Stochastic Processes in Biophysics (2017 Stat. Phys. Winter School)

***Nonequilibrium Statistical Mechanics*,**
Robert Zwanzig (2001) Oxford Univ. Press

- **Langevin eqn (low vs high friction)**
- **Langevin simulations (particles, polymer)** **Project 1 & 2**
- **Non-Markovian Langevin eqn. and FDT**
- **Fokker Planck eqn.**
- **First passage time problem (Survival prob. FPT distribution, MFPT)**
- **Kramers' rate (Escape rate from metastable state)**
- **Diffusion in a rough potential**
- **Dynamical processes in the presence of sink (Wilemski-Fixman formalism)**
- **Effect of dynamic disorder on rate processes.**
- **Theory for force spectroscopy (Bell, Evan Evans, Dudko, … Hyeon)**
- **Detecting dynamic disorder using force spectroscopy (dynamic disorder revisited)**

1928-2014

Langevin Equation

&

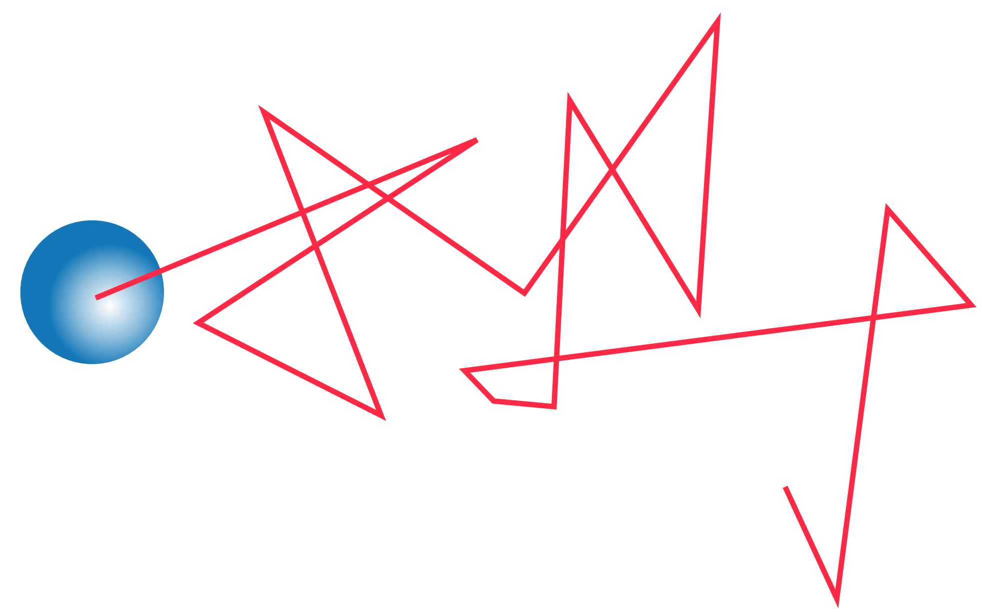
Simulations

Langevin equation

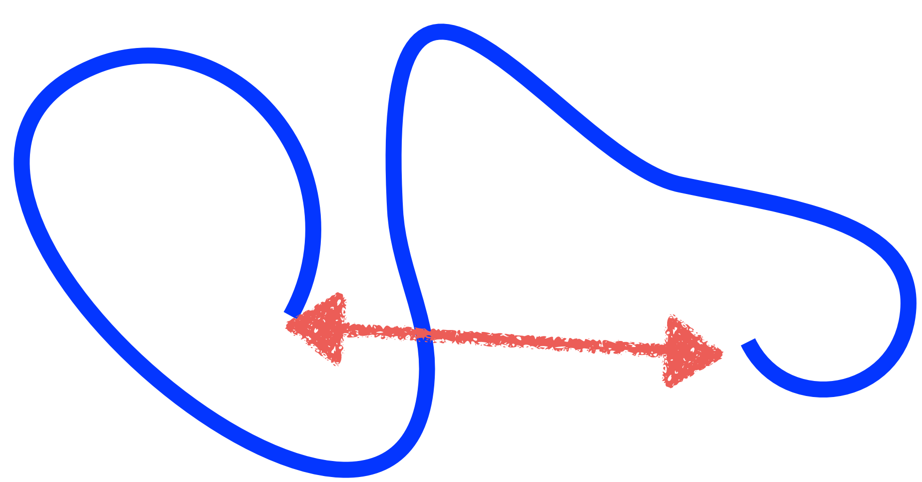
$$m\ddot{x} = -\zeta\dot{x} + \xi(t)$$

$$\langle \xi(t) \rangle = 0$$

$$\langle \xi(t)\xi(t') \rangle = 2B\delta(t - t')$$



$$m\ddot{\vec{R}} = -\zeta\dot{\vec{R}} - \vec{\nabla}U(R) + \vec{\xi}(t)$$



Langevin equation

$$m\ddot{x} = -\zeta\dot{x} + \xi(t)$$

$$\langle \xi(t) \rangle = 0$$

noise strength?

$$\langle \xi(t)\xi(t') \rangle = 2B\delta(t - t')$$

$$m\dot{v} = -\zeta v + \xi(t)$$

$$v(t) = e^{-(\zeta/m)\times t}v(0) + \frac{1}{m}\int_0^t d\tau e^{-(\zeta/m)\times(t-\tau)}\xi(\tau)$$

$$\langle (v(t))^2 \rangle = e^{-2(\zeta/m)\times t}\langle (v(0))^2 \rangle + \frac{2B}{m^2}\int_0^t d\tau_1 \int_0^t d\tau_2 e^{-(\zeta/m)(2t-\tau_1-\tau_2)}\delta(\tau_1 - \tau_2)$$

$$\langle (v(t))^2 \rangle = e^{-2(\zeta/m)\times t}\langle (v(0))^2 \rangle + \frac{2B}{m^2}\frac{m}{2\zeta}(1 - e^{-2\zeta/m\times t})$$

$$\langle v^2(\infty) \rangle = \frac{k_B T}{m} \qquad B = \zeta k_B T$$

Langevin equation

$$m\ddot{x} = -\zeta\dot{x} + \xi(t)$$

$$\langle \xi(t) \rangle = 0$$

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

$$v(t) = e^{-(\zeta/m)\times t}v(0) + \frac{1}{m}\int_0^t d\tau e^{-(\zeta/m)\times(t-\tau)}\xi(\tau)$$

vel. corr.

$$\langle v(t)v(0) \rangle = e^{-(\zeta/m)\times t}\langle (v(0))^2 \rangle \longrightarrow 0 \quad \left(t \gg \frac{m}{\zeta}\right)$$

MSD

$$\langle (\delta x(t))^2 \rangle = \int_0^t ds_1 \int_0^t ds_2 \langle v(s_1)v(s_2) \rangle \;\rightarrow \partial_t \langle (\delta x(t))^2 \rangle = 2\int_0^t ds \langle v(t)v(s) \rangle$$

HW 1: 1. do this algebra

2. show this explicitly using Langevin simulation

$$= \frac{m^2}{\zeta^2}(1 - e^{-(\zeta/m)t})^2\left(v_0^2 - \frac{k_BT}{m}\right) + 2\frac{k_BT}{\zeta}\left(t - \frac{m}{\zeta}(1 - e^{-\zeta/m\times t})\right) \xrightarrow{t\,\rightarrow\,\infty} 2Dt$$

$$\int_0^\infty dt \langle v(t)v(0) \rangle = \frac{k_BT}{\zeta} = D = \frac{1}{3}\int_0^\infty dt \langle \mathbf{v}(t) \cdot \mathbf{v}(0) \rangle$$

Ans 1 Langevin equation

$$m\ddot{x} = -\zeta\dot{x} + \xi(t)$$

$$\langle \xi(t) \rangle = 0$$

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

$$v(t) = e^{-(\zeta/m)\times t} v(0) + \frac{1}{m}\int_0^t d\tau e^{-(\zeta/m)\times(t-\tau)}\xi(\tau)$$

$$\langle (\delta x(t))^2 \rangle = \int_0^t ds_1 \int_0^t ds_2 \langle v(s_1) v(s_2) \rangle$$

$$= \int_0^t ds_1 \int_0^t ds_2 e^{-(\zeta/m)(s_1+s_2)} \langle (v(0))^2 \rangle$$

$$+ \frac{1}{m^2}\int_0^t ds_1 \int_0^t ds_2 \int_0^{s_1} d\tau_1 \int_0^{s_2} d\tau_2 e^{-(\zeta/m)(s_1+s_2-\tau_1-\tau_2)} \langle \xi(\tau_1)\xi(\tau_2) \rangle$$

$$= \frac{m}{2\zeta}\left(e^{-\zeta|s_1-s_2|/m} - e^{-\zeta(s_1+s_2)/m}\right)$$

$$= \frac{m^2}{\zeta^2}(1 - e^{-(\zeta/m)t})^2 \langle (v(0))^2 \rangle + \frac{2\zeta k_B T}{m^2}\int_0^t ds_1 \int_0^t ds_2 \boxed{\int_0^{\min(s_1,s_2)} d\tau e^{-(\zeta/m)(s_1+s_2-2\tau)}}$$

$$= \frac{m^2}{\zeta^2}(1 - e^{-(\zeta/m)t})^2 \left(v_0^2 - \frac{k_B T}{m}\right) + 2\frac{k_B T}{\zeta}\left(t - \frac{m}{\zeta}(1 - e^{-\zeta/m\times t})\right) \longrightarrow 2Dt$$

Langevin equation (high damping or $\frac{t}{(m/\zeta)} \gg 1$)

$$\cancel{m\ddot{x}} = -\zeta \dot{x} + \xi(t)$$

$$\langle \xi(t) \rangle = 0$$

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

$$\dot{x}(t) = \xi(t)/\zeta$$

$$x(t) - x(0) = \frac{1}{\zeta}\int_0^t d\tau \xi(\tau)$$

$$\begin{aligned}
\langle (\delta x(t))^2 \rangle &= \frac{1}{\zeta^2}\int_0^t d\tau \int_0^t d\tau' \langle \xi(\tau)\xi(\tau') \rangle \\
&= \frac{2k_B T}{\zeta}\int_0^t d\tau \int_0^t d\tau' \delta(\tau - \tau') \\
&= 2Dt
\end{aligned}$$

Langevin Simulation (at low friction, $\zeta t/m \ll 1$: MD)

$$m\ddot{x}_i = -\zeta \dot{x}_i + F_{i,c}(t) + \Gamma_i(t) = F_i(t) \qquad F_{i,c}(x_i(t)) = -\frac{dU(\{x\})}{dx_i}$$

$$\langle \Gamma_i(t) \rangle = 0 \qquad \langle \Gamma_i(t)\Gamma_j(t') \rangle = 2\zeta k_B T \delta_{ij}\delta(t-t')$$

Algorithm

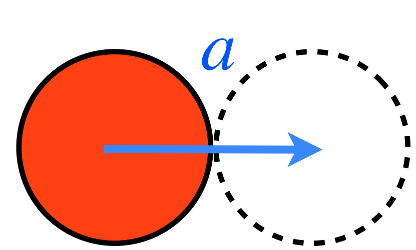
$$\zeta = 0.05 m \tau_L^{-1} \qquad h = 0.0025 \tau_L \qquad P(\Gamma_i) \sim \exp\left(-\frac{\Gamma_i^2}{4\zeta k_B T / h}\right)$$

position: $x_i(t+h) = x_i(t) + \dot{x}_i(t)h + \frac{F_i(t)}{2m}h^2$

velocity: $\dot{x}_i(t+h) = \left(1 - \frac{h\zeta}{2m}\right)\left(1 - \frac{h\zeta}{2m} + \left(\frac{h\zeta}{2m}\right)^2\right)\dot{x}_i(t)$

$$+ \frac{h}{2m}\left(1 - \frac{h\zeta}{2m} + \left(\frac{h\zeta}{2m}\right)^2\right)\left[F_{i,c}(t+h) + \Gamma_i(t+h) + F_{i,c}(t) + \Gamma_i(t)\right] + \cdots$$

$$\frac{3k_BT}{m} = \frac{1}{N}\sum_i \left(\dot{x}_i^2 + \dot{y}_i^2 + \dot{z}_i^2\right)$$



τ_L : intrinsic time scale

$$\frac{ma}{\tau_L^2} \sim \frac{\varepsilon}{a} \qquad \tau_L = \left(\frac{ma^2}{\varepsilon}\right)^{1/2}$$

Verlet algorithm (derivation)

$$m\ddot{x}_i = -\zeta \dot{x}_i + F_{i,c}(t) + \Gamma_i(t) = F_i(t)$$

$$x_i(t+h) = x_i(t) + \dot{x}_i(t)h + \frac{F_i(t)}{2m}h^2$$ **position**

$$\dot{x}_i(t+h) = \dot{x}_i(t) + \ddot{x}_i(t)h + \frac{\boxed{\dot{F}_i(t)}}{2m}h^2$$ **velocity**

$$\ddot{x}_i(t) = -\frac{\zeta}{m}\dot{x}_i(t) + \frac{1}{m}\left(F_{i,c}(t) + \Gamma_i(t)\right)$$

$$\dot{F}_i(t) = \frac{1}{h}\left(F_i(t+h) - F_i(t)\right)$$

$$= \frac{1}{h}\left(-\zeta\dot{x}_i(t+h) + F_{i,c}(t+h) + \Gamma_i(t+h) + \zeta\dot{x}_i(t) - F_{i,c}(t) - \Gamma_i(t)\right)$$

$$\dot{x}_i(t+h) = \dot{x}_i(t) - \frac{\zeta h}{m}\dot{x}_i(t) + \frac{h}{m}\left(F_{i,c}(t) + \Gamma_i(t)\right)$$
$$+ \frac{h}{2m}\left(-\zeta\dot{x}_i(t+h) + F_{i,c}(t+h) + \Gamma_i(t+h) + \zeta\dot{x}_i(t) - F_{i,c}(t) - \Gamma_i(t)\right)$$

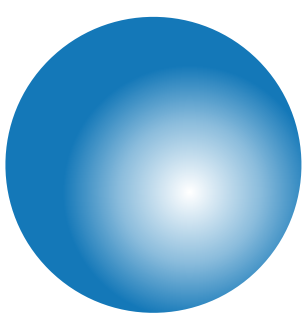
$$\left(1 + \frac{\zeta h}{2m}\right)\dot{x}_i(t+h) = \left(1 - \frac{\zeta h}{2m}\right)\dot{x}_i(t) + \frac{h}{2m}\left(F_{i,c}(t+h) + \Gamma_i(t+h) + F_{i,c}(t) + \Gamma_i(t)\right)$$

$$\dot{x}_i(t+h) = \left(1 - \frac{h\zeta}{2m}\right)\left(1 - \frac{h\zeta}{2m} + \left(\frac{h\zeta}{2m}\right)^2\right)\dot{x}_i(t)$$
$$+ \frac{h}{2m}\left(1 - \frac{h\zeta}{2m} + \left(\frac{h\zeta}{2m}\right)^2\right)\left[F_{i,c}(t+h) + \Gamma_i(t+h) + F_{i,c}(t) + \Gamma_i(t)\right] + \cdots$$

Code for low-friction LD

```
main(){
  initialize();
  step=0;
  while(step<stepsim){
    iteration();
    step++;
  }
}
```

```
#include "header.h"
#define halfh   h/2.0
#define vfact   h*(1.0-zeta*halfh)
#define ffact   h*halfh
#define aux1    halfh*(1.0-h*zeta/2.0)
#define aux2    (1.0-h*zeta/2+(h*zeta)*(h*zeta)/4.0)/h
extern void rforce(), force(), update();
void iteration(){
  int i;
  for(i=1;i<=L;i++){
    C[i].Dx=vfact*C[i].vx+ffact*C[i].fx;
    C[i].Dy=vfact*C[i].vy+ffact*C[i].fy;
    C[i].Dz=vfact*C[i].vz+ffact*C[i].fz;
    C[i].x=C[i].x+C[i].Dx;
    C[i].y=C[i].y+C[i].Dy;
    C[i].z=C[i].z+C[i].Dz;
  }
  rforce();
  force();
  for(i=1;i<=L;i++){
    C[i].vx=aux2*C[i].Dx+aux1*C[i].fx;
    C[i].vy=aux2*C[i].Dy+aux1*C[i].fy;
    C[i].vz=aux2*C[i].Dz+aux1*C[i].fz;
  }
  record_something();
}
```



$$x_i(t+h) = x_i(t) + \dot{x}_i(t)h + \frac{F_i(t)}{2m}h^2$$

$$\dot{x}_i(t+h) = \left(1-\frac{h\zeta}{2m}\right)\left(1-\frac{h\zeta}{2m}+\left(\frac{h\zeta}{2m}\right)^2\right)\dot{x}_i(t)$$

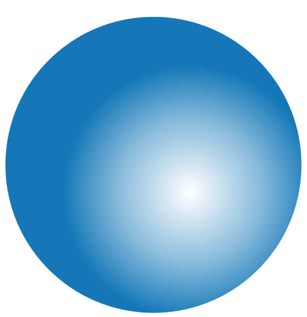
$$+\frac{h}{2m}\left(1-\frac{h\zeta}{2m}+\left(\frac{h\zeta}{2m}\right)^2\right)\left[F_{i,c}(t+h)+\Gamma_i(t+h)+F_{i,c}(t)+\Gamma_i(t)\right]+O\left(\left(\frac{h\zeta}{2m}\right)^4\right)$$

Code for low-friction LD

```
main(){
   initialize();
   step=0;
   while(step<stepsim){
      iteration();
      step++;
   }
}
```

```
void rforce(){
  double var;
  var=sqrt(2.0*temp*zeta/h);
  for(i=1;i<=L;i++){
    C[i].fx=var*gasdev(&mseed);
    C[i].fy=var*gasdev(&mseed);
    C[i].fz=var*gasdev(&mseed);
  }
}
```

$$\xi_\alpha = \sqrt{\frac{2\zeta k_B T}{h}} \mathcal{N}(0,1)$$



Langevin Simulation (at high friction, $\zeta t/m \gg 1$: BD simulation)

$$\cancel{m\ddot{x}_i} = -\zeta \dot{x}_i + F_{i,c}(t) + \Gamma_i(t) = F_i(t) \qquad F_{i,c}(x_i(t)) = -\frac{dU(\{x\})}{dx_i}$$

$$\longrightarrow \boxed{\zeta \dot{x}_i = F_{i,c}(t) + \Gamma_i(t)}$$

$$\langle \Gamma_i(t) \rangle = 0$$

$$\langle \Gamma_i(t) \Gamma_j(t') \rangle = 2\zeta k_B T \delta_{ij} \delta(t - t')$$

Algorithm

position:

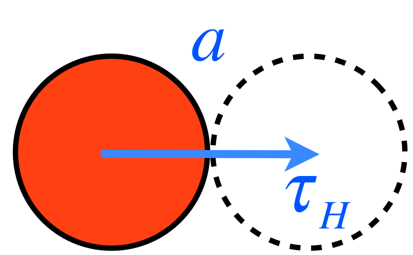
$$x_i(t+h) = x_i(t) + (F_{i,c}(t) + \Gamma_i(t)) \frac{h}{\zeta}$$

$$\zeta = (50 - 100) m \tau_L^{-1}$$

$$h = 0.02 \tau_L$$

$$P(\Gamma_i) \sim \exp\left(-\frac{\Gamma_i^2}{4\zeta k_B T / h} \right)$$

$$\left\langle (\delta x)^2 \right\rangle = 2Dh = 2\frac{k_B T}{\zeta} h$$

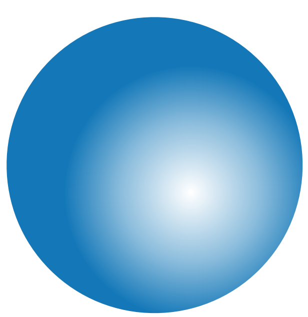


τ_H : Brownian time

$$\zeta \frac{a}{\tau_H} \sim \frac{kT}{a} \qquad \tau_H = \frac{\zeta a^2}{k_B T} = \frac{\zeta (\tau_L^2 / m \times \varepsilon)}{k_B T} = \left[\frac{\zeta (\tau_L / m) \varepsilon}{k_B T} \right] \tau_L$$

Code for high friction LD (BD)

```
main(){
   initialize();
   step=0;
   while(step<stepsim){
      iteration();
      step++;
   }
}
```



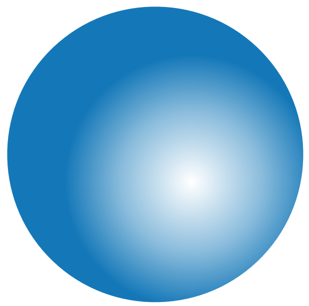
```
void iteration(){
  for(i=1;i<=L;i++){
    C[i].x=C[i].x+C[i].fx*h/zeta;
    C[i].y=C[i].y+C[i].fy*h/zeta;
    C[i].z=C[i].z+C[i].fz*h/zeta;
  }
  rforce();
  force();
  record_something();
}
```

$$x(t+h) = x(t) + f_x(t)/\zeta \times h$$

```
void rforce(){
  double var;
  var=sqrt(2.0*temp*zeta/h);
  for(i=1;i<=L;i++){
    C[i].fx=var*gasdev(&mseed);
    C[i].fy=var*gasdev(&mseed);
    C[i].fz=var*gasdev(&mseed);
  }
}
```

$$\xi_\alpha = \sqrt{\frac{2\zeta k_B T}{h}} \mathcal{N}(0,1)$$

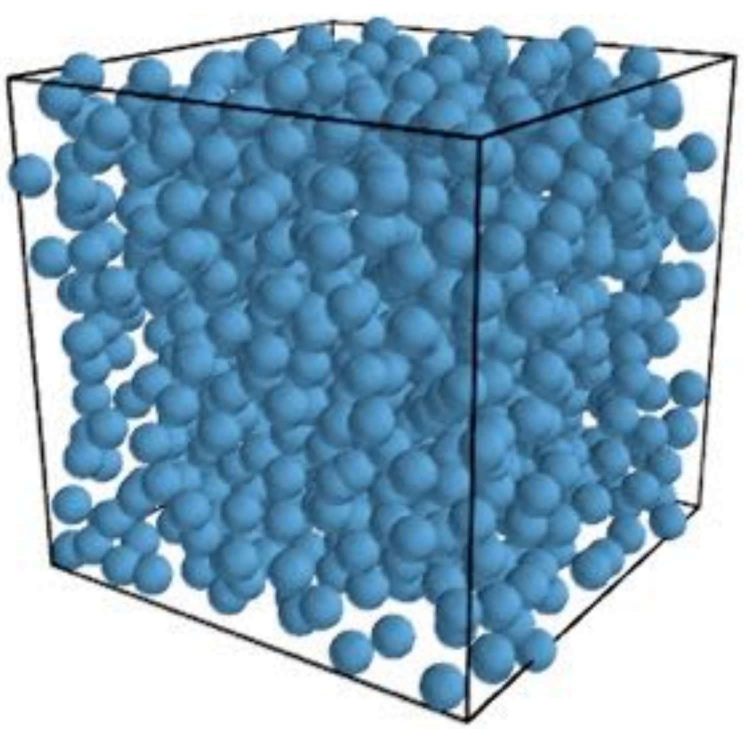
Single particle



$$U_{\text{int}}(\vec{r}_1) = 0$$

→translational motion only

Many particles (Lennard-Jones fluid)



$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i<j} \varepsilon\left((\sigma / r_{i,j})^{12} - 2(\sigma / r_{i,j})^{6}\right)$$

Alder, B. J. & Wainwright, T. E.
Phase transition for a hard sphere system.
J. Chem. Phys. 27, 1208–1209 (1957).

Project 2

Simulate and obtain

$$C(t) = \langle \mathbf{V}(t) \cdot \mathbf{V}(0) \rangle / \langle \mathbf{V}^2(0) \rangle$$

$$D(\phi) = \frac{1}{3} \int_0^\infty dt \langle \mathbf{V}(t) \cdot \mathbf{V}(0) \rangle (\phi)$$

and show

$$C(t) \to t^{-3/2}$$

(hydrodynamic tail)

and discuss freezing volume fraction

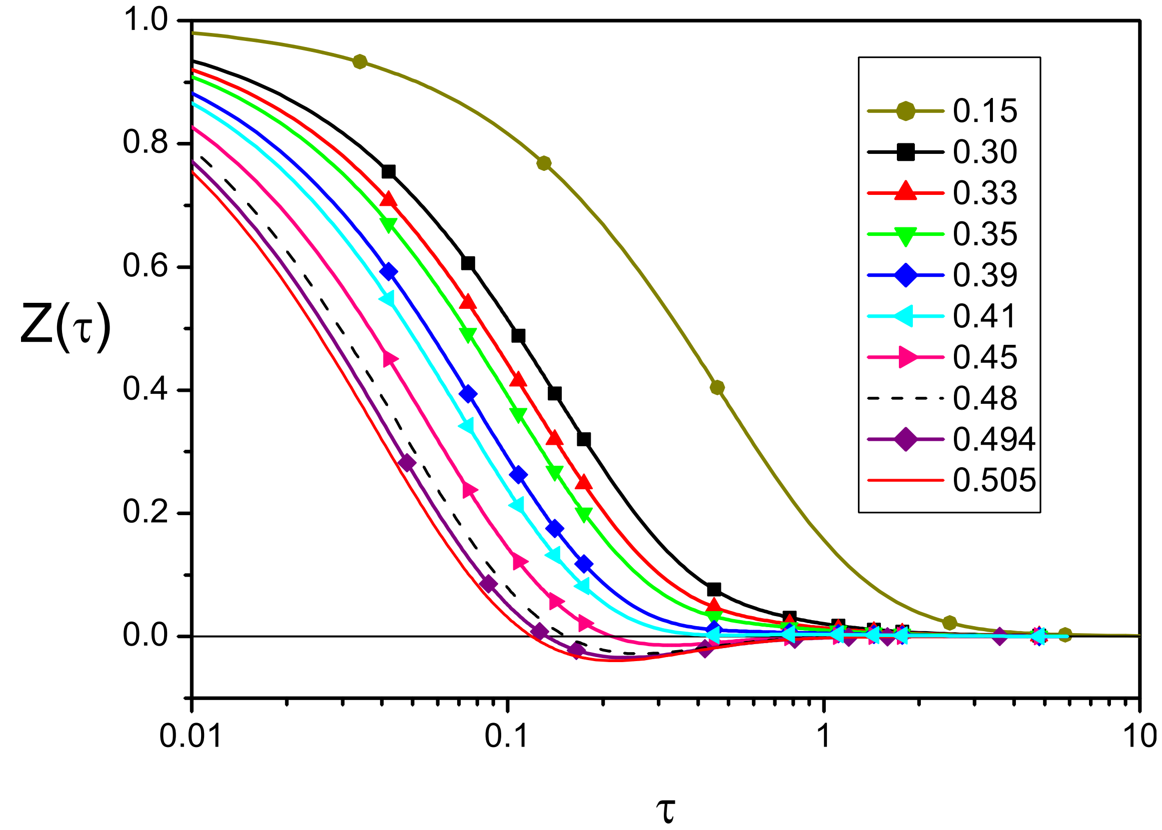
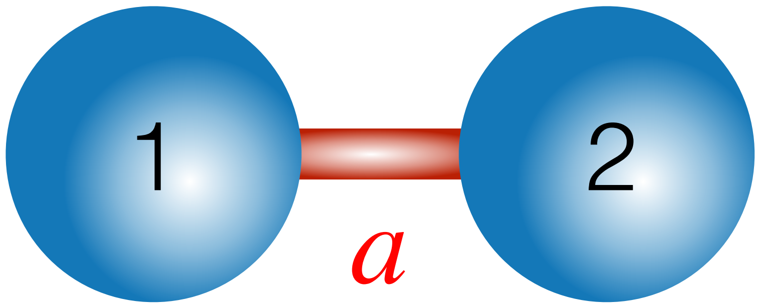


FIG. 1 (color online). A plot of the velocity autocorrelation function $Z(\tau)$ versus $\log\tau$ (symbols are defined in the legend), calculated from one component hard-sphere molecular dynamics simulations of fluids at various volume fractions ϕ = (volume of all the spheres divided by the total system volume). For $\phi \geq 0.45$ the VAF becomes negative, so in order to expose the long-time behavior, double logarithmic plots of $|Z(\tau)|$ are needed (see Fig. 2).

Dimer $\rightarrow$ bond stretching



$$U_{\text{int}}(\vec{r}_1, \vec{r}_2) = \frac{k_r}{2}(r_{1,2} - a)^2$$

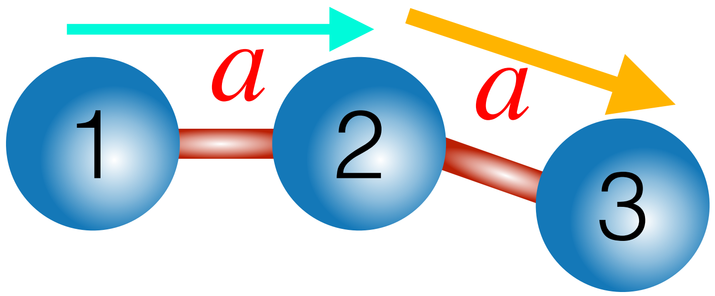
$$r_{1,2} = \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2}$$

$$f_{1,x} = -\frac{\partial U}{\partial x_1} = -\frac{dU}{dr_{1,2}}\frac{dr_{1,2}}{dx_1}$$

$$= -k_r(r_{1,2} - a)\frac{(x_1 - x_2)}{r_{1,2}}$$

$$f_{2,x} = -f_{1,x}$$

Trimer →bond stretching, bending



$$U_{int}(\vec{r}_1,\vec{r}_2,\vec{r}_3) = U_{\text{bond}}(\vec{r}_1,\vec{r}_2,\vec{r}_3) + U_{\text{bend}}(\vec{r}_1,\vec{r}_2,\vec{r}_3)$$

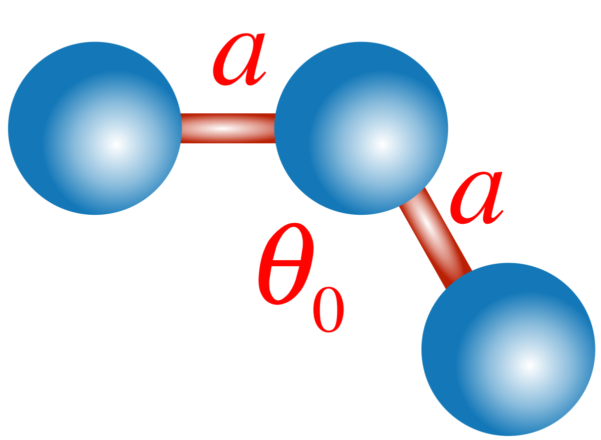
$$U_{\text{bond}}(\vec{r}_1,\vec{r}_2,\vec{r}_3) = \frac{k_r}{2}\left[(r_{1,2}-a)^2 + (r_{2,3}-a)^2\right]$$

$$U_{\text{bend}}(\vec{r}_1,\vec{r}_2,\vec{r}_3) = -k_a(\hat{n}_{1,2}\cdot\hat{n}_{2,3}) = -k_a\frac{\vec{r}_{1,2}\cdot\vec{r}_{2,3}}{|\vec{r}_{1,2}||\vec{r}_{2,3}|} = -k_a\cos\theta \approx k_a\theta^2/2 + \text{const}$$

$$f_{1,x} = -\frac{\partial U_{\text{bend}}}{\partial x_1} = -k_a\left(-\frac{(x_3-x_2)}{|\vec{r}_{1,2}||\vec{r}_{2,3}|} + \frac{\vec{r}_{1,2}\cdot\vec{r}_{2,3}}{|\vec{r}_{1,2}|^2|\vec{r}_{2,3}|}\frac{(x_2-x_1)}{|\vec{r}_{1,2}|}\right)$$

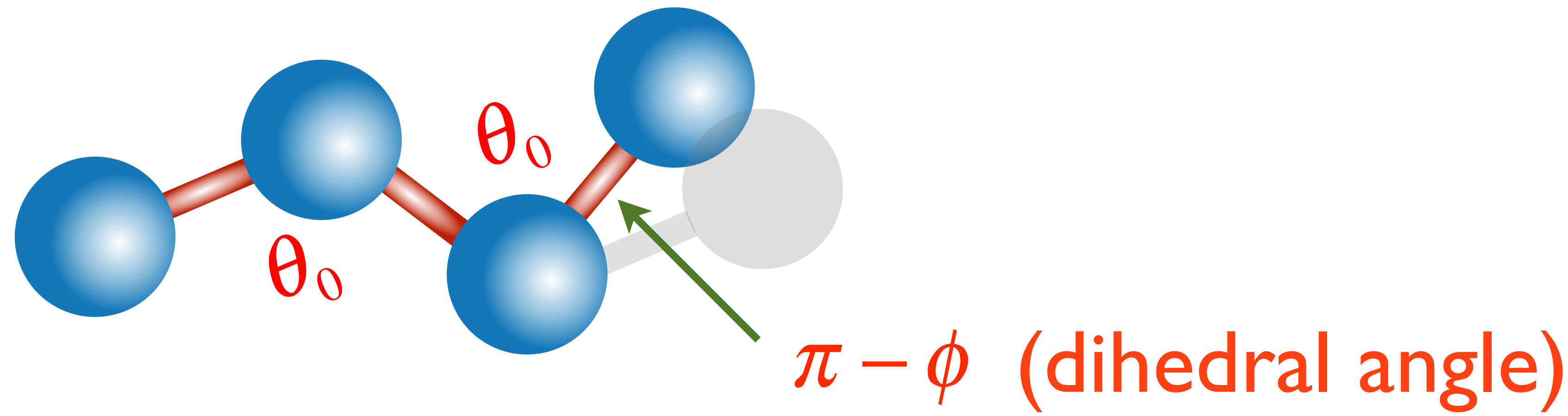
$$f_{3,x} = -\frac{\partial U_{\text{bend}}}{\partial x_3} = -k_a\left(\frac{(x_2-x_1)}{|\vec{r}_{1,2}||\vec{r}_{2,3}|} - \frac{\vec{r}_{1,2}\cdot\vec{r}_{2,3}}{|\vec{r}_{1,2}||\vec{r}_{2,3}|^2}\frac{(x_3-x_2)}{|\vec{r}_{2,3}|}\right)$$

$$f_{2,x} = -\frac{\partial U_{\text{bend}}}{\partial x_2} = -f_{1,x} - f_{3,x}$$



$$U_{\text{int}}(\vec{r}_1,\vec{r}_2,\vec{r}_3) = \sum_{i=1}^{2}\frac{k_r}{2}(r_{i,i+1}-a)^2 + \frac{k_\theta}{2}(\theta-\theta_0)^2$$

N=4

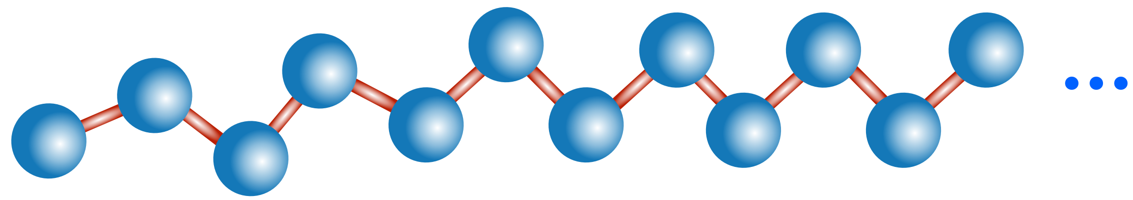


$$U_{\text{int}}(\vec{r}_1,\vec{r}_2,\vec{r}_3,\vec{r}_4)=\sum_{i=1}^{3}\frac{k_r}{2}(r_{i,i+1}-a)^2+\sum_{i=1}^{2}\frac{k_\theta}{2}(\theta_i-\theta_0)^2+\sum_{n=1,3}K_\phi\left(1+\cos\left(n\phi-\delta\right)\right)$$

→bond-stretching, bending, torsion

⋮

Polymer (N>>1)



$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2$$

Gaussian chain (random flight chain)

Freely jointed chain $(k_r \gg 1)$

$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2 - \sum_{i=1}^{N-2} k_a \hat{r}_{i,i+1} \cdot \hat{r}_{i+1,i+2}$$

Semiflexible chain

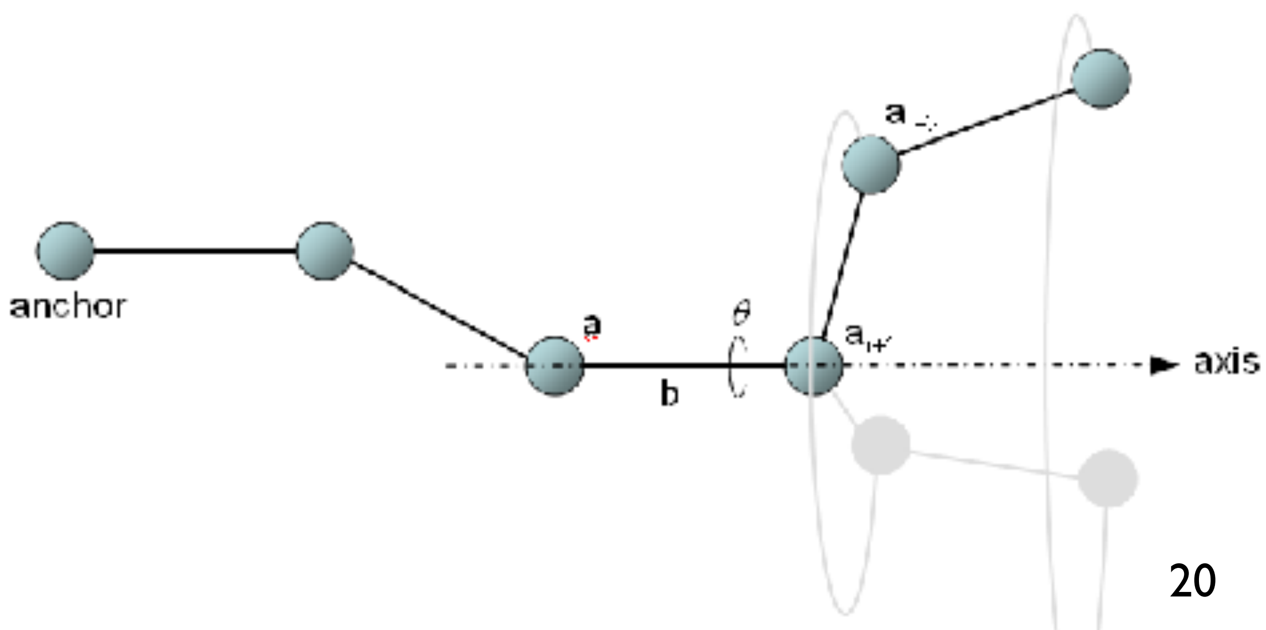
$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2 + \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \varepsilon \left(\frac{\sigma}{r_{i,j}} \right)^{12}$$

Self-avoiding chain

Code for simulation

```
main(){
   initialize();
   step=0;
   while(step<stepsim){
      calc_force();
      calc_random_force();
      position_update();
      step++;
   }
}
```

```
calc_force(){
   bond();
   angle();
   torsion();
      :
      :
   LJ();
   electrostatic();
}
```



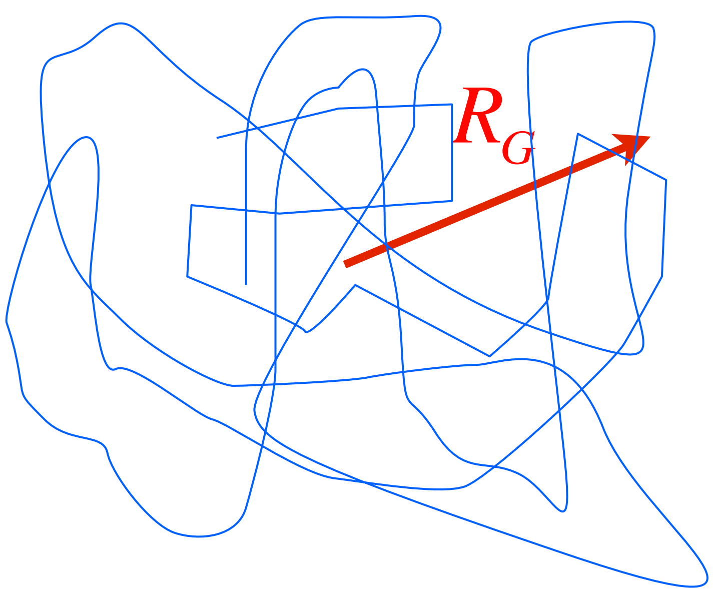
$$U_{\mathrm{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2 + \boxed{\varepsilon_h \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left[\left(\frac{\sigma}{r_{i,j}} \right)^{12} - 2\left(\frac{\sigma}{r_{i,j}} \right)^{6} \right]} + \boxed{\varepsilon_l \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left(\frac{\sigma}{r_{i,j}} \right)^{12}}$$

attraction (A) repulsion (R)

