

# Kramers theory of reaction kinetics

Winter School for Theoretical Chemistry and Spectroscopy  
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# Hans Kramers



Hendrik Anthony Kramers  
1894 – 1952

1911 HBS, 1912 staatsexamen, 1916 doctoraal wis- en natuurkunde  
1916 Arrived unannounced in Kopenhagen to do PhD with Niels Bohr  
1919 promotion in Leiden (Ehrenfest), married in 1920  
Lector in Kopenhagen  
1926 Professor theoretical physics in Utrecht  
1934 Professor in Leiden (chair of Ehrenfest), professor in TU-Delft

Physica VII, no 4

April 1940

## BROWNIAN MOTION IN A FIELD OF FORCE AND THE DIFFUSION MODEL OF CHEMICAL REACTIONS

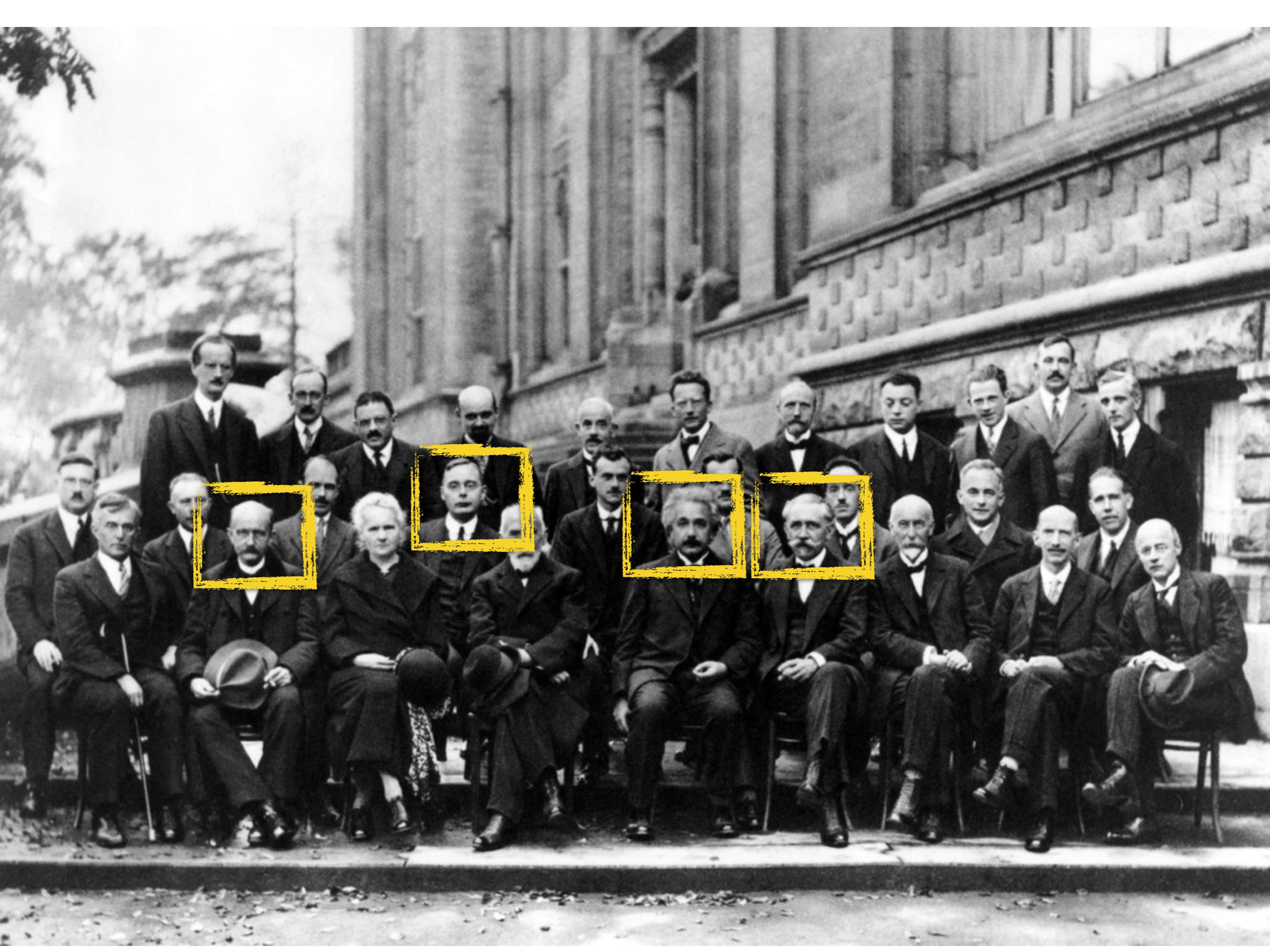
by H. A. KRAMERS

Leiden

### Summary

A particle which is caught in a potential hole and which, through the shuttling action of Brownian motion, can escape over a potential barrier yields a suitable model for elucidating the applicability of the transition state method for calculating the rate of chemical reactions.

Physics 7(4),  
April 1940,  
Pages 284-304  
- 8 references



# Outline

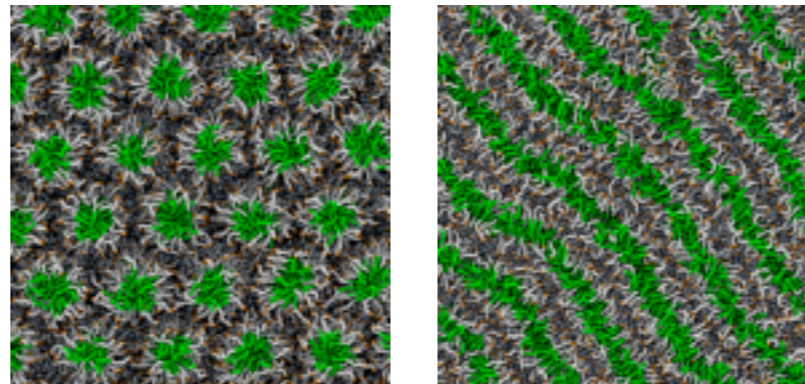
- Intro Kramers theory
- Transition State Theory
- The Langevin equation
- The Fokker-Planck equation
- Kramers reaction kinetics
- high-friction vs low-friction limit
- memory, Grote-Hynes theory
  
- Bennet-Chandler approach
- Reactive Flux
- Transmission coefficient calculation
- Free energy methods
- Summary
- Bibliography

