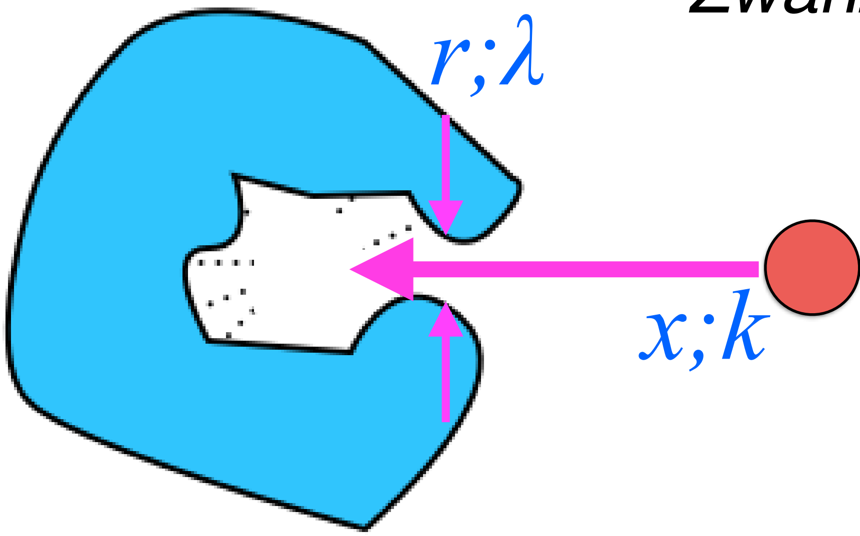

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$$\zeta\partial_t x=-\partial_x U_{\text{eff}}(x;r)+F_x(t)$$

$$\partial_t r=-\lambda r+F_r(t)$$ Binding rate $\sim kr^2$

$$\langle F_x(t)F_x(t')\rangle=2\zeta k_BT\delta(t-t') \qquad \langle F_r(t)F_r(t')\rangle=2\lambda\theta\delta(t-t')$$

(i) $\Sigma(t)\sim e^{-k\langle r^2\rangle t}=e^{-k\theta t}$ $\quad \langle r^2\rangle\equiv\theta$

(ii) $\Sigma(t)\sim\int dre^{-kr^2t}P(r)$

$$\sim\int dre^{-kr^2t}e^{-\frac{r^2}{2\theta}}\sim(1+2k\theta t)^{-1/2}$$

- Some Basics : Rate processes

- Types of disorder in dynamical processes : Quenched vs Dynamic disorder

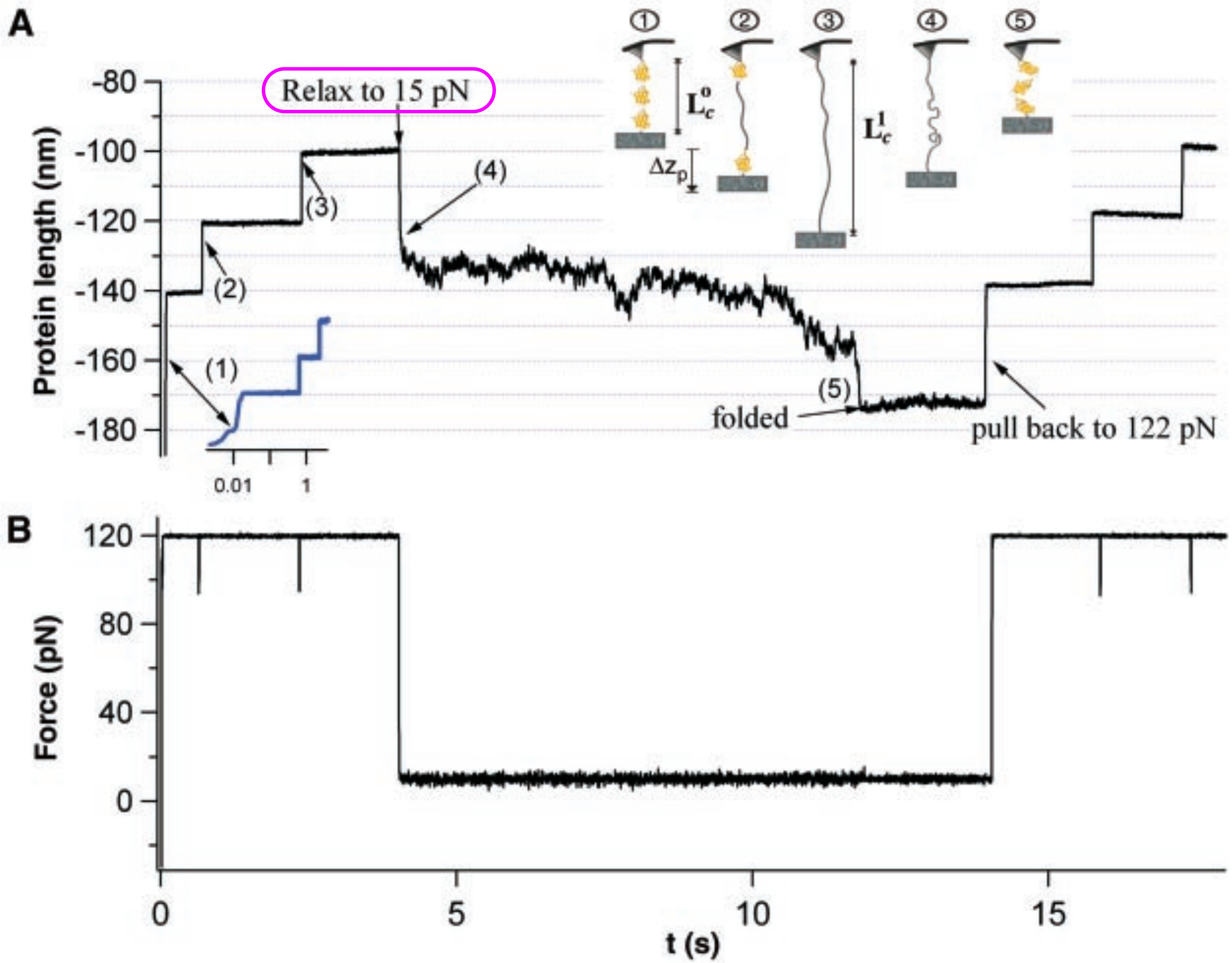
- Polymer relaxation (Protein folding under tension, Expanding sausage model)

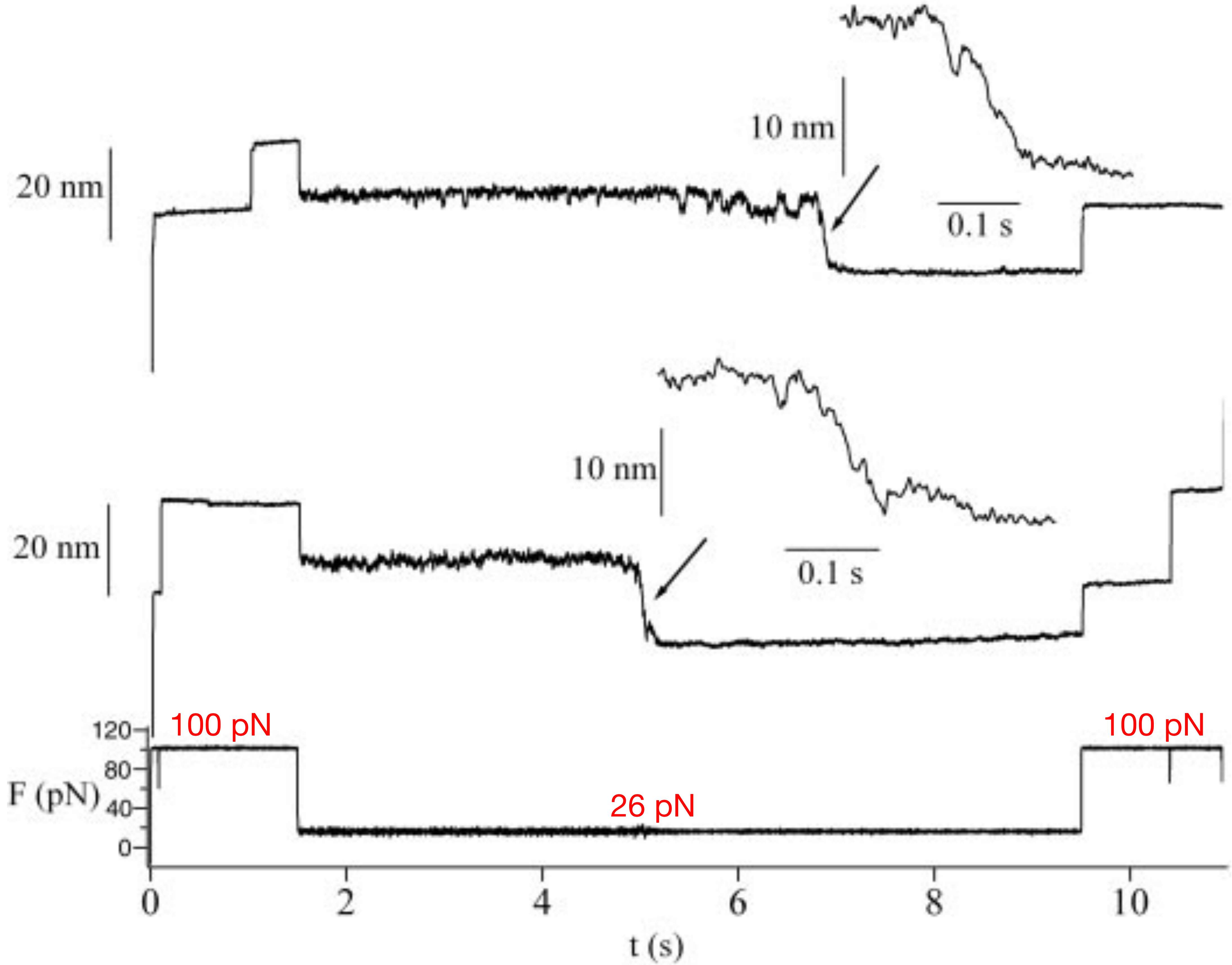
- Broken ergodicity : Heterogeneity in biomolecular dynamics

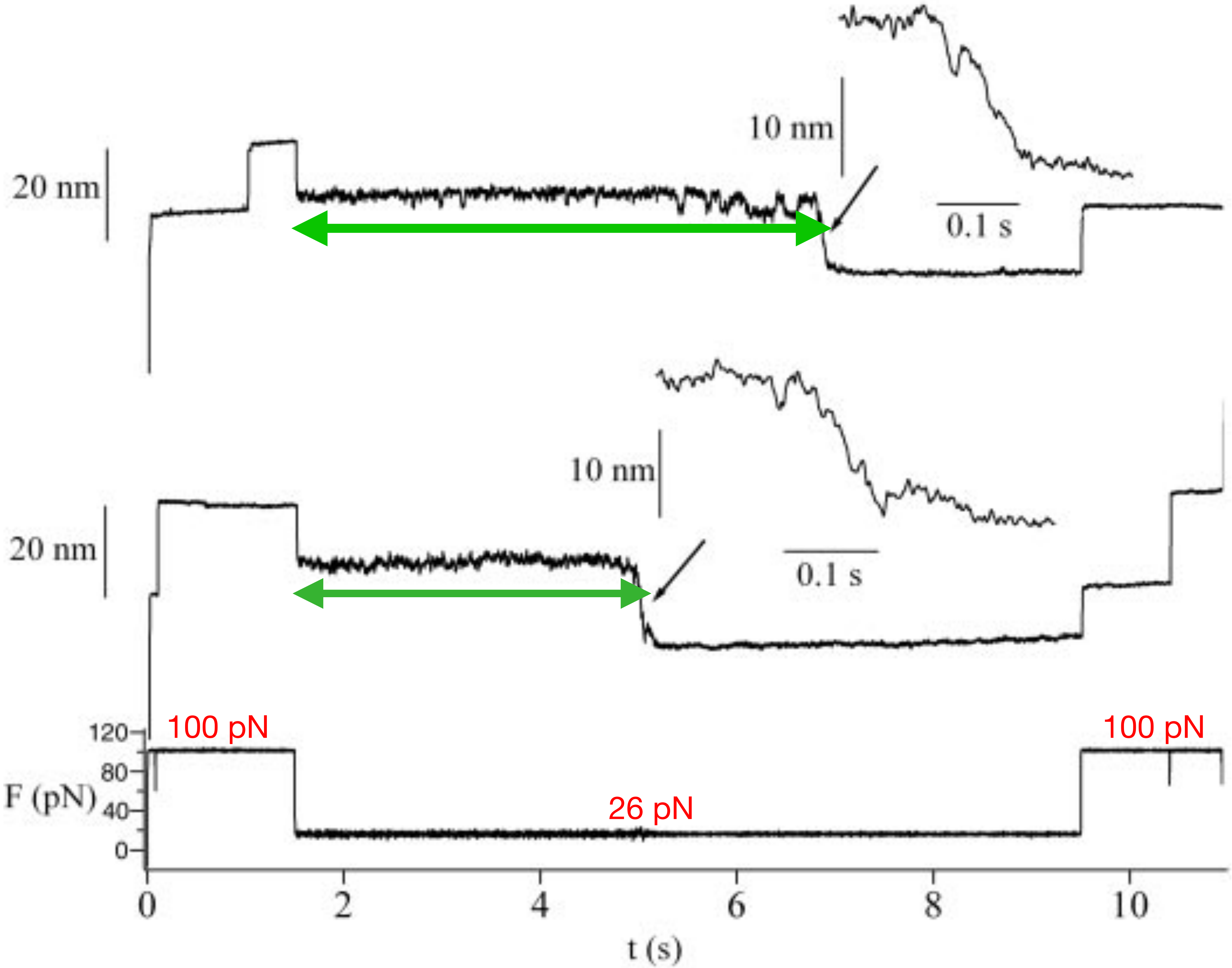
Force-Clamp Spectroscopy Monitors the Folding Trajectory of a Single Protein

Julio M. Fernandez* and Hongbin Li

Science (2004)




10 nm
0.1 s
20 nm
10 nm
0.1 s
20 nm
100 pN
100 pN
26 pN
F (pN)
120
80
40
0
0
2
4
6
8
10
t (s)



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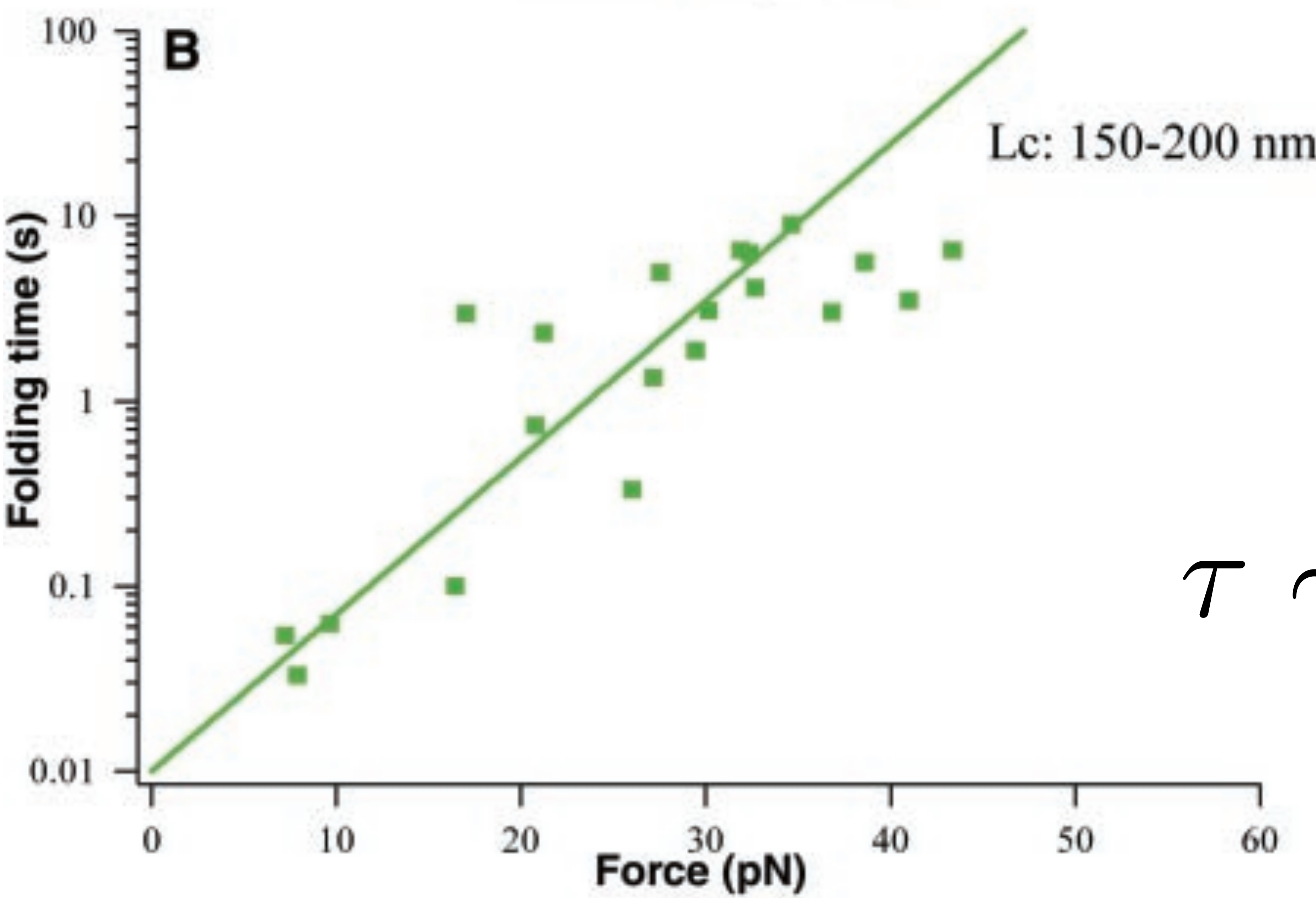
10
t (s)



B
Lc: 150-200 nm
Folding time (s)
100
10
1
0.1
0.01
0
10
20
30
40
50
60
Force (pN)

$$\tau \sim e^{f}$$

Proc. Natl. Acad. Sci. USA
Vol. 96, pp. 7916–7921, July 1999

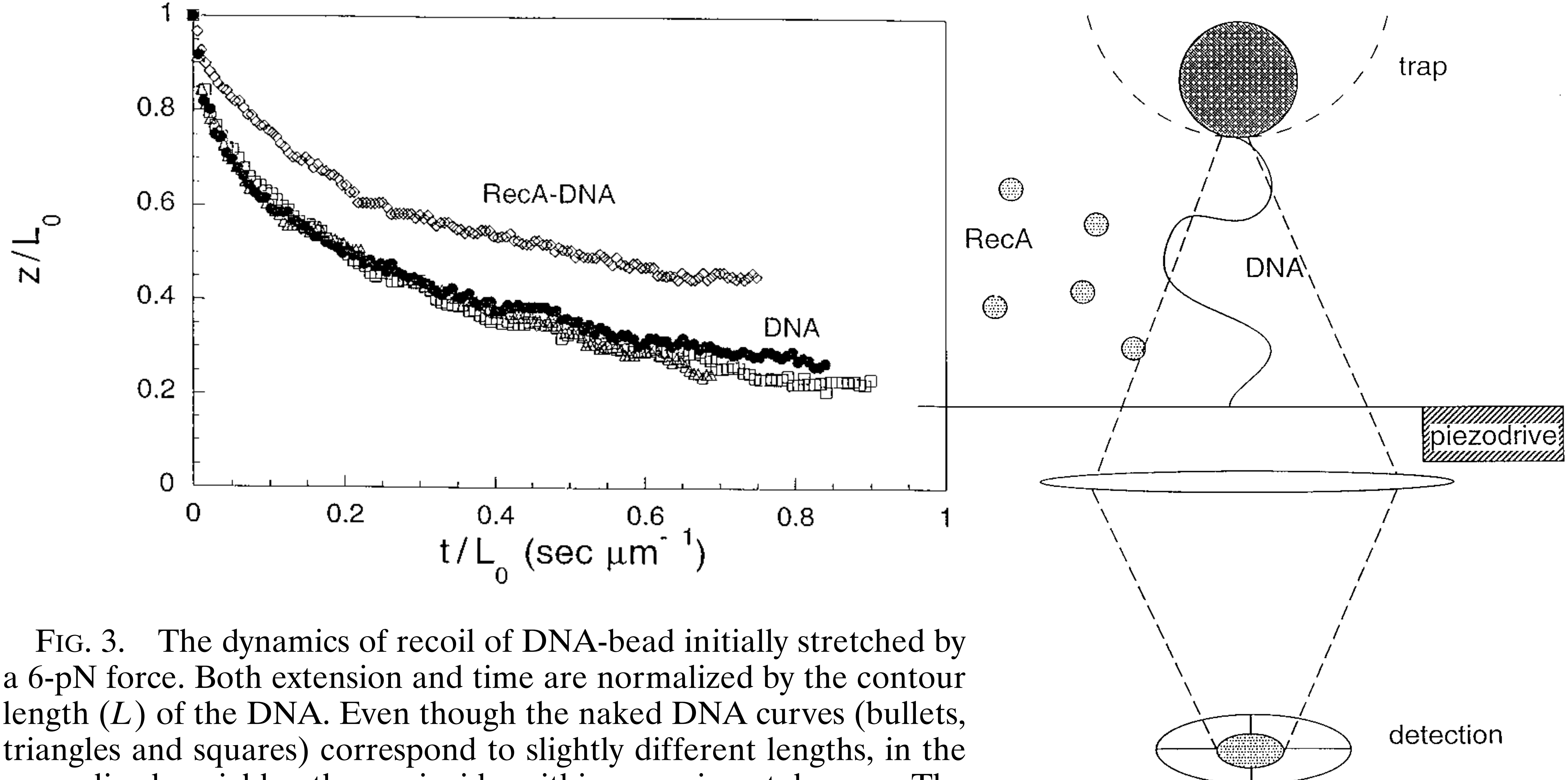
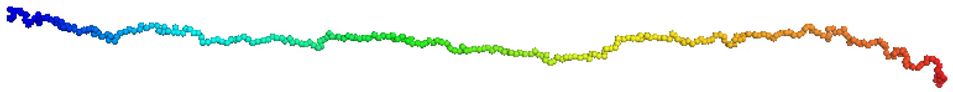
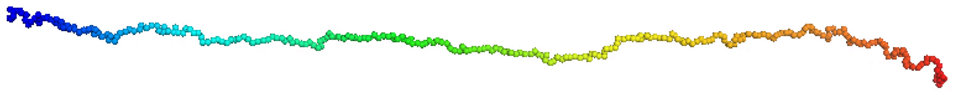
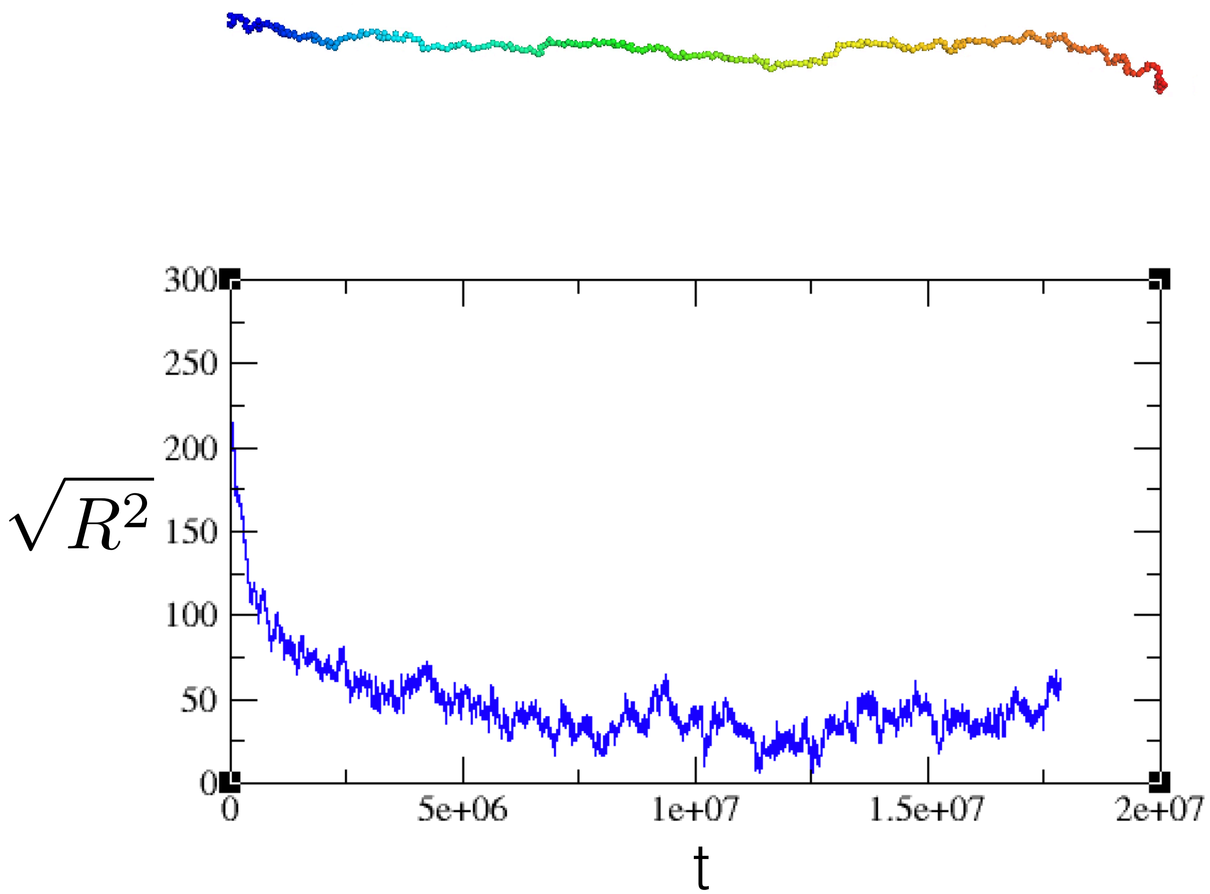


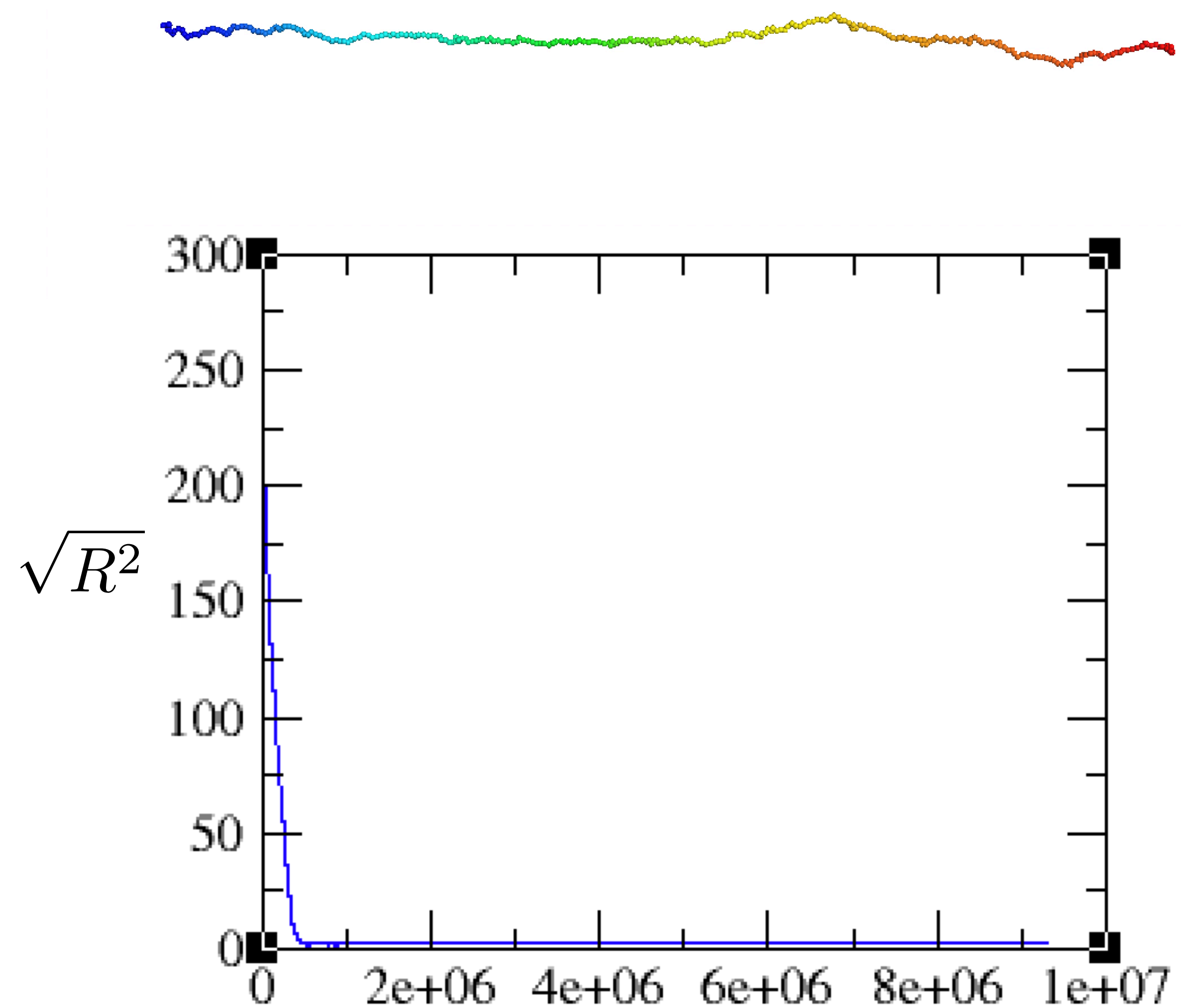
FIG. 3. The dynamics of recoil of DNA-bead initially stretched by a 6-pN force. Both extension and time are normalized by the contour length (L) of the DNA. Even though the naked DNA curves (bullets, triangles and squares) correspond to slightly different lengths, in the normalized variables they coincide within experimental error. The recoil is much slower when DNA is fully covered with RecA-ATP[γS] (diamonds).



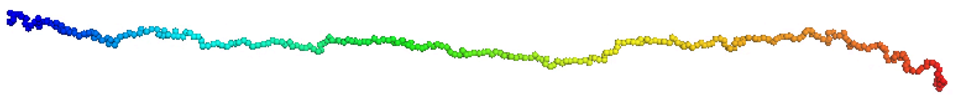


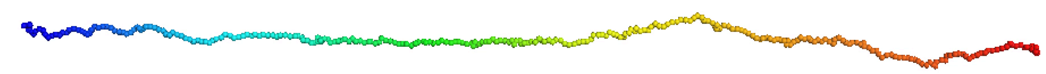



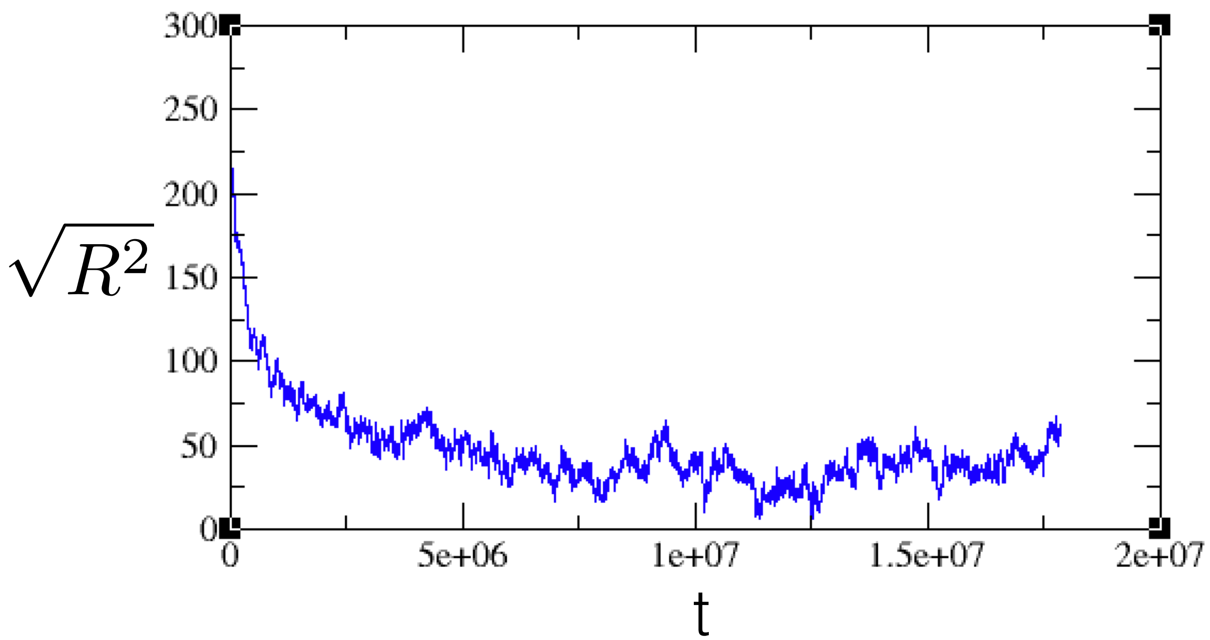
$\sqrt{R^2}$
300
250
200
150
100
50
0
0
5e+06
1e+07
1.5e+07
2e+07
t



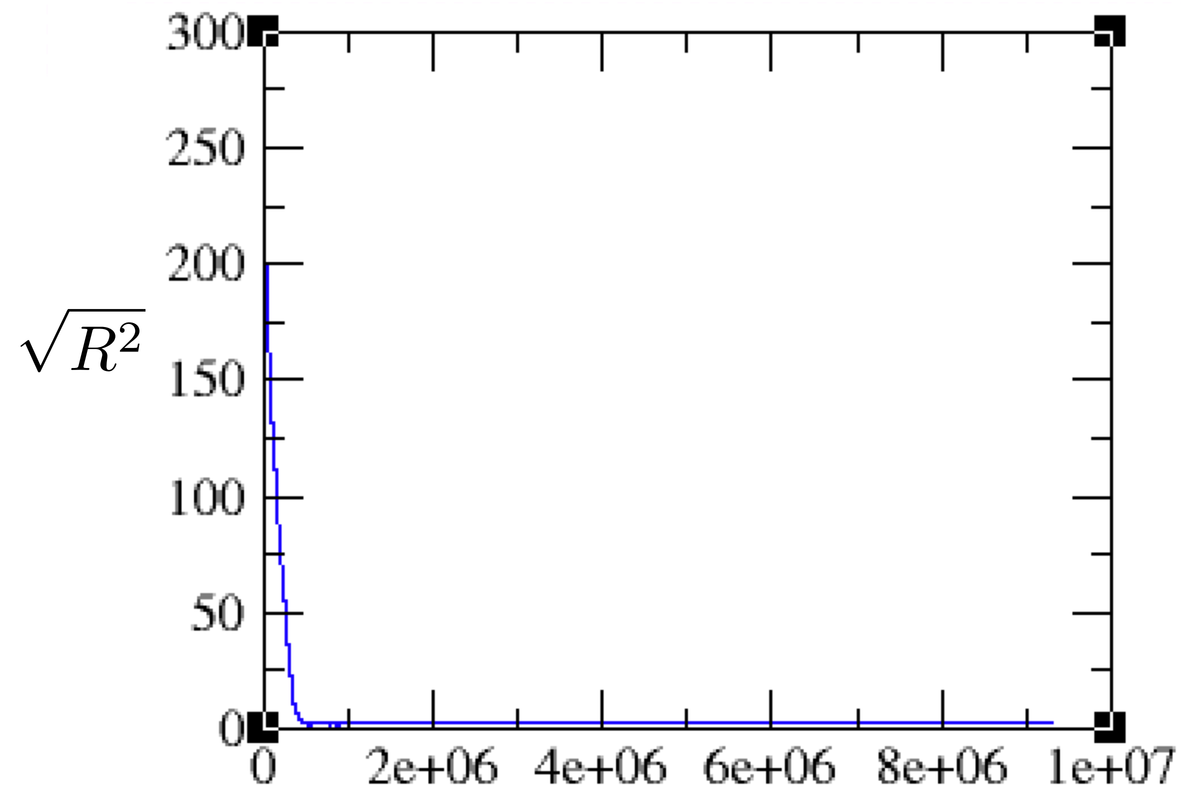
$\sqrt{R^2}$
300
250
200
150
100
50
0
0
2e+06
4e+06
6e+06
8e+06
1e+07



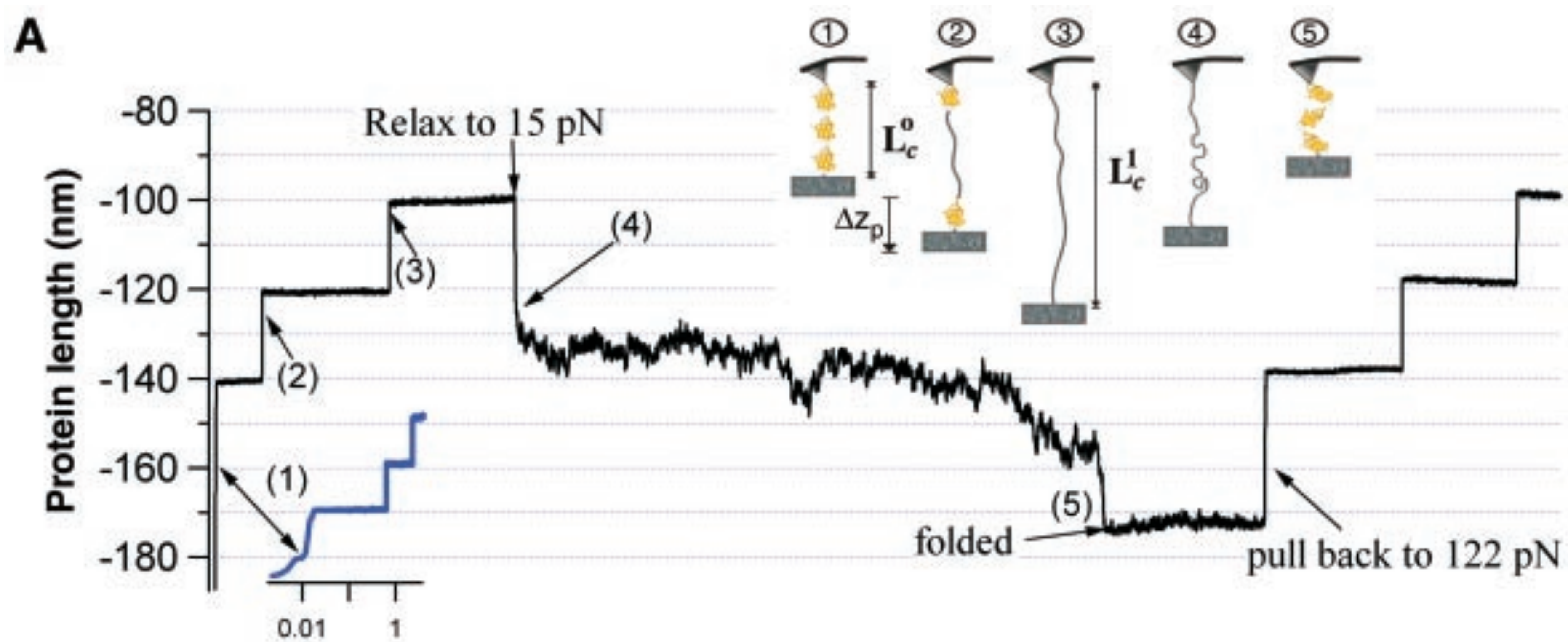




$\sqrt{R^2}$
300
250
200
150
100
50
0
0
5e+06
1e+07
1.5e+07
2e+07
t



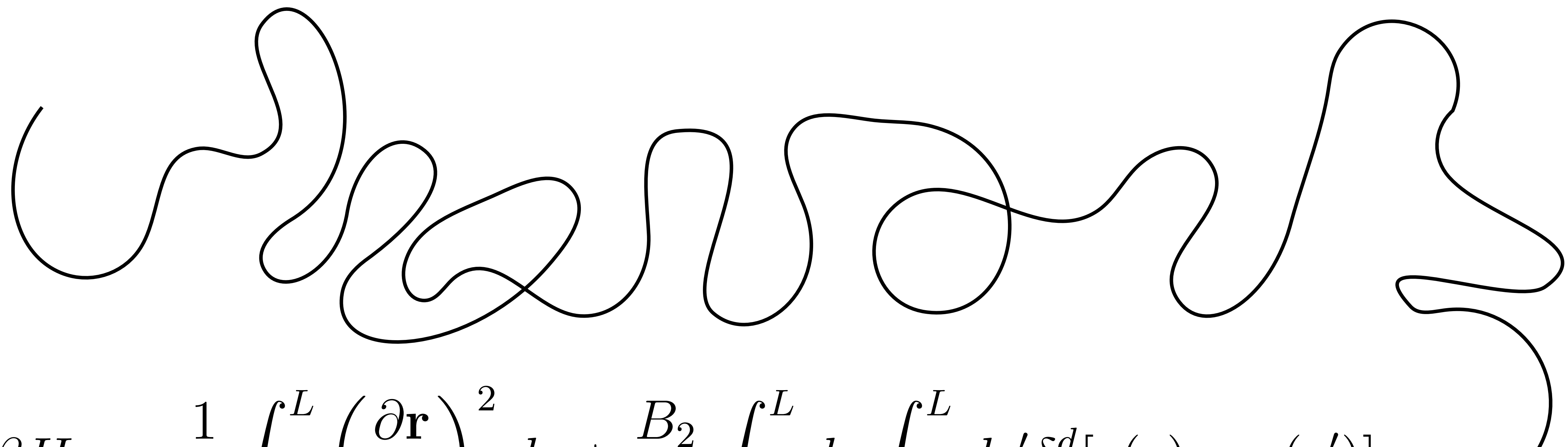
$\sqrt{R^2}$
300
250
200
150
100
50
0
0
2e+06
4e+06
6e+06
8e+06
1e+07



A
Protein length (nm)
-80
-100
-120
-140
-160
-180
Relax to 15 pN
(1)
(2)
(3)
(4)
(5)
folded
pull back to 122 pN
0.01
1
①
②
③
④
⑤
L_c^o
Δz_p
L_c^1

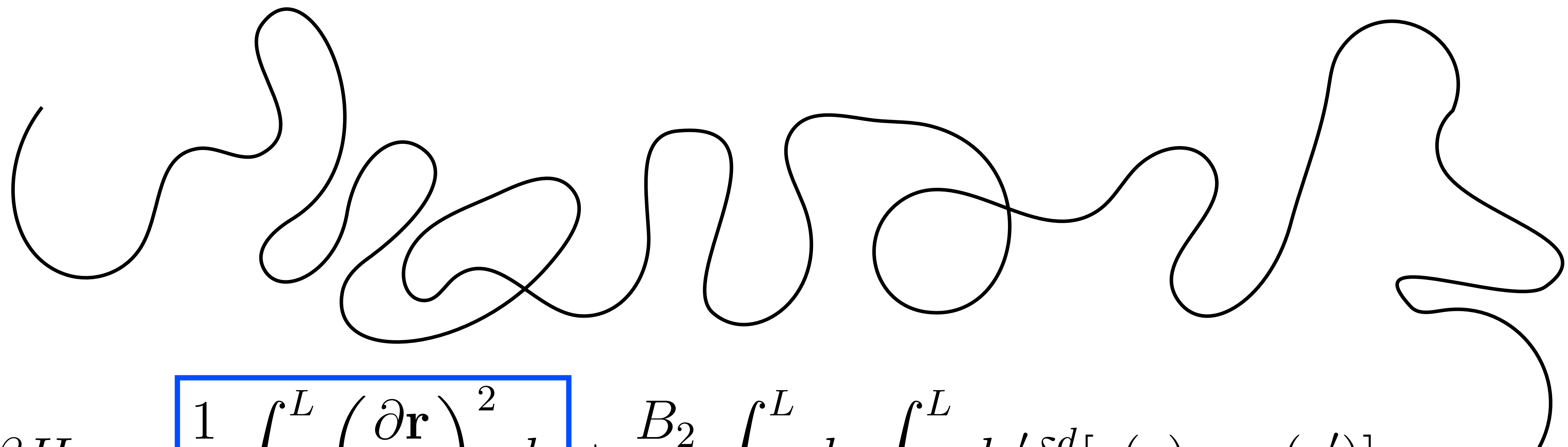
?

Some basics of polymer physics



$$\beta H_{\text{eff}} = \frac{1}{2}\int_0^L \left(\frac{\partial \mathbf{r}}{\partial s}\right)^2 ds + \frac{B_2}{2!}\int_0^L ds \int_0^L ds' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')]$$
$$+ \frac{B_3}{3!}\int_0^L ds \int_0^L ds' \int_0^L ds'' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')]\delta^d[\mathbf{r}(s') - \mathbf{r}(s'')] + \cdots$$

Some basics of polymer physics

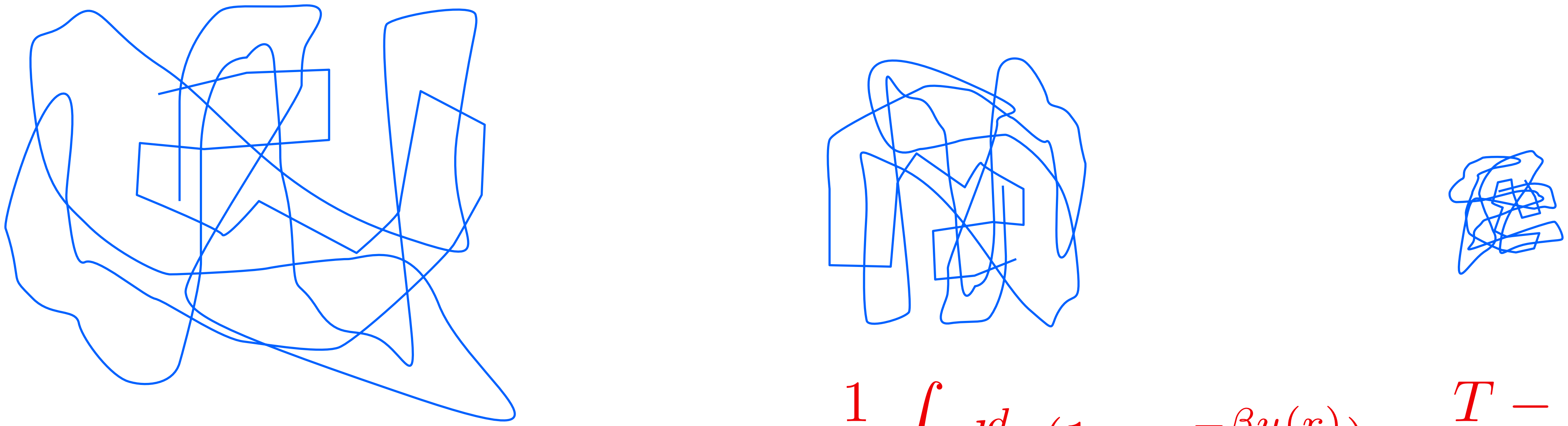


$$\beta H_{\text{eff}} = \boxed{\frac{1}{2}\int_0^L \left(\frac{\partial \mathbf{r}}{\partial s}\right)^2 ds} + \frac{B_2}{2!}\int_0^L ds \int_0^L ds' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')]$$

$$+ \frac{B_3}{3!}\int_0^L ds \int_0^L ds' \int_0^L ds'' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')]\delta^d[\mathbf{r}(s') - \mathbf{r}(s'')] + \cdots$$

$$\frac{k_B T}{2a^2}\sum_{i=1}^{N-1}\left((\mathbf{r}_{i+1} - \mathbf{r}_i)^2 - a^2\right)$$

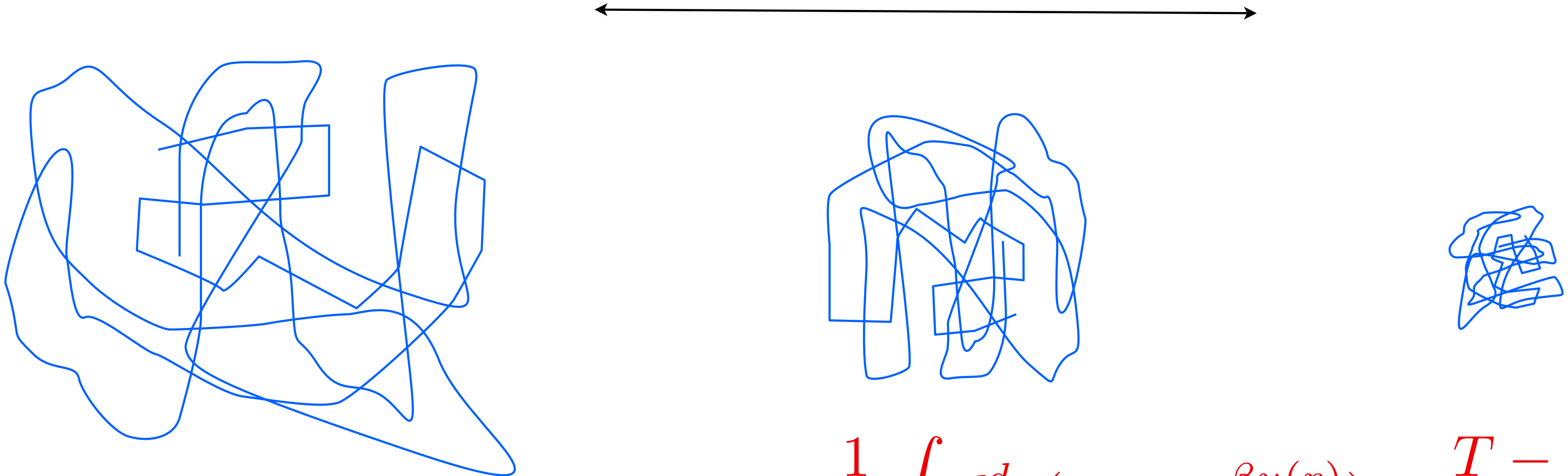
Good (T>Θ)　　　T=Θ　　　poor (T<Θ)



$$= \frac{1}{2}\int d^d r\left(1-e^{-\beta u(r)}\right) \sim \frac{T-\Theta}{\Theta}a^3$$

$$\beta H_{\text{eff}} = \frac{1}{2}\int_0^L \left(\frac{\partial \mathbf{r}}{\partial s}\right)^2 ds + \frac{B_2}{2!}\int_0^L ds\int_0^L ds'\,\delta^d[\mathbf{r}(s)-\mathbf{r}(s')]$$
$$+\frac{B_3}{3!}\int_0^L ds\int_0^L ds'\int_0^L ds''\,\delta^d[\mathbf{r}(s)-\mathbf{r}(s')]\delta^d[\mathbf{r}(s')-\mathbf{r}(s'')]+\cdots$$

Good (T>Θ) T=Θ poor (T<Θ)



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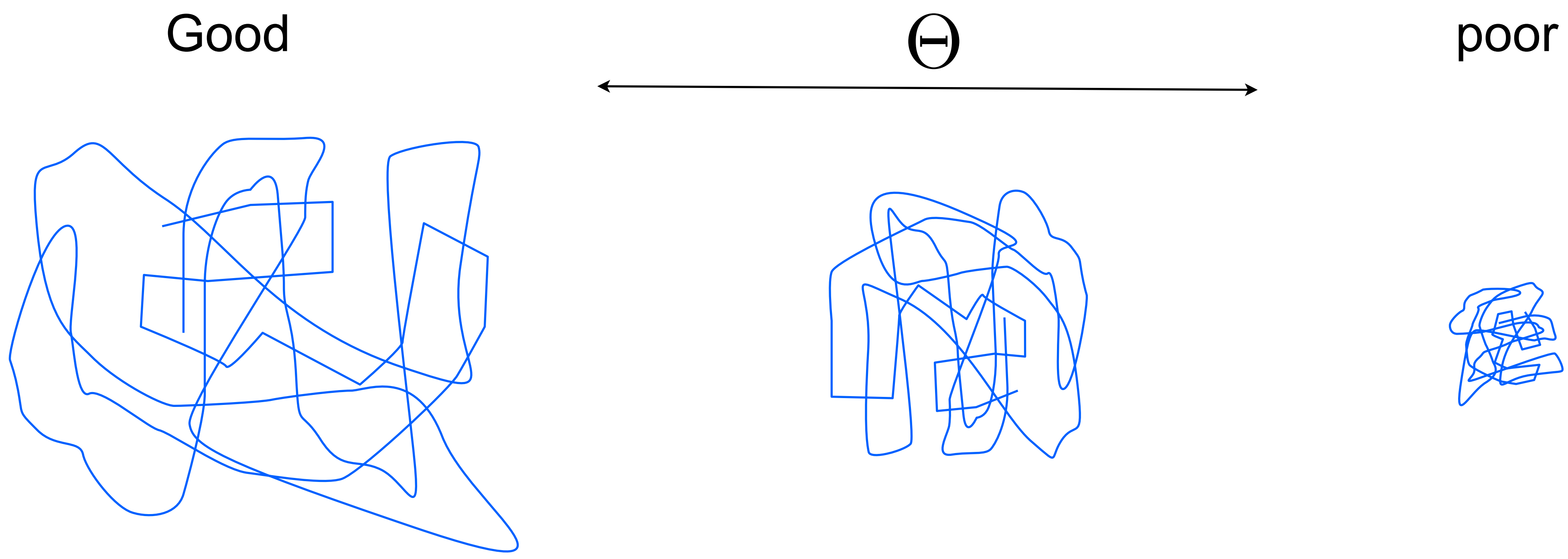
$$+ \frac{B_3}{3!}\int_0^L ds \int_0^L ds' \int_0^L ds'' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')]\delta^d[\mathbf{r}(s') - \mathbf{r}(s'')] + \cdots$$

$$Z = e^{-\beta F} = \int \mathcal{D}[\mathbf{r}(s)] e^{-\beta H_{\text{eff}}} \sim \langle e^{-\beta H_{\text{eff}}} \rangle \geq e^{-\beta \langle H_{\text{eff}} \rangle},$$

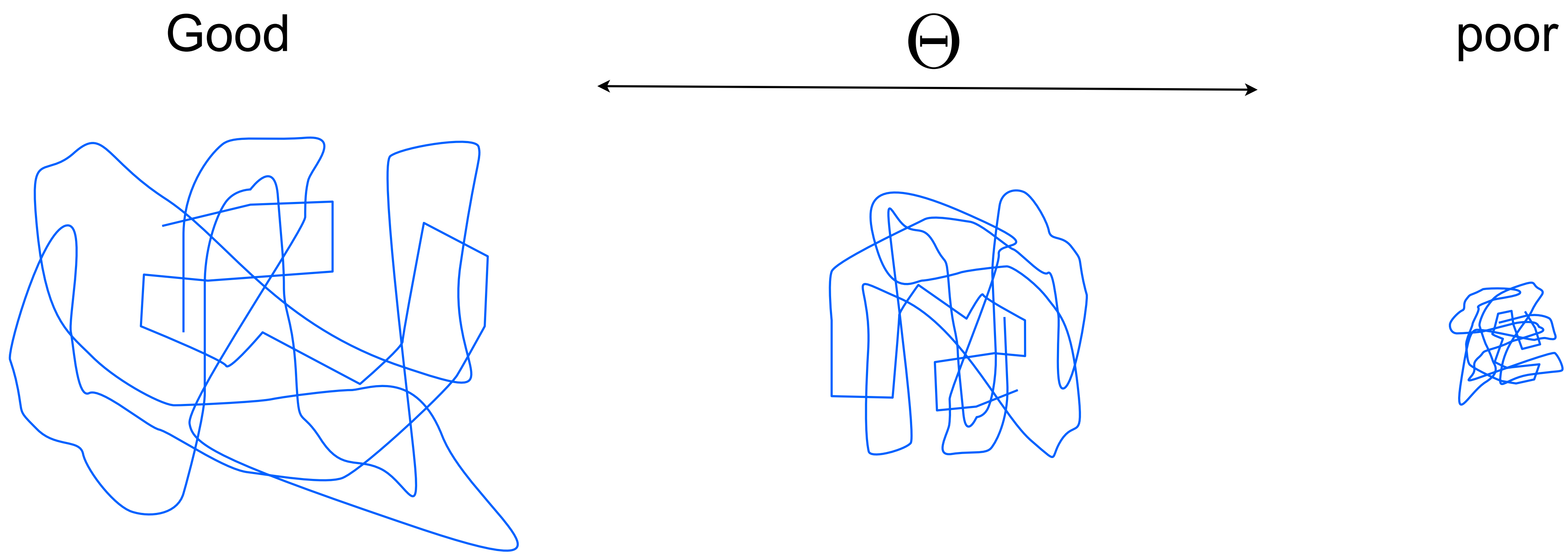
$$\beta F \leq \beta \langle H_{\text{eff}} \rangle$$



$$c(\mathbf{R}) = \int_0^L ds \delta^d[\mathbf{r}(s) - \mathbf{R}]$$

$$\int_0^L ds \int_0^L ds' \delta^d[\mathbf{r}(s) - \mathbf{r}(s')] = \int d^d\mathbf{R} \underbrace{\int_0^L ds \delta^d[\mathbf{r}(s) - \mathbf{R}]}_{=c(\mathbf{R})} \underbrace{\int_0^L ds \delta^d[\mathbf{r}(s') - \mathbf{R}]}_{=c(\mathbf{R})}$$

$$= \int d^d\mathbf{R} c^2(\mathbf{R})$$

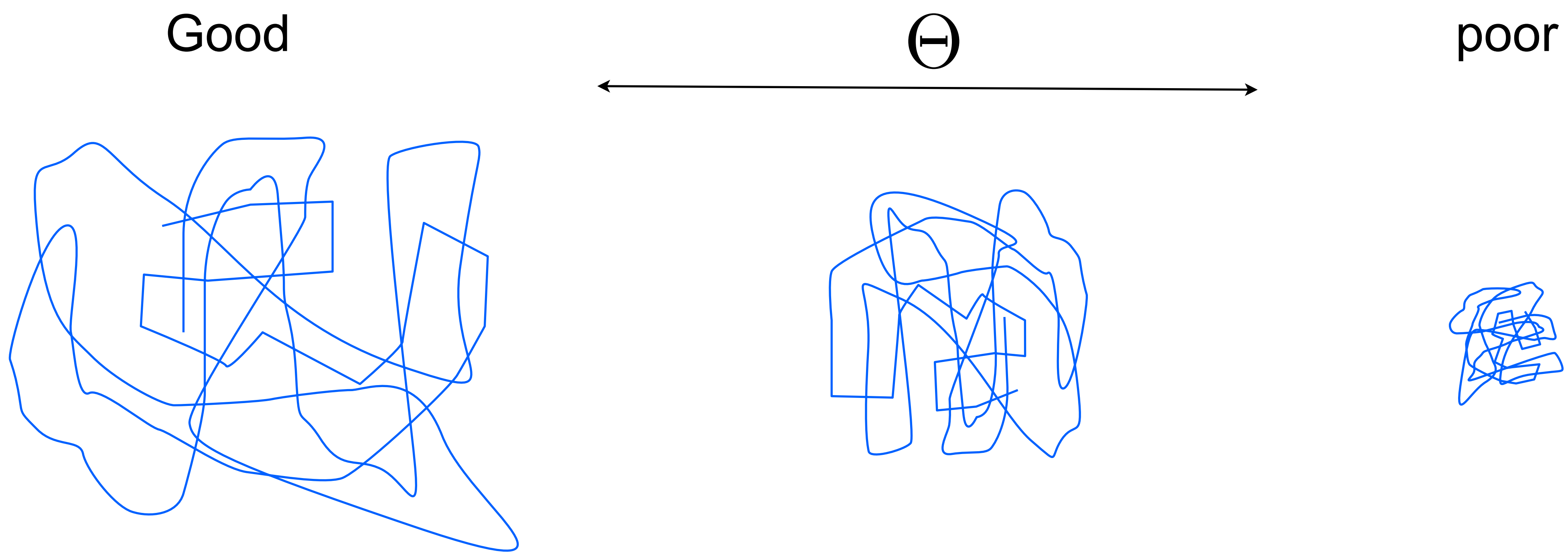


$$\beta F \leq \beta \langle H_{\mathrm{eff}} \rangle$$

$$= \frac{1}{2}\left\langle \int_0^L \left(\frac{\partial \mathbf{r}}{\partial s}\right)^2 ds \right\rangle + \frac{B_2}{2!}\int d^dR \langle c^2(R)\rangle + \frac{B_3}{3!}\int d^dR\langle c^3(R)\rangle + \cdots$$

$$\approx \frac{1}{2}\left(\frac{R^2}{Na^2}\right) + \frac{B_2}{2!}\langle c\rangle^2 R^d + \frac{B_3}{3!}\langle c\rangle^3 R^d + \cdots \qquad \langle c^n\rangle \approx \langle c\rangle^n$$

$$\approx \frac{1}{2}\frac{R^2}{Na^2} + \frac{B_2}{2!}\frac{N^2}{R^d} + \frac{B_3}{3!}\frac{N^3}{R^{2d}} + \cdots \qquad \langle c\rangle = \frac{N}{R^d}$$



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$$\approx \underline{\frac{1}{2}\frac{R^2}{Na^2} + \frac{B_2}{2!}\frac{N^2}{R^d} + \frac{B_3}{3!}\frac{N^3}{R^{2d}} + \cdots} \qquad \langle c\rangle = \frac{N}{R^d}$$