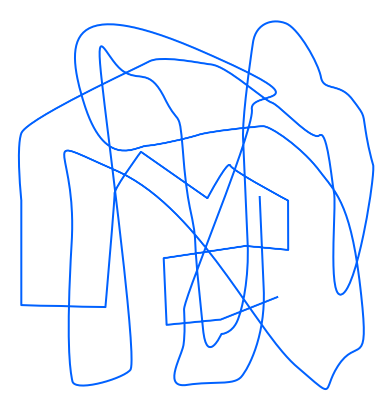
A<<R
Good solvent

A≈R
θ

A>>R
poor solvent



$R_G \sim N^{0.58}$



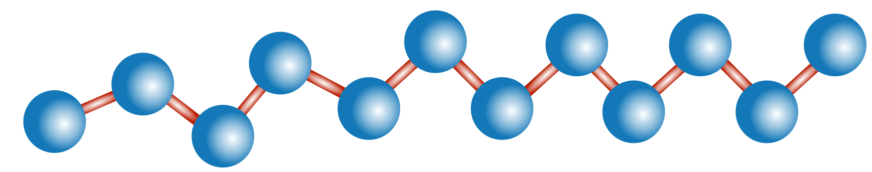
$R_G \sim N^{1/2}$

$R_G \sim N^{1/3}$

Gaussian Phantom chain

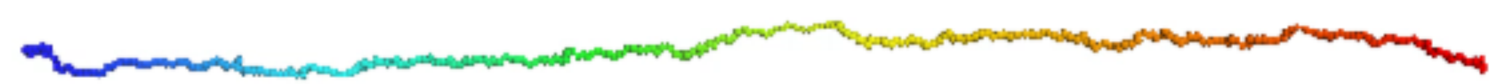
Flexible polymer at θ-condition

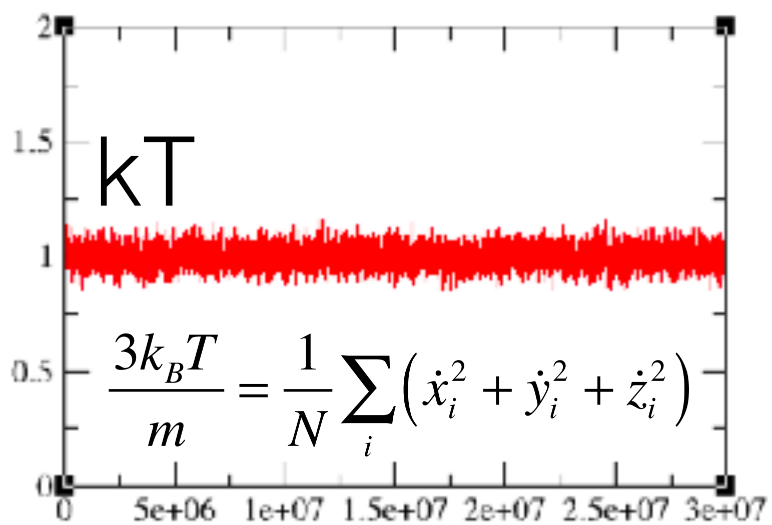
$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2$$

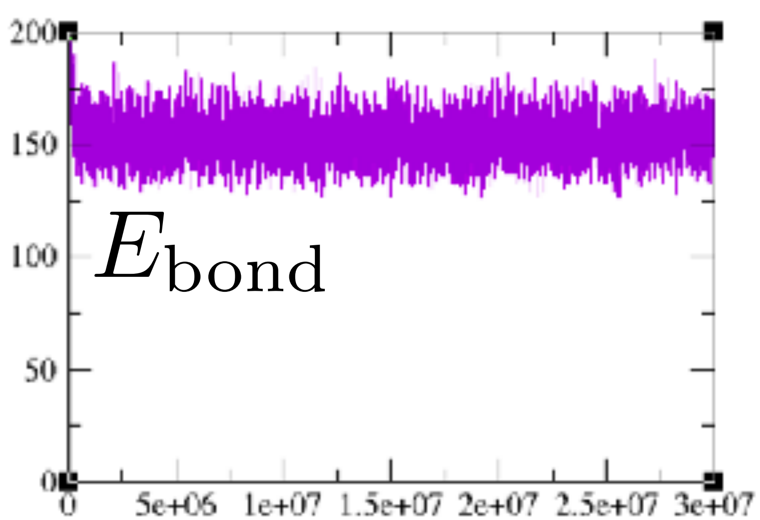


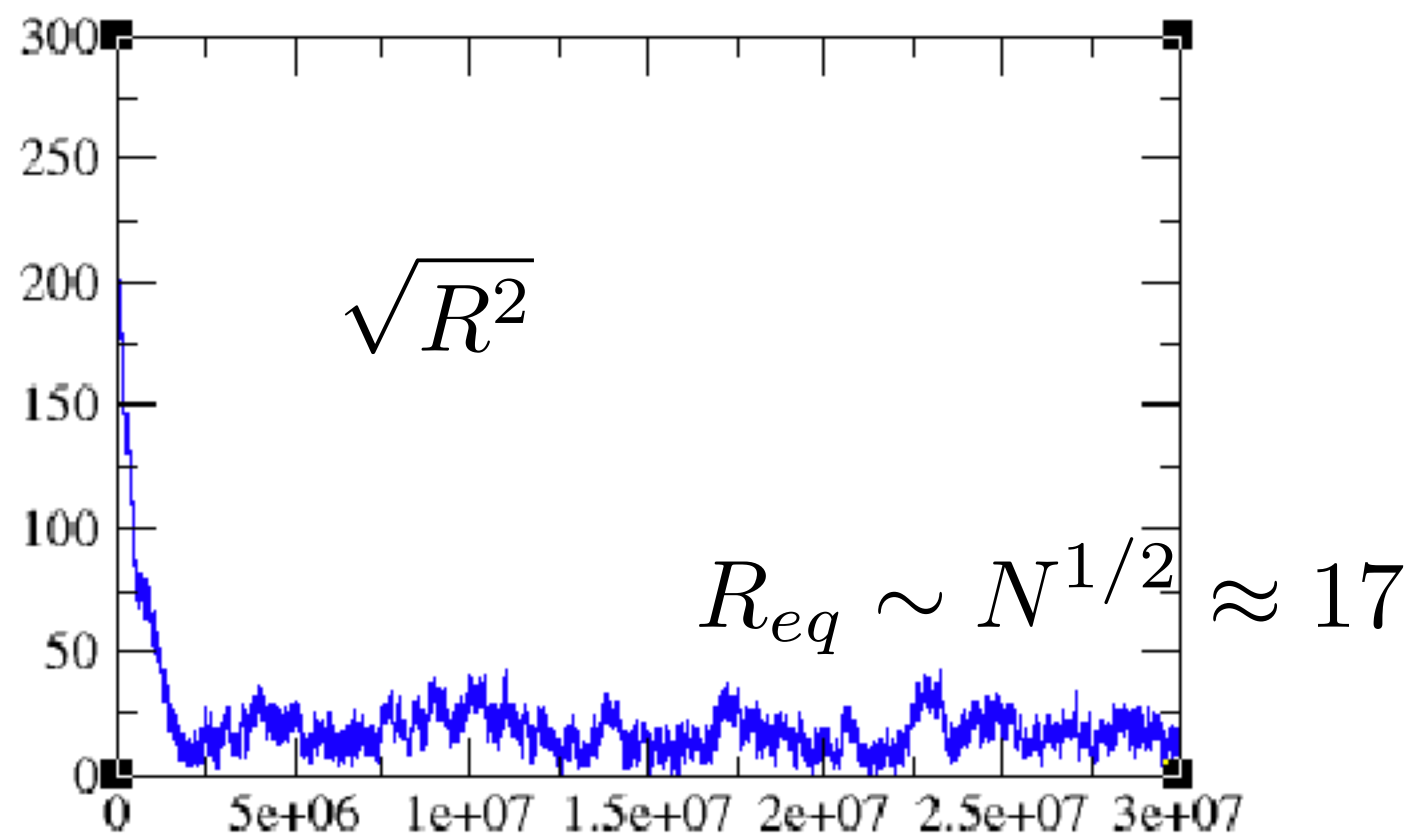
$N = 300$

$$\Delta F = \underbrace{\Delta E}_{=0} - T\underbrace{\Delta S}_{>0}$$







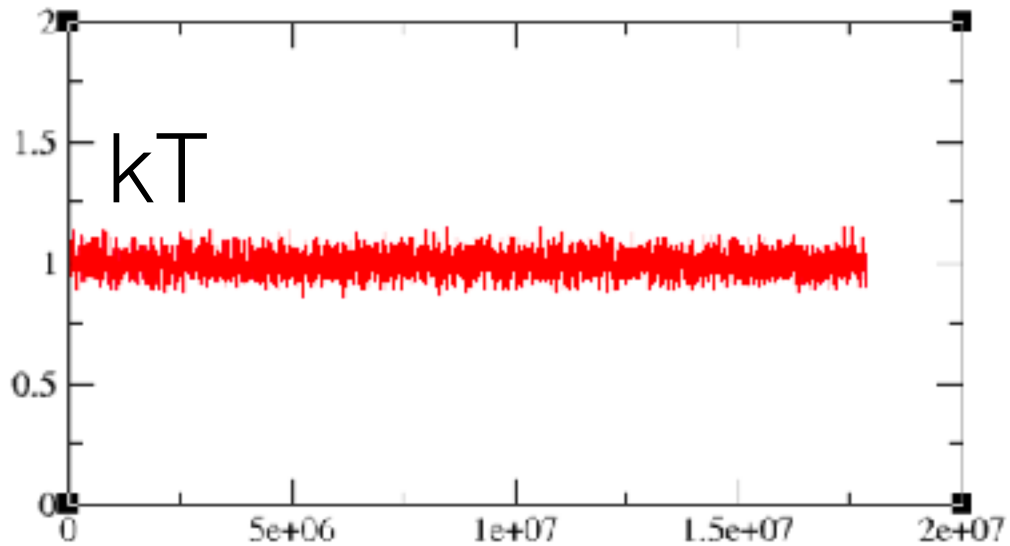


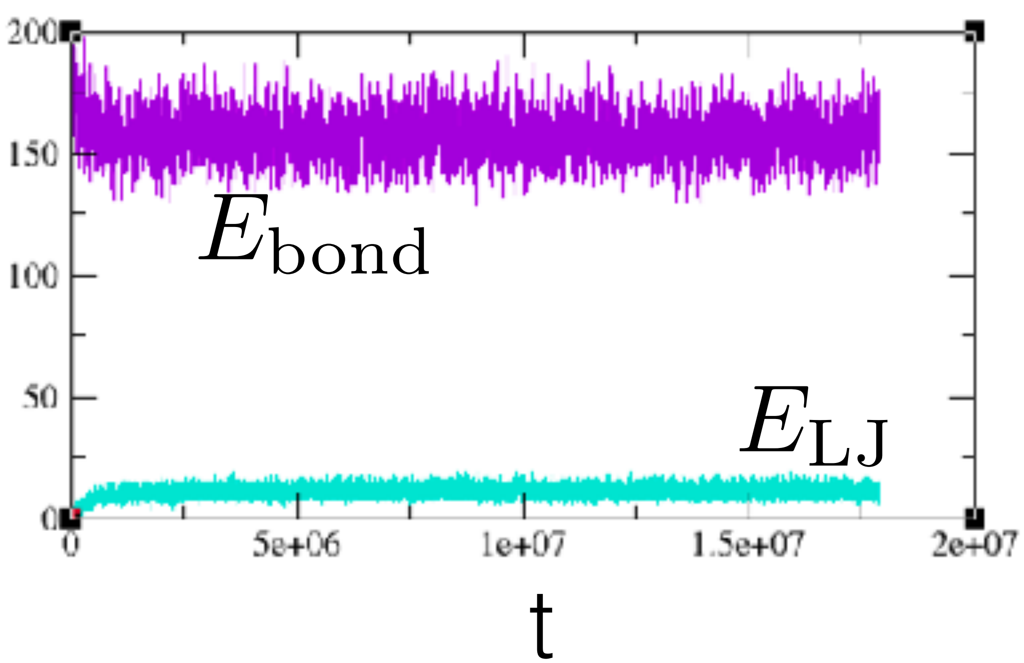
Flexible polymer in good solvent (SAW)

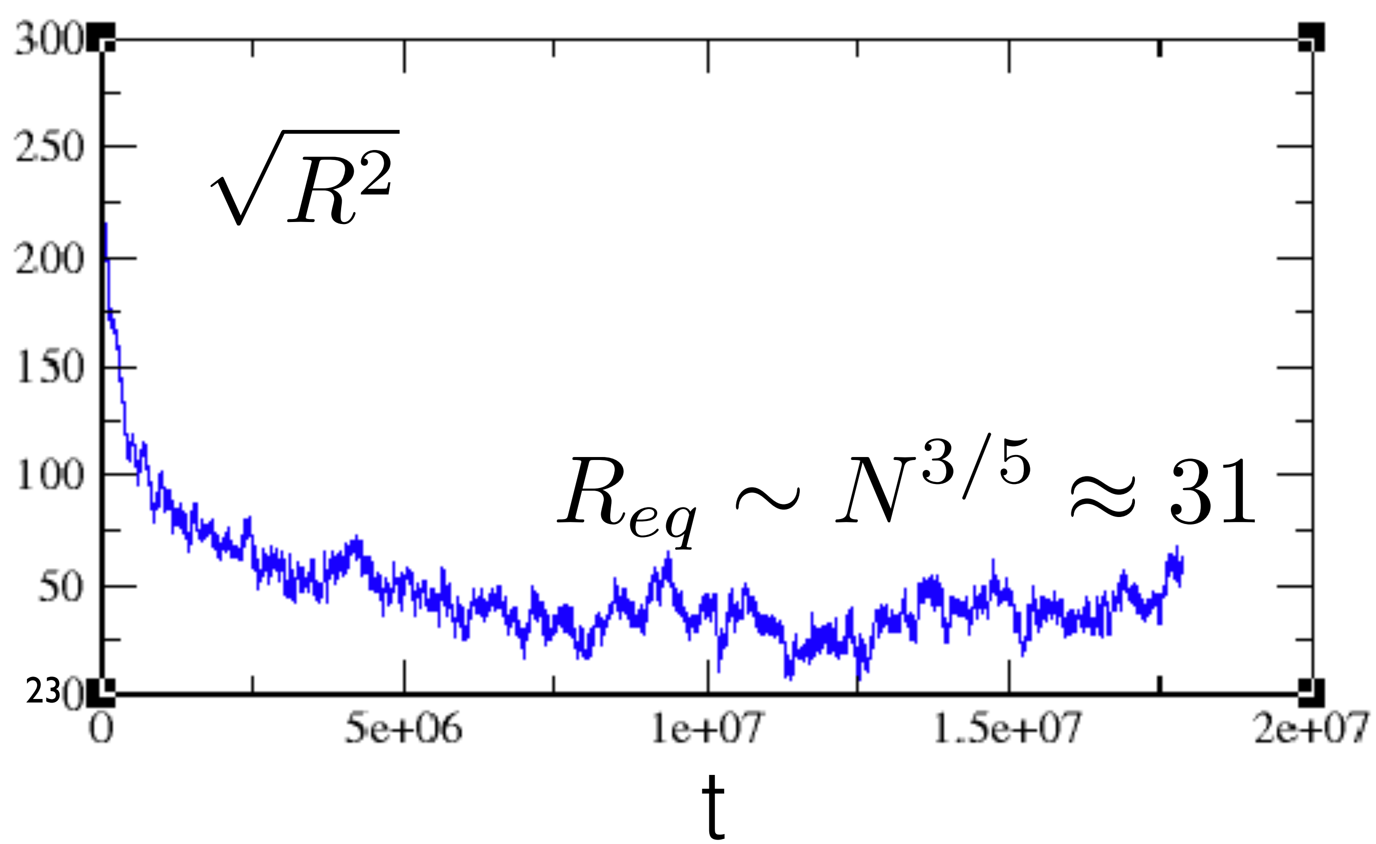
$N = 300$

$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2 + \varepsilon_l \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left(\frac{\sigma}{r_{i,j}} \right)^{12}$$

Monomers are mutually repulsive.





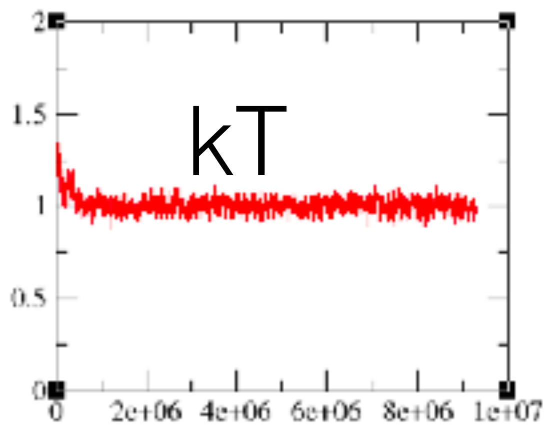


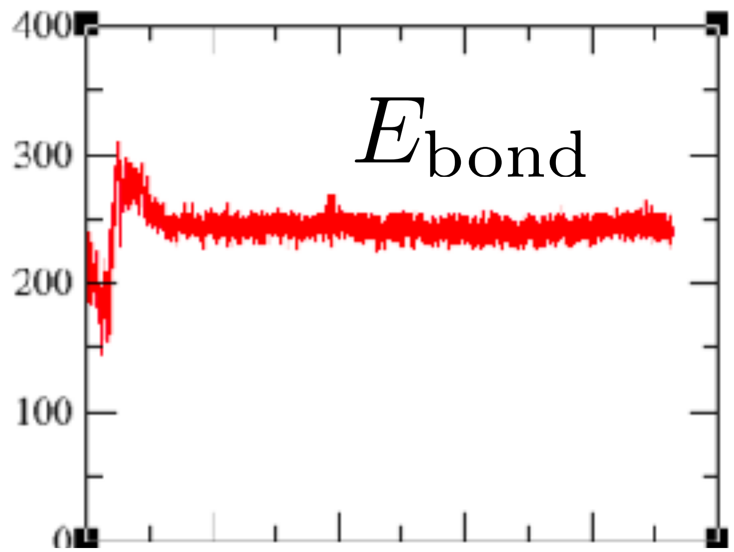
Collapse of flexible polymer in poor solvent

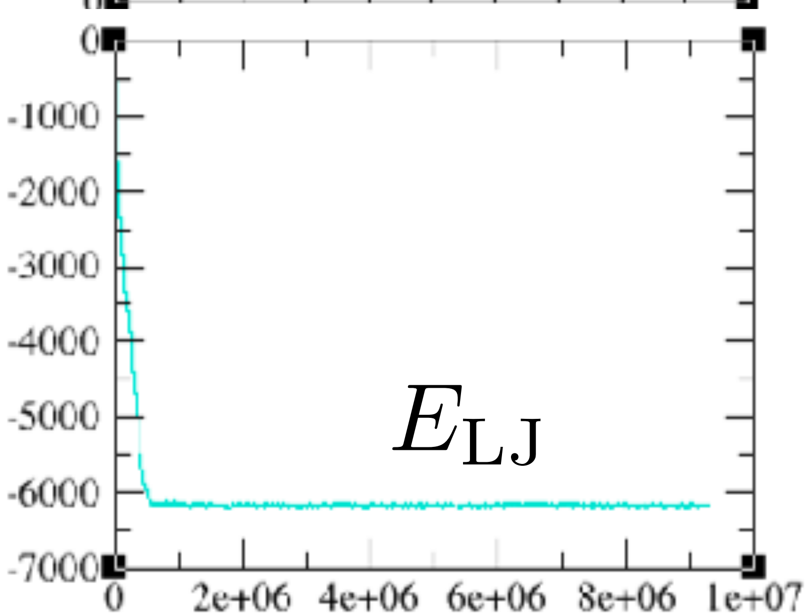
$N = 300$

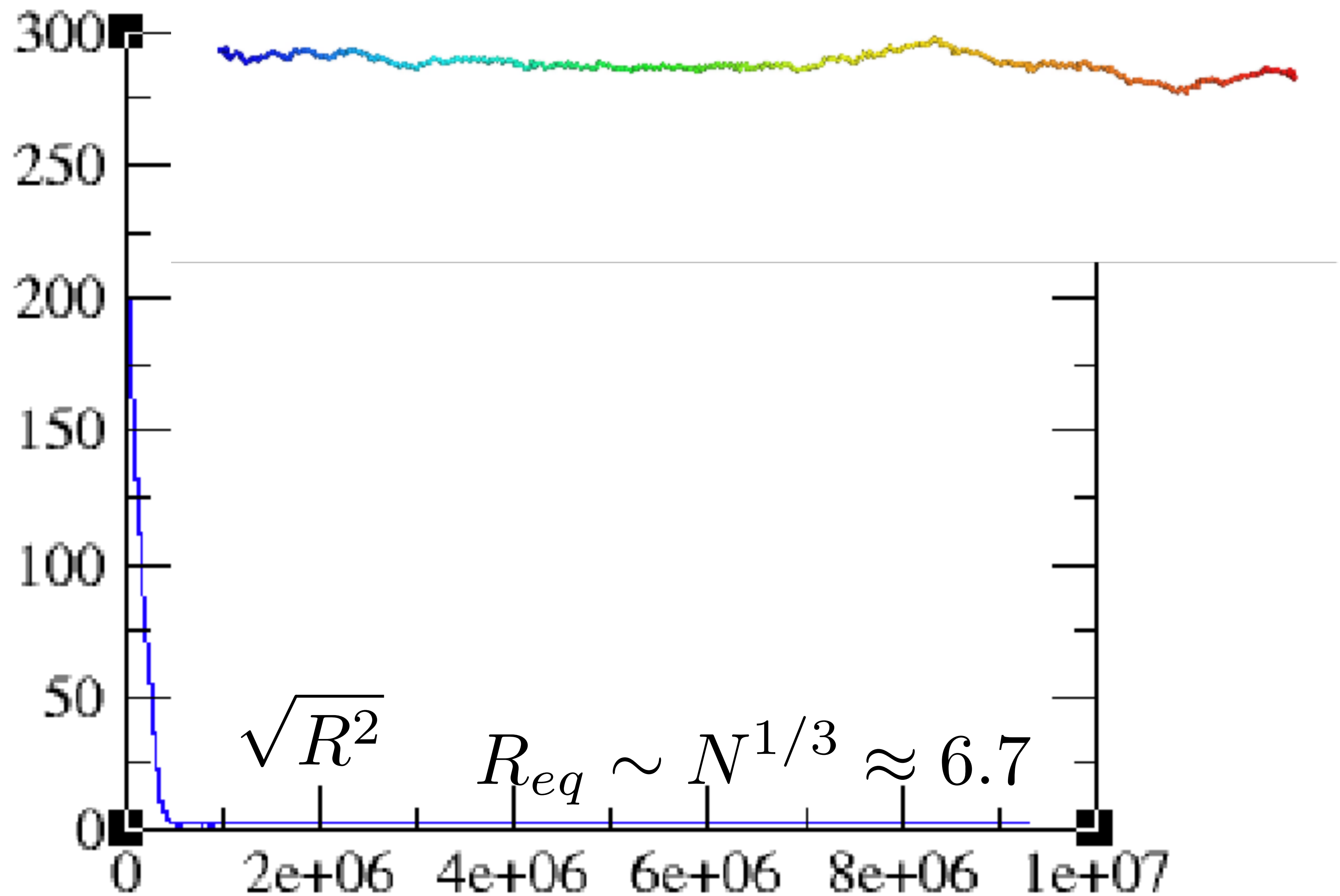
$$U_{\text{int}}(\{\vec{r}_i\}) = \sum_{i=1}^{N} \frac{k_r}{2}(r_{i,i+1} - a)^2 + \varepsilon_h \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left[\left(\frac{\sigma}{r_{i,j}} \right)^{12} - 2 \left(\frac{\sigma}{r_{i,j}} \right)^{6} \right]$$

Monomers are mutually attractive.



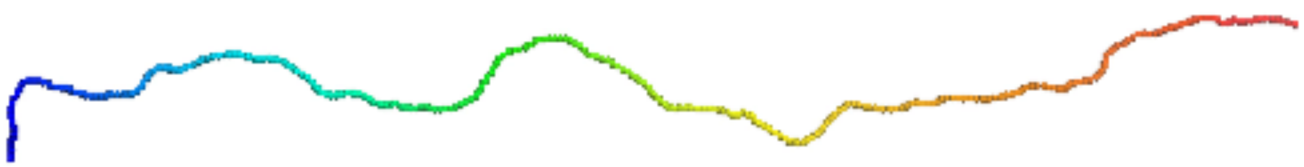




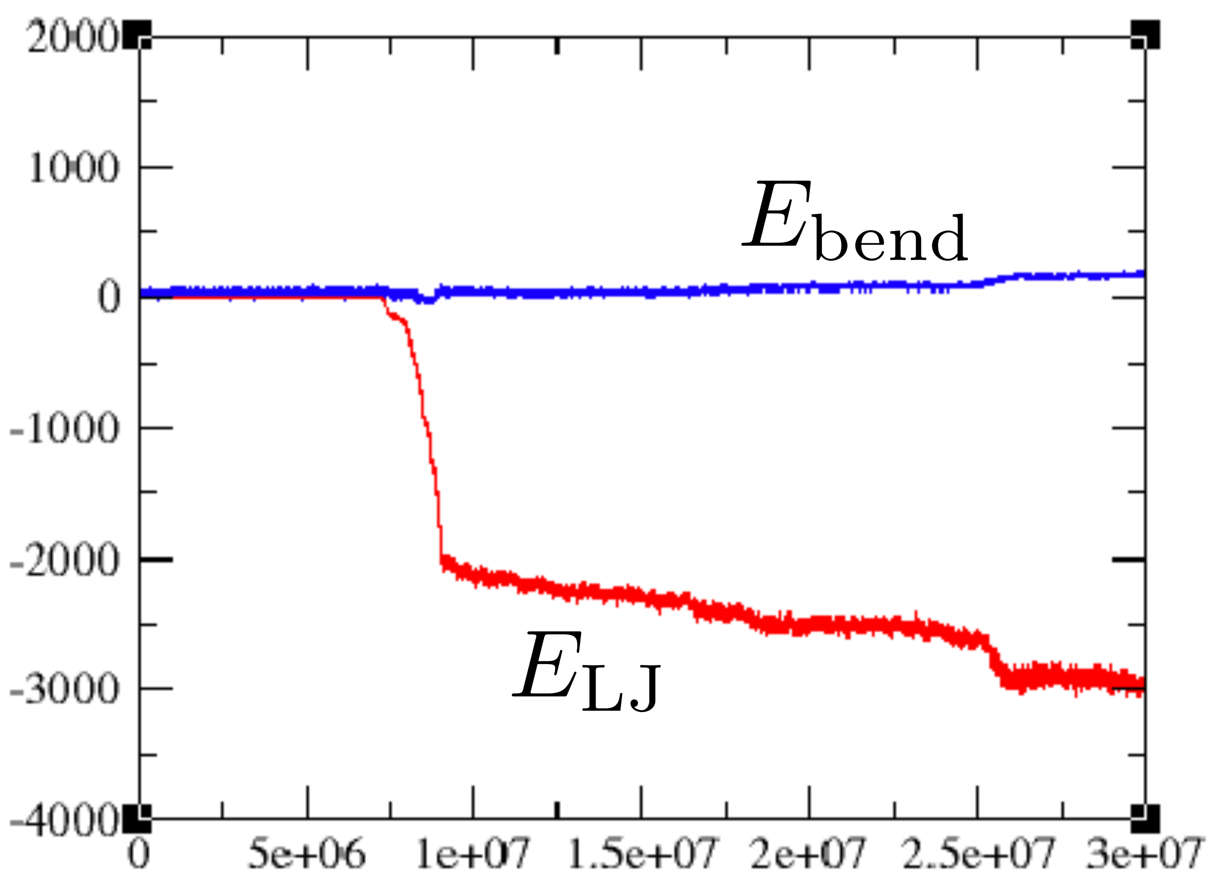


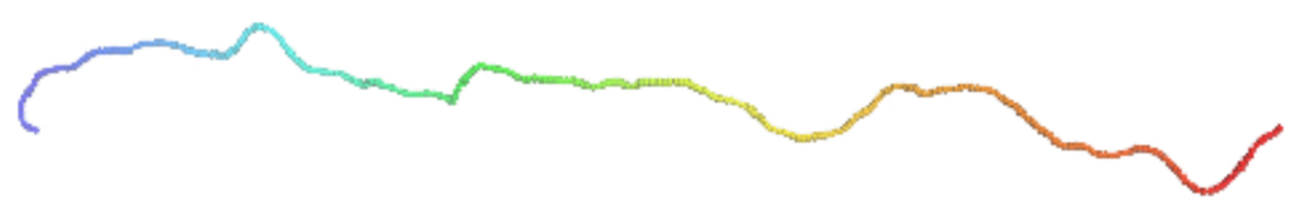
Collapse of semiflexible polymer in poor solvent

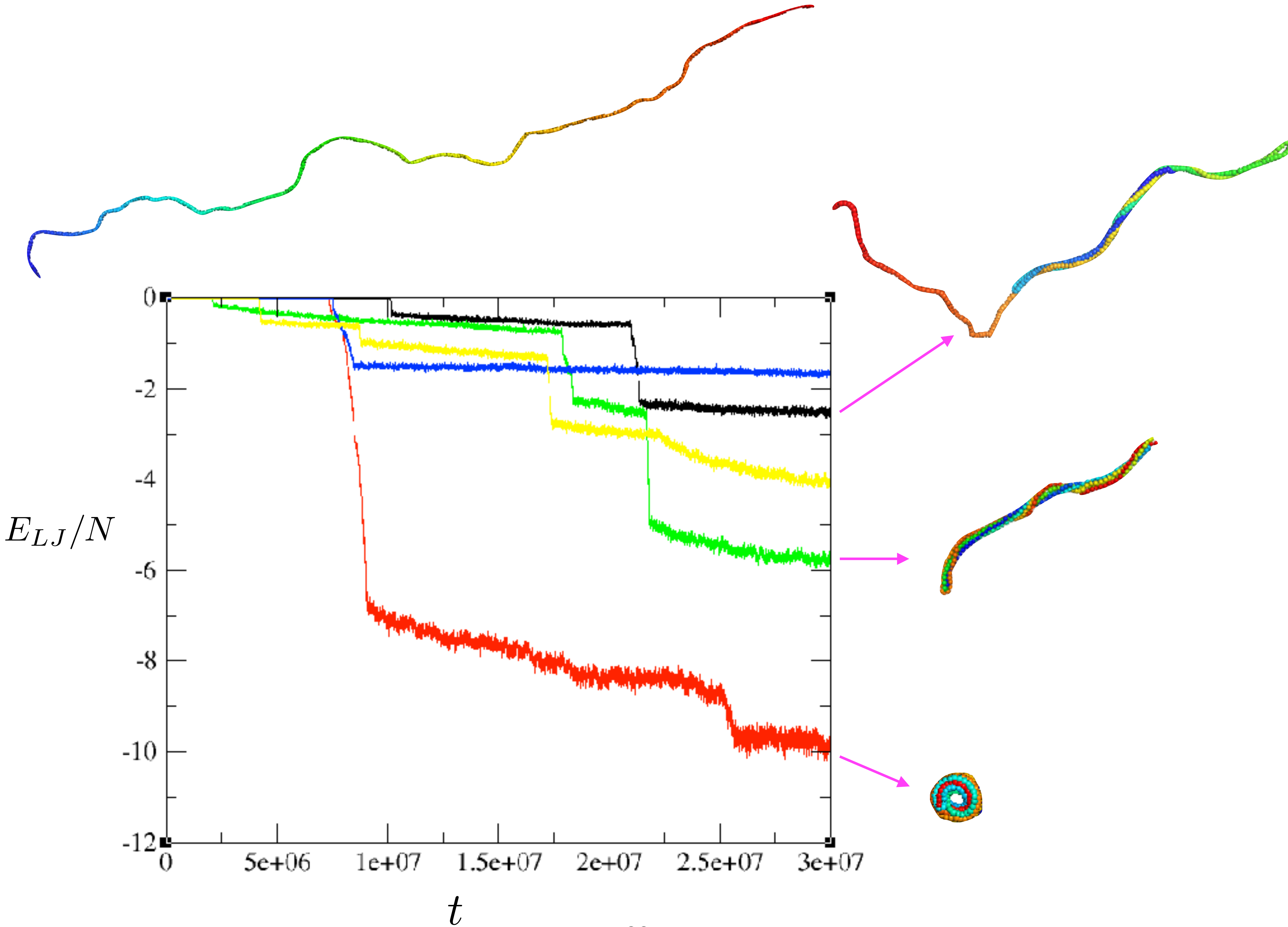
$$U_{\mathrm{int}(\{\vec{r}_i\})=\sum_{i=1}^{N}-1} \frac{k_r}{2}(r_{i,i+1}-a)^2 - \sum_{i=1}^{N-2} k_\theta \hat{r}_{i,i+1}\cdot\hat{r}_{i+1,i+2} + \sum_{i=1}^{N-3}\sum_{j=i+3}^{N} \epsilon_h\left[(\sigma/r_{i,j})^{12} - 2(\sigma/r_{i,j})^6\right]$$



$$k_r = 80k_BT/a^2$$
$$k_\theta = 40k_BT$$
$$\epsilon_h = 1.5k_BT$$

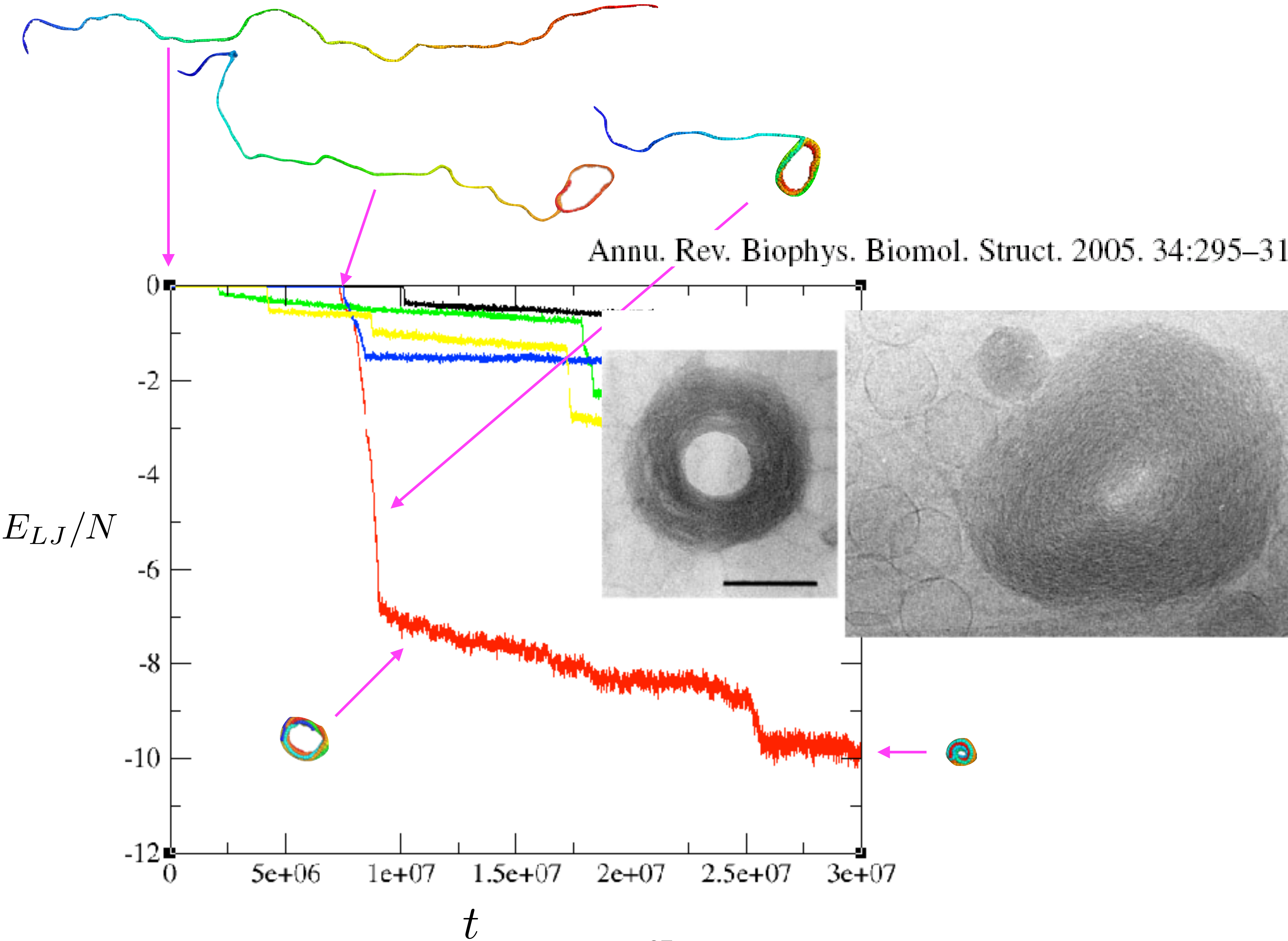






0
-2
-4
-6
-8
-10
-12
0
5e+06
1e+07
1.5e+07
2e+07
2.5e+07
3e+07
E_{LJ}/N
t

Annu. Rev. Biophys. Biomol. Struct. 2005. 34:295–318

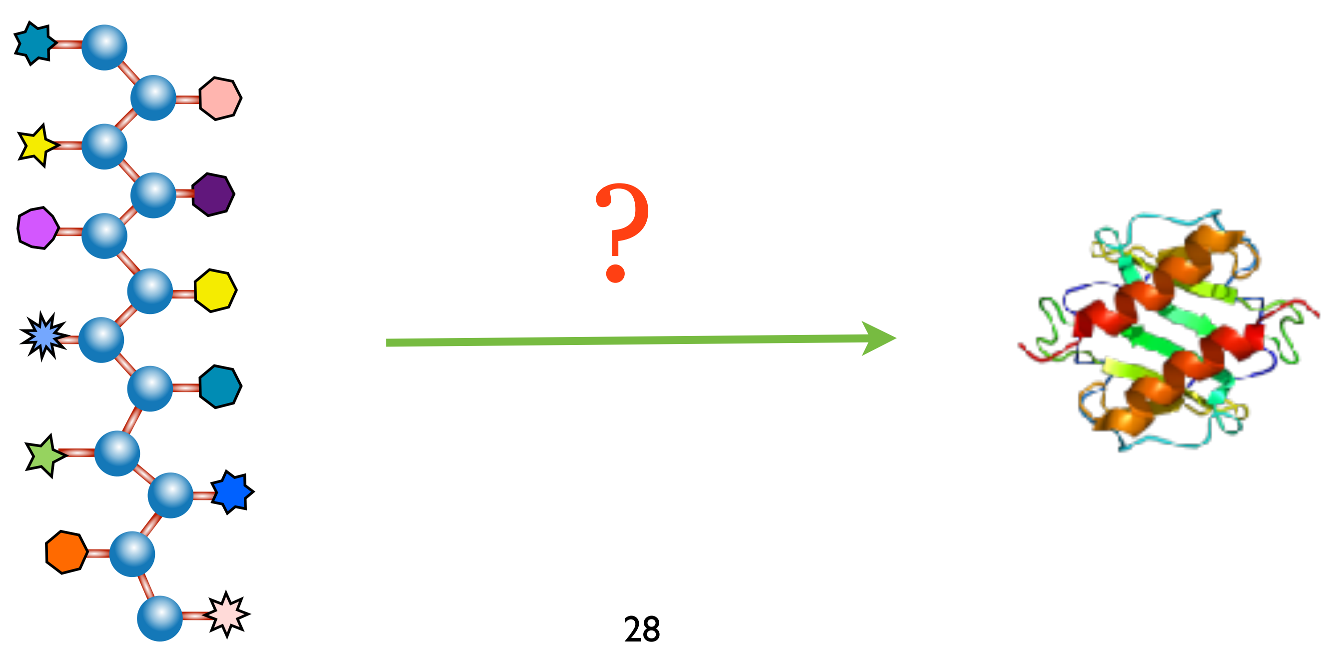


“Design” biopolymers, ...a protein

$$U_{tot} = \sum_{bond} K_r\left(r - r_o\right)^2 + \sum_{angle} K_\theta\left(\theta - \theta_o\right)^2 + \sum_{torsion} K_\phi\left(1 + \cos\left(n\phi - \delta\right)\right)$$

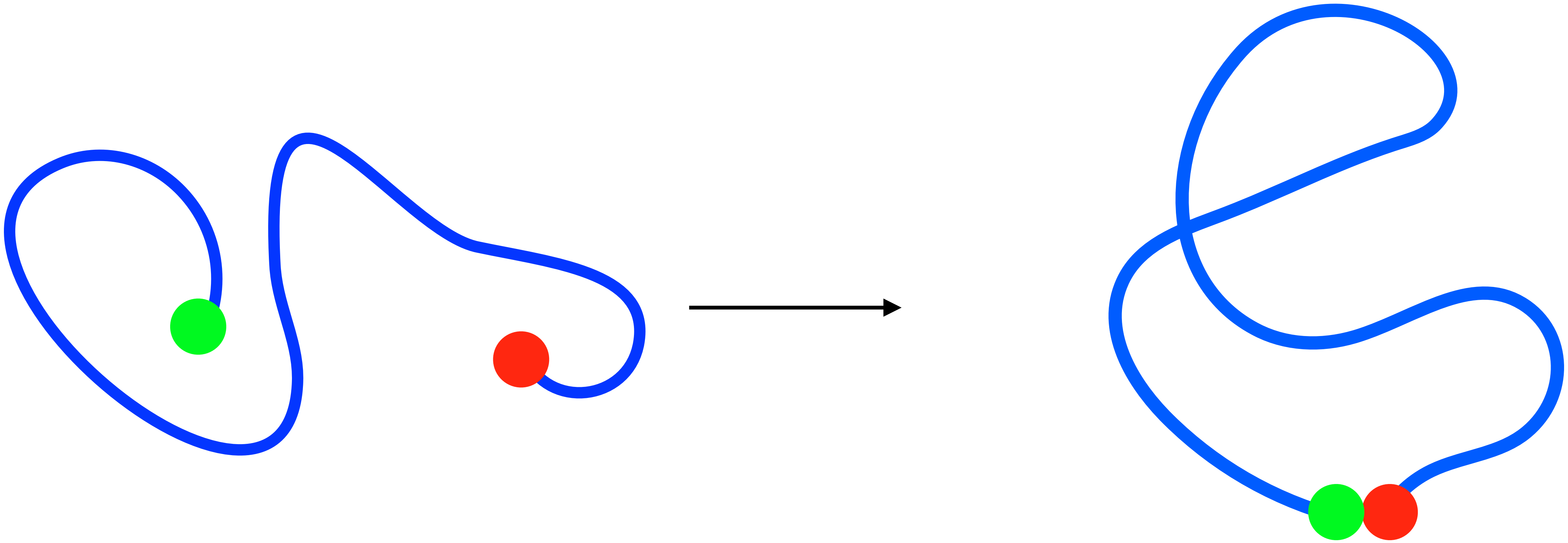
$$+ \sum_{improper} K_\varphi\left(\varphi - \varphi_o\right)^2 + \sum_{Urey-Bradley} K_{UB}\left(r_{1,3} - r_{1,3o}\right)^2 + \sum_{torsion} K_\phi\left(1 + \cos\left(n\phi - \delta\right)\right)$$

$$+ \sum_{nonbonded}\left\{\frac{q_i q_j}{4\pi\varepsilon r_{ij}} + \varepsilon_{ij}\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - 2\left(\frac{\sigma}{r_{ij}}\right)^{6}\right]\right\} + \sum_{i=1}^{N-1}\sum_{j=i+1}^{N}\left(\frac{\sigma}{r_{i,j}}\right)^{12}$$



Project 1

Q: Scaling relation of the mean looping time with the length of polymer? (Theory & Simulation ?)



$$\tau \sim N^{\alpha}$$

Non-Markovian Langevin eq. - Memory effect

$$m\dot{v} = -\zeta v - U'(x) + \xi(t)$$

$$-\zeta v(t) \to -\int_{-\infty}^{t} d\tau K(t-\tau)v(\tau) = -\int_{0}^{\infty} d\tau K(\tau)v(t-\tau)$$

$$U(x) = (1/2)m\omega^2 x^2 \qquad \dot{x} = p/m$$

$$\dot{p} = -m\omega^2 x - \zeta(p/m) + F_p(t) \qquad p(-\infty) = 0$$

$$\langle x^2\rangle_{eq} = \frac{k_B T}{m\omega^2}$$

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

$$p(t) = \int_{-\infty}^{t} d\tau e^{-(\zeta/m)(t-\tau)}(-m\omega^2 x(\tau) + F_p(\tau))$$

$$\dot{x}(t) = -\int_{-\infty}^{t} d\tau \underbrace{e^{-(\zeta/m)(t-\tau)}\omega^2}_{K(t-\tau)} x(\tau) + \underbrace{\int_{-\infty}^{t} d\tau e^{-(\zeta/m)(t-\tau)} F_p(\tau)/m}_{F_x(t)}$$

$$\dot{x}(t) = -\int_{0}^{\infty} d\tau K(\tau)x(t-\tau) + F_x(t)$$

$$\boxed{\langle F_x(t)F_x(t')\rangle = \frac{k_B T}{m}e^{-\zeta|t-t'|/m} = \langle x^2\rangle_{eq} K(|t-t'|)}$$

Show !!