# Molecular Transitions are Rare Events

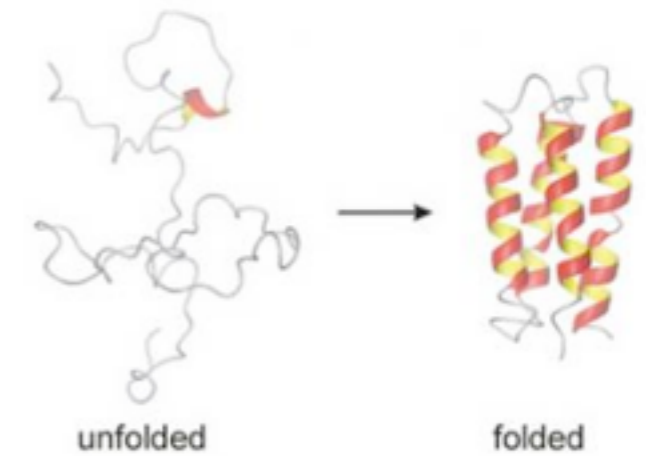
chemical reactions



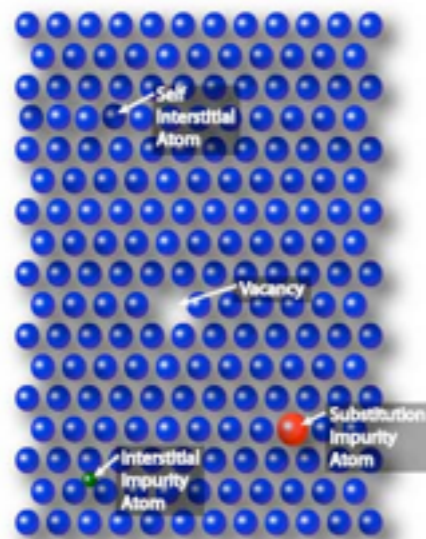
phase transitions



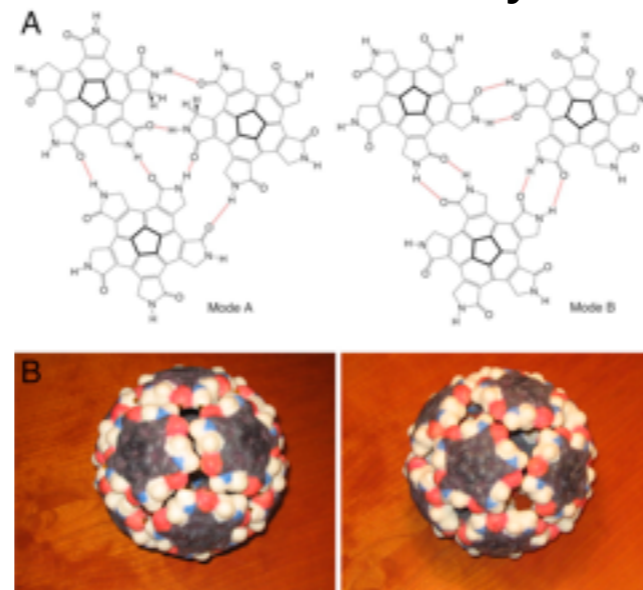
protein folding



defect diffusion



self-assembly



stock exchange crash

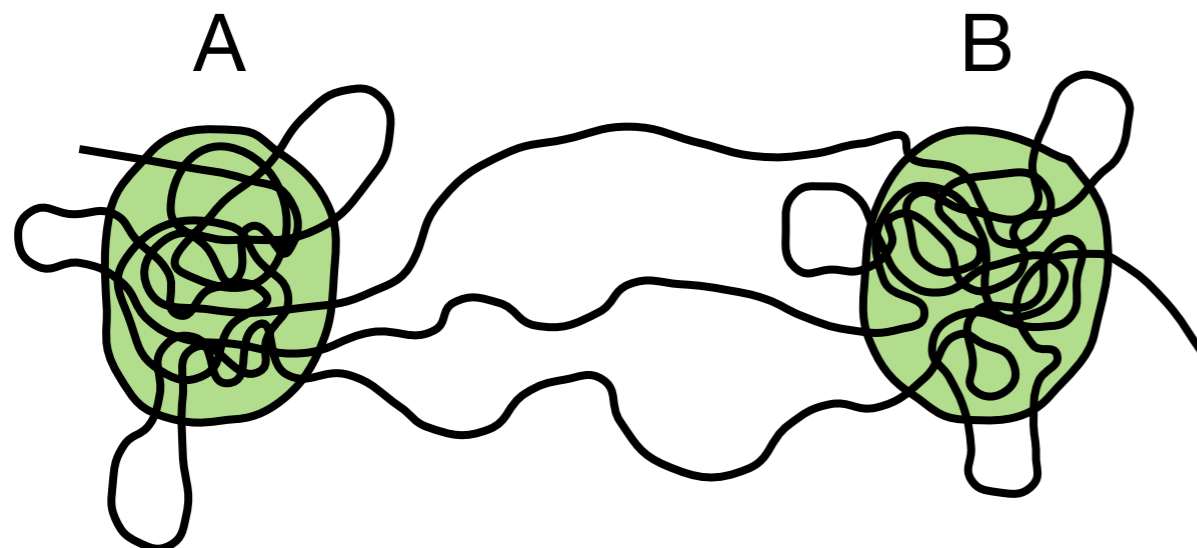


# Rare Events

- Molecular transitions are not rare in every day life
- They are only rare events with respect to the femto-second timescale of atomic motions
- Modeling activated transitions by straightforward simulation would be extremely costly (takes forever)
- Advanced methods: Transition state theory (TST), Bennet-Chandler (Reactive Flux) approach, Transition Path Sampling (TPS), Free energy methods, Parallel Tempering, String Method,.....

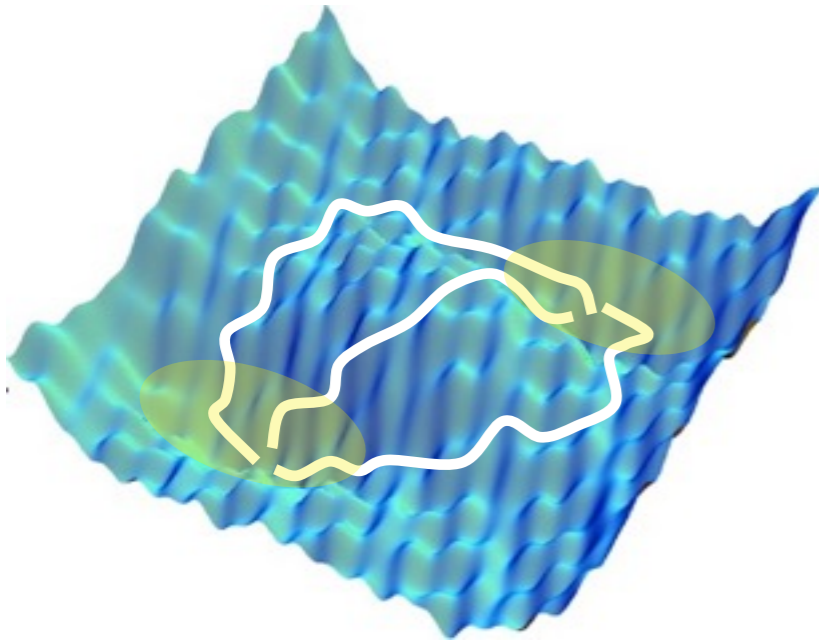


*A very long trajectory*



- A and B are (meta-)stable states, i.e. attractive basins
- transitions between A and B are rare
- transitions can happen fast
- system loses memory in A and B

## Free energy landscape



P.G. Bolhuis, D. Chandler,  
C. Dellago, P.L. Geissler

*Annu. Rev. Phys. Chem* 2002

# Rare Events

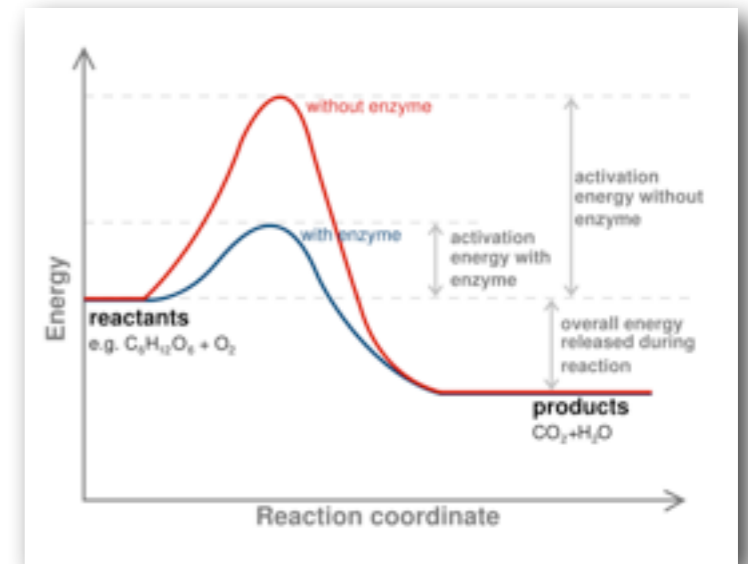
The free energy has local minima separated by barriers