Flory free energy

Marginal solvent (slightly below Θ)

$$\beta F(R) \sim \frac{R^2}{Na^2} + \frac{B_2}{2}\frac{N^2}{R^d} + \frac{B_3}{6}\frac{N^3}{R^{2d}} + \cdots$$

$$R \sim aN^{1/2}$$

$$B_2 \sim \tau a^3 \quad \left(\tau = \frac{\Delta T}{\theta} < 0\right)$$

$$B_3 \sim a^6$$

Marginal solvent (slightly below Θ)

$$\beta F(R) \sim \frac{R^2}{Na^2} + \boxed{\frac{B_2}{2}\frac{N^2}{R^d}} + \boxed{\frac{B_3}{6}\frac{N^3}{R^{2d}}} + \cdots$$

$$R \sim aN^{1/2} \qquad \sim \tau a^{3-d} N^{2-d/2} \qquad \sim a^{6-2d} N^{3-d}$$

$$B_2 \sim \tau a^3 \quad \left(\tau = \frac{\Delta T}{\theta} < 0\right)$$

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$$B_2 \sim \tau a^3 \quad \left(\tau = \frac{\Delta T}{\theta} < 0\right) \qquad |\tau| > N^{-1/2} \quad (d=3)$$

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$$\Delta T > \frac{\theta}{N^{1/2}}$$

Condition to feel the attraction

$$N > \left(\frac{\theta}{\Delta T}\right)^2$$

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$$R \sim aN^{1/2} \qquad \sim \tau a^{3-d} N^{2-d/2} \qquad \sim a^{6-2d} N^{3-d}$$

$$B_2 \sim \tau a^3 \quad \left(\tau = \frac{\Delta T}{\theta} < 0\right) \qquad |\tau| > N^{-1/2} \quad (d=3)$$

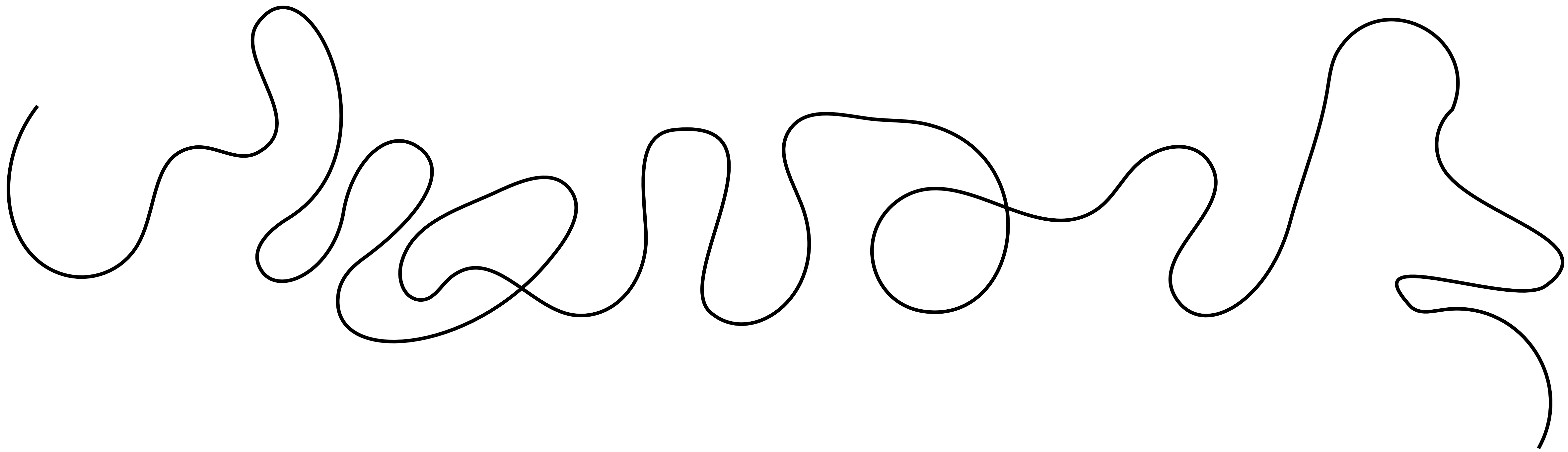
$$B_3 \sim a^6$$

$$\Delta T > \frac{\theta}{N^{1/2}}$$

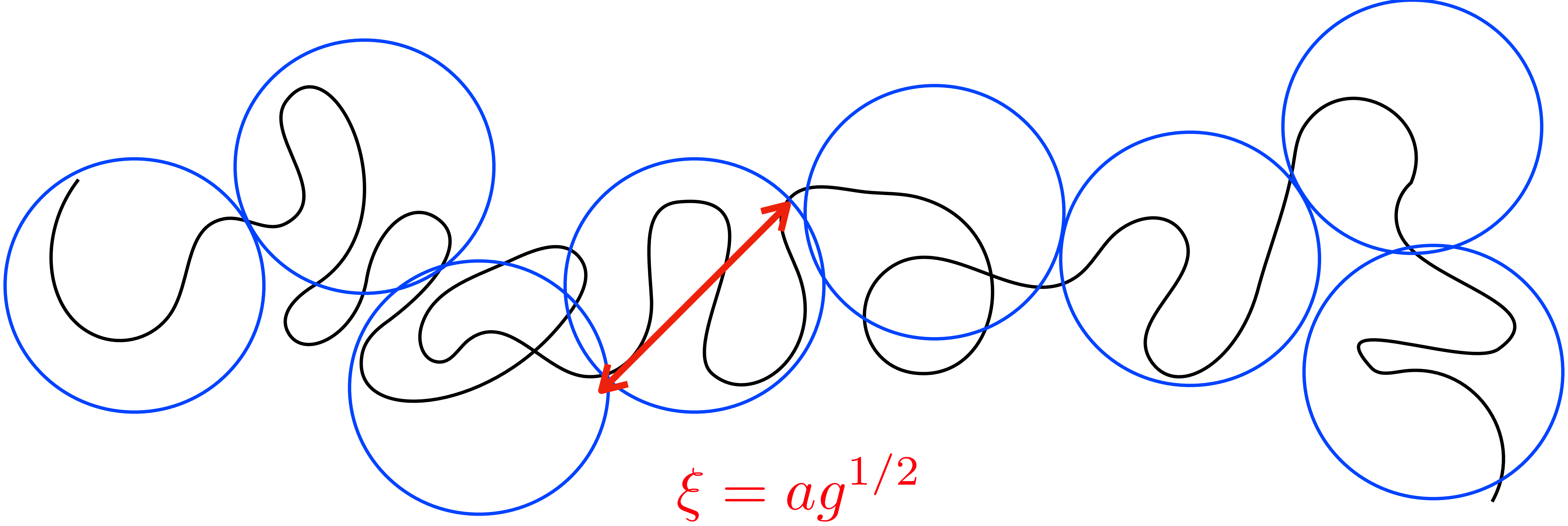
Condition to feel the attraction

$$N > \left(\frac{\theta}{\Delta T}\right)^2$$

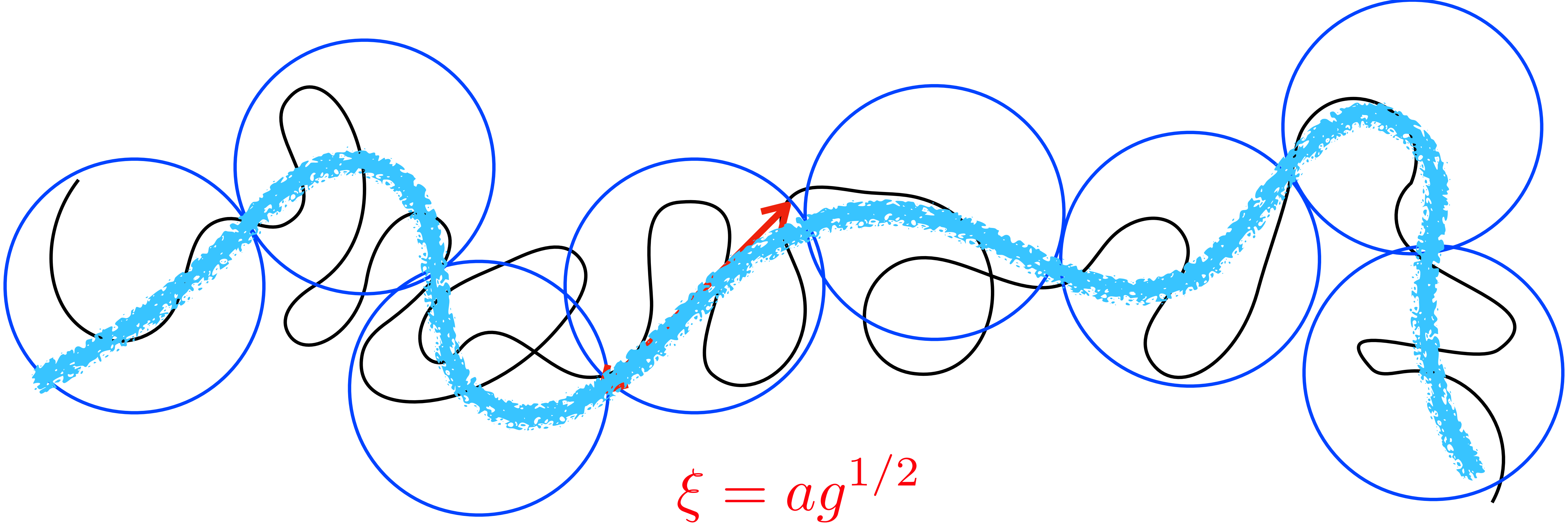
$$g = \left(\frac{\theta}{\Delta T}\right)^2 \qquad \xi = a g^{1/2}$$



$$g = \left(\frac{\theta}{\Delta T}\right)^2 \qquad \xi = a g^{1/2}$$

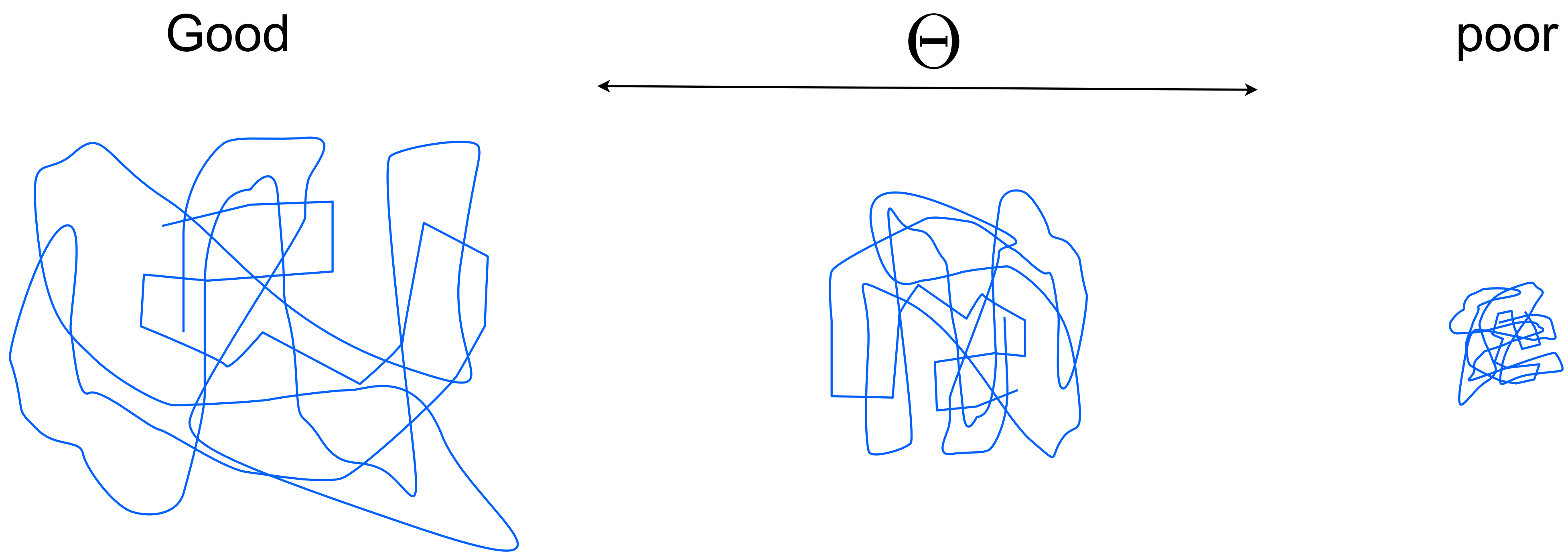


$$g = \left(\frac{\theta}{\Delta T}\right)^2 \qquad \xi = ag^{1/2}$$

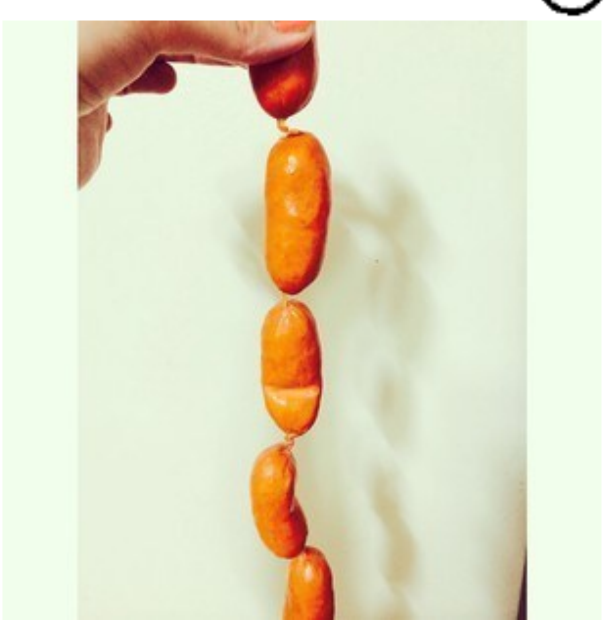


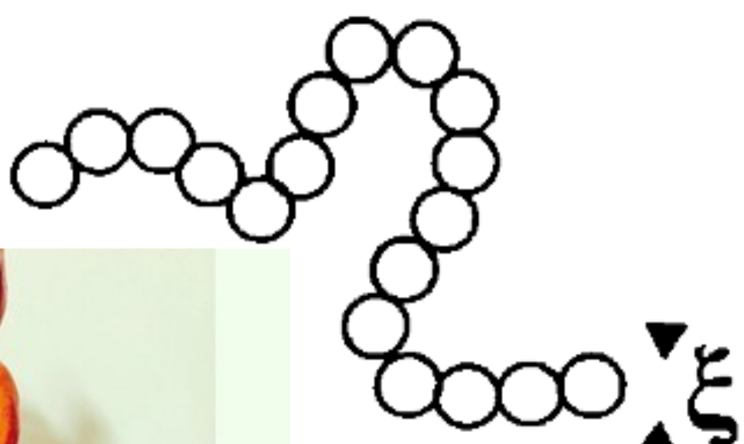
$$L_0 = \left(\frac{N}{g}\right)\xi$$

$$g = \left(\frac{\theta}{\Delta T}\right)^2 \qquad \xi = ag^{1/2}$$

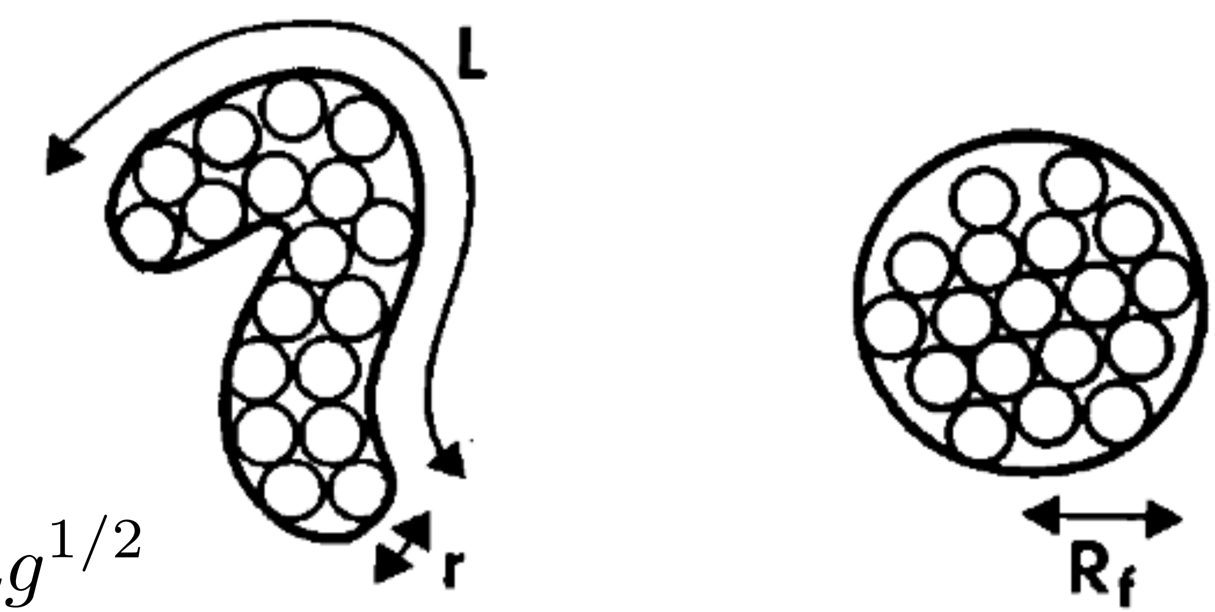


P. G. de Gennes' "expanding sausage model"





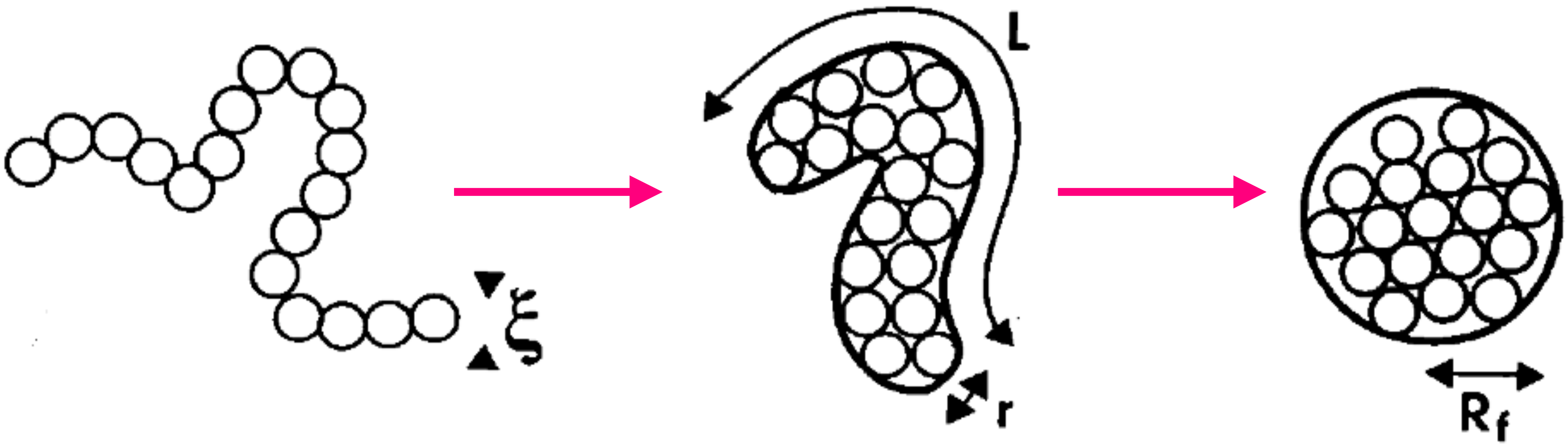
$$\xi = a g^{1/2}$$



Kinetics of collapse for a flexible coil

P. G. de Gennes

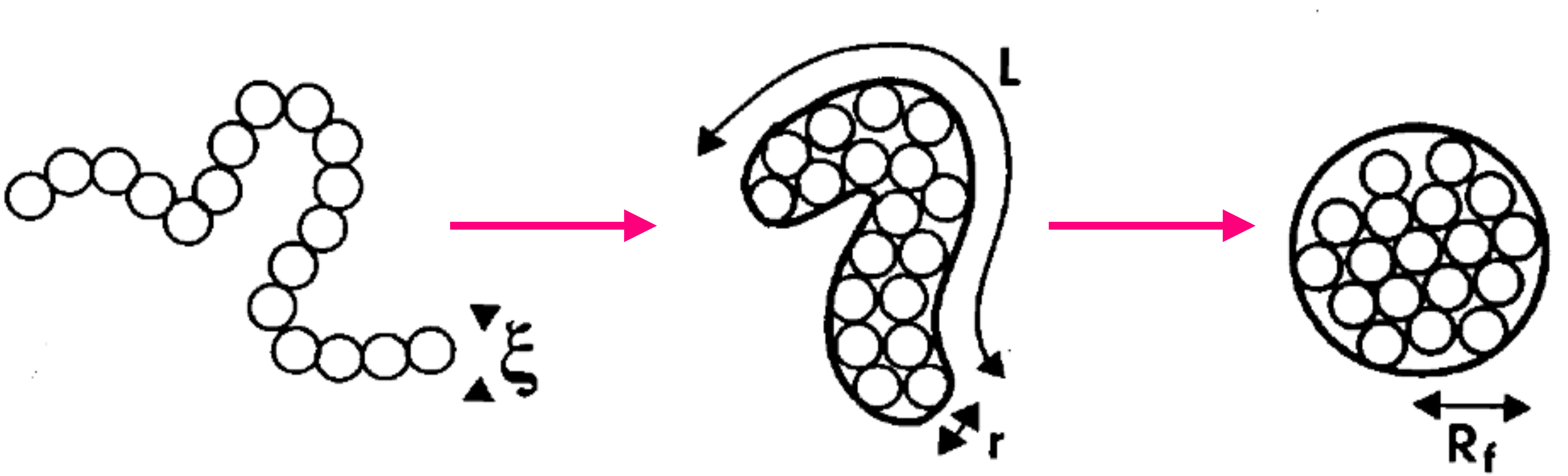
J. Physique Lett. **46** (1985) L-639 - L-642



Kinetics of collapse for a flexible coil

P. G. de Gennes *J. Physique Lett.* **46** (1985) L-639 - L-642

$$F = \gamma A \qquad \gamma = k_B T/\xi^2 \qquad A \sim 2\pi r L$$



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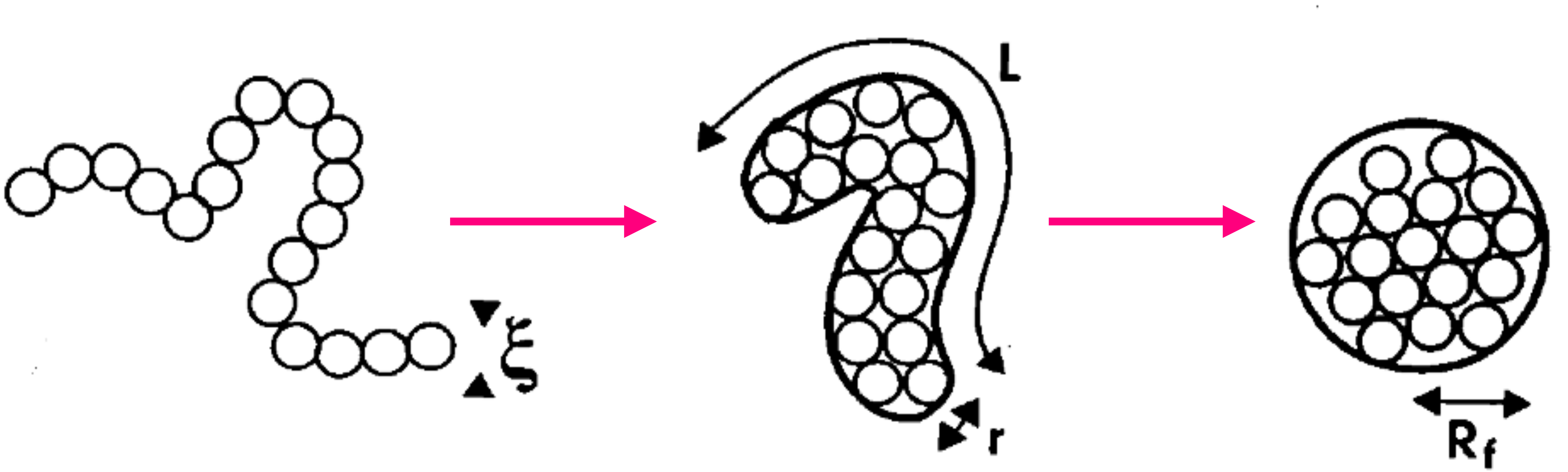
$$\Omega = \pi r^2 L = \pi \xi^2 L_0$$



Kinetics of collapse for a flexible coil

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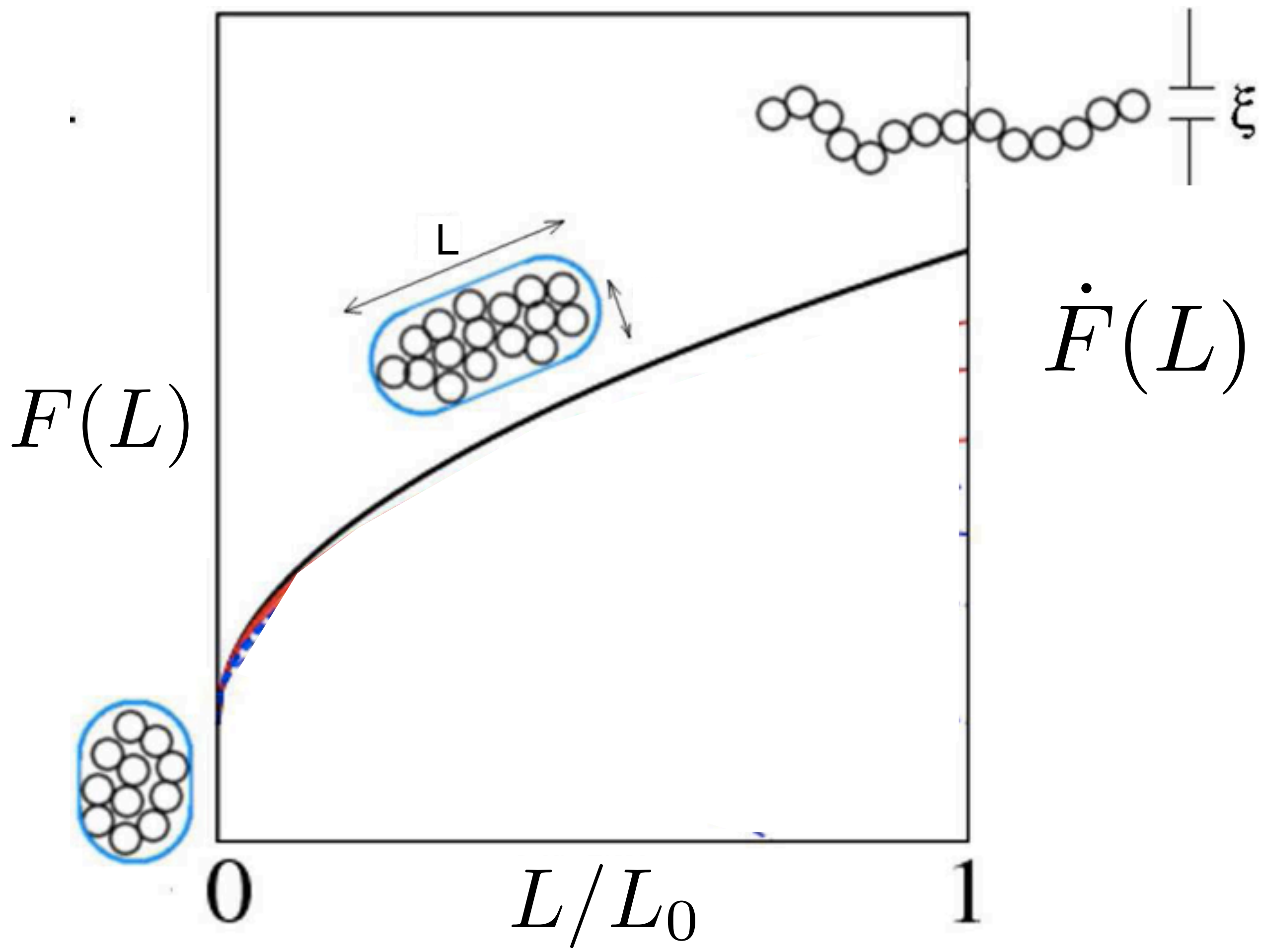
$$F = \gamma A \qquad \gamma = k_B T/\xi^2 \qquad A \sim 2\pi r L$$

$$\Omega = \pi r^2 L = \pi \xi^2 L_0$$

$$F(L) = \gamma 2\sqrt{\pi\Omega} L^{1/2}$$

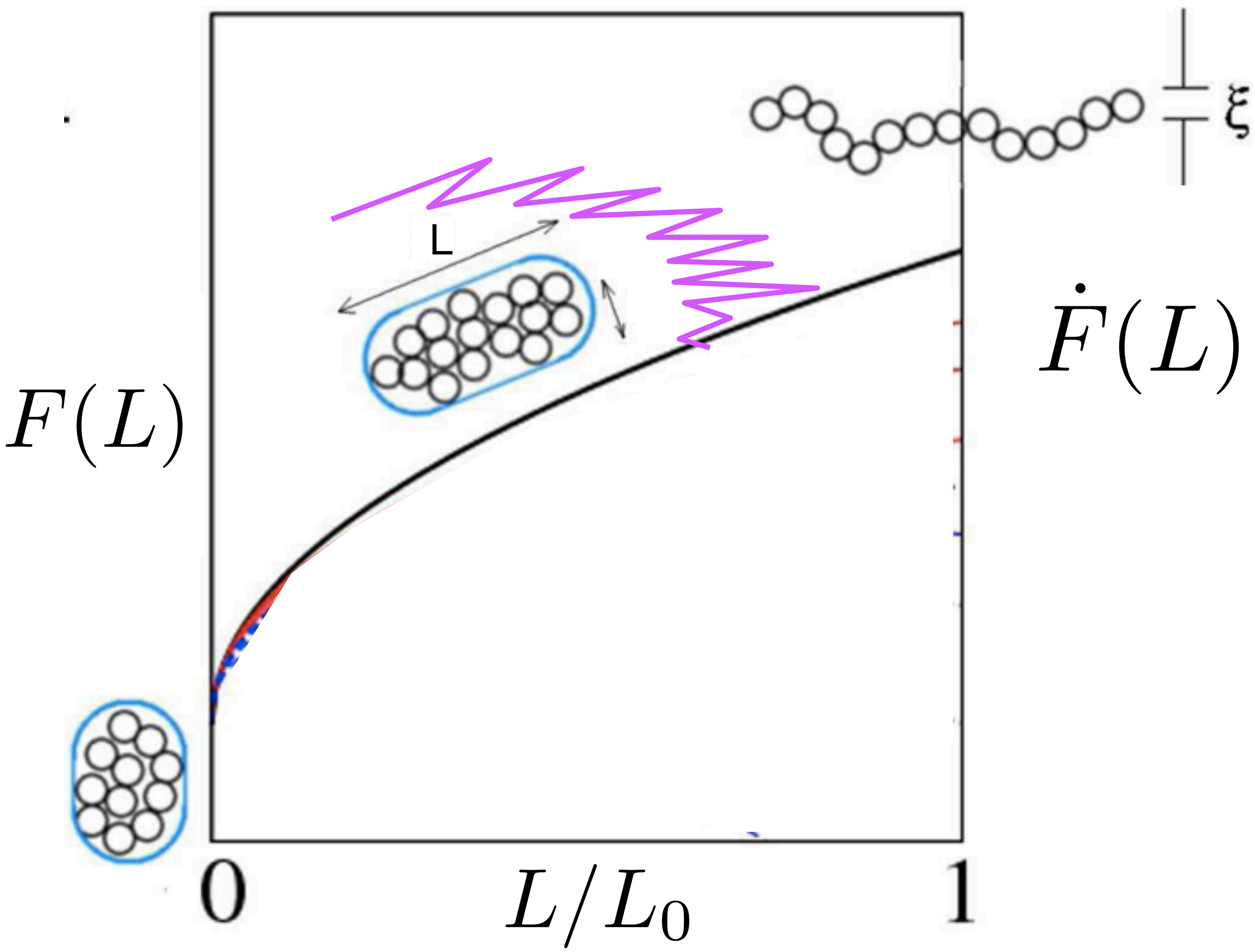


$$\dot{F}(L) = -T\dot{S}(L) \sim -\gamma V^2 \sim -\eta L \dot{L}^2$$

$$\gamma\sqrt{\pi\Omega}L^{-1/2}\dot{L} = -\eta L \dot{L}^2$$

$$L^{3/2}dL = -\frac{\gamma\sqrt{\pi\Omega}}{\eta}dt$$

$$L(t) = L_0(1 - t/\tau_c)^{2/5}$$



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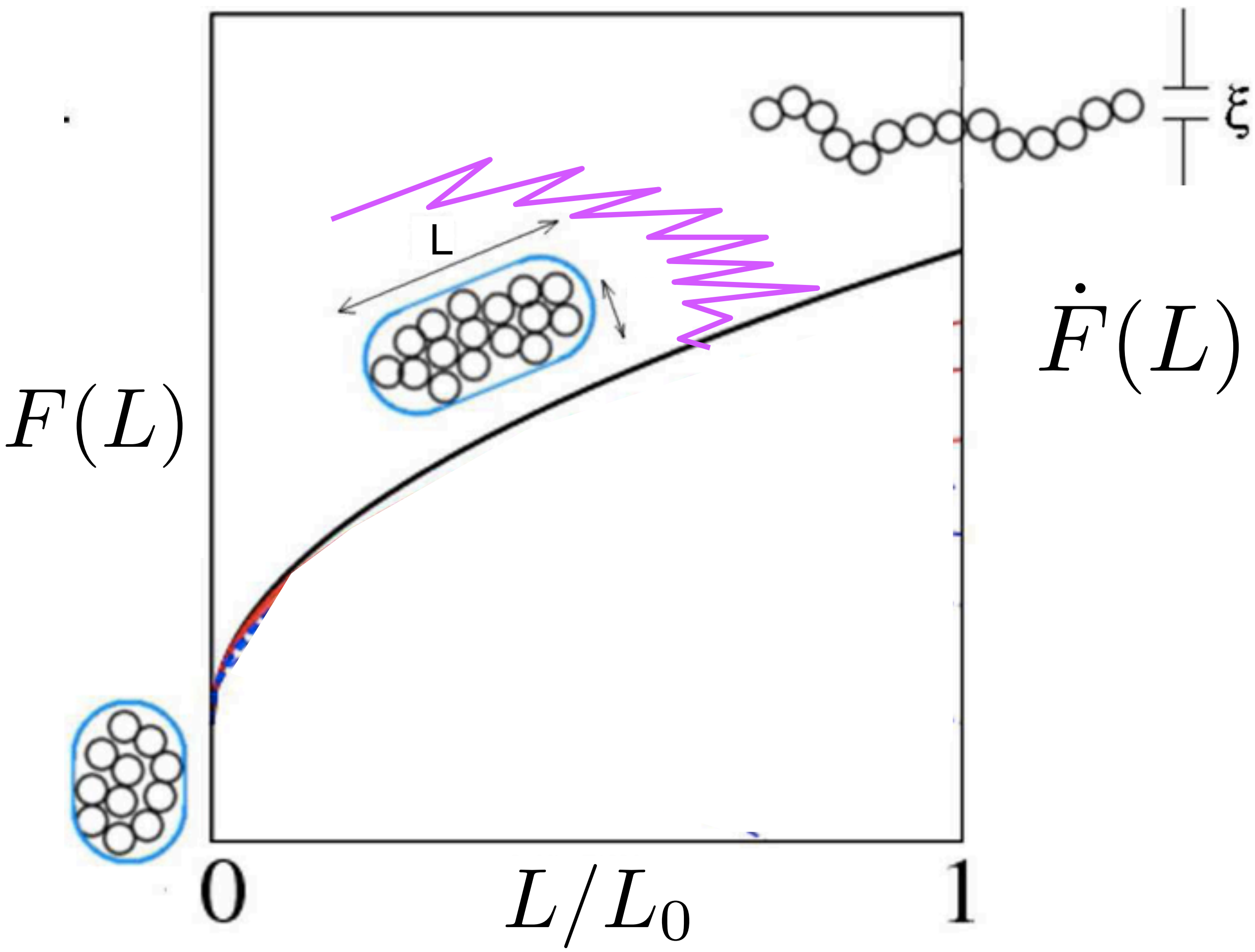

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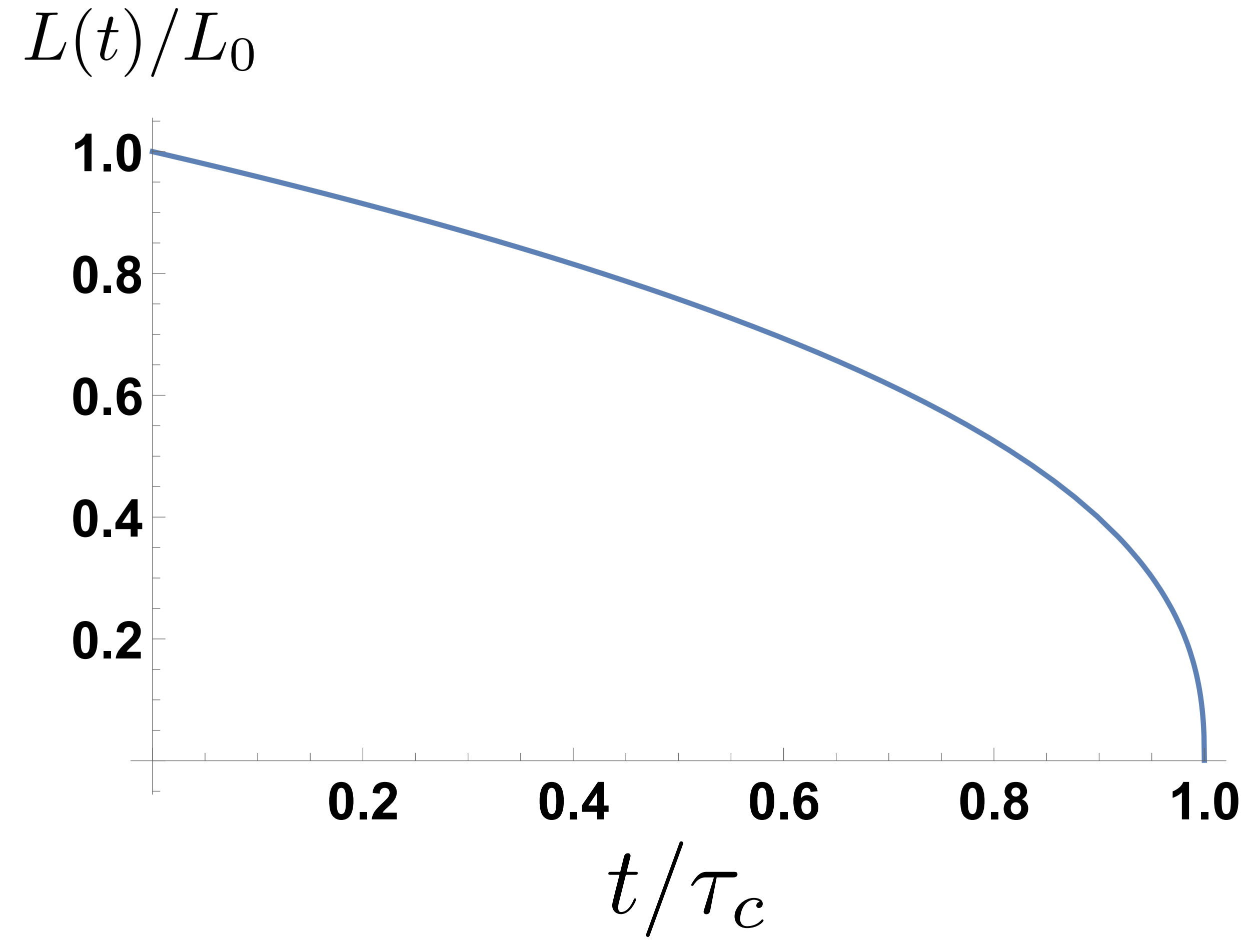

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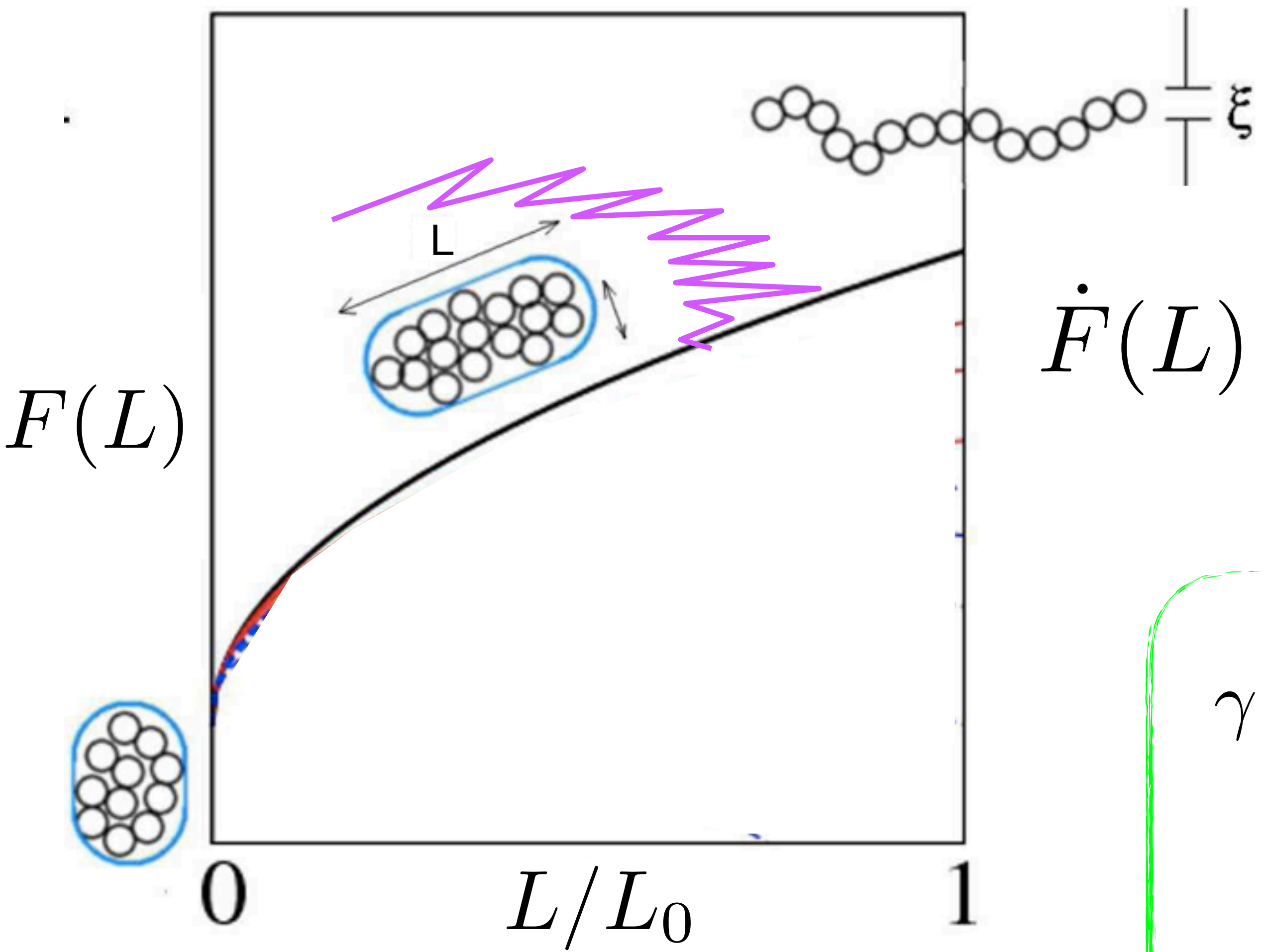


$$\dot{F}(L) = \underline{-T\dot{S}(L) \sim -\gamma V^2 \sim -\eta L \dot{L}^2}$$

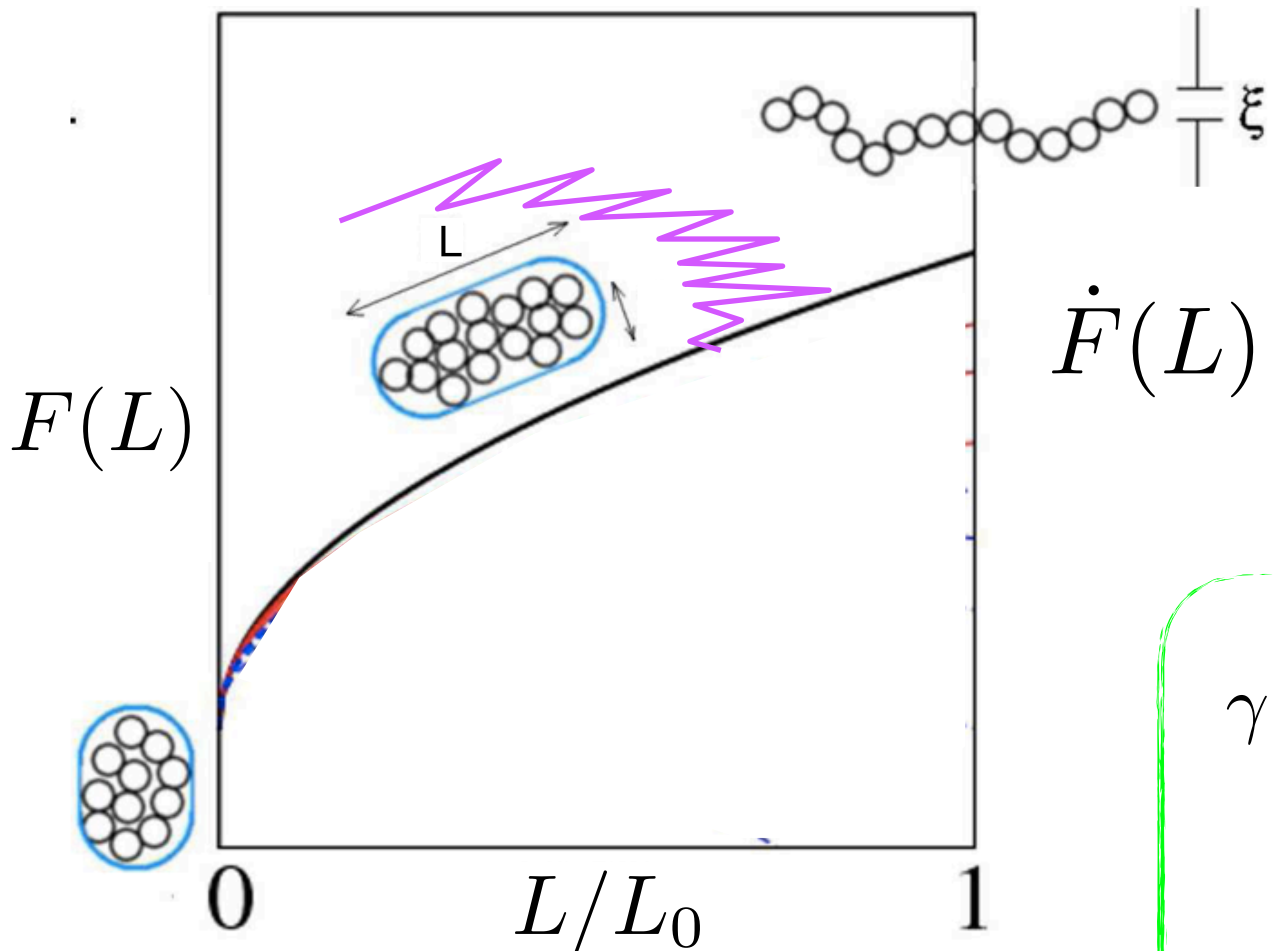
$$L(t) = L_0(1 - t/\tau_c)^{2/5}$$

$$\gamma = \frac{k\theta}{\xi^2} \qquad \Omega = \pi \xi^2 L_0 \qquad L_0 = (N/g)\xi$$

$$\xi = a g^{1/2} \qquad g = \left(\frac{\theta}{\Delta T}\right)^2$$

$$\tau_c = \frac{\eta L_0^{5/2}}{\gamma\sqrt{\pi\Omega}} \sim \frac{\eta a^3}{k\theta} N^2 \left(\frac{\Delta T}{\theta}\right)$$

The greater quench (ΔT) leads to a slower relaxation



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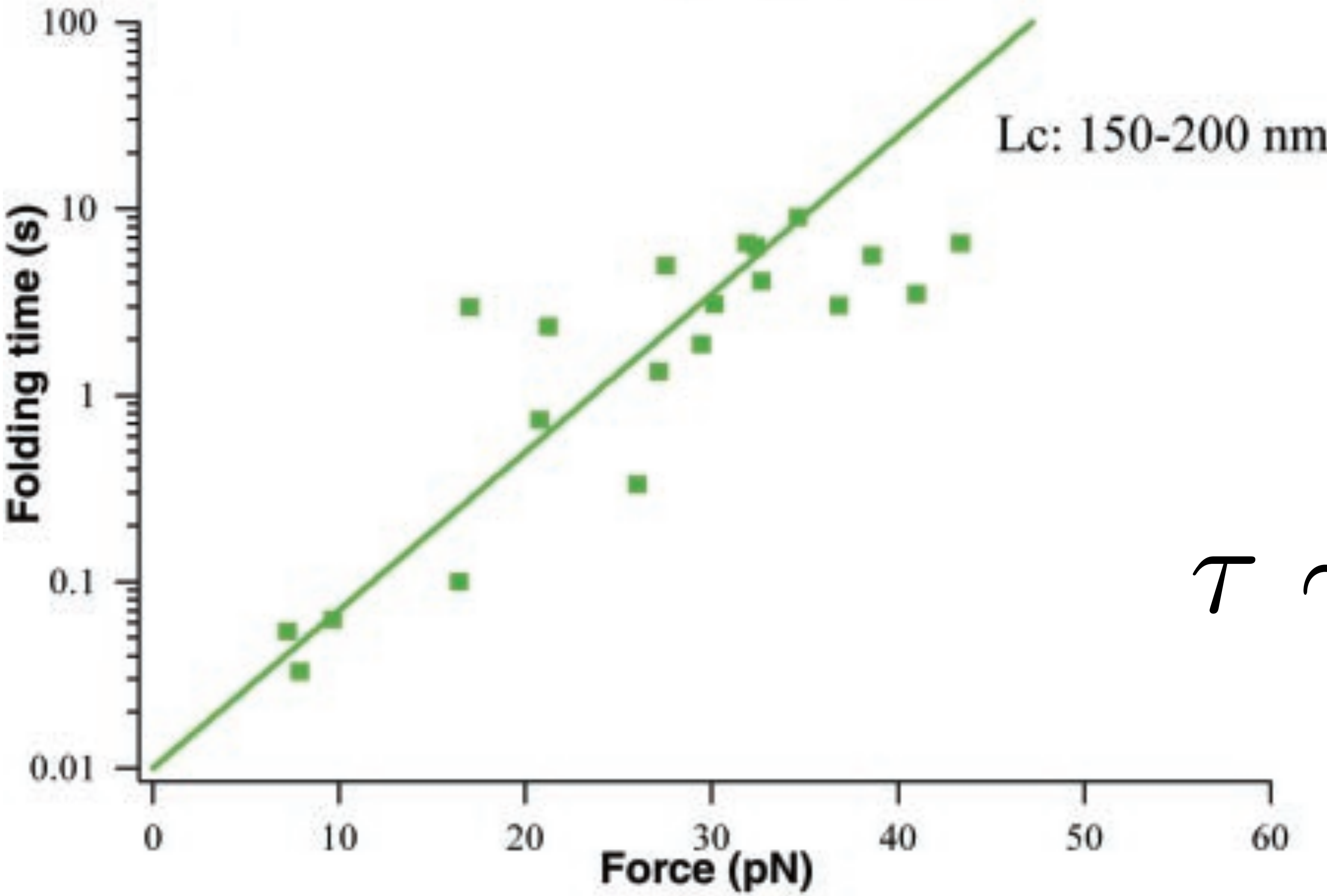
$$L(t) = L_0 (1 - t/\tau_c)^{2/5}$$

$\sim TR$

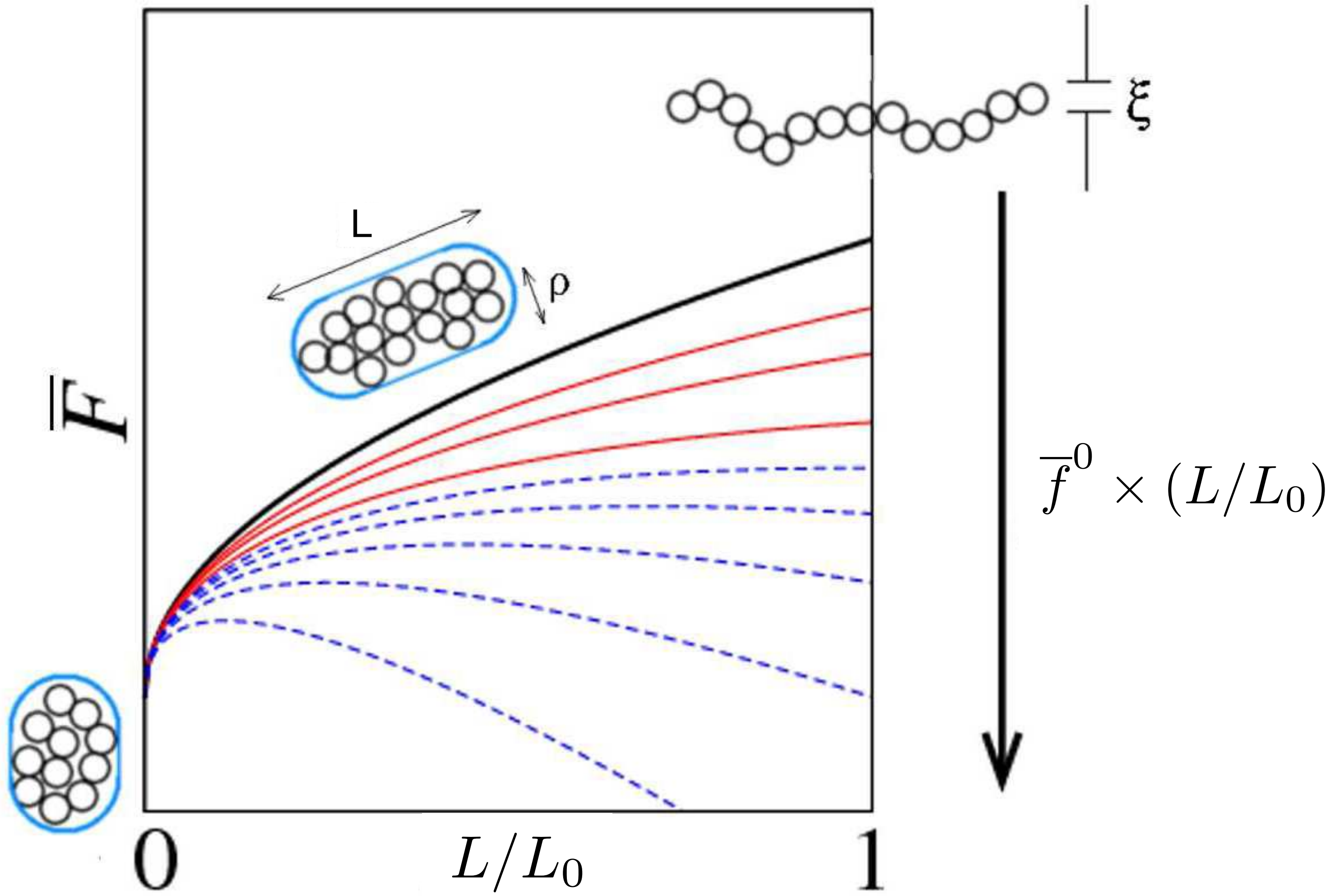
$$\tau_c = \frac{\eta L_0^{5/2}}{\gamma \sqrt{\pi \Omega}} \sim \boxed{\frac{\eta a^3}{k\theta} N^2} \left(\frac{\Delta T}{\theta}\right)$$