Ans)

$$\langle F_x(t)F_x(t')\rangle = \langle x^2\rangle_{eq} K(|t-t'|)$$

$$\begin{aligned}
\langle F_x(t)F_x(t')\rangle &= \frac{1}{m^2}\int_{-\infty}^{t}\int_{-\infty}^{t'} d\tau_1 d\tau_2 e^{-(\zeta/m)(t-\tau_1)} e^{-(\zeta/m)(t'-\tau_2)} \langle F_p(\tau_1)F_p(\tau_2)\rangle \\
&= \frac{2\zeta k_B T}{m^2}\int_{-\infty}^{t}\int_{-\infty}^{t'} d\tau_1 d\tau_2 e^{-(\zeta/m)(t+t'-\tau_1-\tau_2)} \delta(\tau_1-\tau_2) \\
&= \frac{2\zeta k_B T}{m^2}\int_{-\infty}^{\min(t,t')} d\tau e^{-(\zeta/m)(t+t'-2\tau)} \\
&= \frac{2\zeta k_B T}{m^2}\frac{m}{2\zeta} e^{-(\zeta/m)(t+t'-2\min(t,t'))} = \frac{k_B T}{m} e^{-\zeta|t-t'|/m}
\end{aligned}$$

Markovian system of equations

$$\boxed{\begin{aligned}\dot{x} &= p/m \\ \dot{p} &= -m\omega^2 x - \zeta(p/m) + F_p(t)\end{aligned}}$$

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

removal of fast variable, reduction of dimension (or projection)

non-Markovian

$$\boxed{\dot{x}(t) = -\int_0^\infty d\tau K(\tau) x(t-\tau) + F_x(t)}$$

$$\omega^2 e^{-\zeta\tau/m} \xrightarrow{\zeta\tau/m \gg 1} \frac{m\omega^2}{\zeta}\delta(\tau)$$

$$\langle F_x(t) F_x(t') \rangle = \langle x^2 \rangle_{eq} K(|t-t'|)$$

Fluctuation-Dissipation theorem (FDT)

$$\frac{k_B T}{m} e^{-\zeta|t-t'|/m} \xrightarrow[\zeta|t-t'|/m \gg 1]{} \frac{2k_B T}{\zeta}\delta(t-t')$$

$$\boxed{\dot{x}(t) = -m\omega^2 x(t)/\zeta + \sqrt{2D}\eta(t)}$$

Markovian

$$\frac{\partial \mathbf{a}(t)}{\partial t} = \mathcal{L} \cdot \mathbf{a}(t)$$

Method of projection operator (Mori-Zwanzig formalism)

$$\mathcal{L} = \mathbf{P}\mathcal{L} + (1 - \mathbf{P})\mathcal{L}$$

$$e^{t\mathcal{L}} = e^{t(1-\mathbf{P})\mathcal{L}} + \int_0^t ds e^{(t-s)\mathcal{L}} \mathbf{P}\mathcal{L} e^{t(1-\mathbf{P})\mathcal{L}}$$

$$\frac{\partial A(t)}{\partial t} = i\Omega A(t) - \int_0^t ds K(s) \cdot A(t-s) + F(t)$$

$$\langle F(t) F^*(t') \rangle = K(t - t') \cdot \langle A A^* \rangle_{eq}$$

Operator algebra

$$e^{t\mathcal{L}} = e^{t(1-\mathbf{P})\mathcal{L}} + \int_0^t ds e^{(t-s)\mathcal{L}}\mathbf{P}\mathcal{L}e^{t(1-\mathbf{P})\mathcal{L}}$$

$$[z-(A+B)]^{-1} = \{(z-A)[1-(z-A)^{-1}B]\}^{-1}$$

$$= [1-(z-A)^{-1}B]^{-1}(z-A)^{-1}$$

$$= [1+(z-A)^{-1}B+(z-A)^{-1}B(z-A)^{-1}B+\cdots](z-A)^{-1}$$

$$= (z-A)^{-1}+(z-A)^{-1}B(z-A)^{-1}+(z-A)^{-1}B(z-A)^{-1}B(z-A)^{-1}+\cdots$$

$$= (z-A)^{-1}+\{(z-A)^{-1}+(z-A)^{-1}B(z-A)^{-1}+\cdots\}B(z-A)^{-1}$$

$$= (z-A)^{-1}+[z-(A+B)]^{-1}B(z-A)^{-1}$$

$$e^{t(A+B)} = e^{tA} + \int_0^t ds e^{(t-s)(A+B)}Be^{tA}$$

Fokker-Planck equation

Continuity equation in phase space

$$\partial_t \rho(\mathbf{x},t) + \nabla_{\mathbf{x}} \cdot (\dot{\mathbf{x}}\rho(\mathbf{x},t)) = 0$$

$$\boxed{\frac{\partial f}{\partial t} + \frac{\partial}{\partial \Gamma}(\dot{\Gamma} f) = 0}$$

$$f = f(\Gamma, t) \qquad \int f(\Gamma,t)d\Gamma = 1$$

$$\Gamma \equiv (\vec{q}_1, \vec{q}_2, \ldots, \vec{q}_N, \vec{p}_1, \vec{p}_2, \ldots, \vec{p}_N)$$

$$\frac{\partial f}{\partial t} + \dot{\Gamma}\frac{\partial f}{\partial \Gamma} + f\frac{\partial \dot{\Gamma}}{\partial \Gamma} = 0$$

$$\sum_i \left(\frac{\partial \dot{q}_i}{\partial q_i} + \frac{\partial \dot{p}_i}{\partial p_i}\right) = \sum_i \left(\frac{\partial^2 H}{\partial q_i \partial p_i} - \frac{\partial^2 H}{\partial p_i \partial q_i}\right) = 0$$

0 for Hamiltonian system $\vec{\nabla} \cdot \vec{V} = 0$

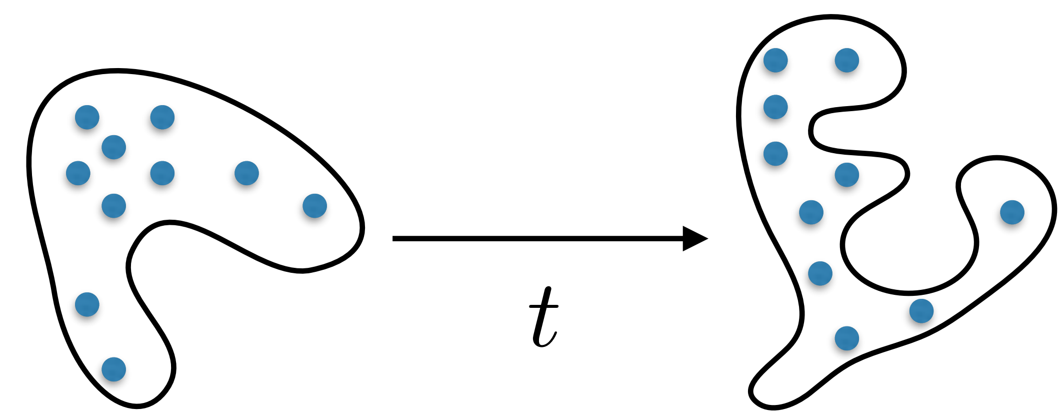
Liouville theorem

Phase space density is constant along the dynamic trajectory in phase space

$$\frac{df}{dt} = \boxed{\frac{\partial f}{\partial t} + \dot{\Gamma} \cdot \frac{\partial f}{\partial \Gamma} = 0}$$

Liouville equation

● $(\{q\},\{p\})[= (\vec{q}_1, \vec{q}_2, \ldots, \vec{q}_N, \vec{p}_1, \vec{p}_2, \ldots, \vec{p}_N)]$



$$\frac{df(\{q\},\{p\},t)}{dt} = \frac{\partial f}{\partial t} + \sum_i \frac{\partial f}{\partial q_i}\frac{dq_i}{dt} + \sum_i \frac{\partial f}{\partial p_i}\frac{dp_i}{dt} = 0$$

$$\partial_t f = -\mathcal{L} f$$

$$f(\Gamma, t) = e^{-\mathcal{L}t} f(\Gamma, 0)$$

Fokker-Planck equation $\mathbf{a}(t) \longrightarrow \rho(\mathbf{a},t)$

stochastic variable

prob. density

$$\partial_t \mathbf{a}(t) = \mathbf{v}(\mathbf{a}) + \mathbf{F}(t) \qquad \langle \mathbf{F}(t) \rangle = 0 \qquad \langle \mathbf{F}(t)\mathbf{F}(t') \rangle = 2\mathbf{B}\delta(t-t')$$

$$\partial_t \rho(\mathbf{a},t) + \partial_{\mathbf{a}} \cdot (\dot{\mathbf{a}}\rho(\mathbf{a},t)) = 0$$: continuity equation

---

$$\partial_t \rho(\mathbf{a},t) + \partial_{\mathbf{a}} \cdot (\mathbf{v}(\mathbf{a})\rho(\mathbf{a},t) + \mathbf{F}(t)\rho(\mathbf{a},t)) = 0$$

$$\partial_t \rho(\mathbf{a},t) + \mathcal{L}\rho(\mathbf{a},t) = -\partial_{\mathbf{a}} \cdot (\mathbf{F}(t)\rho(\mathbf{a},t))$$

$$\rho(\mathbf{a},t) = e^{-\mathcal{L}t}\rho(\mathbf{a},0) - \int_0^t d\tau e^{-\mathcal{L}(t-\tau)}\partial_{\mathbf{a}} \cdot (\mathbf{F}(\tau)\rho(\mathbf{a},\tau))$$

$$\partial_t \overline{\rho}(\mathbf{a},t) + \mathcal{L}\overline{\rho}(\mathbf{a},t) = \int_0^t d\tau e^{-\mathcal{L}(t-\tau)}\partial_{\mathbf{a}} \cdot \overline{\mathbf{F}(t)\mathbf{F}(\tau)} \cdot \partial_{\mathbf{a}}(\overline{\rho}(\mathbf{a})) = \partial_{\mathbf{a}} \cdot \mathbf{B} \cdot \partial_{\mathbf{a}}\overline{\rho}(\mathbf{a},t)$$

$$\boxed{\partial_t \overline{\rho}(\mathbf{a},t) = \frac{\partial}{\partial \mathbf{a}} \cdot \mathbf{B} \cdot \frac{\partial}{\partial \mathbf{a}}\overline{\rho}(\mathbf{a},t) - \frac{\partial}{\partial \mathbf{a}} \cdot (\mathbf{v}(\mathbf{a},t)\overline{\rho}(\mathbf{a},t))} \qquad \partial_t \overline{\rho} = \mathcal{L}_{FP}\overline{\rho}$$

Fokker Planck equation $\quad (x,p) \longrightarrow \rho(x,p,t)$

$$m\ddot{x} = -\zeta\dot{x} - \frac{dU(x)}{dx} + \xi(t)$$

$$\dot{x} = p/m$$
$$\dot{p} = -\zeta(p/m) - dU(x)/dx + \xi(t)$$

$$\partial_t\rho + \partial_x(\dot{x}\rho) + \partial_p(\dot{p}\rho) = 0$$: continuity equation

---

$$\partial_t\rho + \underline{\partial_x(p/m \times \rho) + \partial_p(-\zeta(p/m)\rho - (dU(x)/dx)\rho)} = -\partial_p(\xi(t)\rho)$$

$$\partial_t\rho + \underline{\mathcal{L}}\rho = -\partial_p(\xi(t)\rho)$$

$$\overline{\xi(t)\xi(\tau)} = 2\zeta k_B T\delta(t-\tau)$$

$$\rho(x,p,t) = e^{-\mathcal{L}t}\rho(x,p,0) - \int_0^t d\tau e^{-\mathcal{L}(t-\tau)}\xi(\tau)\partial_p\rho(x,p,\tau)$$

$$\partial_t\overline{\rho} + \mathcal{L}\overline{\rho} = \int_0^t d\tau e^{-\mathcal{L}(t-\tau)}\overline{\xi(t)\xi(\tau)}\partial_p^2\overline{\rho}(\tau)$$

$$\partial_t\overline{\rho} = \zeta k_B T\partial_p^2\overline{\rho} + \partial_p\left[\left(\frac{\zeta p}{m} + \frac{dU(x)}{dx}\right)\overline{\rho}\right] - \partial_x\left(\frac{p}{m}\overline{\rho}\right)$$

Klein-Kramers eqn.

Fokker-Planck equation

$$x \longrightarrow \rho(x,t)$$

$$\dot{x} = -\frac{1}{\zeta}\frac{dU(x)}{dx} + \frac{\xi(t)}{\zeta}$$

$$\partial_t \rho + \partial_x(\dot{x}\rho) = 0$$: continuity equation

---

$$\partial_t \rho = \frac{k_B T}{\zeta}\partial_x^2 \rho + \partial_x\left(\frac{1}{\zeta}\frac{dU(x)}{dx}\rho\right)$$

$$\partial_t \rho = D\frac{\partial^2 \rho}{\partial x^2} + \frac{\partial}{\partial x}\left(\frac{U'(x)}{\zeta}\rho\right)$$ **Smoluchowski equation**

$$\partial_t \rho = D\partial_x(\partial_x + \beta U'(x))\rho = -\partial_x j$$

$$j = j_{\mathrm{diff}} + j_{\mathrm{adv}} \qquad j_{\mathrm{diff}} = -D\partial_x \rho$$

$$j_{\mathrm{adv}} = v\rho$$

SUMMARY of Fokker-Planck eqn.

$$m\ddot{x} = -\zeta\dot{x} - \frac{dU(x)}{dx} + \xi(t) \qquad\qquad \longrightarrow \rho(x,p,t)$$

Klein-Kramers eqn.

$$\partial_t\overline{\rho} = \zeta k_B T \partial_p^2 \overline{\rho} + \partial_p \left[\left(\frac{\zeta p}{m} + \frac{dU(x)}{dx} \right) \overline{\rho} \right] - \partial_x \left(\frac{p}{m}\overline{\rho} \right)$$

$$\dot{x} = -\frac{1}{\zeta}\frac{dU(x)}{dx} + \frac{\xi(t)}{\zeta} \qquad\qquad \longrightarrow \rho(x,t)$$

Smoluchowski equation

$$\partial_t\rho = D\frac{\partial^2\rho}{\partial x^2} + \frac{\partial}{\partial x}\left(\frac{U'(x)}{\zeta}\rho\right)$$

Survival Probability, $S(t)$

First Passage time distribution, $P_{\mathrm{FPT}}(t)$

Mean first passage time, $\tau = \int_0^\infty tP_{\mathrm{FPT}}(t)dt$

Kramers Escape Rate Theory

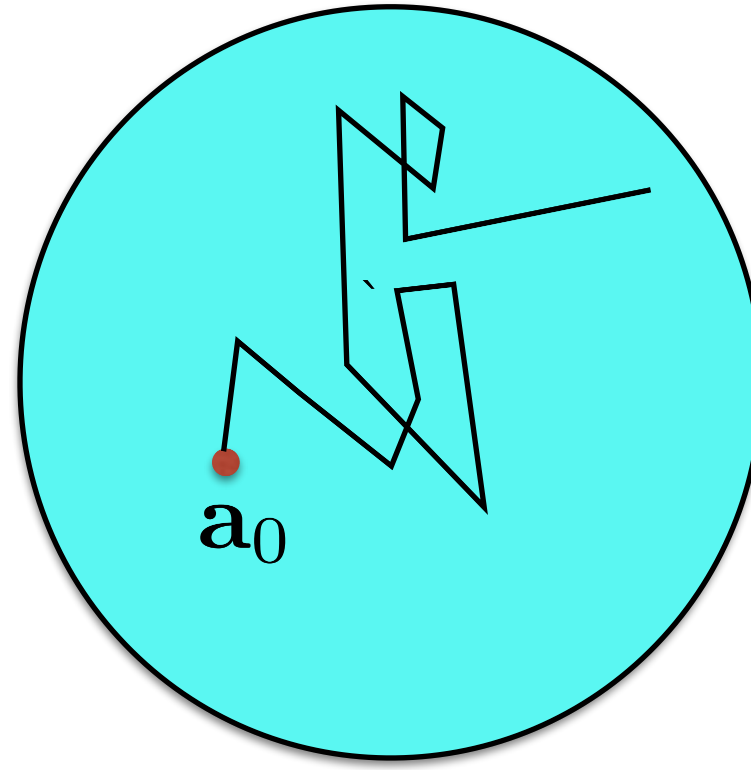
$$P_{\mathrm{FPT}}(t) = -\frac{dS(t)}{dt}$$

$$S(t) = 1 - \int_0^t d\tau P_{\mathrm{FPT}}(\tau) \qquad S(0) = 1 \qquad S(\infty) = 0$$

$$\tau = \int_0^\infty tP_{\mathrm{FPT}}(t)dt = \int_0^\infty S(t)dt$$

$$\partial_t P(\mathbf{a}, t; \mathbf{a}_0) = \mathcal{L}_{FP} P(\mathbf{a}, t; \mathbf{a}_0)$$

$$S(t; \mathbf{a}_0) = \int_V d\mathbf{a} P(\mathbf{a}, t; \mathbf{a}_0)$$



∂V (absorbing boundary)

$$P(\mathbf{a}, \infty) \to 0$$

$$\begin{aligned}
\tau(\mathbf{a}_0) &= \int_0^\infty dt S(t; \mathbf{a}_0) \\
&= \int_0^\infty dt \int_V d\mathbf{a} e^{t\mathcal{L}_{FP}} \delta(\mathbf{a} - \mathbf{a}_0) \\
&= \int_0^\infty dt \int_V d\mathbf{a} \delta(\mathbf{a} - \mathbf{a}_0) \left(e^{t\mathcal{L}_{FP}^\dagger} 1 \right) \\
&= \int_V d\mathbf{a} \delta(\mathbf{a} - \mathbf{a}_0) \left(\int_0^\infty dt \left(e^{t\mathcal{L}_{FP}^\dagger} 1 \right) \right)
\end{aligned}$$

$$\tau(\mathbf{a}) = \int_0^\infty e^{t\mathcal{L}_{FP}^\dagger} dt$$

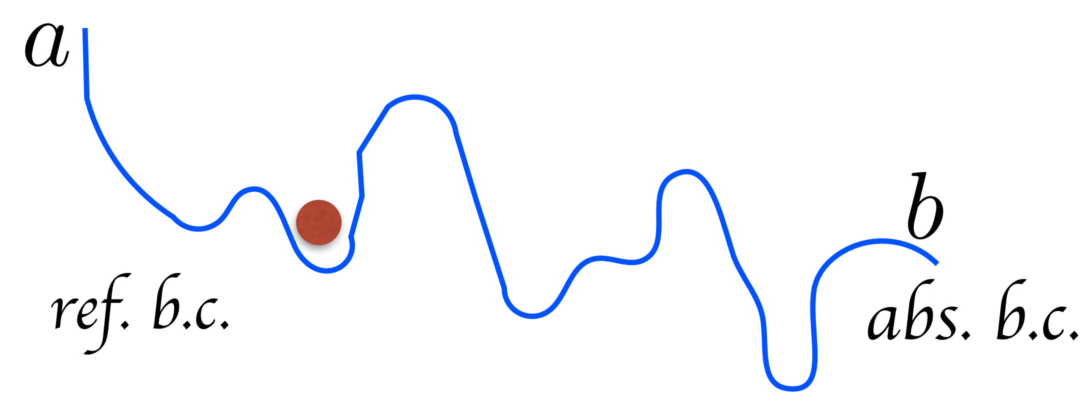
$$\begin{aligned}
\mathcal{L}_{FP}^\dagger \tau(\mathbf{a}) &= \int_0^\infty \partial_t (e^{t\mathcal{L}_{FP}^\dagger}) dt \\
&= [e^{t\mathcal{L}_{FP}^\dagger}]_0^\infty = -1
\end{aligned}$$

$$\mathcal{L}_{FP}^\dagger \tau(\mathbf{a}) = -1$$

$$\mathcal{L}_{FP} = D\partial_x e^{-\beta U(x)}\partial_x e^{\beta U(x)} = D(\partial_x^2 + \beta\partial_x U'(x))$$

$$\mathcal{L}_{FP}^{\dagger} = De^{\beta U(x)}\partial_x e^{-\beta U(x)}\partial_x = D(\partial_x^2 - \beta U'(x)\partial_x)$$

$$De^{\beta U(x)}\partial_x e^{-\beta U(x)}\partial_x \tau(x) = -1$$



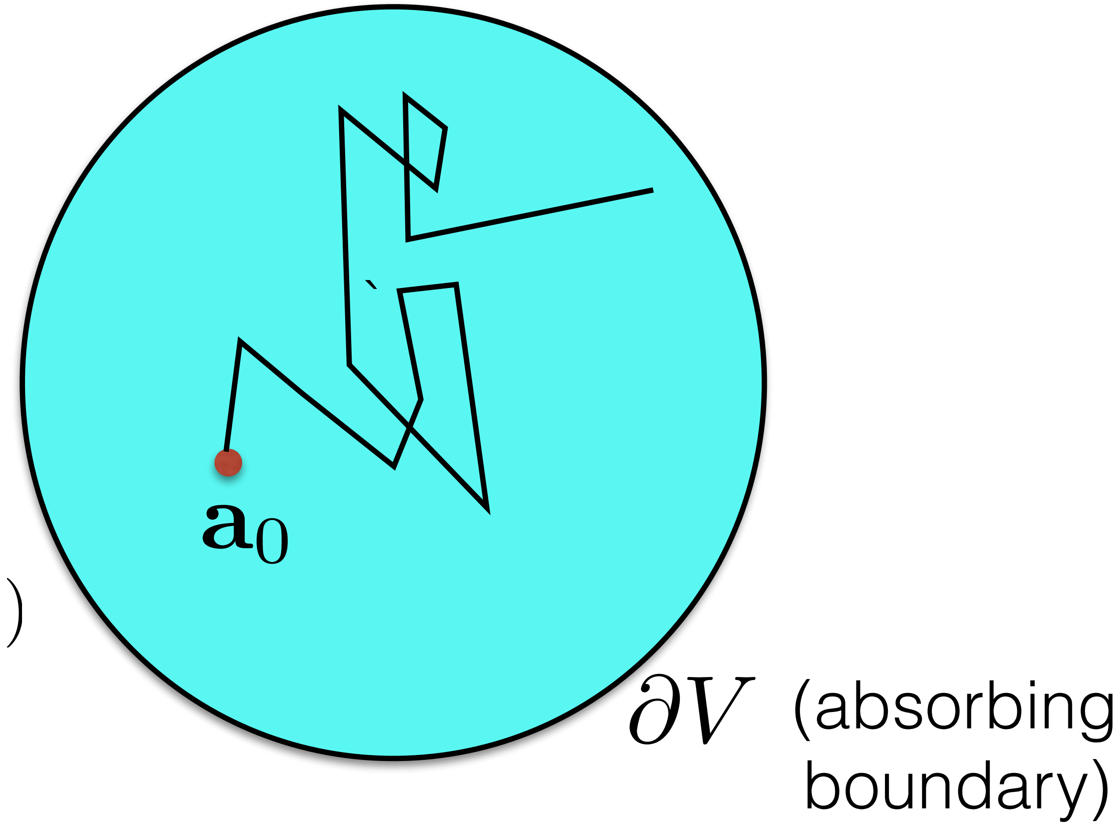
$$e^{-\beta U(x)}\partial_x \tau(x) - e^{-\beta U(a)}\partial_x \tau(x)|_{x=a} = -\frac{1}{D}\int_a^x dx e^{-\beta U(x)}$$

$$\tau(b) - \tau(x) = -\int_x^b dy \frac{1}{D} e^{\beta U(y)} \int_a^y dz e^{-\beta U(z)}$$

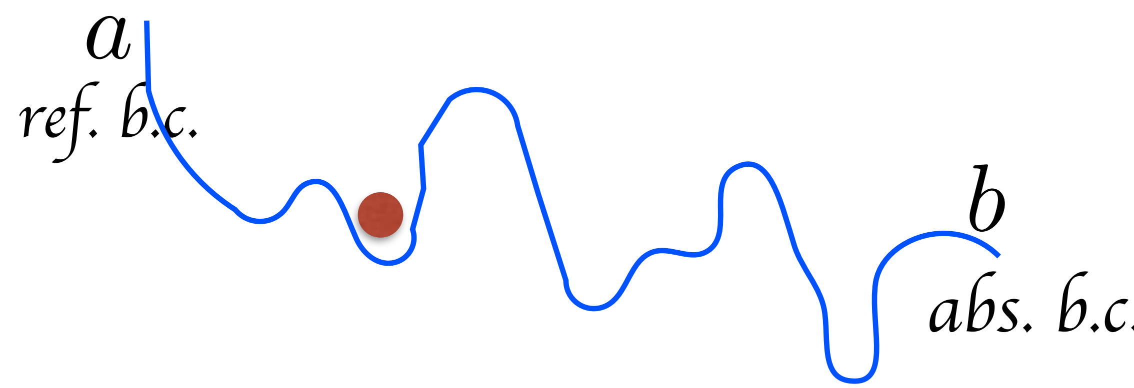
$$\boxed{\tau(x) = \frac{1}{D}\int_x^b dy e^{\beta U(y)} \int_a^y dz e^{-\beta U(z)}}$$

$$\mathcal{L}_{FP}^{\dagger}(\mathbf{a}_0) = -1$$

$$\mathcal{L}_{FP}^{\dagger} = De^{\beta U(x)}\partial_x e^{-\beta U(x)}\partial_x = D(\partial_x^2 - \beta U'(x)\partial_x)$$



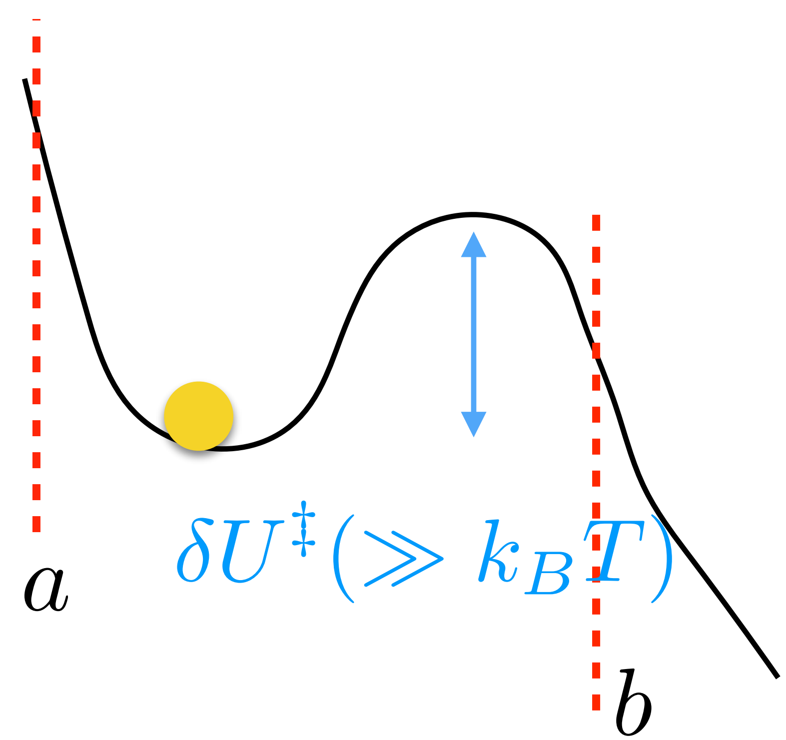
$$\boxed{\tau(x) = \frac{1}{D}\int_x^b dy e^{\beta U(y)} \int_a^y dz e^{-\beta U(z)}}$$



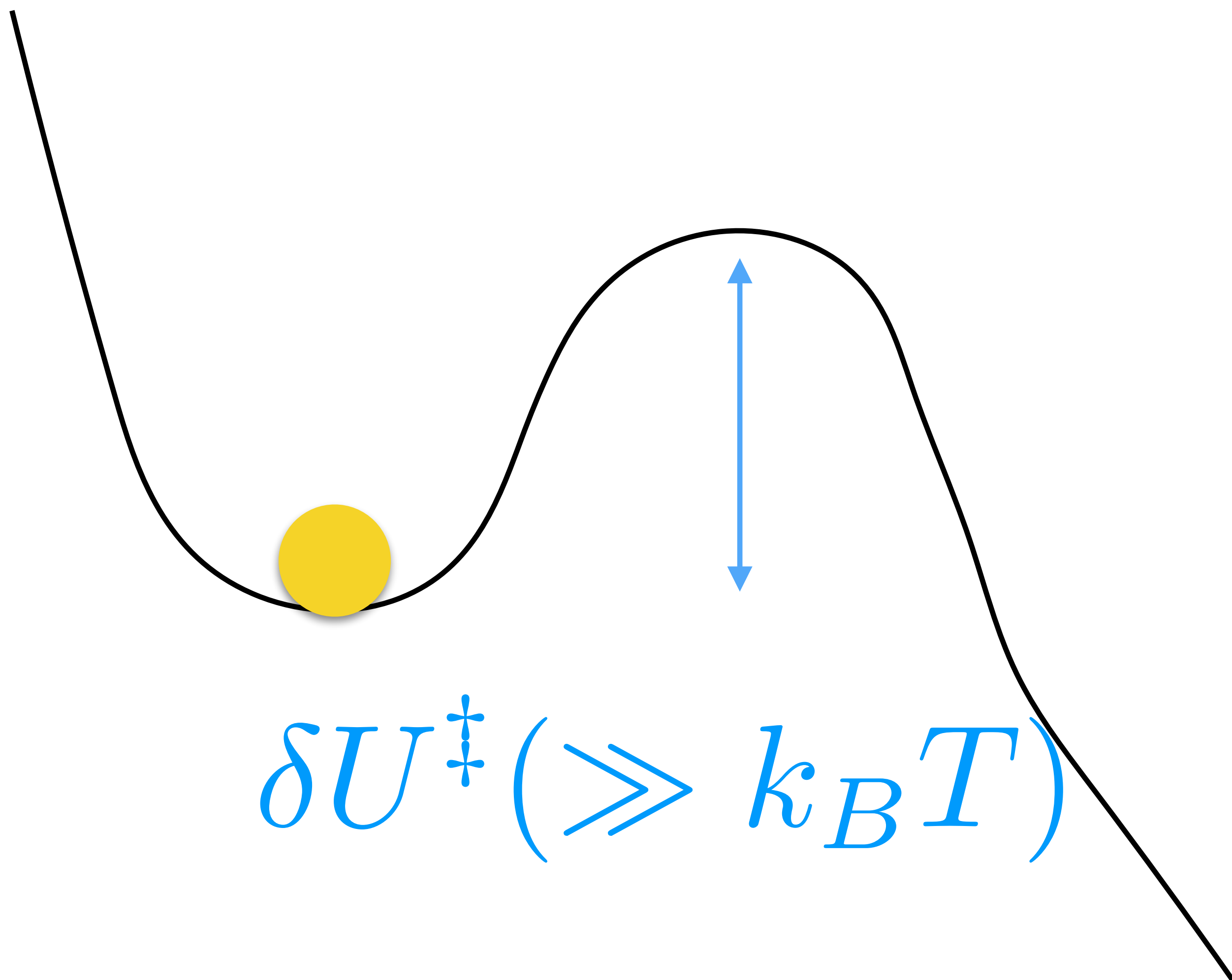
$$U(x) \approx U(x_{ts}) - \frac{1}{2}m\omega_{ts}^2(x - x_{ts})^2$$

$$U(x) \approx U(x_0) + \frac{1}{2}m\omega_0^2(x - x_0)^2$$

$$\tau_{KR} = \frac{2\pi k_B T}{Dm\omega_{ts}\omega_0}e^{\beta\delta U^{\ddagger}}$$



Kramers Rate



$$k = Ae^{-\delta U^{\ddagger}/k_B T}$$

$$k_{TST} = \frac{k_B T}{h} e^{-\beta \delta U^{\ddagger}}$$

$$m\ddot{x} = -\zeta \dot{x} - \frac{dU(x)}{dx} + \xi(t)$$

Kramers equation (high friction)

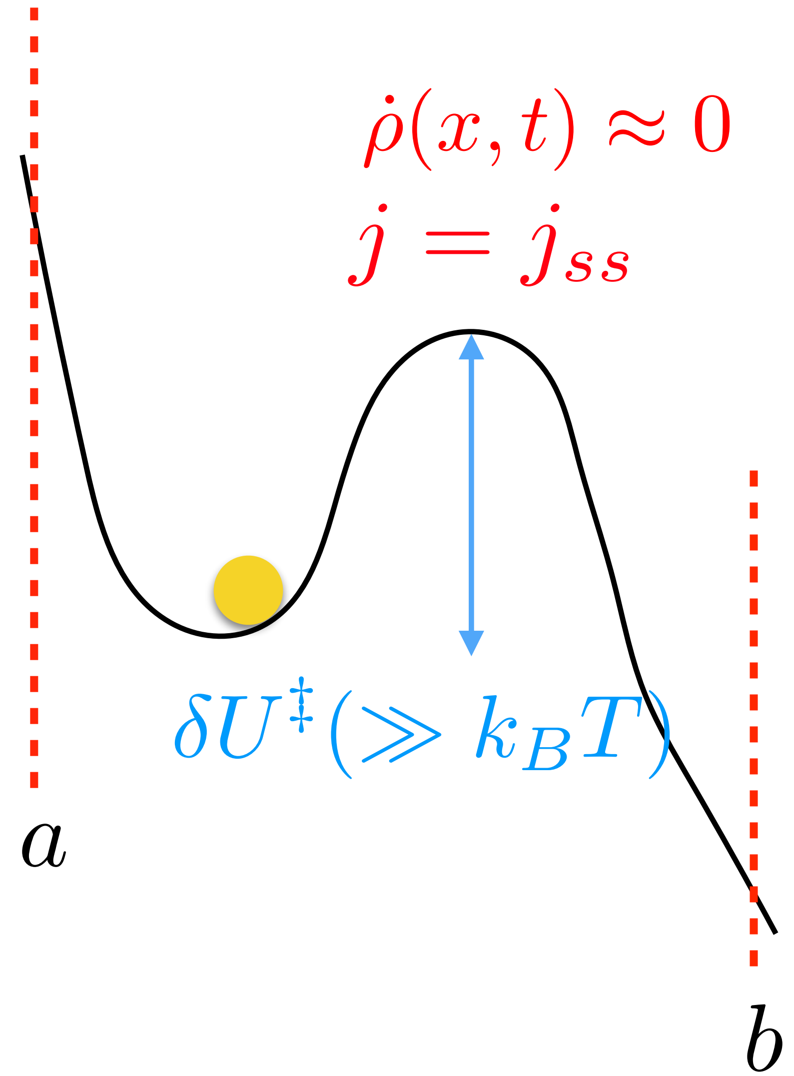
$$\partial_t \rho = D\partial_x(\partial_x + \beta U'(x))\rho = -\partial_x j$$

$$j = -D(\partial_x + \beta U'(x))\rho = -De^{-\beta U(x)}\partial_x e^{\beta U(x)}\rho$$

$$-\frac{j}{D}\int_x^b dx e^{\beta U(x)} = e^{\beta U(b)}\rho(b) - e^{\beta U(x)}\rho(x)$$

$$\frac{j}{D}\int_a^x dy e^{-\beta U(y)}\int_y^b dz e^{\beta U(z)} = \int_a^x dx \rho(x) = N$$

$$j = N/\tau$$



$$\boxed{\delta U^\ddagger / k_B T \gg 1}$$

$$\tau = \frac{1}{D}\int_a^x dy e^{-\beta U(y)}\int_y^b dz e^{\beta U(z)} \quad \to \frac{2\pi k_B T}{Dm\omega_{ts}\omega_0}e^{\beta\delta U^\ddagger}$$