Many possible transition paths via meta-stable states

Projection on reaction coordinate shows FE profile with transition state barrier

Reaction rate depends exponentially on the barrier height

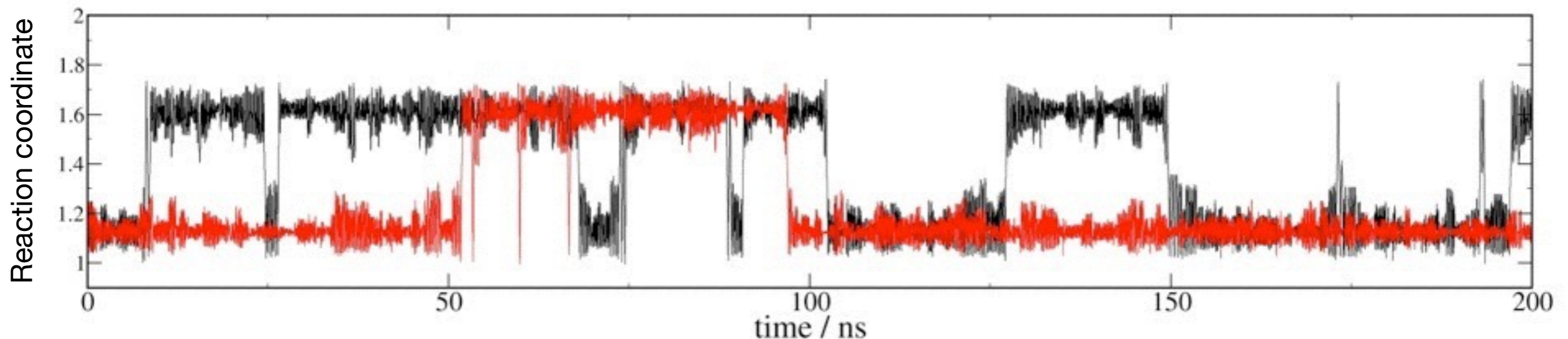
## Transition State



$$k = k_0 e^{-\Delta G/kT}$$

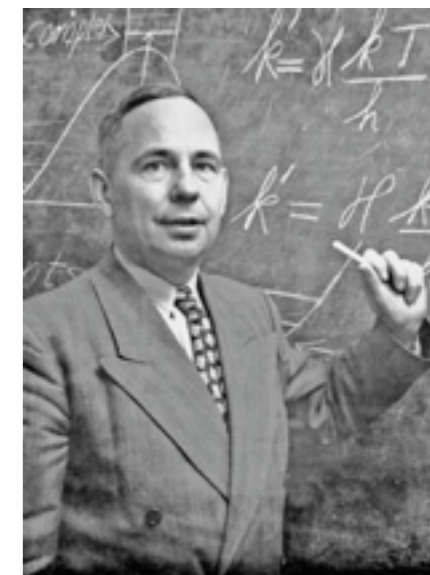
Arrhenius equation

## A long trajectory

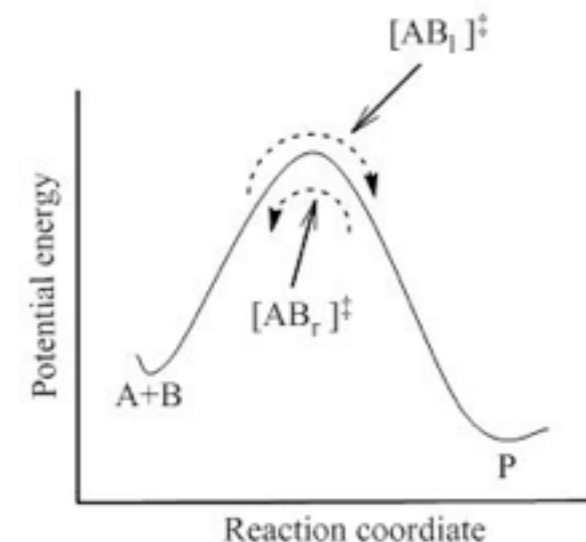


# Transition State Theory

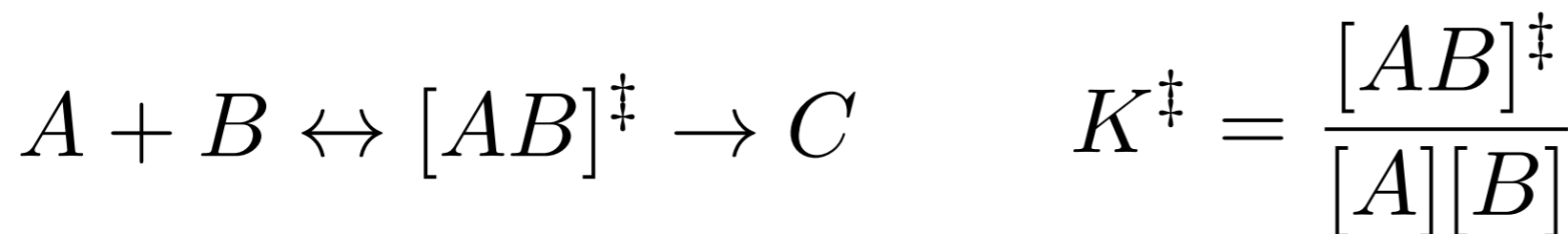
- Derived by Henry Eyring and by Meredith Gwynne Evans and Michael Polanyi in 1935
- Explains Arrhenius equation (1889)  $k = Ae^{-E_a/RT}$   
(van't Hoff 1884)
- Activated complex is in quasi equilibrium with reactants
- All reactants that reach the activated complex state, continue to products



*Henry Eyring*



*probability to reach the transition state*



$$k = k^\ddagger K^\ddagger = \kappa \frac{k_B T}{h} e^{-\Delta G^\ddagger / RT}$$

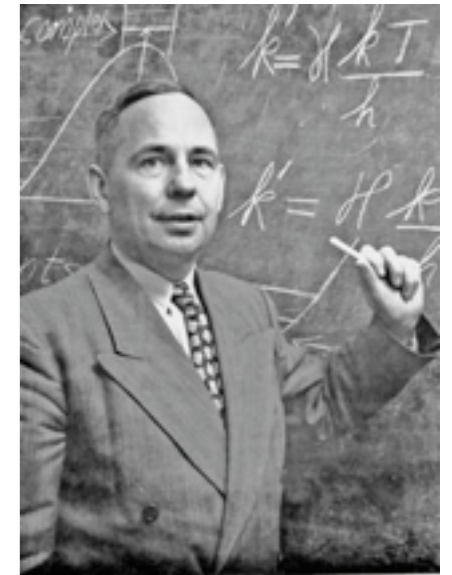
↙ *frequency*

*- rate is frequency of unstable mode times the TS probability*  
*- transmission factor is  $\kappa=1$  in TST (correction for barrier recrossings)*

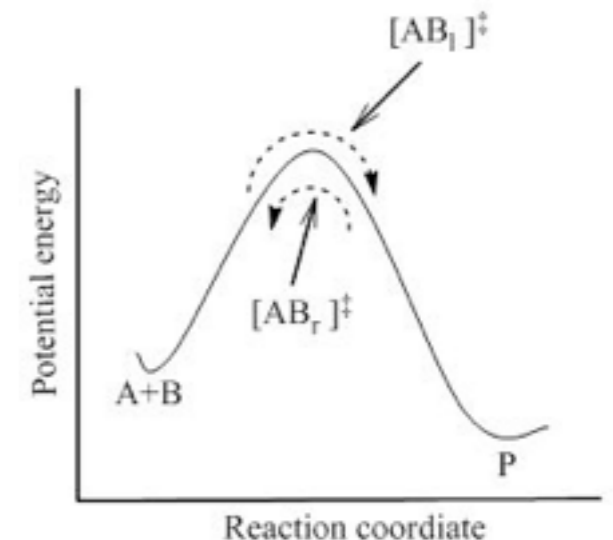


# Transition State Theory

- what is a transition state? activated structure, critical nucleus, entropic bottleneck,...
- where does the prefactor ( $\kappa$  dependence) come from?
- TST rate is an upper limit for the true rate
- The actual rate is slower than the TST estimate due to recrossing
- recrossing occurs due to a bad estimate for the TS (dividing surface) / hidden slow variables (aka the reaction coordinate problem) and/or due to noisy dynamics from the environment
- is  $\kappa$  just a cheating factor or does it have a physical meaning?