The greater quench (ΔT) leads to a slower relaxation



100
10
1
0.1
0.01
Folding time (s)
0
10
20
30
40
50
60
Force (pN)
Lc: 150-200 nm

$$\tau \sim e^{f}$$



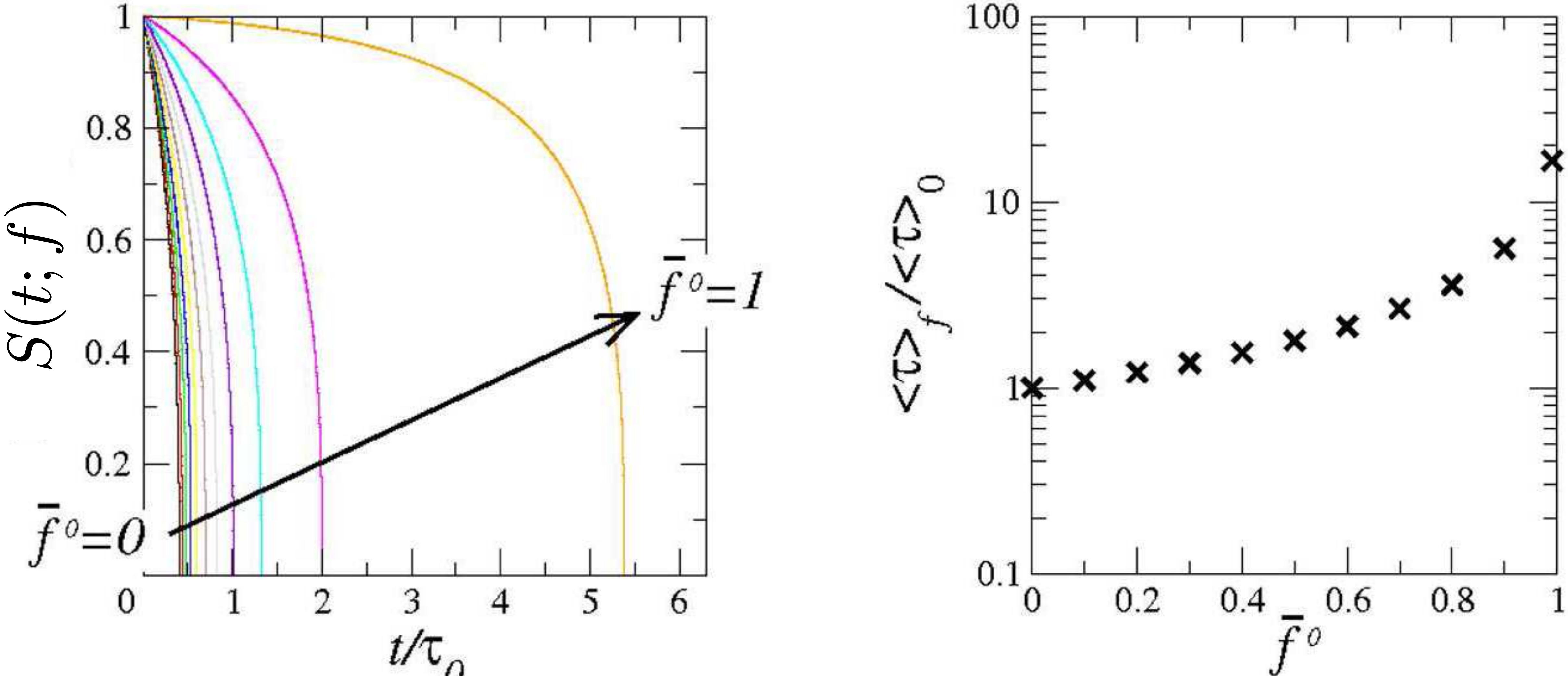
$$\overline{f}^0 \equiv f\tau_0/\eta L_0^2$$

$$\tau_0 \equiv \frac{\eta \xi^2 L_0^{5/2}}{k_B T\sqrt{\pi\Omega}}$$

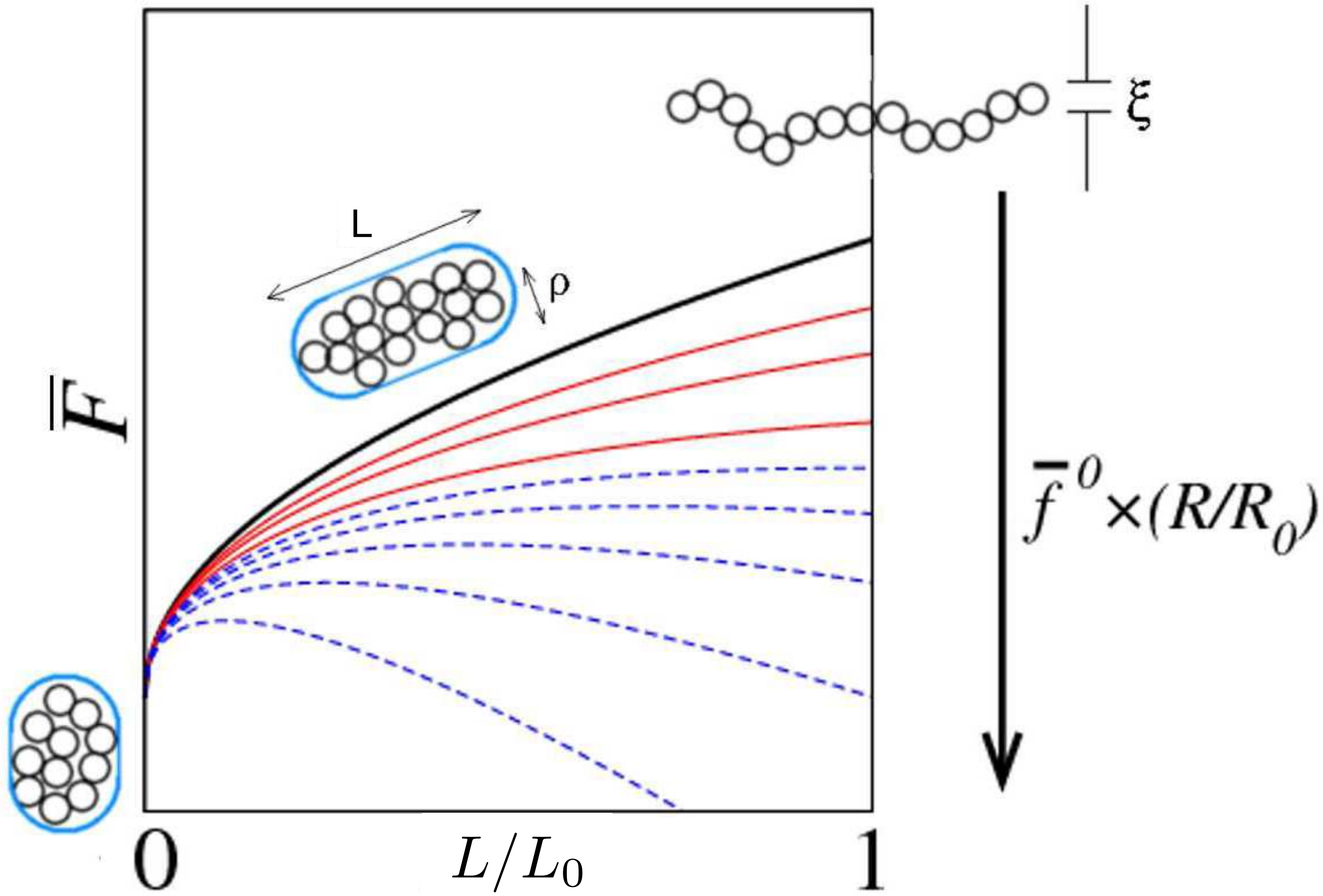
$$F(L) = \frac{k_B T}{\xi^2} 2\sqrt{\pi\Omega} L^{1/2} - fL$$

$$\left(\gamma\sqrt{\pi\Omega}L^{1/2} - f\right)\dot{L} = -\eta L \dot{L}^2$$

$$t/\tau_0 = \int_1^{L/L_0} \frac{x^{3/2}dx}{\overline{f}^0 x^{1/2} - 1} \Longrightarrow S(t)\,[= L(t)/L_0]$$



$$\langle \tau \rangle_f = \int_0^{t^*} S(t;f)dt$$



$$\overline{f}^{\,0} \equiv f\tau_0/\eta L_0^2$$

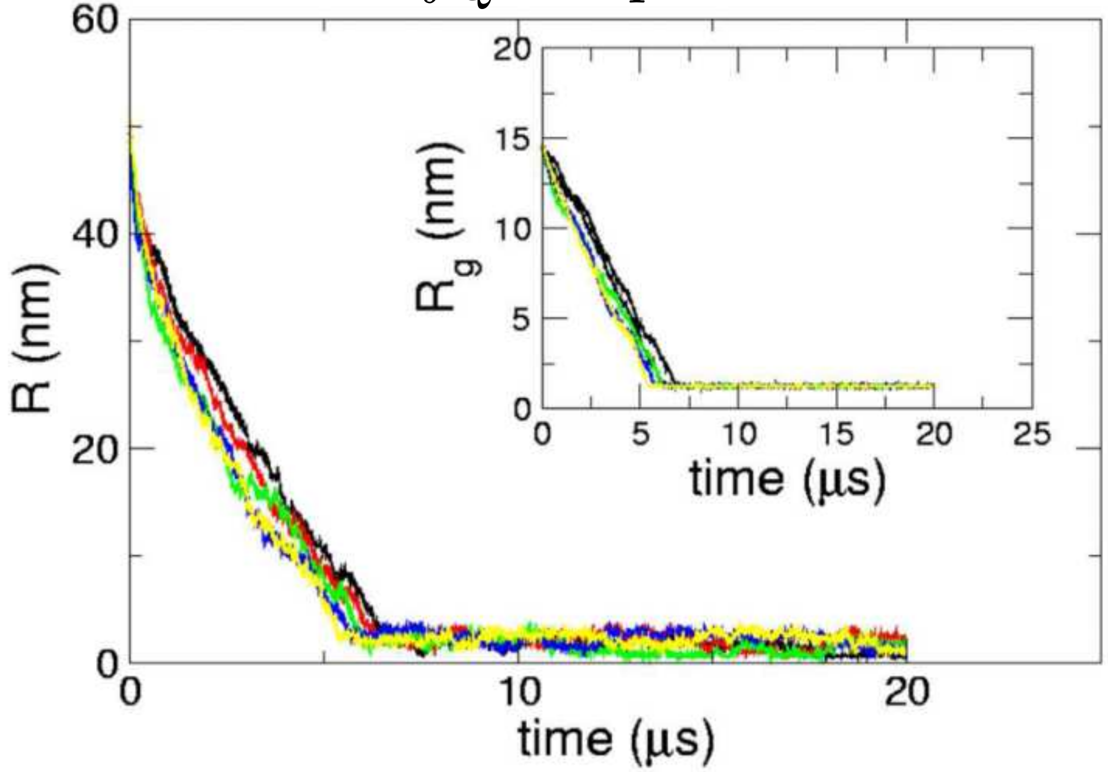
$$\tau_0 \equiv \frac{\eta\xi^2 L_0^{5/2}}{k_B T\sqrt{\pi\Omega}}$$

For $\quad \overline{f}^{\,0} \geq 1$

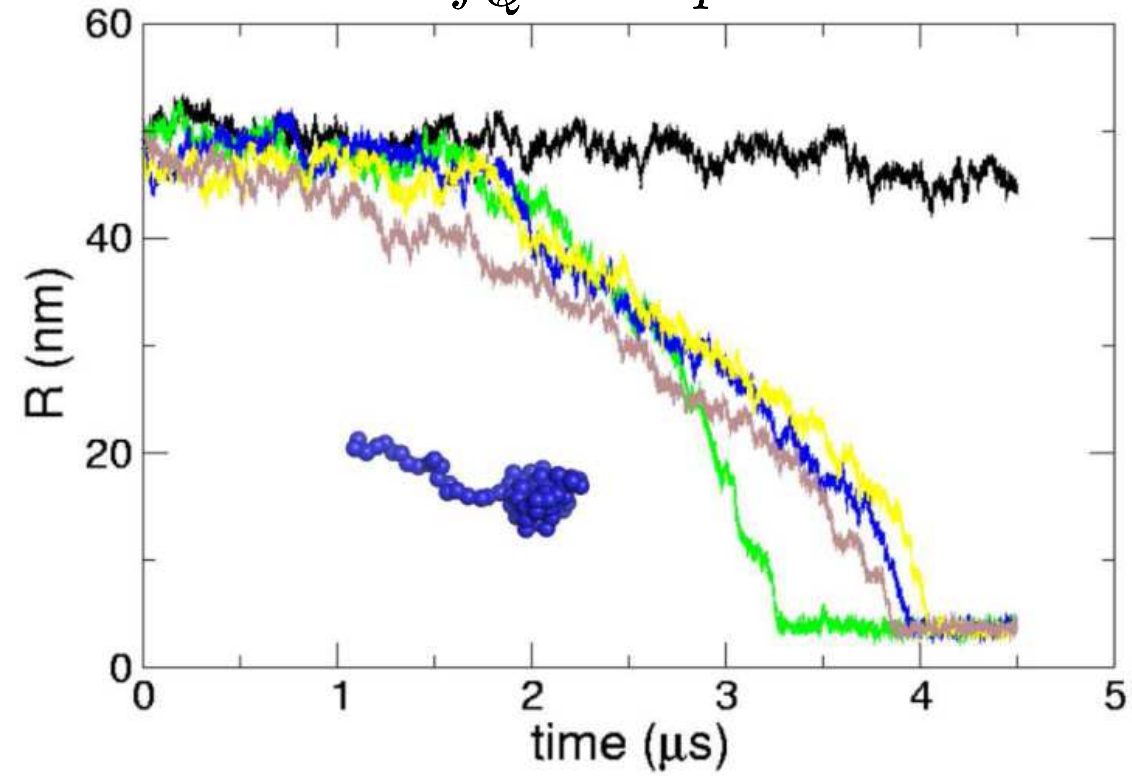
$$\delta\overline{F}^{\ddagger} = \overline{F}(L^{TS}/L_0) - \overline{F}(1) = 1/\overline{f}^{\,0} - 2 + \overline{f}^{\,0}$$

$$\tau_F \sim \exp\left[\frac{1}{\overline{f}^{\,0}} - 2 + \overline{f}^{\,0}\right],$$

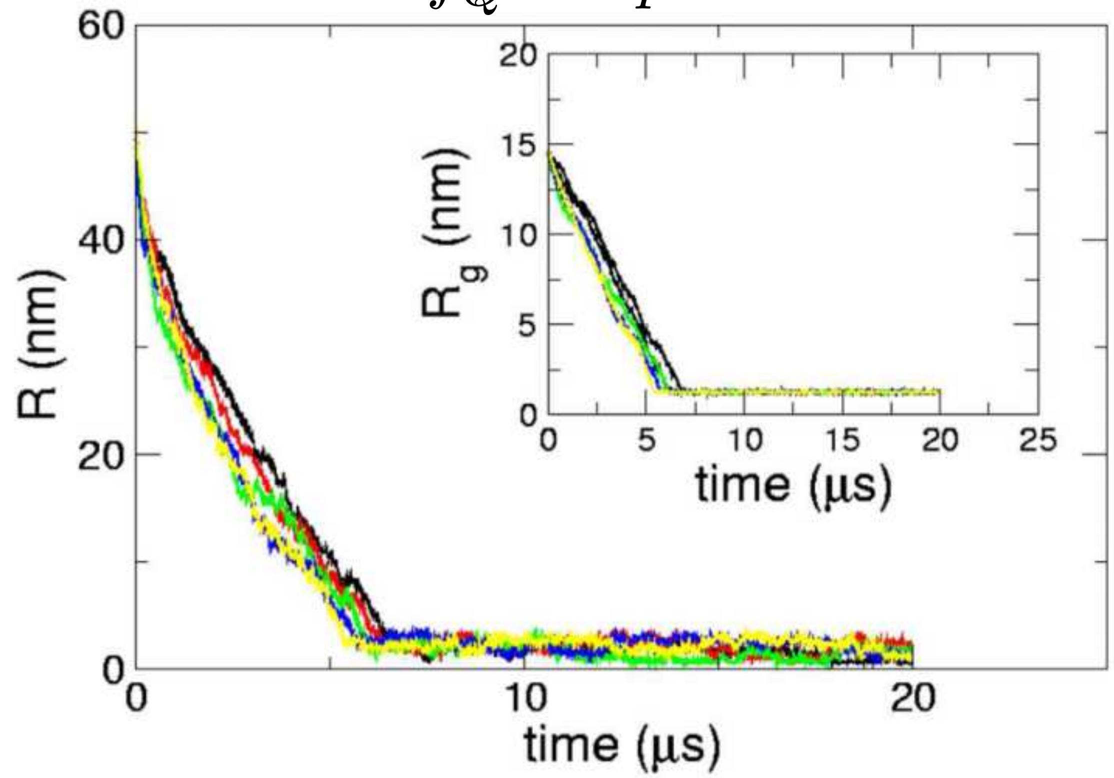
$\rightarrow f_Q = 4pN$



$\rightarrow f_Q = 75pN$



$\rightarrow f_Q = 4pN$



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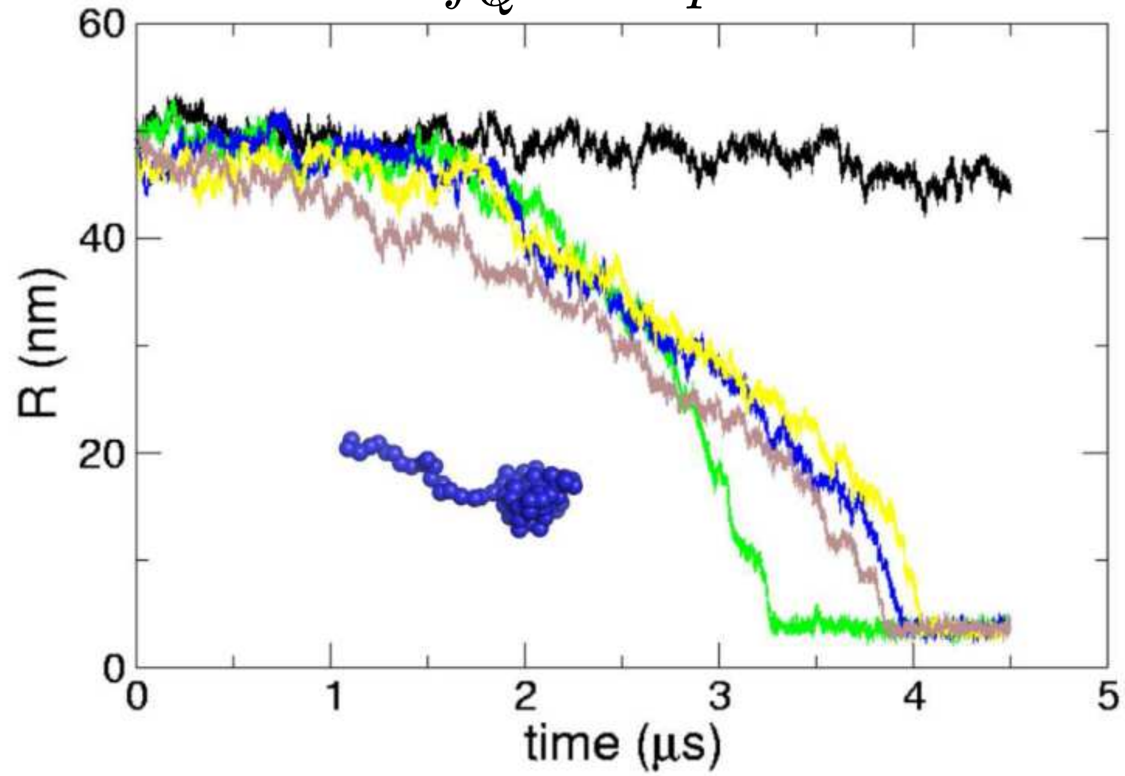
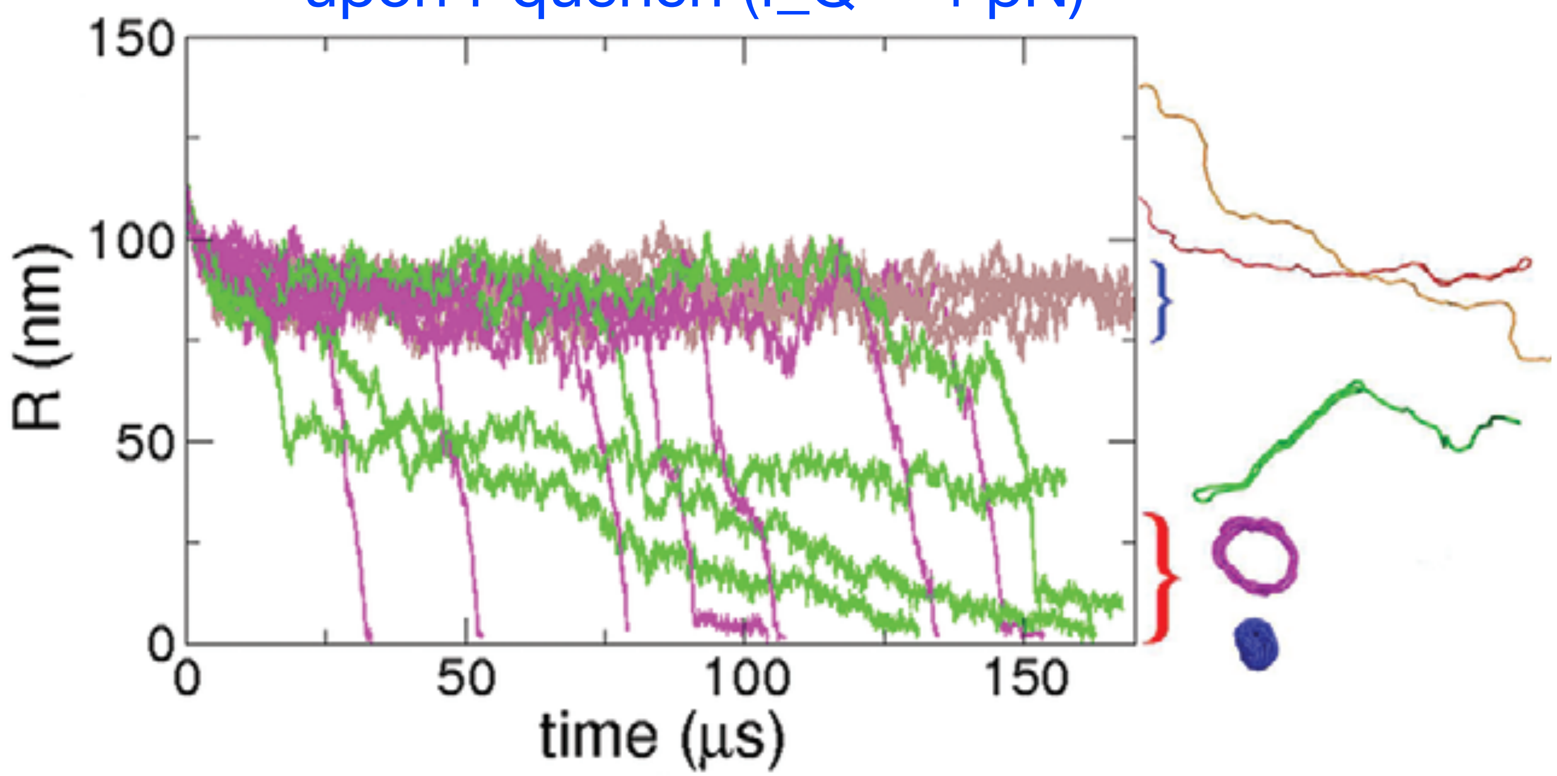
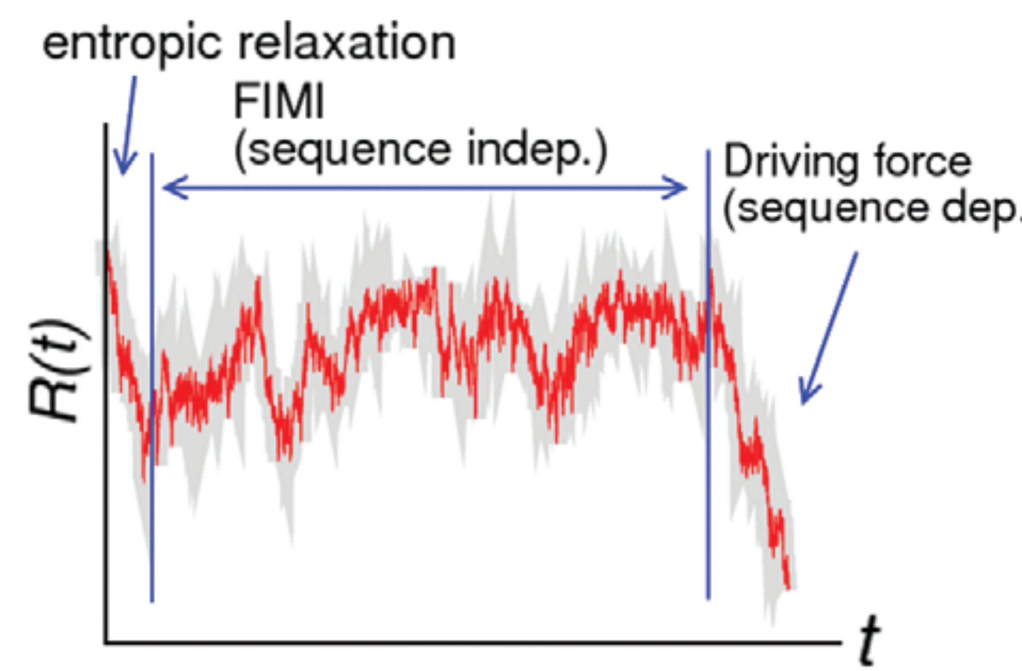


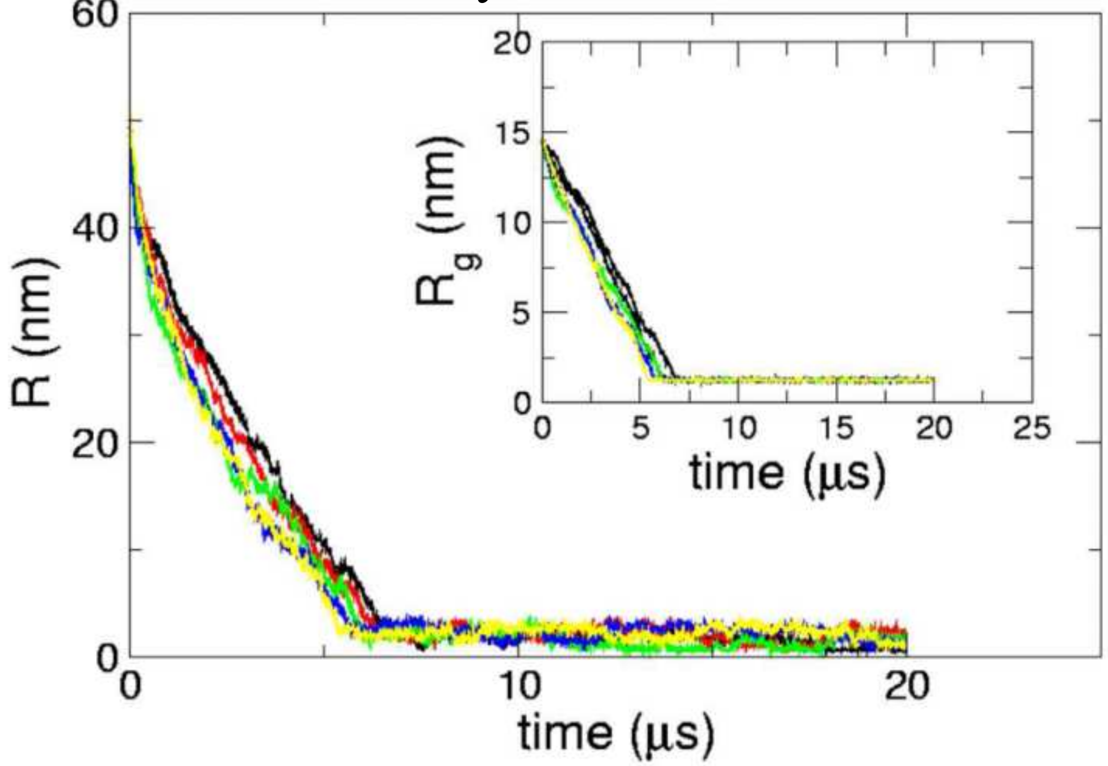
Semiflexible chain in poor solvent
upon f-quench (f_Q = 4 pN)



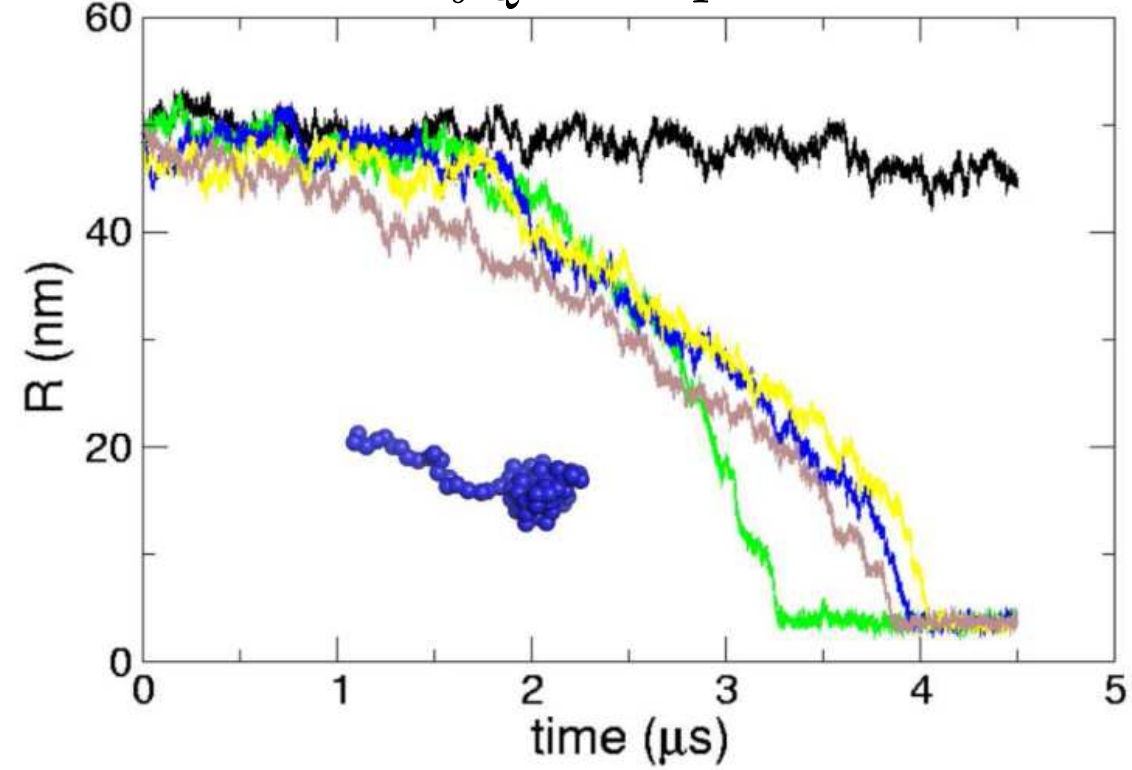


Proc. Natl. Acad. Sci. USA. (2009) 106: 20288

$\rightarrow f_Q = 4pN$



$\rightarrow f_Q = 75pN$



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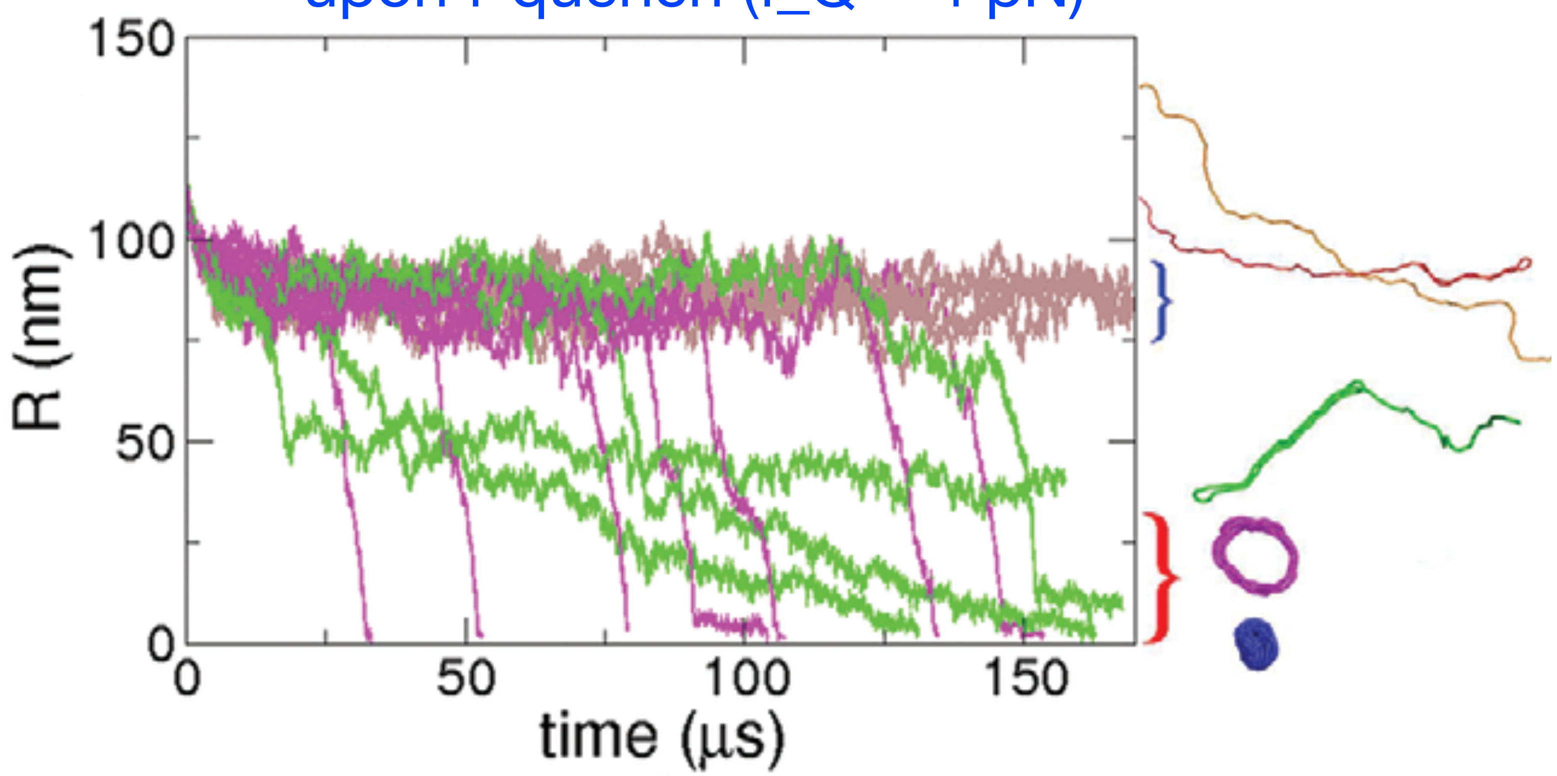
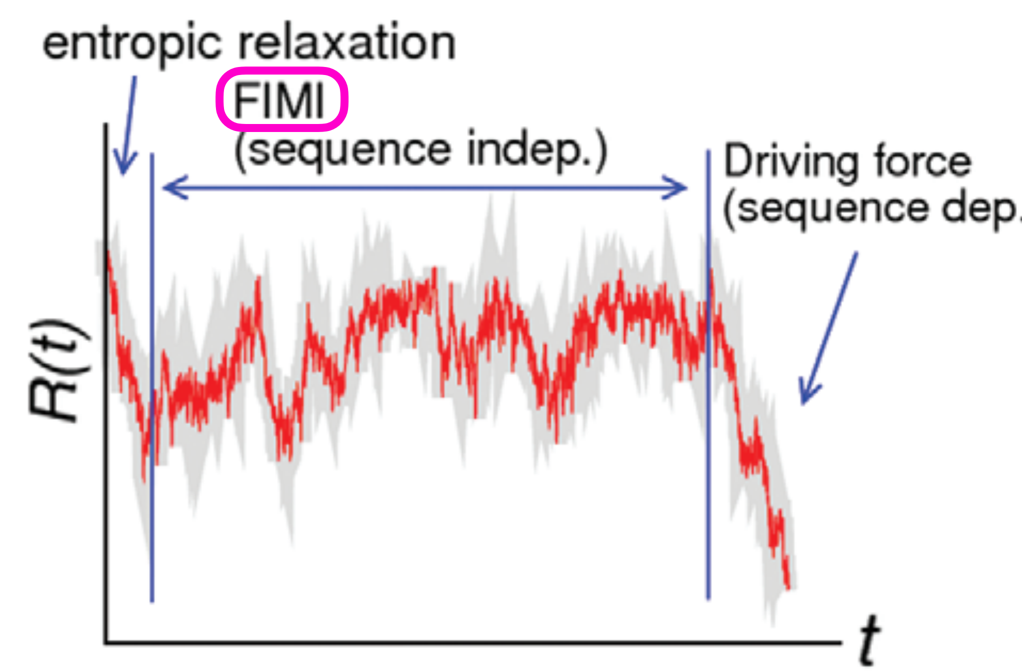


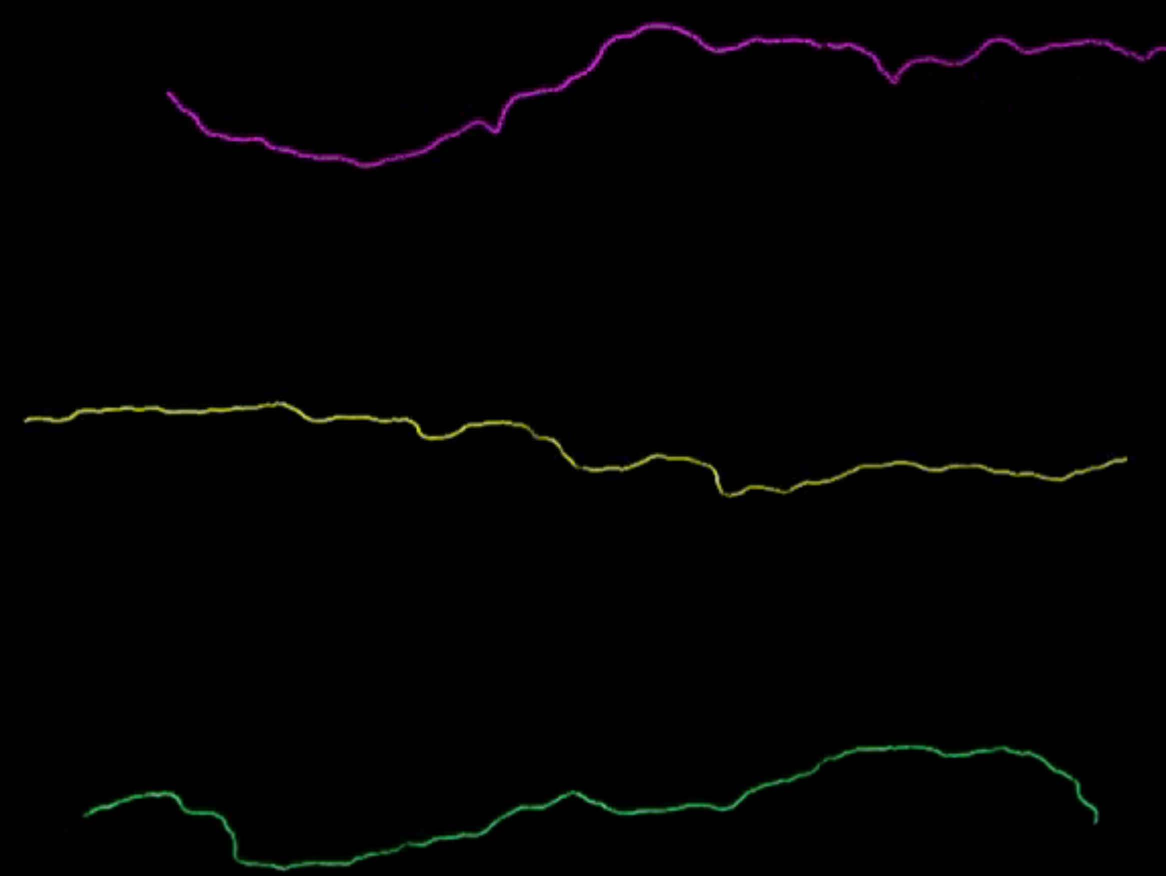
Force-Induced Metastable Intermediate



Proc. Natl. Acad. Sci. USA. (2009) 106: 20288

Collapse dynamics of a stretched semiflexible chain under poor solvent condition

$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N-1} \frac{k_r}{2}(r_{i,i+1} - a)^2 - \sum_{i=1}^{N-2} \frac{k_\theta}{2} \hat{r}_{i,i+1} \cdot \hat{r}_{i+1,i+2} + \varepsilon_h \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left[\left(\frac{\sigma}{r_{i,j}} \right)^{12} - 2\left(\frac{\sigma}{r_{i,j}} \right)^{6} \right] - f(z_N - z_0)$$



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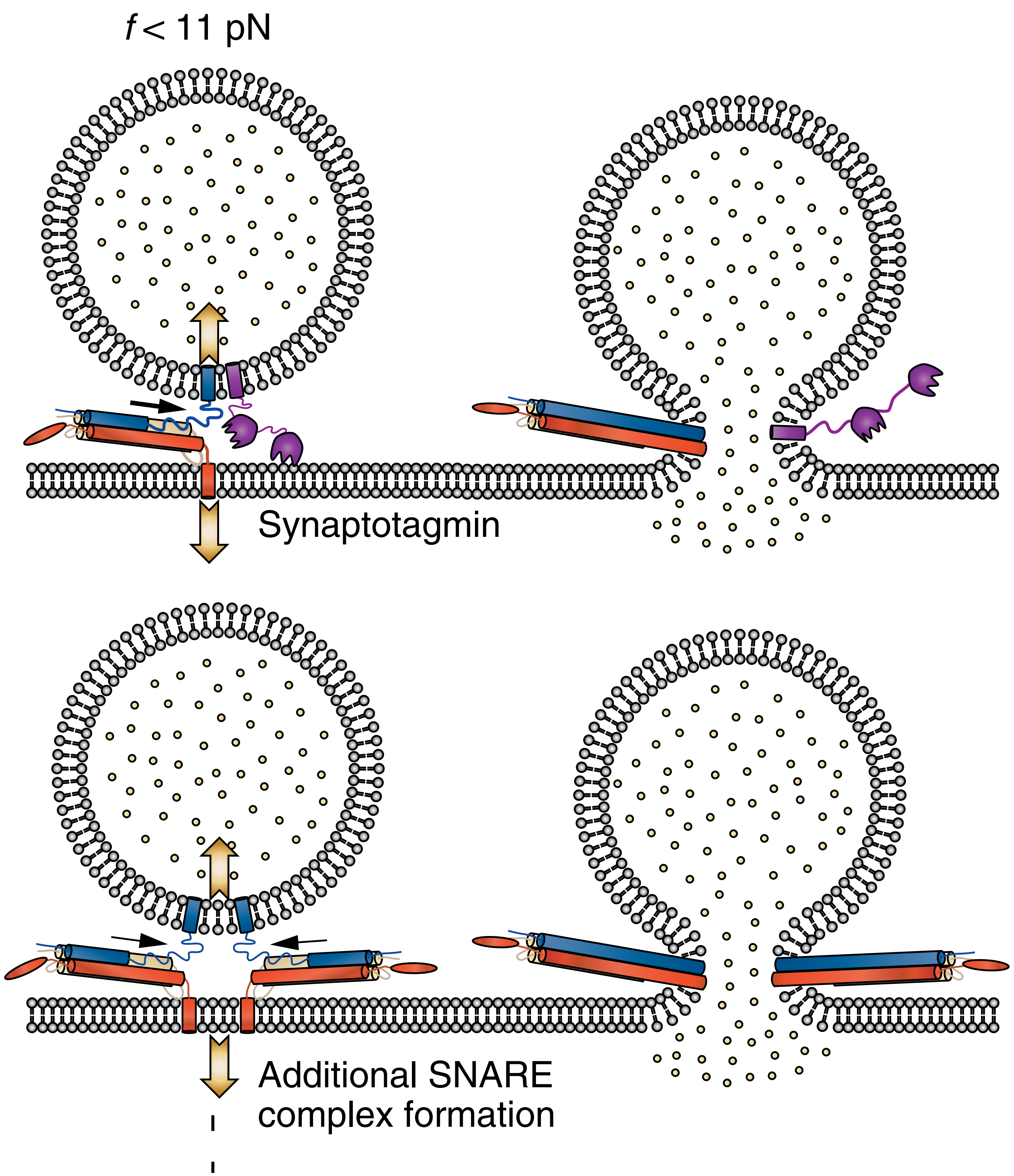
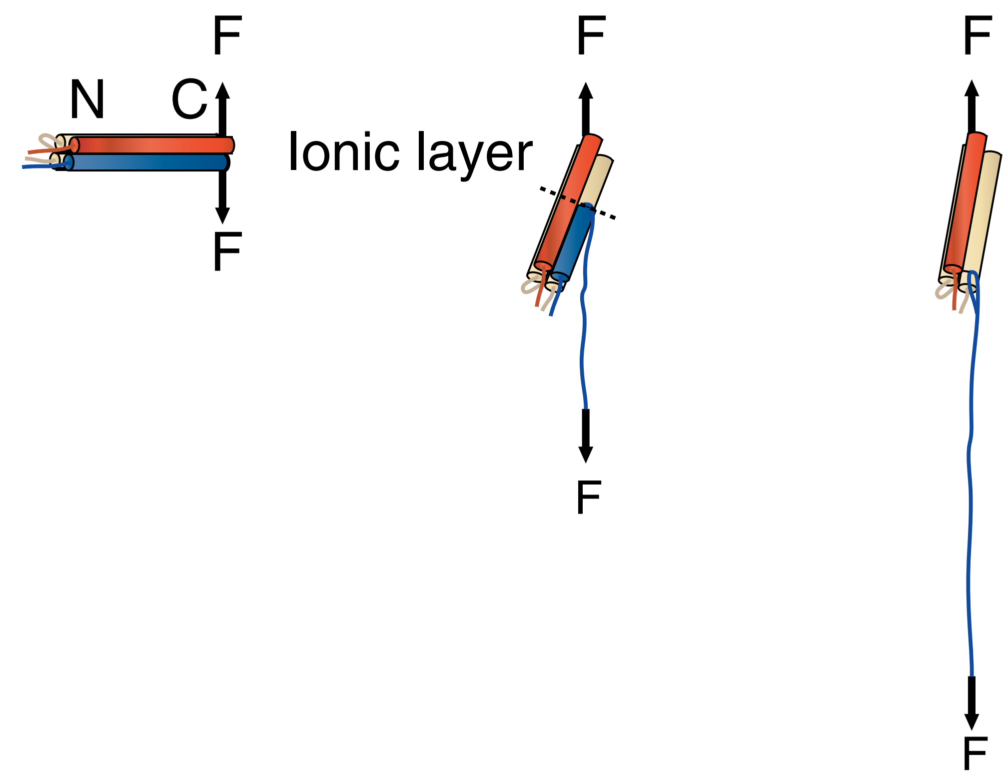
Toroid formation from the chain end

Toroid formation from the middle of the chain

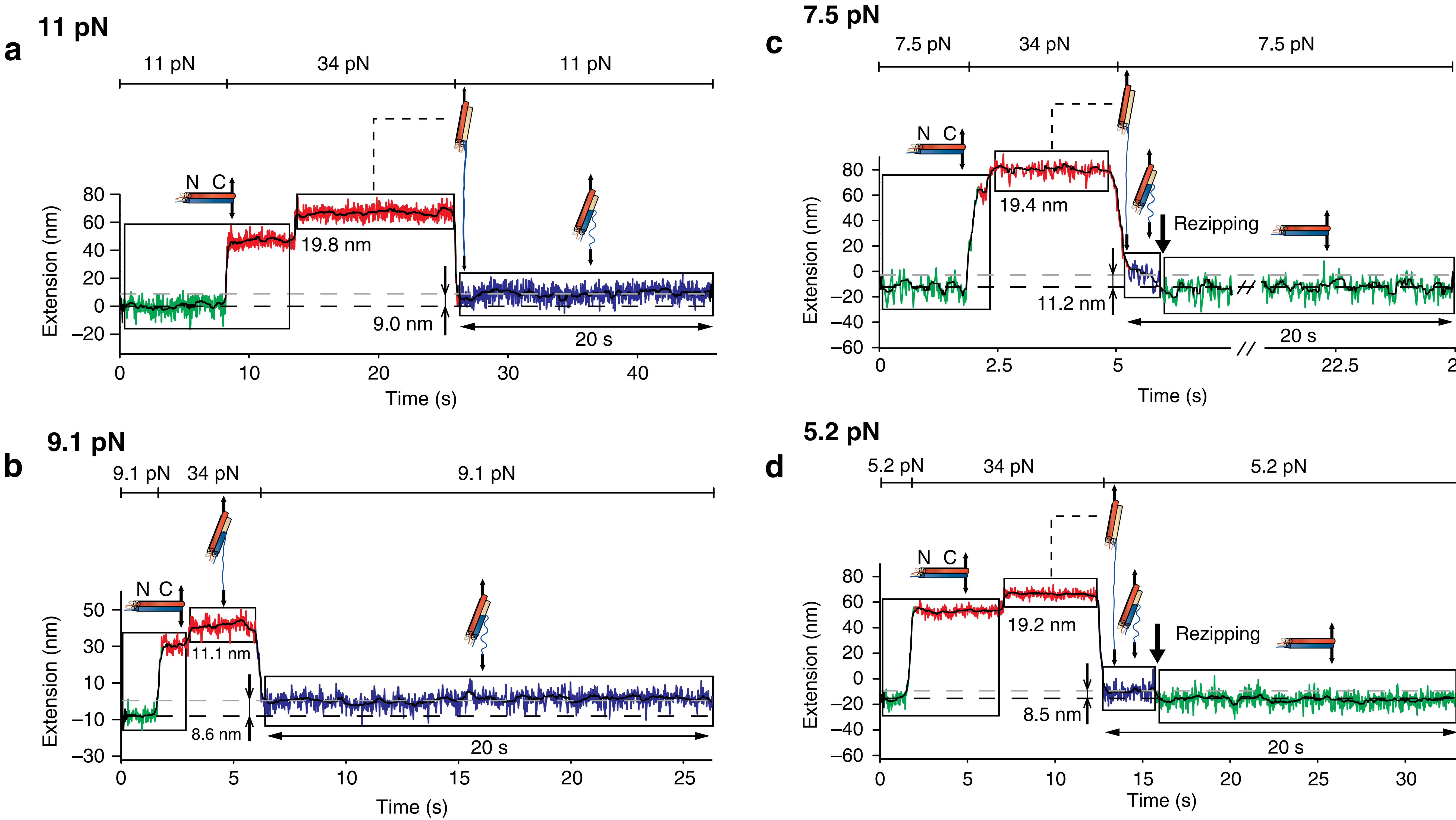
Racquet formation

SNARE





Nat. Comm. (2013) 4:1705



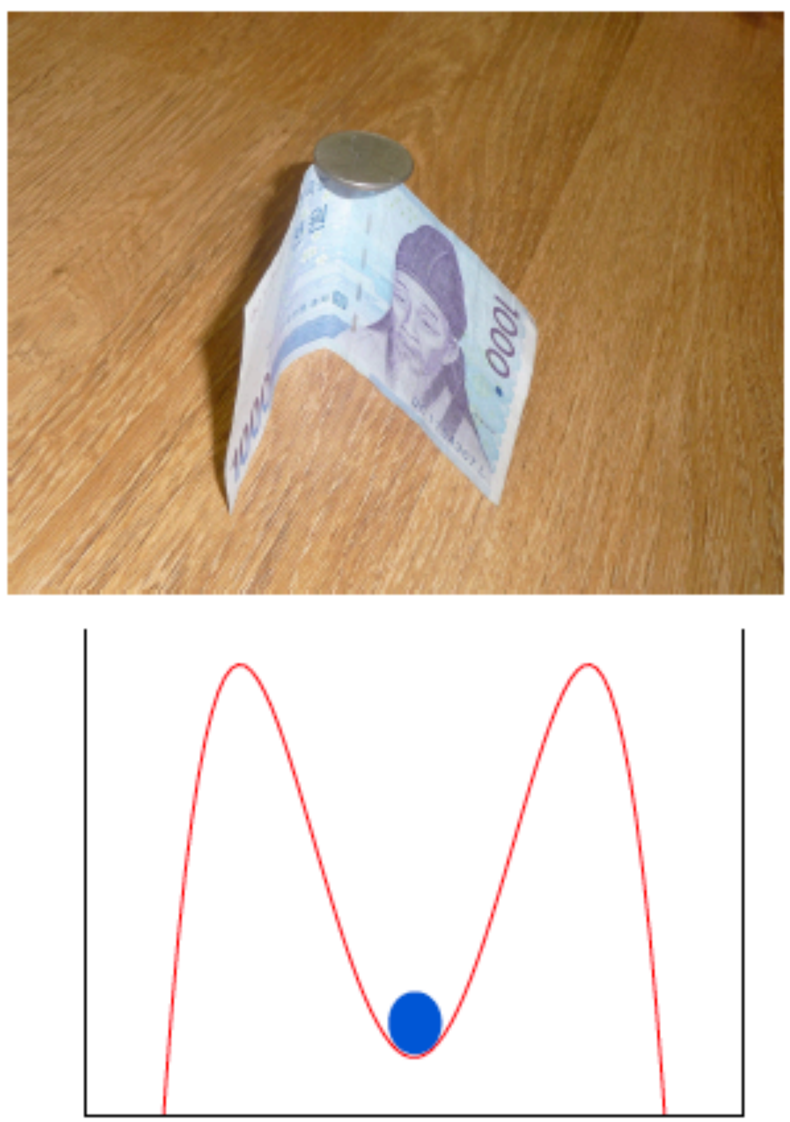
Nat. Comm. (2013) 4:1705

Metastability

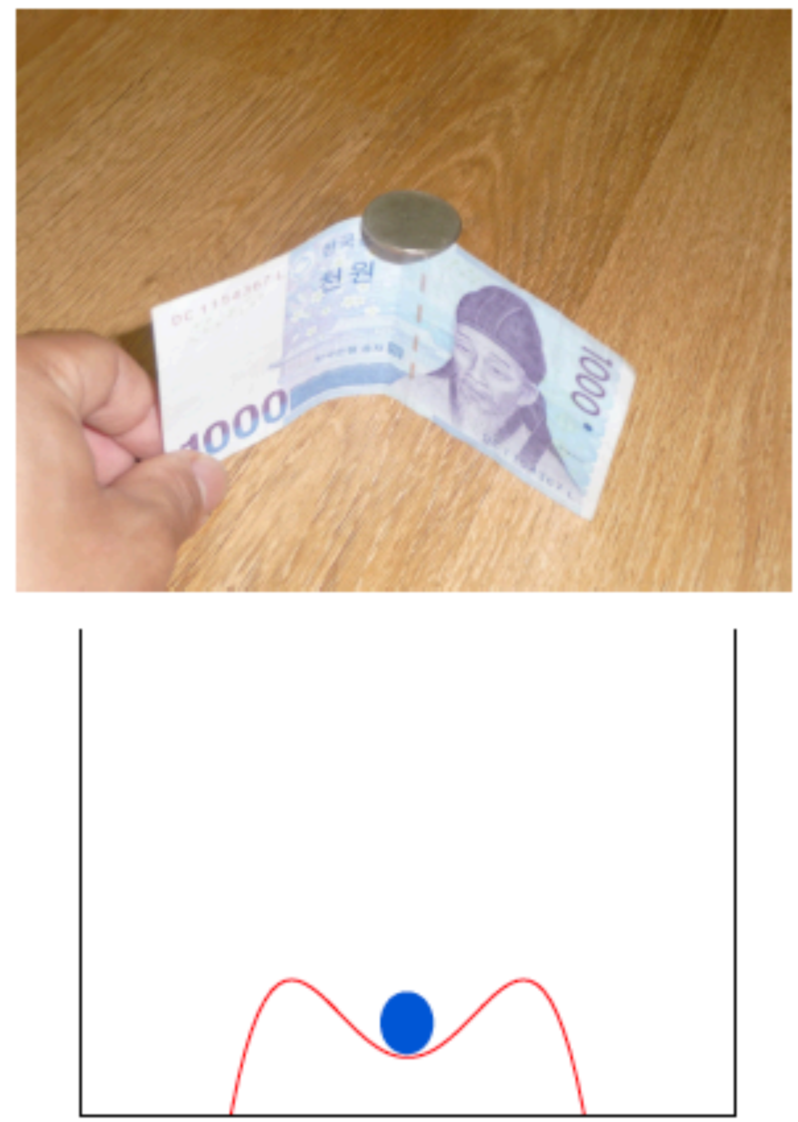
c

Metastability

A



B



C

- Relaxation dynamics along the gradient of effective free energy potentials (free energy reduction = entropy production)

$$\dot{F}(L) \approx -\eta L \dot{L}^2 \quad \longrightarrow \quad (S(t) = L(t)/L(0))$$

$$\tau = \int_0^\infty dt S(t)$$

- Escape dynamics from metastable intermediates.

$$\tau \sim \exp\left(-\beta \Delta F^{\ddagger}\right)$$

- Some Basics : Rate processes
- Types of disorder in dynamical processes : Quenched vs Dynamic disorder
- Polymer relaxation (Protein folding under tension, Expanding sausage model)
- Broken ergodicity : Heterogeneity in biomolecular dynamics

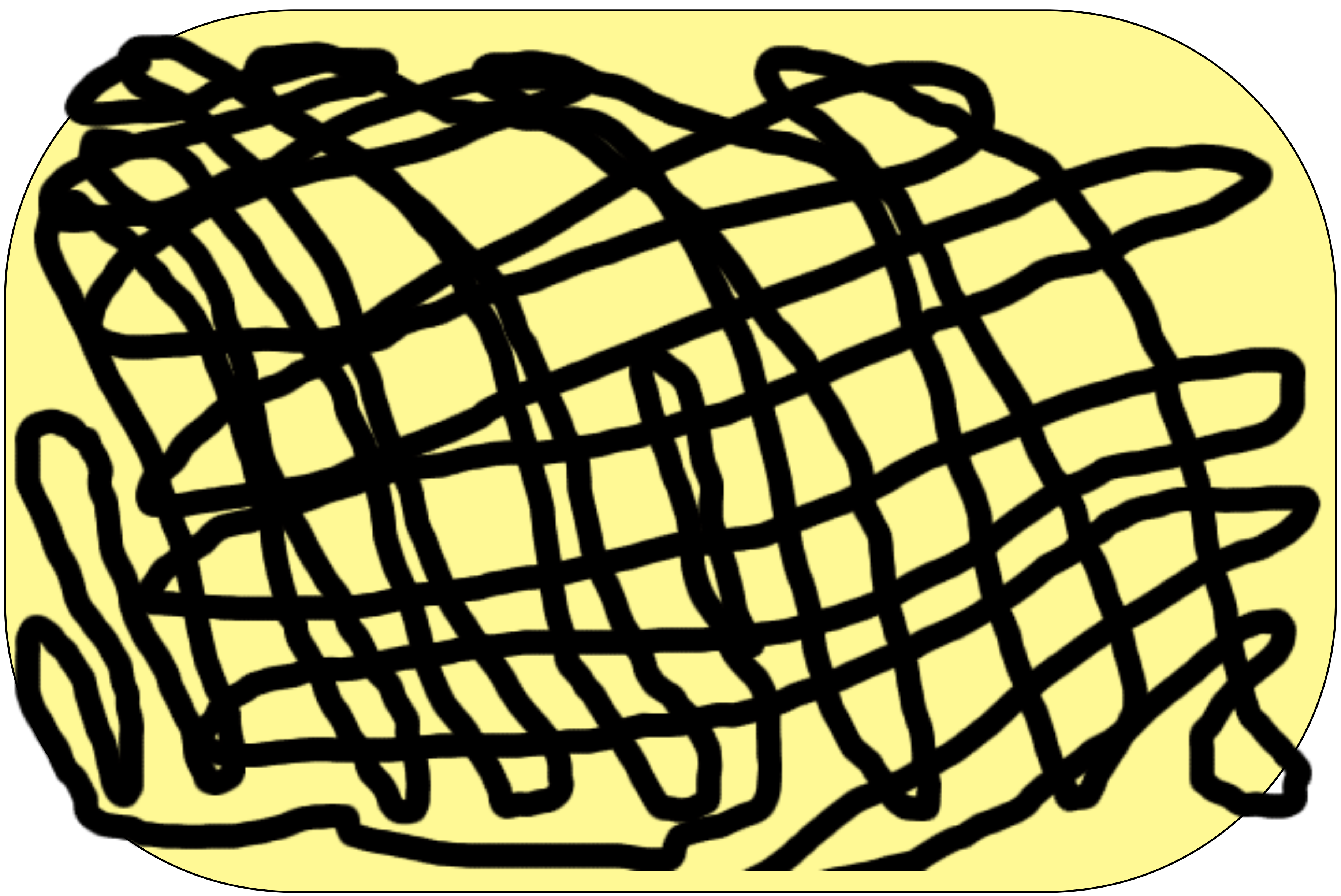
Ergodicity

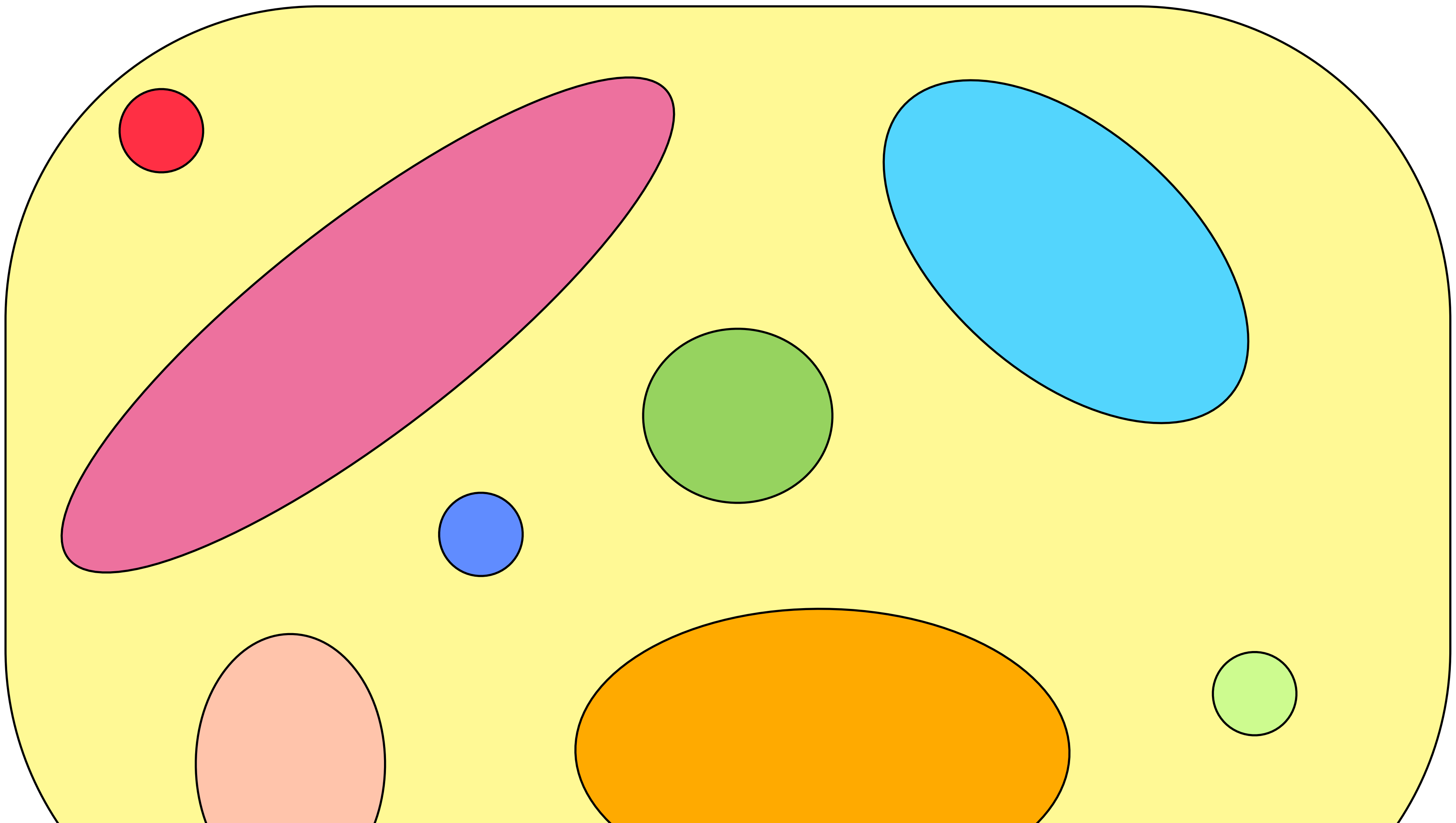
Starting from almost all initial points, the phase-space trajectory will explore many regions of phase-space over the time scale of a laboratory experiment. If this time scale is sufficiently long allowing the trajectory to sample the entire phase space, then the time average of the dynamic quantity over this time scale is equal to the ensemble average.