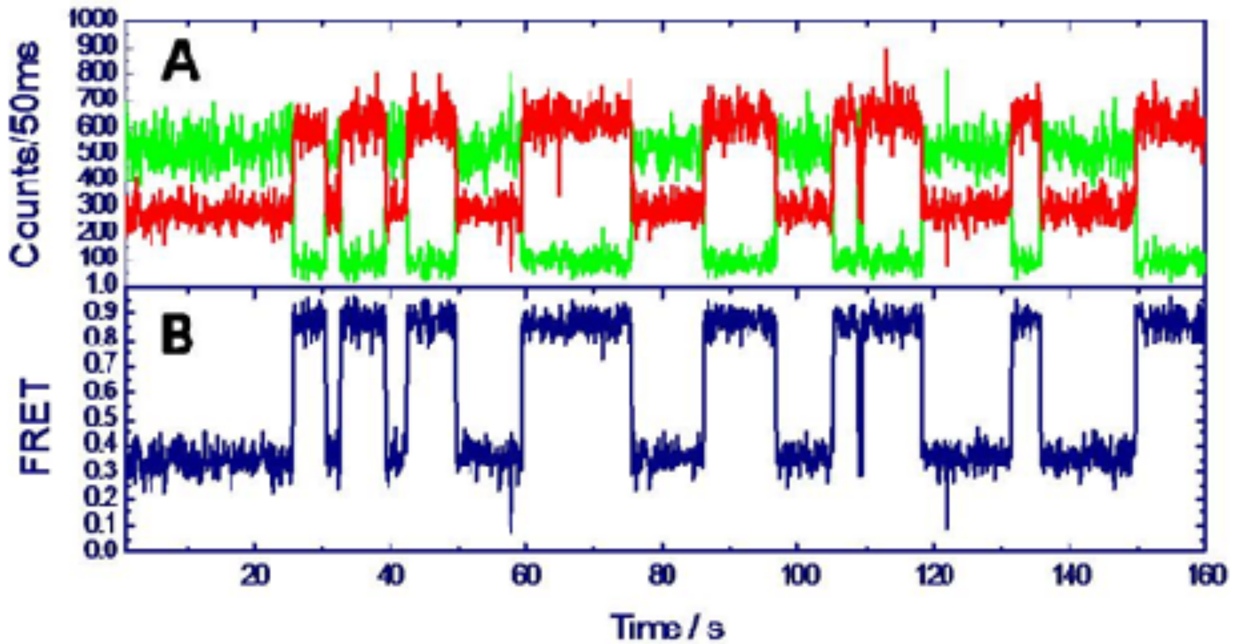
$k(=\tau^{-1})$

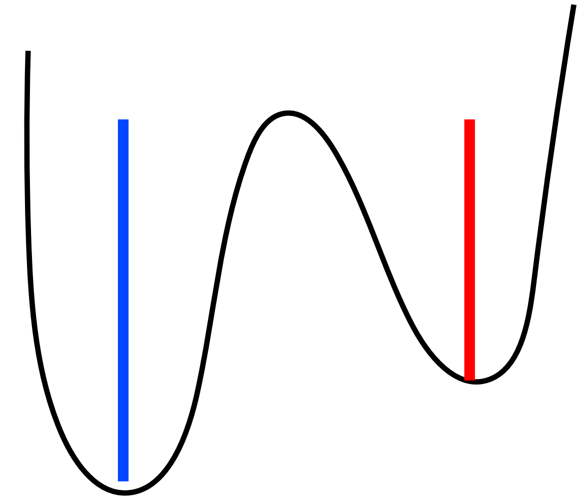
flux-over-population

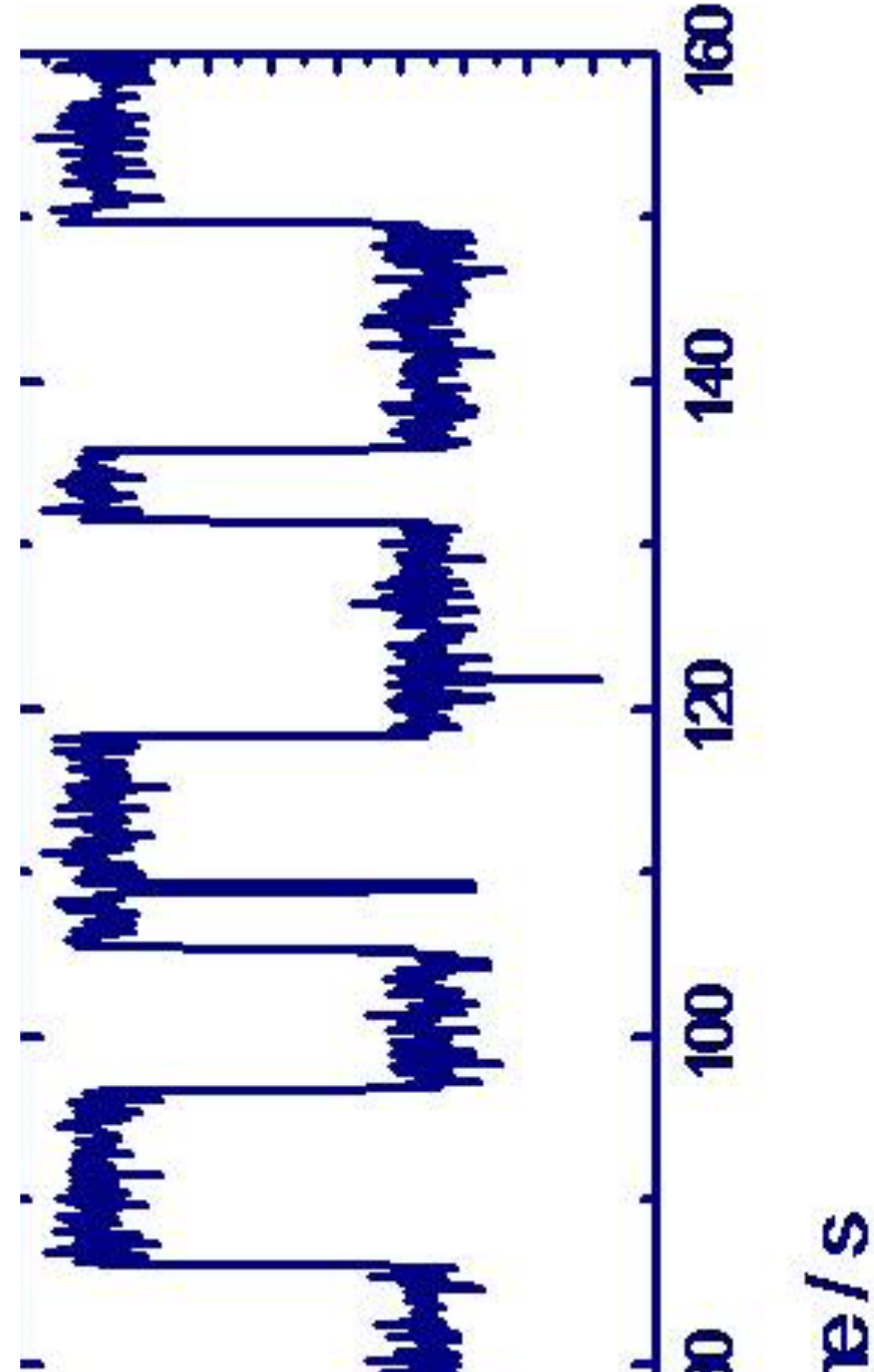
$$\boxed{k_{KR} = \frac{\omega_{ts}\omega_0}{2\pi\gamma}e^{-\beta\delta U^\ddagger}}$$

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

$$\zeta = m\gamma$$







$$\boxed{k_{\rightarrow} = \kappa e^{-\beta \Delta G^{\ddagger}_{\rightarrow}}}$$

$$\boxed{k_{\leftarrow} = \kappa e^{-\beta \Delta G^{\ddagger}_{\leftarrow}}}$$

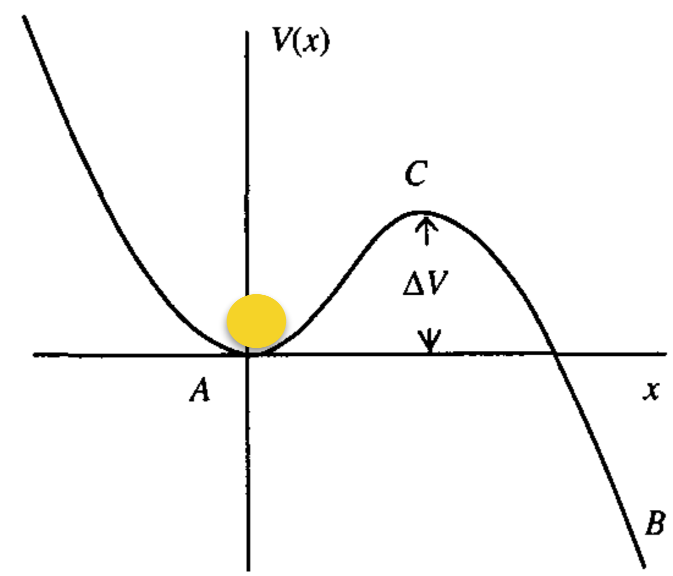
$$K_{eq} = \frac{k_{\rightarrow}}{k_{\leftarrow}} = e^{-\beta \Delta G}$$

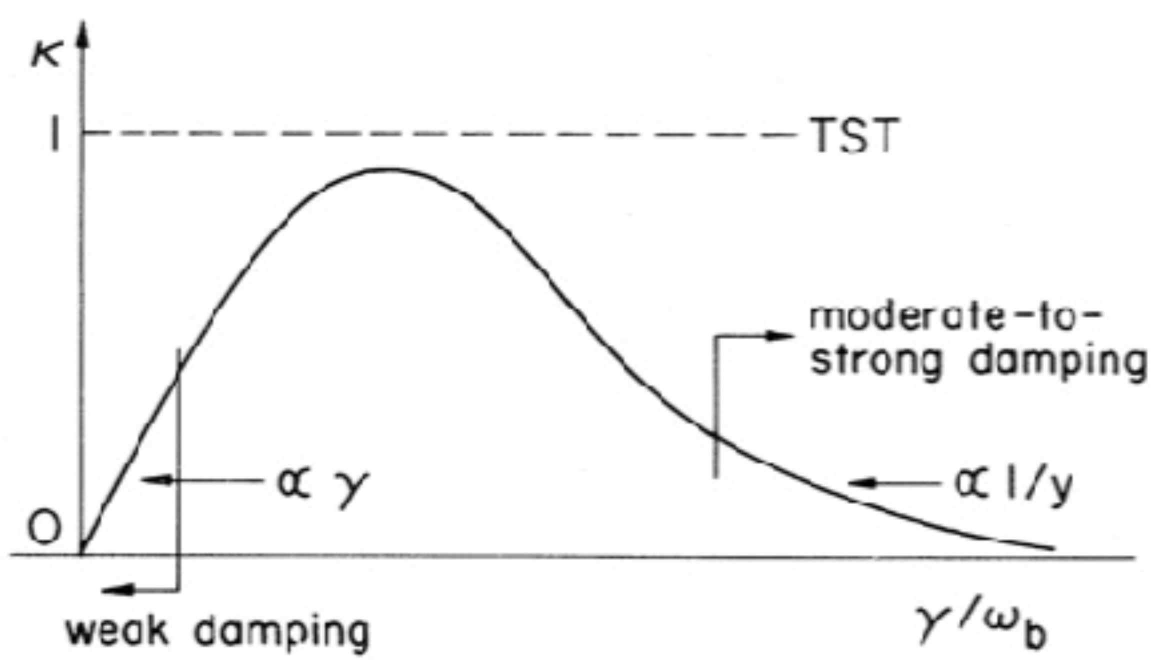
Kramers Escape Rate Theory (noise-induced transition)

cf. $k_{TST} = \dfrac{k_B T}{h} e^{-\beta \delta U^{\ddagger}}$

no coupling to bath

$$k_{KR} = \begin{cases} \text{Intermediate-to-high damping (IHD)} \\ \left[\sqrt{\dfrac{\gamma^2}{4} + \omega_{ts}^2} - \dfrac{\gamma}{2}\right] \dfrac{\omega_0}{2\pi\omega_{ts}} e^{-\beta \Delta U^{\ddagger}} \xrightarrow[2\omega_{ts}/\gamma \ll 1]{} \dfrac{\omega_{ts}\omega_0}{2\pi\gamma} e^{-\beta\delta U^{\ddagger}} \\ \cancel{\cdots\cdots\xrightarrow[\gamma/2\omega_{ts} \ll 1]{} \dfrac{\omega_0}{2\pi} e^{-\beta\delta U^{\ddagger}}} \\ \text{very low damping (VLD)} \\ \gamma I(E_{ts}) \ll k_B T \\ \dfrac{\omega_0}{2\pi} \dfrac{\gamma I(E_{ts})}{k_B T} e^{-\delta U^{\ddagger}/k_B T} \end{cases}$$





Kramers, *Physica* (1940) 7, 284
Grote & Hynes, *J. Chem. Phys.* (1980) 73, 2715
Hanggi, Talkner, Borkovec, *RMB* (1990)

Separation of time scale (or thermal equil. at A) should be ensured $\delta U^{\ddagger}/k_B T \gg 1$

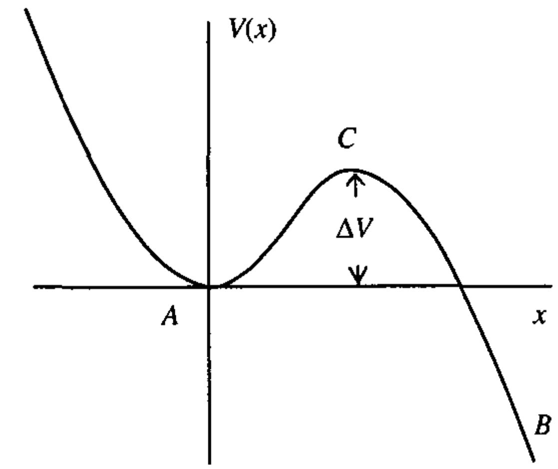
Klein-Kramers eqn.

$$\partial_t \rho = \underbrace{-(p/m)\partial_x \rho + U'(x)\partial_p \rho}_{-\mathcal{L}_o \rho} + \underbrace{\zeta k_B T \partial_p((p/mk_BT)\rho + \partial_p \rho)}_{\zeta k_B T \partial_p \rho_{eq} \partial_p (\rho/\rho_{eq})}$$

$$H = p^2/2m + U(x)$$

$$\rho_{eq} = e^{-(\frac{p^2}{2m} + U(x))/k_BT}/Q$$

$$g(E;t) = \int dx \int dp \delta(H(x,p) - E)\rho(x,p;t)$$



$$\partial_t g(E,t) = \frac{\partial}{\partial E} D(E) g_{eq}(E) \frac{\partial}{\partial E} \frac{g(E,t)}{g_{eq}(E)} \quad (\mathcal{L}_o H = 0)$$

$$\begin{aligned} D(E) &= \zeta k_B T \frac{\int dx \int dp (p/m)^2 \delta(H-E)}{\int dx \int dp \delta(H-E)} \\ &= \frac{2\zeta k_B T}{m} \frac{\int dx \sqrt{E - U(x)}}{\int dx \frac{1}{\sqrt{E-U(x)}}} \\ &= \frac{\zeta k_B T I(E)}{m} \left(\frac{dI(E)}{dE} \right)^{-1} \\ &= \frac{\zeta k_B T}{m} I(E) \frac{\omega_0}{2\pi} \end{aligned}$$

cf. $\partial_t \rho(x,t) = \partial_x D(x) e^{-\beta U(x)} \partial_x e^{\beta U(x)} \rho(x,t)$

$$\tau(x) = \int_x^b dy \frac{e^{\beta U(y)}}{D(y)} \int_a^y dz e^{-\beta U(z)}$$

$$\tau(E) = \int_E^{E_C} dE' \frac{1}{D(E') g_{eq}(E')} \int_0^{E'} dE g_{eq}(E)$$

$$= \frac{2\pi m k_B T}{\zeta} \frac{1}{\omega_0 I(E_C)} e^{\beta E_C} \longrightarrow k_{KR}^{\mathrm{VLD}} = \frac{\omega_0}{2\pi} \frac{\gamma I(E_{ts})}{k_B T} e^{-\beta \delta U^{\ddagger}}$$

Extension of Kramers' Theory to Multi-dimension

J. S. Langer *Ann. Phys.* (1969), 54, 258

$$k = \frac{\lambda_+}{2\pi}\left[\frac{\det F^{(A)}}{\left|\det F^{(S)}\right|}\right]^{1/2} \exp\left(-\beta F^{\ddagger}(f)\right) \qquad F \approx F^{S,A} + \frac{1}{2}\sum_{i,j}\frac{\partial^2 F^{S,A}}{\partial\eta_i \partial\eta_j}(\eta_i - \eta_i^{S,A})(\eta_j - \eta_j^{S,A})$$

flux-over-population from
multi-dimensional Fokker-Planck eq.

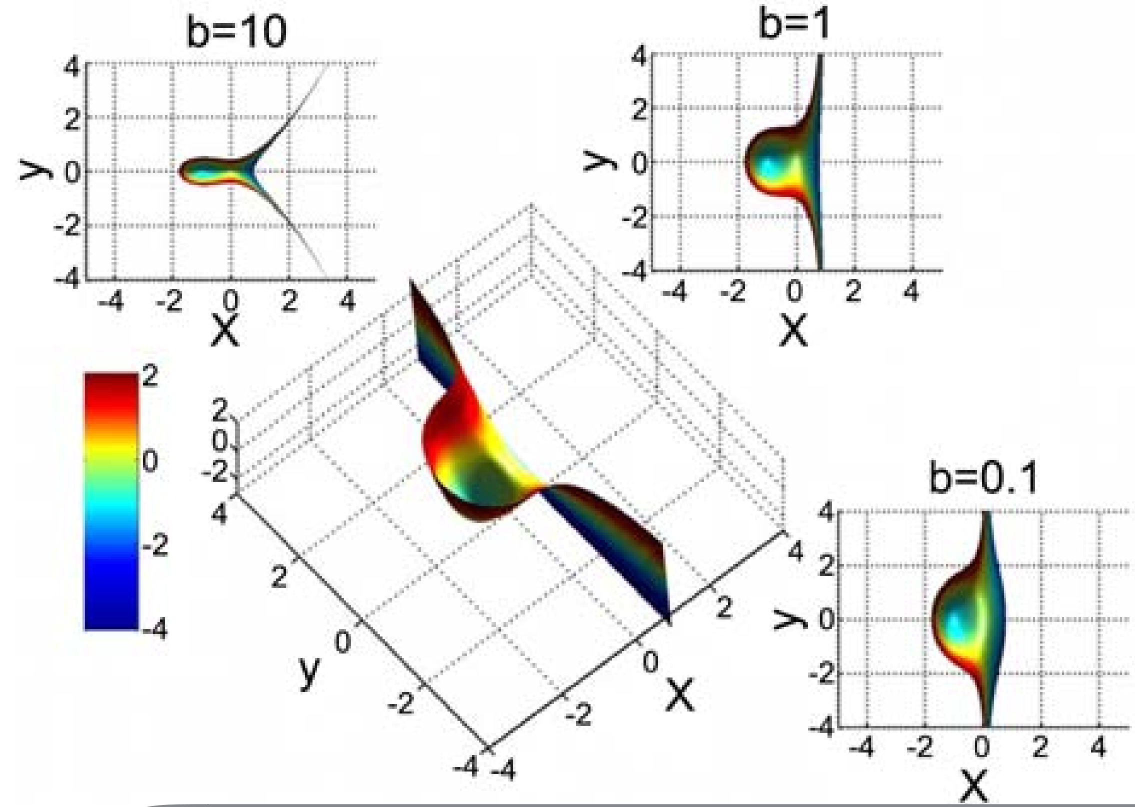
λ_+ : deterministic growth rate
at the saddle point
(Largest eigenvalue of
Matrix *Me*)

$$\dot{\eta}_i = -\sum_j M_{ij}\frac{\partial H}{\partial \eta_j}$$: Hamilton's equation of motion

$$\frac{\partial H}{\partial \eta_j} = \sum_k \left(\frac{\partial^2 H}{\partial \eta_j \eta_k}\right)_{S,A} \delta\eta_k^{S,A} = \sum_k e_{jk}\delta\eta_k^{S,A}$$

$$\dot{\eta}_i = -\sum_{j,k} \underline{M_{ij}e_{jk}}\delta\eta_k$$

e.g. Hyeon, *BKCS* (2012) 33, 897



$$F(x,y) = -F^{\ddagger}\left[2\left(\frac{x}{x^{\ddagger}}\right)^3 + 3\left(\frac{x}{x^{\ddagger}}\right)^2\right] - \kappa\left[\left(\frac{x}{x^{\ddagger}}\right) - b\right]y^2$$

$$H(x,y,p_x,p_y) = \frac{p_x^2}{2m} + \frac{p_y^2}{2m} + F(x,y)$$

$$\dot{x} = \frac{\partial H}{\partial p_x} \qquad \dot{y} = \frac{\partial H}{\partial p_y}$$

$$\dot{p}_x = -m\zeta_{xx}p_x - \frac{\partial F}{\partial x} = -\zeta_{xx}\frac{\partial H}{\partial p_x} - \frac{\partial H}{\partial x}$$

$$\dot{p}_y = -m\zeta_{yy}p_y - \frac{\partial F}{\partial y} = -\zeta_{yy}\frac{\partial H}{\partial p_y} - \frac{\partial H}{\partial y}$$

$$\dot{\eta}_i = -\sum_j M_{ij}\frac{\partial H}{\partial \eta_j}$$

$$\frac{\partial H}{\partial \eta_j} = \sum_k \left(\frac{\partial^2 H}{\partial \eta_j \eta_k}\right)_{S,A} \delta\eta_k^{S,A} = \sum_k e_{jk}\delta\eta_k^{S,A}$$

$$\dot{\eta}_i = -\sum_{j,k} M_{ij}e_{jk}\delta\eta_k$$

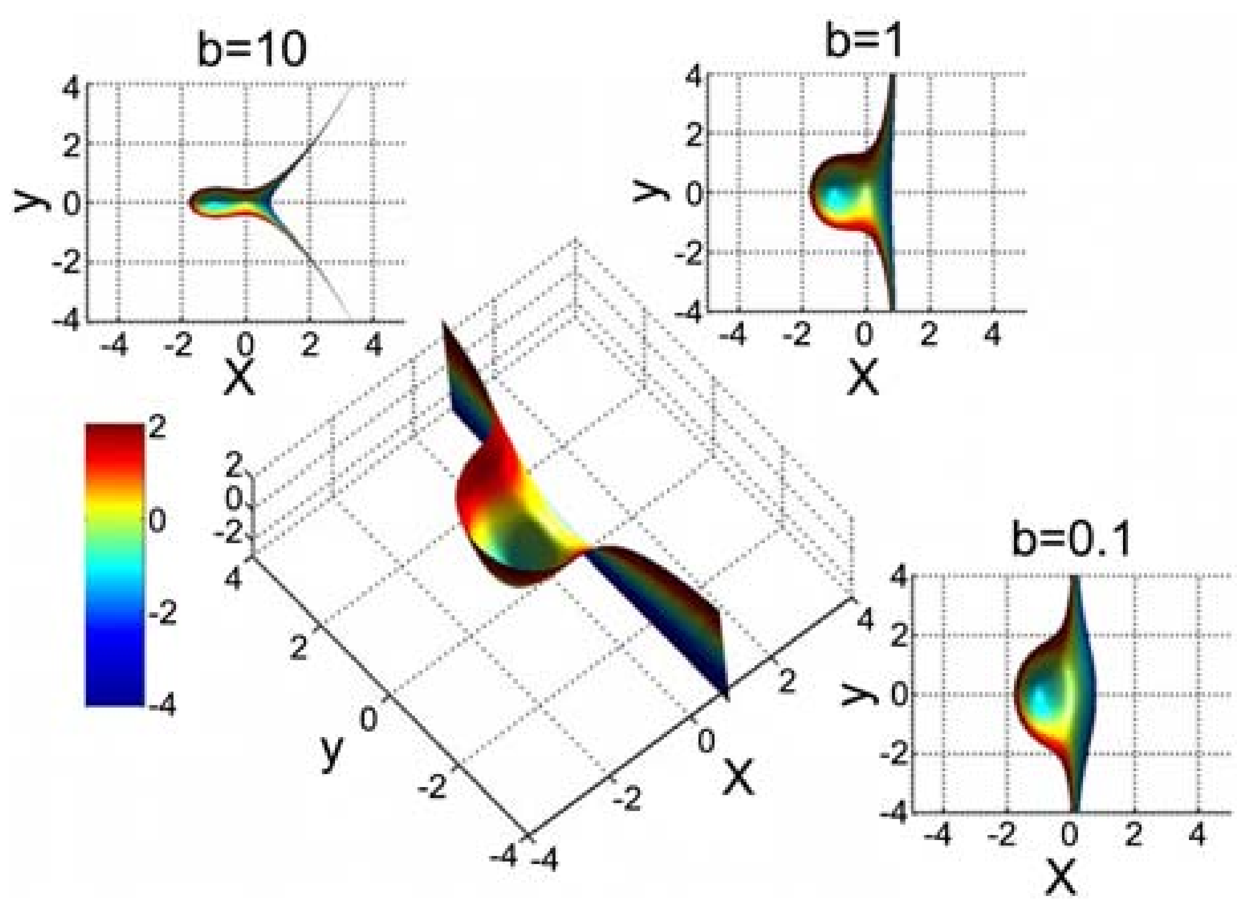
$$\begin{pmatrix} \dot{x} \\ \dot{y} \\ \dot{p}_x \\ \dot{p}_y \end{pmatrix} = -\begin{pmatrix} 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & -1 \\ 1 & 0 & \zeta_{xx} & 0 \\ 0 & 1 & 0 & \zeta_{yy} \end{pmatrix} \begin{pmatrix} \partial H/\partial x \\ \partial H/\partial y \\ \partial H/\partial p_x \\ \partial H/\partial p_y \end{pmatrix} \qquad e^{S,A} = \begin{pmatrix} \mp 6F^{\ddagger}/(x^{\ddagger})^2 & 0 & 0 & 0 \\ 0 & \kappa(2b+1\mp 1) & 0 & 0 \\ 0 & 0 & 1/m & 0 \\ 0 & 1 & 0 & 1/m \end{pmatrix}$$

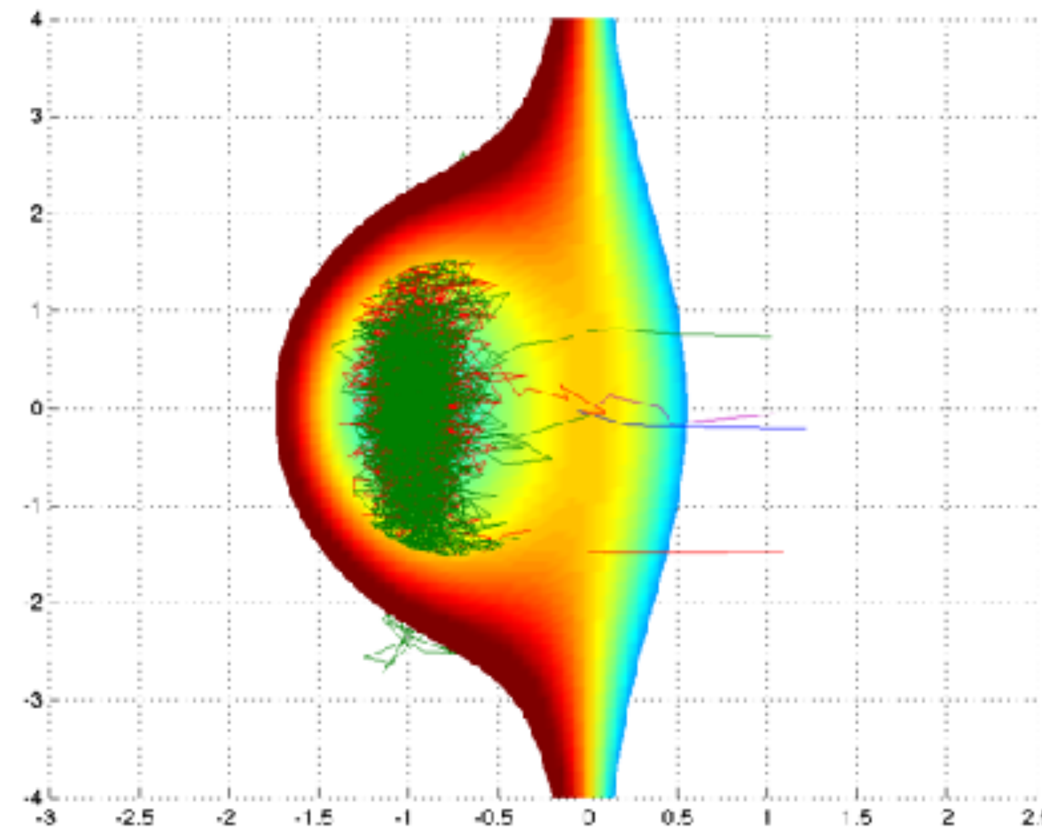
$$\lambda_+ = -\frac{\zeta_{xx}}{2m} + \sqrt{\left(\frac{\zeta_{xx}}{2m}\right)^2 + \frac{6F^{\ddagger}}{m(x^{\ddagger})^2}}$$

Another important condition for Kramers' theory

$$F(x,y) = -F^{\ddagger}\left[2\left(\frac{x}{x^{\ddagger}}\right)^3 + 3\left(\frac{x}{x^{\ddagger}}\right)^2\right] - \kappa\left[\left(\frac{x}{x^{\ddagger}}\right) - b\right]y^2$$

$$k = \frac{\lambda_+}{2\pi}\left[\frac{\det F^{(A)}}{\left|\det F^{(S)}\right|}\right]^{1/2}\exp\left(-\beta F^{\ddagger}(f)\right)$$





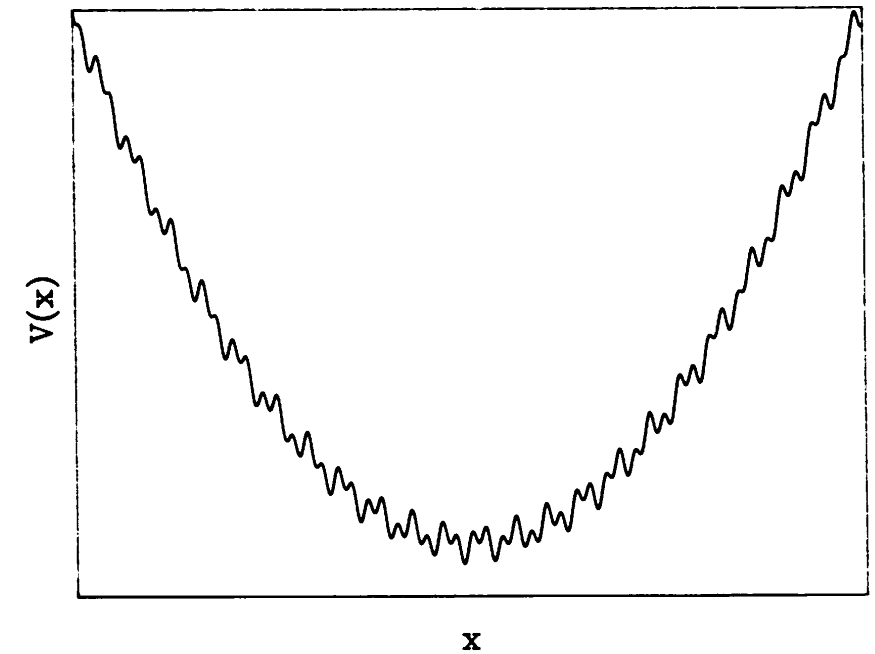
“The saddle point” should be well defined.

Hyeon, *BKCS* (2012) 33, 897

Proc. Natl. Acad. Sci. USA
Vol. 85, pp. 2029–2030, April 1988
Physics

Diffusion in a rough potential

ROBERT ZWANZIG



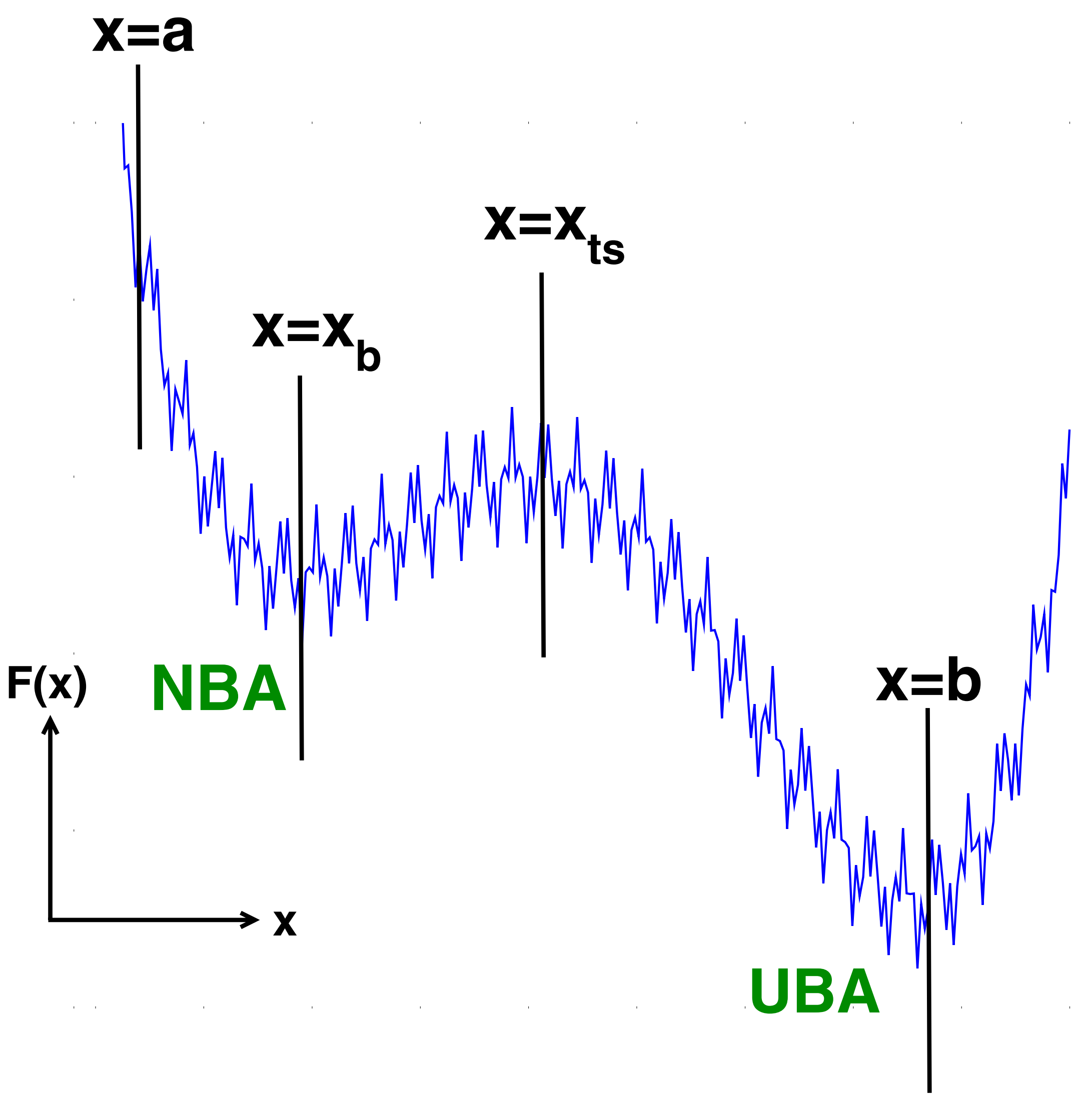
$$\tau = \frac{1}{D}\int_a^x dy e^{-\beta U(y)} \int_y^b dz e^{\beta U(z)}$$

$$\tau = \frac{1}{D}\int_a^x dy e^{-\beta(U_0(y)+\delta U)} \int_y^b dz e^{\beta(U_0(z)+\delta U)}$$

$$\approx \frac{1}{D}\int_a^x dy e^{-\beta U_0(y)}\langle e^{-\beta\delta U}\rangle \int_y^b dz e^{\beta U_0(z)}\langle e^{\beta\delta U}\rangle$$

$$D \to D^* = D\langle e^{-\beta\delta U}\rangle^{-1}\langle e^{+\beta\delta U}\rangle^{-1} \approx De^{-\beta^2\langle(\delta U)^2\rangle}$$

$$D^* = De^{-(\varepsilon/k_B T)^2}$$



$$k = \frac{D^* m\omega_{ts}\omega_b}{2\pi k_B T} e^{-\delta F^\ddagger / k_B T}$$

$$= \frac{D m\omega_{ts}\omega_b}{2\pi k_B T} e^{-\delta F^\ddagger / k_B T} e^{-\varepsilon^2/(k_B T)^2}$$

Dynamical processes in the presence of sink - Wilemski-Fixman formalism

J. Chem. Phys., (1973) , 58 , 4009; ibid (1974), 60, 886

$$\frac{\partial\psi(\{\mathbf{r}_i\},t)}{\partial t} = \mathcal{L}(\{\mathbf{r}_i\})\psi(\{\mathbf{r}_i\},t) - k\mathcal{S}(\{\mathbf{r}_i\})\psi(\{\mathbf{r}_i\},t)$$

$$\tilde{\psi}(\{\mathbf{r}_i\},z) = (z-\mathcal{L}(\{\mathbf{r}_i\})+k\mathcal{S}(\{\mathbf{r}_i\}))^{-1}\psi(\{\mathbf{r}_i\},0)$$

$$= \left(1-\frac{1}{z-\mathcal{L}(\{\mathbf{r}_i\})}k\mathcal{S}(\{\mathbf{r}_i\})+\cdots\right)\frac{1}{z-\mathcal{L}(\{\mathbf{r}_i\})}\psi(\{\mathbf{r}_i\},0)$$

$$= \frac{1}{z-\mathcal{L}(\{\mathbf{r}_i\})}\psi(0) - \frac{1}{z-\mathcal{L}(\{\mathbf{r}_i\})}k\mathcal{S}(\{\mathbf{r}_i\})\tilde{\psi}(\{\mathbf{r}_i\},z)$$

$$\psi(\{\mathbf{r}_i\},t) = e^{t\mathcal{L}}\psi(0) - k\int_0^t d\tau e^{(t-\tau)\mathcal{L}(\{\mathbf{r}_i\})}\mathcal{S}(\{\mathbf{r}_i\})\psi(\{\mathbf{r}_i\},\tau)$$

cf. $e^{t(A+B)} = e^{tA} + \int_0^t dse^{(t-s)(A+B)}Be^{tA}$

$$= e^{-t\mathcal{L}}\psi(0) - k\int_0^t d\tau\int d\{\mathbf{r}'_i\}\underline{\left[e^{(t-\tau)\mathcal{L}(\{\mathbf{r}_i\})}\delta(\{\mathbf{r}_i\}-\{\mathbf{r}'_i\})\right]}\,\mathcal{S}(\{\mathbf{r}'_i\})\psi(\{\mathbf{r}'_i\},\tau)$$

$\psi(\{\mathbf{r}_i\},0) = \psi_{eq}(\{\mathbf{r}_i\})$

$$= \psi_{eq}(\{\mathbf{r}_i\}) - k\int_0^t d\tau\int d\{\mathbf{r}'_i\}\mathcal{G}(\{\mathbf{r}_i\},t|\{\mathbf{r}'_i\},\tau)\mathcal{S}(\{\mathbf{r}'_i\})\psi(\{\mathbf{r}'_i\},\tau)$$

$$\psi(\{\mathbf{r}_i\},t) = \psi_{eq}(\{\mathbf{r}_i\}) - k\int_0^t d\tau \int d\{\mathbf{r}'_i\}\mathcal{G}(\{\mathbf{r}_i\},t|\{\mathbf{r}'_i\},\tau)\mathcal{S}(\{\mathbf{r}'_i\})\psi(\{\mathbf{r}'_i\},\tau)$$

$$\Big\downarrow \int d\{\mathbf{r}_i\}\mathcal{S}(\{\mathbf{r}_i\}) \qquad\qquad \mu(t) \equiv \int d\{\mathbf{r}_i\}\mathcal{S}(\{\mathbf{r}_i\})\psi(\{\mathbf{r}_i\},t)$$

$$\mu(t) = \mu_{eq} - k\int_0^t d\tau \int d\{\mathbf{r}_i\}\int d\{\mathbf{r}'_i\}\mathcal{S}(\{\mathbf{r}_i\})\mathcal{G}(\{\mathbf{r}_i\},t|\{\mathbf{r}'_i\},\tau)\mathcal{S}(\{\mathbf{r}'_i\})\psi(\{\mathbf{r}'_i\},\tau)$$

$$\Big\downarrow \quad \frac{\psi(\{\mathbf{r}'_i\},t)}{\psi_{eq}(\{\mathbf{r}'_i\})} \approx \frac{\int d\{\mathbf{r}'_i\}\mathcal{S}(\{\mathbf{r}'_i\})\psi(\{\mathbf{r}'_i\},t)}{\int d\{\mathbf{r}'_i\}\mathcal{S}(\{\mathbf{r}'_i\})\psi_{eq}(\{\mathbf{r}'_i\})} = \frac{\mu(t)}{\mu_{eq}}$$

closure approximation

(cf. local equilibrium approx.)