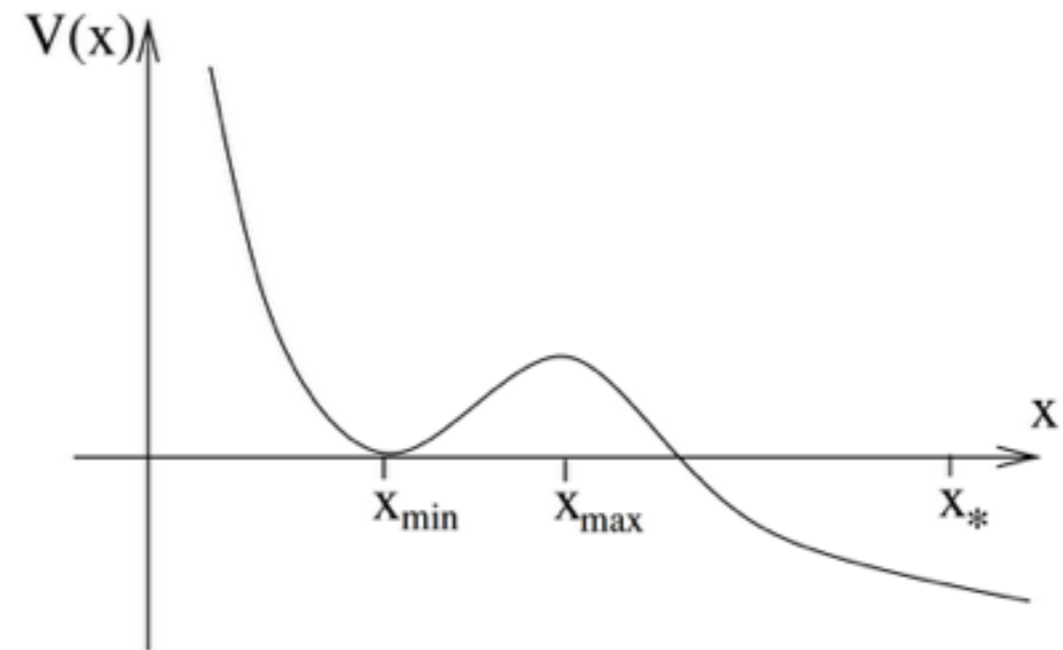


*Henry Eyring*



# Separation of time scales

- Suppose a coordinate  $X$  describes the reaction progress
- $X$  is coupled to environment
- the coupling makes the dynamics of  $X$  stochastic (not deterministic)
- to escape from the reactant well,  $X$  (=random walker) must acquire enough energy from the bath
- this energy must be lost again after passing the barrier



- The escape time depends on the size of the fluctuations  $(X(t) - \langle X \rangle)^2$
- $E_{\text{noise}} \ll E_{\text{barrier}} \Rightarrow E^a/RT \gg 1$

*relaxation time  $\tau_s$*

*escape time  $\tau_e = 1/k$*

$$\tau_s \approx 2\pi \sqrt{m_{\text{eff}} / \left( \frac{d^2V}{dX^2} \right)} \ll \tau_e = \tau_s \exp(E^a / k_B T)$$

# Diffusion

Density of particles:  $\rho(\mathbf{r}, t)$

Current density:

$$\mathbf{j}(\mathbf{r}, t) = \rho(\mathbf{r}, t)\mathbf{v}(\mathbf{r}, t)$$

A gradient in the density leads to a current:

$$\mathbf{j} = -D\nabla\rho \quad \text{Fick's law}$$

$D$  diffusion coefficient

Mean square displacement:

$$\langle x^2(t) \rangle = 2Dt$$

- also end-to-end distance
- ballistic motion:  $x^2(t) \rightarrow t^2$

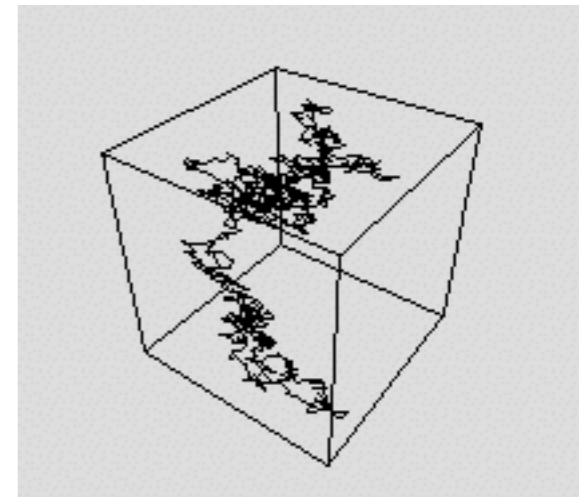
Velocity auto correlation function:

$$D = \int_0^\infty d\tau \langle v_x(\tau)v_x(0) \rangle$$

ensemble average  $\langle \dots \rangle$



Diffusion of particles due to a concentration gradient



Self-diffusion of a particle seen as a random walk

# Langevin equation

*mass x acceleration = force*

$$m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

*U is external  
potential*

*viscous drag  
 $\gamma$  is friction  
(dissipation)*

*random  
collisions*

Describes Brownian motion

random motion of small particles (pollen grains) in a solvent due to thermal fluctuations (Brown 1828)



Paul Langevin  
1872-1946



Robert Brown  
1773-1858

# Illustration with Octave/Matlab script

$$m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

```
% brownian_2d.m simulates a two-dimensional Brownian motion

N=10000;           % number of steps to take
T=70;             % maximum time
h=T/N;           % time step
t=(0:h:T);       % t is the vector [0 1h 2h 3h ... Nh]
sigma = 1.0;     % strength of noise

x=zeros(size(t)); % place to store x locations
y=zeros(size(t)); % place to store y locations

x(1)=0.0;        % initial x location
y(1)=0.0;        % initial y location
for i=1:N        % take N steps
    x(i+1)=x(i)+sigma*sqrt(h)*randn;
    y(i+1)=y(i)+sigma*sqrt(h)*randn;
end;

plot(x,y);
grid on          % add a grid to axes
% axis([0 T -3 8]); % set axis limits
```