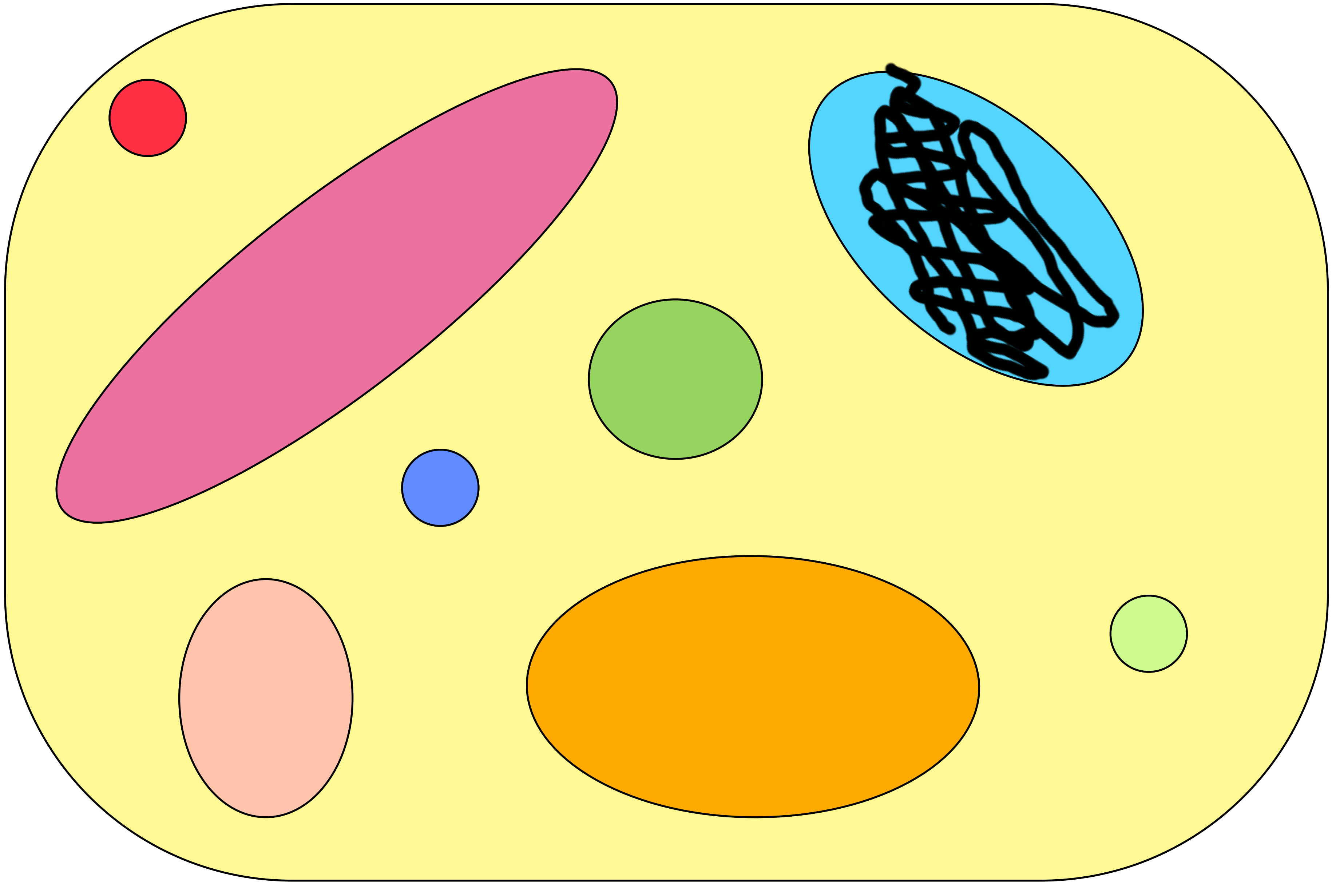
$$\overline{F}(\Gamma)\left[=\lim_{T\to\infty}\frac{1}{T}\int_0^T F(\Gamma_t)dt\right]=\langle F(\Gamma)\rangle\left[=\sum_i p_i F(\Gamma_i)\right]$$

Ergodicity

However, if a system has many metastable states, its phase trajectories may be trapped in some subset of its total phase space for long times. Consequently, the “real” behaviors often deviate from the predictions based on the usual Gibbs formalism.

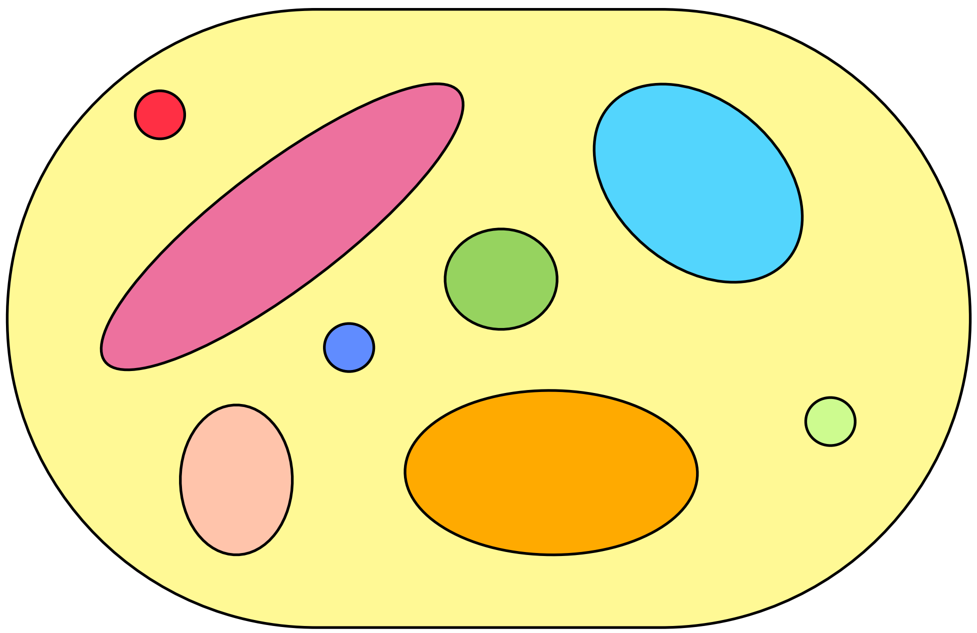






"Broken ergodicity" R. G. Palmer (1972) *Adv. Phys.*

$$\mathcal{T}_{obs} \ll \tau_{sample} \sim \exp\left(aN_{sys}\right)$$



$$\exp\left(-\beta\Delta F^{\ddagger}\right) = \frac{Z[\partial\Gamma^{\alpha}]}{Z[\Gamma^{\alpha}]}$$

$$0 \approx \omega_0 \exp\left(-\beta\Delta F^{\ddagger}\right) \times \mathcal{T}_{obs} \leq p_0$$

… confined in subregion α

$$\Gamma = \cup_{\alpha}\Gamma^{\alpha}$$

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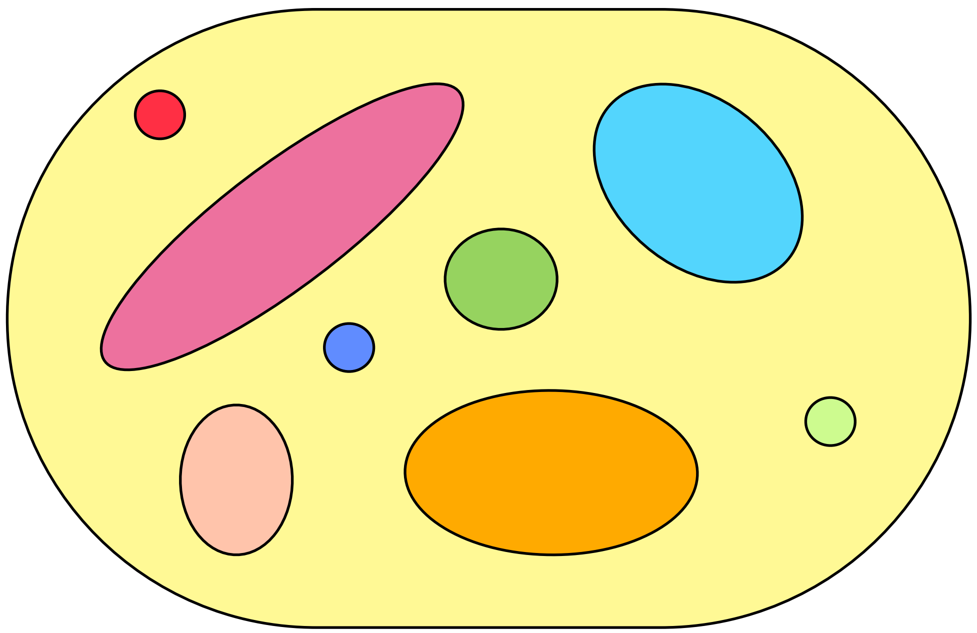

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Each Γ^{α} (component) is internally ergodic.

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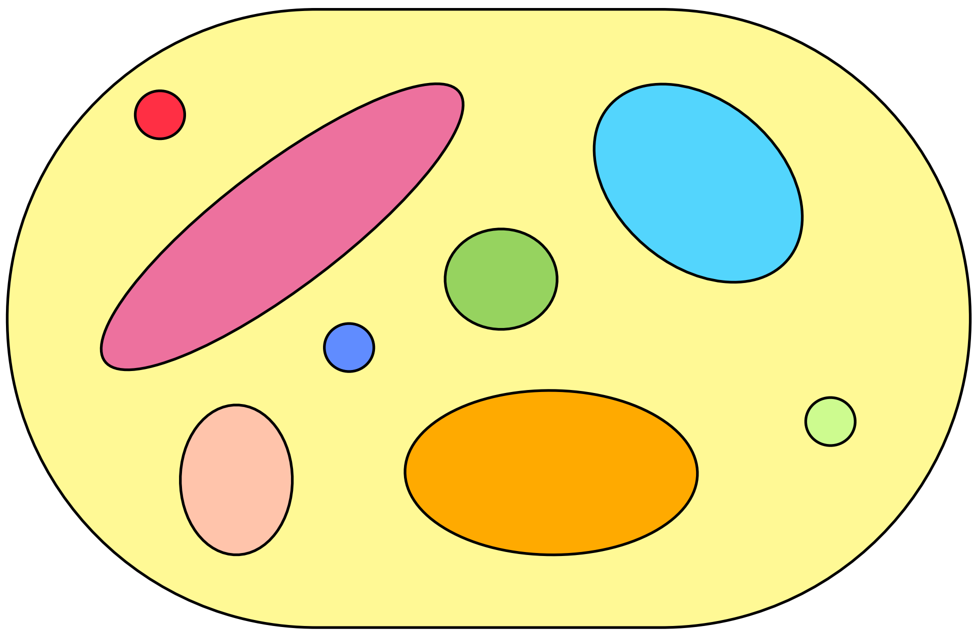

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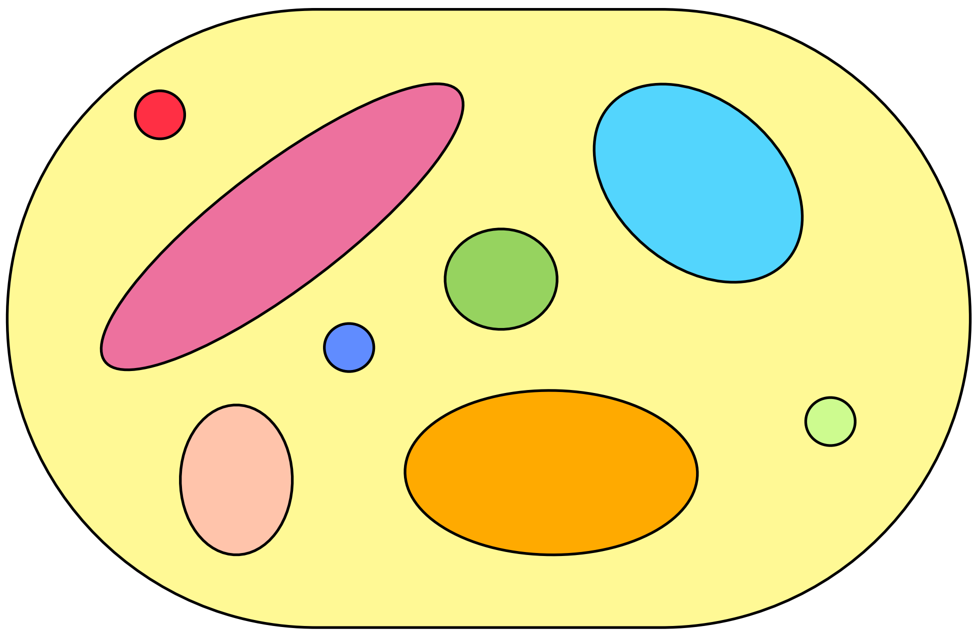

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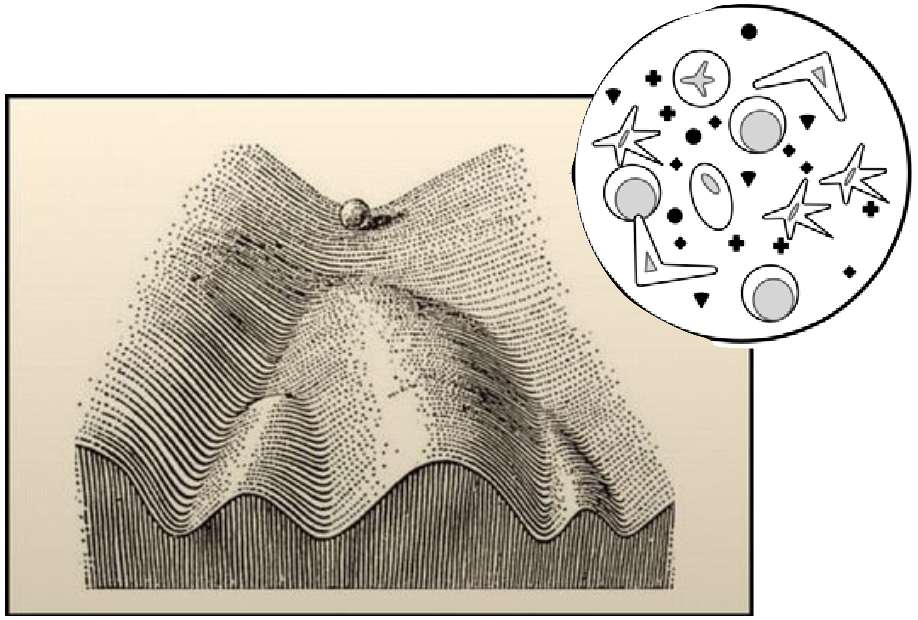
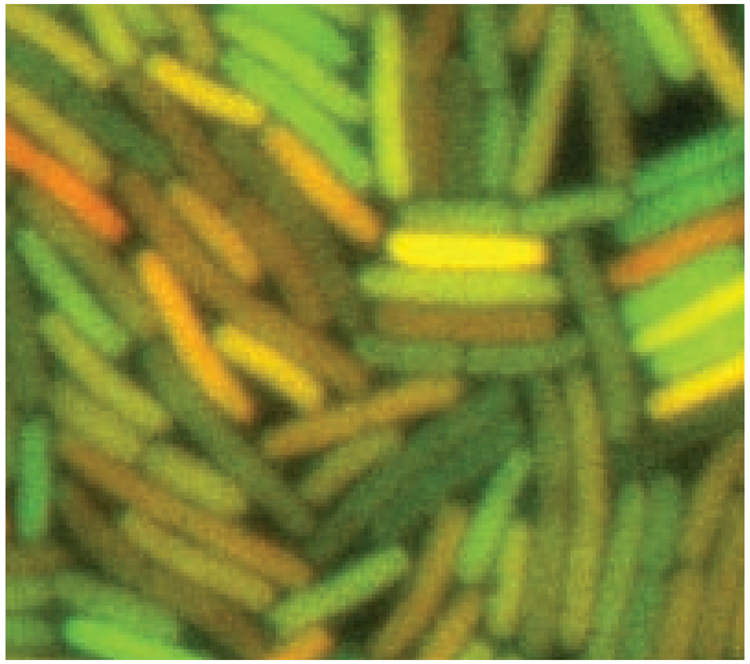
Each Γ^α (component) is internally ergodic.

Component characterization

Cell-to-cell variability
Cancer cell heterogeneity

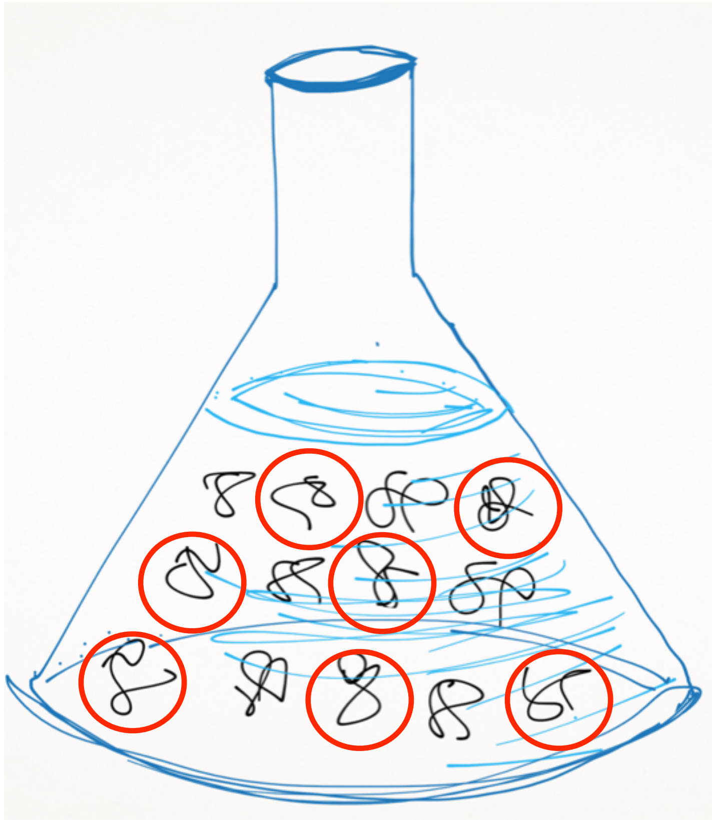


Waddington's epigenetic landscape

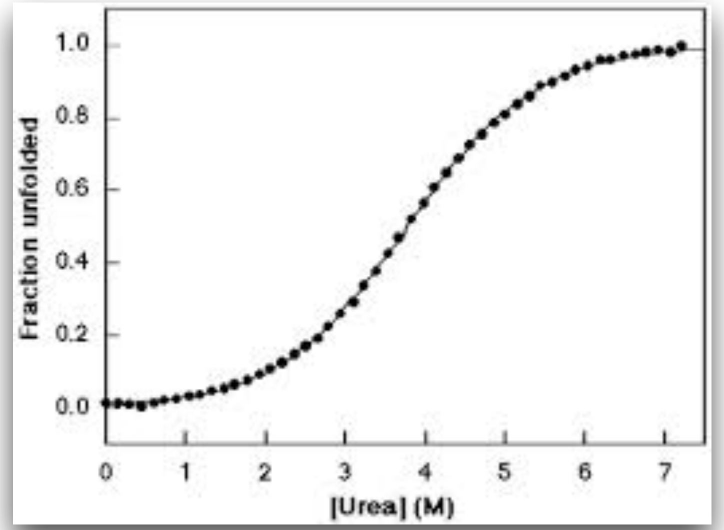


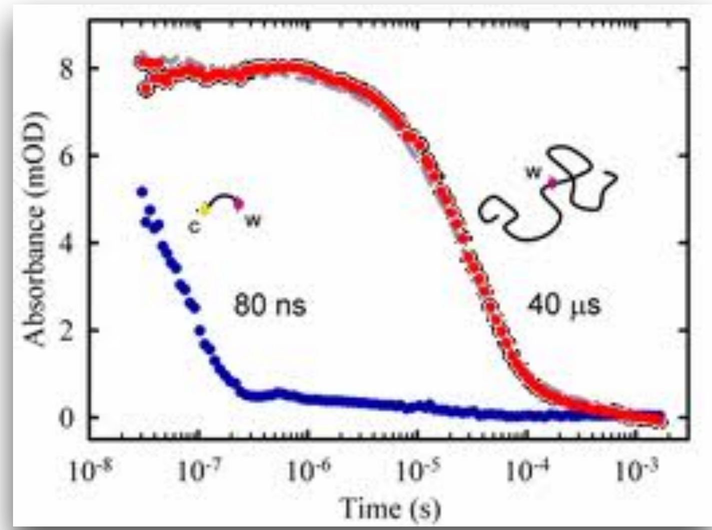
Elowitz et al. Science (2002)

Biomolecules ....



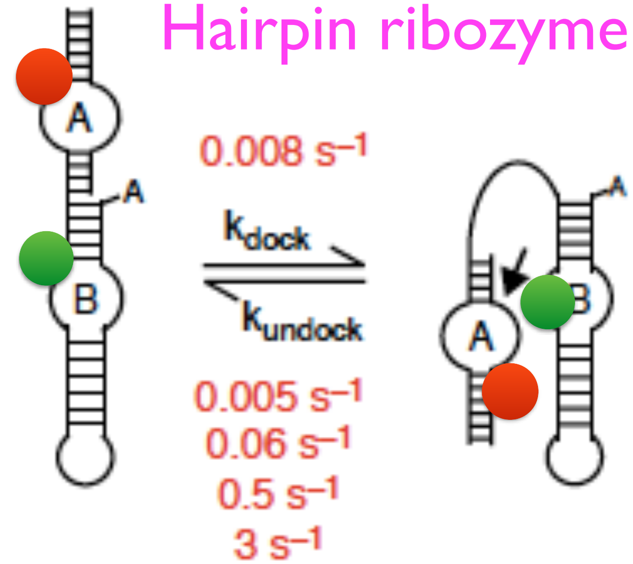
Ensemble Exp.



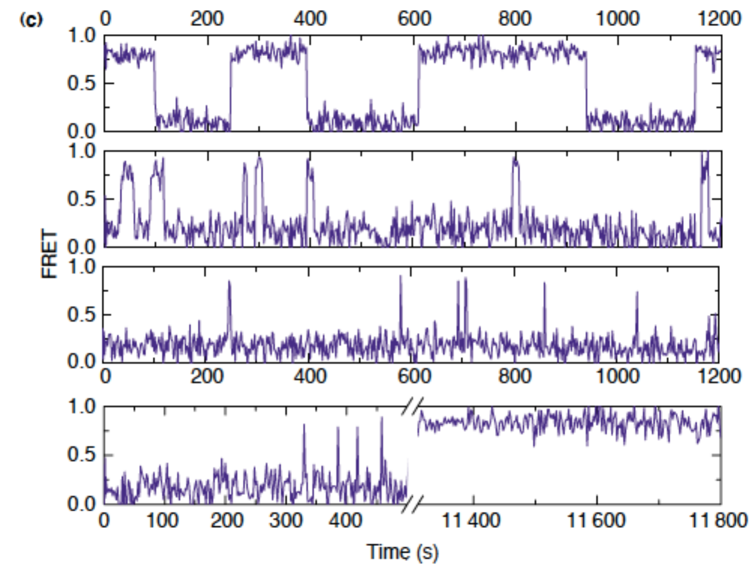


Molecule-to-molecule variation (Molecular heterogeneity)

Hairpin ribozyme

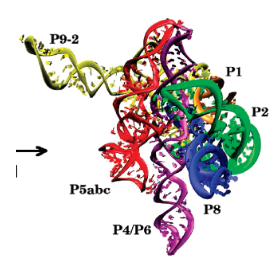


Zhuang et al. Science (2002)

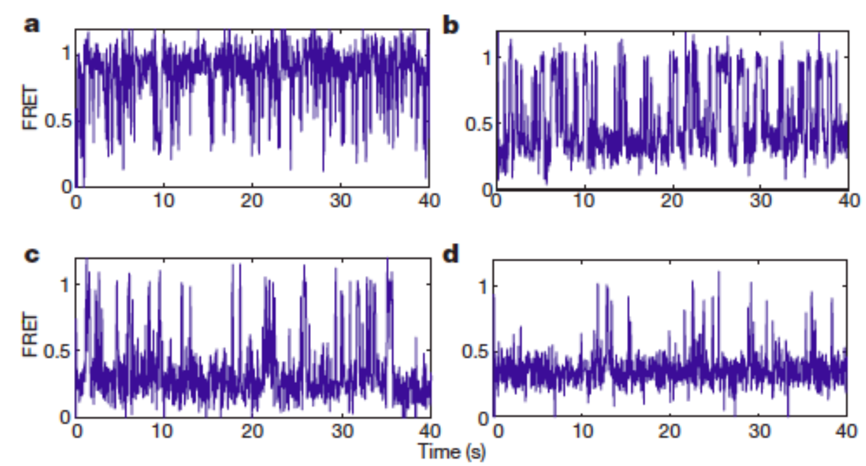


T. therm. group I intron ribozyme

Solomatin et al. (2010) Nature

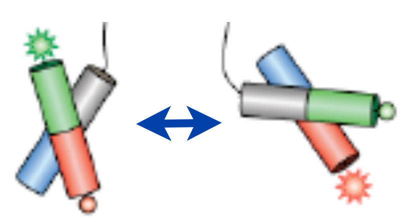


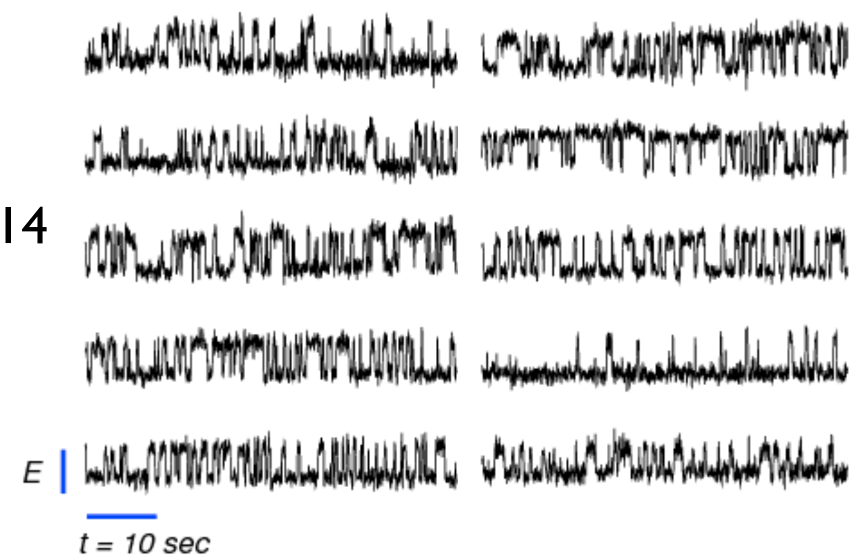
(~400 nt ribozyme)

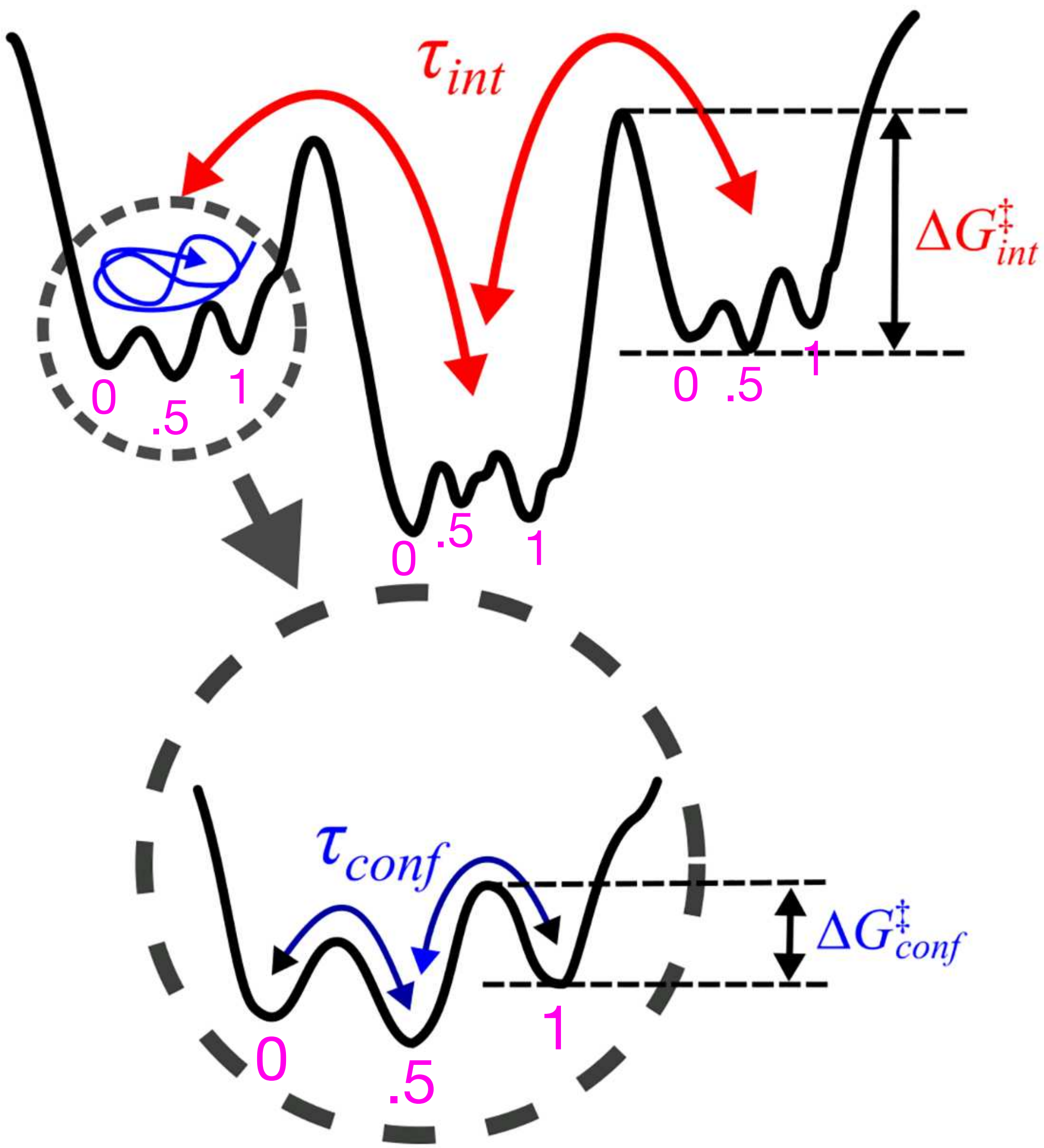


Holliday Junctions

Nat. Chem. (2012) 4, 907-914





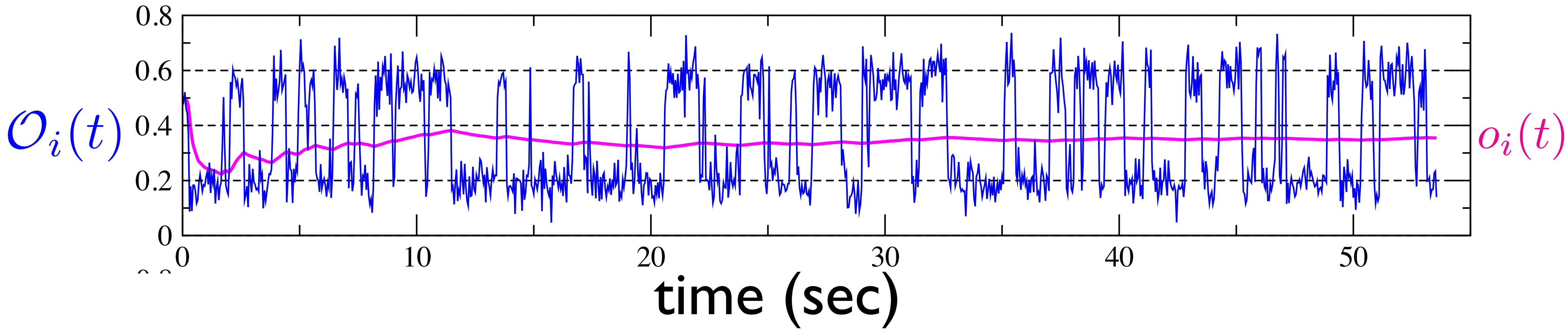


(i) $\tau_{conf} \ll T_{obs} \ll \tau_{int}$;

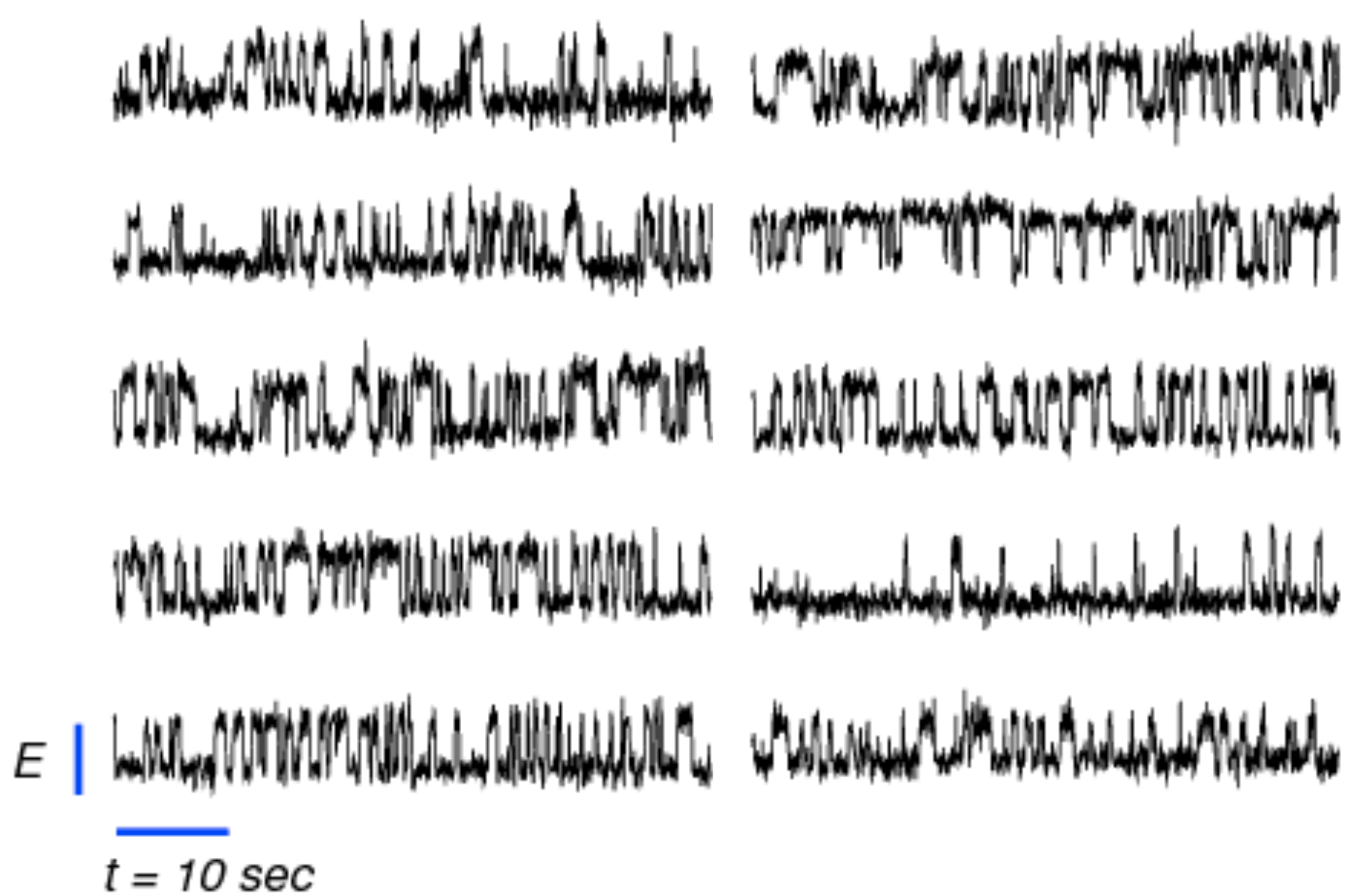
(ii) $\tau_{conf} \ll \tau_{int} \ll T_{obs}$

Component characterization !!

Partition the ensemble of molecules into its own internally ergodic component.



$$o_i(t) \equiv \frac{1}{t}\int_0^t ds\,\mathcal{O}_i(s)$$



Thirumalai, Mountain, Kirkpatrick (1989) Phys. Rev. A

$$\Omega_{\mathcal{O}}(t) = \frac{1}{N}\sum_{i=1}^{N}(o_i(t) - \overline{o(t)})^2 :$$ ergodic measure (fluctuation metric)

$$o_i(t) \equiv \frac{1}{t}\int_0^t ds\mathcal{O}_i(s)$$

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$$\lim_{t\to\infty} \Omega_{\mathcal{O}}(t) \to 0$$ should be satisfied for ergodic system

Thirumalai, Mountain, Kirkpatrick (1989) Phys. Rev. A

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=

$$\overline{o(t)} \equiv \frac{1}{N}\sum_{i=1}^{N} o_i(t) = \langle \mathcal{O} \rangle$$

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$$\Omega_{\mathcal{O}}(t) = \frac{1}{t^2}\int_0^t ds_1 \int_0^t ds_2 \frac{1}{N}\sum_{i=1}^{N}(\mathcal{O}_i(s_1) - \langle \mathcal{O} \rangle)(\mathcal{O}_i(s_2) - \langle \mathcal{O} \rangle)$$

Thirumalai, Mountain, Kirkpatrick (1989) Phys. Rev. A

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$$= \frac{1}{t^2}\int_0^t ds_1 \int_0^t ds_2 C(s_1, s_2)$$

Thirumalai, Mountain, Kirkpatrick (1989) Phys. Rev. A

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$$\xrightarrow{t\to\infty} \langle\mathcal{O}\rangle \qquad\qquad = \langle\mathcal{O}\rangle$$

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$$\Omega_{\mathcal{O}}(t) = \frac{1}{t^2}\int_0^t ds_1\int_0^t ds_2 \boxed{\frac{1}{N}\sum_{i=1}^{N}(\mathcal{O}_i(s_1) - \langle\mathcal{O}\rangle)(\mathcal{O}_i(s_2) - \langle\mathcal{O}\rangle)}$$

$$= \frac{1}{t^2}\int_0^t ds_1\int_0^t ds_2 C(s_1, s_2)$$

$C(s_1, s_2) \approx C(|s_1 - s_2|)$

Thirumalai, Mountain, Kirkpatrick (1989) Phys. Rev. A

$$\Omega_{\mathcal{O}}(t) = \frac{1}{N}\sum_{i=1}^{N}(o_i(t) - \overline{o(t)})^2:$$ ergodic measure (fluctuation metric)

$$o_i(t) \equiv \frac{1}{t}\int_0^t ds\mathcal{O}_i(s) \qquad = \qquad \overline{o(t)} \equiv \frac{1}{N}\sum_{i=1}^{N} o_i(t)$$

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Thirumalai, Mountain, Kirkpatrick (1989) Phys. Rev. A

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For an ergodic system, D_O is an "effective diffusion constant" in a space projected onto the observable *O*

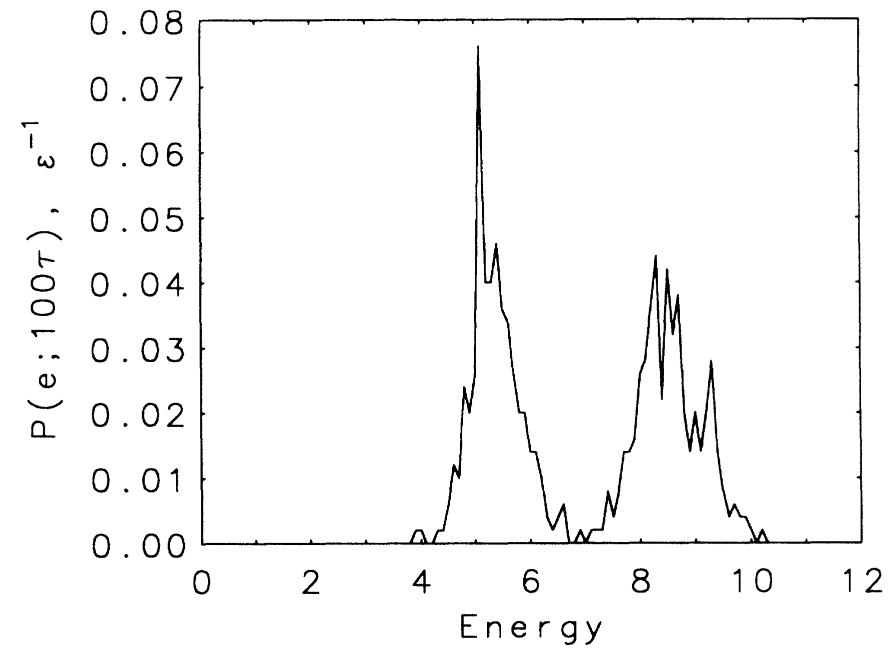
: a speed of mixing (equilibration)

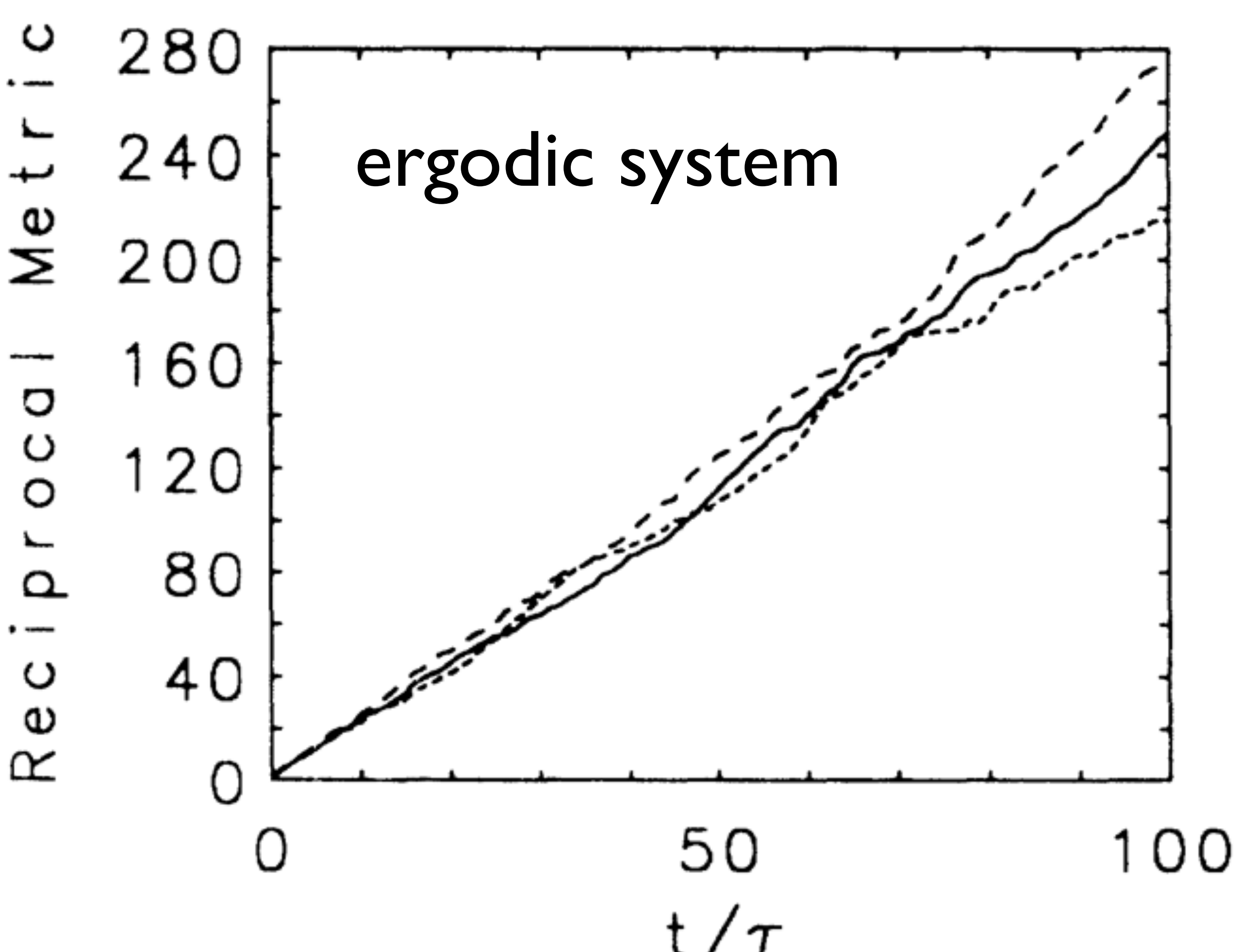
Ergodic convergence properties of supercooled liquids and glasses

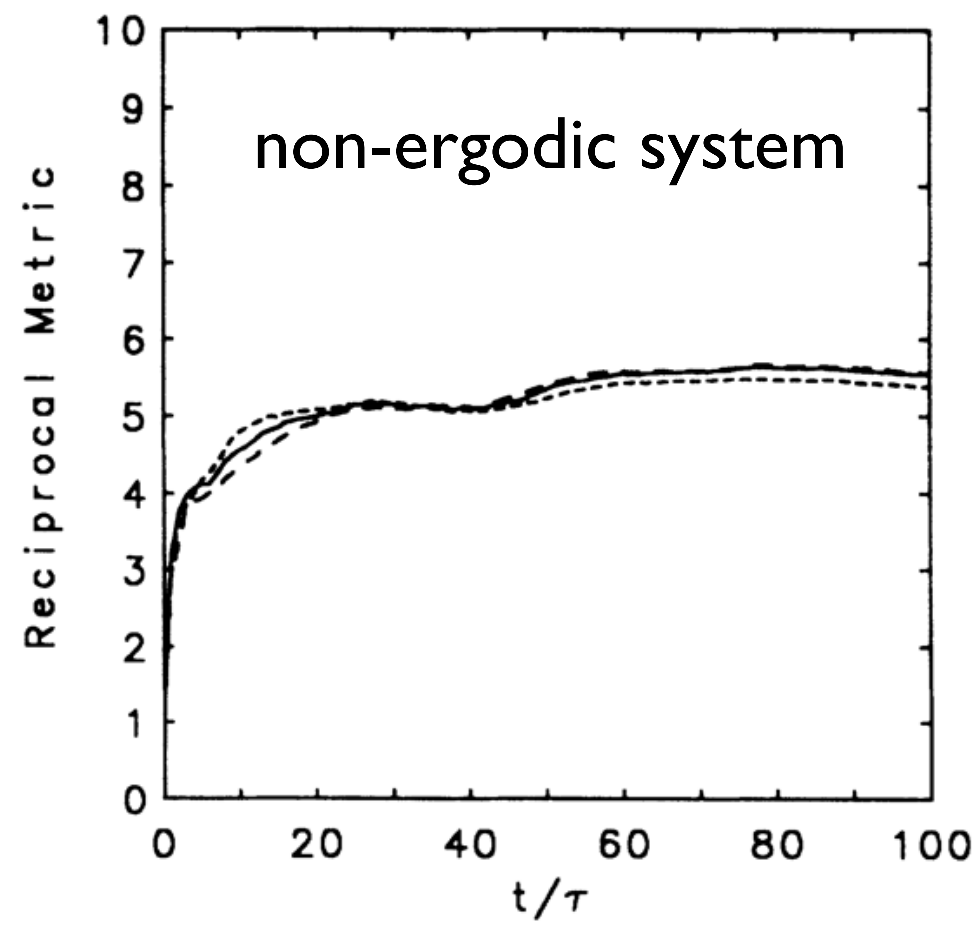
Binary fluids

Thirumalai & Mountain, PRA (1990) 42:4574

$$\frac{\Omega_{\mathcal{O}}(0)}{\Omega_{\mathcal{O}}(t)} \sim D_{\mathcal{O}} t$$







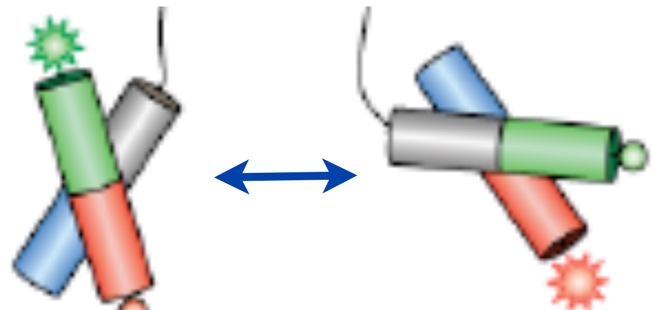
Examples

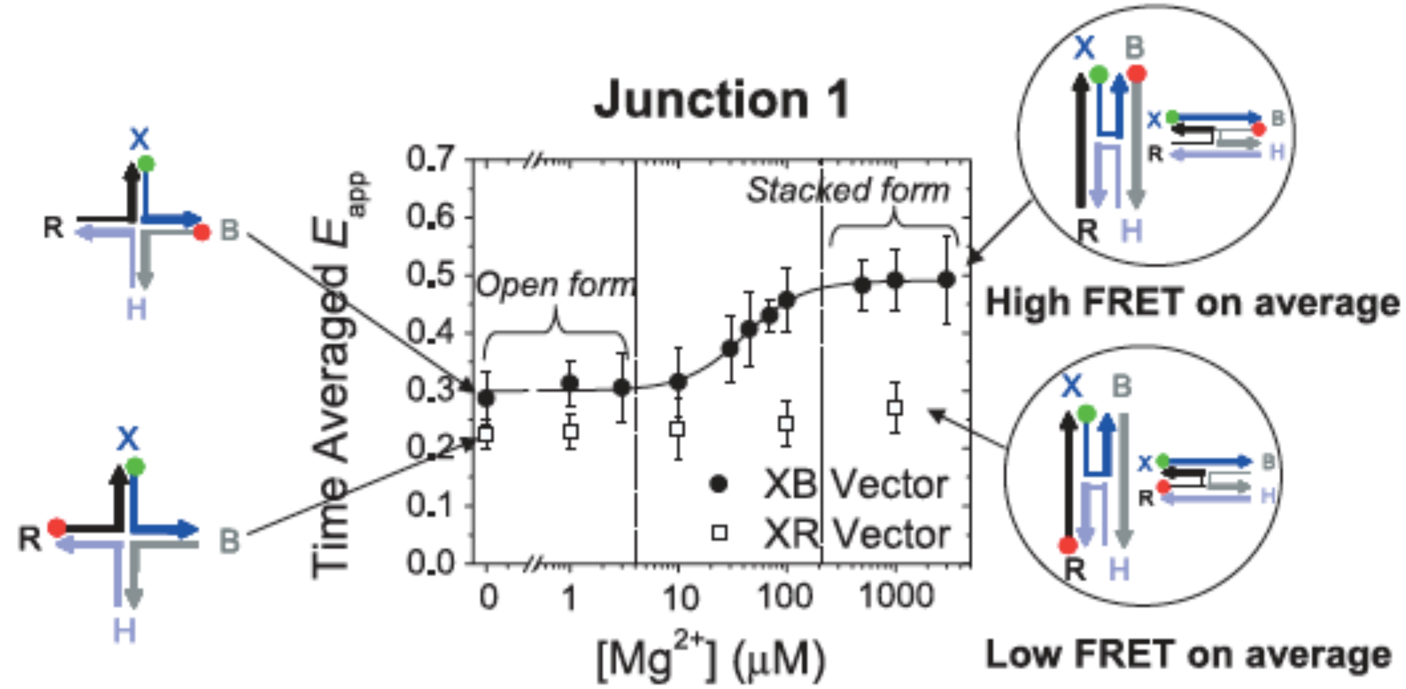
- Dynamics of DNA junction (Holliday junction)
- Molecular motor (kinesin-1)
- RecBCD
- H-DNA

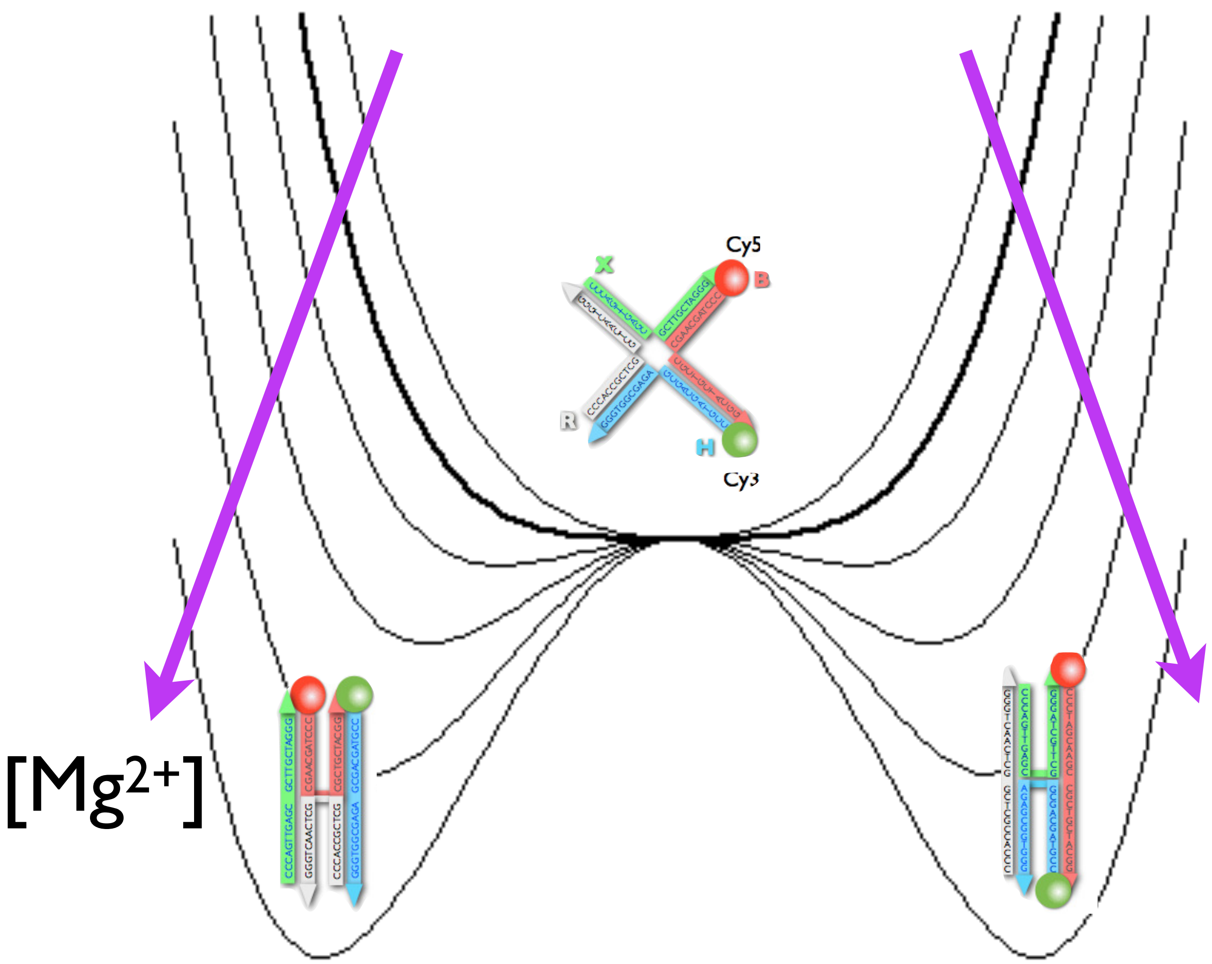
Holliday Junctions

Nat. Chem. (2012) 4, 907-914

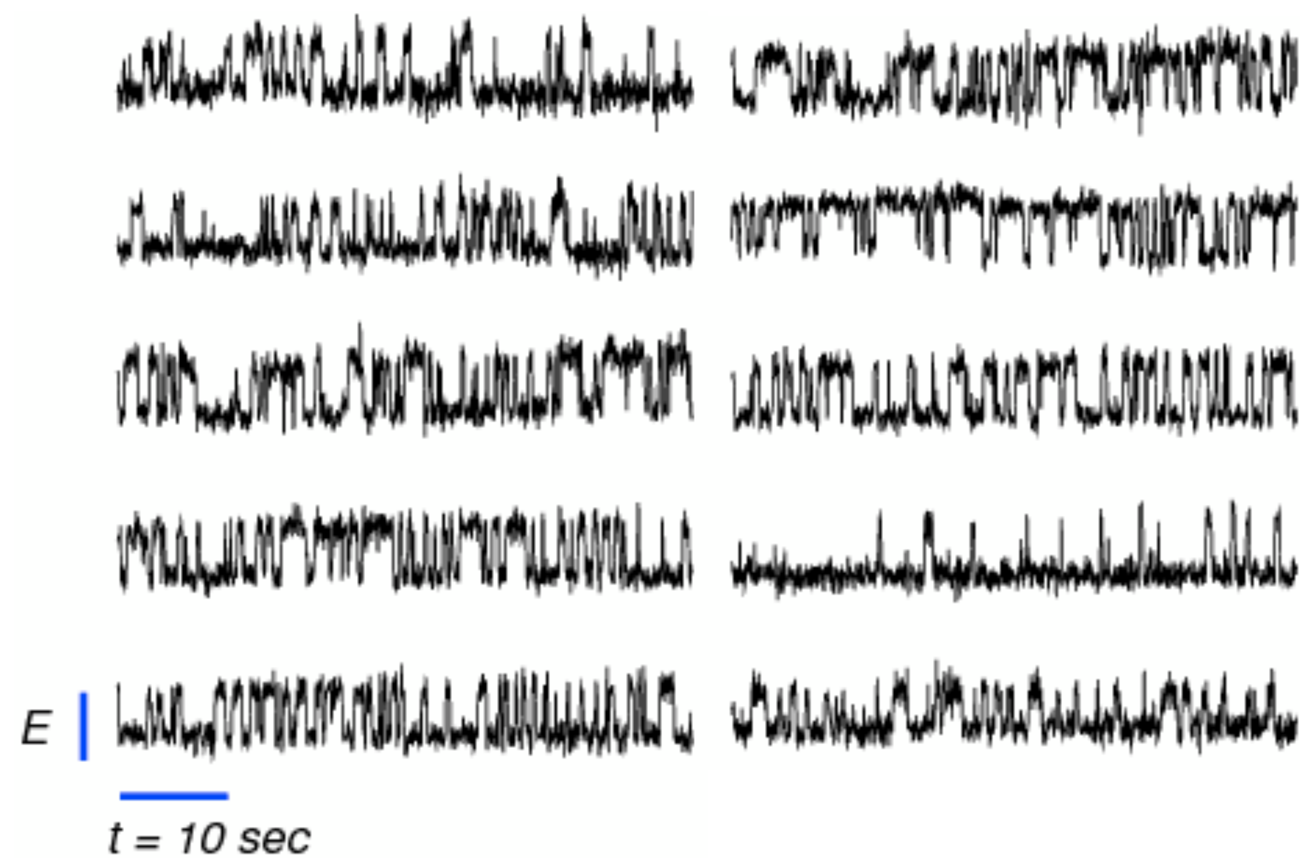
Two state dynamics at $[Mg^{2+}]$=0.5 ~ 50 mM





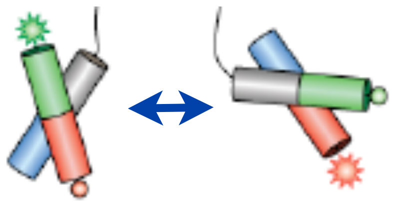


$E_i(t)$



Holliday Junctions

Nat. Chem. (2012) 4, 907-914



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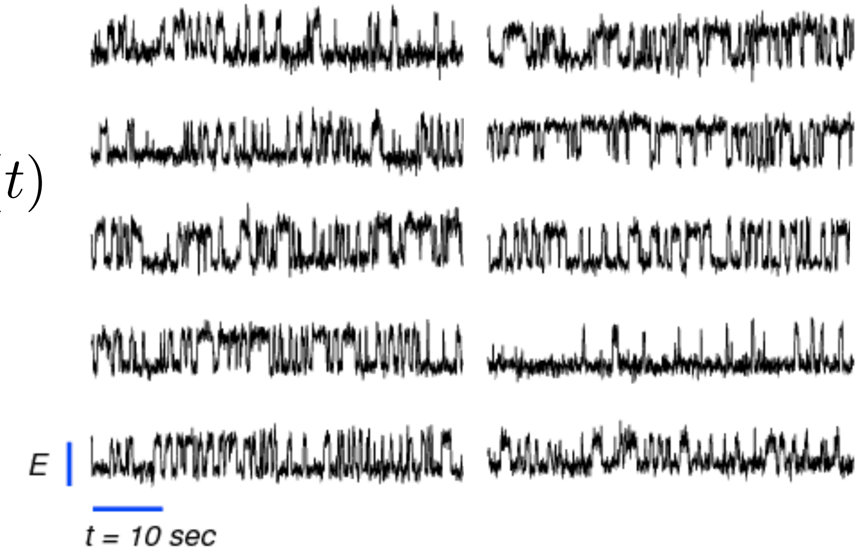
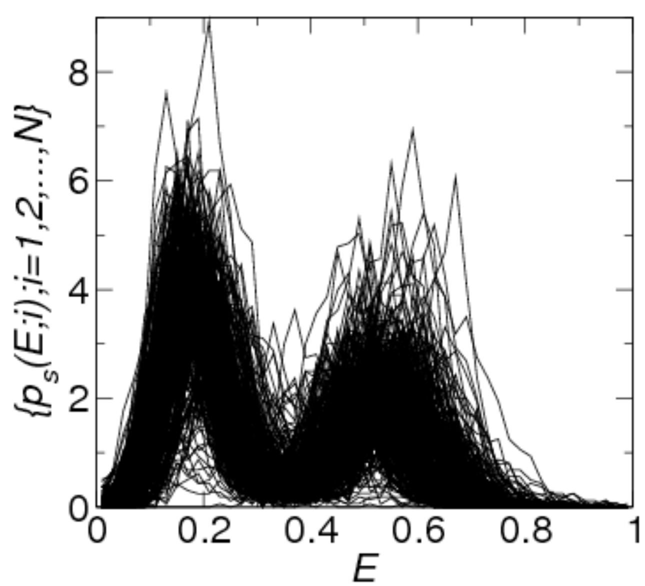
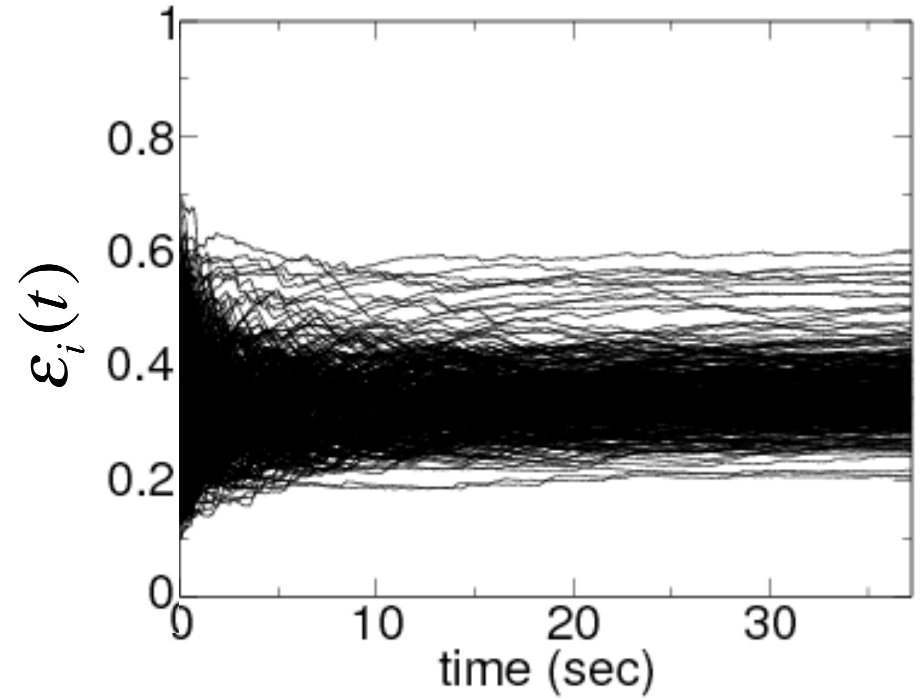
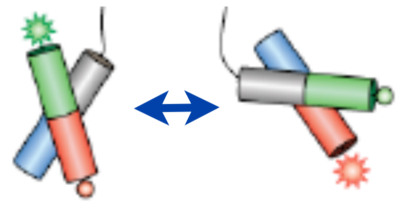