$$\mu(t) \approx \mu_{eq} - k\int_0^t d\tau \underbrace{\left[\int d\{\mathbf{r}_i\}\int d\{\mathbf{r}'_i\}\mathcal{S}(\{\mathbf{r}_i\})\mathcal{G}(\{\mathbf{r}_i\},t|\{\mathbf{r}'_i\},\tau)\mathcal{S}(\{\mathbf{r}'_i\})\psi_{eq}(\{\mathbf{r}'_i\})\right]}_{\equiv C(t,\tau)}(\mu(t)/\mu_{eq})$$

$$C(t,\tau) = C(t-\tau)$$

$$\mu(t) \approx \mu_{eq} - \frac{k}{\mu_{eq}}\int d\tau C(t-\tau)\mu(\tau)$$

$$\boxed{\mu(t) \approx \mu_{eq} - \frac{k}{\mu_{eq}} \int d\tau C(t-\tau)\mu(\tau)} \longrightarrow \tilde{\mu}(z) = z^{-1}\left(1 + \frac{k}{\mu_{eq}}\tilde{C}(z)\right)^{-1}\mu_{eq}$$

Our objective is to compute **mfpt**

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

$$\phi(t) = \int d\{\mathbf{r}_i\}\psi(\{\mathbf{r}_i\}, t)$$

$$\frac{\partial \psi(\{\mathbf{r}_i\}, t)}{\partial t} = \mathcal{L}(\{\mathbf{r}_i\})\psi(\{\mathbf{r}_i\}, t) - k\mathcal{S}(\{\mathbf{r}_i\})\psi(\{\mathbf{r}_i\}, t)$$

$$\frac{\partial \phi(t)}{\partial t} = -k\mu(t) \longrightarrow \tilde{\phi}(z) = z^{-1}(1 - k\tilde{\mu}(z))$$

$$\langle t \rangle = \int_0^\infty dt \phi(t) = \lim_{z\to 0} \tilde{\phi}(z) = \lim_{z\to 0} (1 - k\tilde{\mu}(z)) \left(1 + \frac{k}{\mu_{eq}}\tilde{C}(z)\right) \frac{\tilde{\mu}(z)}{\mu_{eq}}$$

$$= \lim_{z\to 0} \left(1 + \frac{k}{\mu_{eq}}\tilde{C}(z) - k \underbrace{\tilde{\mu}(z)\left(1 + \frac{k}{\mu_{eq}}\tilde{C}(z)\right)}_{\mu_{eq}/z}\right) \frac{\tilde{\mu}(z)}{\mu_{eq}}$$

$$\langle t\rangle = \int_0^\infty dt\phi(t) = \lim_{z\to 0}\tilde{\phi}(z) = \lim_{z\to 0}\left(1-k\tilde{\mu}(z)\right)\left(1+\frac{k}{\mu_{eq}}\tilde{C}(z)\right)\frac{\tilde{\mu}(z)}{\mu_{eq}}$$

$$\frac{\partial\phi(t)}{\partial t} = -k\mu(t)$$

$$\phi(\infty)-\phi(0) = -k\int_0^\infty dt\mu(t)$$

$$-1 = -k\tilde{\mu}(0)$$

$$= \lim_{z\to 0}\left(1+\frac{k}{\mu_{eq}}\tilde{C}(z) - k\,\underbrace{\tilde{\mu}(z)\left(1+\frac{k}{\mu_{eq}}\tilde{C}(z)\right)}_{\mu_{eq}/z}\right)\frac{\tilde{\mu}(z)}{\mu_{eq}}$$

$$= \lim_{z\to 0}\left(1+\frac{k}{\mu_{eq}}\left(\tilde{C}(z)-\frac{\mu_{eq}^2}{z}\right)\right)\frac{\tilde{\mu}(z)}{\mu_{eq}}$$

$$\langle t\rangle = \frac{1}{k\mu_{eq}} + \int_0^\infty dt\left(\frac{C(t)}{\mu_{eq}^2}-1\right)$$

$$C(t) = \int d\{\mathbf{r}_i\}\int d\{\mathbf{r}_i'\}\mathcal{S}(\{\mathbf{r}_i\})\mathcal{G}(\{\mathbf{r}_i\},t|\{\mathbf{r}_i'\},\tau)\mathcal{S}(\{\mathbf{r}_i'\})\psi_{eq}(\{\mathbf{r}_i'\}) \to C(\infty) = \mu_{eq}^2$$

$$\boxed{\langle t\rangle = \frac{1}{k\mu_{eq}} + \int_0^\infty dt\left(\frac{C(t)}{C(\infty)}-1\right)}$$

Polymer looping time from WF formalism

$$\langle t \rangle = \frac{1}{k\mu_{eq}} + \int_0^\infty dt \left(\frac{C(t)}{C(\infty)} - 1 \right) \xrightarrow{k \to \infty} \langle t \rangle = \int_0^\infty dt \left(\frac{C(t)}{C(\infty)} - 1 \right)$$

$$\mathcal{S}(\{\mathbf{r}_i\}) = \frac{\delta(r - \sigma)}{4\pi\sigma^2}$$

$$C(t) = \int d\{\mathbf{r}_i\} \int d\{\mathbf{r}_i'\} \mathcal{S}(\{\mathbf{r}_i\}) \mathcal{G}(\{\mathbf{r}_i\}, t | \{\mathbf{r}_i'\}, \tau) \mathcal{S}(\{\mathbf{r}_i'\}) \psi_{eq}(\{\mathbf{r}_i'\})$$

$$\int \left(\prod_{i=1}^{N*} d\mathbf{r}_i \right) \mathcal{G}(\{\mathbf{r}_i\}, t | \{\mathbf{r}_i'\}, 0) \equiv G(r, t | r_0, 0)$$

$C(t) = G(\sigma, t | \sigma, 0)$: returning prob. to r=σ after time t

$$\langle t \rangle = \int_0^\infty dt \left(\frac{G(\sigma, t | \sigma, 0)}{P_{loop}(\sigma)} - 1 \right)$$

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

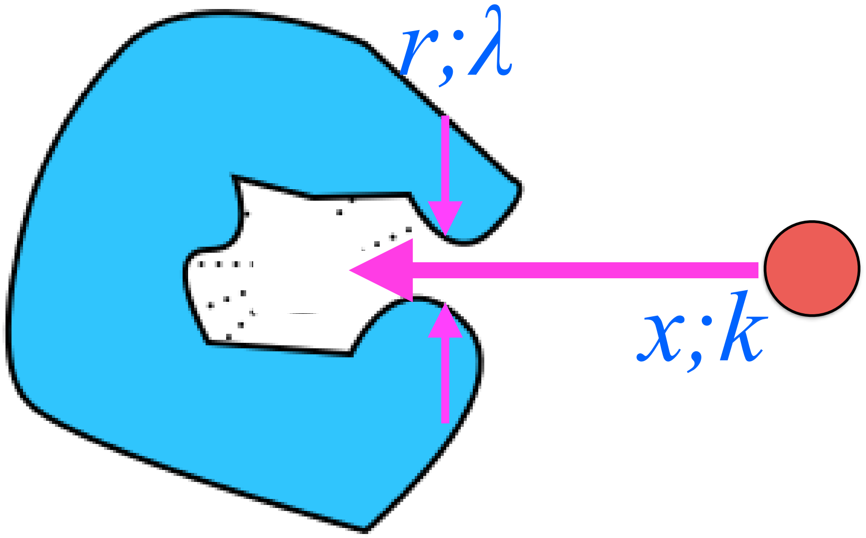
Kinetics from disordered systems:
Binding kinetics of CO to myoglobin in 80s by Frauenfelder & colleagues ….

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

Non-exponential (power-law) binding kinetics, Σ(t)

Fluctuating bottleneck model

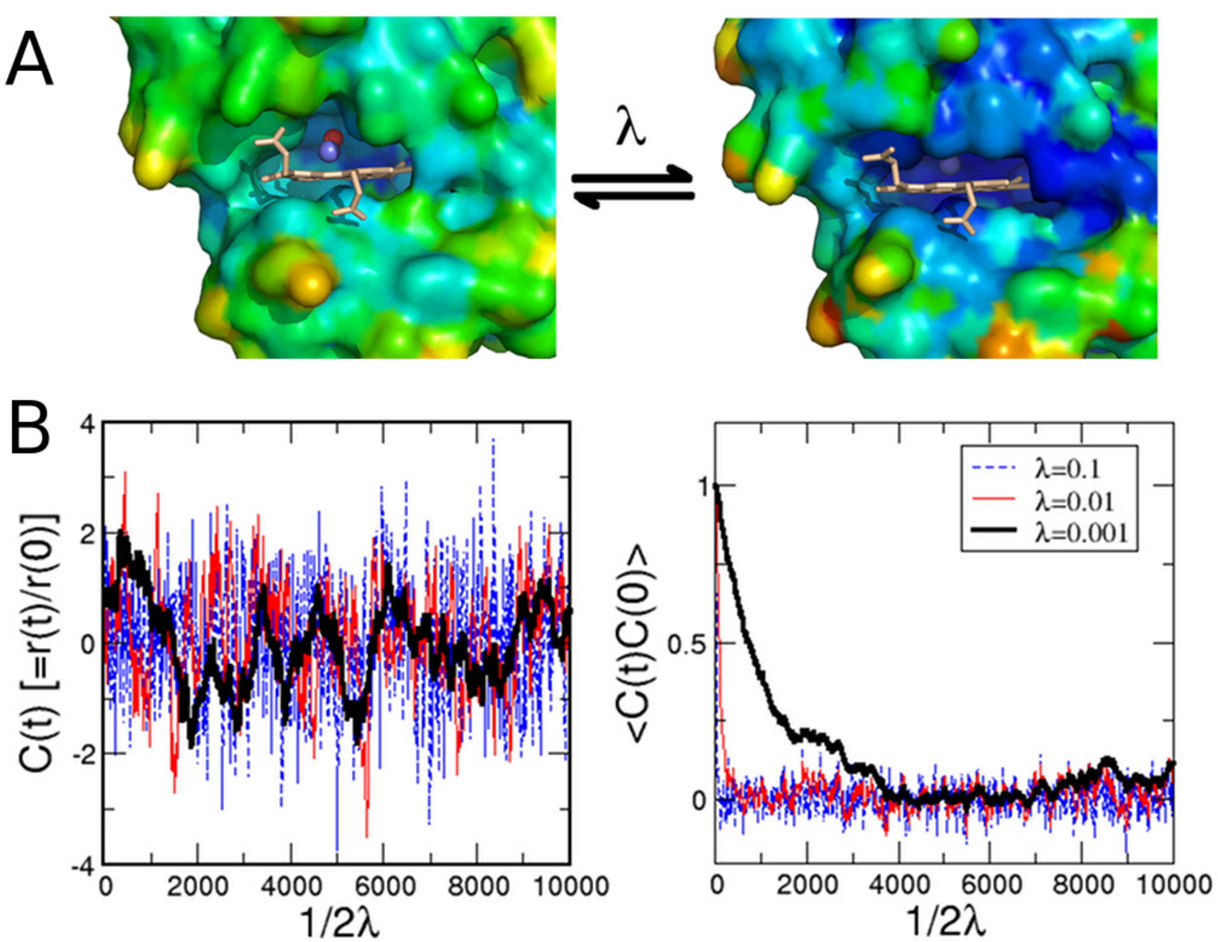
- Zwanzig (1992) JCP.



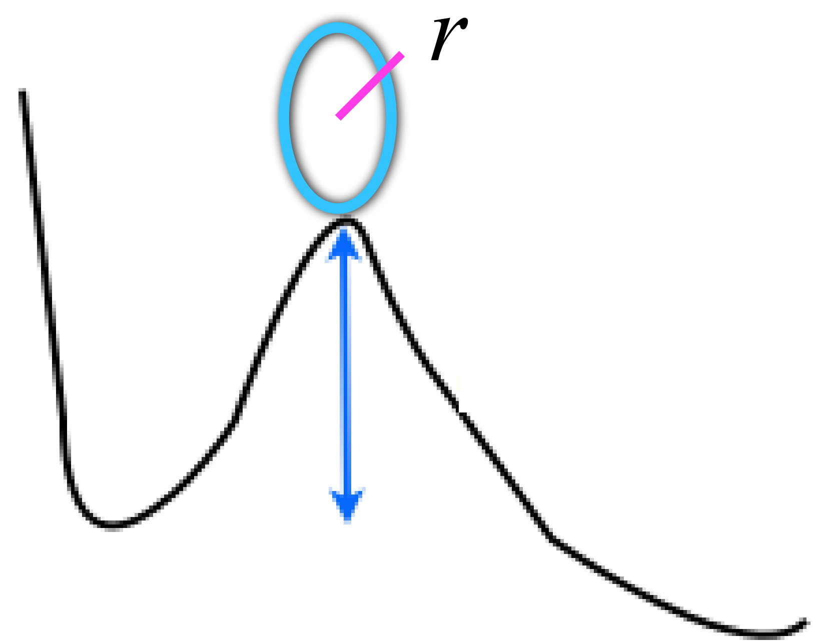
$$\zeta \partial_t x = -\partial_x U_{\text{eff}}(x; r) + F_x(t)$$

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

Binding rate ~ kr^2



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



$$\frac{dC}{dt} = -K(r)C$$

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

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

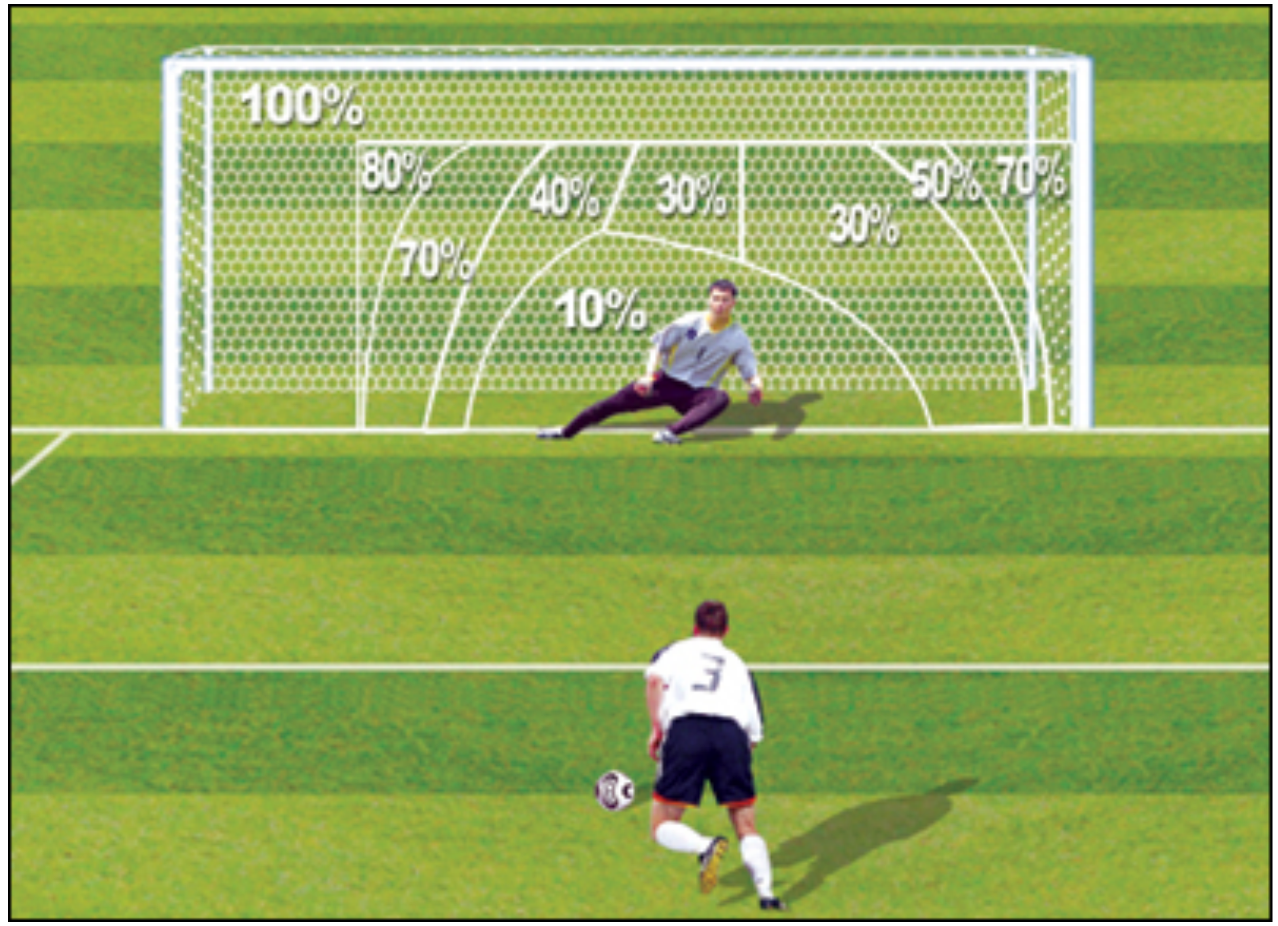
$$\lambda \to \infty \qquad kr^2 \to k\theta$$

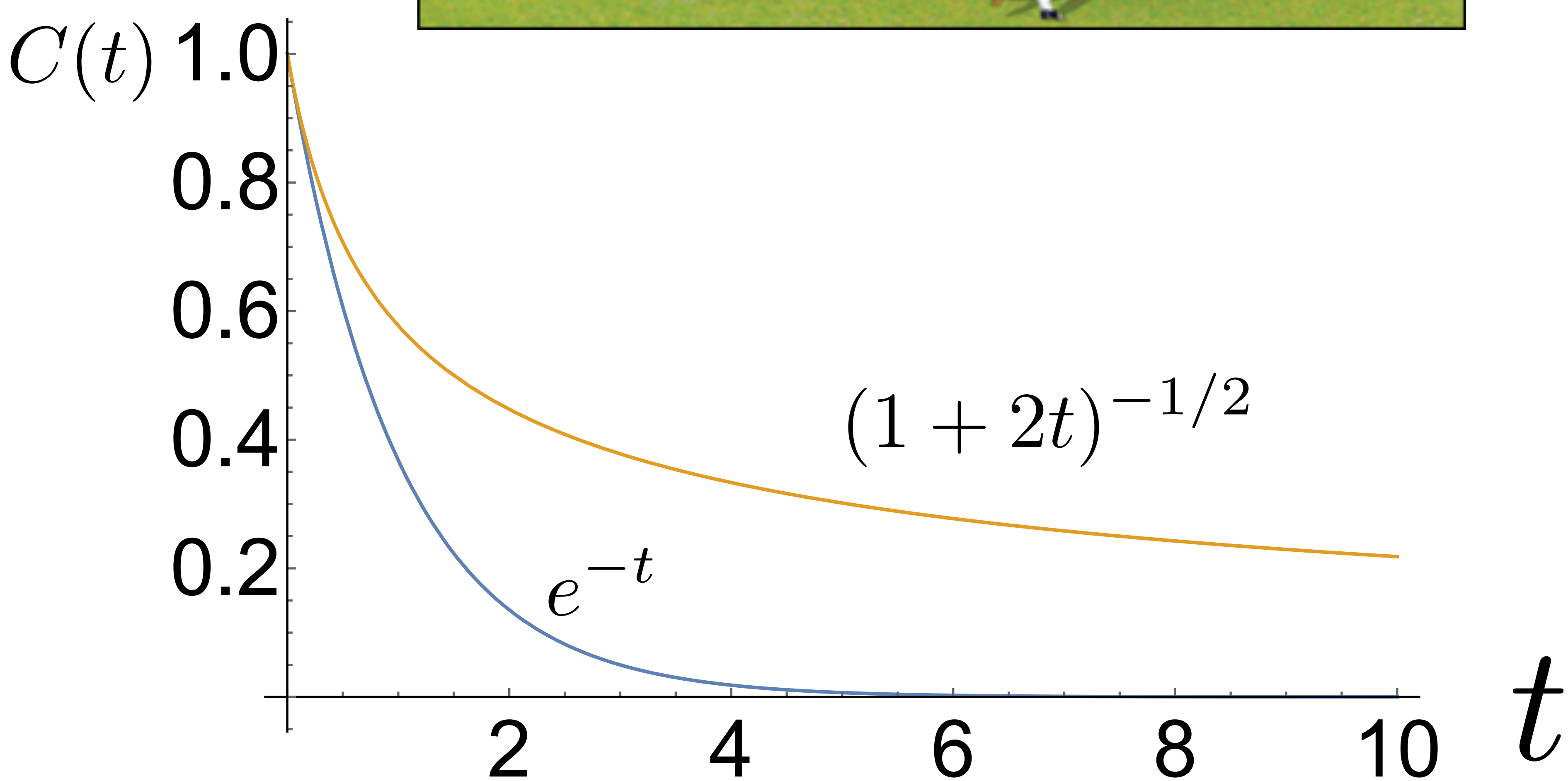
$$C(t) = e^{-k\theta t}$$

$$\lambda \to 0$$

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

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


100%
80%
40%
30%
50%
70%
70%
30%
10%
3


$C(t)$
1.0
0.8
0.6
0.4
0.2
$(1+2t)^{-1/2}$
e^{-t}
2
4
6
8
10
t

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

$$\partial_t r = -\lambda r + F_r(t) \qquad \langle F_r(t) F_r(t') \rangle = 2B\delta(t - t')$$

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

---

1. Determine the noise strength of $F_r(t)$ $\quad B = ?$

$$r(t) = e^{-\lambda t} r(0) + \int_0^t d\tau e^{-\lambda(t-\tau)} F_r(\tau)$$

$$\langle r^2(t) \rangle = e^{-2\lambda t} \langle r^2(0) \rangle + 2B \int_0^t d\tau_1 \int_0^t d\tau_2 e^{-\lambda(2t - \tau_1 - \tau_2)} \delta(\tau_1 - \tau_2)$$

$$\longrightarrow \quad B = \lambda\theta$$

2. Obtain the Fokker Planck eqn. $\quad \partial_t \overline{\rho} = \mathcal{L}_x \overline{\rho} + \mathcal{L}_r \overline{\rho}$

$$\partial_t \rho + \partial_x(\dot{x}\rho) + \partial_r(\dot{r}\rho) = 0$$

$$\partial_t \rho + (\mathcal{L}_x^o + \mathcal{L}_r^o)\rho + \partial_x(F_x(t)/\zeta \times \rho) + \partial_r(F_r(t)\rho) = 0$$

$$\rho(x, r, t) = e^{-\mathcal{L}^o t} - \int_0^t d\tau e^{\mathcal{L}^o (t-\tau)} [\partial_x(F_x(\tau)/\zeta \times \rho(\tau)) + \partial_r(F_r(\tau)\rho(\tau))]$$

$$\boxed{\partial_t \overline{\rho} = \underbrace{D\partial_x(\partial_x + \beta U'(x))}_{\mathcal{L}_x}\overline{\rho} + \underbrace{\lambda\theta\partial_r(\partial_r + r/\theta)}_{\mathcal{L}_r}\overline{\rho}}$$

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

$$\partial_t r = -\lambda r + F_r(t) \qquad \langle F_r(t) F_r(t') \rangle = 2B\delta(t-t')$$

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

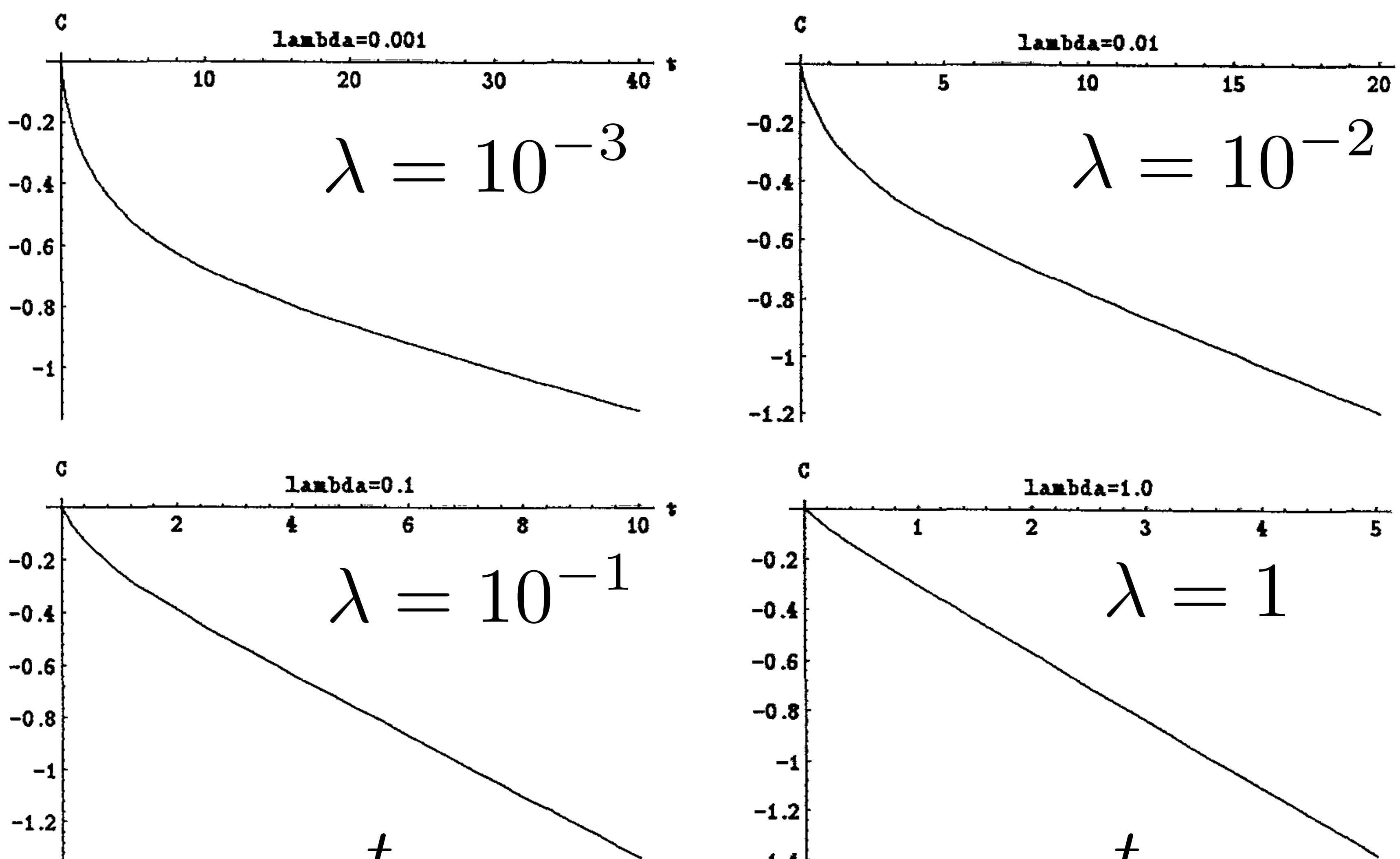
where $S = \left(1 + \frac{4k\theta}{\lambda}\right)^{1/2}$ and $E = e^{-2\lambda S t}$.

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

show this !

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

$(k\theta = 1)$



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

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

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

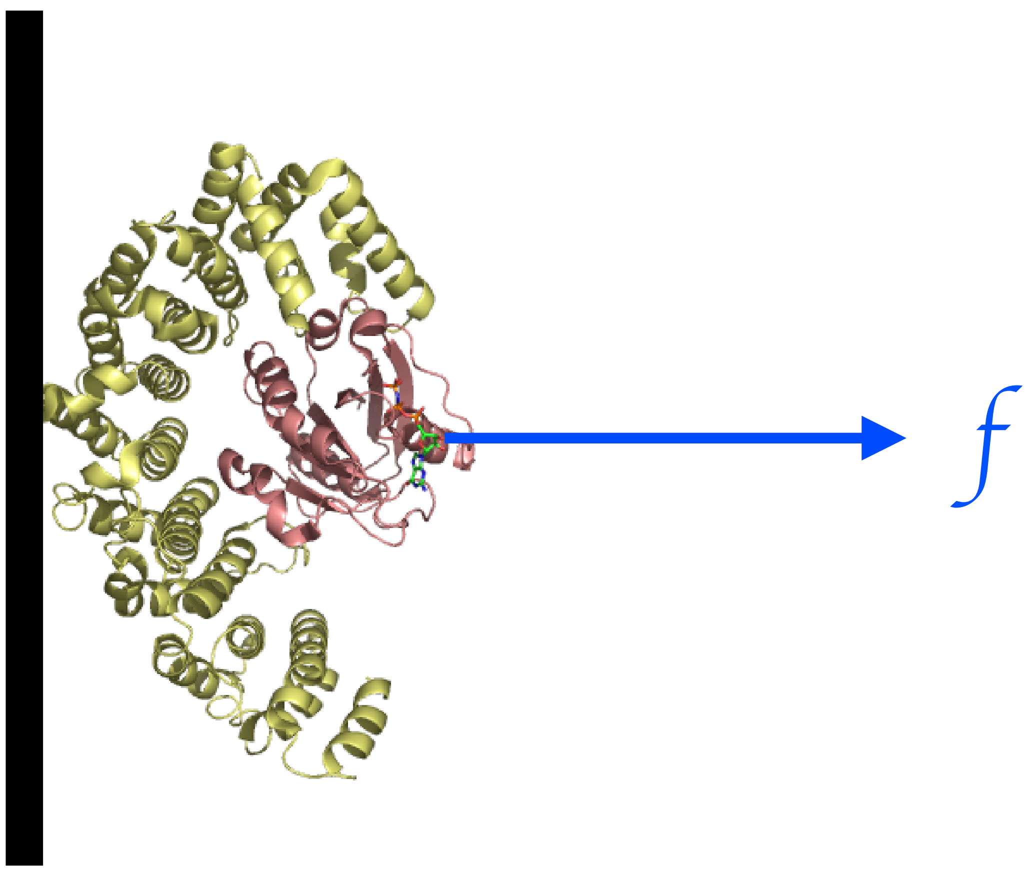
$$\mu_n = \frac{\lambda}{2}(S-1) + 2n\lambda S$$

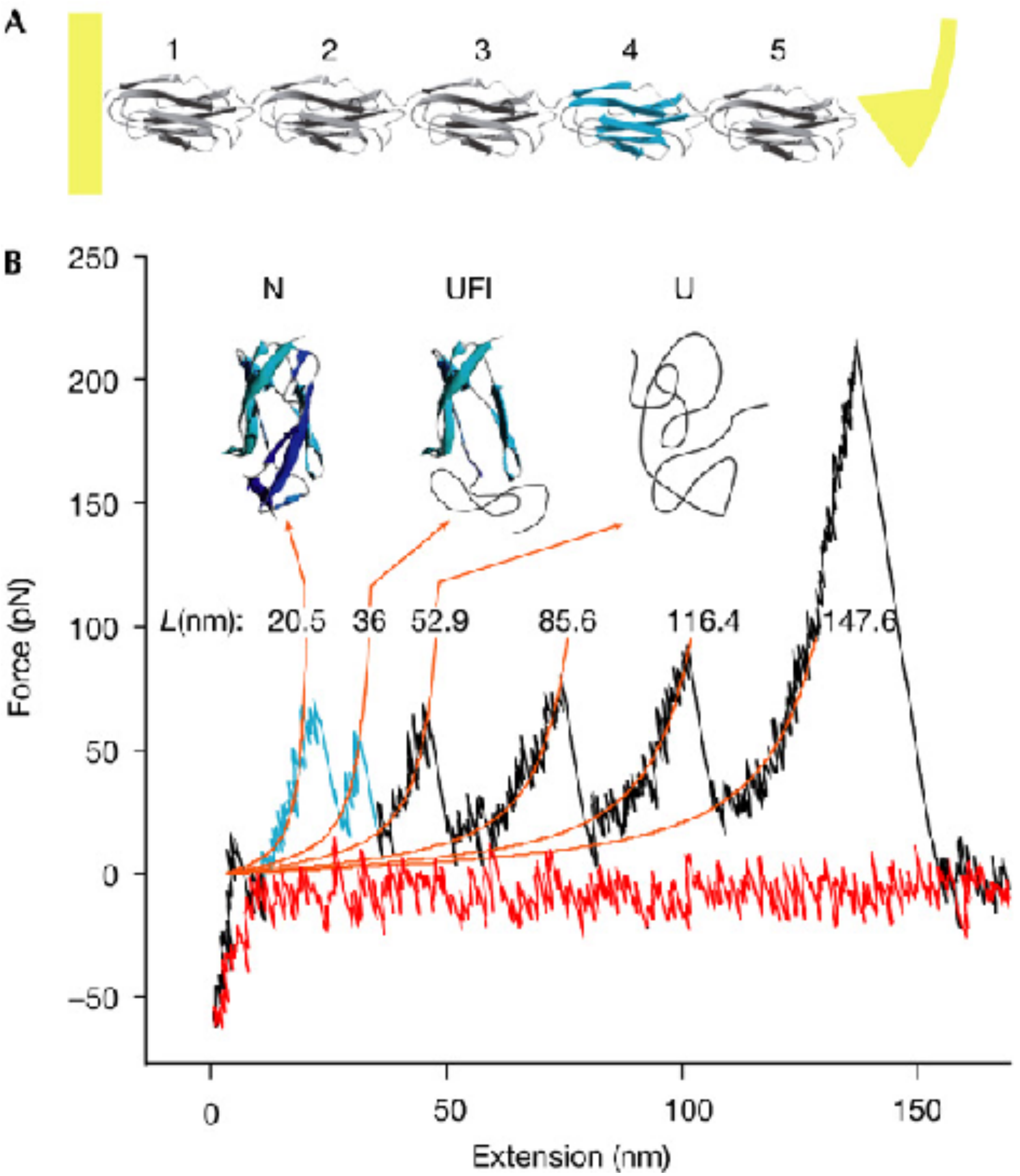
$$\mu_0 = \frac{\lambda}{2}(S-1) = \frac{\lambda}{2}\left(\left(1+\frac{4k\theta}{\lambda}\right)^{1/2} - 1\right)$$

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

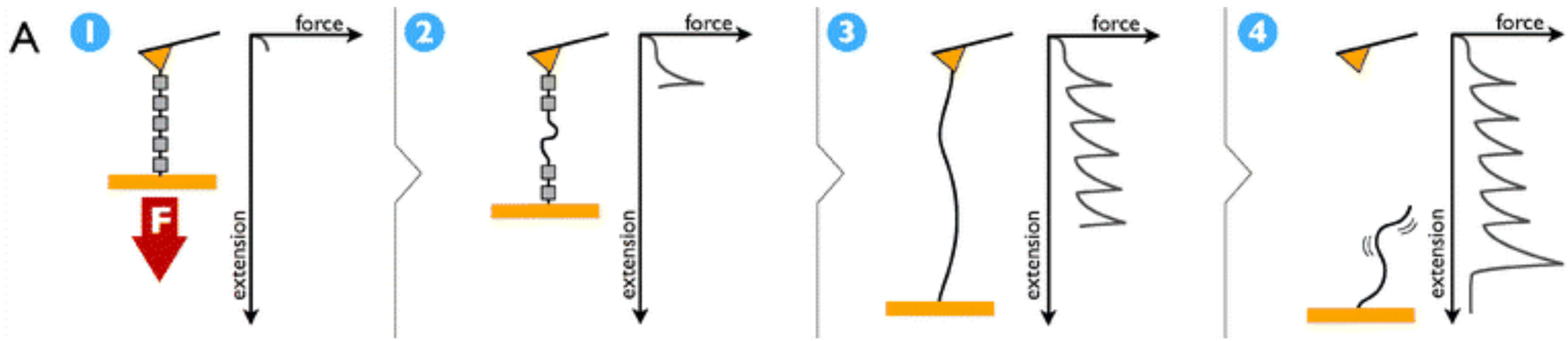
$$\mu_0(\lambda \to 0) \approx (k\theta\lambda)^{1/2} \sim \eta^{-1/2}$$

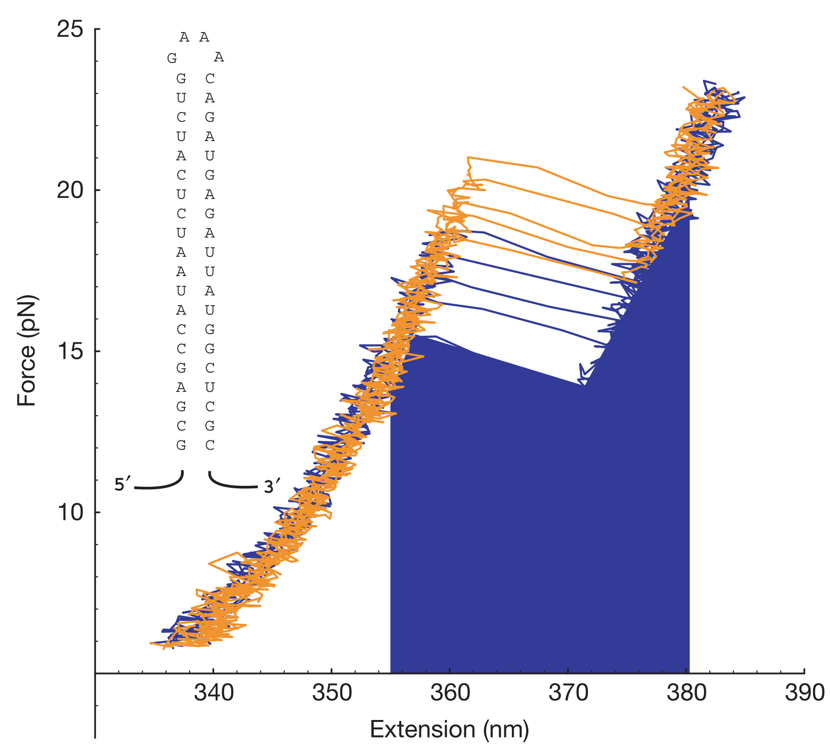
Force spectroscopy

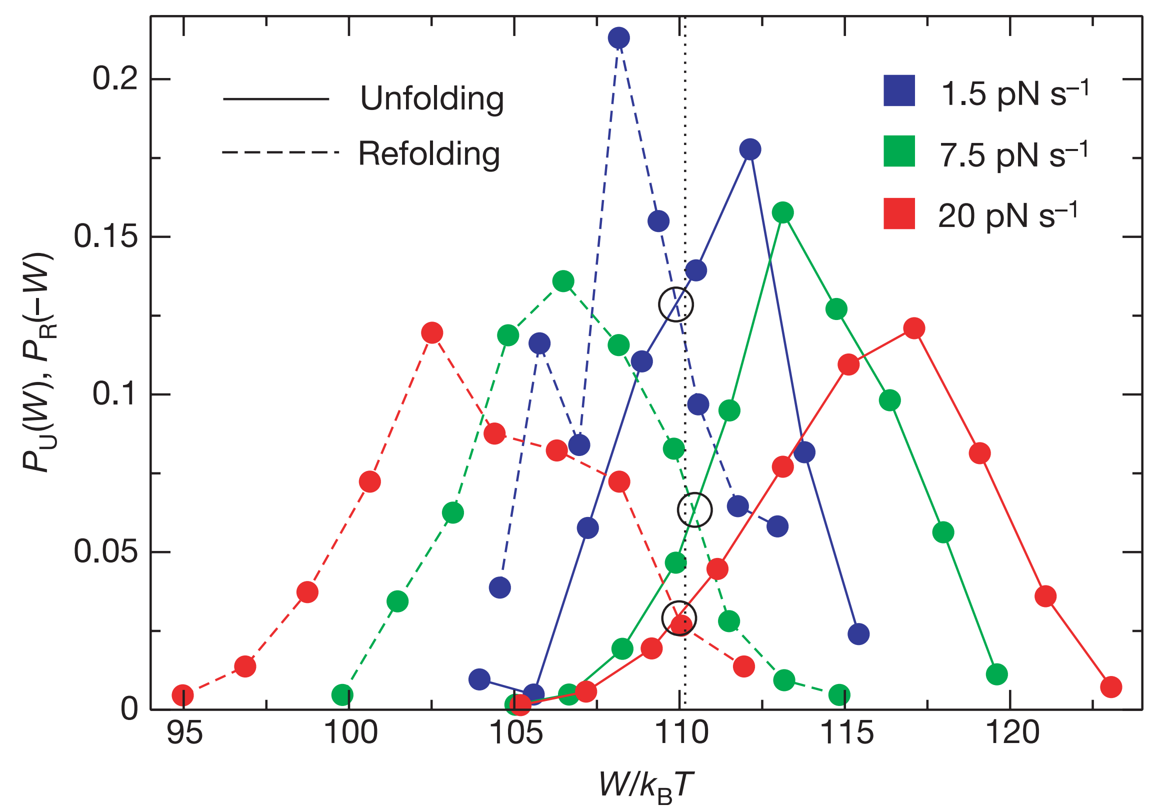




Force spectroscopy

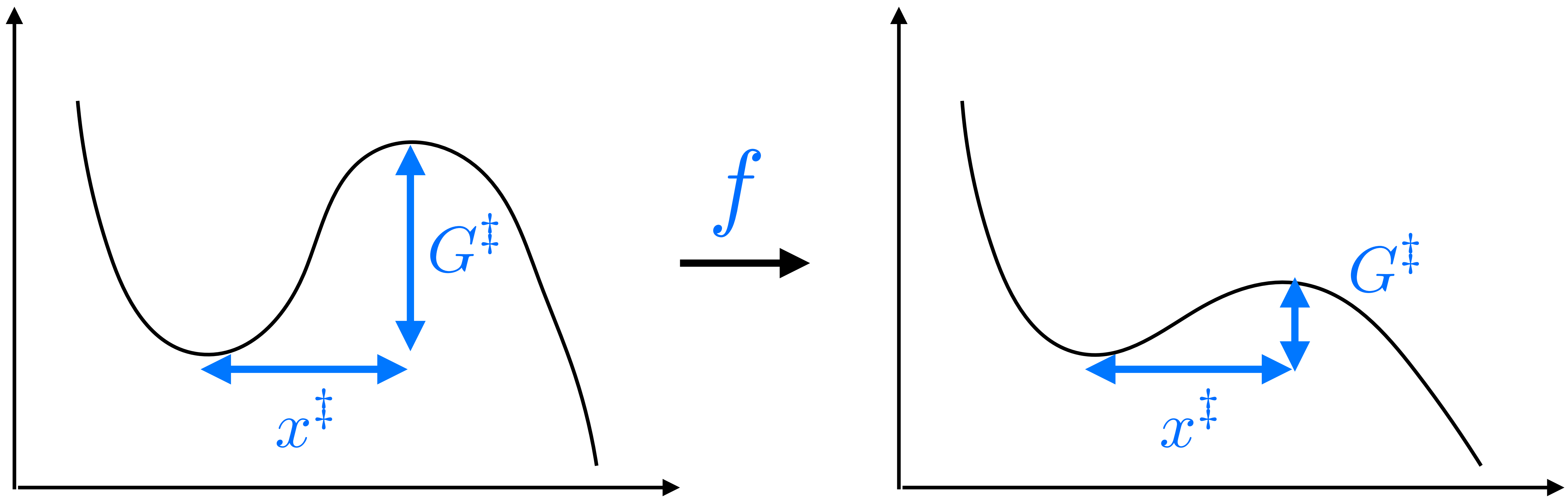






$$\langle e^{-\beta W} \rangle = e^{-\beta \Delta F}$$

Force spectroscopy



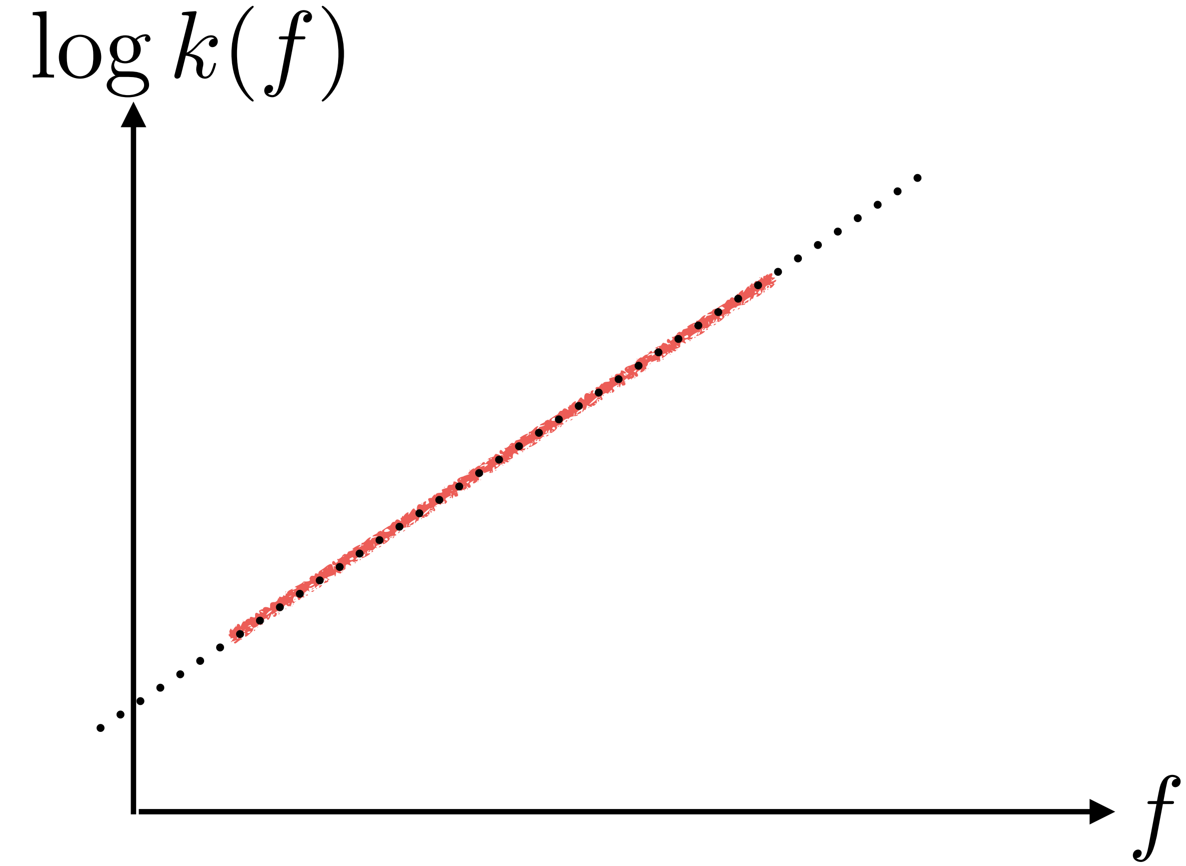
$$G^\ddagger \longrightarrow G^\ddagger - f x^\ddagger$$