# Illustration with Octave/Matlab script

$$m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

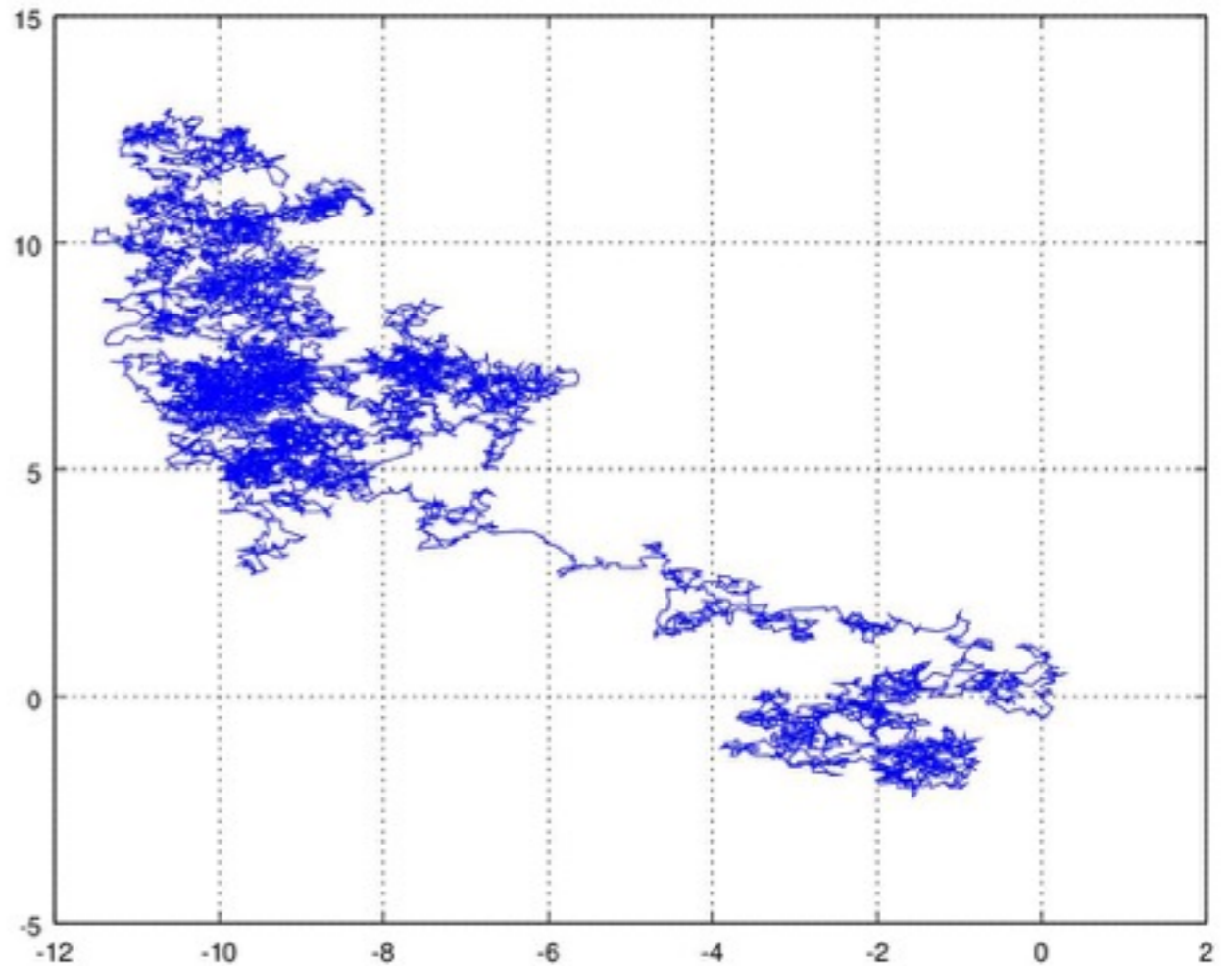
```
% brownian_2d.m simulates a two-d

N=10000;           % number of
T=70;             % maximum t
h=T/N;           % time step
t=(0:h:T);       % t is the
sigma = 1.0;     % strength

x=zeros(size(t)); % place to
y=zeros(size(t)); % place to

x(1)=0.0;        % initial x
y(1)=0.0;        % initial y
for i=1:N        % take N st
    x(i+1)=x(i)+sigma*sqrt(h)*ran
    y(i+1)=y(i)+sigma*sqrt(h)*ran
end;

plot(x,y);
grid on          % add a grid to axes
% axis([0 T -3 8]); % set axis limits
```



# Langevin equation

Stokes formula for viscous drag:

$$\gamma = -6\pi\eta\alpha$$

$$f_d = -\gamma v$$

- laminar flow (small velocities)
- spherical particle with radius  $\alpha$
- $\gamma$  is the friction
- $1/\gamma$  is the mobility
- $\eta$  is the dynamic viscosity
- $v$  is the velocity of the particle

Equation of motion with only drag and random forces:

$$m \frac{d\mathbf{v}(t)}{dt} = -6\pi\eta\alpha\mathbf{v}(t) + \zeta(t)$$

- Langevin equation without  $\nabla V$
- stochastic differential equation
- what do we know about  $\zeta(t)$ ?
  - $\langle \zeta(t) \rangle = 0$
  - $\langle \zeta(t)\zeta(t') \rangle = 2D\gamma^2\delta(t-t')$
  - (white noise, Wiener process)
  - (Markovian dynamics vs memory)

Taking the ensemble average:

$$m \frac{d\langle \mathbf{v}(t) \rangle}{dt} = -6\pi\eta\alpha\langle \mathbf{v}(t) \rangle$$

- since average random force is zero

which implies:  $\langle \mathbf{v}(t) \rangle = \mathbf{v}(0) e^{-t/\tau}$

- relaxation time of initial perturbation  
 $\tau = m/(6\pi\eta\alpha)$

# strong friction

Particle in a very viscous solvent:

$$\gamma \frac{dx}{dt} = \zeta(t)$$

$$- m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

- *particle is driven by fluctuating solvent*
- *no inertial motion  $\rightarrow m=0$*
- *no external potential*

solving the differential equation:

$$x(t) = x(0) + \frac{1}{\gamma} \int_0^t dt' \zeta(t')$$

- *since  $\langle \zeta(t) \rangle = 0$*
- *unsurprisingly:  $\langle x(t) \rangle = \langle x(0) \rangle$*
- *consider many paths from  $x(0)$*

what about the variance?

$$\langle (x(t) - x(0))^2 \rangle = \frac{1}{\gamma^2} \int_0^t dt'_1 \int_0^t dt'_2 \langle \zeta(t'_1) \zeta(t'_2) \rangle$$

- *$x(0)$  to the left and square both sides*

$$\langle (x(t) - x(0))^2 \rangle = 2Dt$$

- *particle gets  $10^{16}$  (gas) to  $10^{20}$  (liquid) kicks per sec.*
- *kicks are very fast and considered uncorrelated*
- *$\langle \zeta(t) \zeta(t') \rangle = 2D\gamma^2 \delta(t - t')$*



# weaker friction

Particle in a less viscous solvent:

$$\langle \mathbf{v}(t) \rangle = \mathbf{v}(0) e^{-\gamma t/m}$$

$$- m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

- inertial motion  $\rightarrow m > 0$
- still no external potential
- $\tau = m/\gamma$

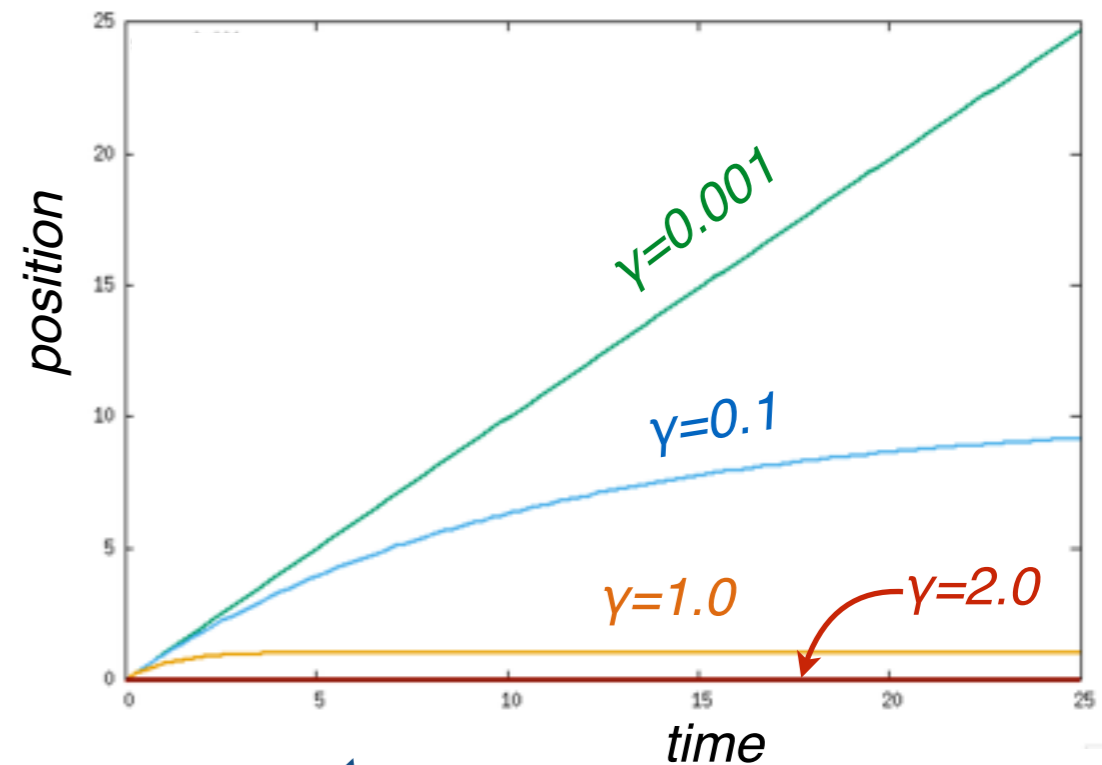
For the position we use:

$$x(t) = x(0) + \int_0^t dt' v(t')$$

take the ensemble average

$$\langle x(t) \rangle = x(0) + \int_0^t dt' \langle v(t') \rangle$$

$$\langle x(t) \rangle = x(0) + \frac{m}{\gamma} v(0) (1 - e^{-\gamma t/m})$$



# Fluctuation-dissipation

$$m \frac{d\mathbf{v}(t)}{dt} = -6\pi\eta\alpha\mathbf{v}(t) + \zeta(t)$$

dissipation of kinetic energy into heat of the bath

conversion of heat into kinetic energy of the particle

Velocity auto correlation in weak friction:

$$\langle v_x(t_1)v_x(t_2) \rangle = \frac{D\gamma}{m} e^{-\gamma(t_2-t_1)/m}$$

- decays to zero with  $\tau=m/\gamma$
- i.e. correlated when  $t_2 - t_1 < m/\gamma$