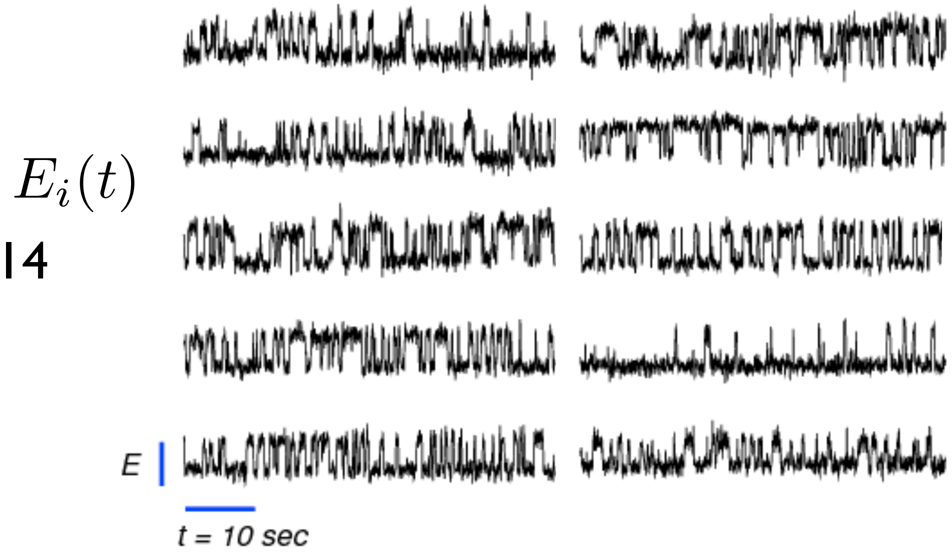


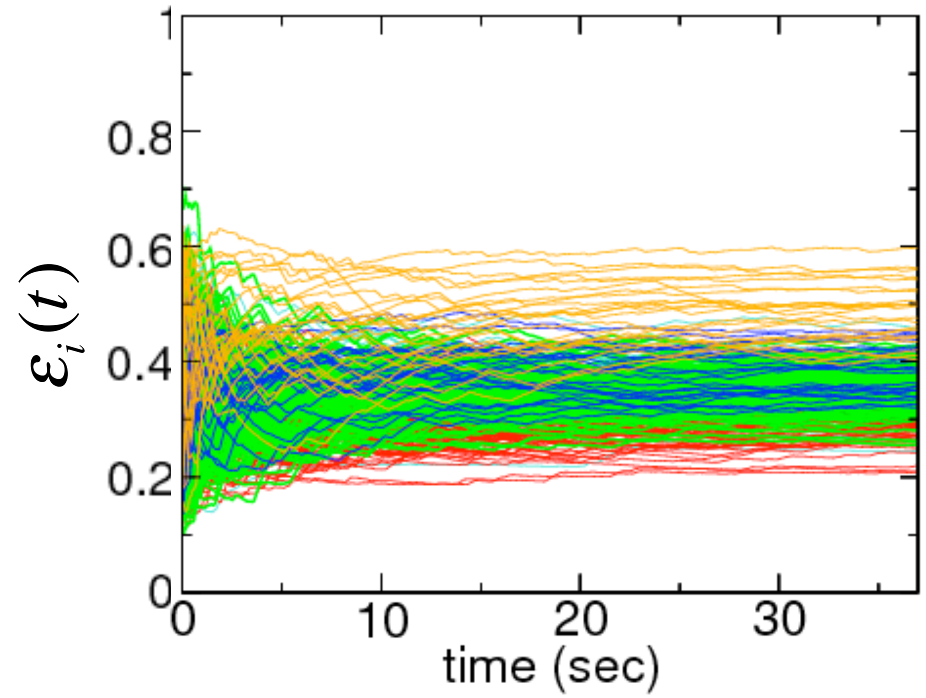


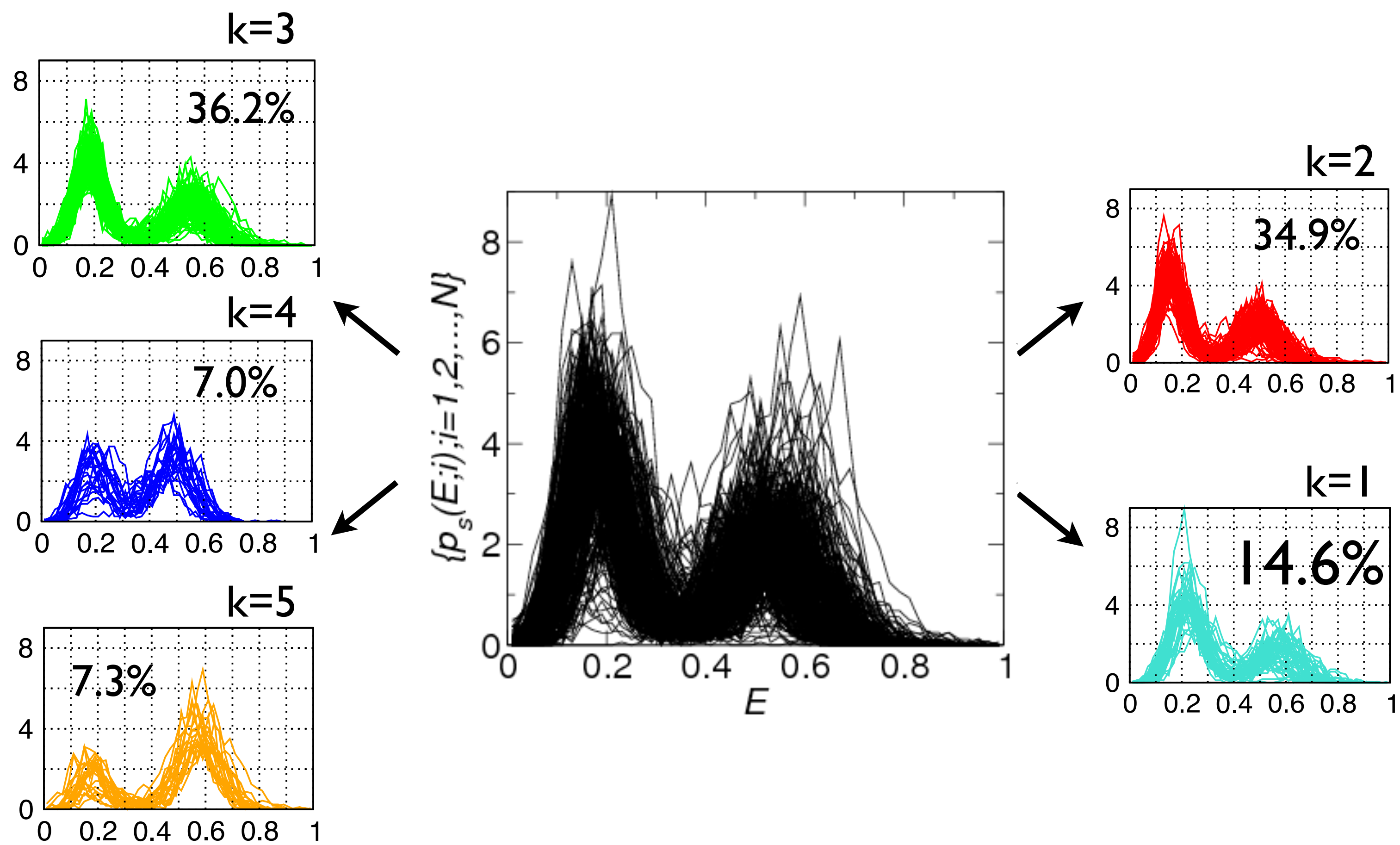
Holliday Junctions

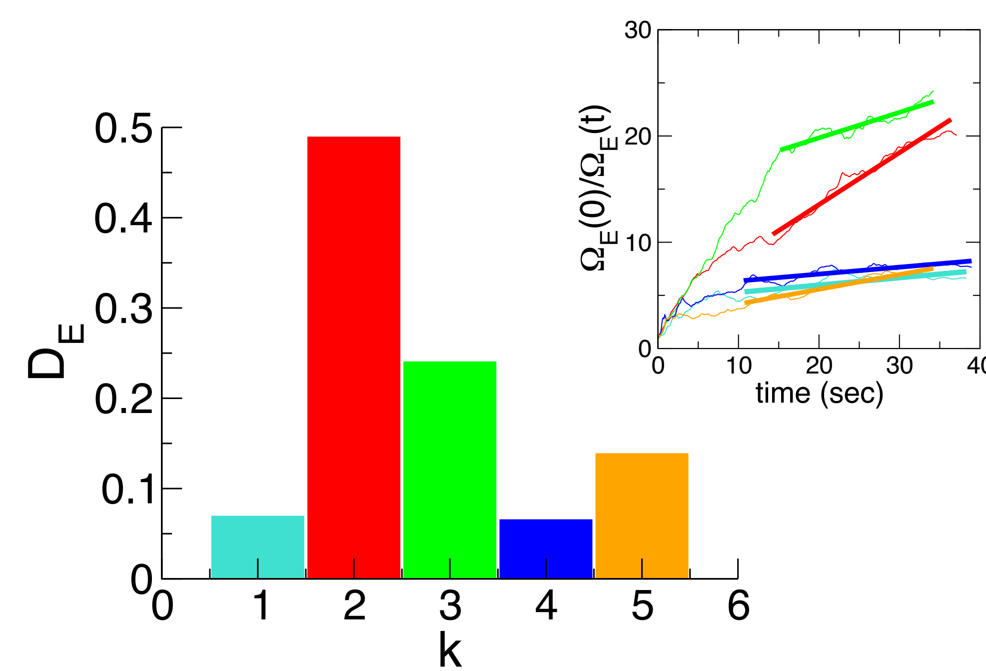
Nat. Chem. (2012) 4, 907-914





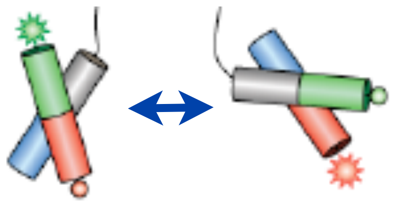


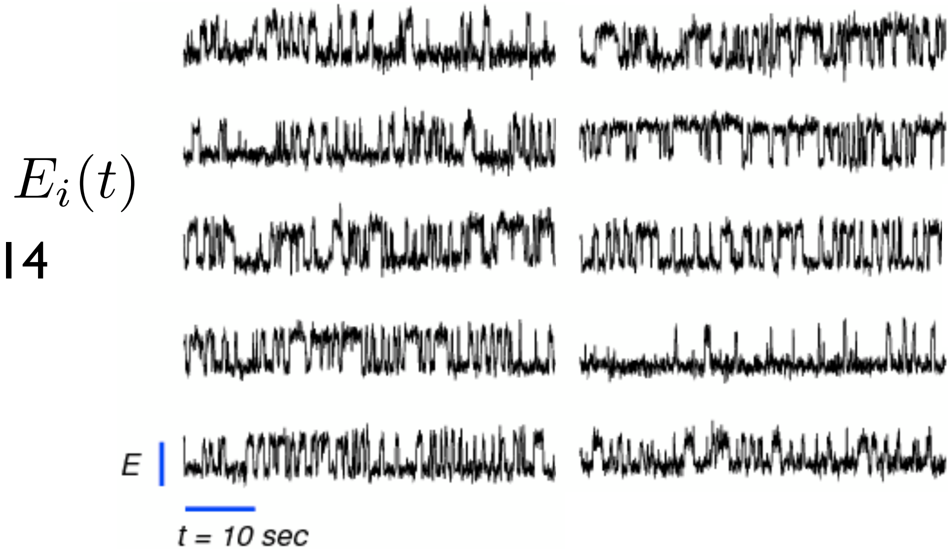


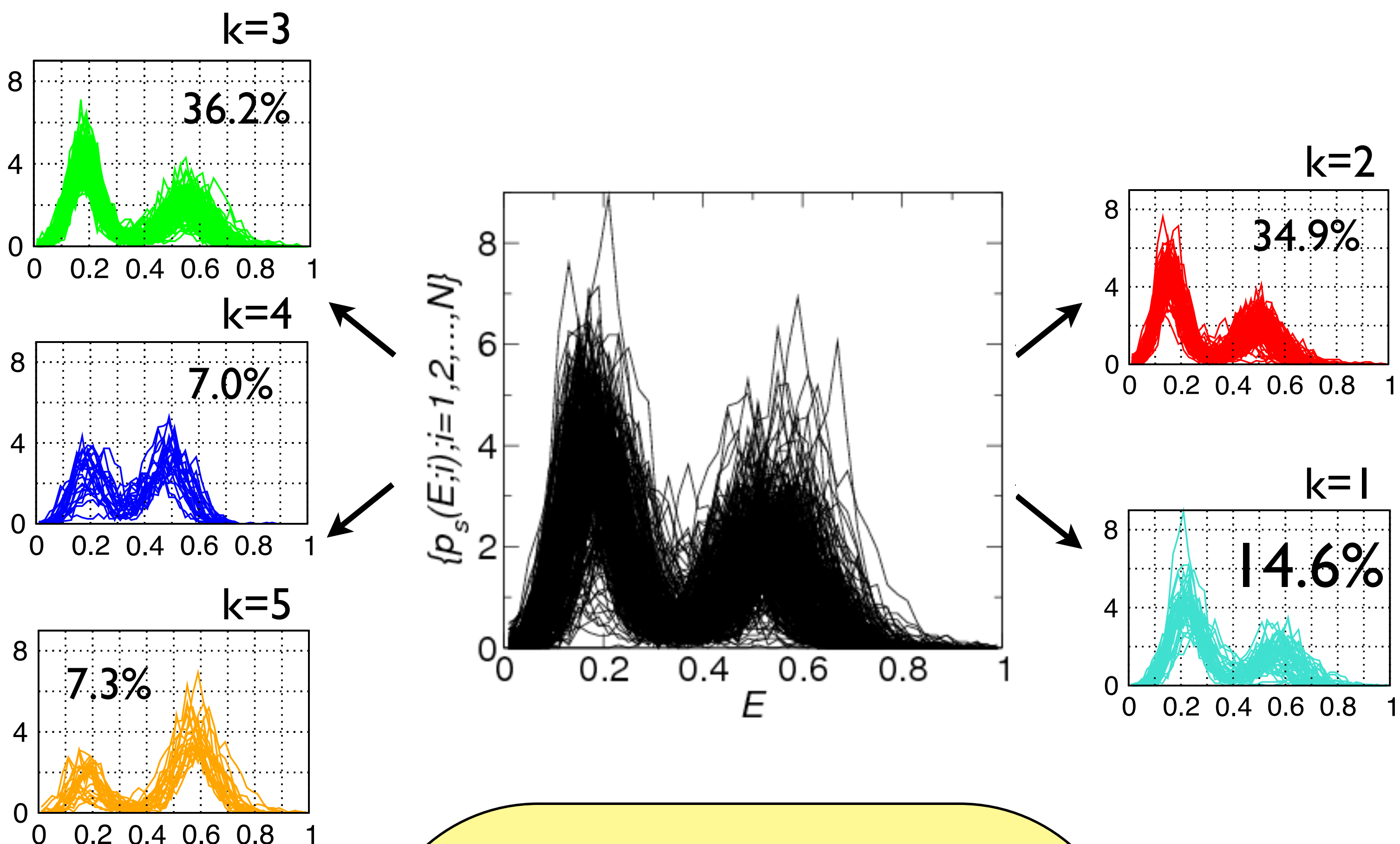


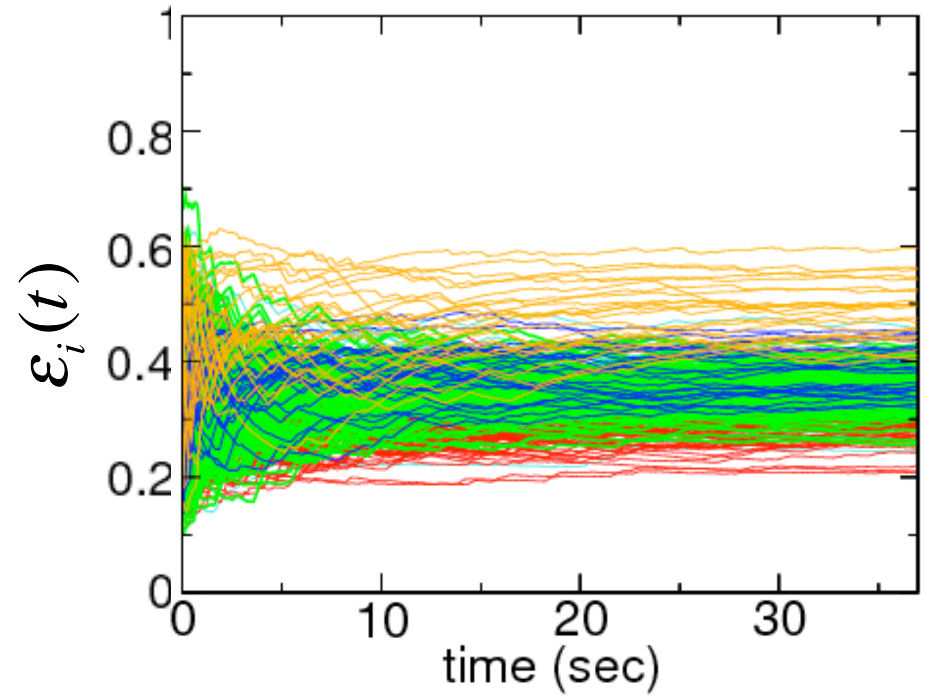
Holliday Junctions

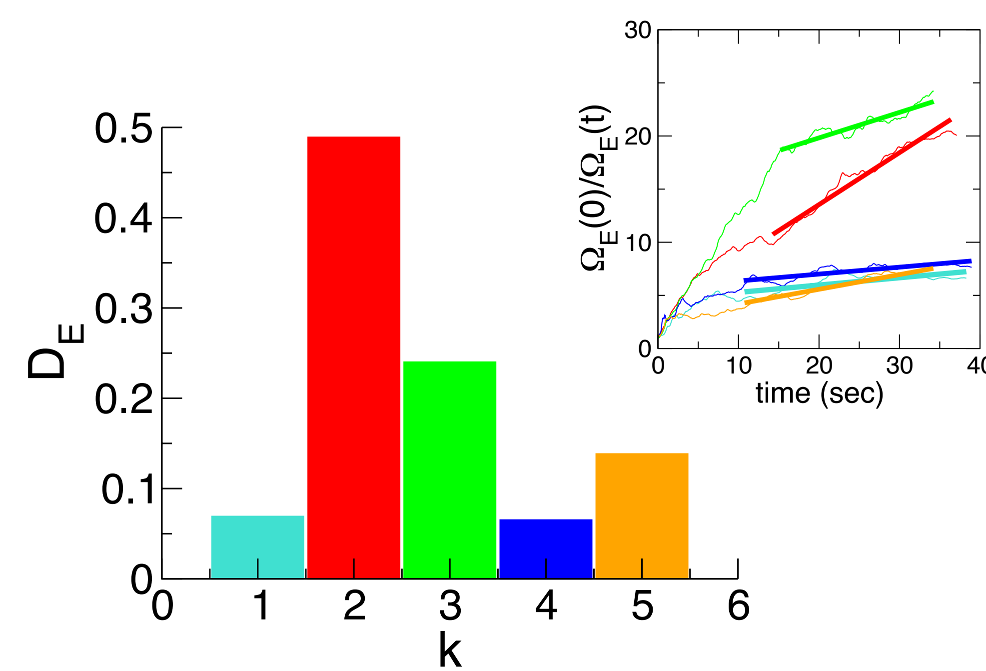
Nat. Chem. (2012) 4, 907-914

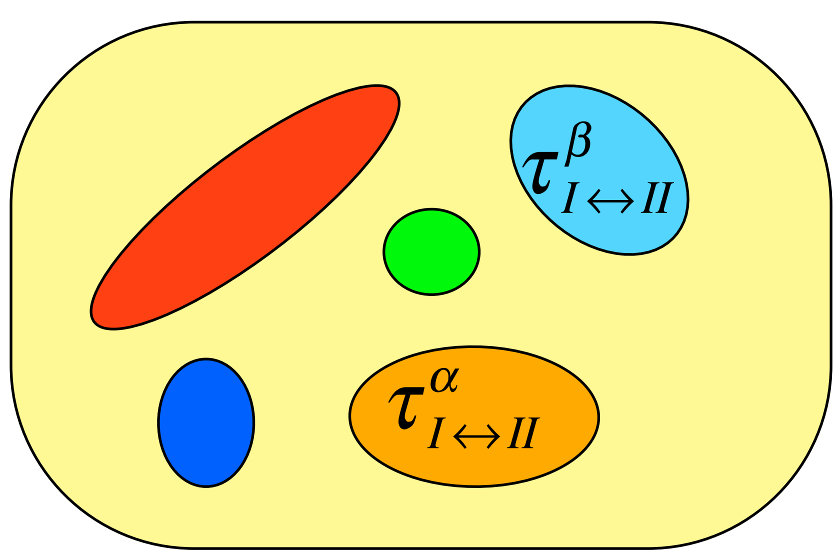




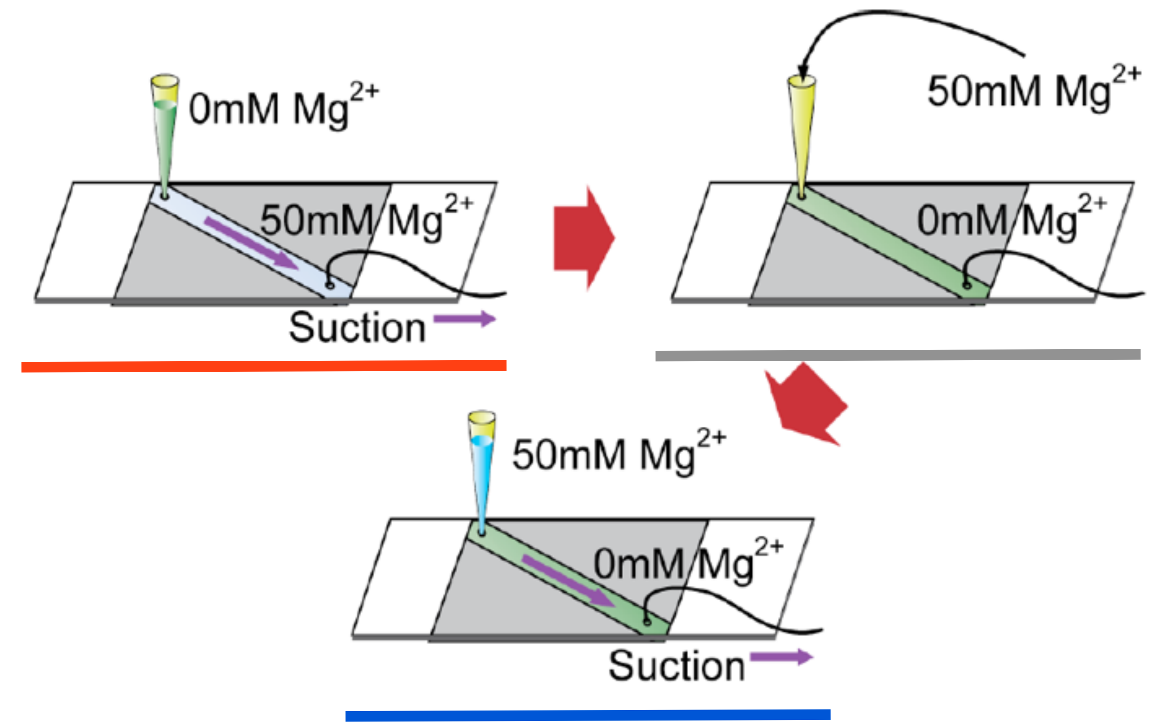


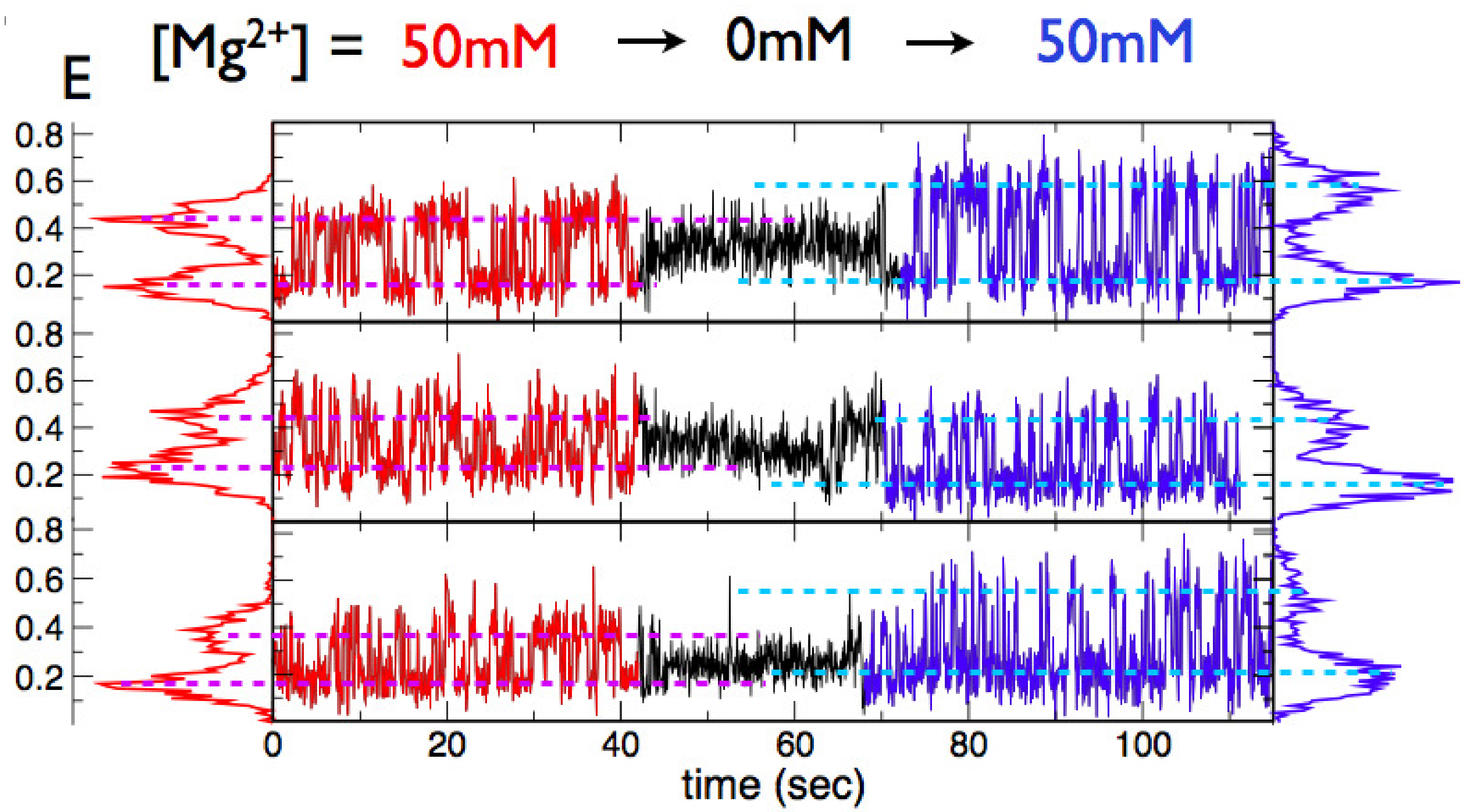






An annealing experiment using $\boxed{Mg^{2+}\text{-pulse}}$ facilitates interconversion between different patterns within the time trace of a single HJ

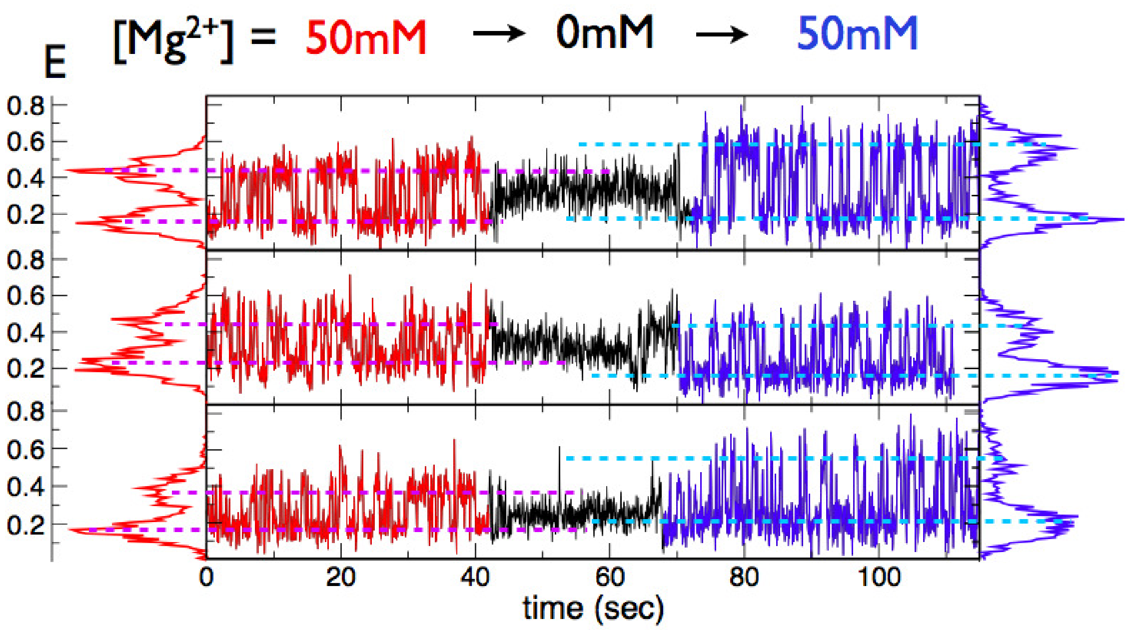


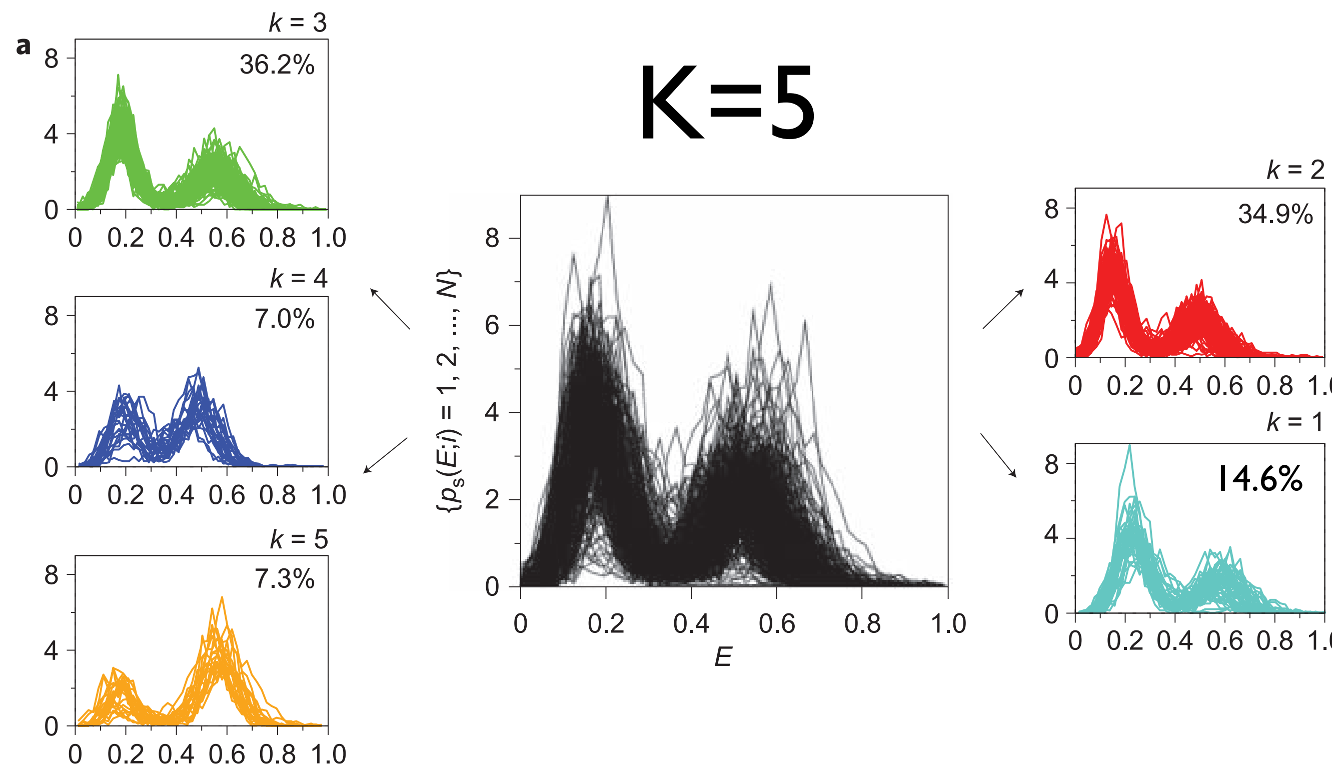


This excludes possible scenarios such as

1. Effect of surface immobilization
2. slow relaxation dynamics of dye conformation due to different environment.
3. covalent modifications

Nature Chem. (2012) 4:907-914

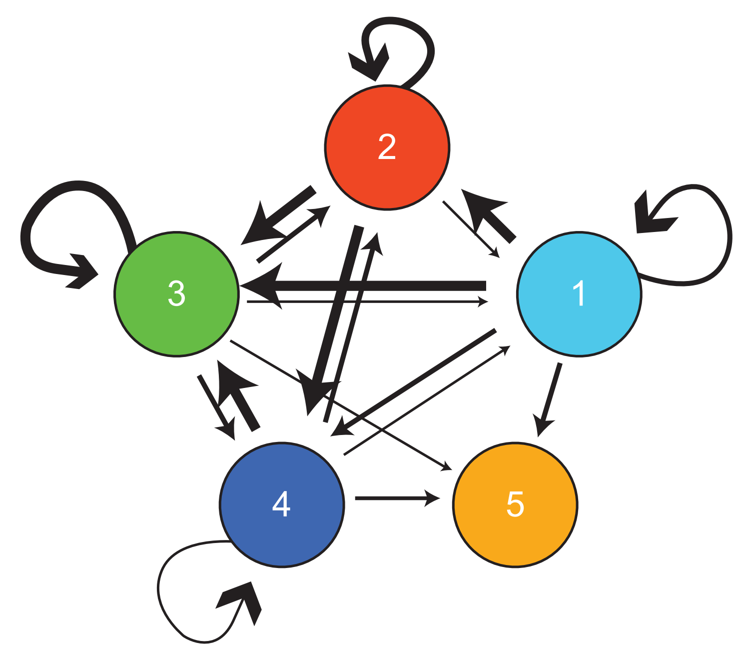




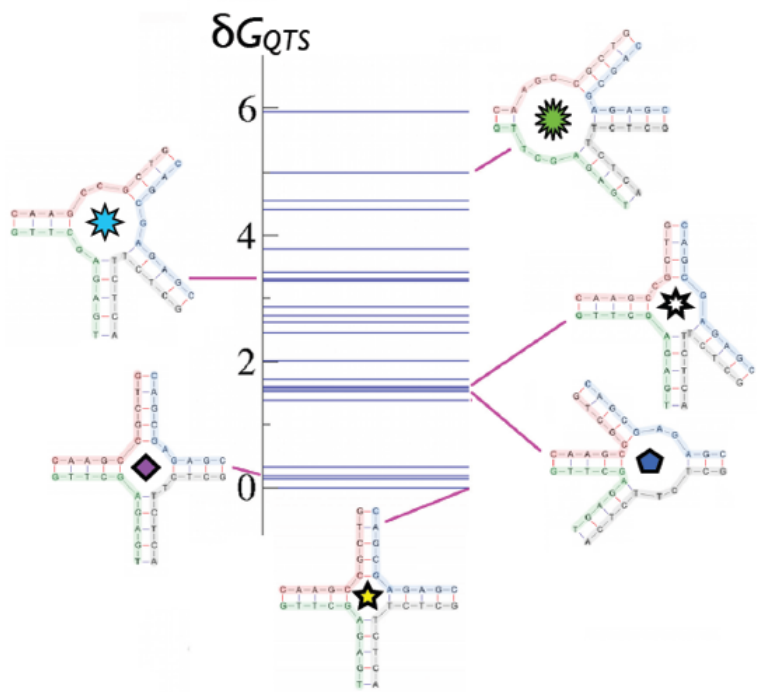
Mg^{2+} pulse resets the "memory" of dynamics ...

Mg^{2+} ions are the culprit of heterogeneity.

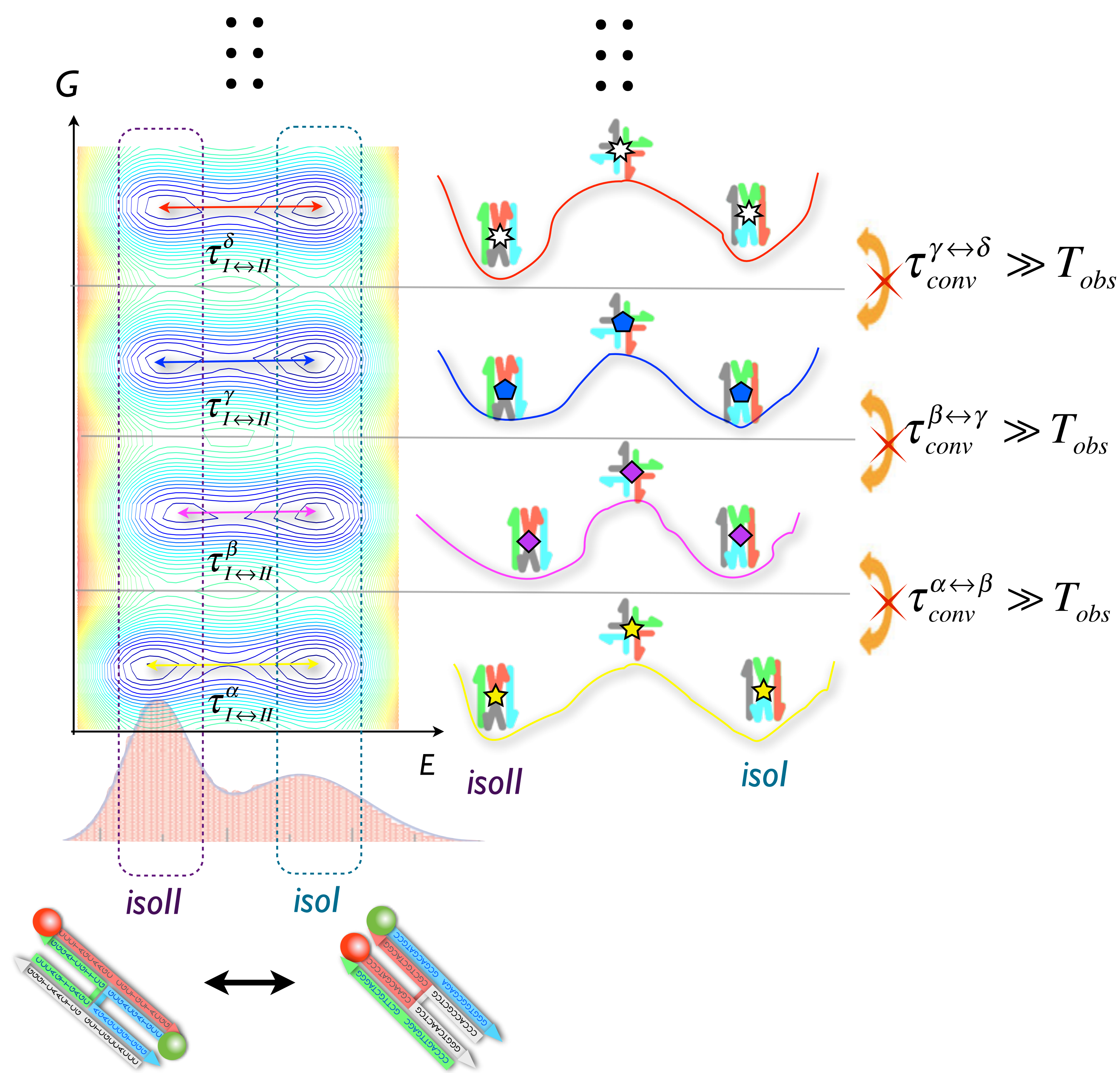
	1	2	3	4	5	
1	14	6	10	2	2	(34)
2	1	29	14	6	0	(50)
3	1	6	24	4	1	(36)
4	1	5	11	8	3	(28)
5	0	0	0	0	0	(0)
	(17)	(46)	(59)	(20)	(6)	

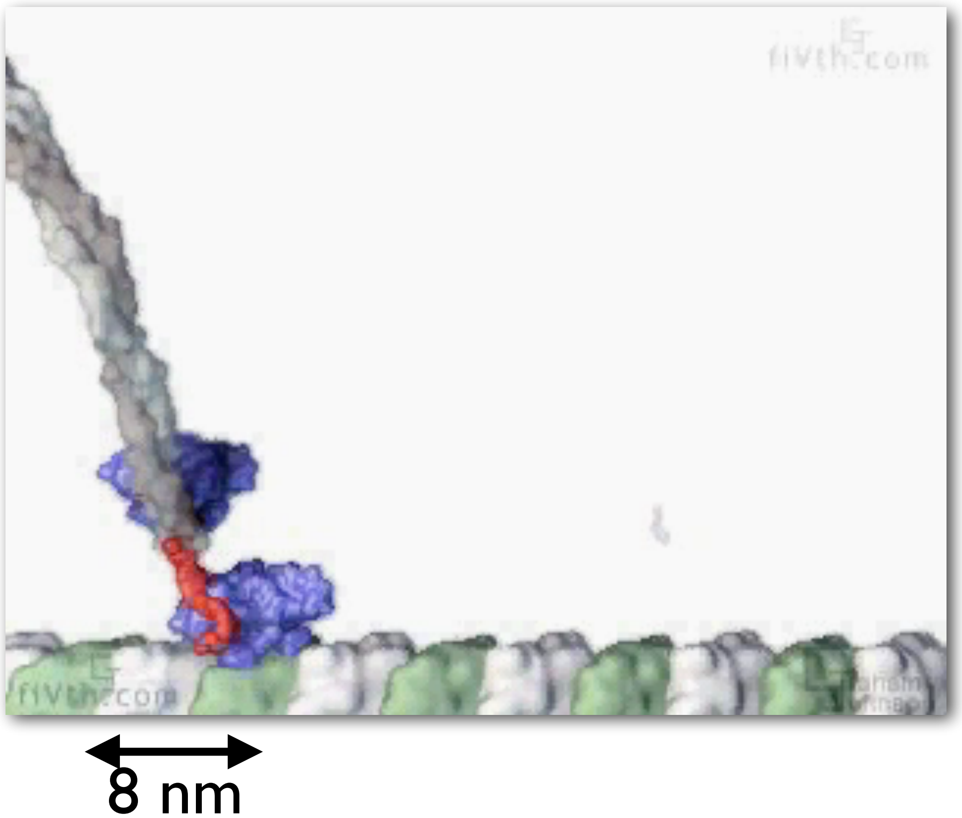


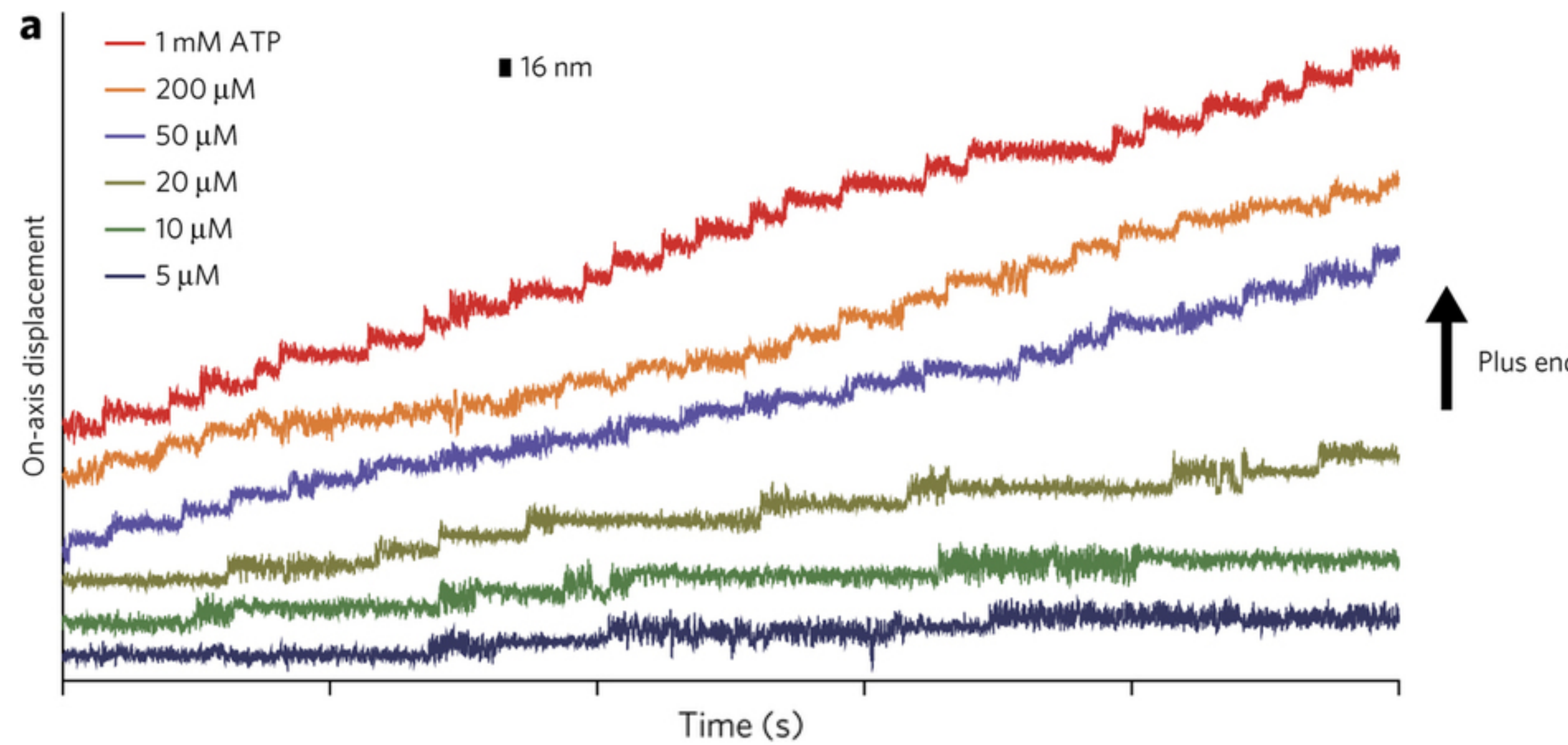
Mg^{2+} ions create kinetically disjoint conformational sub-ensemble of HJ by specifically binding to the internal multiloop and freezing it



$$\tau^{\xi}_{I\leftrightarrow II} \ll T_{obs} \ll \tau^{\xi\leftrightarrow\eta}_{conv}$$







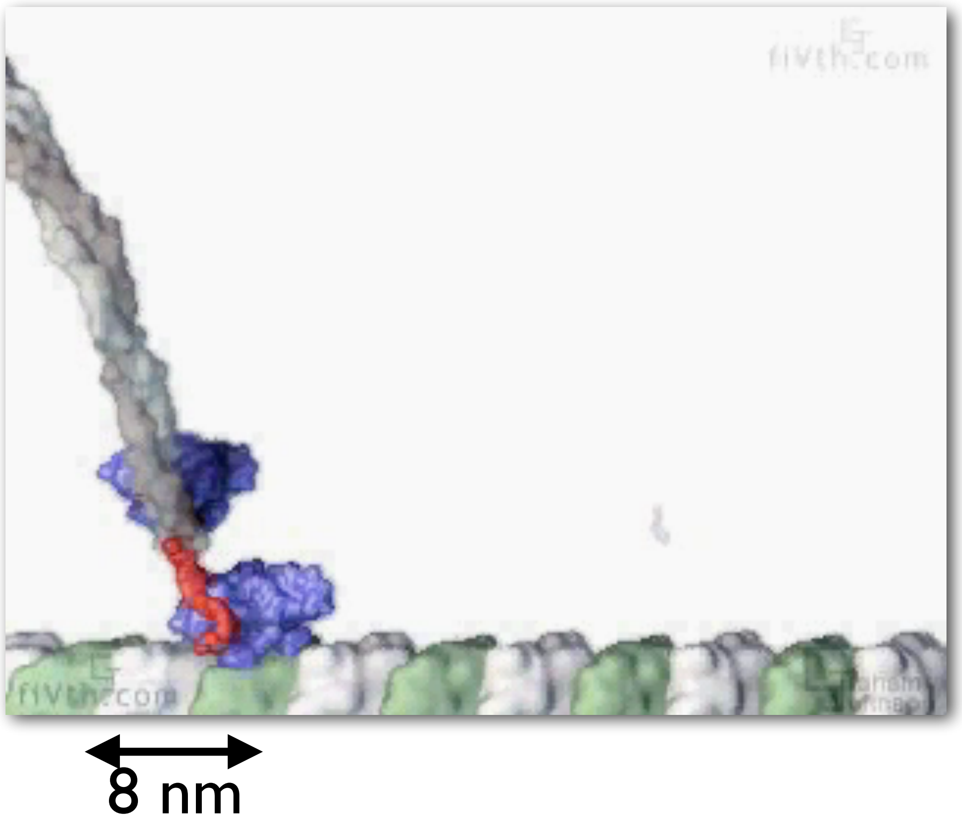
Tomishige and colleague
Nat. Chem. Biol. **12**, 290–297 (2016)

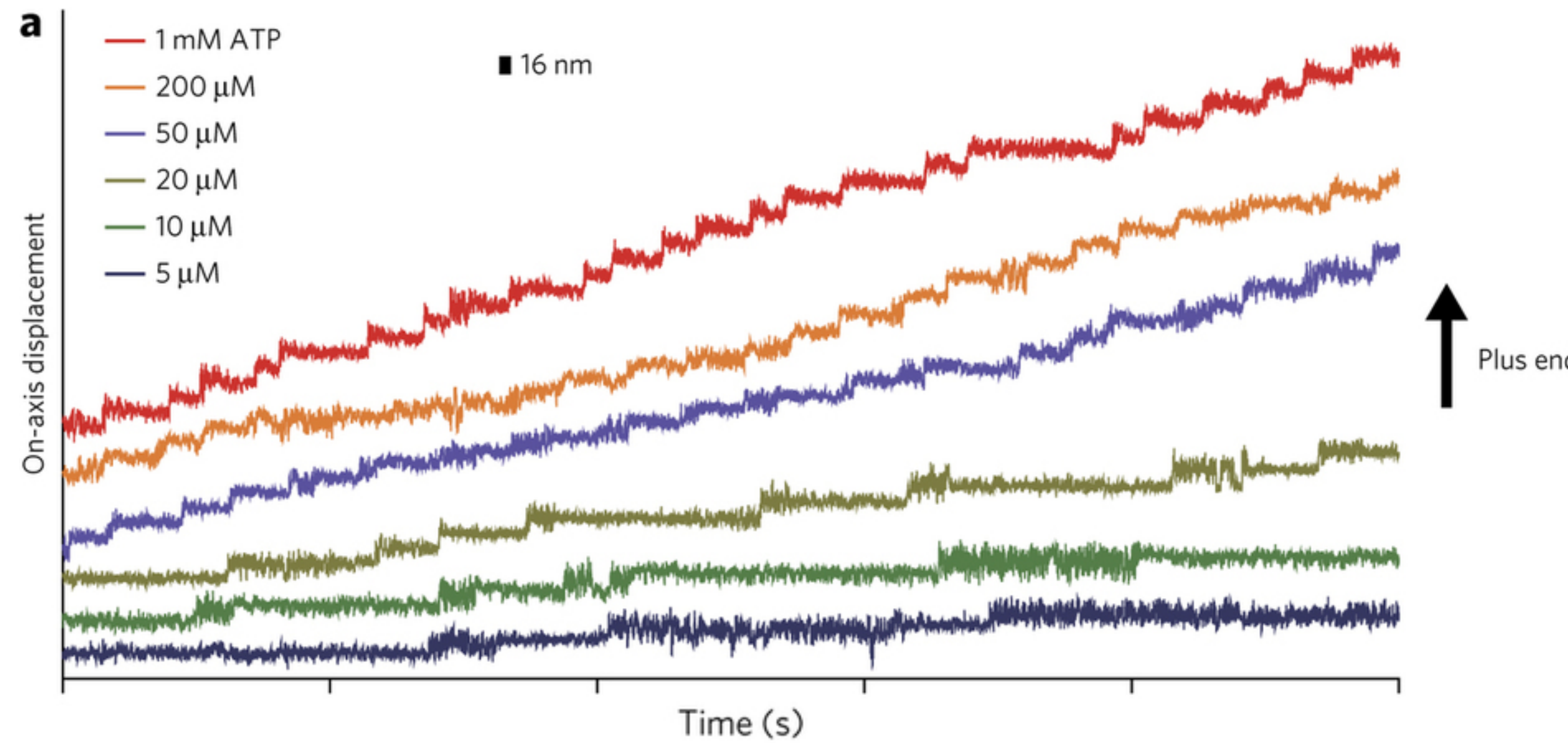
Kinesin-1

at saturating ATP conc. (c > 1 mM), in vitro

- mean velocity, V ~ 800 nm/s
- mean travel distance, L ~ 1 μm (finite processivity)
- Step size: d ~ 8 nm
- Ave. stepping time: τ ~ 10 ms.

Block, Cross, Yanagida, Ishiwata, Vale …. etc.