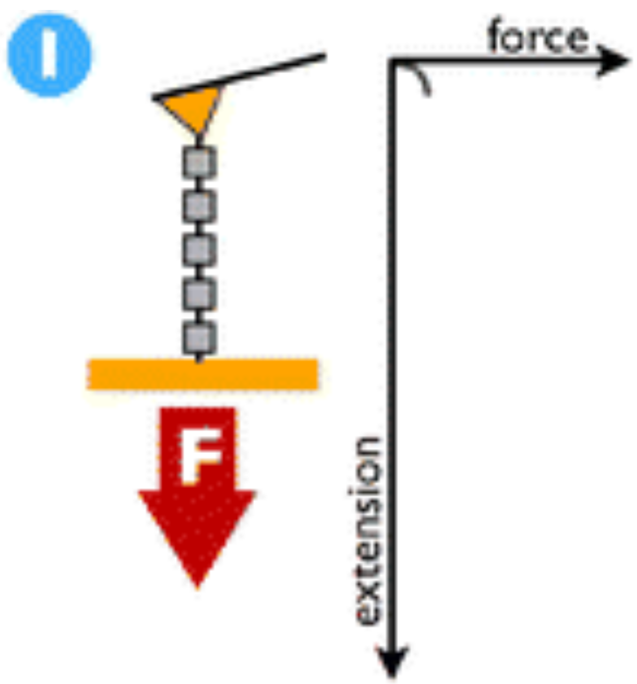
$$k_{KR} = \frac{\omega_{ts}\omega_0}{2\pi\gamma} e^{-\beta G^\ddagger} \longrightarrow k_{KR}(f) = \frac{\omega_{ts}\omega_0}{2\pi\gamma} e^{-\beta G^\ddagger} e^{\beta f x^\ddagger}$$

Model for specific adhesion of cells to cells, G.I.Bell, *Science* (1978)

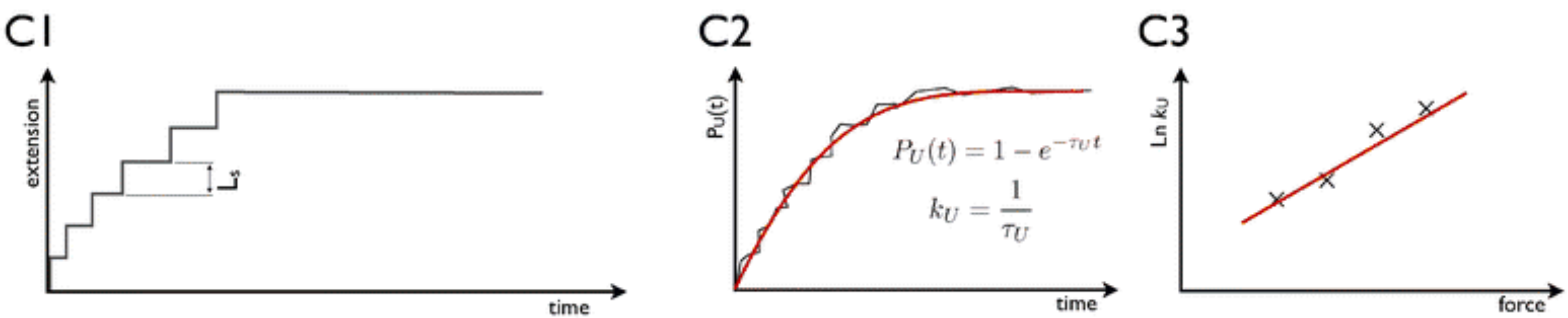
$$k(f) = k e^{\beta f x^{\ddagger}} \quad \text{(Bell model)}$$

$$\log k(f) = \log k + (x^{\ddagger}/k_B T) f$$





force clamp exp.

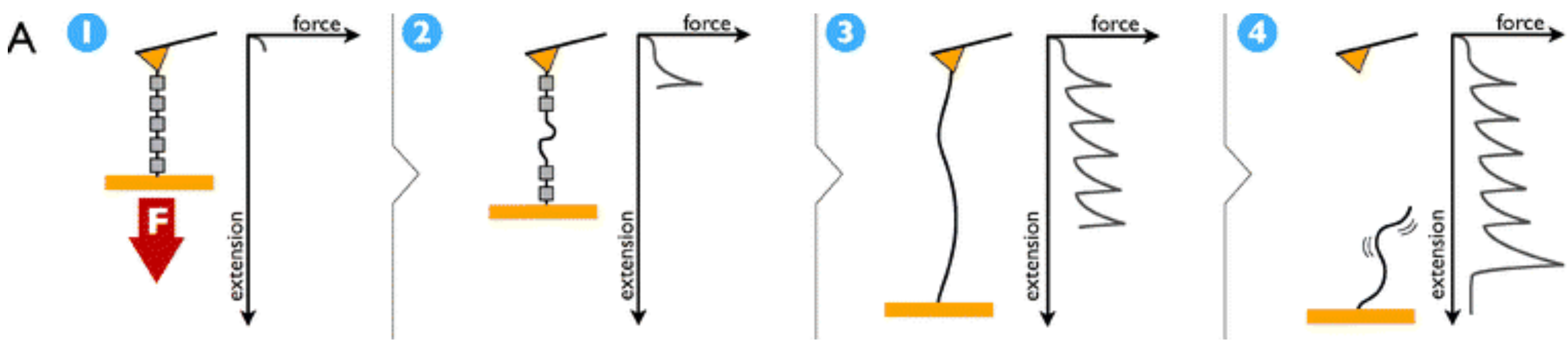


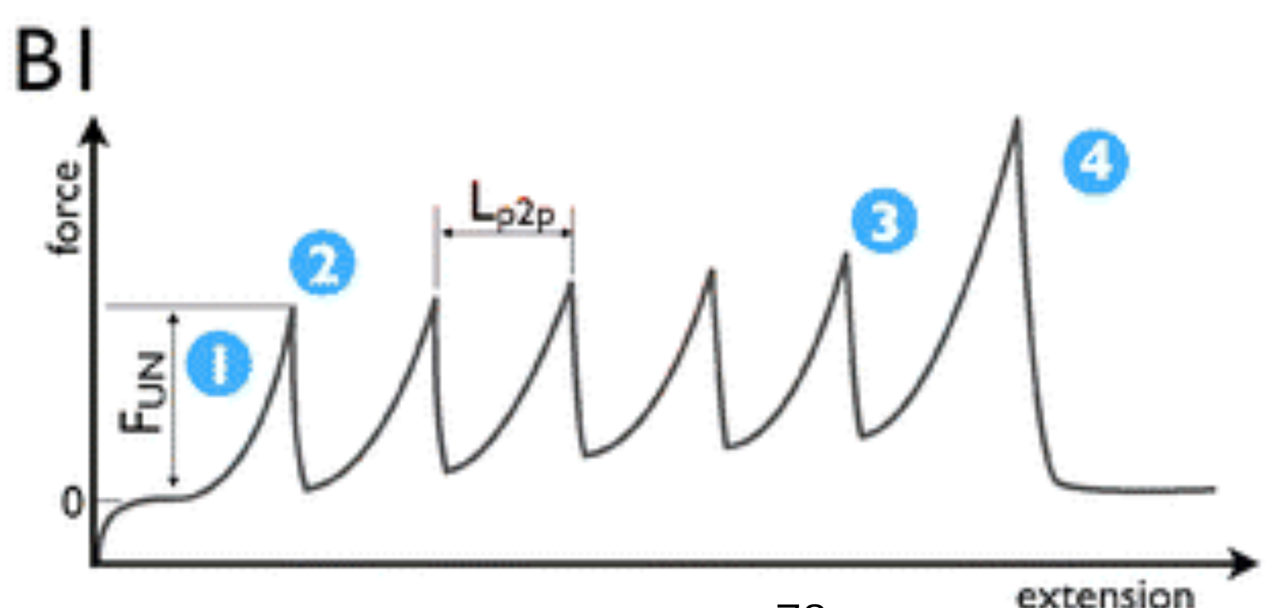
force ramp exp. (dynamic force spectroscopy)

$$f = r_f \times t$$

$$r_f = df/dt : \text{ loading rate}$$
$$= KV$$

$$P(f) = r_f^{-1} P(t)$$





force ramp exp. (dynamic force spectroscopy)

$$f = r_f \times t$$

$r_f = df/dt$: loading rate

$= KV$

$$P(f) = r_f^{-1} P(t)$$

---

	rupture force distribution			rupture time distribution
$P(f)$	unbinding force distribution	$\longleftrightarrow$	$P(t)$	unbinding time distribution
	unfolding force distribution			unfolding time distribution

at ramping force

$$P(f) = r_f^{-1} P(t)$$

force ramp exp. (dynamic force spectroscopy)

$$f = r_f \times t$$

$$r_f = df/dt : \text{ loading rate}$$
$$= KV$$

$$P(f) = r_f^{-1} P(t)$$

$$\frac{dS(t)}{dt} = -k(t)S(t) \longrightarrow S(t) = e^{-\int_0^t d\tau k(\tau)}$$

$$S(f) = e^{-\frac{1}{r_f}\int_0^f df' k(f')}$$

$$P(t) = -\partial_t S(t) = k(t)e^{-\int_0^t d\tau k(\tau)} = k(t)S(t)$$

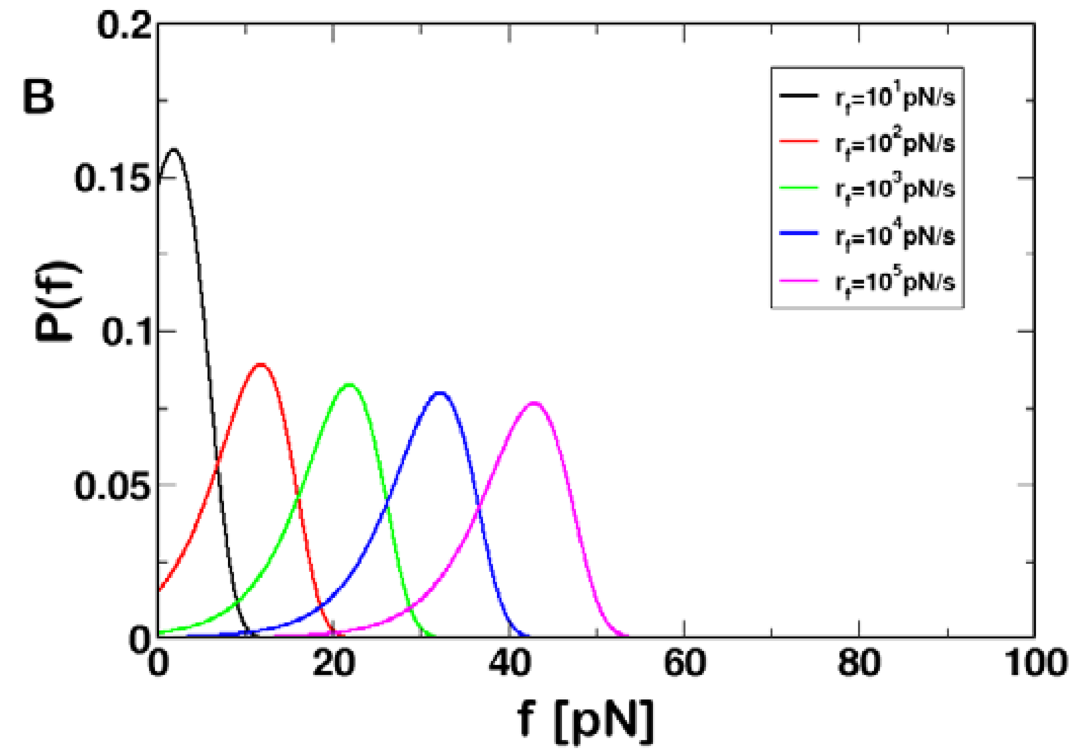
$$P(f) = \frac{1}{r_f}k(f)e^{-\frac{1}{r_f}\int_0^f df k(f)} = \frac{1}{r_f}k(f)S(f)$$

$$P(f) = \frac{1}{r_f} k(f) e^{-\frac{1}{r_f} \int_0^f df\, k(f)} \qquad k(f) = k e^{\beta f x^\ddagger}$$

1. draw $P(f)$ with varying r_f

$$P(f) = \frac{k}{r_f} e^{f/\hat{f}} e^{-\frac{k\hat{f}}{r_f}(e^{f/\hat{f}} - 1)}$$

with $\hat{f} = \frac{k_B T}{x^\ddagger}$

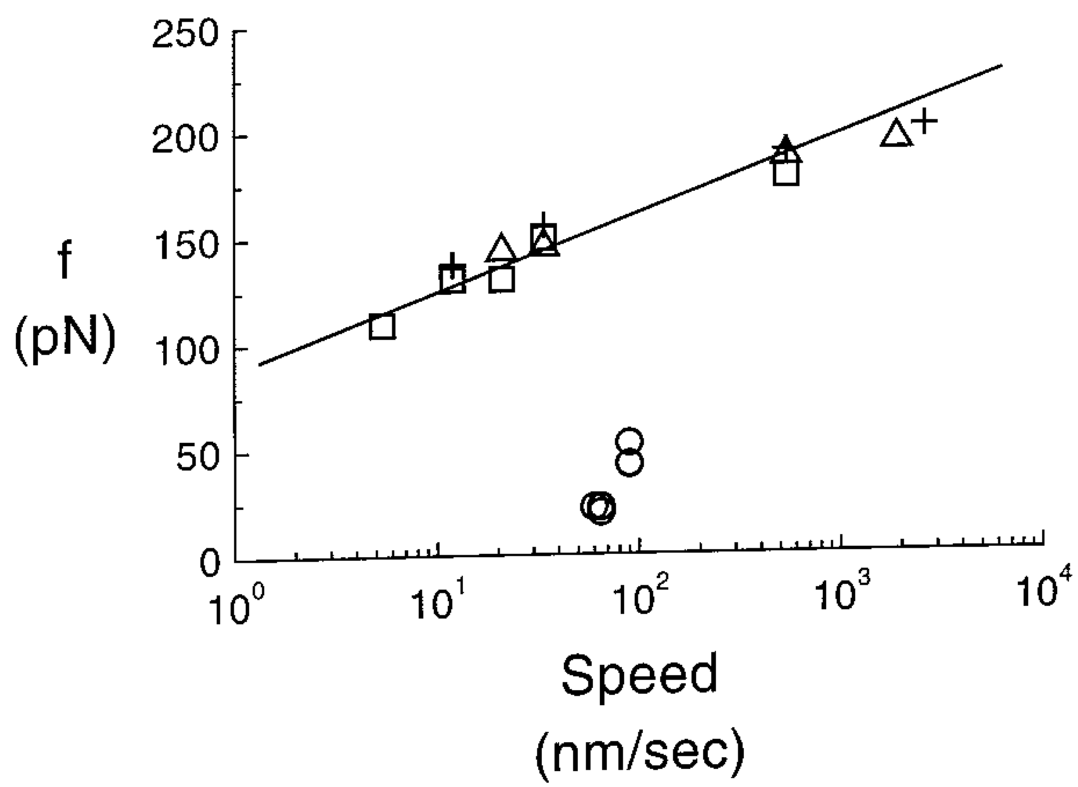


2. How does the most probable rupture force change with r_f ?

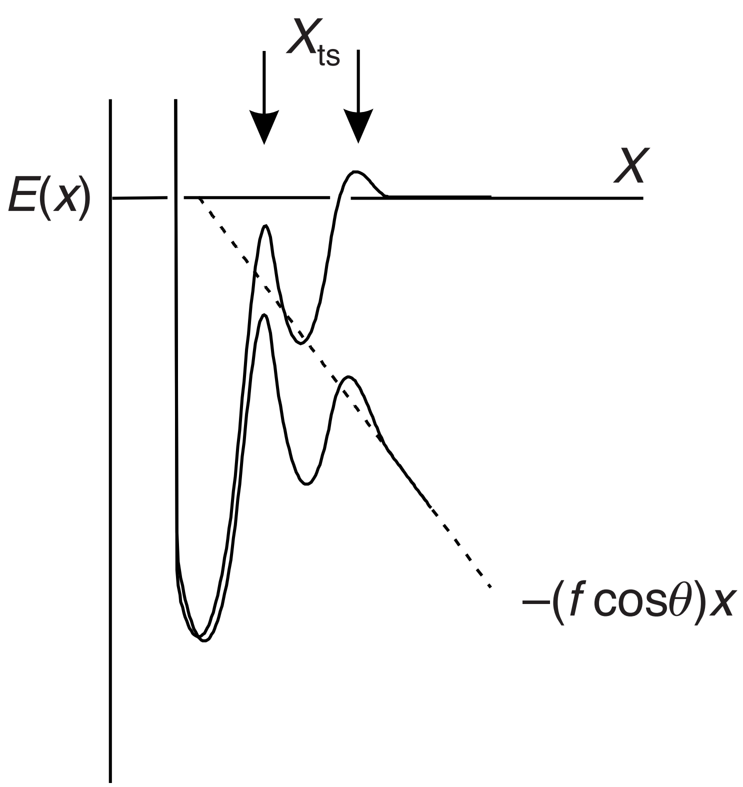
Use $P(f) = \frac{1}{r_f} k(f) S(f) \xrightarrow{P'(f)|_{f=f^*} = 0} r_f k'(f) = [k(f)]^2$

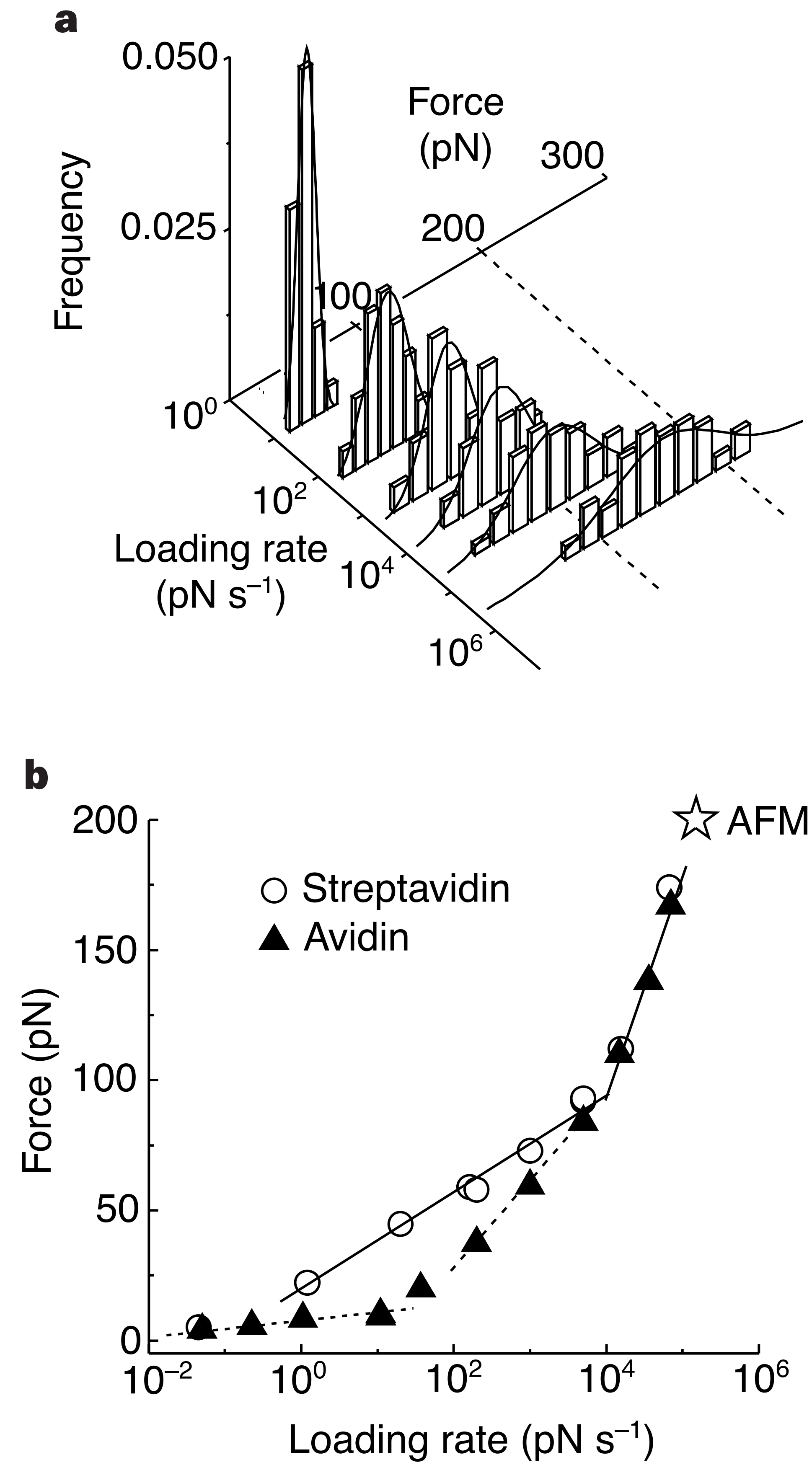
$$f^* = \frac{k_B T}{x^\ddagger} \log r_f + \frac{k_B T}{x^\ddagger} \log \frac{x^\ddagger}{k_B T}$$

Dynamic strength of molecular adhesion bonds, Evans & Ritchie, *Biophys. J.* (1997)

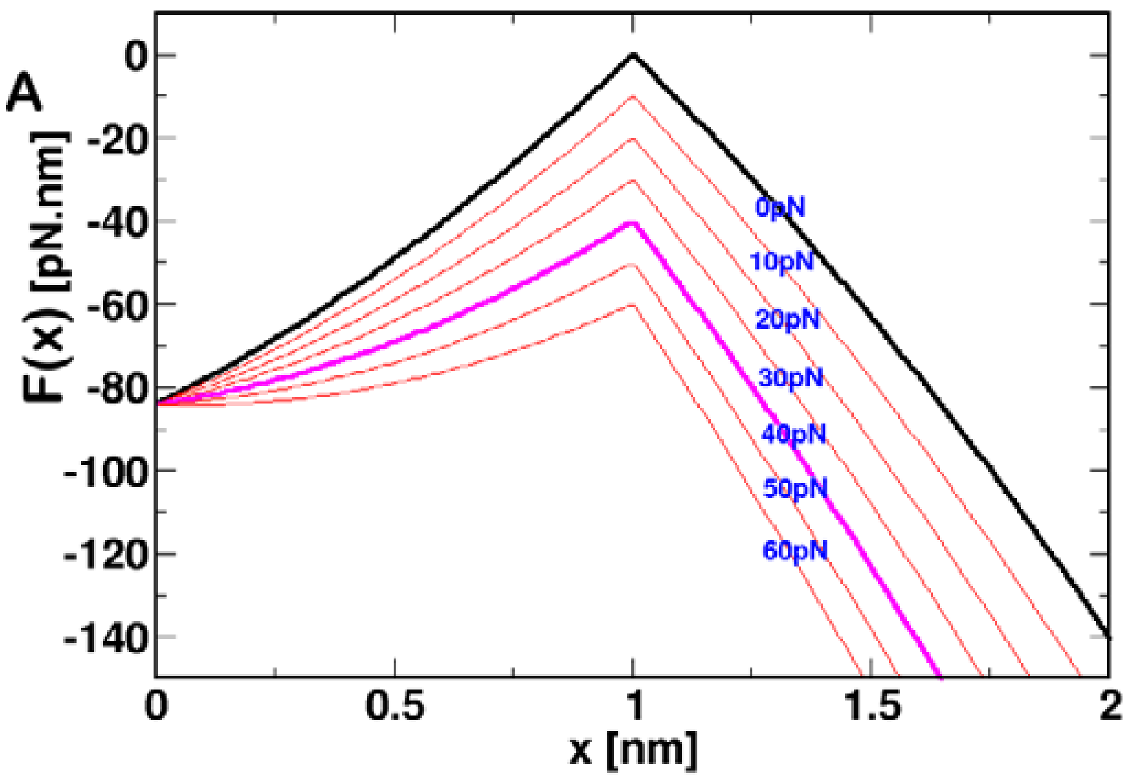


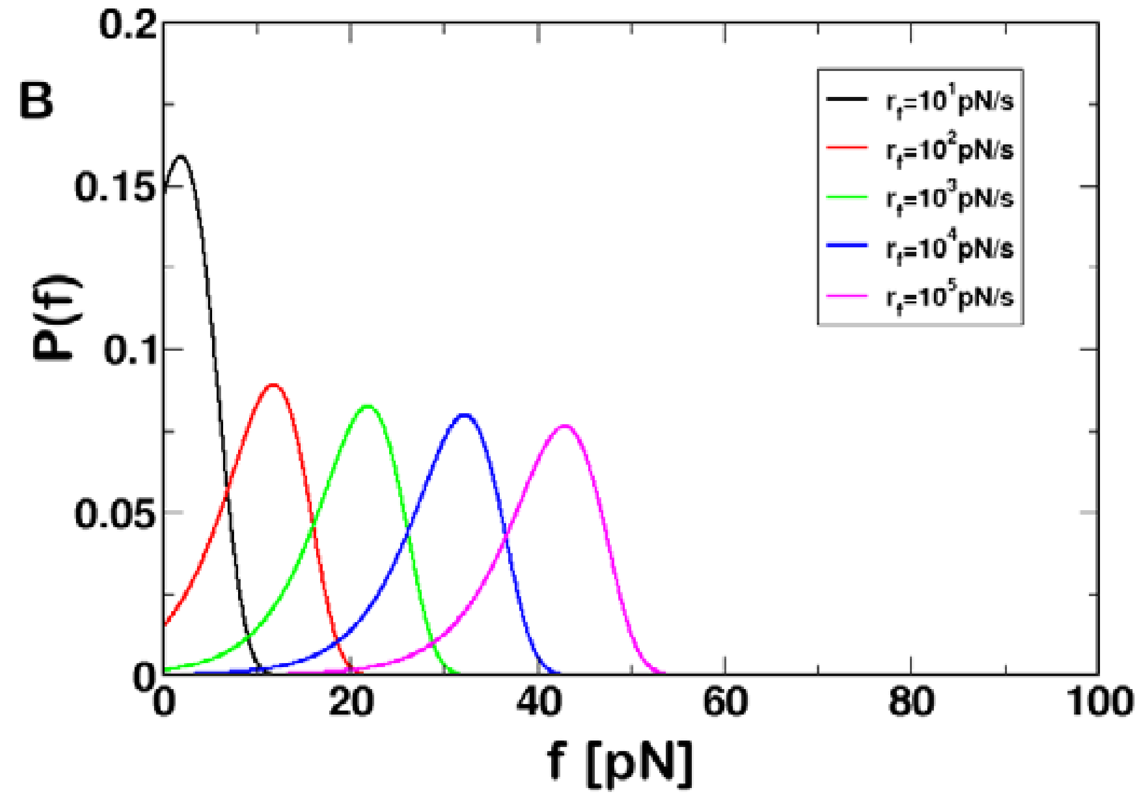
$$f^* = \frac{k_B T}{x^\ddagger} \log r_f + \frac{k_B T}{x^\ddagger} \log \frac{x^\ddagger}{k_B T}$$

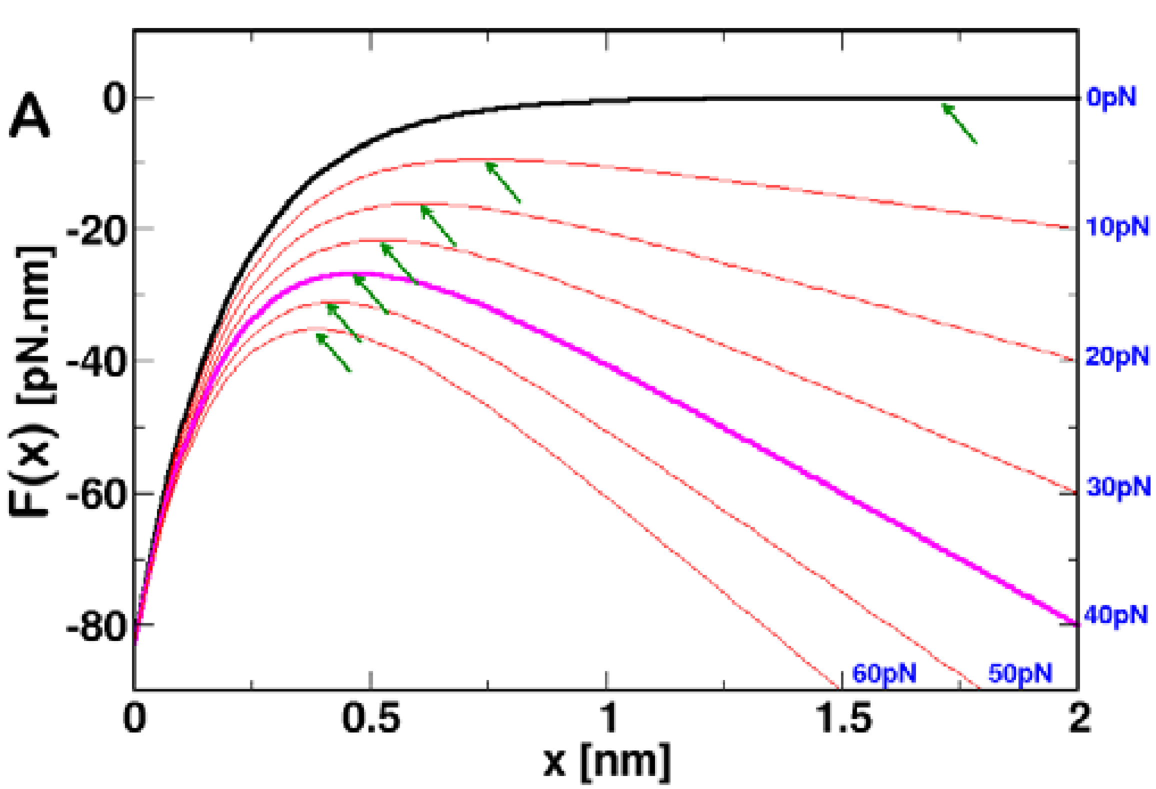


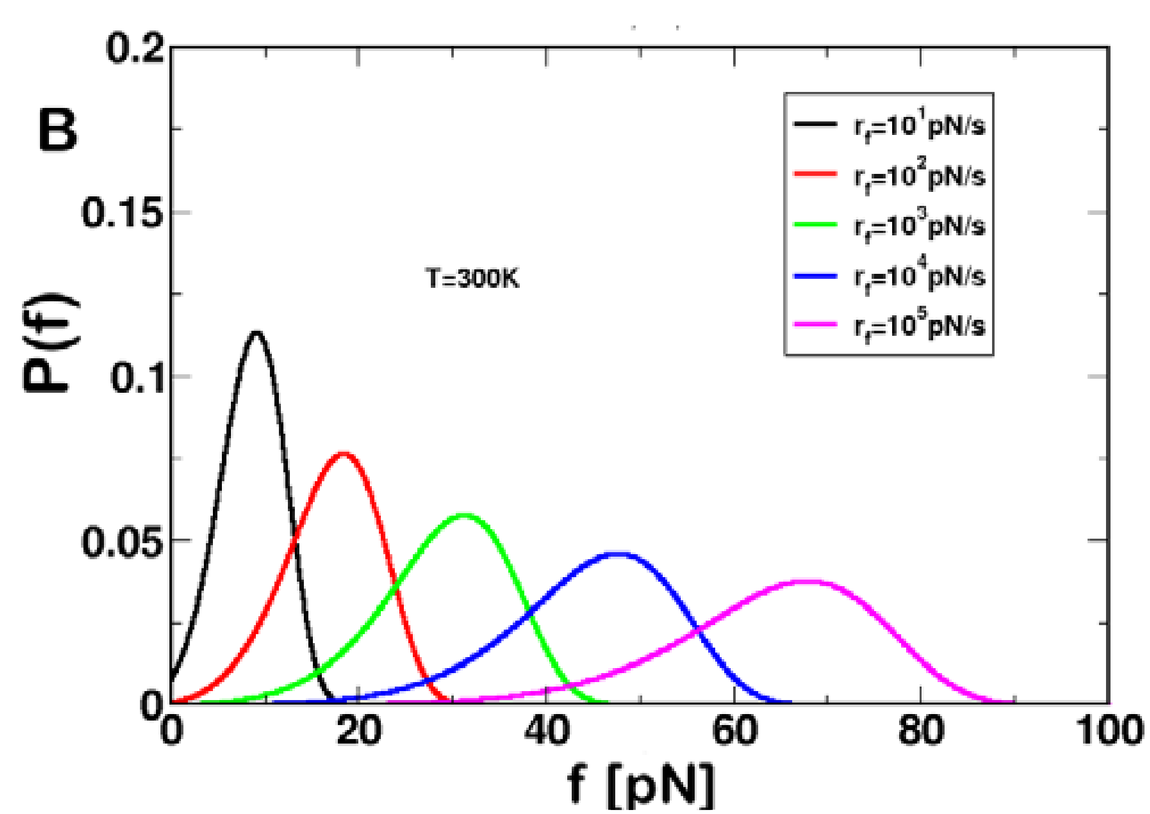


Evans and coworkers, Nature (1999) 397, 50

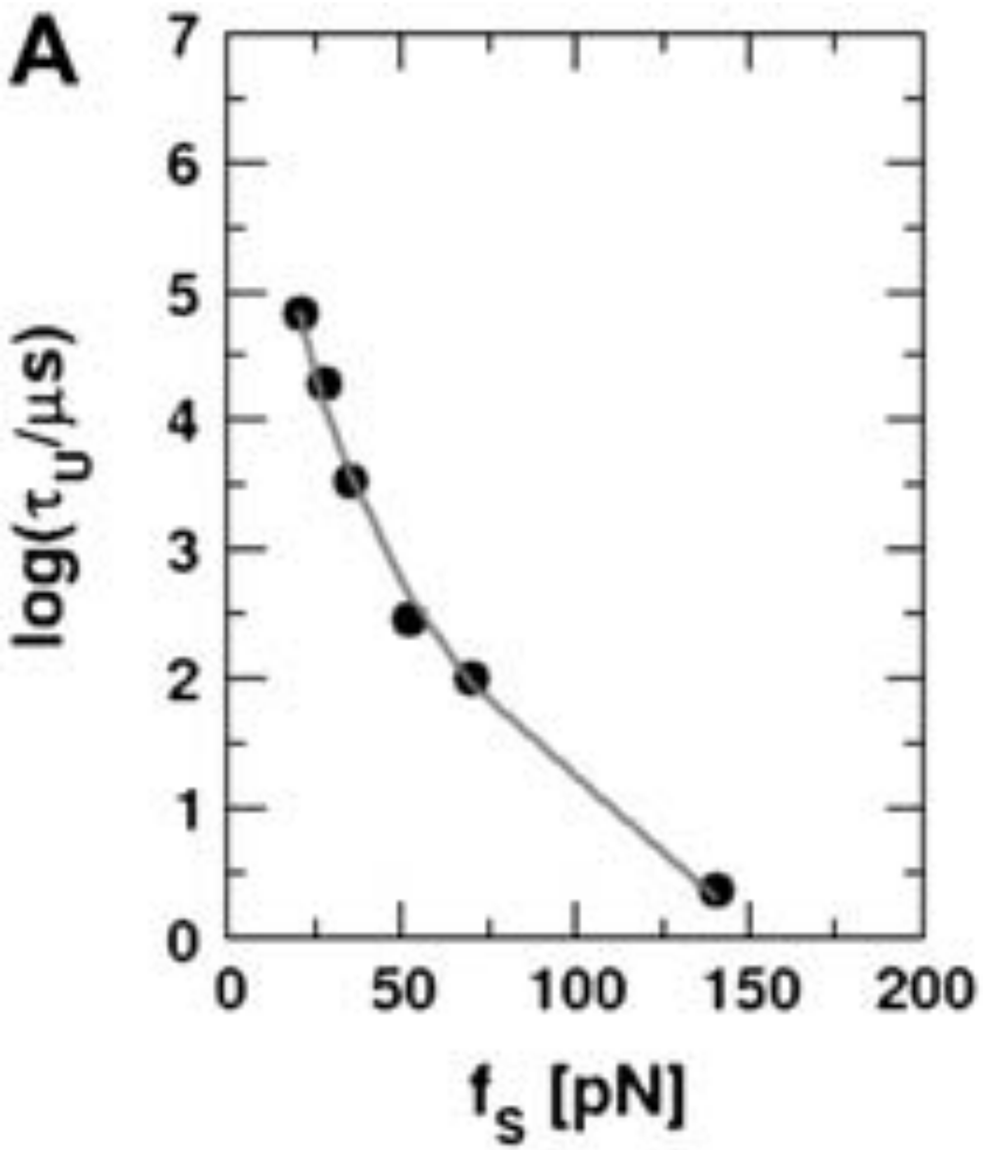




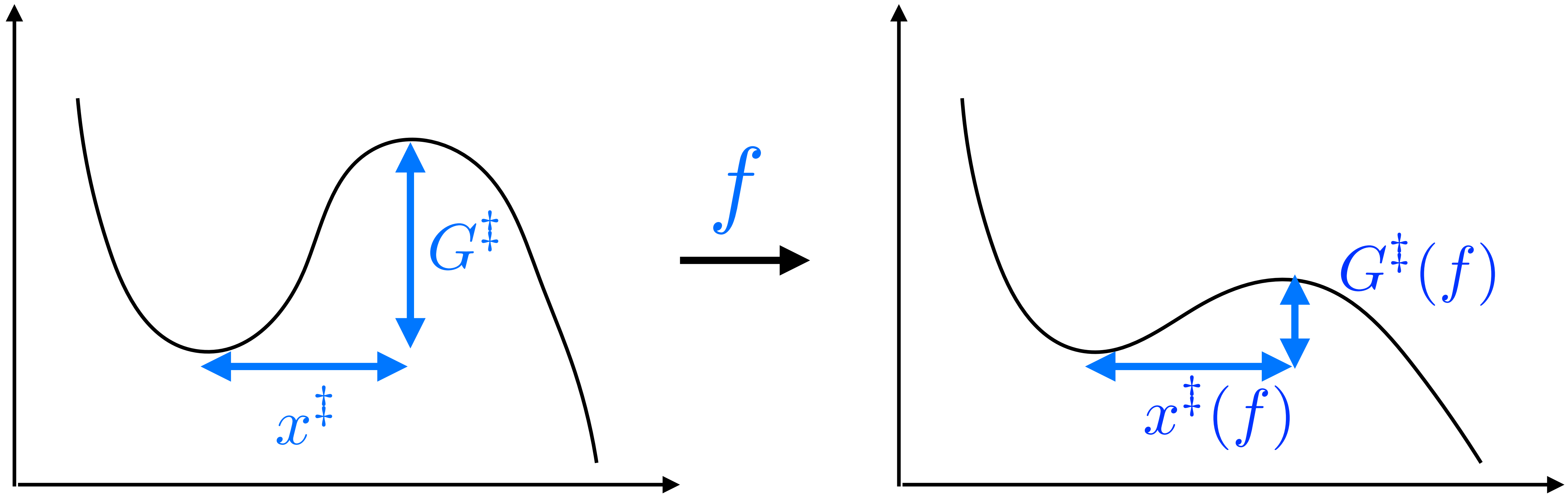




J. Phys. Cond. Matt. (2007) 19, 113101



$$\log k(f) = \log k + (x^{\ddagger}/k_B T) f$$

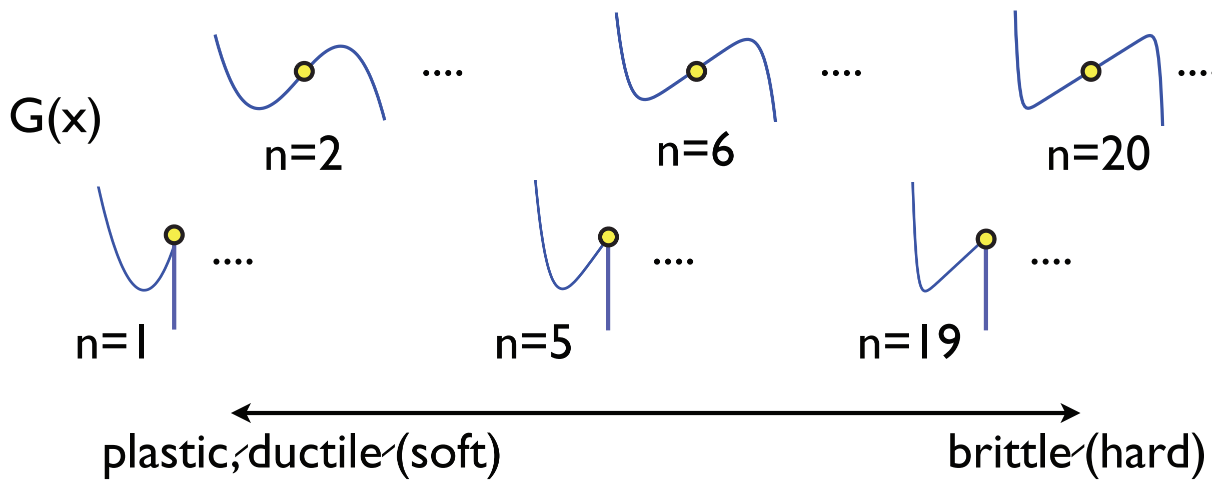


$$G(x) = f_c(x - x_c) - A(x - x_c)^3 \; - f(x - x_c)$$
$$= (f_c - f)(x - x_c) - A(x - x_c)^3$$
$$= \epsilon f_c(x - x_c) - A(x - x_c)^3$$