Gives also the kinetic energy:

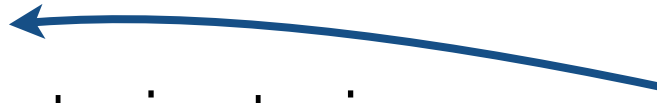
$$E_{\text{kin}} = \frac{1}{2} m \langle \mathbf{v}(t)^2 \rangle = \frac{3D\gamma}{2}$$

- $\langle v_x(t)v_x(t) \rangle = \frac{D\gamma}{m}$
- equipartition theorem:  $E_{\text{kin}} = \frac{3}{2} k_B T$
- **fluctuation-dissipation theorem:** there is a relation between the kicking and the friction!

Einstein relation:  $D = \frac{k_B T}{\gamma}$

- combine with MSD -> determine  $k_B$ !
- $\langle \mathbf{x}^2 \rangle = \frac{k_B T}{\pi\eta\alpha} t$
- Jean Baptiste Perrin 1926 Nobel prize

# Fokker-Planck

Integrating the Langevin equation from an initial point  $(\mathbf{x}_0, t_0)$  results in a stochastic trajectory. What is the probability to arrive at point  $\mathbf{x}$  at time  $t$ ?  $\longrightarrow P(\mathbf{x}, t | \mathbf{x}_0, t_0)$  

- we could integrate over all possible trajectories
- or try to predict how the probability evolves

E.g. strong friction case:  $\gamma \frac{dx}{dt} = \zeta(t)$        $m \frac{d^2x}{dt^2} = -\frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$

$\langle \mathbf{x}(0) \rangle = 0, \quad \langle \mathbf{x}^2(t) \rangle = 6Dt$       - (now in 3 dimensions)

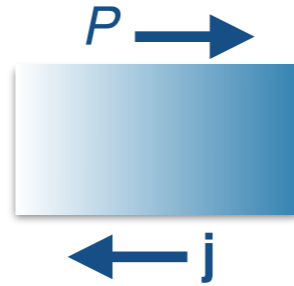
The distribution that gives this variance is a Gaussian:

$$P(\mathbf{x}, t) = \left( \frac{1}{4\pi Dt} \right)^{3/2} e^{-\mathbf{x}^2 / 4Dt} \quad - \text{prefactor from: } \int d^3x P(\mathbf{x}, t) = 1$$

Solution of diffusion equation:  $\frac{\partial P}{\partial t} = D \nabla^2 P$       - simplest Fokker-Planck equation

# Diffusion equation

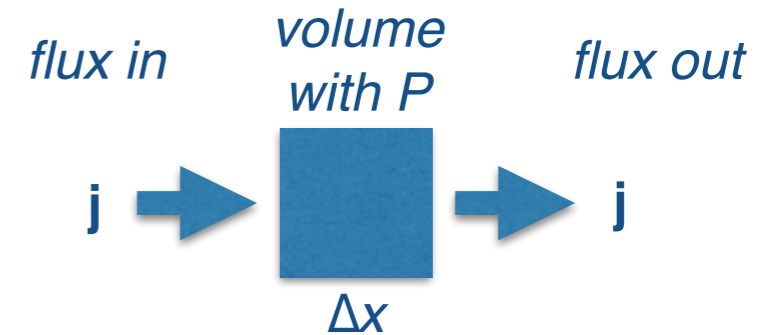
Fick's law:  $\mathbf{j} = -D\nabla P$



- *current probability (or current density)*

$$\mathbf{j}(\mathbf{x}, t) = P(\mathbf{x}, t)\mathbf{v}(\mathbf{x}, t)$$

Conservation law:  $\frac{\partial P}{\partial t} = -\frac{\partial \mathbf{j}}{\partial \mathbf{x}}$



Combine:  $\frac{\partial P}{\partial t} = D\nabla^2 P$

Solution of diffusion equation:

$$P(\mathbf{x}, t) = \left(\frac{1}{4\pi Dt}\right)^{3/2} e^{-\mathbf{x}^2/4Dt}$$

# Illustration with Octave/Matlab script

$$P(\mathbf{x}, t) = \left(\frac{1}{4\pi Dt}\right)^{3/2} e^{-\mathbf{x}^2/4Dt}$$

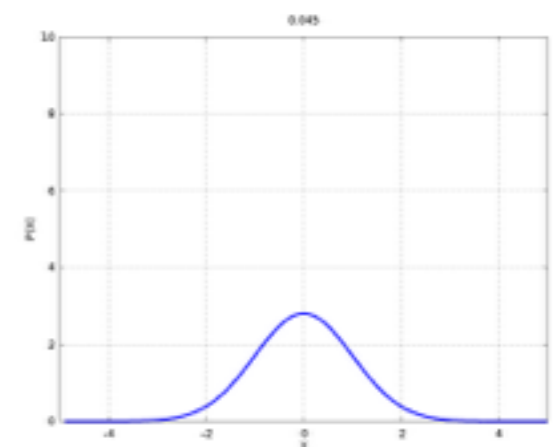
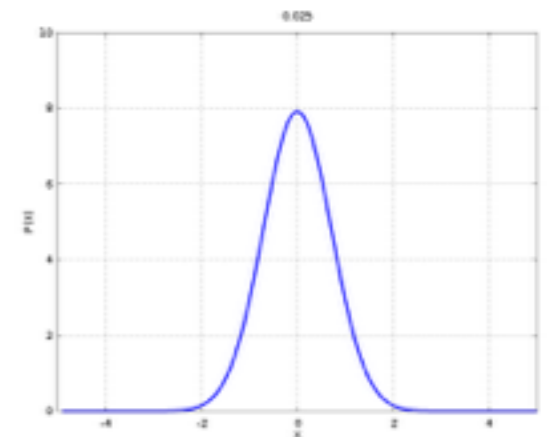
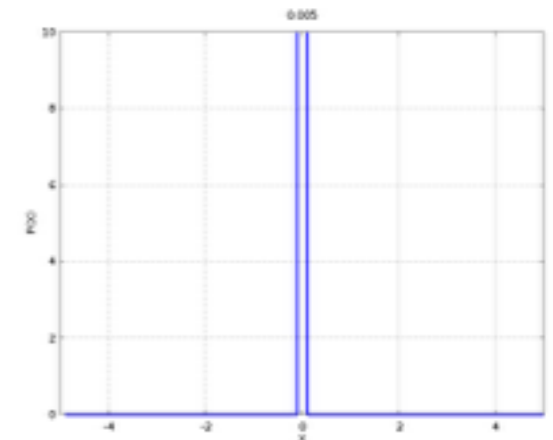
```
% Script to plot diffusion equation
clear;
clf;

N=1000;           % number of steps to take
T=50;            % maximum time
h=T/N;           % time step
nx=100;          % size of xgrid
xmin=-5.0;
xmax=5.0;
dx=(xmax-xmin)/nx;
x=zeros(size(nx)); % place to store x locations
y=zeros(size(nx)); % place to store y locations
sigma = 0.01;     % strength of noise
D=1.0*4*3.14159265;
t=0.00001;

for it=1:T
    for ix=1:nx
        x(ix)=xmin + ix*dx;
        y(ix)= (1.0/(D*t))^(3/2) * exp(-(x(ix)^2)/(4*D*t));
    end;

    plot(x,y,"linewidth"), hold on;
    title(num2str(it*h));
    xlabel ("X");
    ylabel ("P(X)");
    axis([xmin xmax 0.0 10.0]);
    grid on;
    pause(1);

    t=t+h;
end;
```