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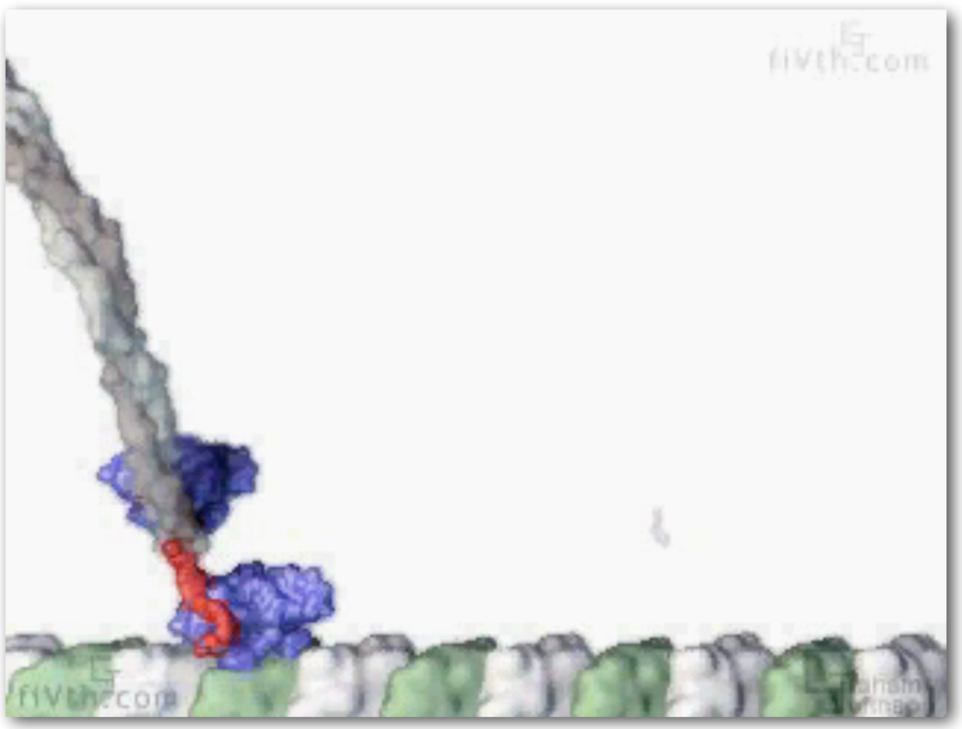
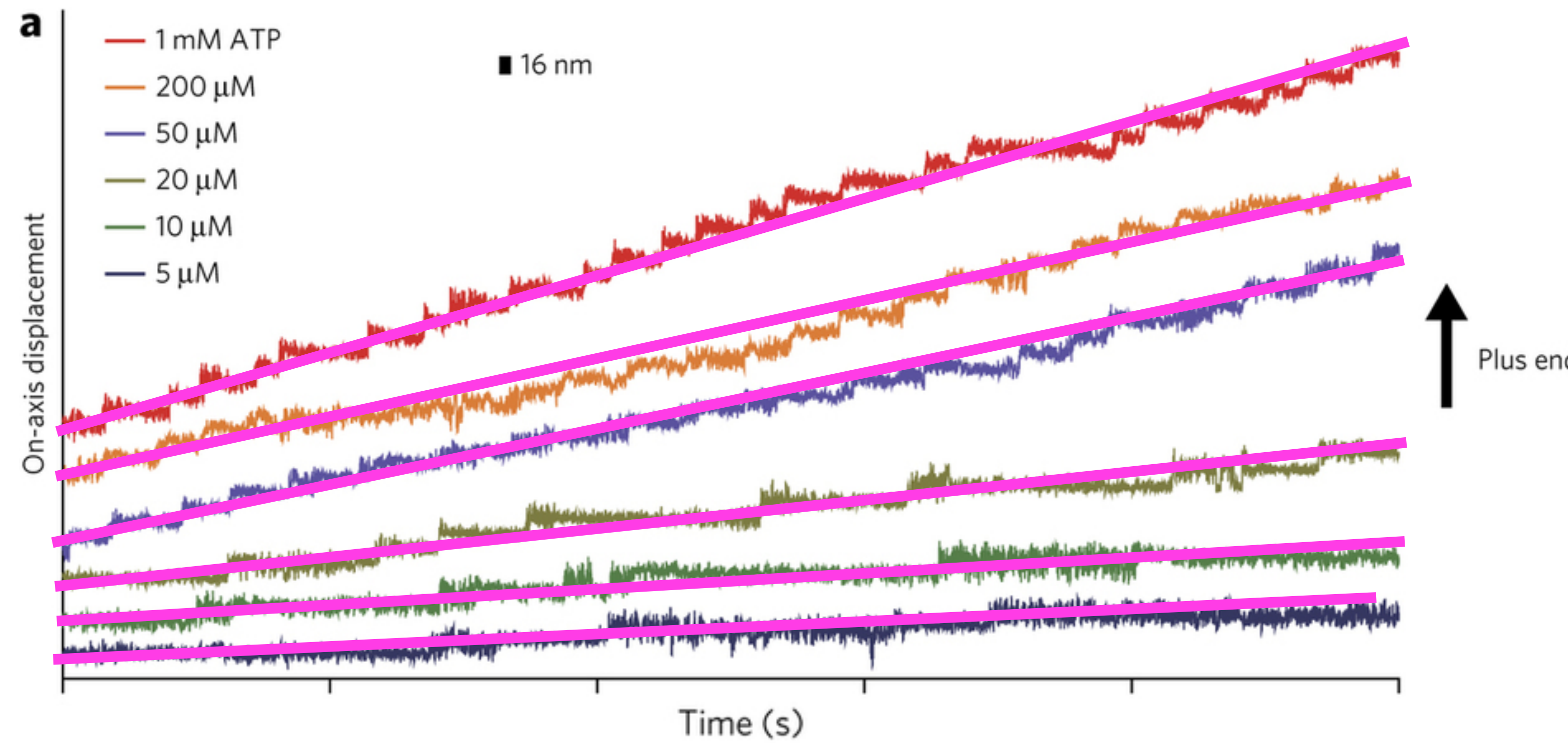


8 nm



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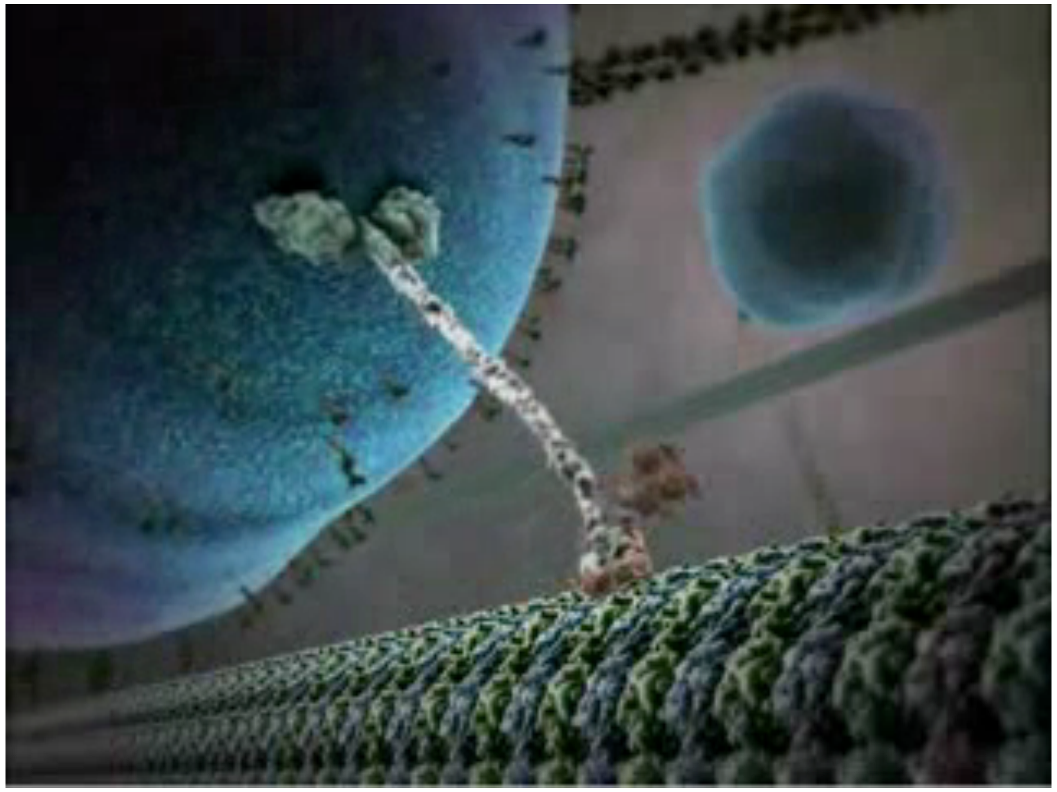
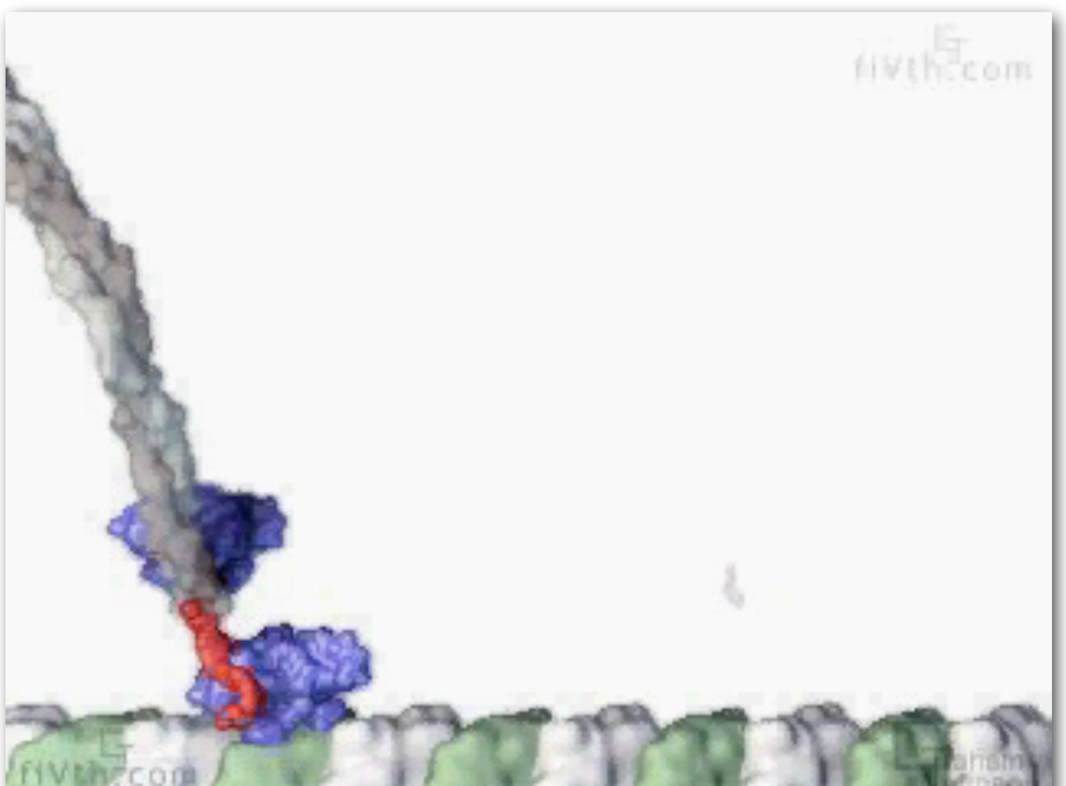
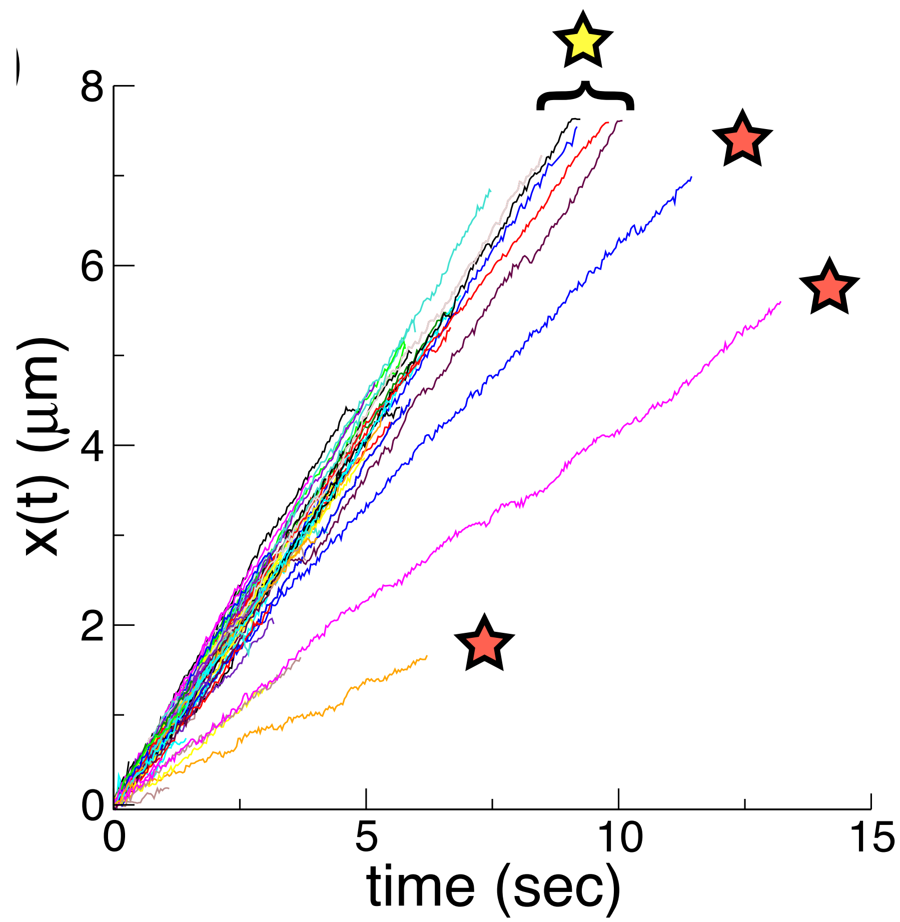
Quenched disorder in time traces of molecular motors (driven system)





KINESIN



Traffic (2017)

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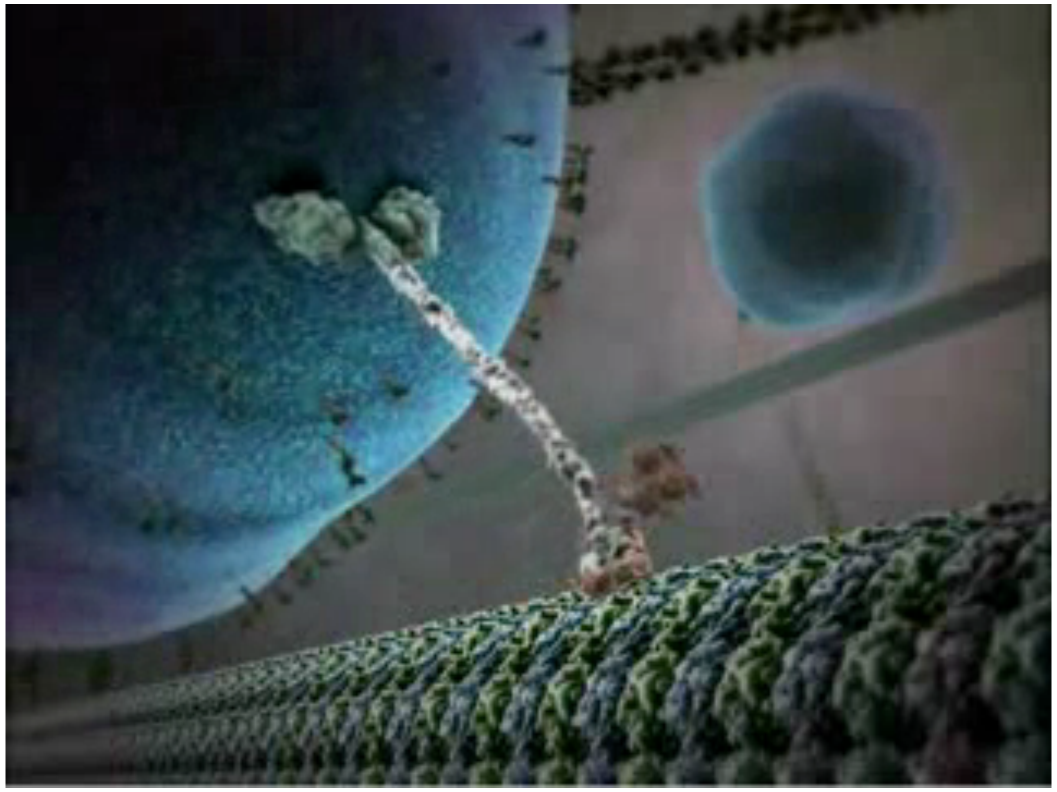
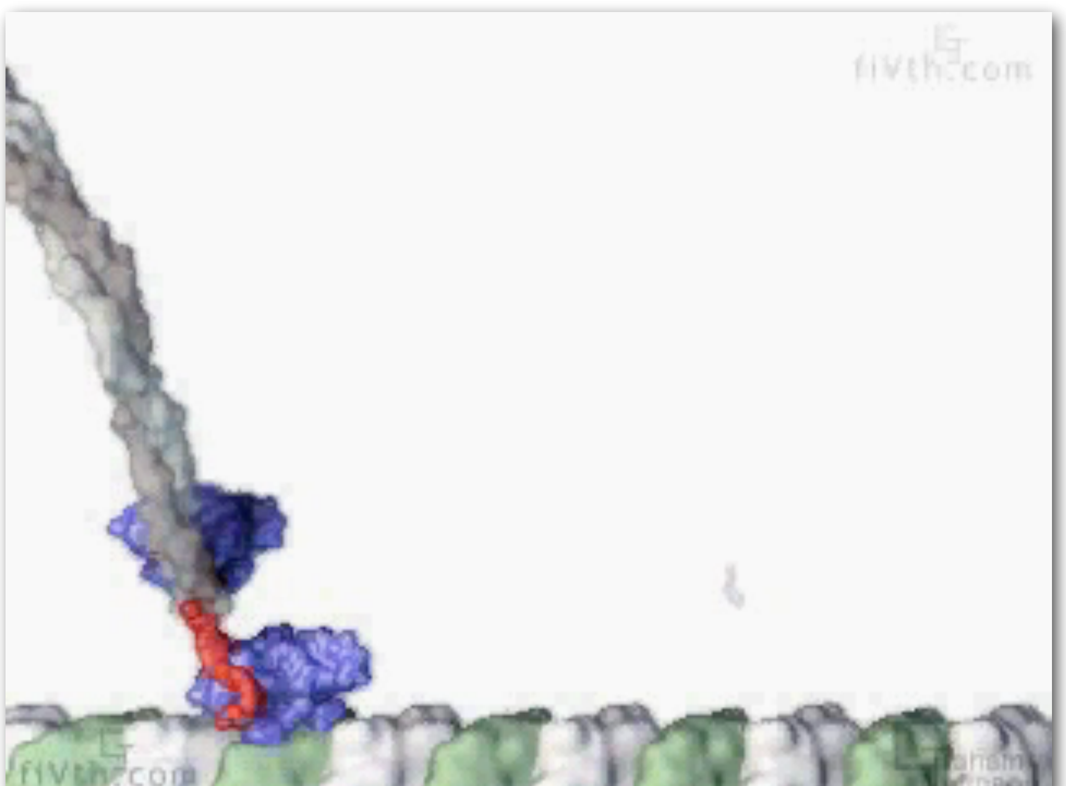
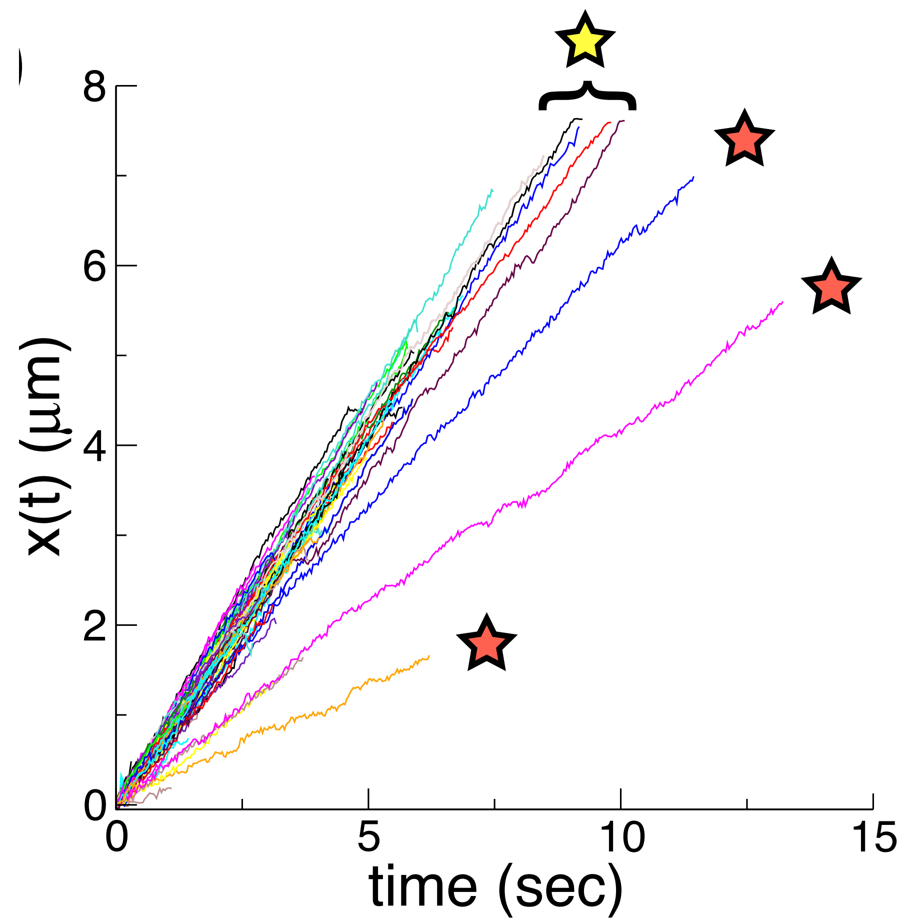


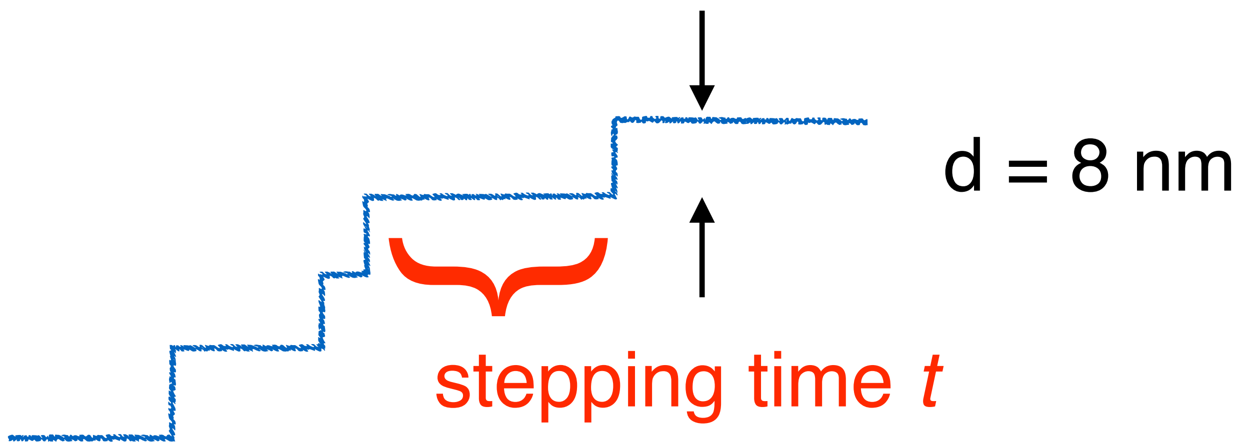


KINESIN



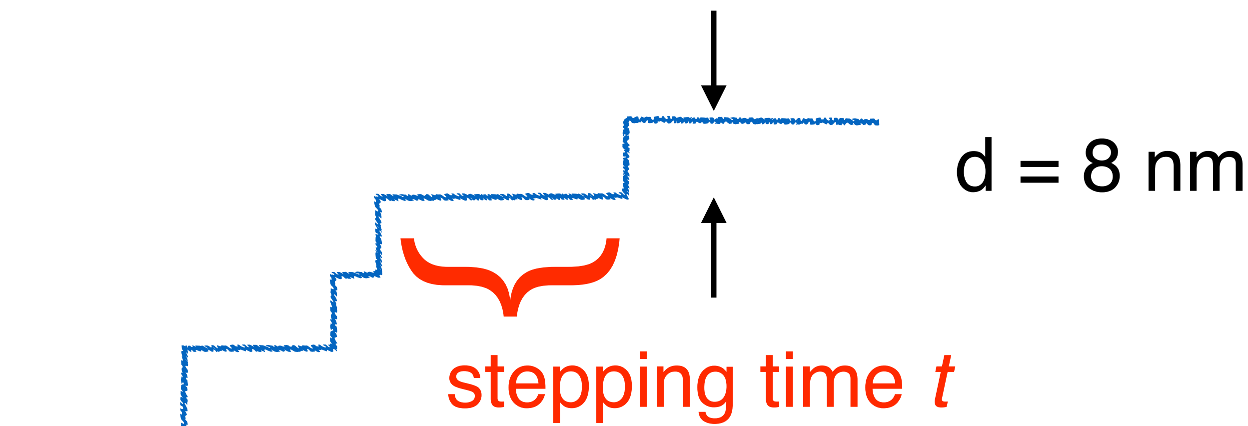
Traffic (2017)

Kaseda et al. *Nat. Cell Biol.* (2003) 5, 1079



$\psi(t)$: stepping time distribution

slope = mean velocity, V ~ d/<t>



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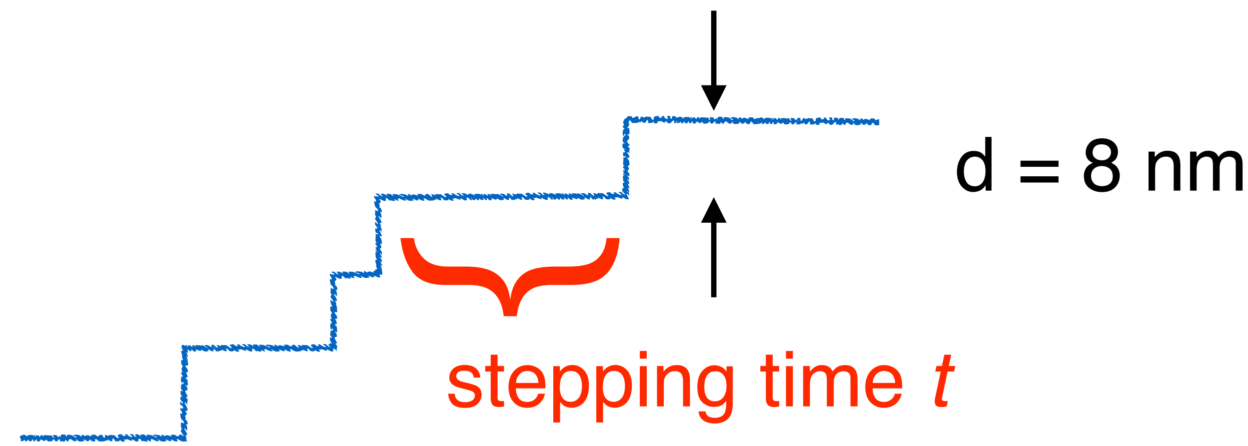
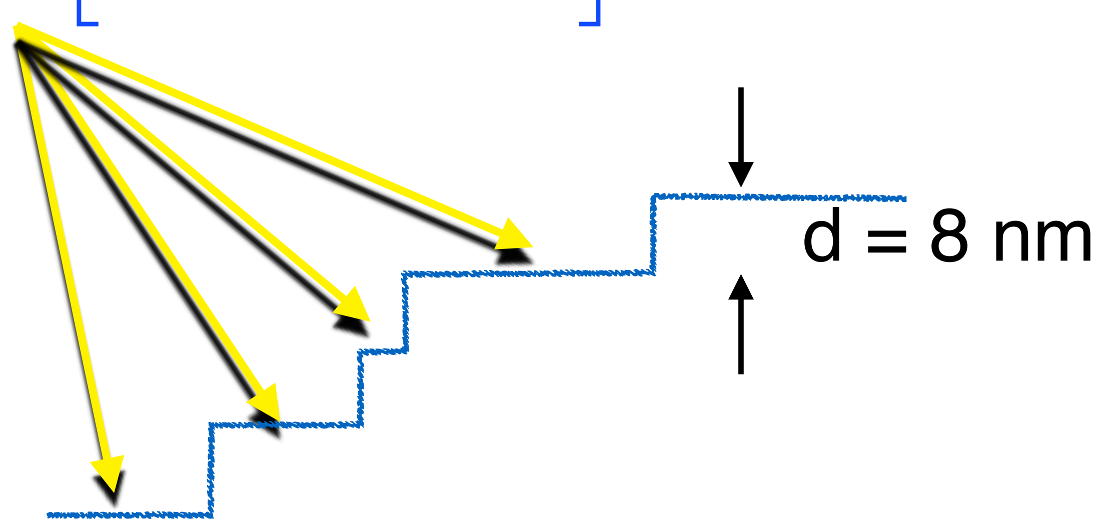
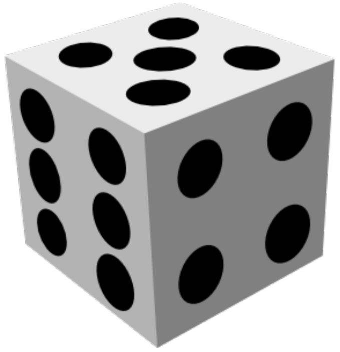


$\psi(t)$: stepping time distribution

$$\psi(t)\left[= \tau^{-1}e^{-t/\tau}\right](\tau = 10 \text{ msec})$$

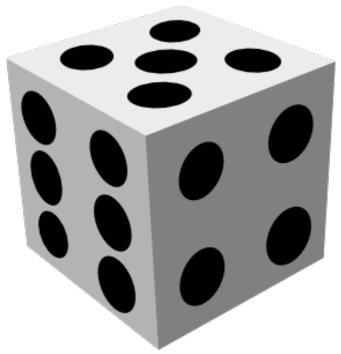


$t = \text{dwell time}$



$$\boldsymbol{\Psi}(1)=\boldsymbol{\Psi}(2)=\ldots=\boldsymbol{\Psi}(6)=1/6$$

$$\langle i \rangle = 1\times(1/6) + 2\times(1/6) + \ldots + 6\times(1/6) = 3.5$$



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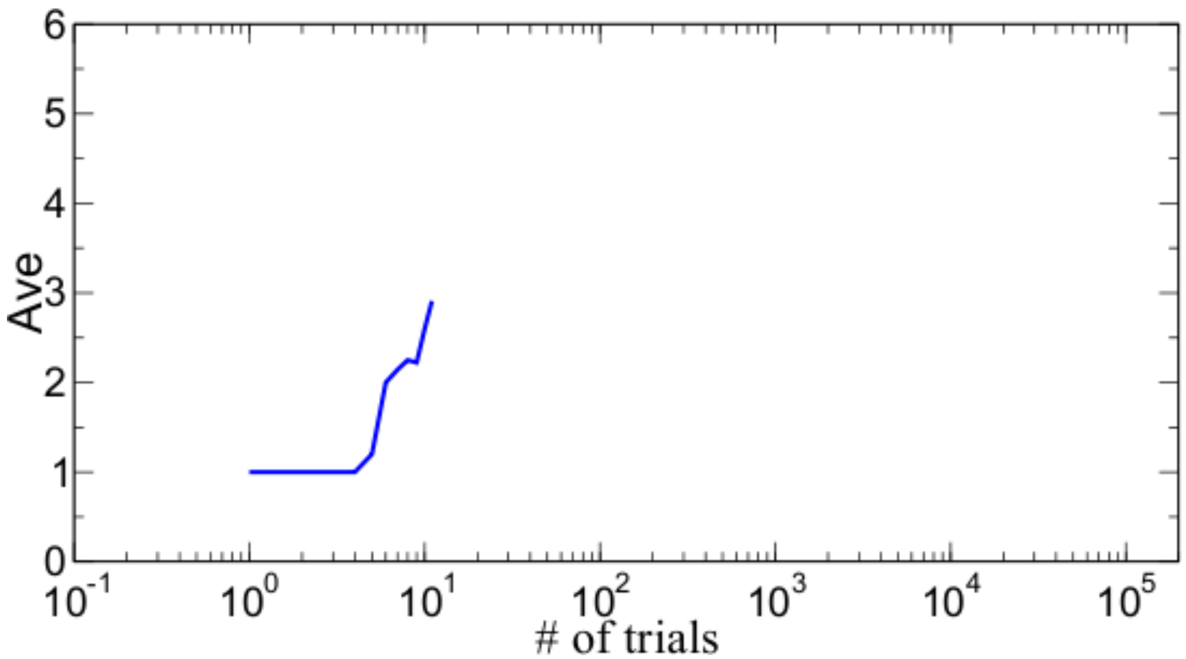
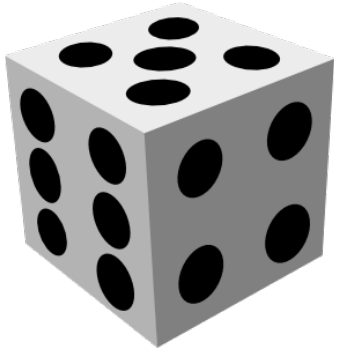


3.5



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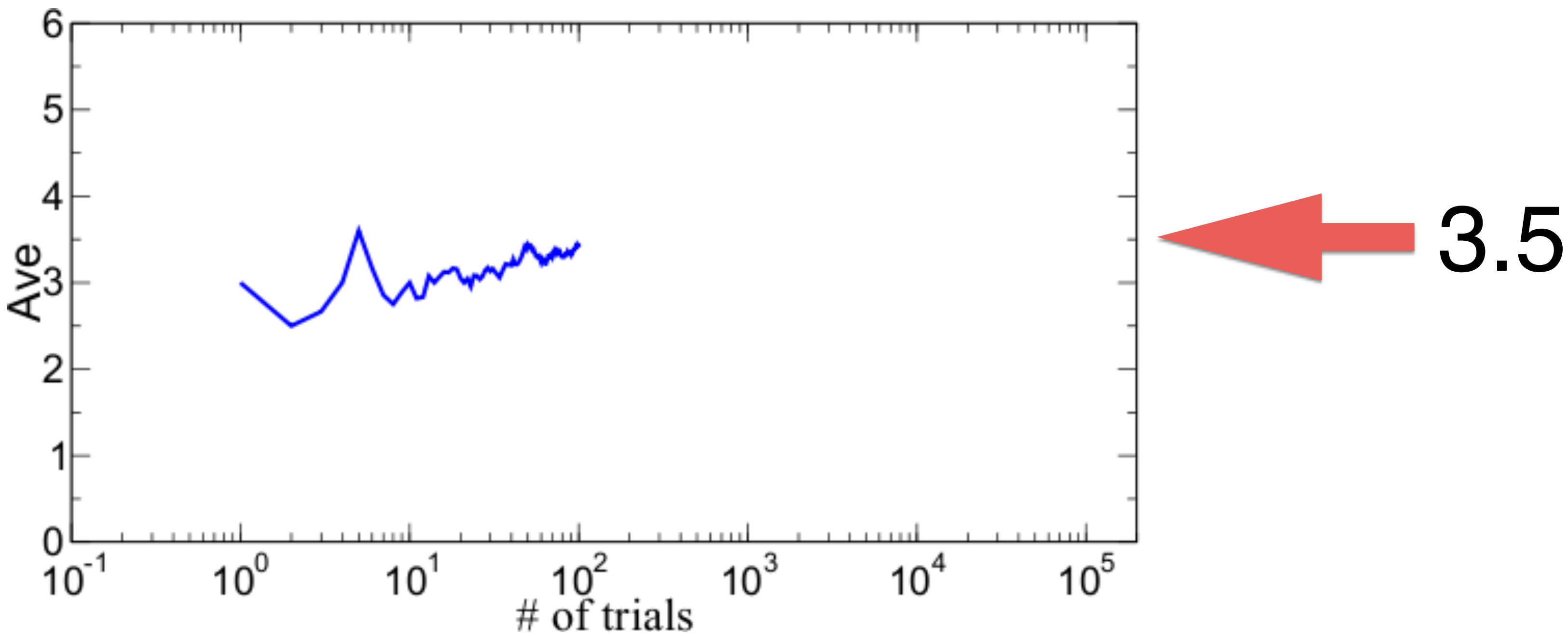

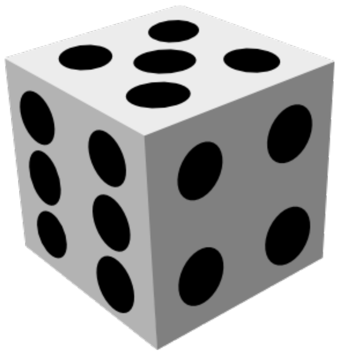

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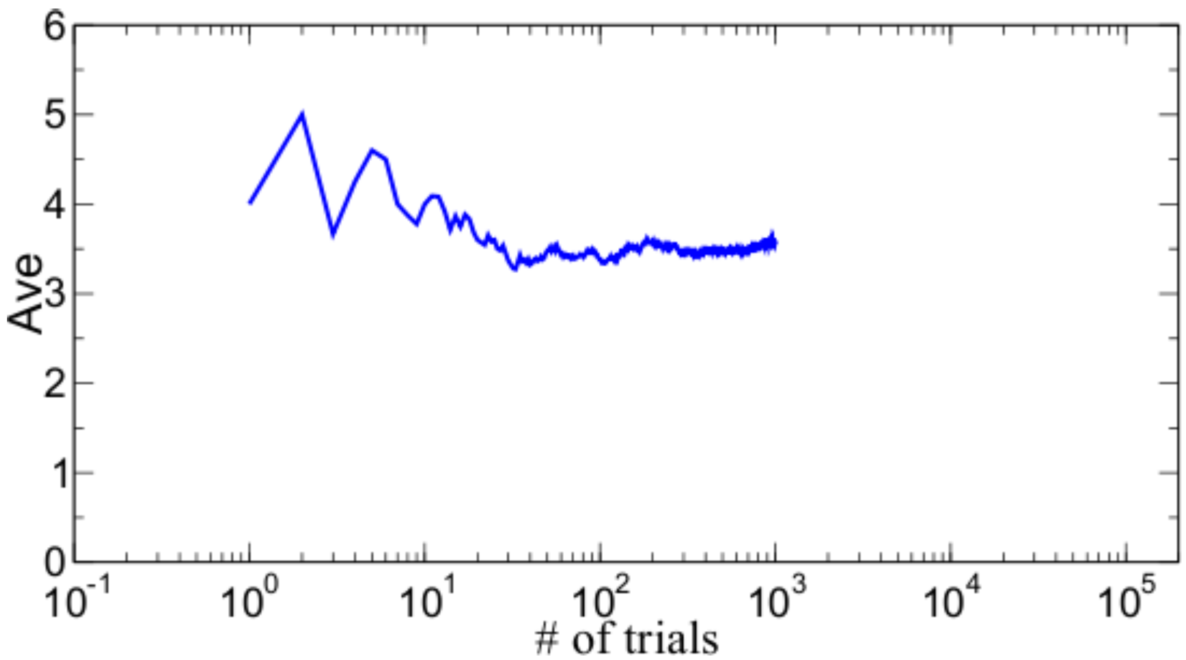

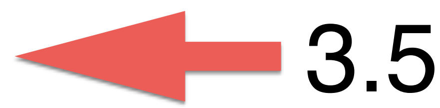

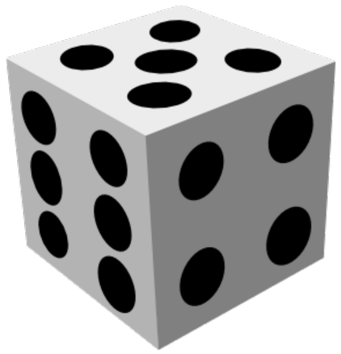

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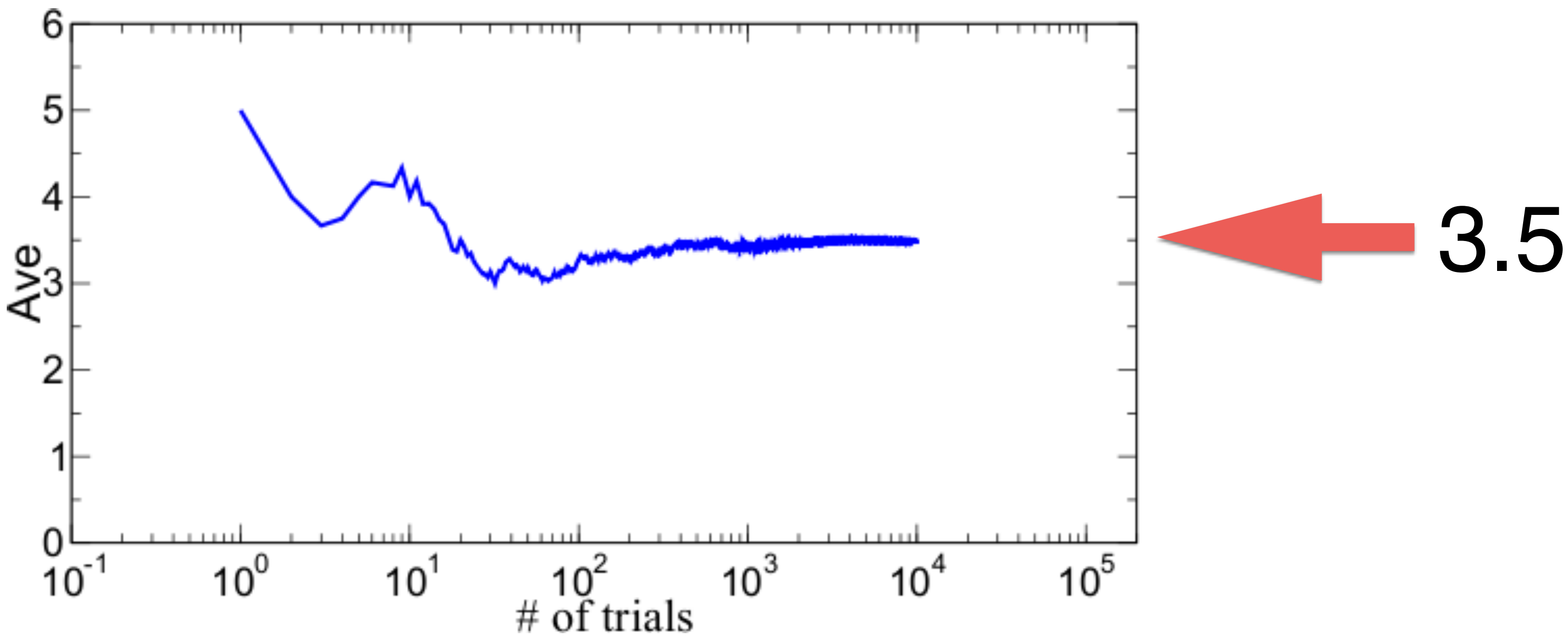

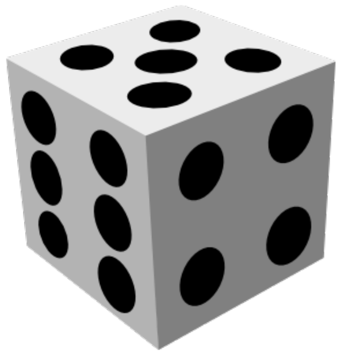

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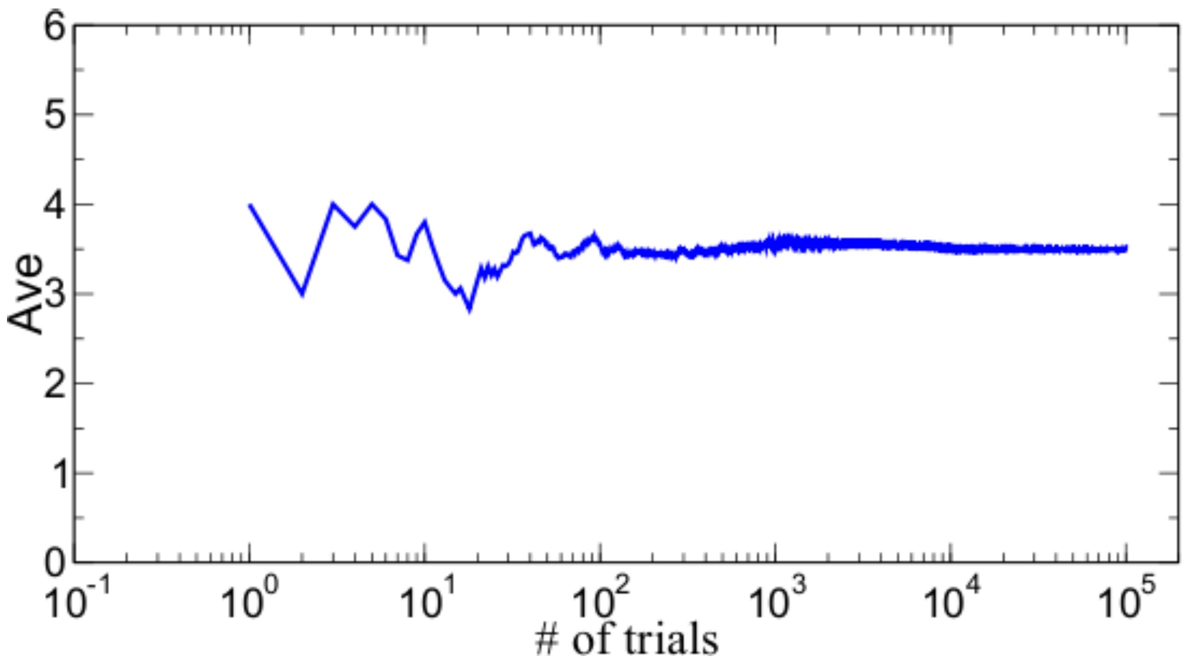

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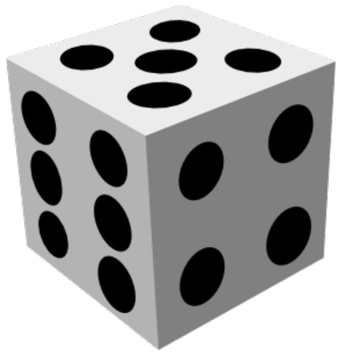

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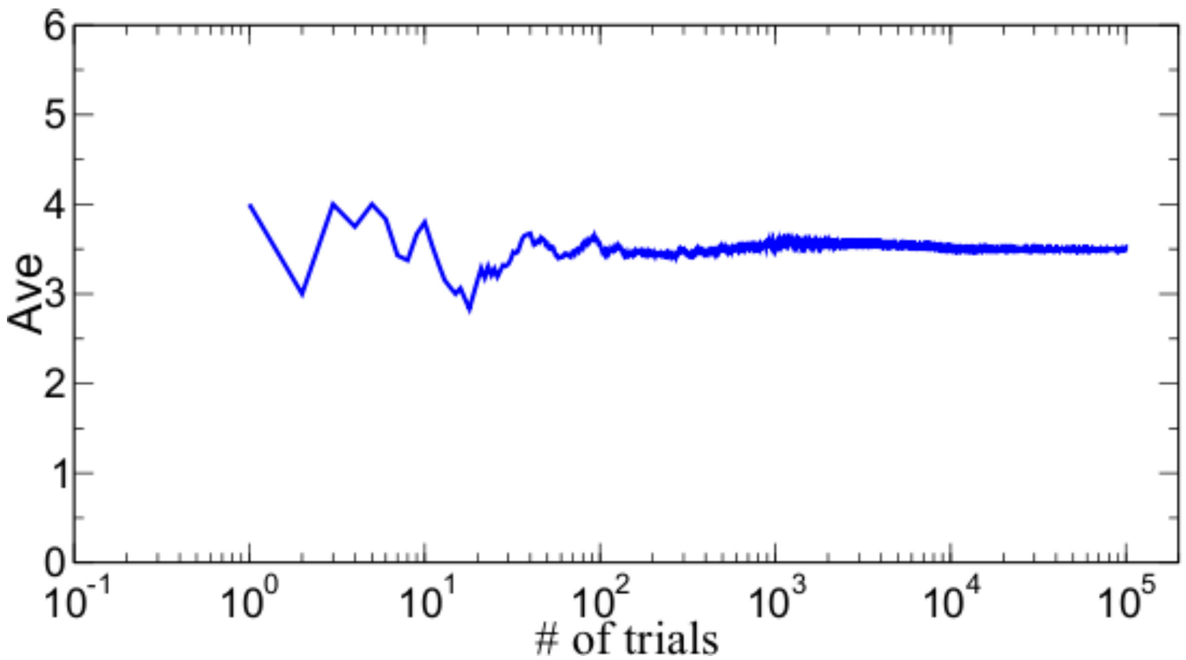
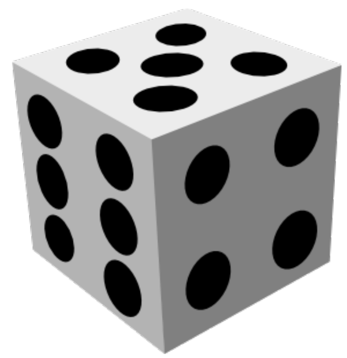


3.5

The law of large numbers !!!



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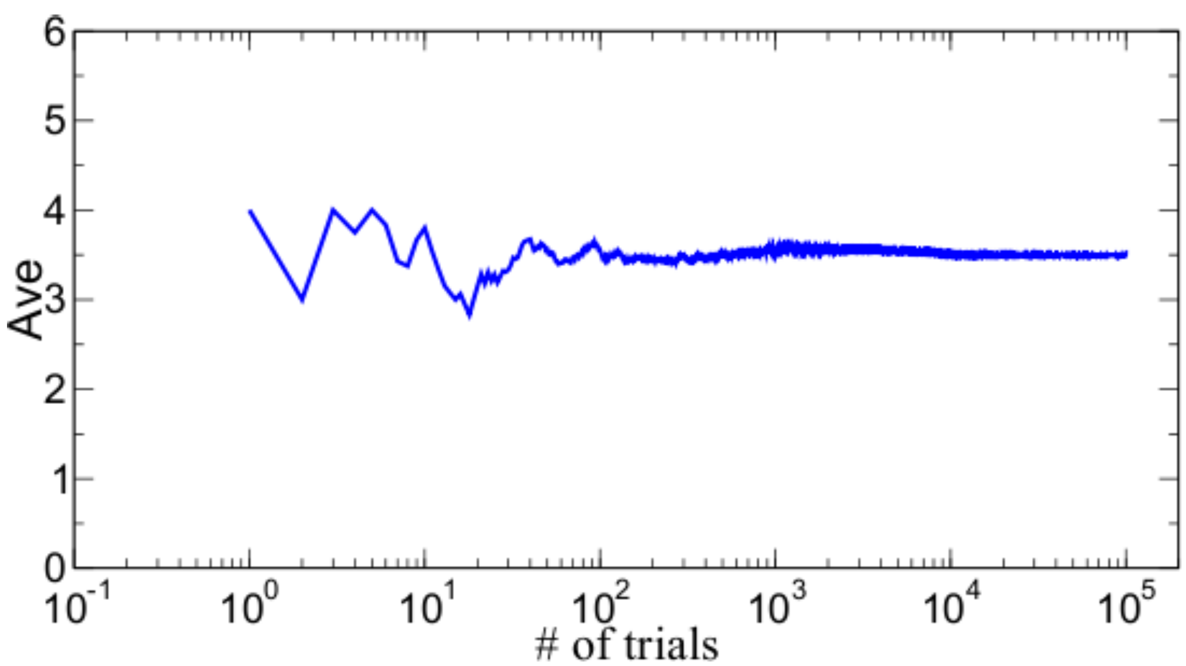

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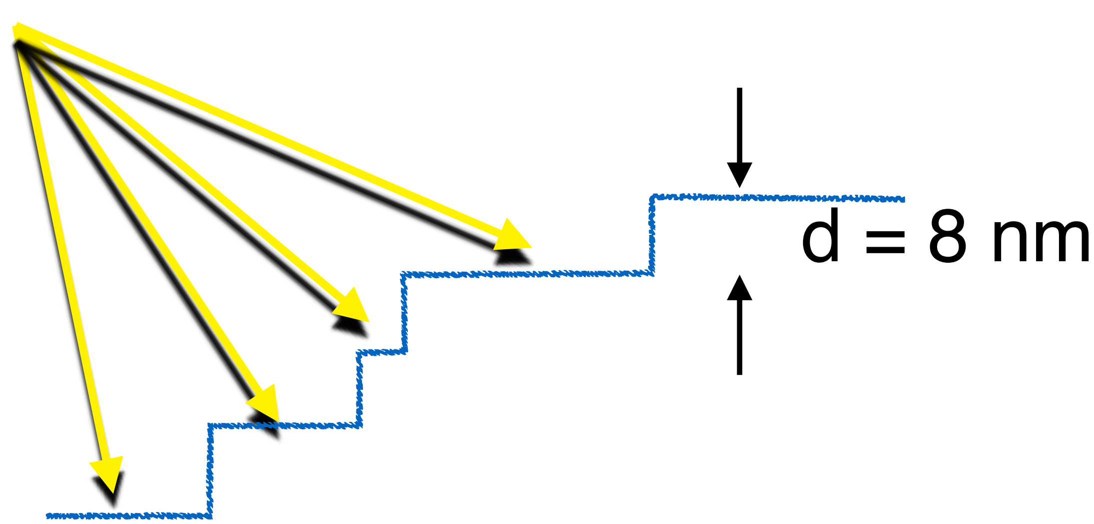
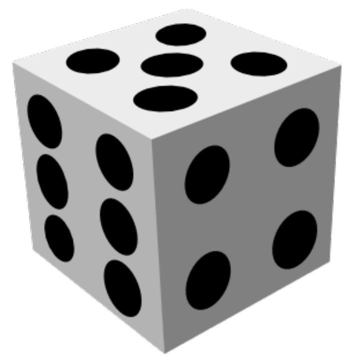
The law of large numbers !!!

$\psi(t)$



$t = \text{dwell time}$

$$\langle t \rangle = \frac{1}{N}\sum_{i=1}^{N} t_i := \int_0^\infty t\psi(t)dt$$



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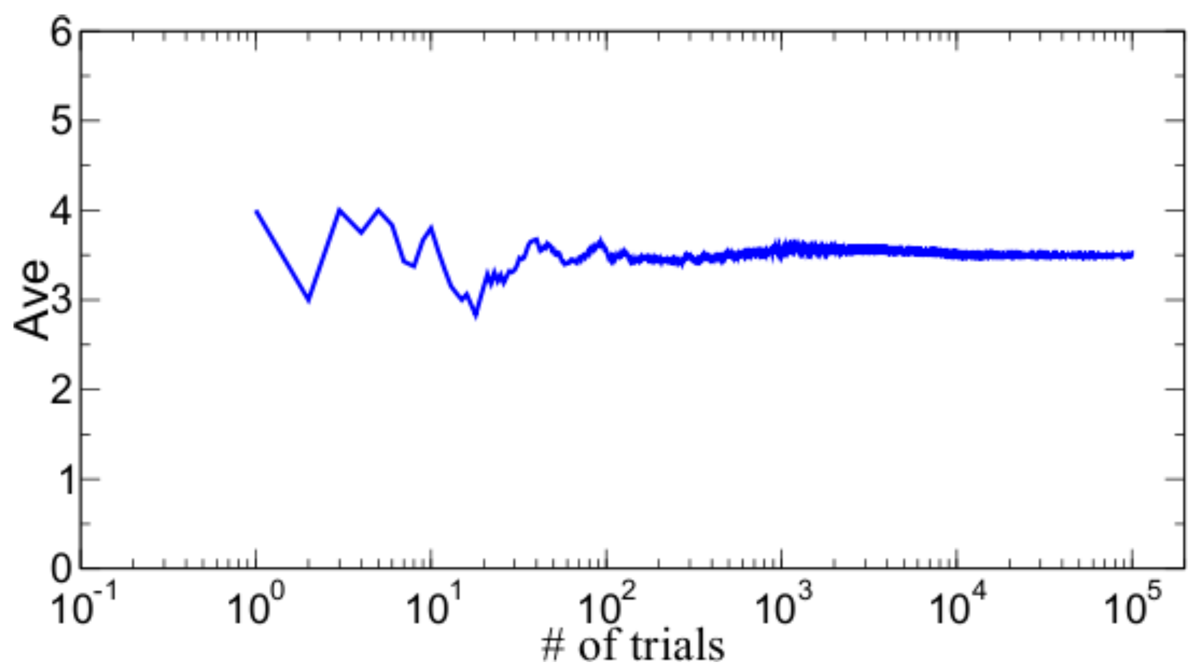

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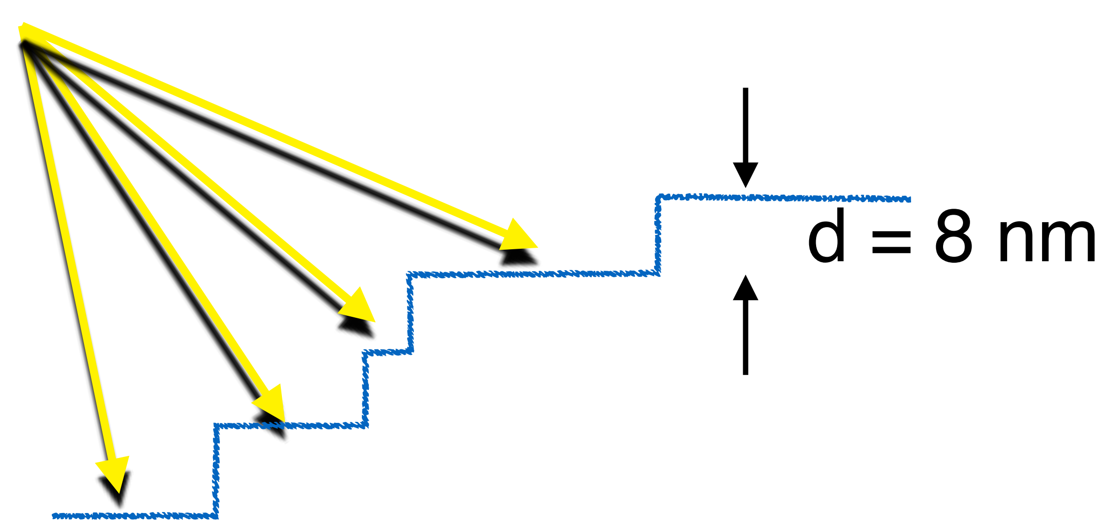

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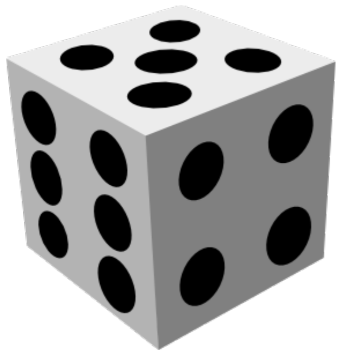

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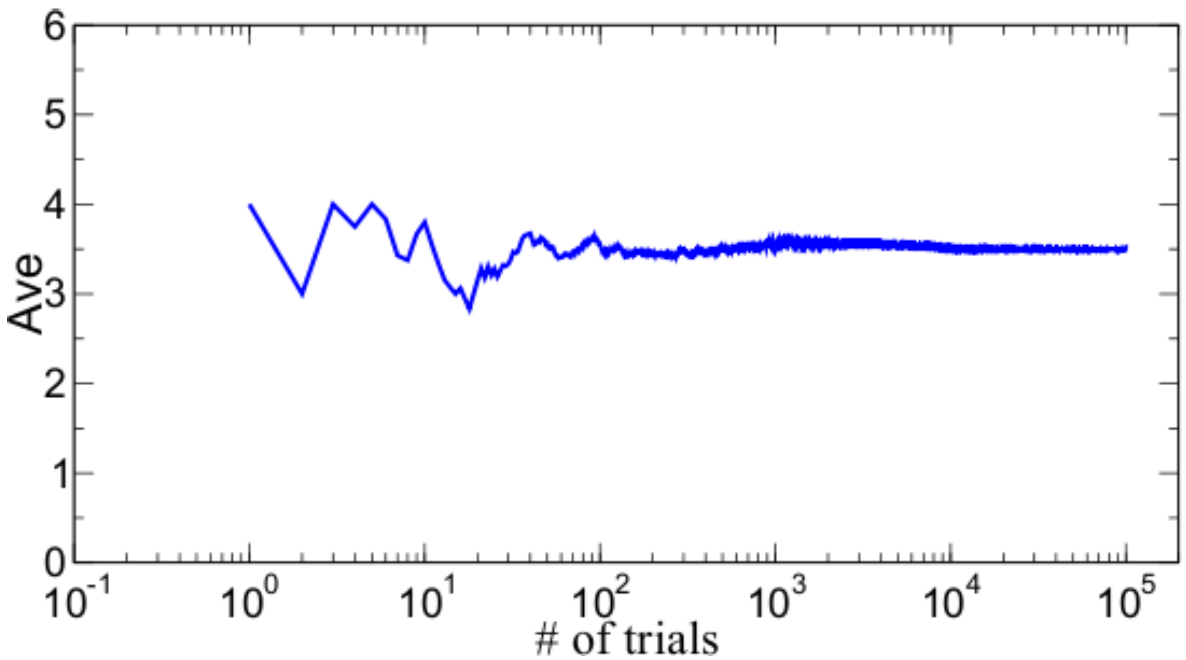

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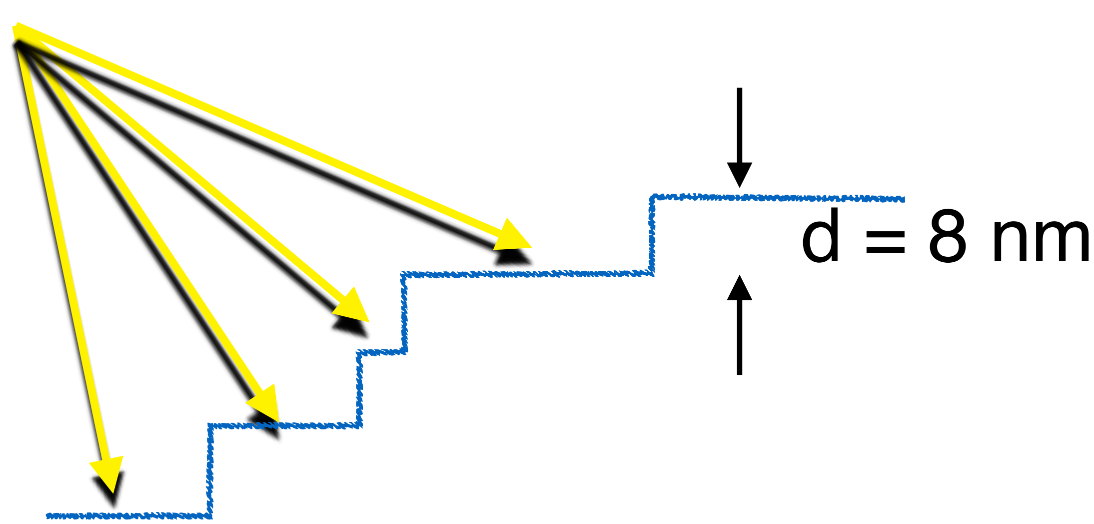

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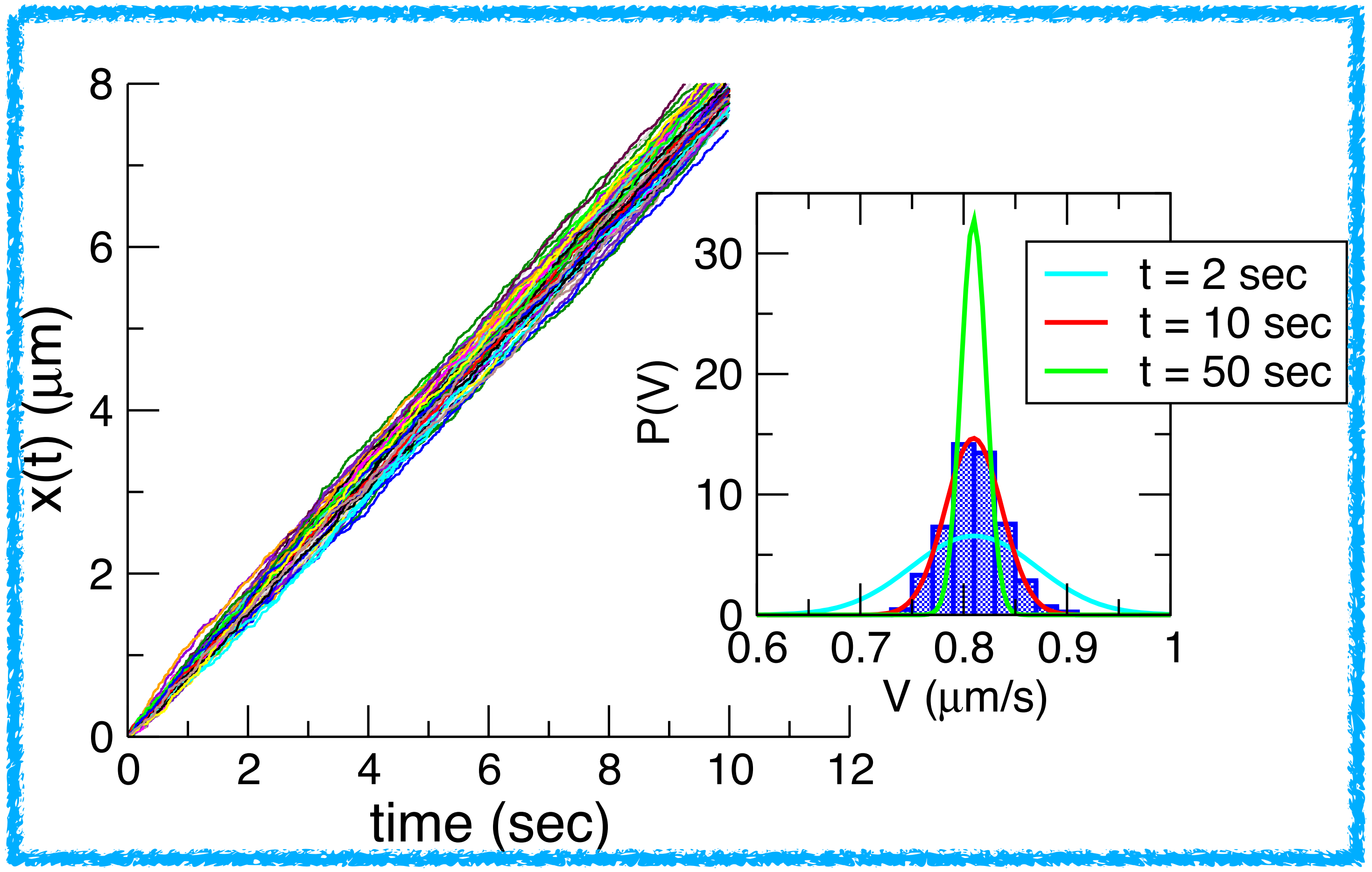
$$\frac{d}{\langle t\rangle} = \frac{8\ \text{nm}}{10\ \text{msec}} = \overline{V} = 800\ \text{nm/s}$$



Computer-generated time traces obtained by assuming that stepping time for each step is i.i.d.