$$x_\pm = x_c \pm (f_c/3A)^{1/2}\epsilon^{1/2}$$
$$x^\ddagger = x_+ - x_-$$
$$G^\ddagger = G(x_+) - G(x_-)$$

$$x^\ddagger(f)/x^\ddagger = \epsilon^{1/2}$$
$$G^\ddagger(f)/G^\ddagger = \epsilon^{3/2}$$
$$\epsilon = 1 - f/f_c$$

$$k(\epsilon) = \kappa\epsilon \exp\left(-\beta G^\ddagger \epsilon^{3/2}\right)$$



$$f_c = \frac{n+1}{n} G^{\ddagger}/x^{\ddagger}$$

$$G(x) = G(x_c) + f_c(x - x_c) + \frac{(-1)^{n+1}M}{(n+1)!}(x - x_c)^{n+1}$$

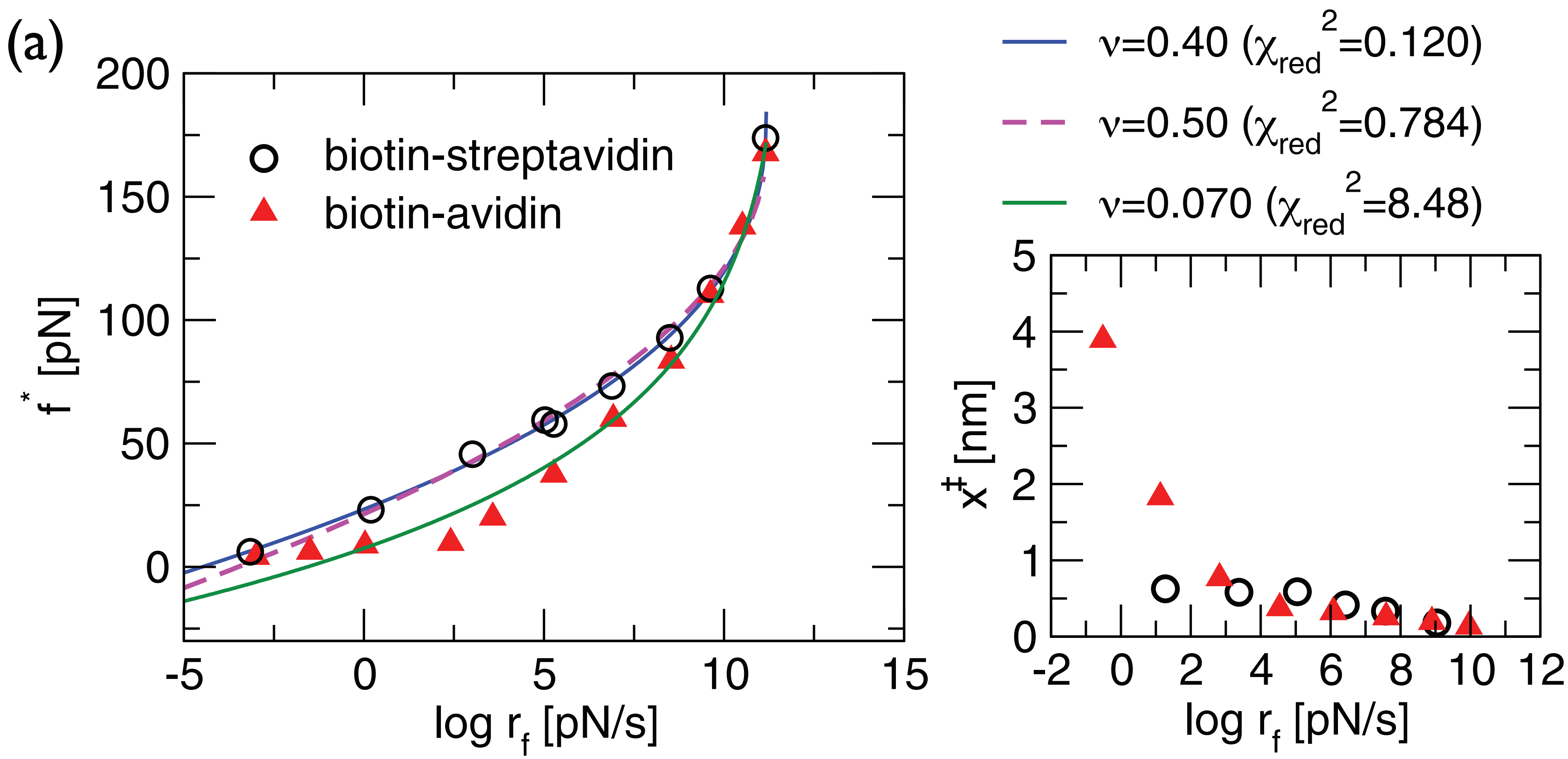
$$k(\varepsilon) = \kappa\,\varepsilon^{\alpha(n)} \exp\left(-\beta G^{\ddagger}\varepsilon^{(n+1)/n}\right), \quad \alpha(n) = \chi(1 - n^{-1})$$

$$k'(f^*) = \frac{1}{r_f}[k(f^*)]^2$$

$$\varepsilon^{\frac{n+1}{n}} = \frac{-1}{\beta G^{\ddagger}} \log\left[\frac{r_f x^{\ddagger}}{\kappa k_B T}\varepsilon^{1/n-\alpha(n)}\left(1 - \frac{1}{\beta G^{\ddagger}}\frac{n\alpha(n)}{n+1}\varepsilon^{-\frac{n+1}{n}}\right)\right].$$

$$f^* \approx f_c\left[1 - \left(-\frac{k_B T}{G^{\ddagger}}\log\frac{r_f x^{\ddagger}}{\kappa k_B T}\right)^{\nu}\right] \qquad \nu = \frac{n}{n+1}$$

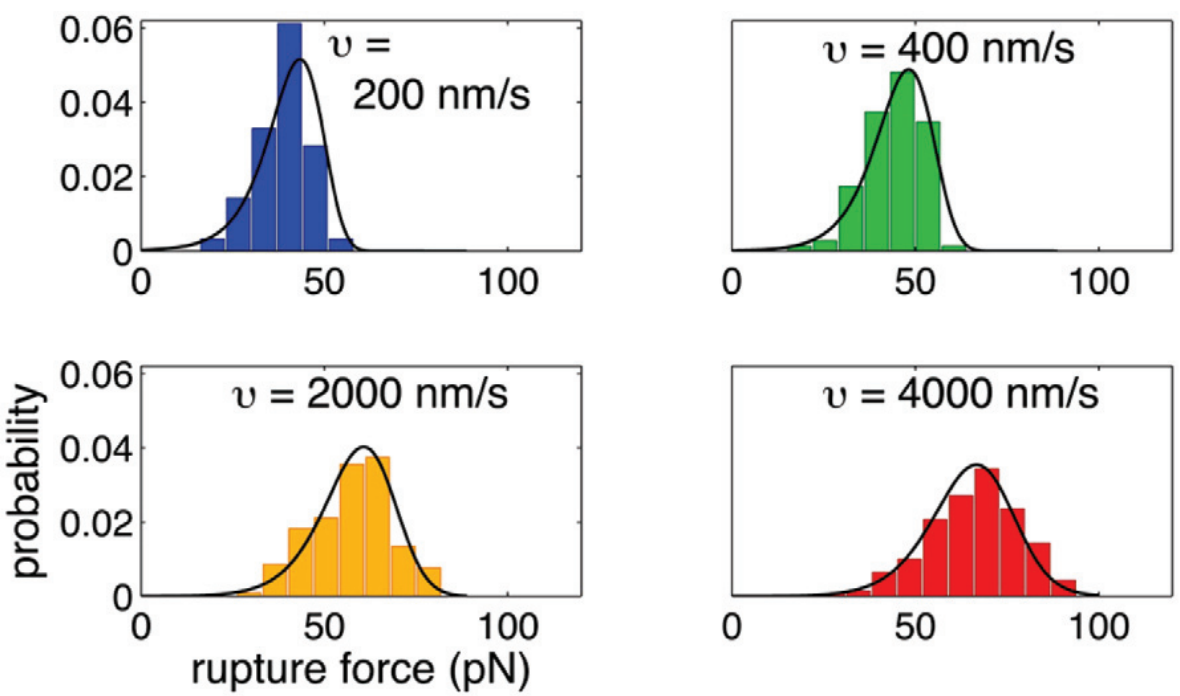
J. Chem. Phys. (2012) 137, 055103

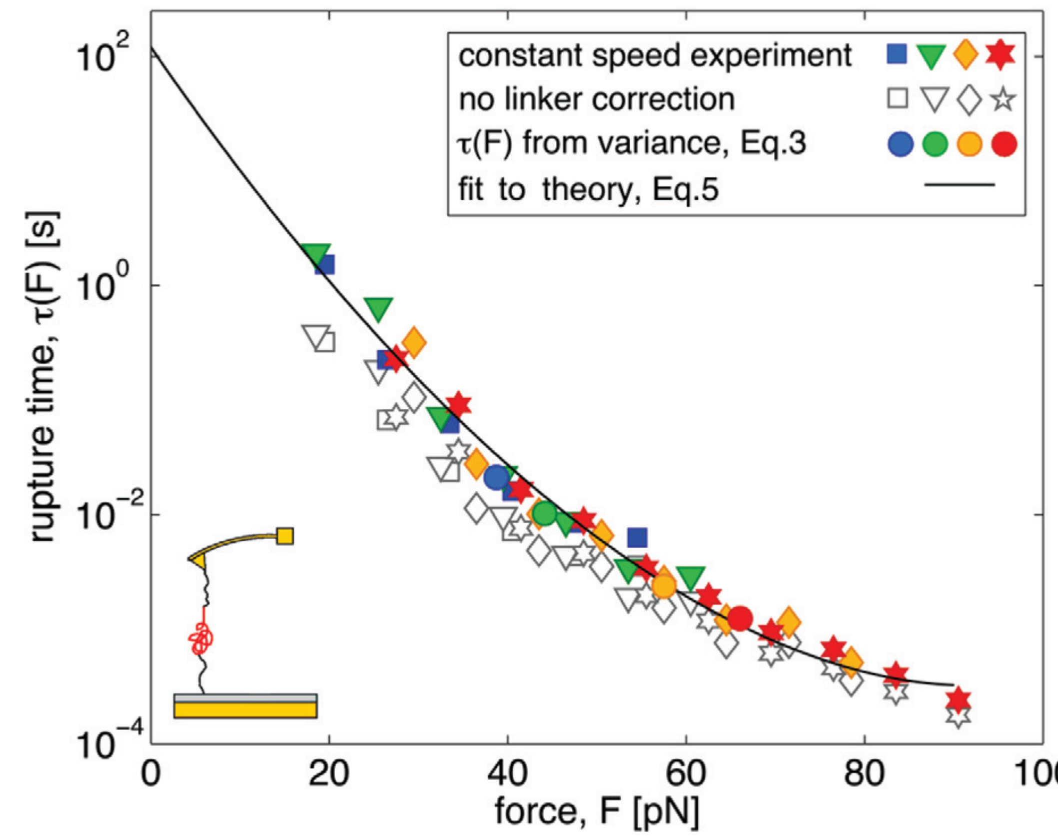


$$f^* \approx f_c \left[1 - \left(-\frac{k_B T}{G^\ddagger} \log \frac{r_f x^\ddagger}{\kappa k_B T} \right)^\nu \right] \qquad 1/2 \le \nu \le 1$$

J. Chem. Phys. (2012) 137, 055103

$$P(f) = r_f^{-1} k(f) S(f) \longrightarrow k(f) = \frac{r_f P(f)}{1 - \int_0^f P(f')df'}$$





$$P(f) \longrightarrow k(f)$$

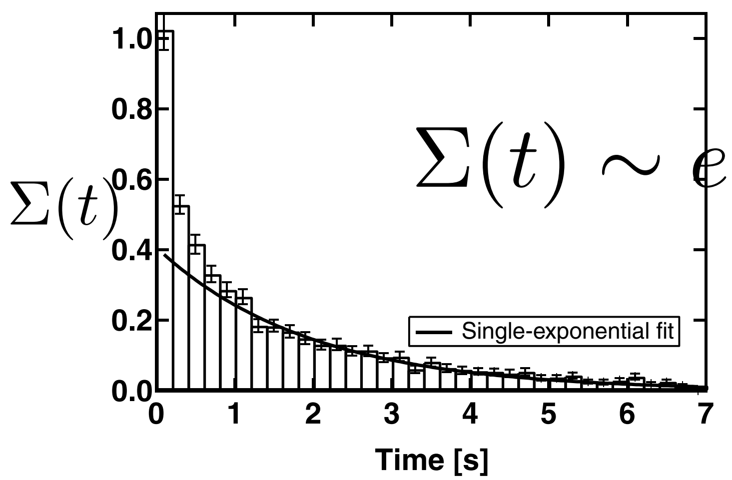
info. from force ramp exp.

info. from force clamp exp.

Dudko et al. PNAS (2008)

Detecting molecular dynamic disorder using force spectroscopy

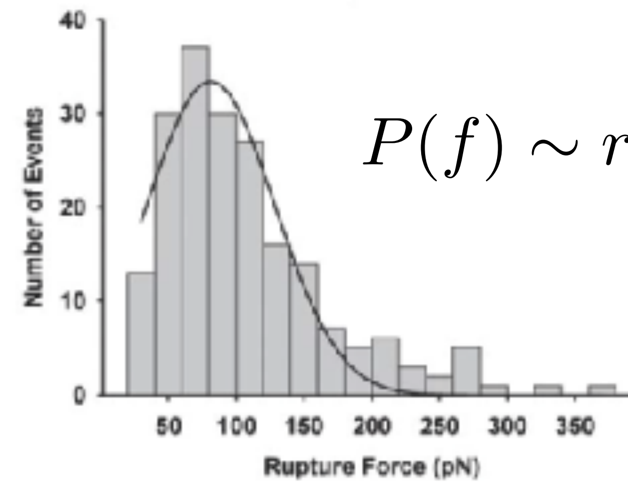
e.g. single molecule force spectroscopy (force-clamp, force-ramp)



$$\Sigma(t) \sim e^{-k(f)\times t}$$

poly-Ub
(Fernandez, Brujic, ….)

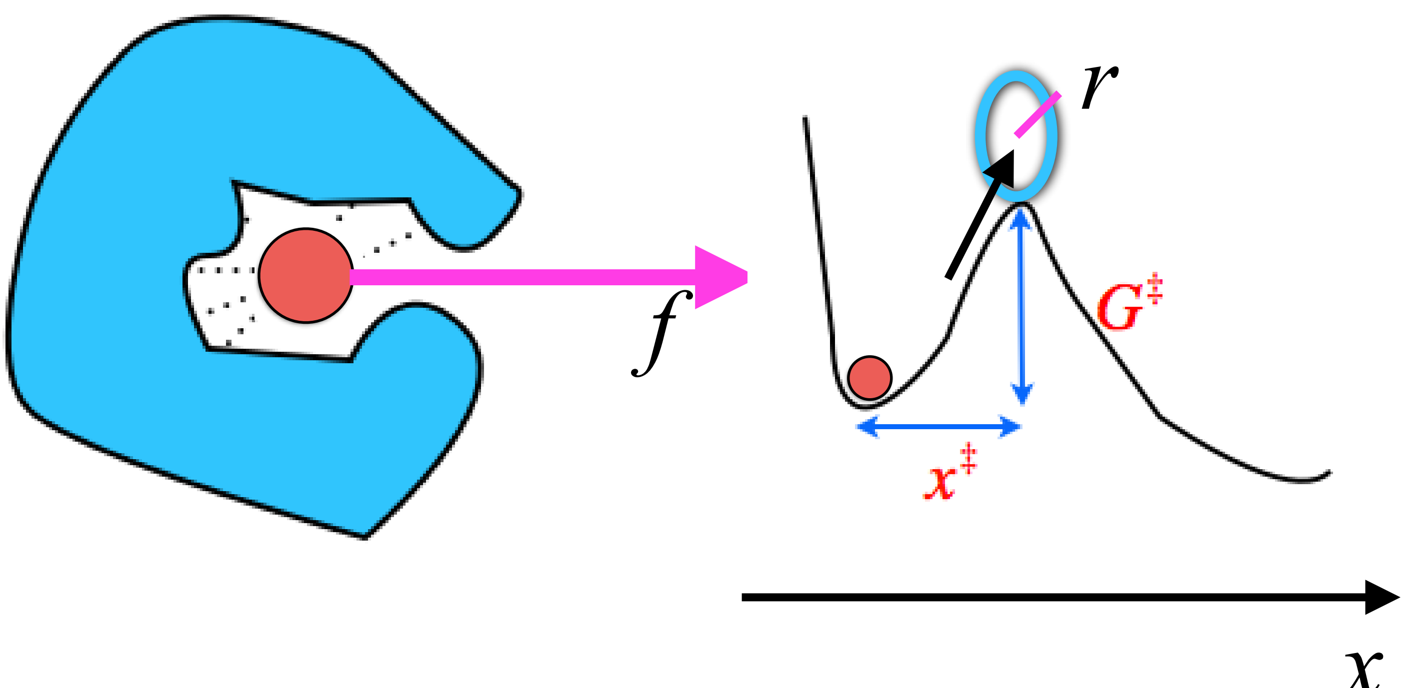
Kuo et al. PNAS 2010



$$P(f) \sim r_f^{-1} e^f \exp\left(-e^{f/r_f}\right)$$

Evidences of molecular disorder?

Force dynamics + Fluctuating bottleneck model (Zwanzig)



k(f) vs λ
(i) k(f) << λ : annealed disorder
(ii) k(f) >> λ : quenched disorder
(iii) k(f) ~ λ : dynamical disorder

$$k(f) = k_0 e^{f\Delta x^{\ddagger}/k_BT}$$

(Bell model)

$$\zeta\partial_t x = -\partial_x U_{\mathrm{eff}}(x;r) + F_x(t) \qquad U_{eff}(x) = U(x) - fx$$

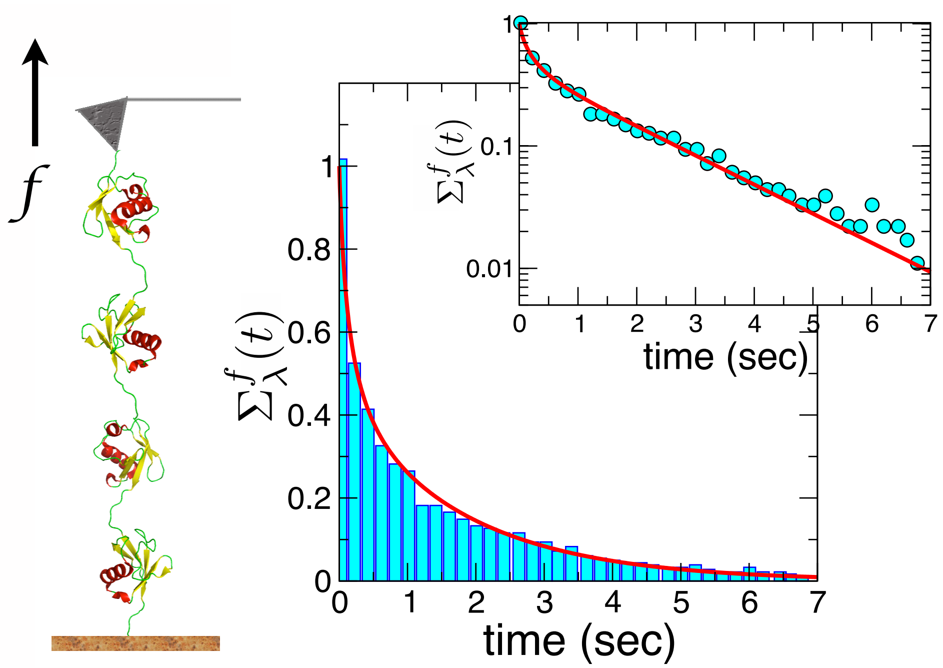
$$\partial_t r = -\lambda r + F_r(t)$$

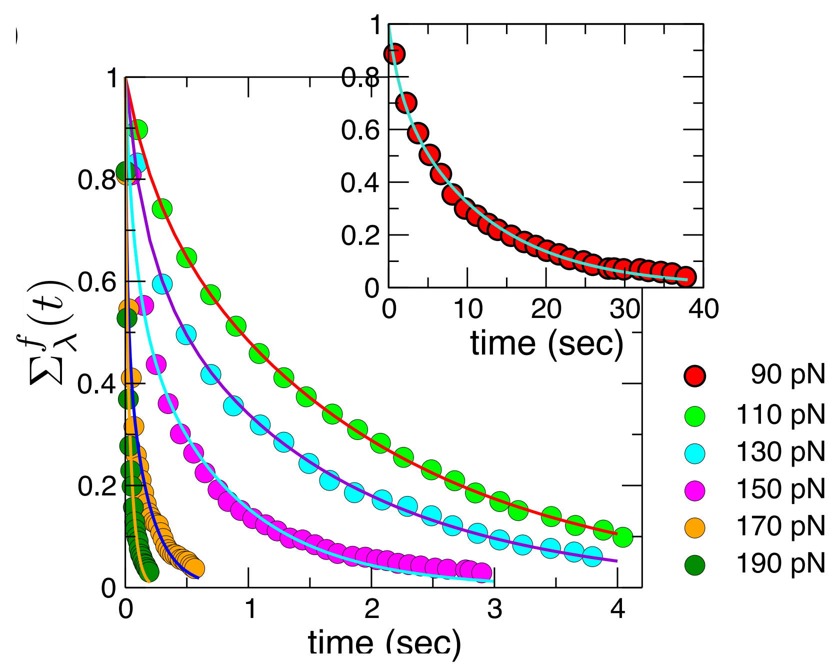
Zwanzig, J. Chem. Phys. (1992)
J. Phys. Cond. Matt. (2007) 113101
Phys. Rev. Lett. (2014) 112, 138101

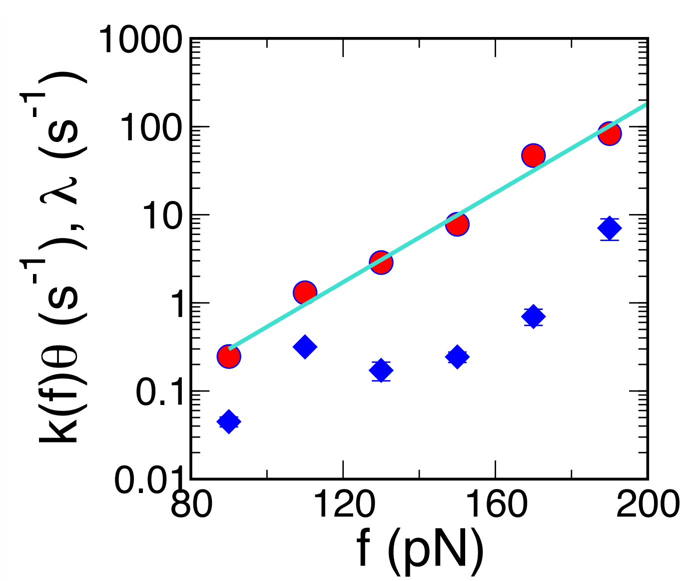
Unbinding (unfolding) kinetics at constant force, f (force-clamp)

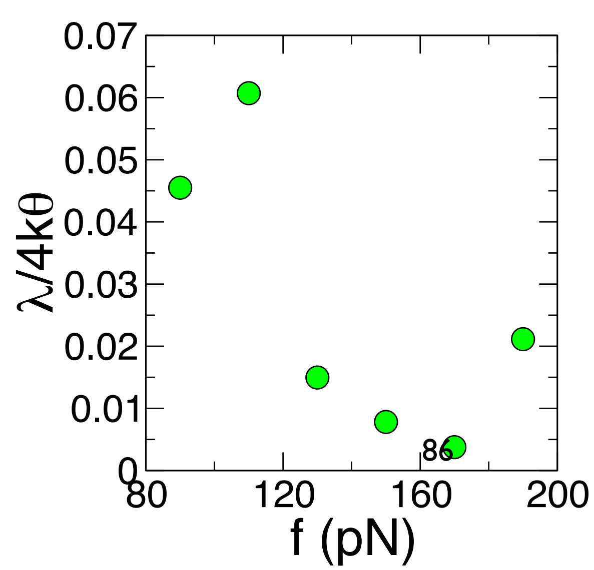
$$\boxed{\Sigma_{\lambda}^{f}(t)=e^{-\frac{\lambda}{2}(S-1)t}\left[\frac{(S+1)^2-(S-1)^2E}{4S}\right]^{-1/2}} \sim \begin{cases} e^{-k(f)\theta t} & :\lambda \gg k(f) \\ (1+2k(f)\theta t)^{-1/2} & :\lambda \ll k(f) \end{cases}$$

Reanalyze the unfolding data of polyubiquitin under force-clamp (Kuo et al. PNAS 2010)





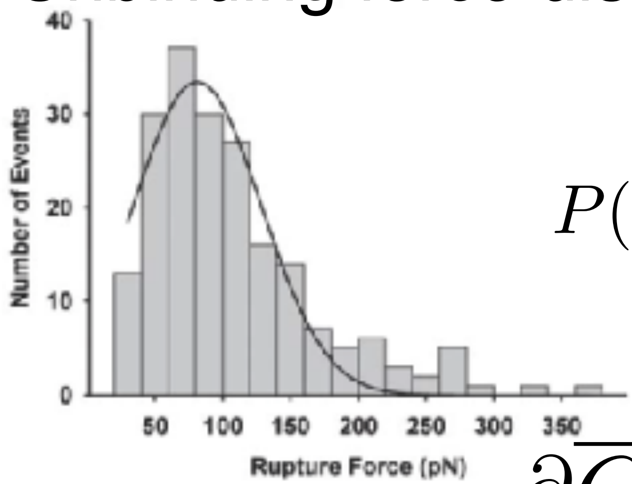




$$\frac{\lambda}{4k\theta} \ll 1$$

Phys. Rev. Lett. (2014) 112, 138101

Unbinding force distribution at constant loading rate, γ (force-ramp)



$$P(f) \sim r_f^{-1} e^{f} \exp\left(-e^{f/r_f}\right)$$

$$\frac{\partial \overline{C}(r,t)}{\partial t} = \boxed{\mathcal{L}(r)}\,\overline{C}(r,t) - \boxed{\mathcal{S}(r,t)}\,\overline{C}(r,t)$$

$$\mathcal{L}(r) = \lambda\theta\partial_r\left(\partial_r + r/\theta\right) \qquad \mathcal{S}(r,t) = k(f(t))r^2 = k_0 e^{\tilde{\gamma}t} r^2$$

$$\overline{C}(r,t) = \sqrt{\frac{2}{\pi\theta}}\left[\frac{\mathcal{I}(\rho)}{\mathcal{I}(\rho_0)}\right]^{-1/2} \exp\left[\frac{\lambda t}{2} - \frac{r^2}{4\theta}\left\{1 + \kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)}\right\}\right],$$

$$\Sigma_\lambda^\gamma(t) = \int_0^\infty dr\overline{C}(r,t) = \frac{1}{\sqrt{2\theta}}\frac{e^{\nu(t)}}{\sqrt{\mu(t)}} = \sqrt{2}e^{\frac{\lambda t}{2}}\left[\frac{\mathcal{I}(\rho)}{\mathcal{I}(\rho_0)}\right]^{-1/2}\left[1 + \kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)}\right]^{-1/2}.$$

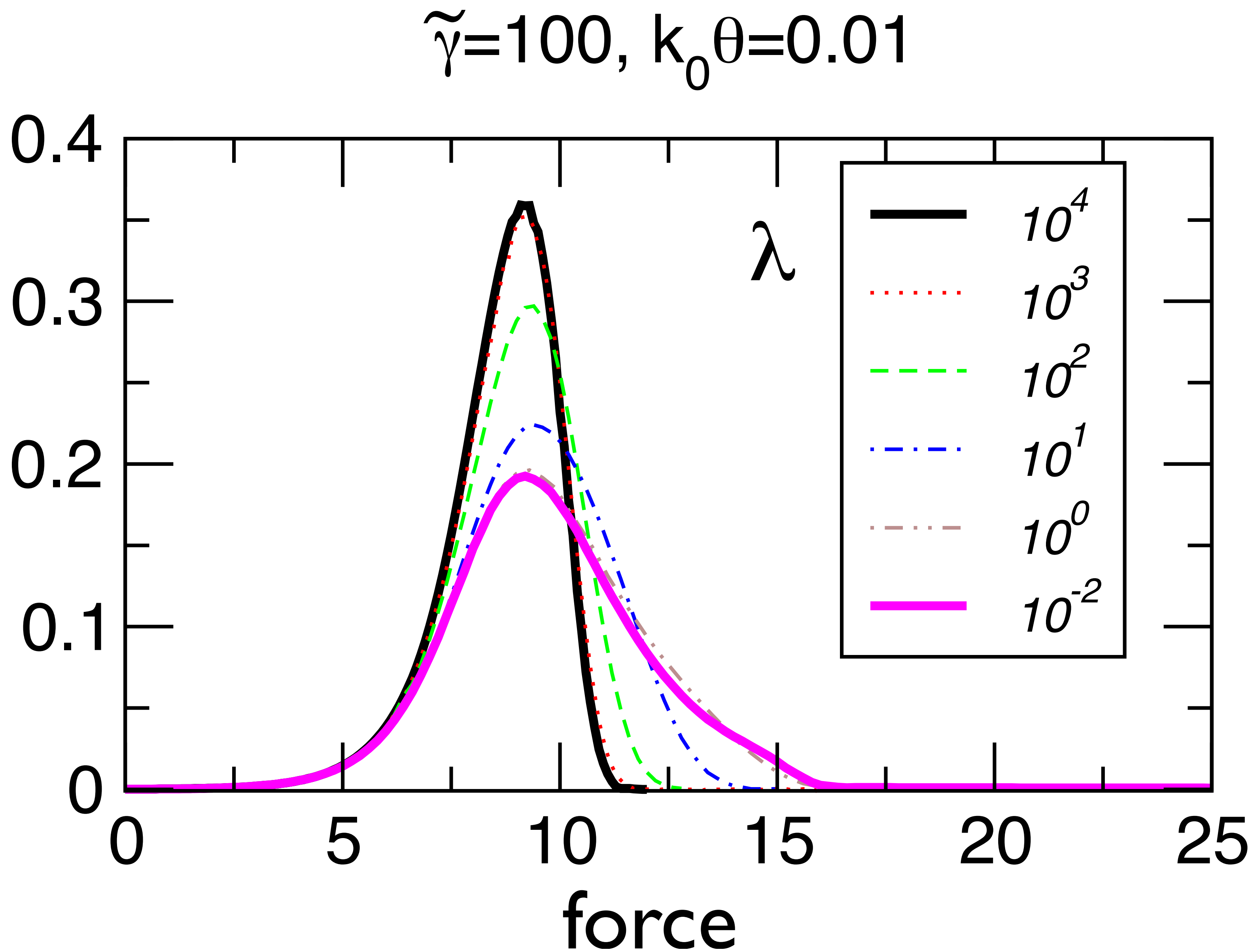
$$P_\lambda(t) = \frac{\lambda e^{\lambda t/2}}{\sqrt{2}}\left[\kappa^2(t)\frac{\mathcal{I}''(\rho)}{\mathcal{I}(\rho)} + \frac{1}{\beta}\kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)} - 1\right]\left[\frac{\mathcal{I}(\rho)}{\mathcal{I}(\rho_0)}\right]^{-1/2}\left[1 + \kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)}\right]^{-3/2}.$$

$$\rho = \beta\kappa(t) \qquad \beta = 2\lambda/\tilde{\gamma} \qquad \kappa(t) = \sqrt{4k_0\theta/\lambda}\,e^{t\tilde{\gamma}/2}$$

$$\mathcal{I}(\rho) = \left(\mathcal{I}_\beta'(\rho_0)\mathcal{Q}_\beta(\rho) - \mathcal{Q}_\beta'(\rho_0)\mathcal{I}_\beta(\rho)\right) - [\kappa(0)]^{-1}\left\{\mathcal{I}_\beta(\rho_0)\mathcal{Q}_\beta(\rho) - \mathcal{Q}_\beta(\rho_0)\mathcal{I}_\beta(\rho)\right.$$

$$P_\lambda(t) = \frac{\lambda e^{\lambda t/2}}{\sqrt{2}} \left[\kappa^2(t)\frac{\mathcal{I}''(\rho)}{\mathcal{I}(\rho)} + \frac{1}{\beta}\kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)} - 1\right] \left[\frac{\mathcal{I}(\rho)}{\mathcal{I}(\rho_0)}\right]^{-1/2} \left[1 + \kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)}\right]^{-3/2}.$$

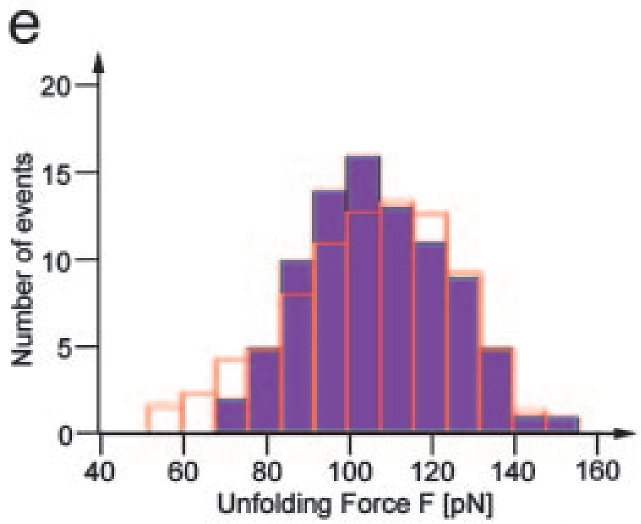
$$(\tilde{f} = \tilde{\gamma} t)$$

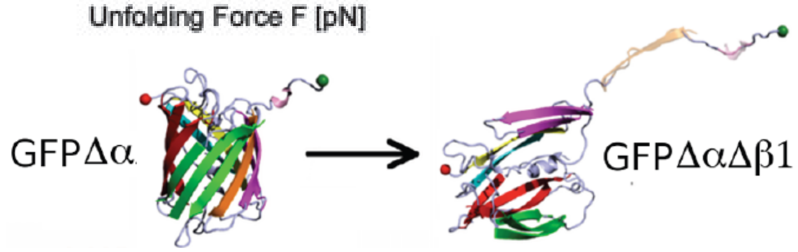


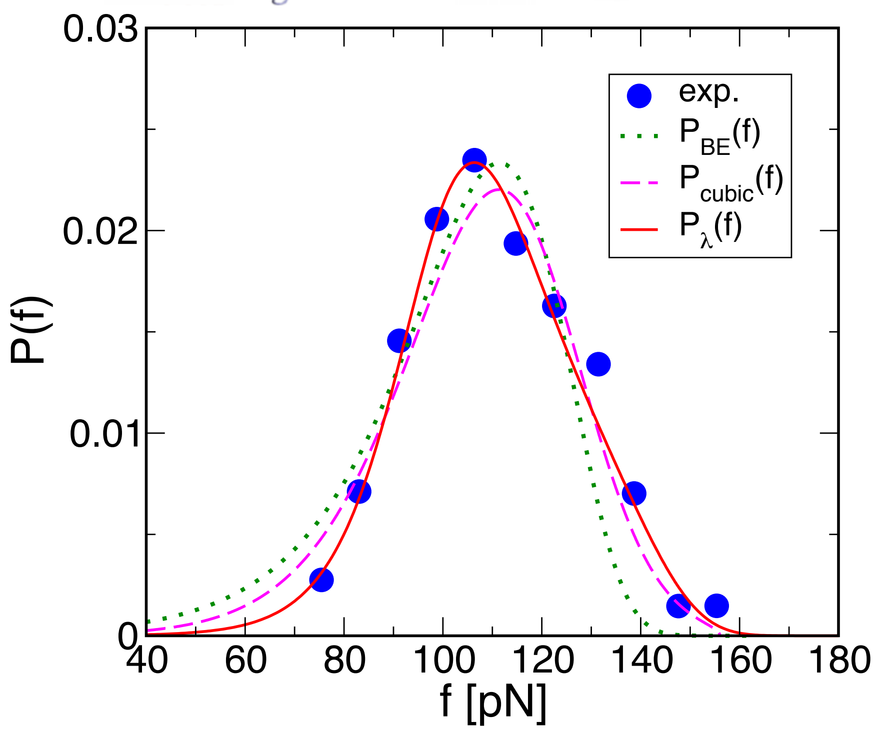
GFP (Green fluorescence proteins)