# Summary part 1

Transition state theory (Eyring, 1935)  $k = \kappa \frac{k_B T}{h} e^{-\Delta G^\ddagger / RT}$

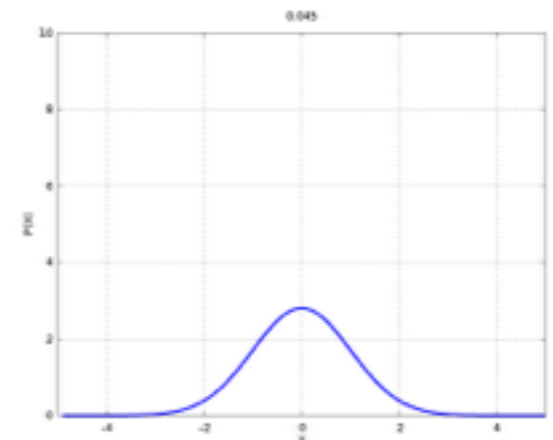
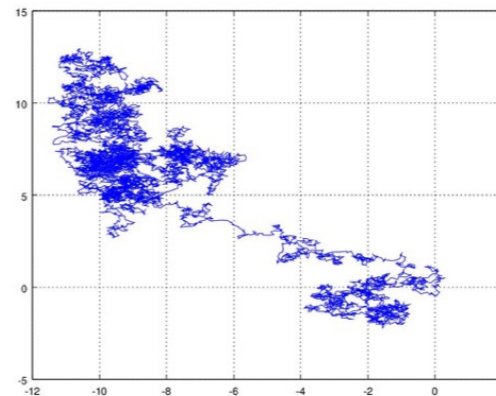
Diffusion, Brownian Motion, Langevin equation:

$$m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

Fluctuation-dissipation theorem, Einstein relation:  $D = \frac{k_B T}{\gamma}$

Diffusion equation, Fokker-Planck equation:  $\frac{\partial P}{\partial t} = D \nabla^2 P$

Matlab/Octave scripting and plotting



# Fokker-Planck

More general: with an external potential:

$$m \frac{d^2 x}{dt^2} = - \frac{dU(x)}{dx} - \gamma \frac{dx}{dt} + \zeta(t)$$

- strong limit  $\rightarrow m=0$

$$\gamma \mathbf{v} = -\nabla V + \zeta(t)$$

$$\delta \mathbf{x} = \mathbf{v} \delta t = -\frac{1}{\gamma} \nabla V \delta t + \frac{1}{\gamma} \int_t^{t+\delta t} dt' \zeta(t')$$

- after a small displacement
- integrate over the random kicks during this small time interval

The expectation value of a small displacement:

$$\langle \delta \mathbf{x} \rangle = -\frac{1}{\gamma} \nabla V \delta t$$

- since  $\langle \zeta(t) \rangle = 0$

The correlation between displacements is also not difficult:

$$\begin{aligned} \langle \delta x_i \delta x_j \rangle &= -\frac{1}{\gamma^2} \langle \partial_i V \partial_j V \rangle \delta t^2 - \delta t \int_t^{t+\delta t} dt' \langle \partial_i V \zeta_j(t') + \partial_j V \zeta_i(t') \rangle + \\ &+ \int_t^{t+\delta t} dt' \int_t^{t+\delta t} dt'' \langle \zeta_i(t') \zeta_j(t'') \rangle \end{aligned}$$

- $i, j$  are different directions
- one integral drops in last term because  $\langle \zeta(t) \rangle = 0$
- 1<sup>st</sup> and 2<sup>nd</sup> terms: order  $(\delta t)^2$

# Fokker-Planck

$$\langle \delta x_i \delta x_j \rangle = -\frac{1}{\gamma^2} \langle \partial_i V \partial_j V \rangle \delta t^2 - \delta t \int_t^{t+\delta t} dt' \langle \partial_i V \zeta_j(t') + \partial_j V \zeta_i(t') \rangle + \int_t^{t+\delta t} dt' \int_t^{t+\delta t} dt'' \langle \zeta_i(t') \zeta_j(t'') \rangle$$

$$\langle \delta x_i \delta x_j \rangle = 2\delta_{ij} D \delta t + \mathcal{O}(\delta t^2)$$

- ignore terms of order  $(\delta t)^2$
- average:  $\langle \delta \mathbf{x} \rangle = -\frac{1}{\gamma} \nabla V \delta t$

So, which probability distribution has this average and variance?

Let's start from the conditional probability:

$$P(\mathbf{x}, t + \delta t | \mathbf{x}', t) = \langle \delta(\mathbf{x} - (\mathbf{x}' + \delta \mathbf{x})) \rangle$$

*probability to be at  $x$  at  $t+dt$ ,  
if we were at  $x'$  at time  $t$*

=

*ensemble average over all  
possible displacements  $\delta x$   
such that go from  $x'$  to  $x$*

We bravely Taylor expand the delta-function at  $\delta x=0$ :

$$P(\mathbf{x}, t + \delta t | \mathbf{x}', t) = \left( 1 + \langle \delta x_i \rangle \frac{\partial}{\partial x'_i} + \frac{1}{2} \langle \delta x_i \delta x_j \rangle \frac{\partial^2}{\partial x'_i \partial x'_j} + \dots \right) \delta(\mathbf{x} - \mathbf{x}')$$

- (what are the derivatives of the delta function???)



# Fokker-Planck

$$P(\mathbf{x}, t + \delta t | \mathbf{x}', t) = \left( 1 + \langle \delta x_i \rangle \frac{\partial}{\partial x'_i} + \frac{1}{2} \langle \delta x_i \delta x_j \rangle \frac{\partial^2}{\partial x'_i \partial x'_j} + \dots \right) \delta(\mathbf{x} - \mathbf{x}')$$

Use the Chapman-Kolmogorov equation:

*at  $t'$ , in-between  $t$  and  $t_0$  the particle had to be somewhere! so, integrate over all possible  $x'$*

$$P(\mathbf{x}, t | \mathbf{x}_0, t_0) = - \int_{-\infty}^{\infty} d^3 \mathbf{x}' \underbrace{P(\mathbf{x}, t | \mathbf{x}', t') P(\mathbf{x}', t' | \mathbf{x}_0, t_0)}$$

*fill in our Taylor expansion:*

$$P(\mathbf{x}, t + \delta t | \mathbf{x}_0, t_0) = P(\mathbf{x}, t | \mathbf{x}_0, t_0) - \frac{\partial}{\partial x'_i} \left( \langle \delta x_i \rangle P(\mathbf{x}, t | \mathbf{x}_0, t_0) \right) + \frac{1}{2} \langle \delta x_i \delta x_j \rangle \frac{\partial^2}{\partial x'_i \partial x'_j} P(\mathbf{x}, t | \mathbf{x}_0, t_0) + \dots$$

- use:  $\langle \delta \mathbf{x} \rangle = -\frac{1}{\gamma} \nabla V \delta t$  and  $\langle \delta x_i \delta x_j \rangle = 2\delta_{ij} D \delta t$

$$P(\mathbf{x}, t + \delta t | \mathbf{x}_0, t_0) = P(\mathbf{x}, t | \mathbf{x}_0, t_0) + \frac{1}{\gamma} \frac{\partial}{\partial x'_i} \left( \frac{\partial V}{\partial x_i} P(\mathbf{x}, t | \mathbf{x}_0, t_0) \right) \delta t + D \frac{\partial^2}{\partial x^2} P(\mathbf{x}, t | \mathbf{x}_0, t_0) \delta t + \dots$$