Theoretically, we get

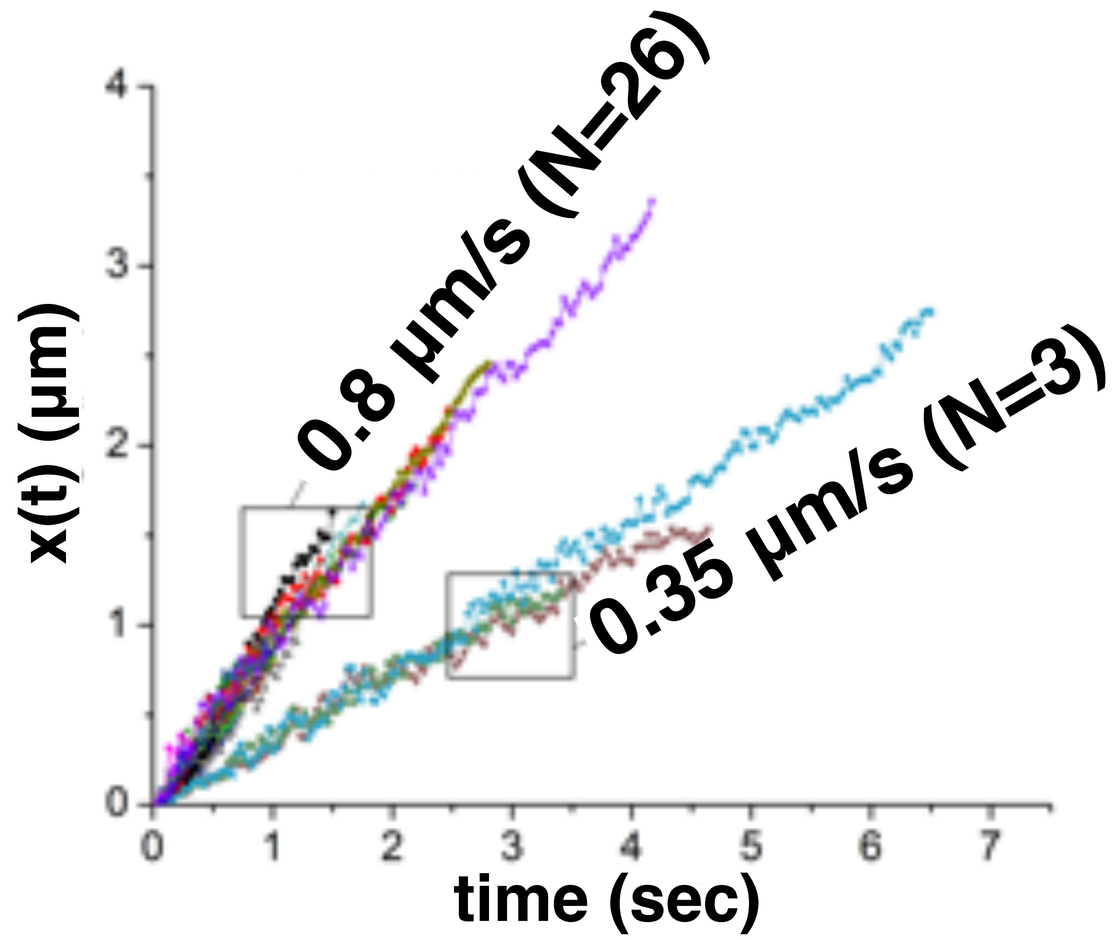
$$P[V(t)] = \left(\frac{t}{4\pi\overline{D}}\right)^{1/2} \exp\left[-\frac{(V(t)-\overline{V})^2}{4\overline{D}/t}\right] \longrightarrow \delta(V(t)-\overline{V})$$

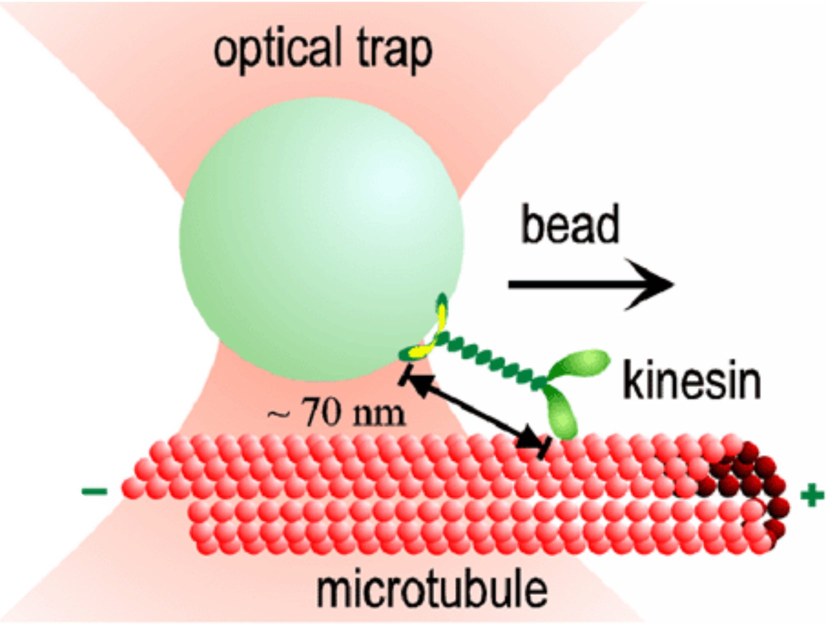
The relative error in the mean velocity when kinesins have taken *n* steps

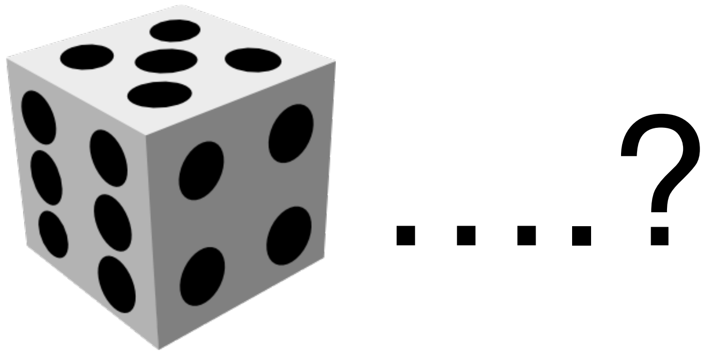
$$\frac{\sqrt{\sigma_V^2}}{\overline{V}} = \frac{(2\overline{D}/t)^{1/2}}{\overline{V}} = \sqrt{\frac{\tau}{t}} = \frac{1}{\sqrt{n}}$$

$$V(n) = \overline{V} \pm \delta\overline{V} = \overline{V} \pm \frac{\overline{V}}{\sqrt{n}}$$

Bead assays, kinesins purified from Drosophila embryos.







The relative error in the mean velocity of homogeneous kinesin:

$$\frac{\sqrt{\sigma_V^2}}{\overline{V}} = \frac{(2\overline{D}/t)^{1/2}}{\overline{V}} = \sqrt{\frac{\tau}{t}} = \frac{1}{\sqrt{n}}$$

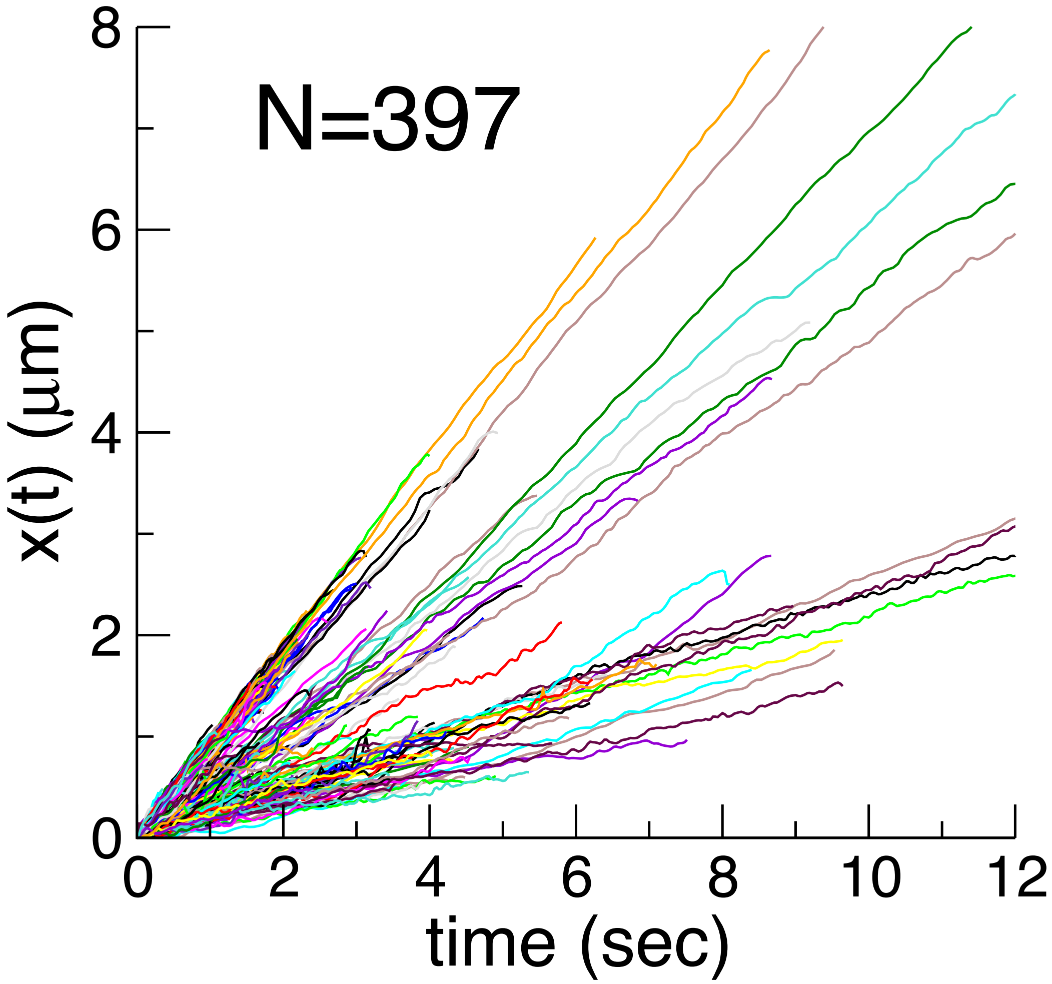
$$n = 400$$
$$V = 800 \pm 40 \text{ nm/s}$$

Questions …

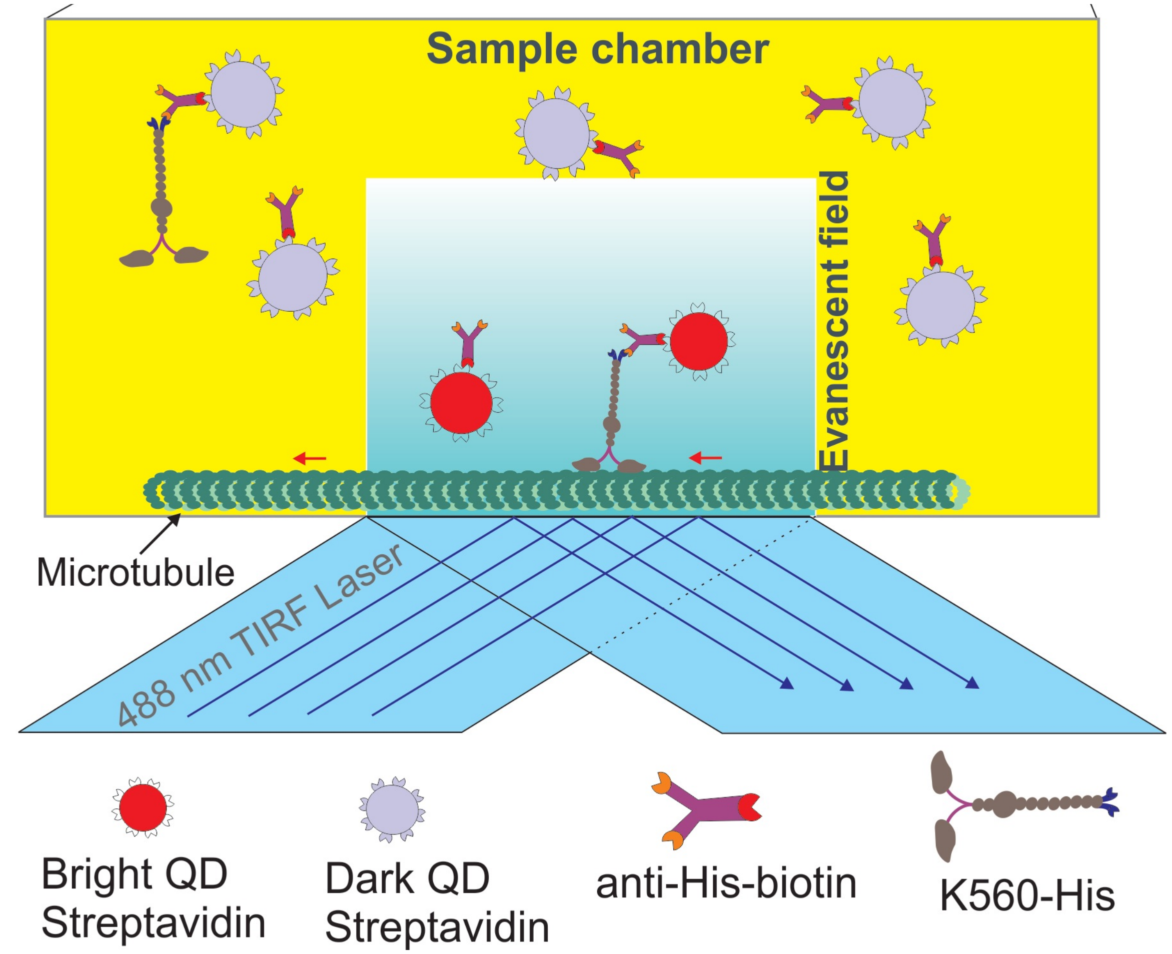
- Why do we observe heterogeneous time traces?
- Post-translational modification, heterogeneity in tail-bead attachment, artifacts in the experiment, … or wrong experiment, … etc.
- Are functional kinesins heterogeneous?

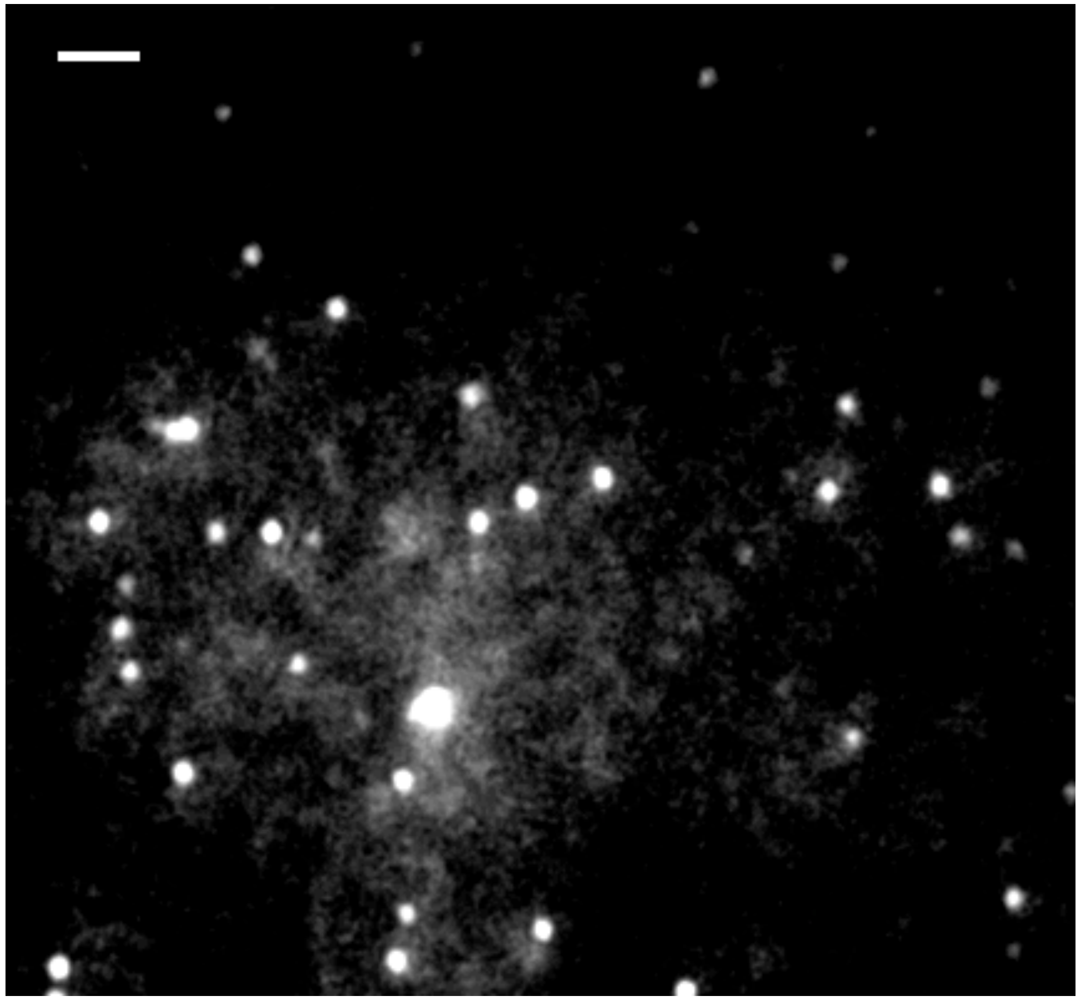
Q-dot assays

kinesins (K560) purified from E. coli.



Specific tail-Qdot attachment.
anti-His-biotin : K560-His





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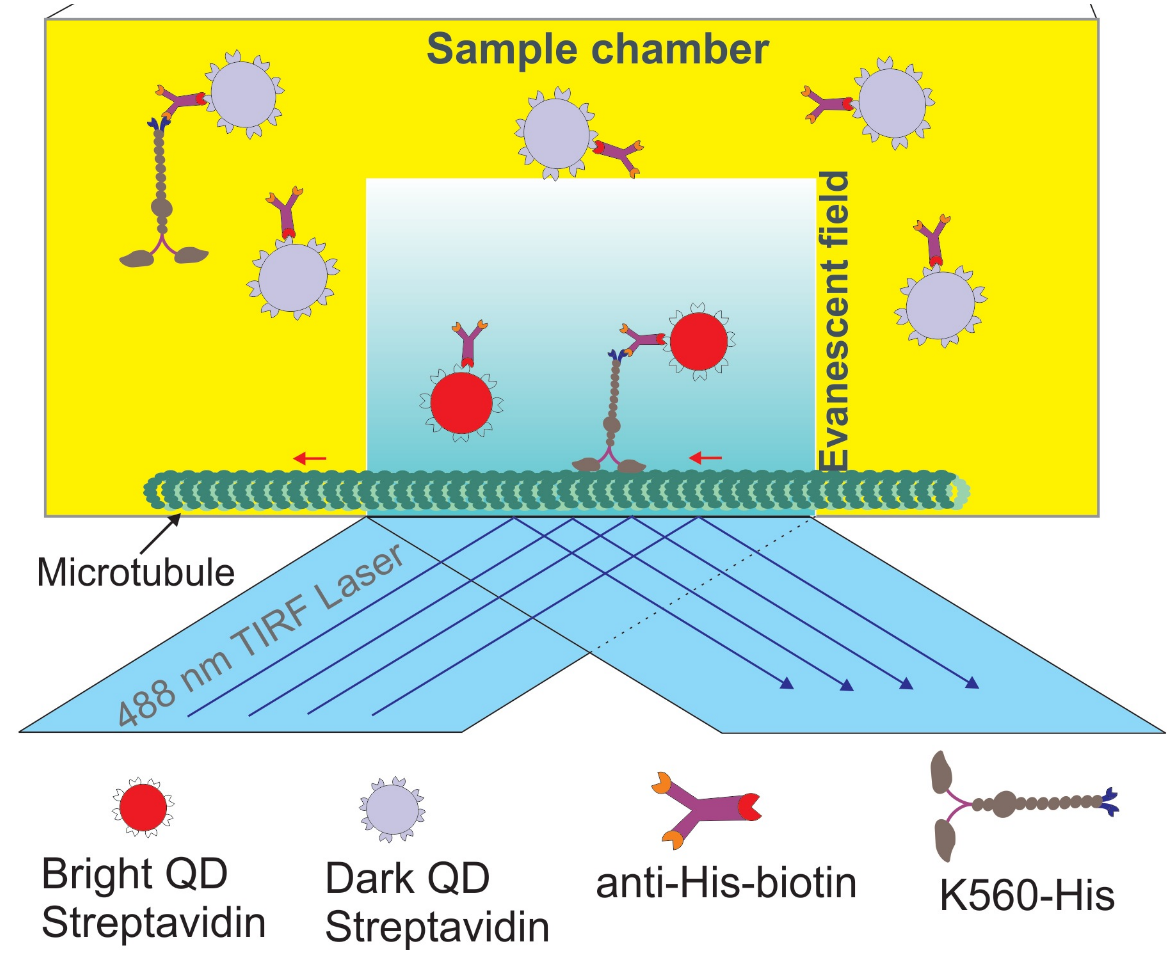

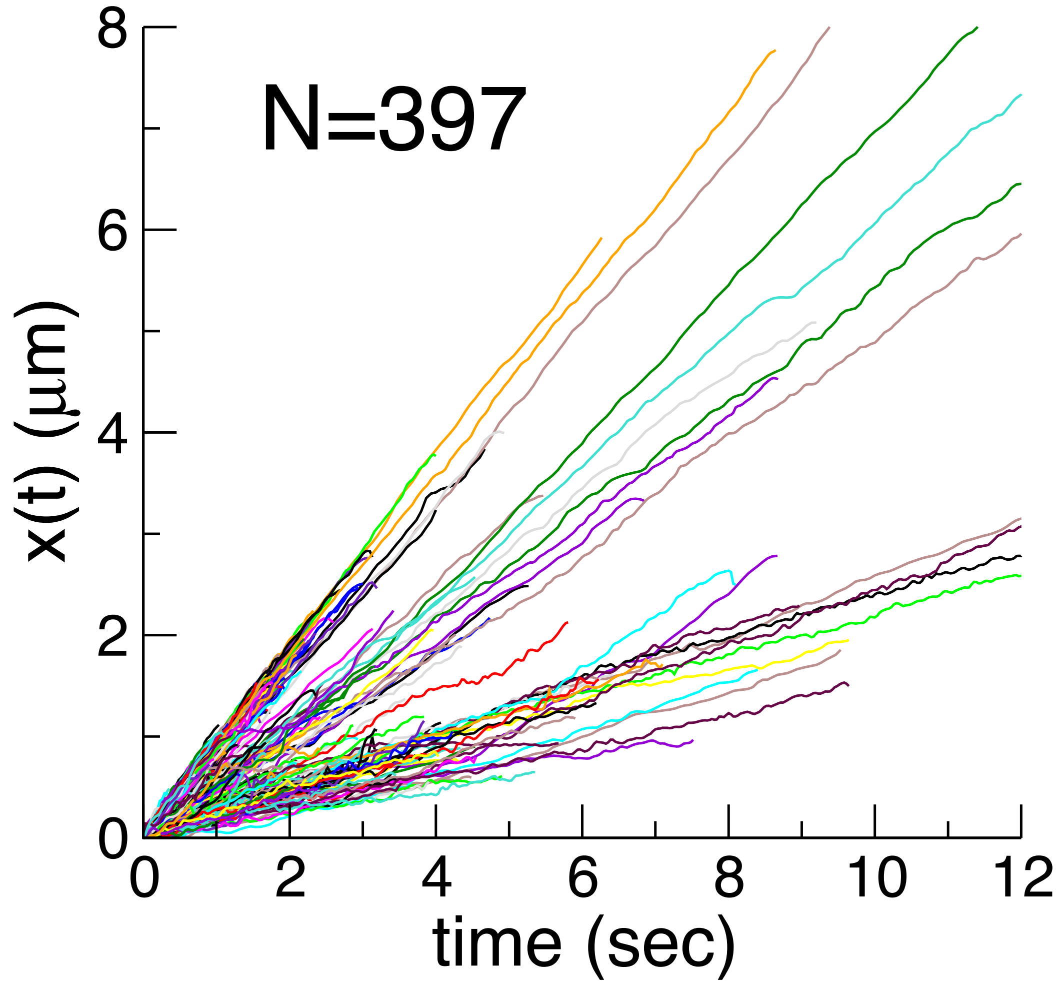

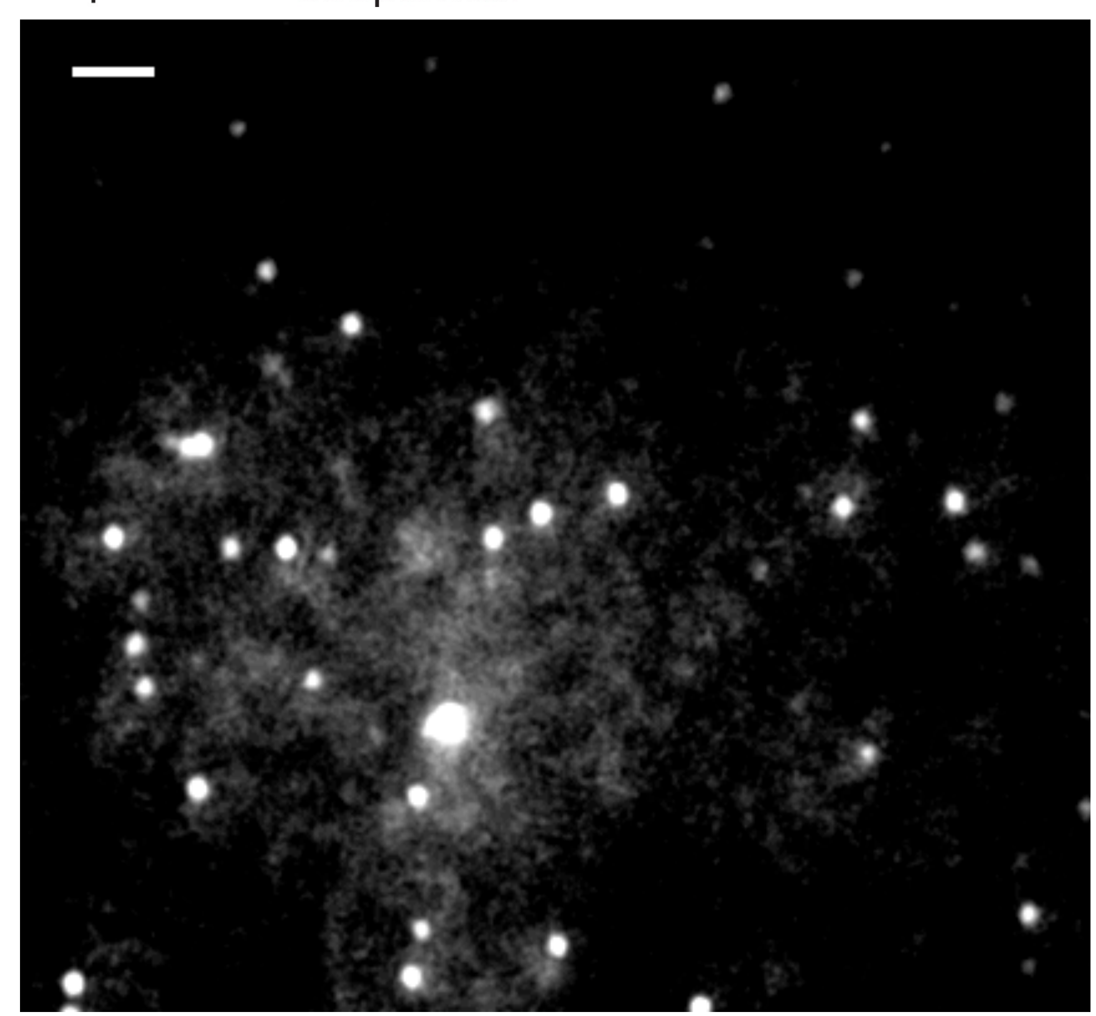

Specific tail-Qdot attachment.
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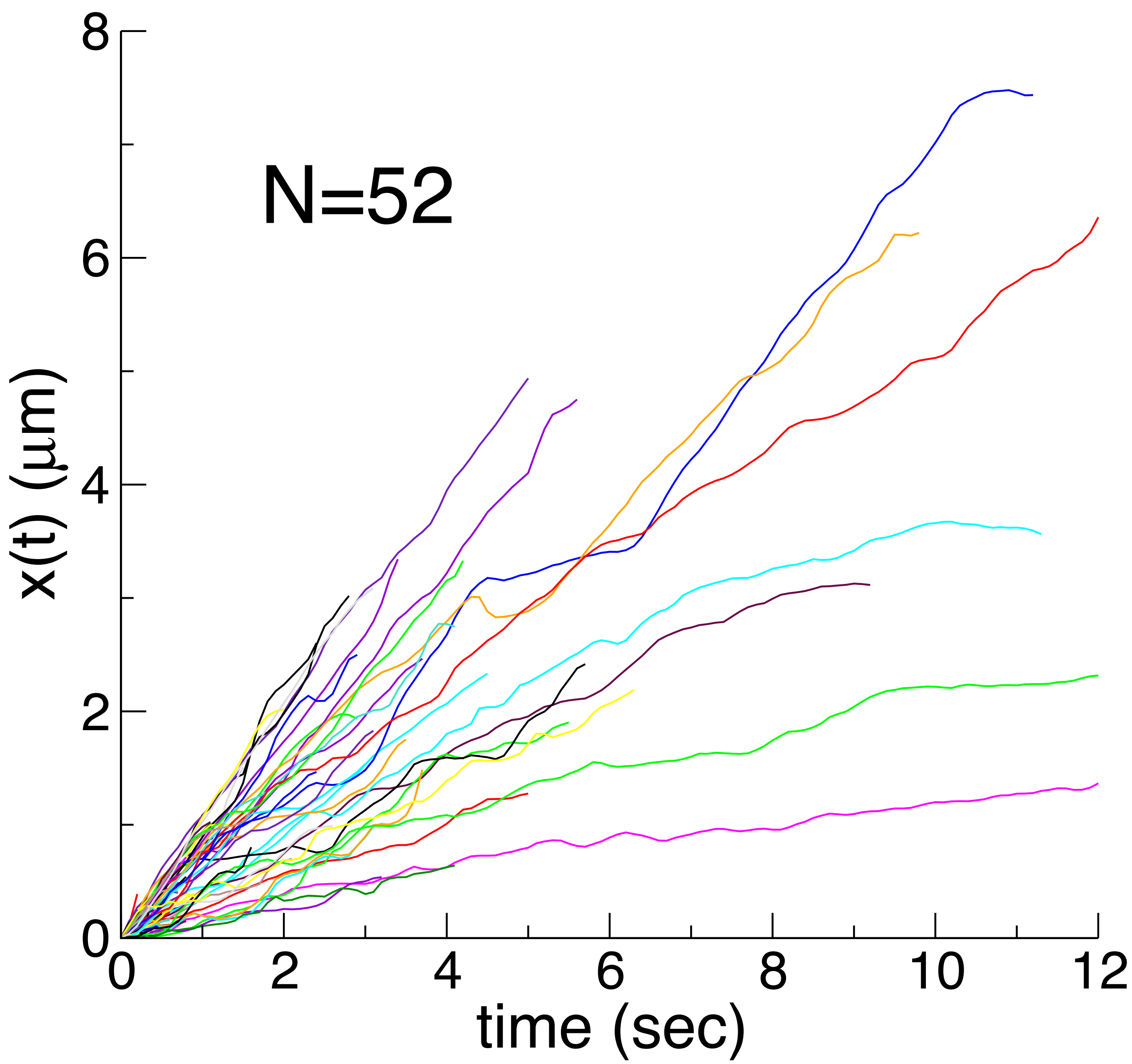
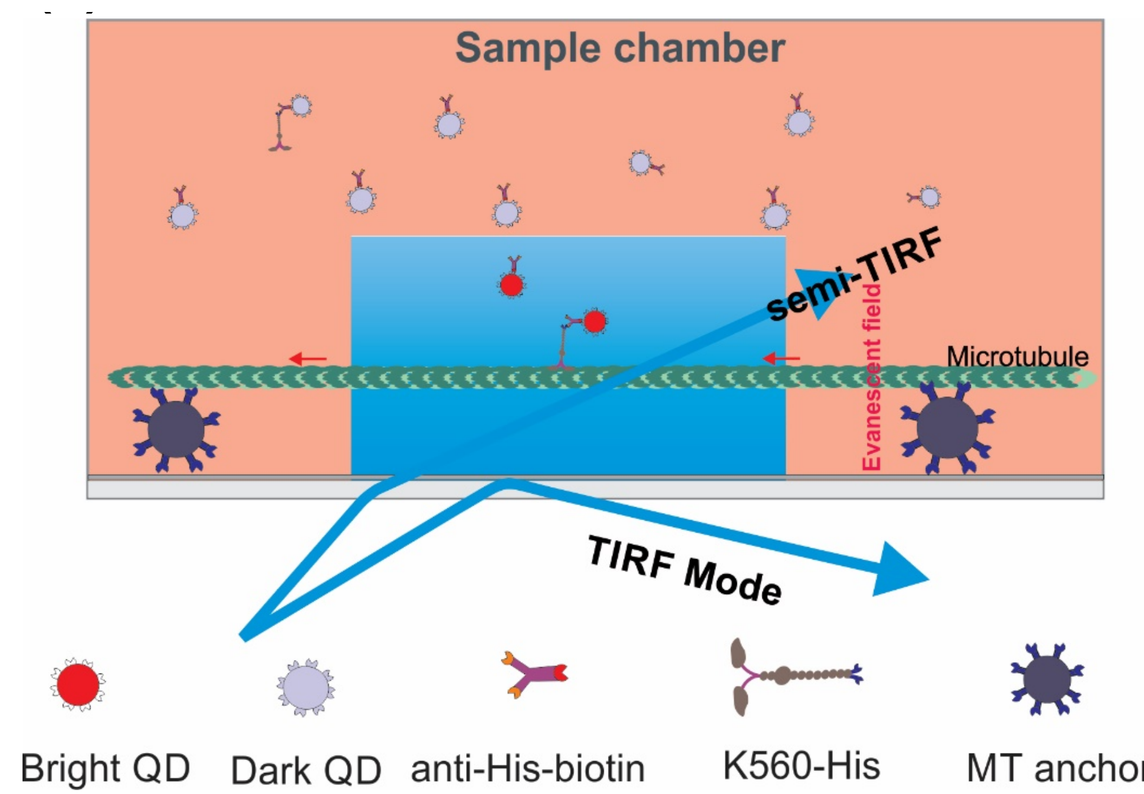
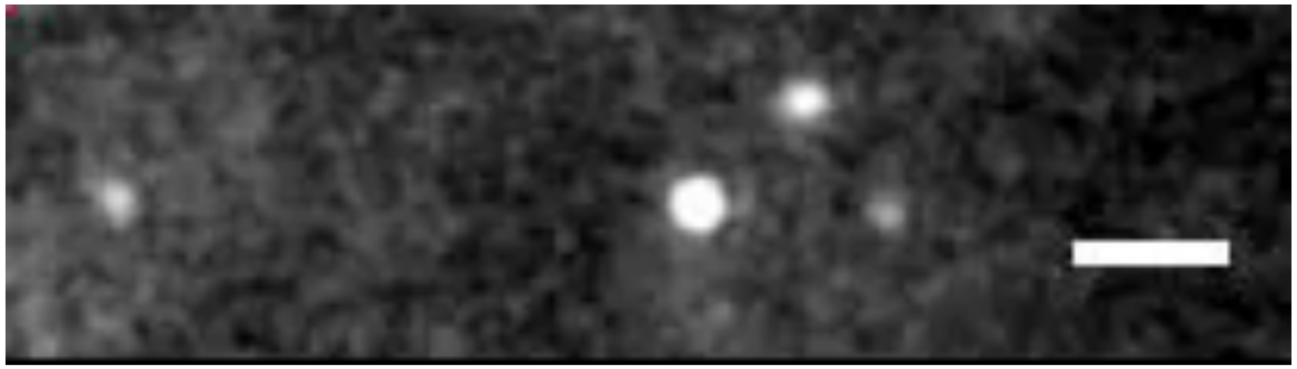
Q-dot assays above surfaces, kinesins (K560) purified from E. coli.

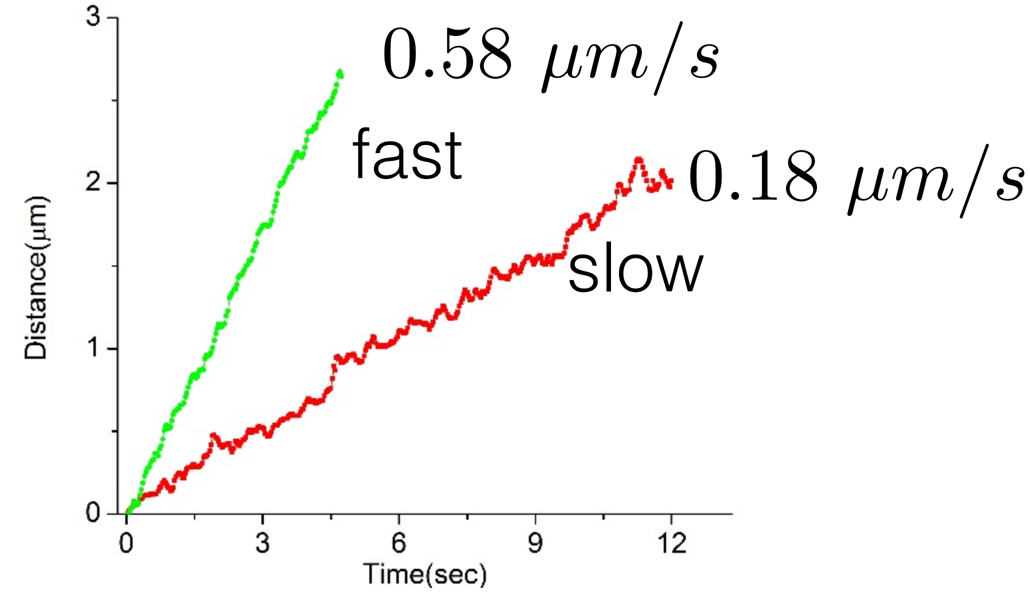


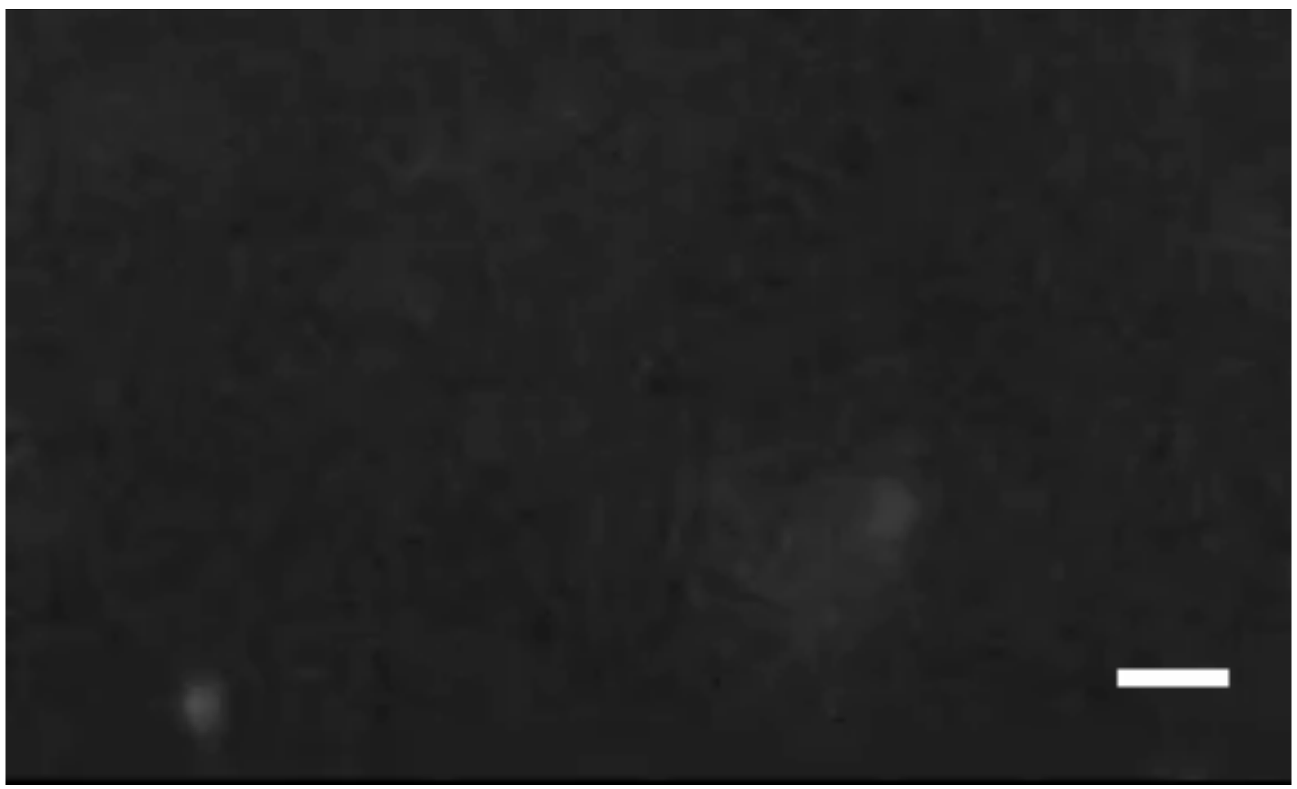


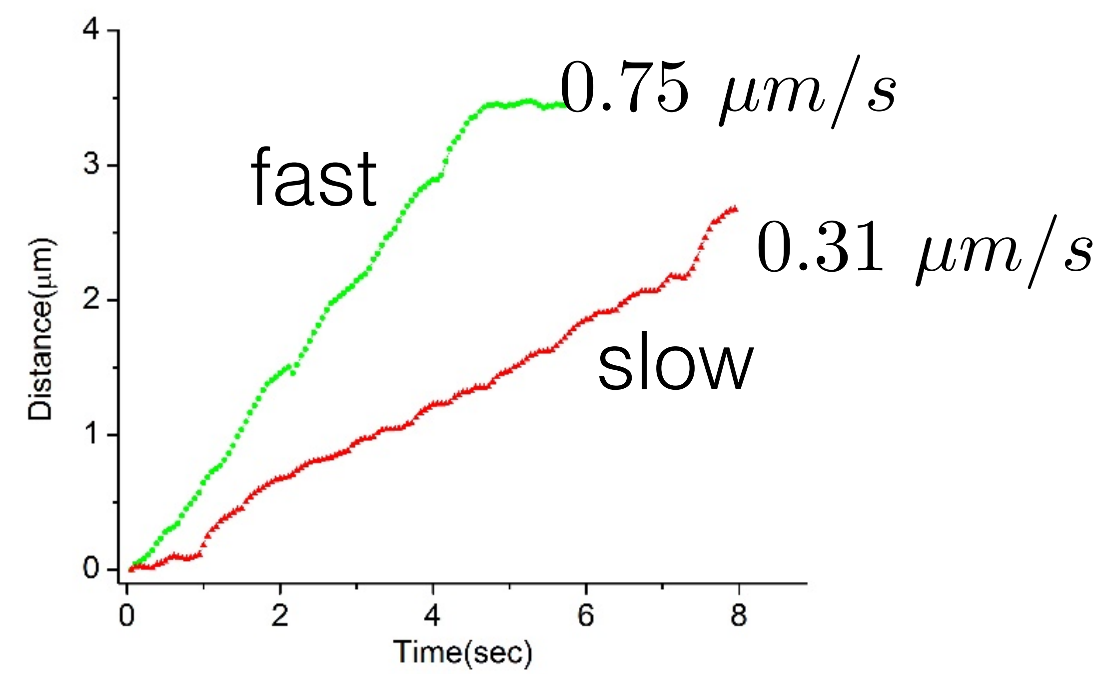
Traffic (2017)

QD-Kinesins (K560) on the same off-surface microtubule









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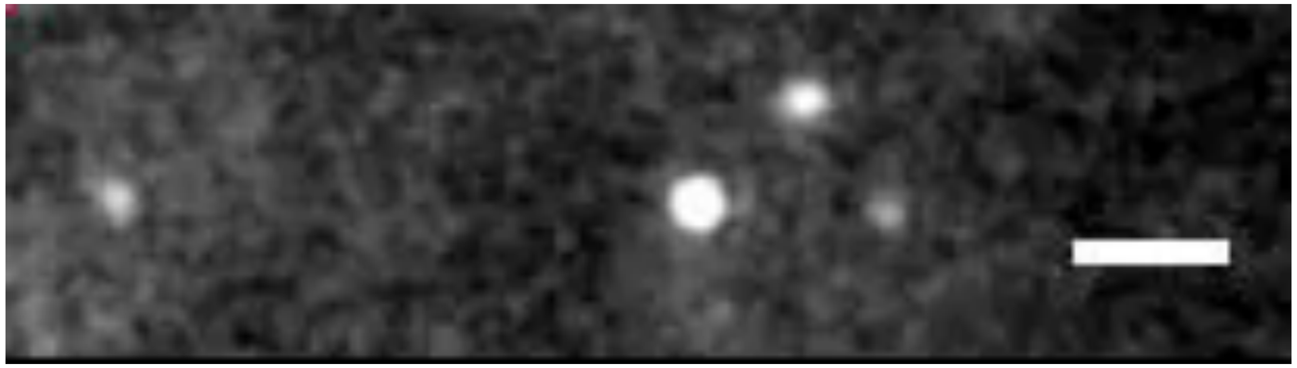

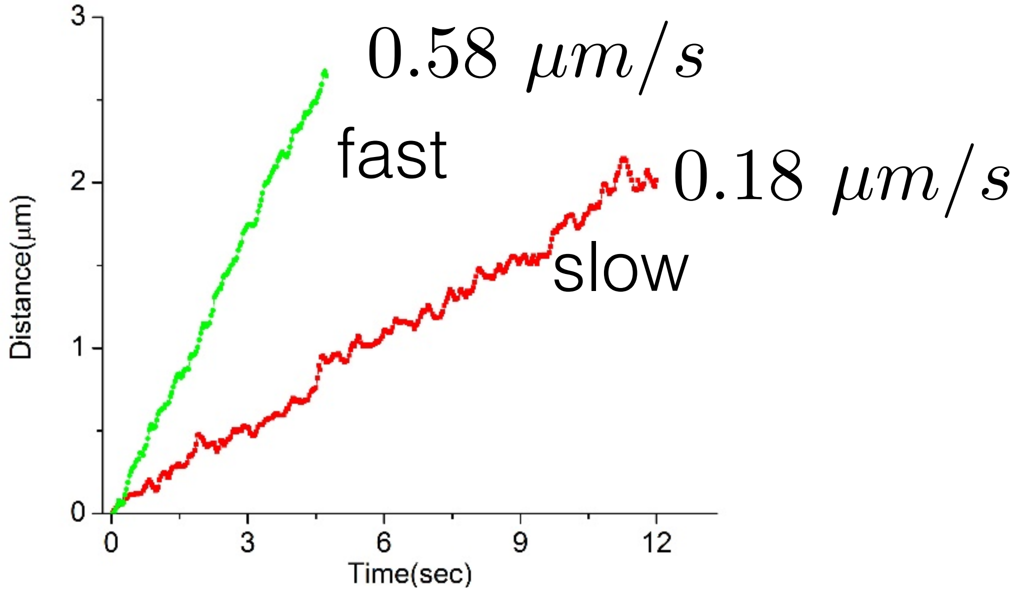

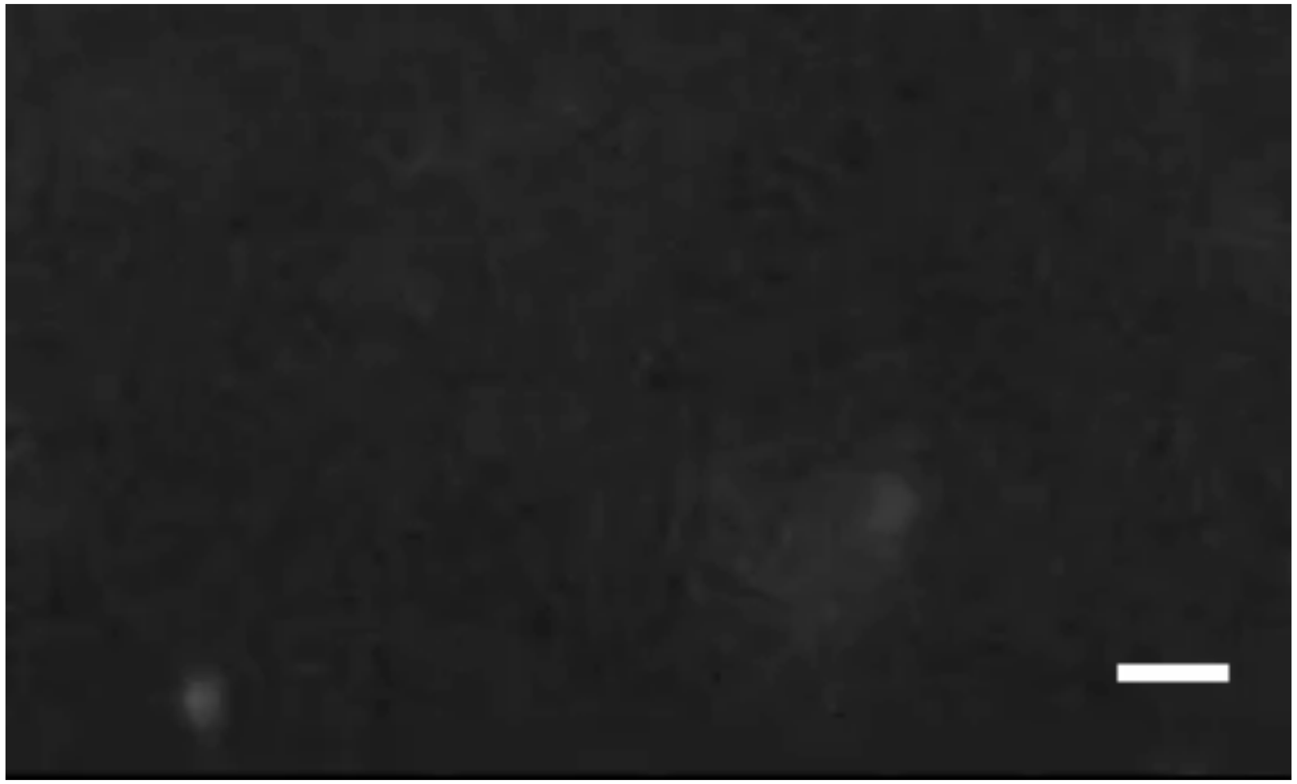

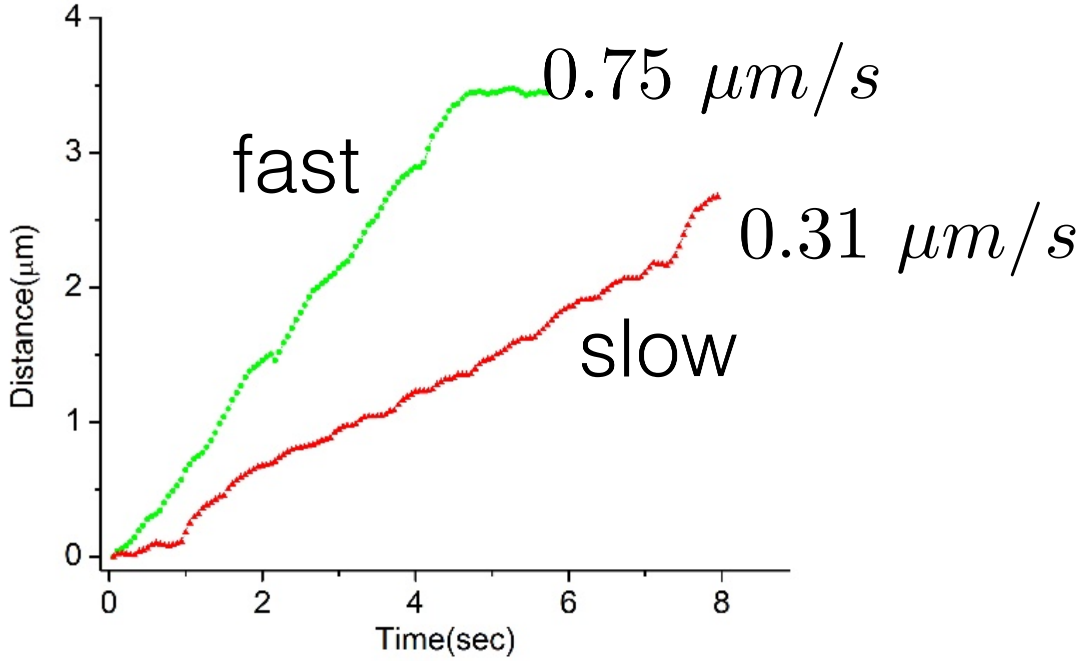

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Traffic (2017)

DNA unwinding heterogeneity by RecBCD results from static molecules able to equilibrate

RecBCD

Bian Liu[1,2,3], Ronald J. Baskin[2] & Stephen C. Kowalczykowski[1,2,3]

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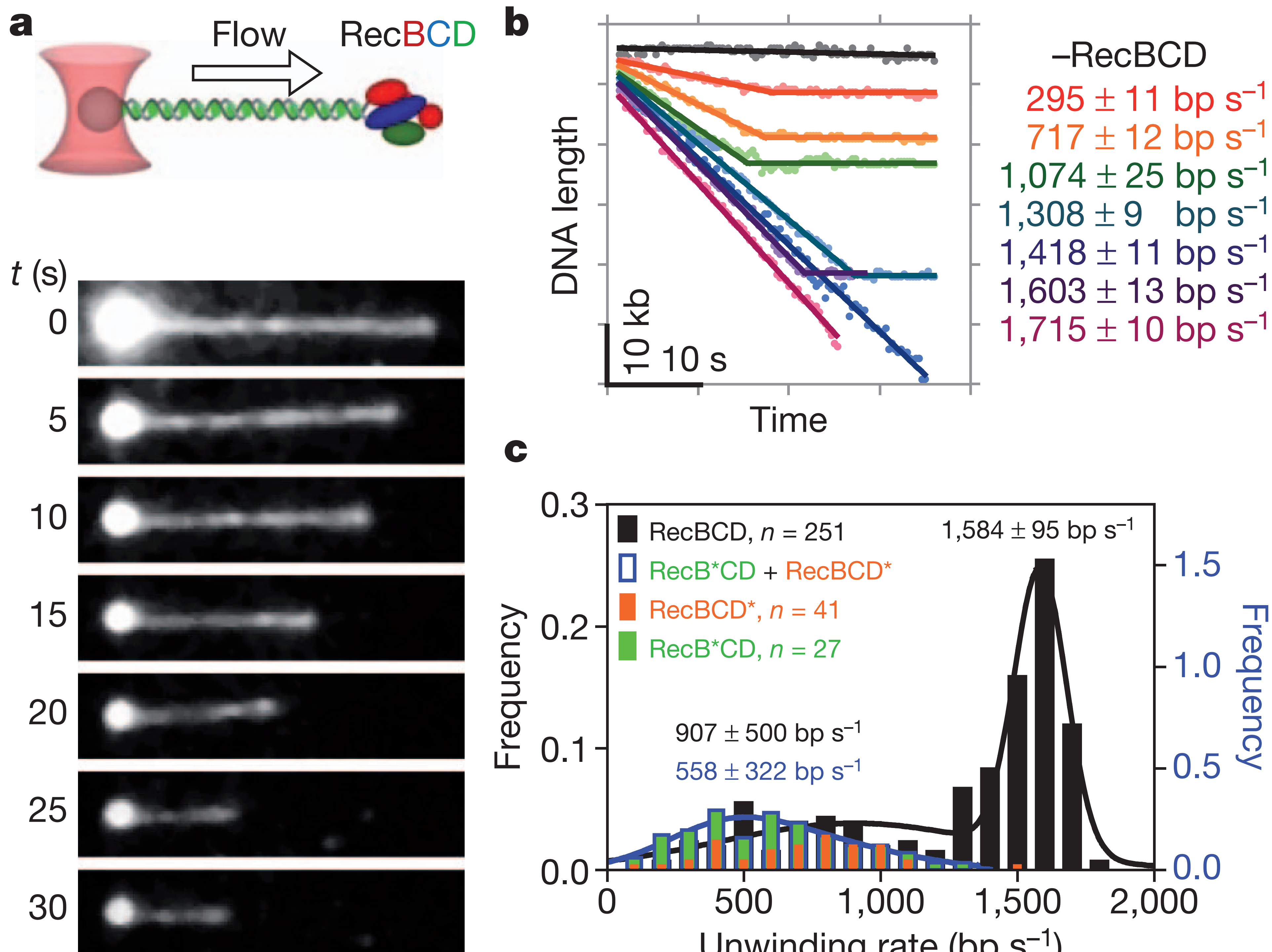
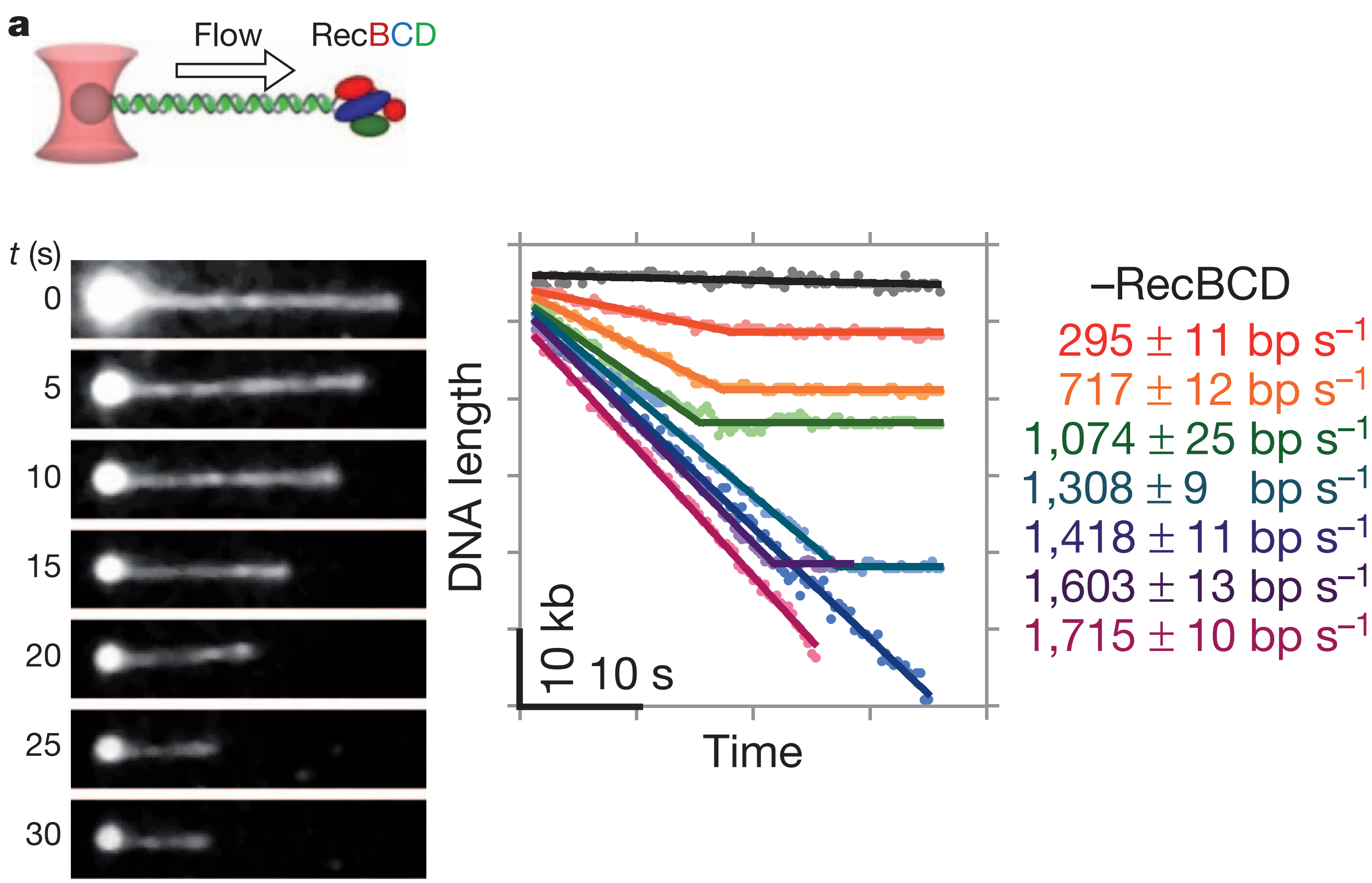
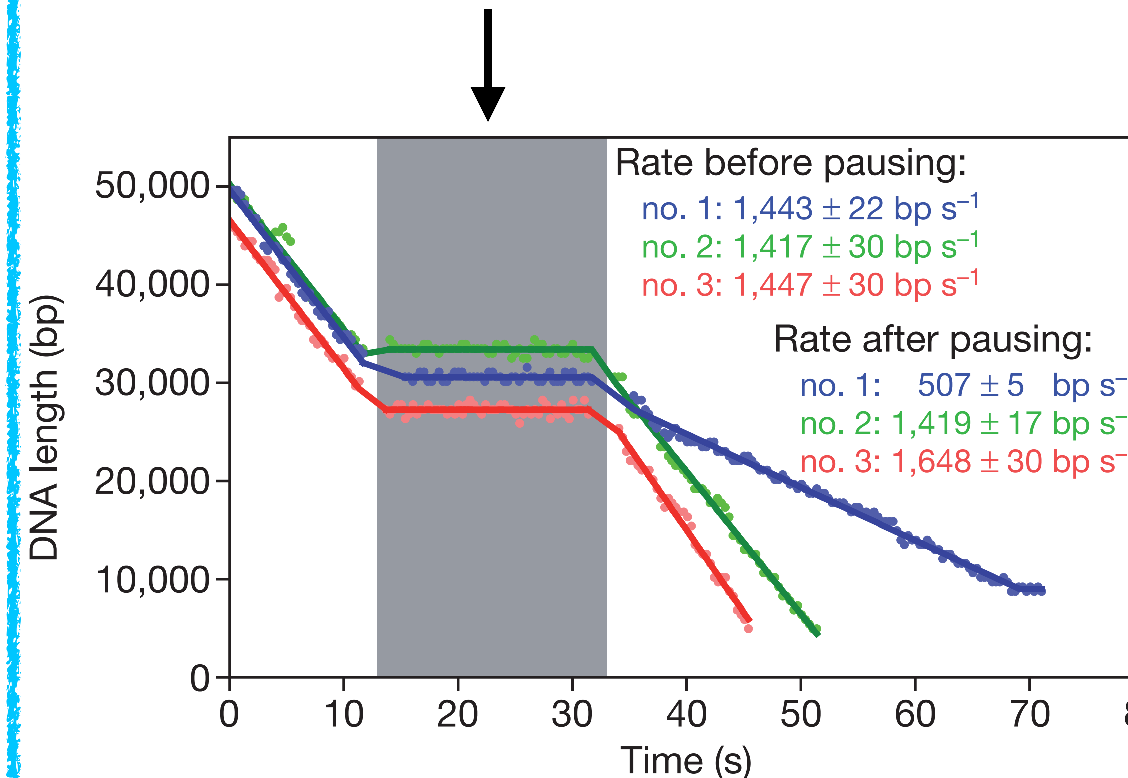


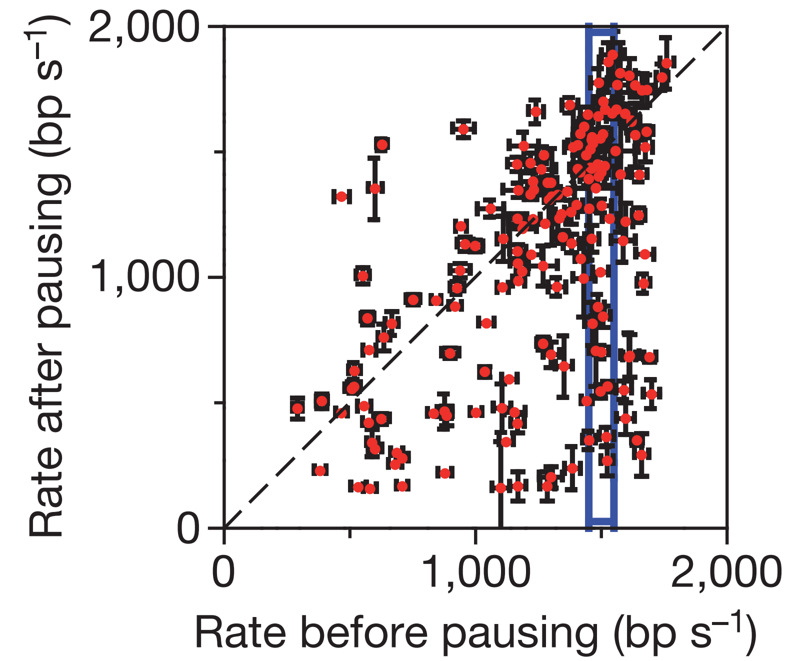
dsDNA unwinding motor RecBCD



Kowalczykowski & coworkders
Nature (2013)

Pause due to *ATP depletion*





— Depletion of ATP can reset the memory of initial condition !!!