Dietz & Rief (2004) PNAS 101:16192

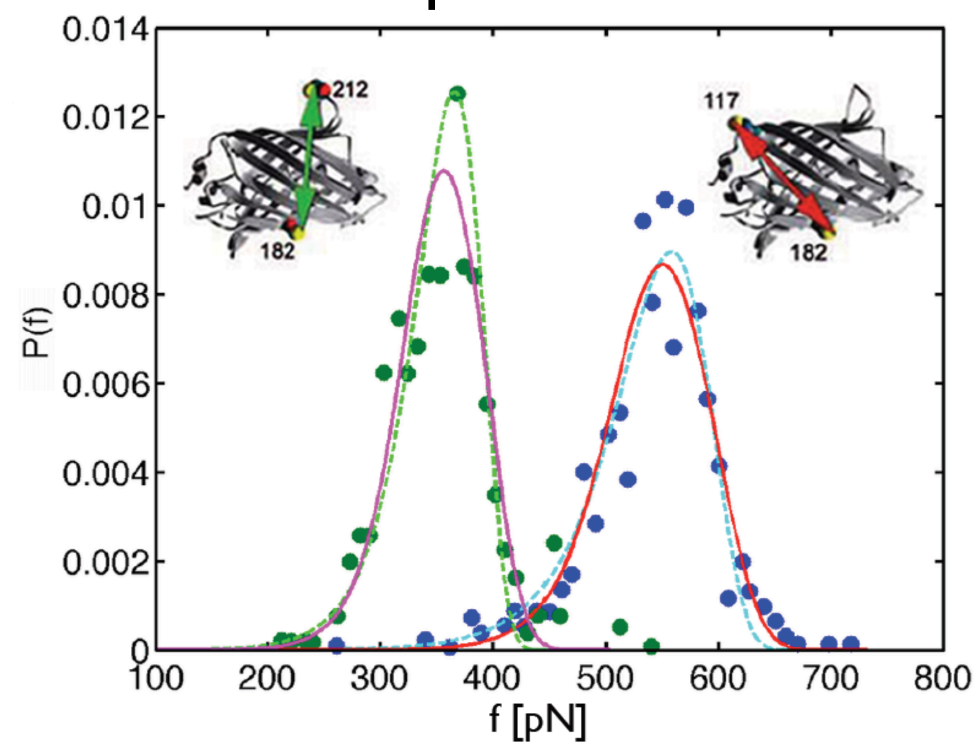
Dietz et al (2006) PNAS 103:12724

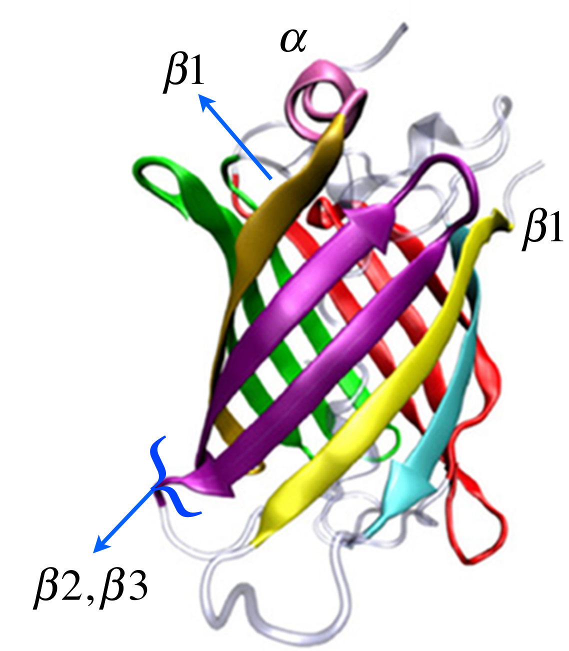






anisotropic deformation





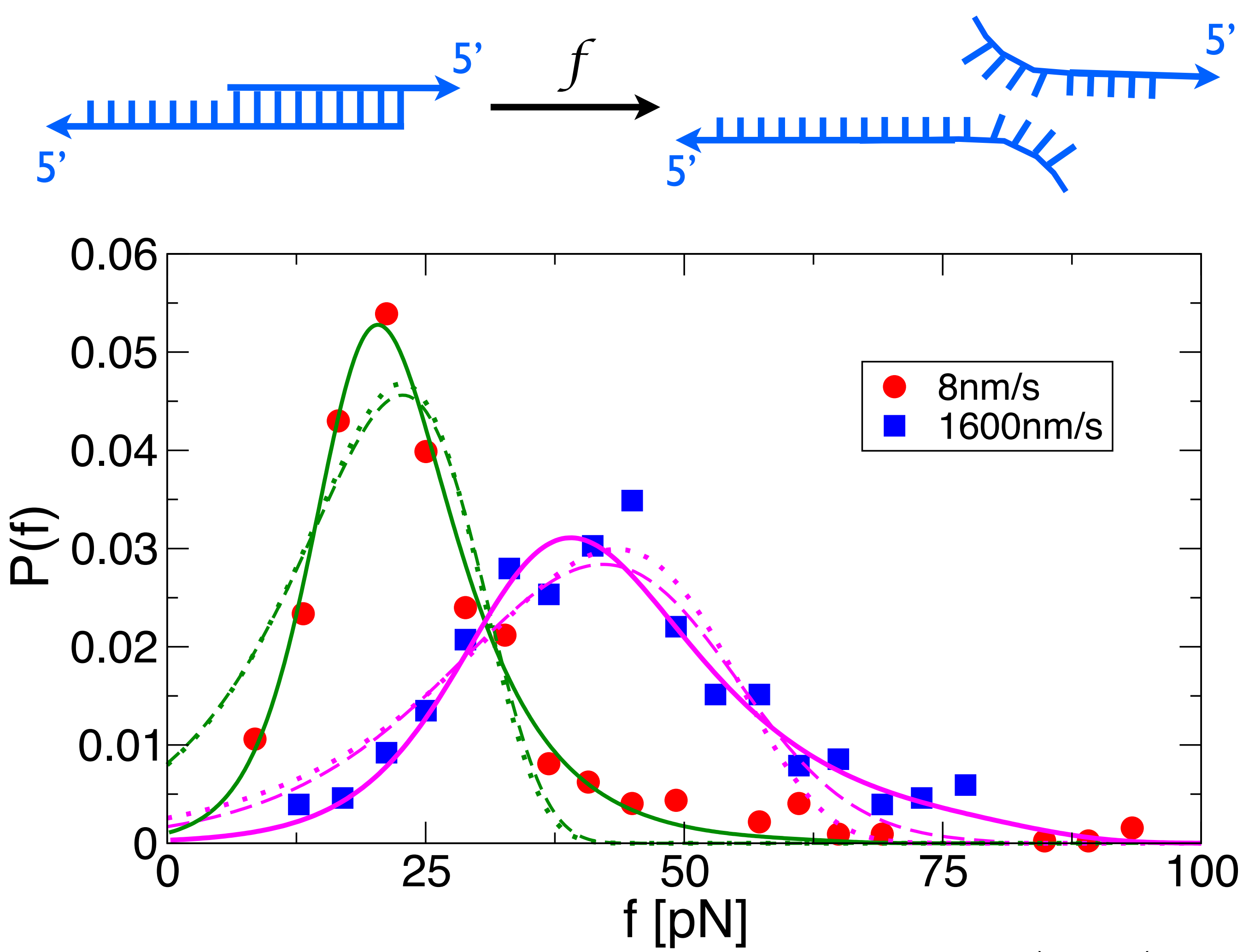
$v = 300\ \mathrm{nm/s},\ k_s = 30\ \mathrm{pN/nm}$

$\Delta x^\ddagger = 0.48$ nm	$\Delta x^\ddagger = 0.14$ nm	$\Delta x^\ddagger = 0.18$ nm
$k_0\theta = 4.5 \times 10^{-3} s^{-1}$	$k_0\theta = 3.3 \times 10^{-5} s^{-1}$	$k_0\theta = 1.0 \times 10^{-3} s^{-1}$
$\lambda = 20 s^{-1}$	$\lambda = 10^3 s^{-1}$	$\lambda = 10^3 s^{-1}$
	(182,212)	(117,182)

Unbinding force distribution at constant loading rate, γ (force-ramp)

$$P_\lambda(t) = \frac{\lambda e^{\lambda t/2}}{\sqrt{2}}\left[\kappa^2(t)\frac{\mathcal{I}''(\rho)}{\mathcal{I}(\rho)} + \frac{1}{\beta}\kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)} - 1\right]\left[\frac{\mathcal{I}(\rho)}{\mathcal{I}(\rho_0)}\right]^{-1/2}\left[1+\kappa(t)\frac{\mathcal{I}'(\rho)}{\mathcal{I}(\rho)}\right]^{-3/2}.$$

$\rho = \beta\kappa(t)$ $\beta = 2\lambda/\tilde{\gamma}$ $\kappa(t) = \sqrt{4k_0\theta/\lambda}\, e^{t\tilde{\gamma}/2}$



T. Strunz, K. Oroszlan, R. Schäfer, and H. Güntherodt, Proc. Natl. Acad. Sci. U.S.A. **96**, 11277 (1999).

$v = 8$ nm/s
$\Delta x^\ddagger = 1.1$ nm
$k_0\theta = 0.017 s^{-1}$
$\lambda = 2.8\times 10^{-5} s^{-1}$

$v = 1600$ nm/s
$\Delta x^\ddagger = 0.66$ nm
$k_0\theta = 0.99 s^{-1}$
$\lambda = 0.48 s^{-1}$

dotted line : Bell
dashed line : DHS
solid line : our theory

Phys. Rev. Lett. (2014) 112, 138101

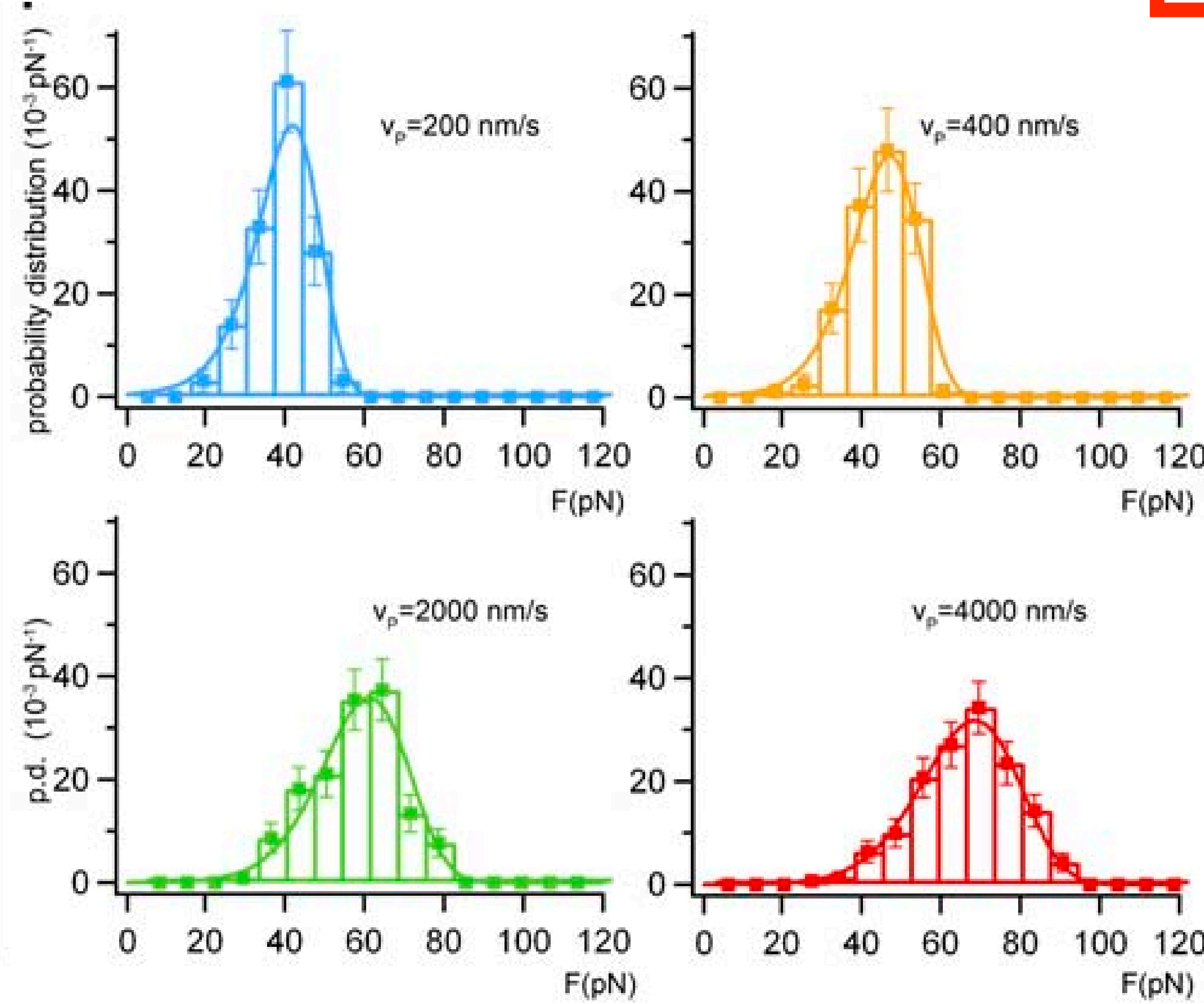
$$\Sigma(f) = e^{-\frac{1}{r_f}\int_0^f df' k(f')}$$

$$r_f = K(f)V = \omega(f)V \qquad V\text{: controlled}$$

$$\Omega_V(f) \equiv -V \log \Sigma(f) = \boxed{\int_0^f df' \, (k(f')/\omega(f'))}$$

indep. of pulling speed (V)

ddFLN4



$$\Sigma(f) = 1 - \frac{1}{r_f}\int_0^f df \, P(f)$$

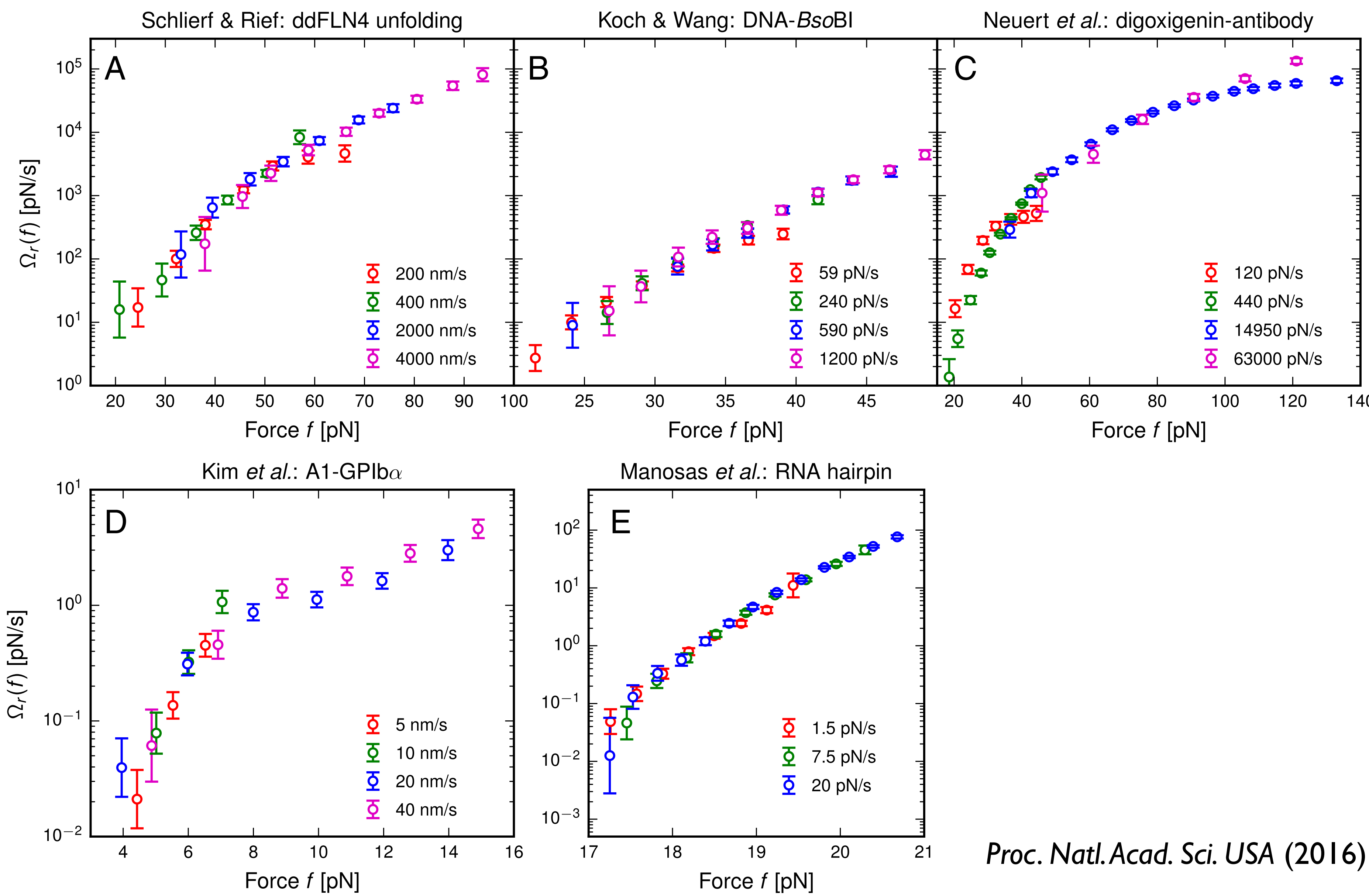
$$r_f = k_m V$$

Schlierf, Rief (2005) Biophys. J.

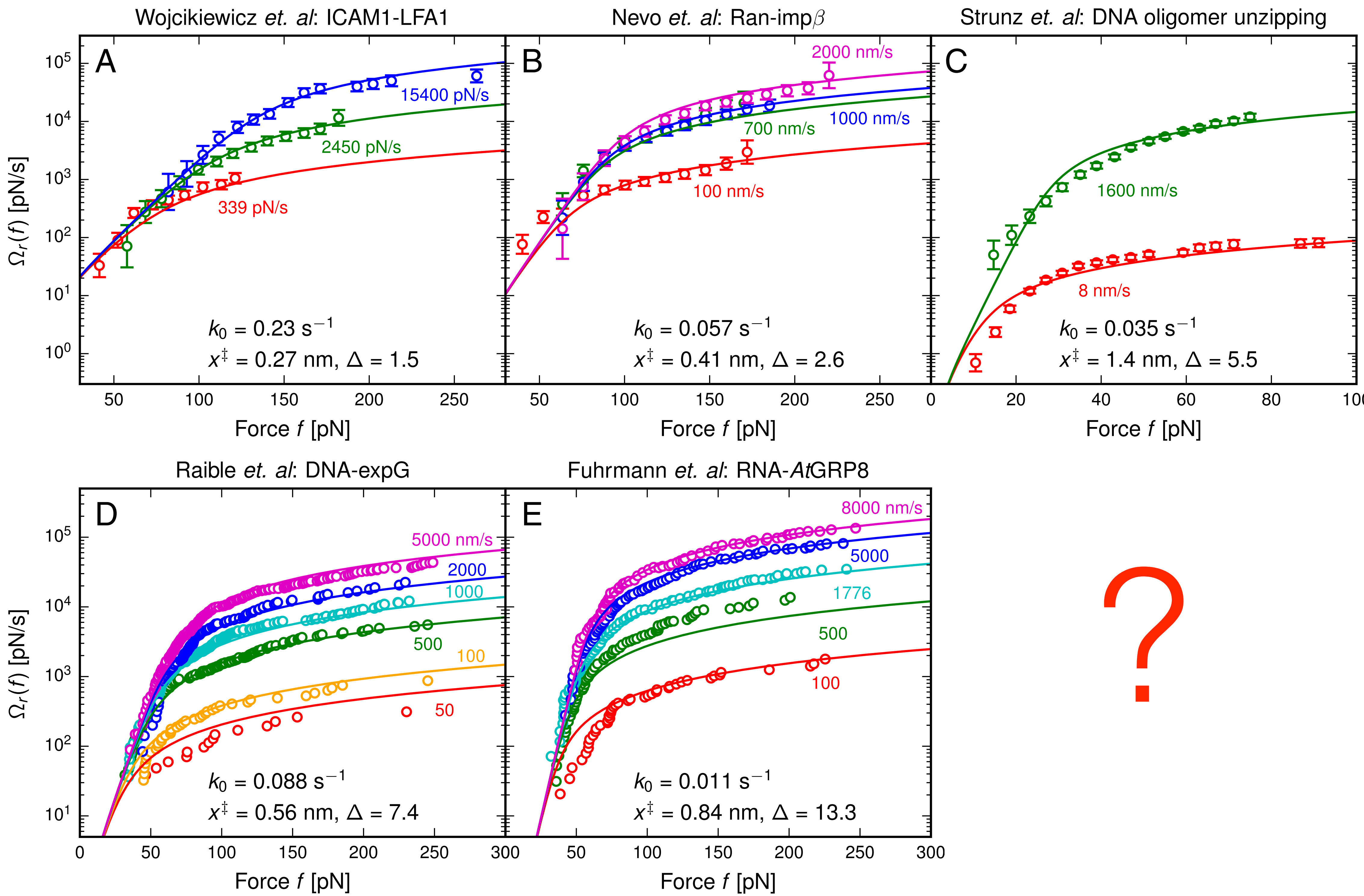
$$\Sigma(f) = e^{-\frac{1}{r_f}\int_0^f df' k(f')}$$

$$r_f = K(f)V = \omega(f)V \qquad V\text{: controlled}$$

$$\Omega_V(f) \equiv -V\log\Sigma(f) = \int_0^f df'\,(k(f')/\omega(f'))$$

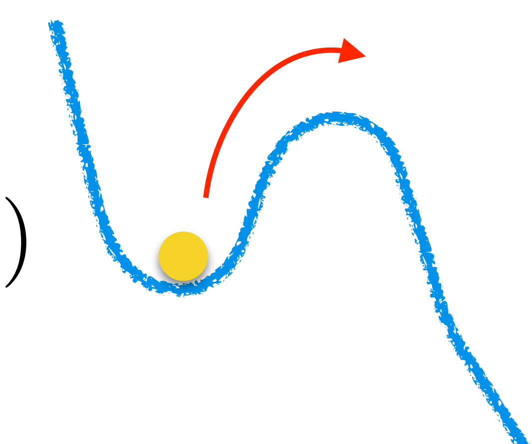


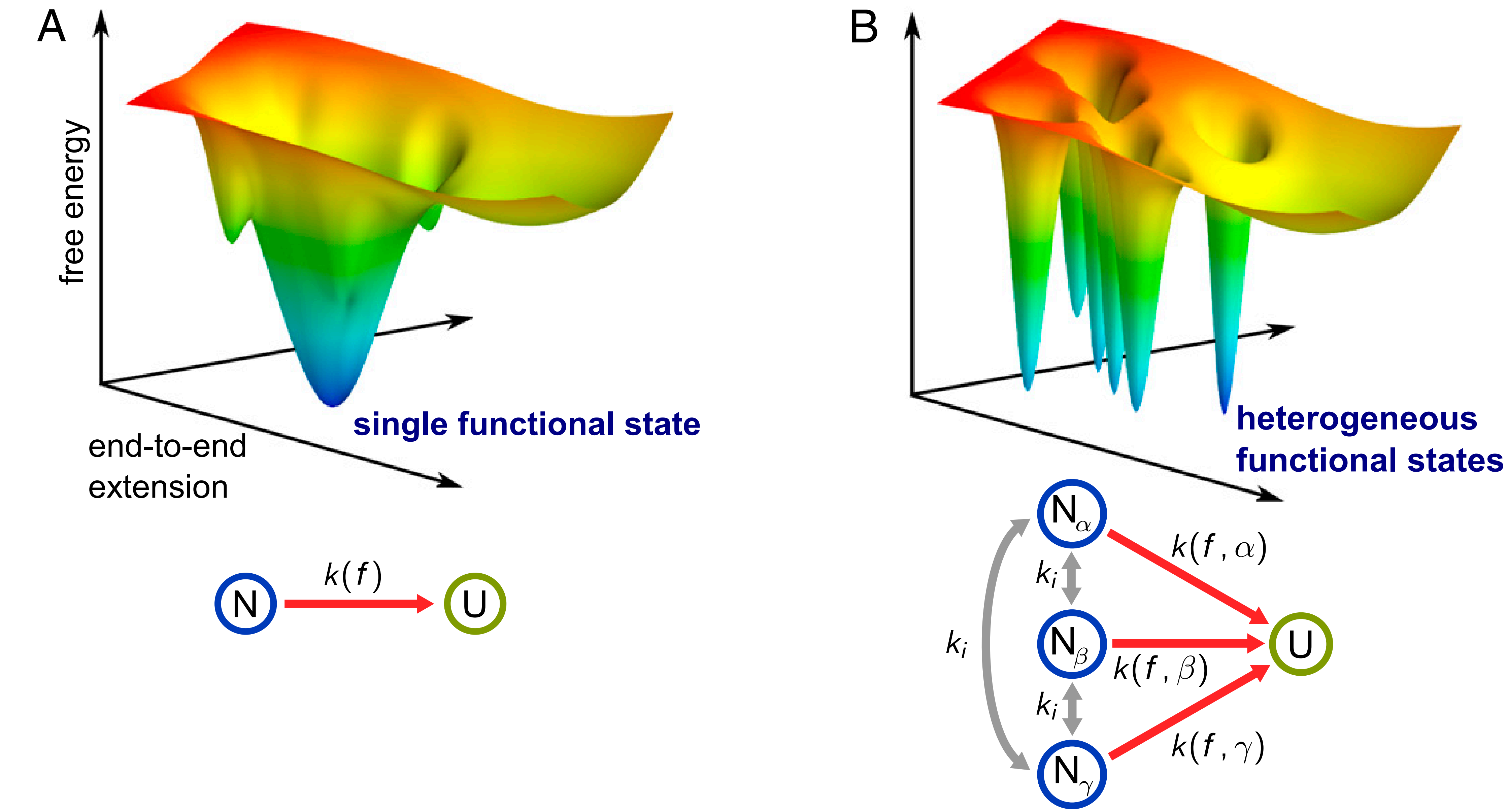
Proc. Natl. Acad. Sci. USA (2016) 113, E3852-E3861



?

$$\Sigma(f) = e^{-\frac{1}{r_f}\int_0^f df' k(f')} \longleftarrow \frac{d\Sigma(t)}{dt} = -k(t)\Sigma(t)$$





$$\Sigma(f) = e^{-\frac{1}{r_f}\int_0^f df' k(f')}$$

$$\Sigma(f) = \langle e^{-\frac{1}{r_f}\int_0^f df' k(f')} \rangle$$

$\langle \ldots \rangle$ **: average over heterogenous native population**

$$\langle \mathcal{O} \rangle = \sum_\alpha p_\alpha \mathcal{O}_\alpha$$

Proc. Natl. Acad. Sci. USA (2016) 113, E3852-E3861

$$\Sigma_{r_f}(f) = \sum_{\alpha} p_\alpha e^{-\frac{1}{r_f}\int_0^f df' k_\alpha(f')} = \langle e^{-\frac{1}{r_f}\int_0^f df' k(f')} \rangle$$

$$\Omega_{r_f}(f) = -r_f \log \Sigma_{r_f}(f) = -r_f \log \langle e^{-\frac{1}{r_f}\overbrace{\boxed{\int_0^f df' k(f')}}^{I(f)}} \rangle$$

$$-r_f \log \langle e^{-I(f)/r_f} \rangle = \langle I(f) \rangle - \frac{1}{2!}\frac{\langle (\delta I(f))^2 \rangle}{r_f} + \cdots = -\sum_{n=1}^{\infty} \frac{(-1)^n}{n!}\frac{\kappa_n(f)}{r_f^{n-1}}$$

$$\kappa_1(f) = \langle I(f) \rangle$$

$$\kappa_2(f) = \langle (\delta I(f))^2 \rangle$$

$$\kappa_n(f) \equiv \frac{\partial^n}{\partial \lambda^n} \log \langle e^{\lambda I(f,\alpha)} \rangle \Big|_{\lambda=0}.$$

$$\boxed{\Delta(f) \equiv \frac{\kappa_2(f)}{\kappa_1^2(f)}}$$

extent of static heterogeneity

$$\Omega_{r_f}(f) = r_f \log \langle e^{-I(f)/r_f} \rangle^{-1} = \frac{r_f}{\Delta(f)} \log \left[1 + \frac{\kappa_1(f)}{r_f} + \cdots \mathcal{O}\left(\frac{1}{r_f^2}\right) \right]^{\Delta(f)}$$

$$\approx \frac{r_f}{\Delta(f)} \log \left[1 + \frac{\kappa_1(f)\Delta(f)}{r_f} \right] \xrightarrow[\Delta(f) \to 0]{} \kappa_1(f)$$

Proc. Natl. Acad. Sci. USA (2016) 113, E3852-E3861

$$\Omega_{r_f}(f) = r_f \log \langle e^{-I(f)/r_f} \rangle^{-1} = \frac{r_f}{\Delta(f)} \log \left[1 + \frac{\kappa_1(f)}{r_f} + \cdots \mathcal{O}\left(\frac{1}{r_f^2} \right) \right]^{\Delta(f)}$$

$$\approx \frac{r_f}{\Delta(f)} \log \left[1 + \frac{\kappa_1(f)\Delta(f)}{r_f} \right] \xrightarrow[\Delta(f) \to 0]{} \kappa_1(f)$$

$$\Sigma(f) = e^{-\Omega_{r_f}(f)/r_f}$$

$$\kappa_1(f) = \langle \int_0^f df' k(f') \rangle = \langle \int_0^f df' k_0 e^{f/\overline{f}} \rangle = k_0 \overline{f} (e^{f/\overline{f}} - 1)$$

$$\Delta(f) = \Delta,$$

$$P(f) = -\frac{d\Sigma(f)}{df} \approx \frac{k_0 e^{f/\overline{f}}}{r_f} \left(1 + \frac{k_0 \overline{f} (e^{f/\overline{f}} - 1)}{r_f} \Delta \right)^{-\frac{1+\Delta}{\Delta}}$$

$$\xrightarrow[\Delta \to 0]{} \frac{k_0}{r_f} e^{f/\overline{f}} e^{-\frac{k_0 \overline{f}}{r_f} (e^{f/\overline{f}} - 1)}$$

Proc. Natl. Acad. Sci. USA (2016) 113, E3852-E3861

Data analysis

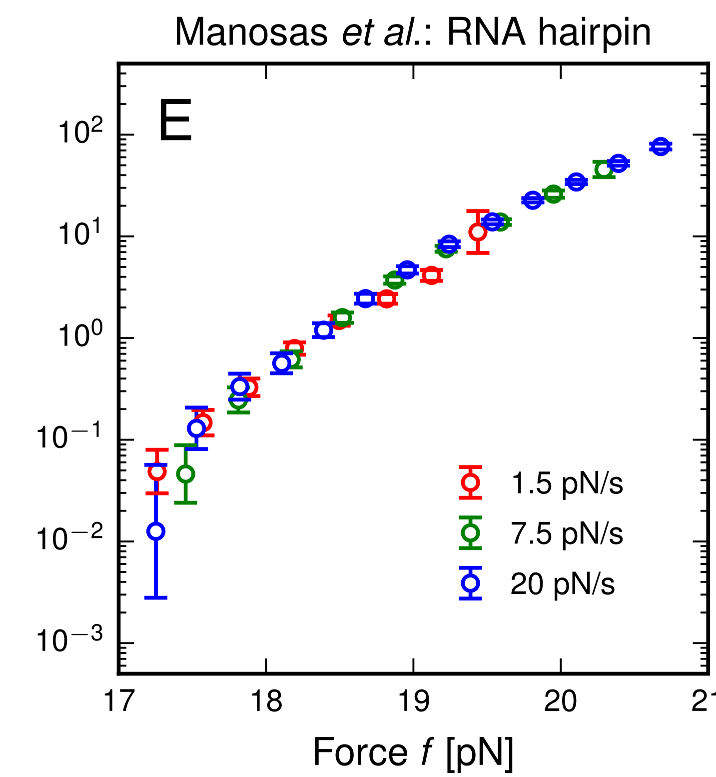
$$\Omega_{r_f}(f) \approx \frac{r_f}{\Delta(f)} \log\left[1 + \frac{\kappa_1(f)\Delta(f)}{r_f}\right]$$

$$\kappa_1(f) = \langle \int_0^f df' k(f') \rangle = \langle \int_0^f df' k_0 e^{f/\overline{f}} \rangle = k_0 \overline{f}(e^{f/\overline{f}} - 1)$$

$$\Delta(f) = \Delta,$$

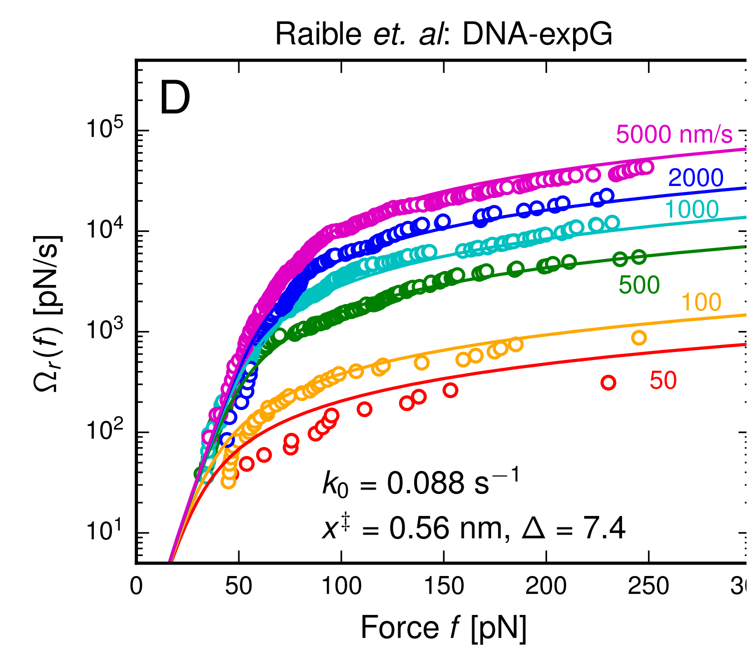
For $\Delta \to 0$ $\qquad \Omega_{r_f}(f) \to \kappa_1(f) = \langle \int_0^f df' k(f') \rangle$

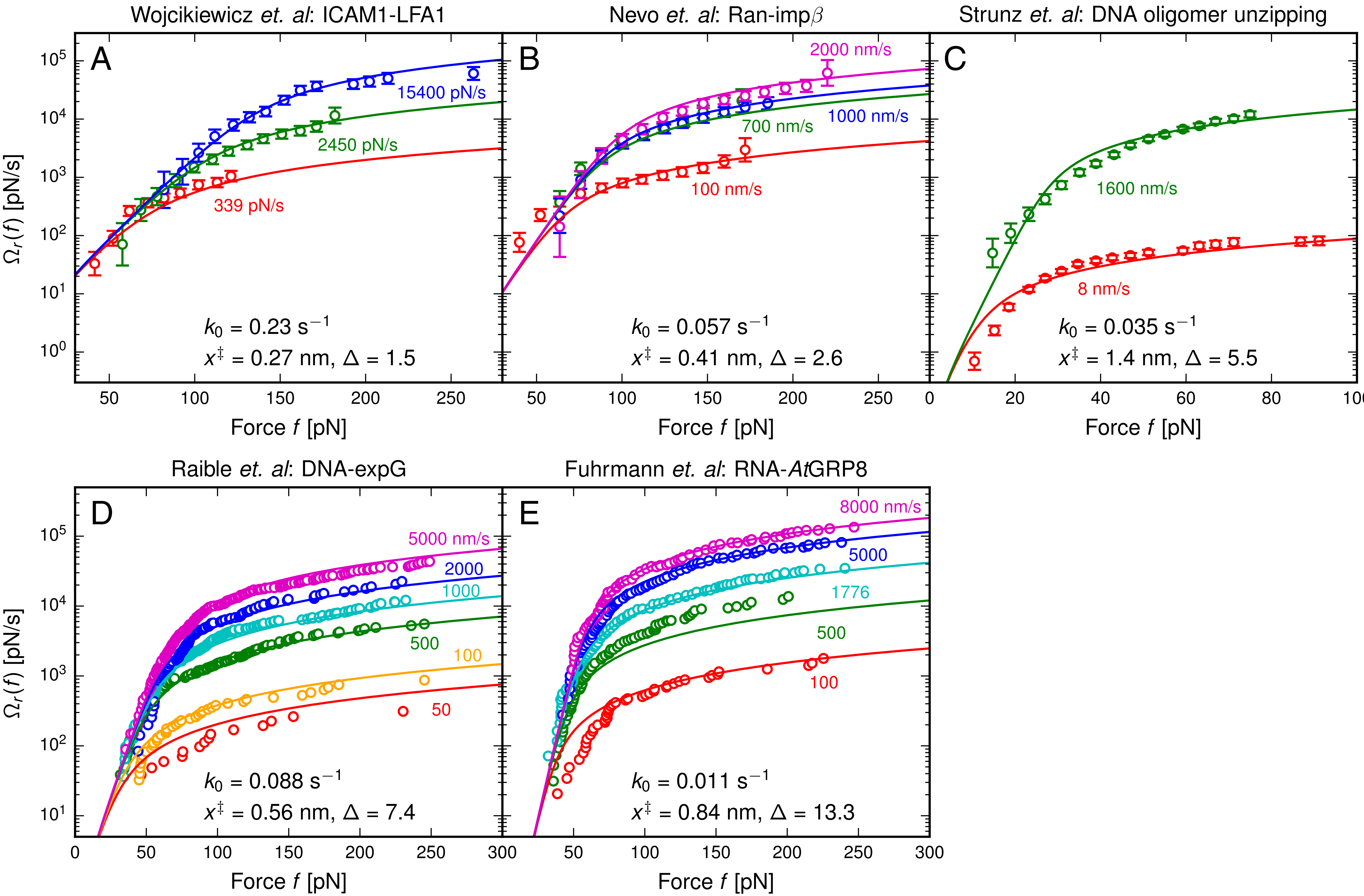
$\Omega_{r_f}(f)$ is r_f-independent !!



For $\Delta \neq 0$ $\qquad \Omega_{r_f}(f) \approx \frac{r_f}{\Delta} \log\left[1 + \frac{\kappa_1(f)\Delta}{r_f}\right]$

$\Omega_{r_f}(f)$ is r_f-dependent, and one can determine Δ by simultaneously fitting data




Wojcikiewicz et. al: ICAM1-LFA1
Nevo et. al: Ran-impβ
Strunz et. al: DNA oligomer unzipping
A
B
C
15400 pN/s
2450 pN/s
339 pN/s
2000 nm/s
1000 nm/s
700 nm/s
100 nm/s
1600 nm/s
8 nm/s
k_0 = 0.23 s^{-1}
$x^\ddagger$ = 0.27 nm, Δ = 1.5
k_0 = 0.057 s^{-1}
$x^\ddagger$ = 0.41 nm, Δ = 2.6
k_0 = 0.035 s^{-1}
$x^\ddagger$ = 1.4 nm, Δ = 5.5
$\Omega_r(f)$ [pN/s]
Force f [pN]
Raible et. al: DNA-expG
Fuhrmann et. al: RNA-AtGRP8
D
E
5000 nm/s
2000
1000
500
100
50
8000 nm/s
5000
1776
500
100
k_0 = 0.088 s^{-1}
$x^\ddagger$ = 0.56 nm, Δ = 7.4
k_0 = 0.011 s^{-1}
$x^\ddagger$ = 0.84 nm, Δ = 13.3