DNA unwinding heterogeneity by RecBCD results from static molecules able to equilibrate

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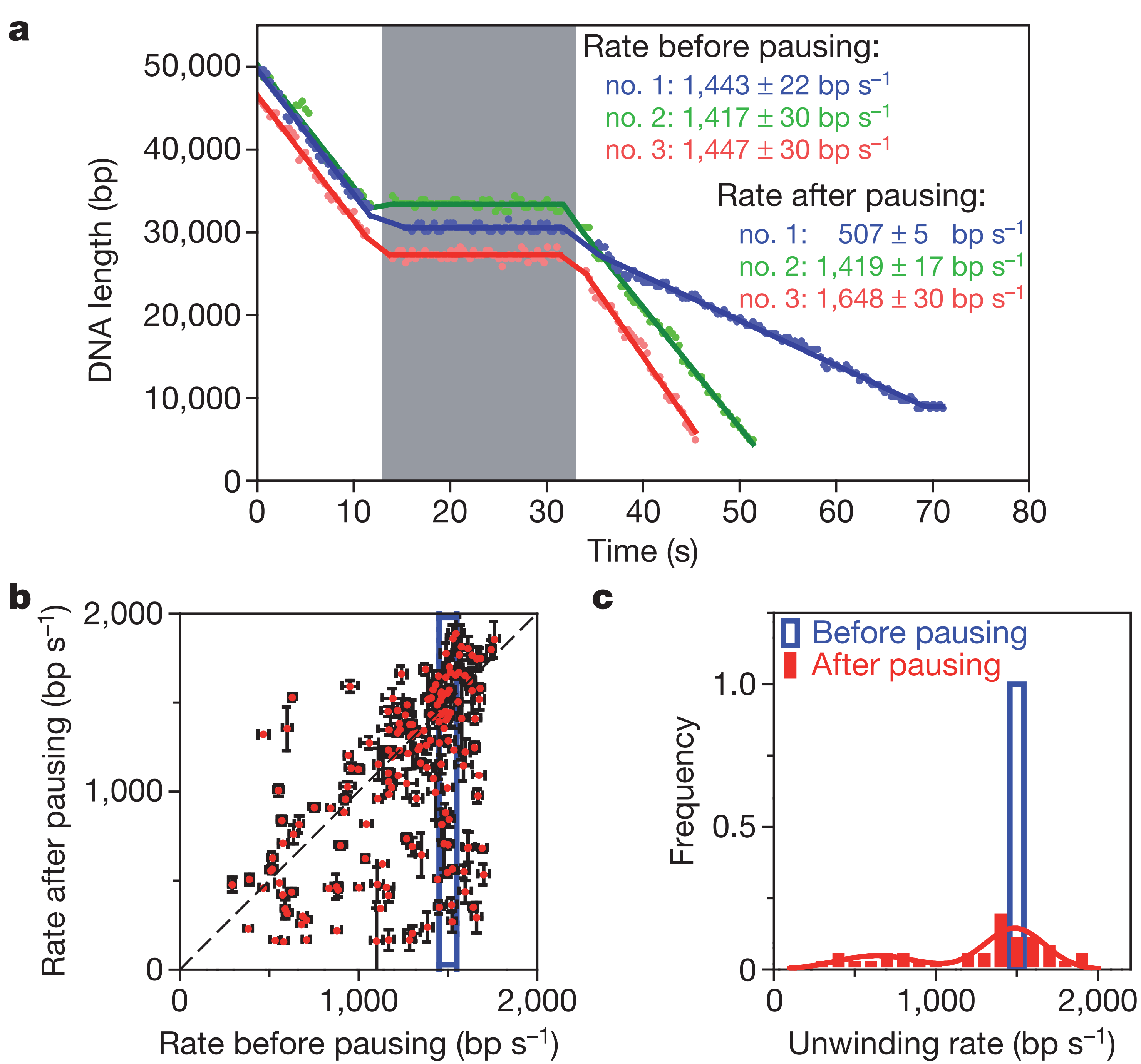
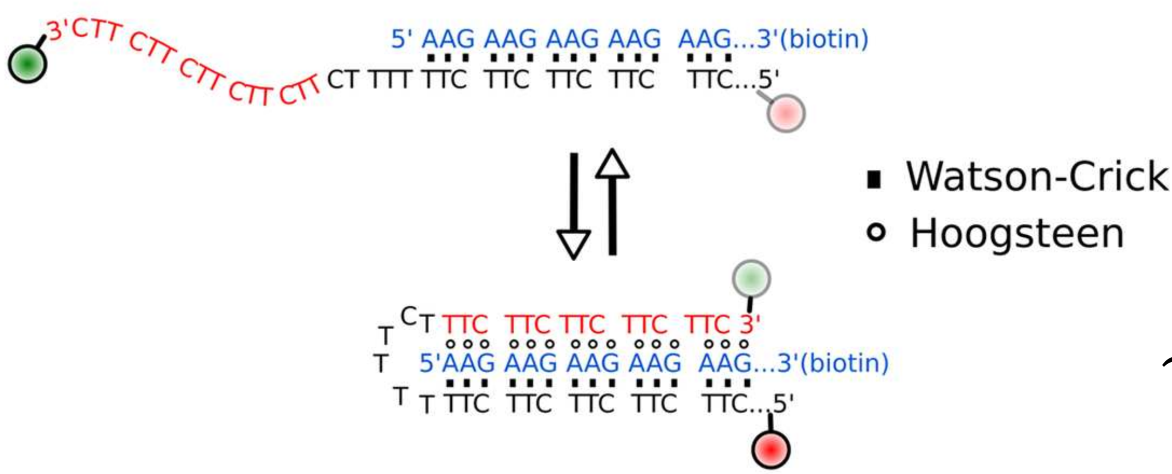
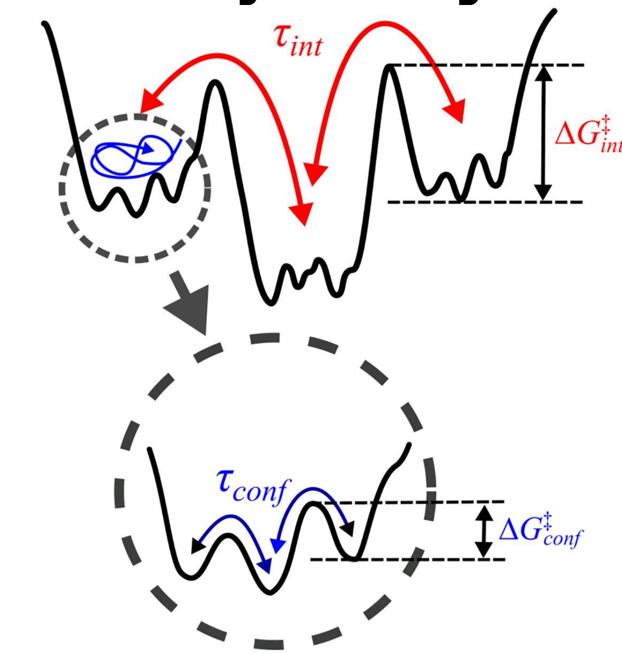
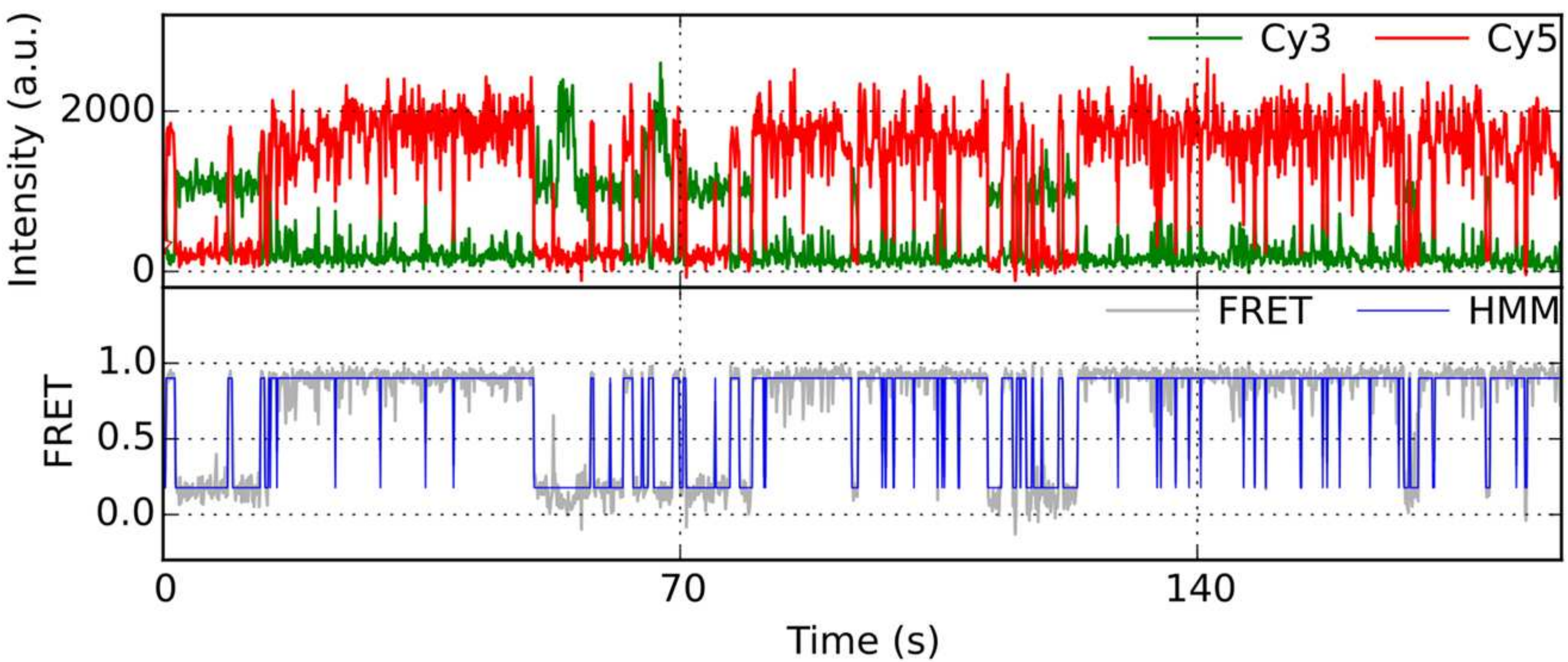


Decoding dynamic disorder in single molecule time trajectory (folding/unfolding of H-DNA)





$$\tau_{conf} \ll \tau_{int} \lesssim T_{obs}$$



Hwang et al. PLoS Comp. Biol. (2016)

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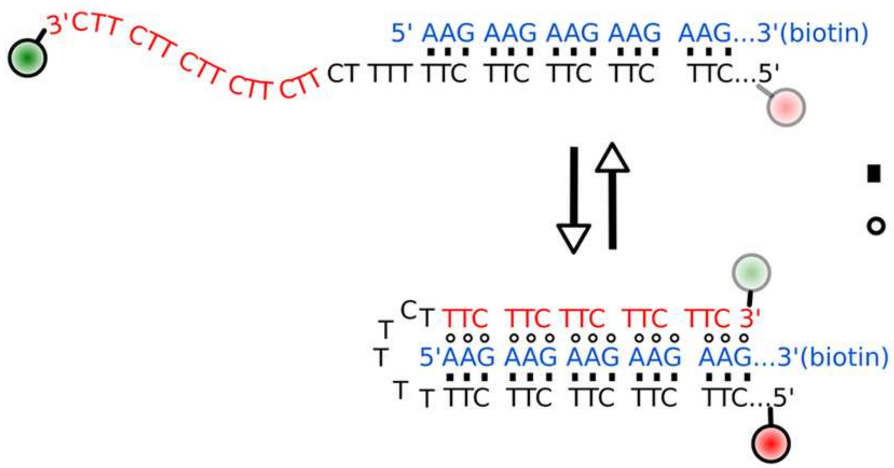

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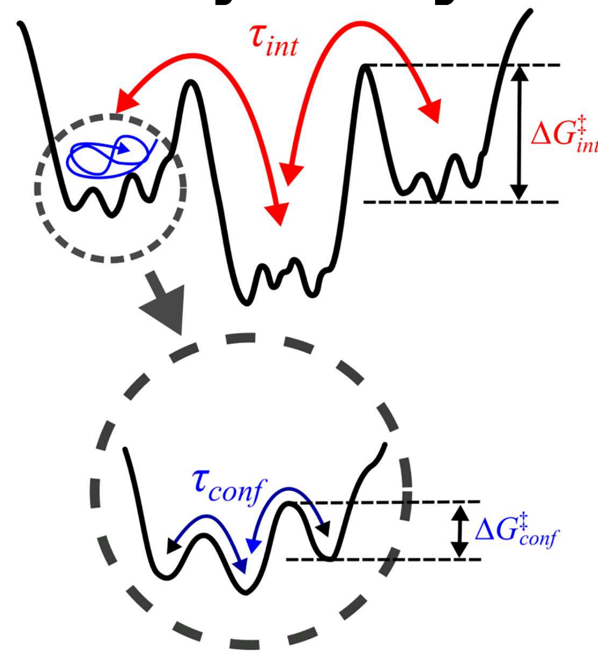

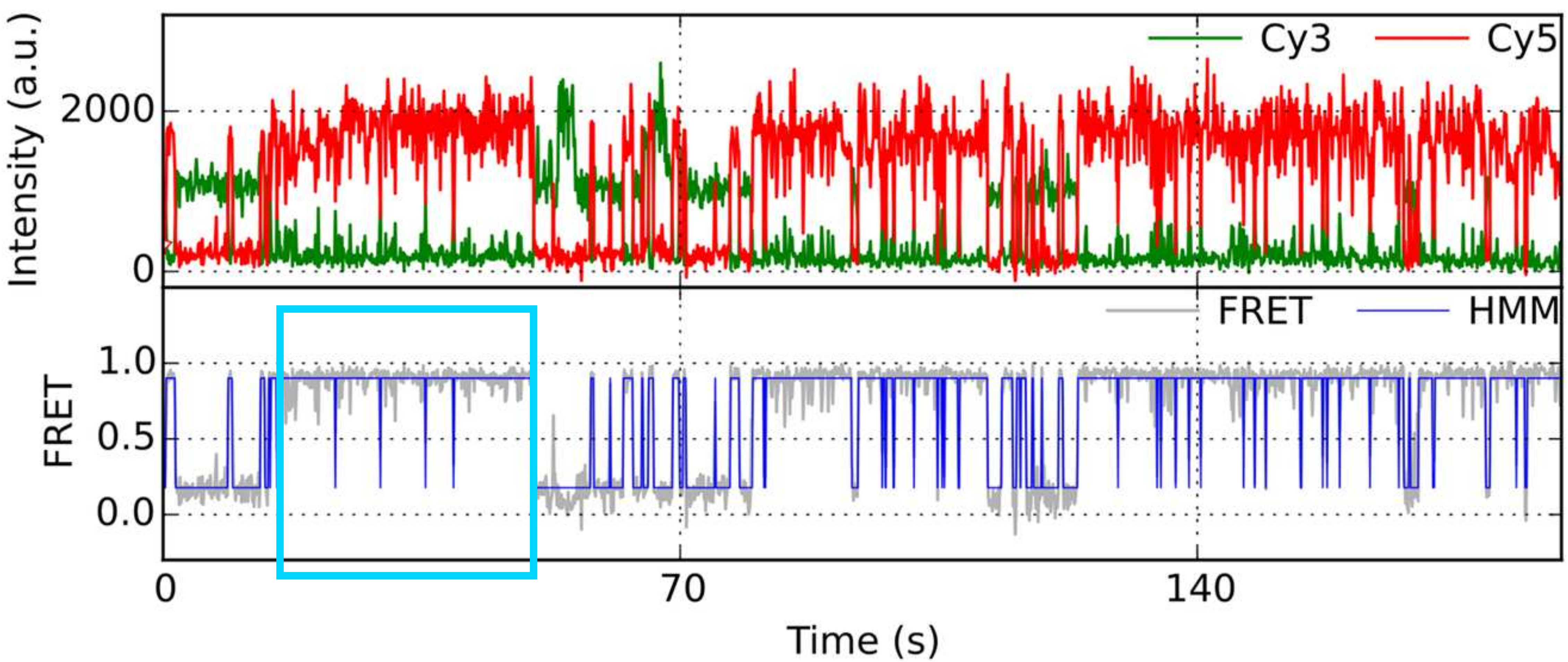

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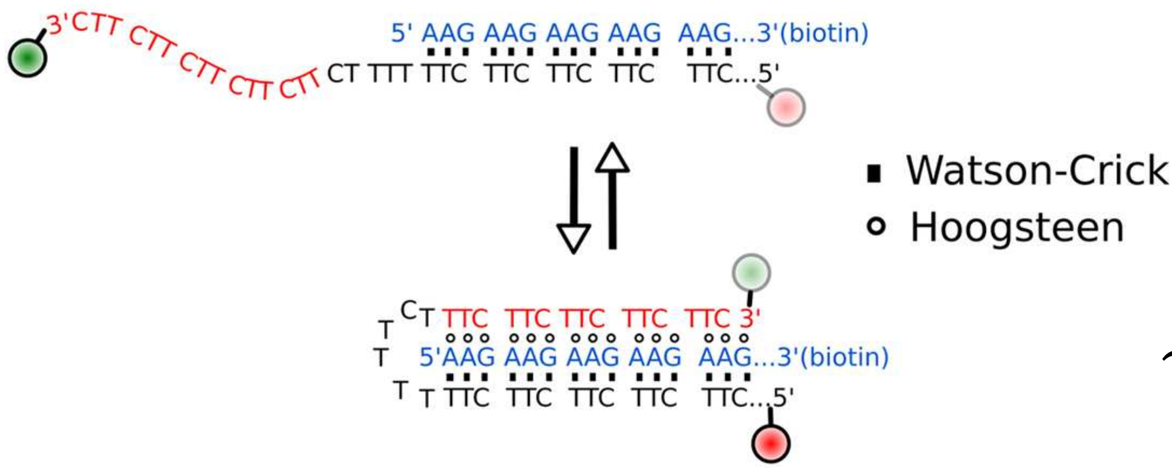

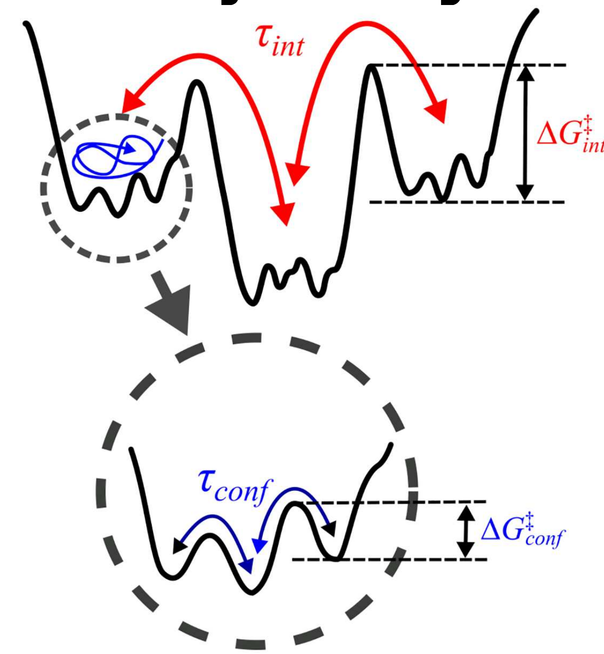

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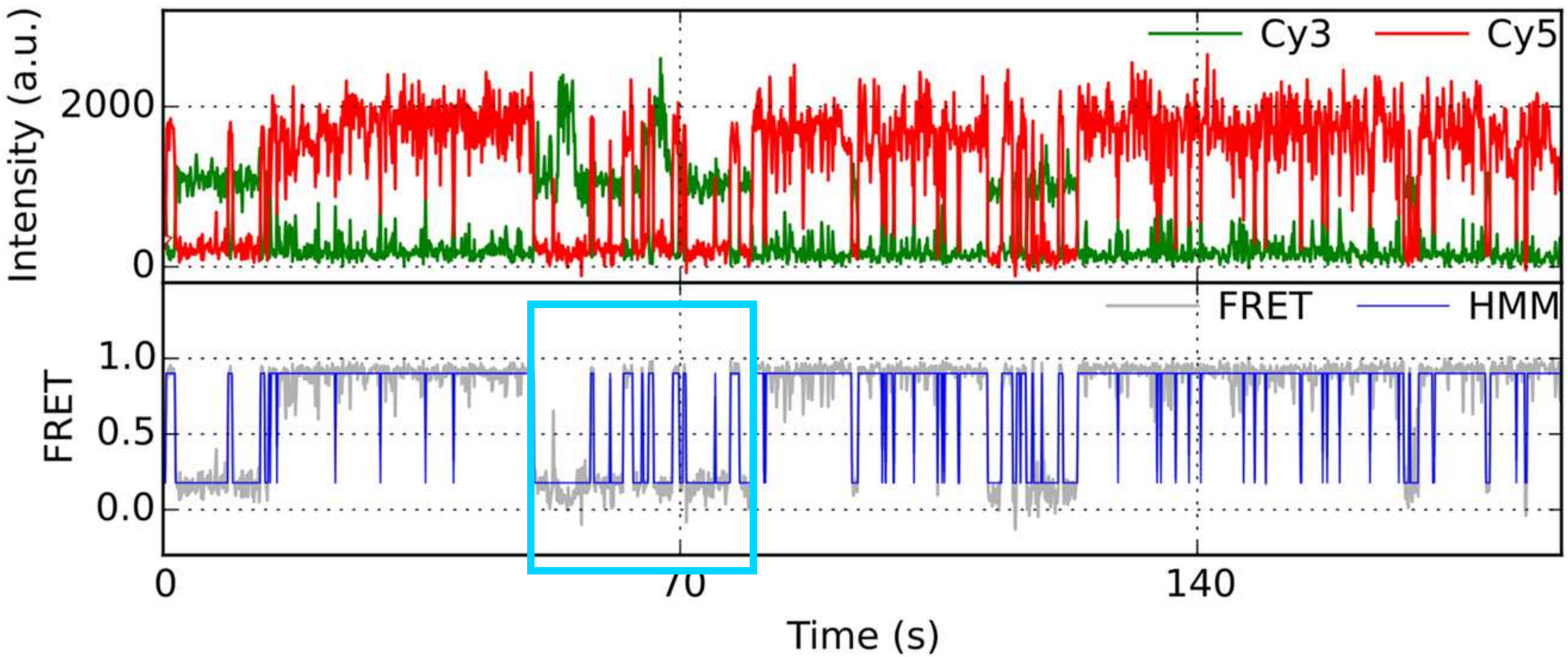

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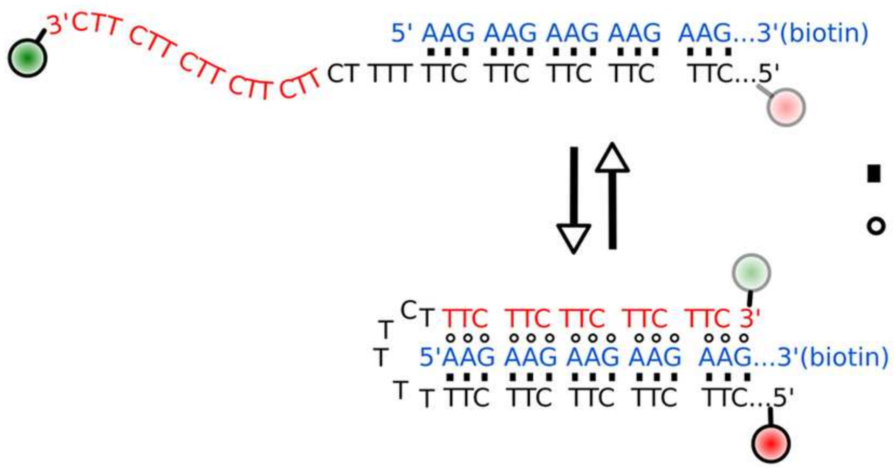

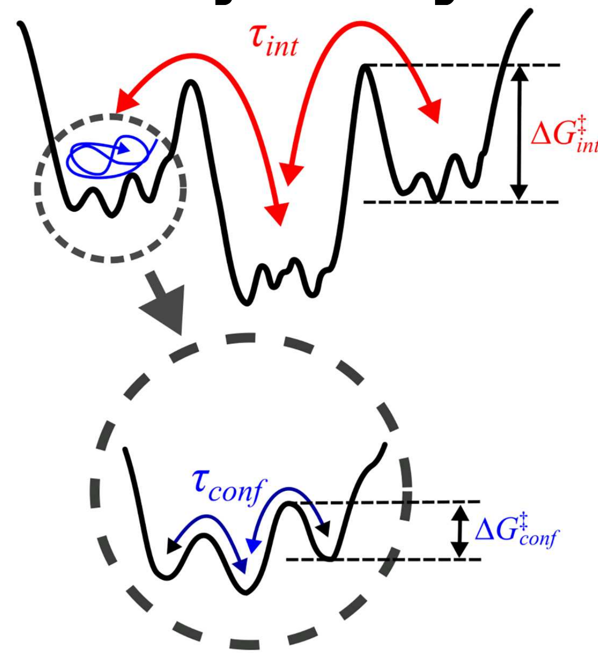

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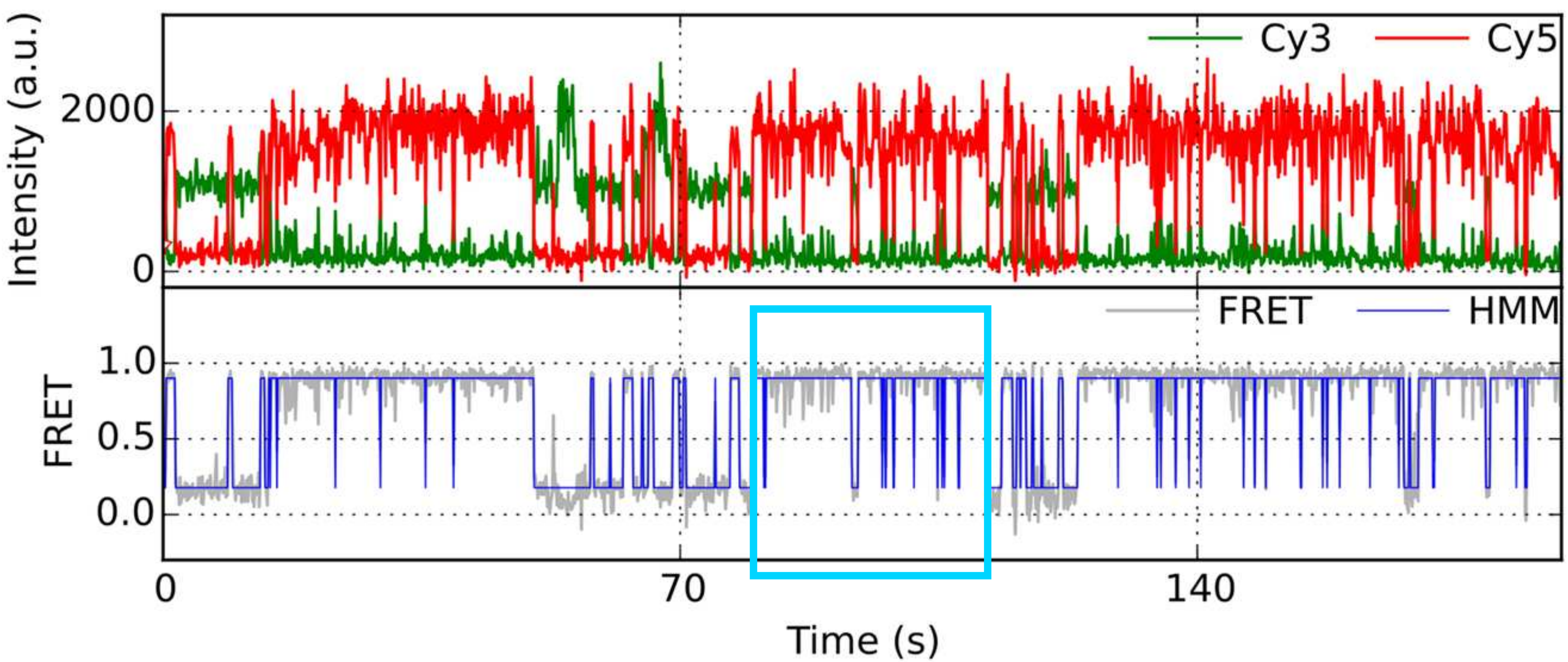
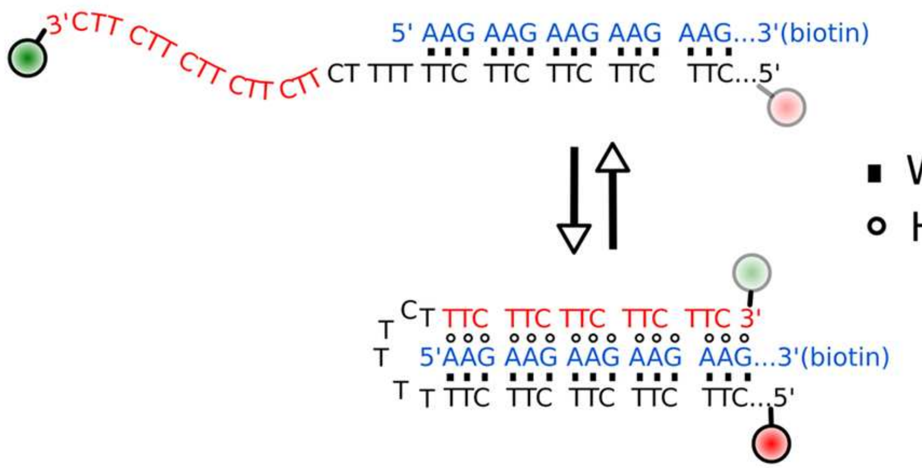
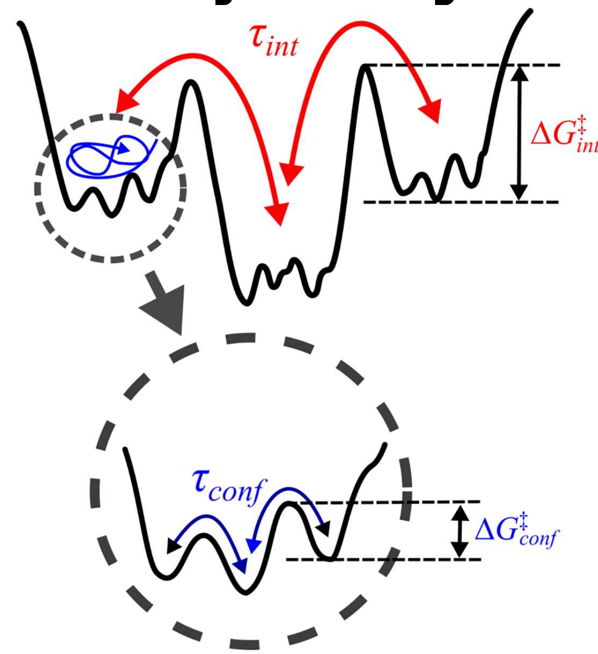


Hwang et al. PLoS Comp. Biol. (2016)

Decoding dynamic disorder in single molecule time trajectory (folding/unfolding of H-DNA)





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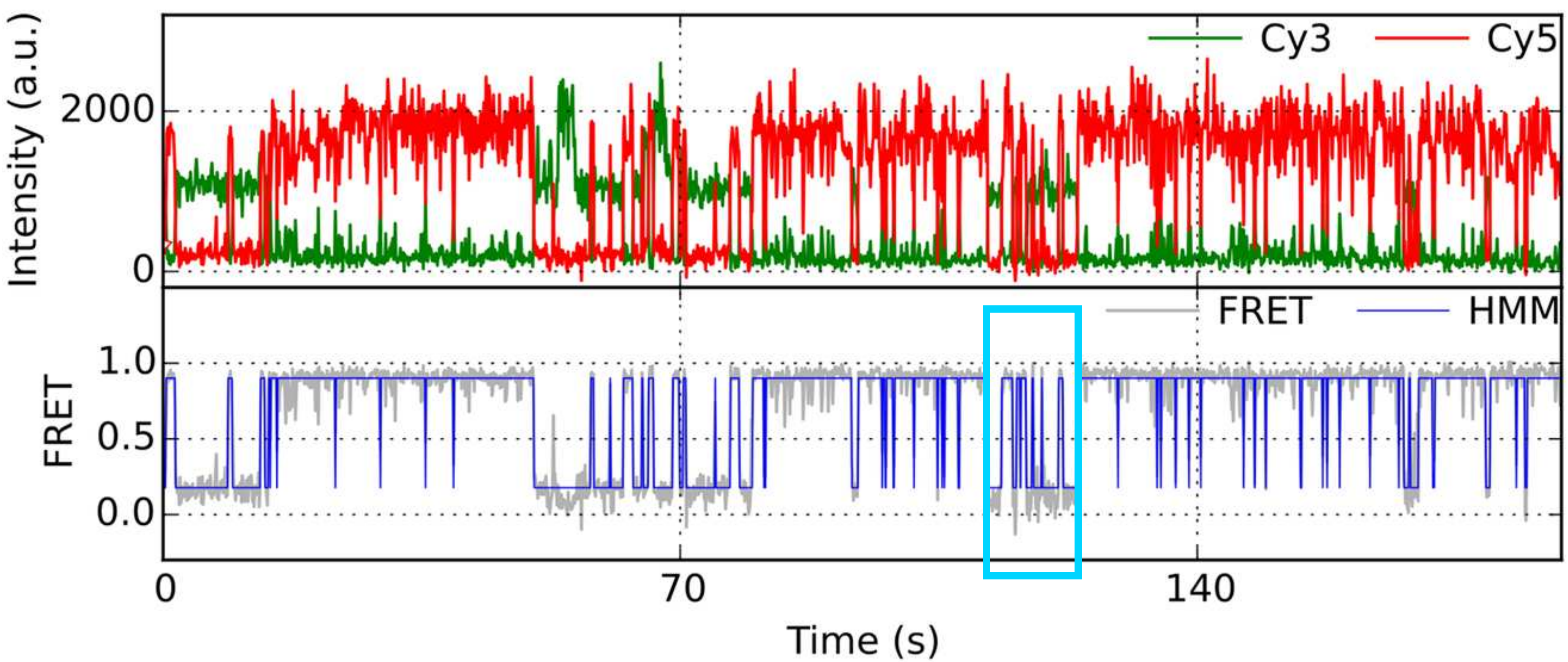

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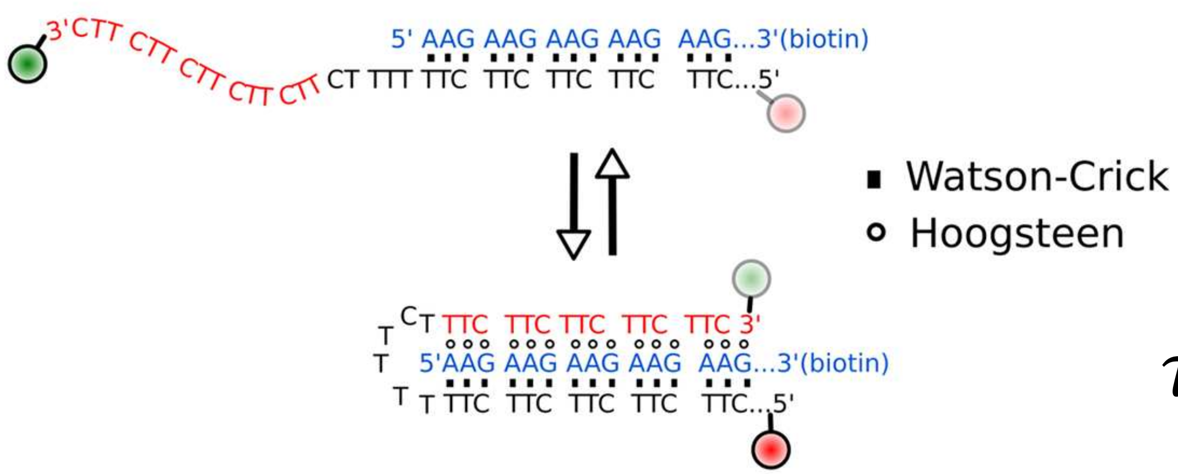

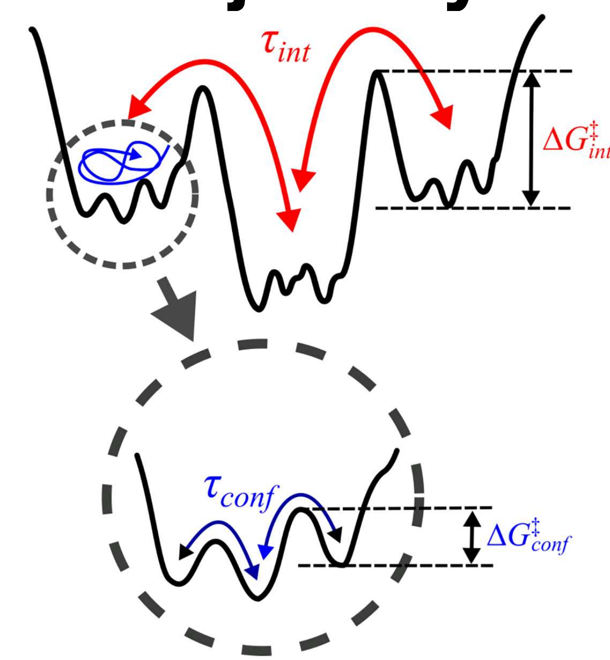

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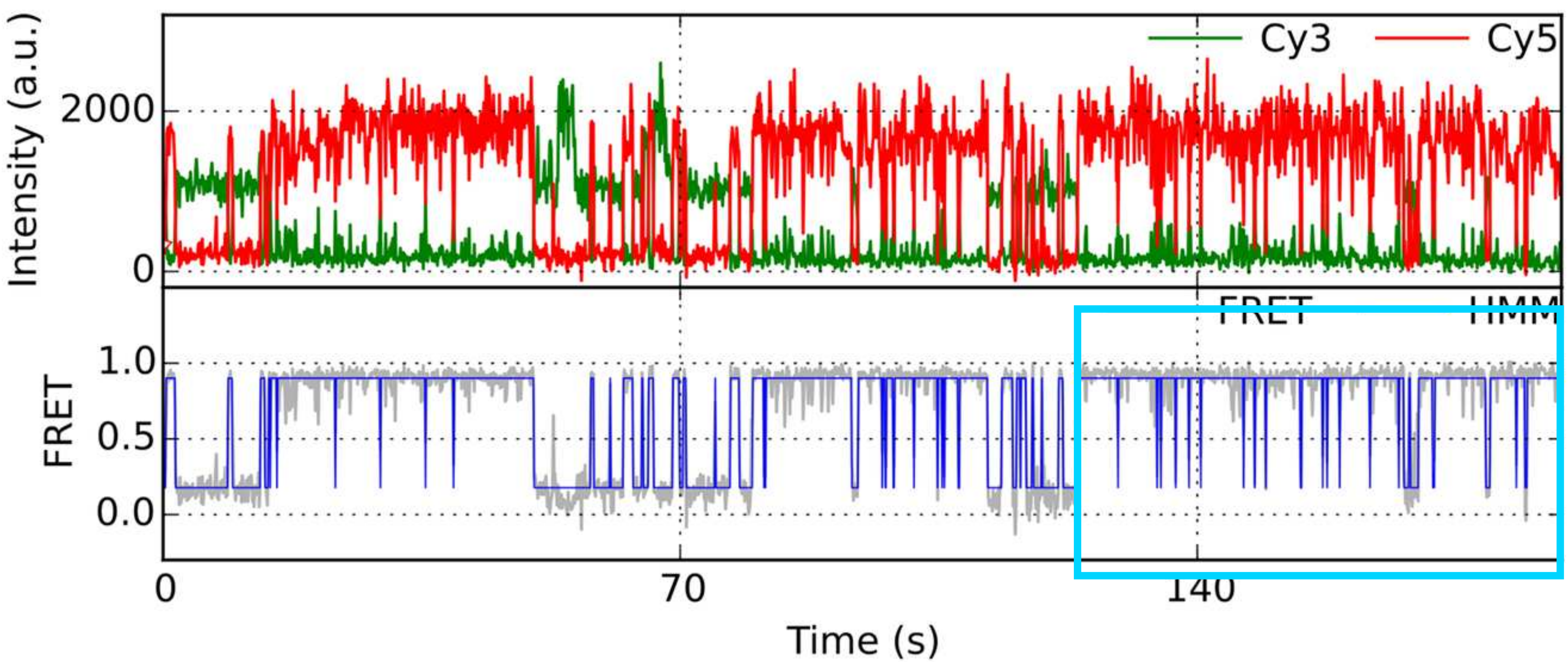

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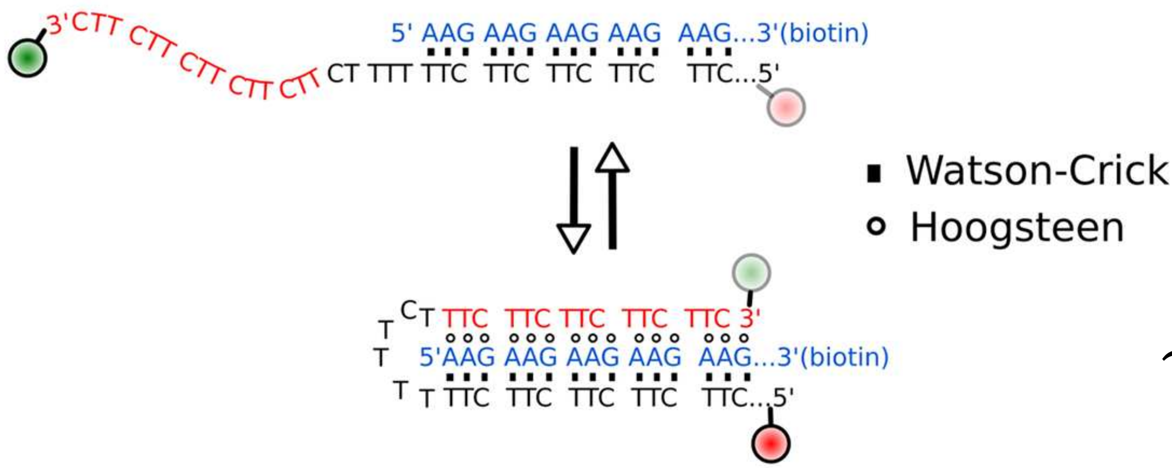

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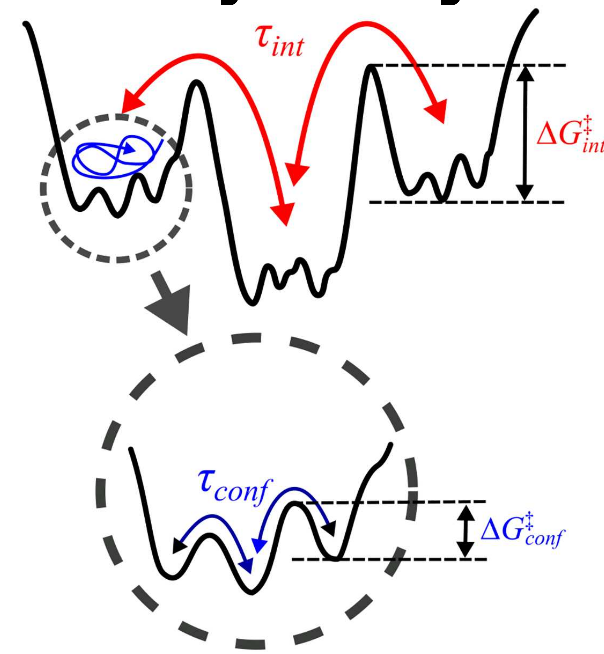

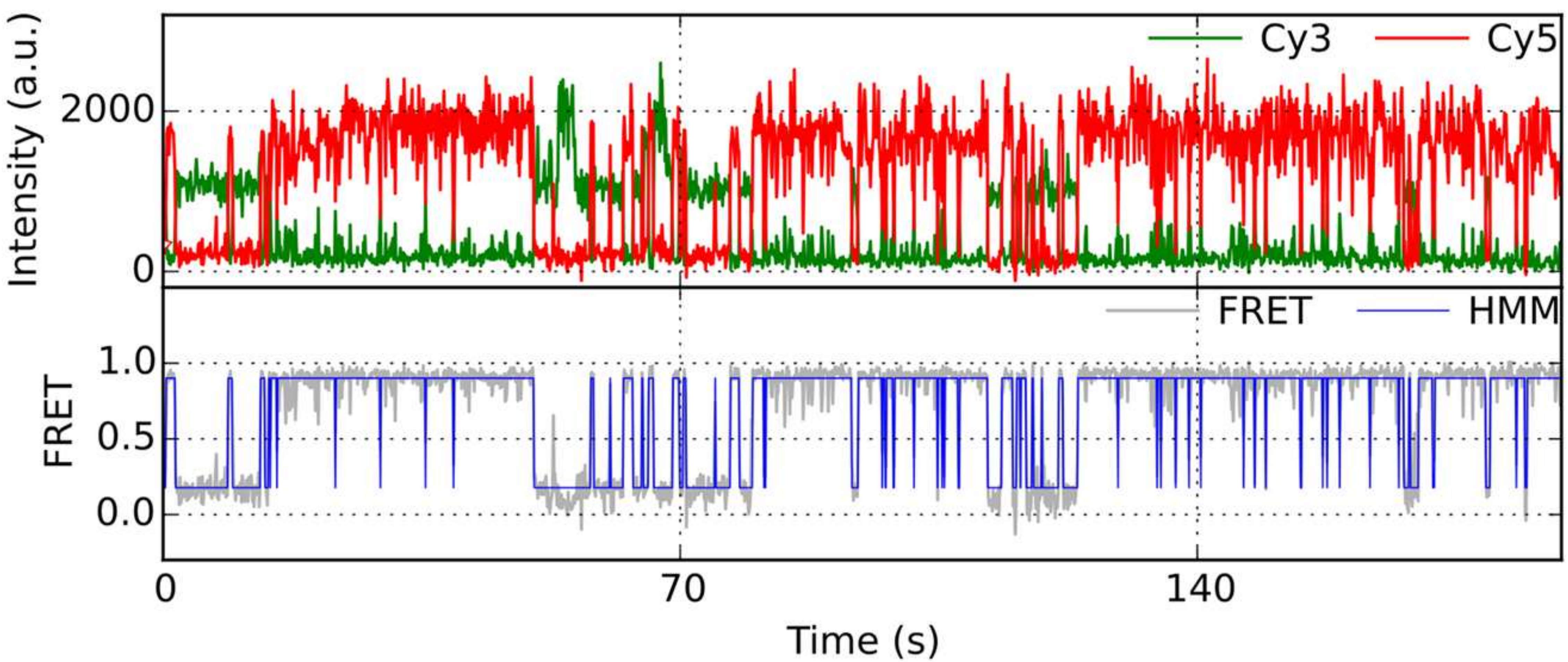

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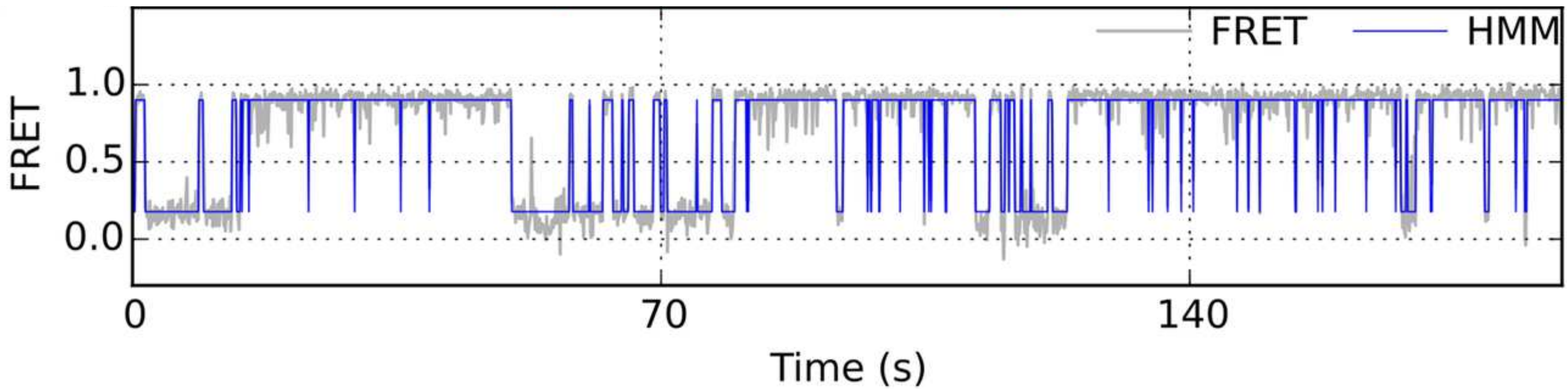
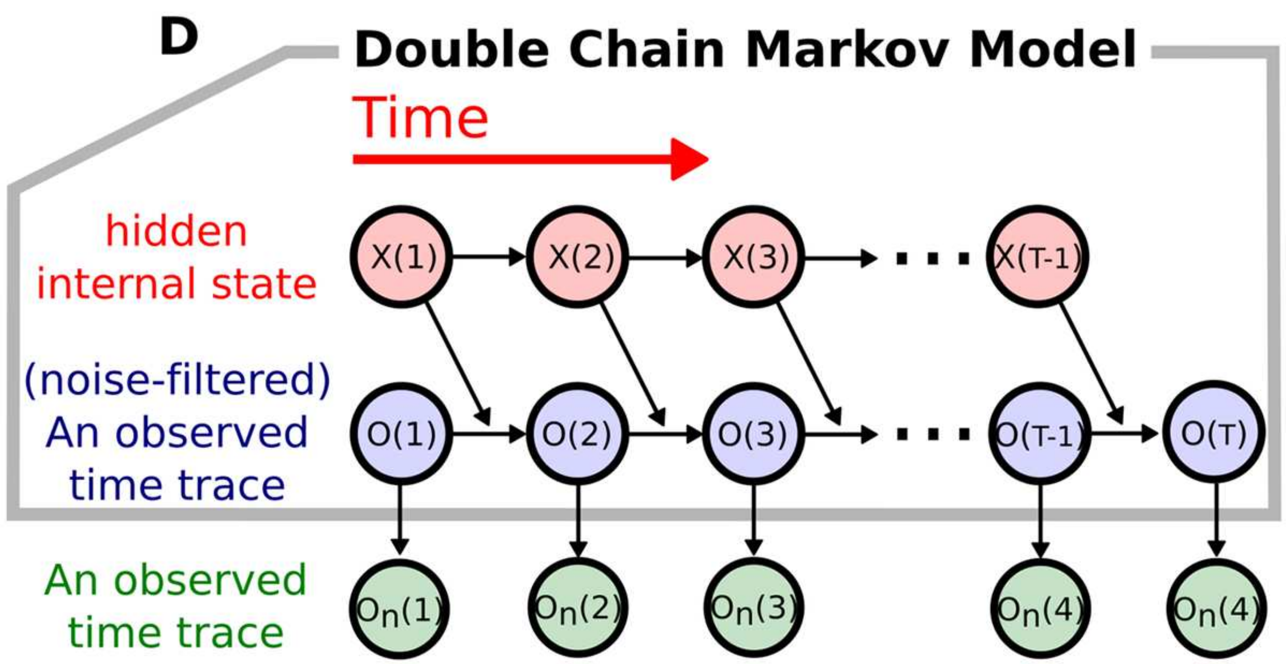


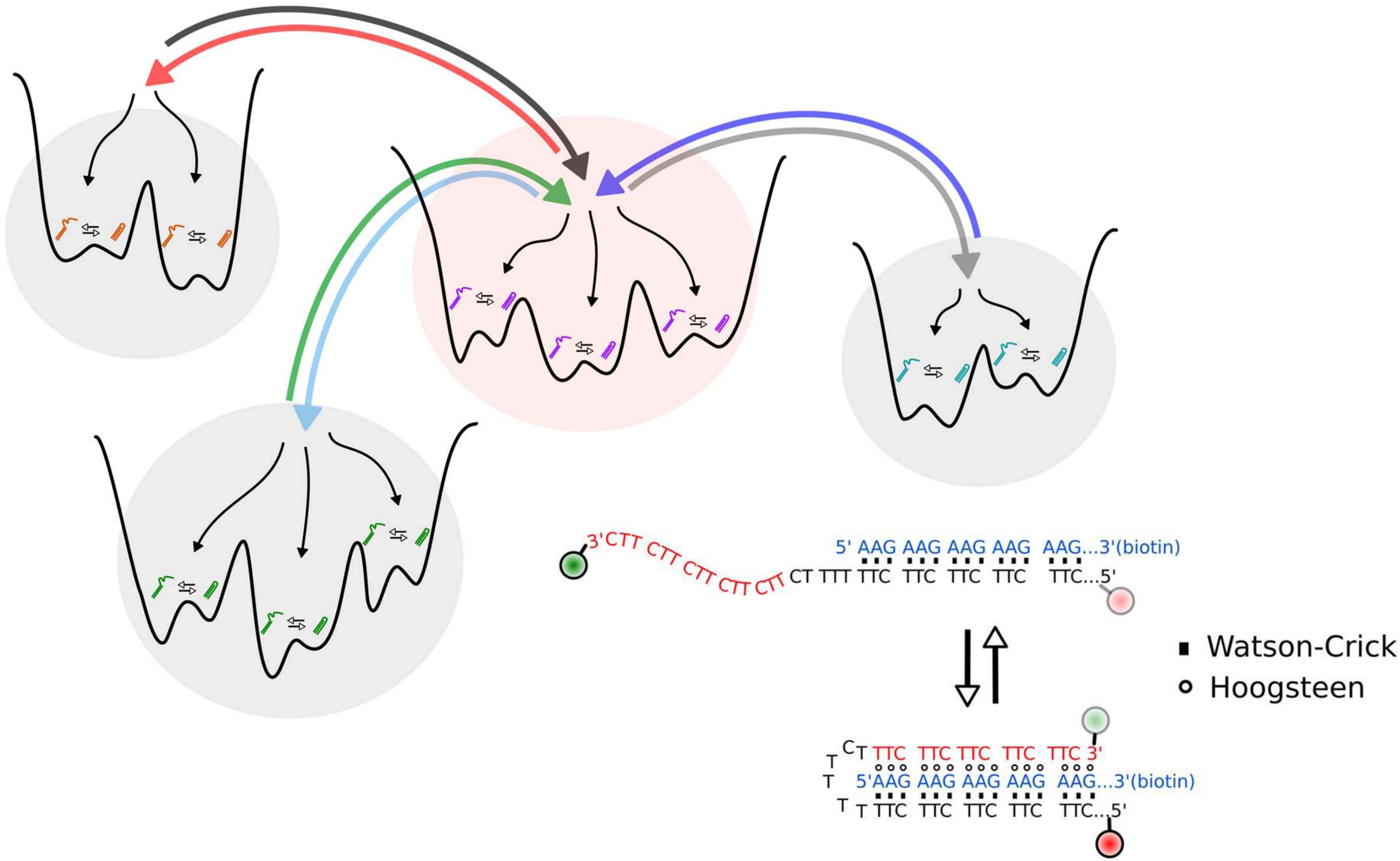


$$A = \begin{pmatrix} \gamma^{(1)\to(1)}\Delta t & \gamma^{(1)\to(2)}\Delta t \\ \gamma^{(2)\to(1)}\Delta t & \gamma^{(2)\to(2)}\Delta t \end{pmatrix}.$$

$$B^{(\mu)} = \begin{pmatrix} k^{(\mu)}_{1\to1}\Delta t & k^{(\mu)}_{1\to2}\Delta t & k^{(\mu)}_{1\to3}\Delta t \\ k^{(\mu)}_{2\to1}\Delta t & k^{(\mu)}_{2\to2}\Delta t & k^{(\mu)}_{2\to3}\Delta t \\ k^{(\mu)}_{3\to1}\Delta t & k^{(\mu)}_{3\to2}\Delta t & k^{(\mu)}_{3\to3}\Delta t \end{pmatrix}.$$

$$P(\boldsymbol{o}|K) = \int P(\boldsymbol{o}|\boldsymbol{\lambda})P(\boldsymbol{\lambda}|K)d\boldsymbol{\lambda} \qquad \text{where } \boldsymbol{\lambda} \equiv (\boldsymbol{\pi}, \boldsymbol{A}, \boldsymbol{B})$$

Goal : determine the most probable sequence of internal state and associated kinetic rates, $\{k^{(\mu)}_{a\to b}\}$ and $\{\gamma^{(\mu)\to(\nu)}\}$



6 kinetic pathways connecting 4 internal states

- Rate processes (parallel processes, kinetic partitioning)

- Types of disorder in dynamical processes :
  Quenched vs Dynamic disorder (fluctuating bottleneck model)

- Slow dynamics due to force-induced metastable intermediate

- Heterogeneity in biomolecular dynamics (component characterization, ergodic measure, ….)