# Fokker-Planck

$$P(\mathbf{x}, t + \delta t | \mathbf{x}_0, t_0) = P(\mathbf{x}, t | \mathbf{x}_0, t_0) + \frac{1}{\gamma} \frac{\partial}{\partial x'_i} \left( \frac{\partial V}{\partial x_i} P(\mathbf{x}, t | \mathbf{x}_0, t_0) \right) \delta t + D \frac{\partial^2}{\partial x^2} P(\mathbf{x}, t | \mathbf{x}_0, t_0) \delta t + \dots$$

Left hand side is also:

- Taylor expansion in  $dt$

$$P(\mathbf{x}, t + \delta t | \mathbf{x}_0, t_0) = P(\mathbf{x}, t | \mathbf{x}_0, t_0) + \frac{1}{\partial t} P(\mathbf{x}, t | \mathbf{x}_0, t_0) \delta t + \dots$$

Combining with previous result gives:

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = \frac{1}{\gamma} \nabla \cdot (P(\mathbf{x}, t) \nabla V(\mathbf{x})) + D \nabla^2 P(\mathbf{x}, t)$$

*drift or transport* *diffusion*

*D here independent of position; otherwise D is inside of  $\nabla^2$*

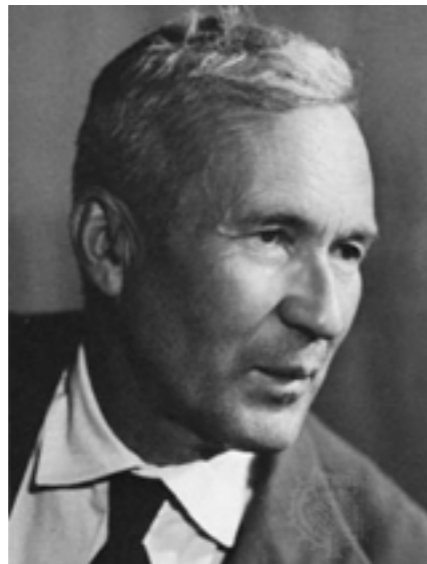
The Fokker-Planck equation  
or Smoluchowski equation  
or Kolomogorov's forward equation



Adriaan Daniël Fokker  
1887 – 1972  
Dutch physicist and musician.



Max Karl Ernst Ludwig Planck,  
1858 – 1947  
German theoretical physicist  
Nobel Prize in Physics (1918)



Andrey Nikolaevich Kolmogorov  
1903 – 1987  
Soviet mathematician



Marian Ritter von  
Smolan Smoluchowski  
1872 – 1917  
Polish physicist

# Fokker-Planck

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = \frac{1}{\gamma} \nabla \cdot (P(\mathbf{x}, t) \nabla V(\mathbf{x})) + D \nabla^2 P(\mathbf{x}, t)$$

FP as a continuity equation:

-  $J$  is probability current or flux

$$\frac{\partial P(\mathbf{x}, t)}{\partial t} = \nabla \mathbf{J} \quad \mathbf{J} = \frac{1}{\gamma} \underbrace{(P(\mathbf{x}, t) \nabla V(\mathbf{x}))}_{\text{drift}} + \underbrace{D \nabla P(\mathbf{x}, t)}_{\text{diffusion}}$$

Helps to see that probability is conserved:

$$\frac{\partial}{\partial t} \int d^3x P = \int d^3x \frac{\partial P}{\partial t} = \int d^3x \nabla \mathbf{J} = 0 \quad \begin{array}{l} - \int d^3x P = 1 \\ - \text{the particle should be somewhere} \end{array}$$

FP tells us how a system evolves:

- for  $V=0$  (diffusion equation), the system spreads out forever
- for generic  $V$ , stationary solutions with  $\nabla \mathbf{J}=0$ :

$$- D = \frac{k_B T}{\gamma}$$

$$P(x) \sim e^{-V(x)/\gamma D} \xrightarrow{\text{Einstein relation}} P(x) \sim e^{-V(x)/k_B T}$$

- Boltzmann distribution!

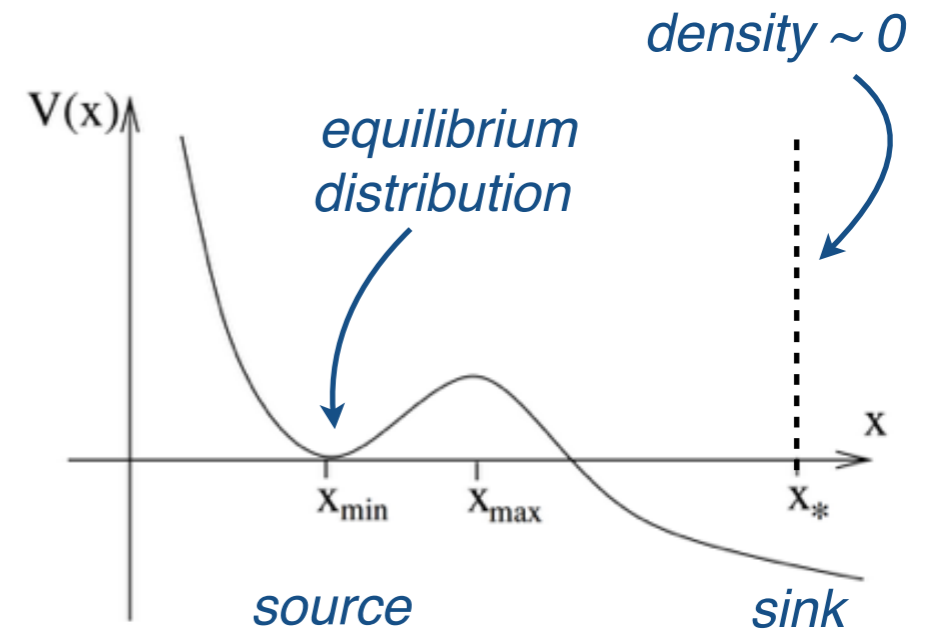
# Escape over a barrier

Thermal escape from 1D potential

$$V(x) \approx \frac{1}{2} \omega_{\min}^2 (x - x_{\min})^2$$

With initial distribution in the left well:

$$P(x, t = 0) = \sqrt{\frac{\omega_{\min}^2}{2\pi k_B T}} e^{-\omega_{\min}^2 (x - x_{\min})^2 / 2k_B T}$$



- initial distribution is not the equilibrium distribution
- there is no equilibrium
- assume small flux

Steady state flux:

$$J = \frac{k_B T}{\gamma} e^{-V(x)/k_B T} \frac{\partial}{\partial x} \left( e^{V(x)/k_B T} P \right)$$

$$\mathbf{J} = \frac{1}{\gamma} (P(\mathbf{x}, t) \nabla V(\mathbf{x})) + D \nabla P(\mathbf{x}, t)$$

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

$$e^{-V/k_B T} \frac{\partial}{\partial x} (P \cdot e^{V/k_B T}) = \frac{1}{k_B T} \frac{\partial V}{\partial x} P + \frac{\partial P}{\partial x}$$

$$J e^{V(x)/k_B T} = \frac{k_B T}{\gamma} \frac{\partial}{\partial x} \left( e^{V(x)/k_B T} P \right)$$

now integrate both sides from  $x_{\min}$  and  $x_*$

# Escape over a barrier

$$\int_{x_{\min}}^{x_*} J e^{V(x)/k_B T} = \int_{x_{\min}}^{x_*} \frac{k_B T}{\gamma} \frac{\partial}{\partial x} (e^{V(x)/k_B T} P) \quad \text{first integrate the right side}$$

$$J \int_{x_{\min}}^{x_*} e^{V(x)/k_B T} = \frac{k_B T}{\gamma} \left[ \underbrace{e^{V(x_{\min})/k_B T} P(x_{\min})}_{\text{at } x_{\min} \text{ } P \text{ is at equilibrium}} - \underbrace{e^{V(x_*)/k_B T} P(x_*)}_{\text{at } x_* \text{ } P \text{ is practically zero}} \right] = \frac{k_B T}{\gamma} \sqrt{\frac{\omega_{\min}^2}{2\pi k_B T}}$$

Next, the integral at the left, which is

dominated by the potential at  $V(x_{\max})$ :  $V(x) \approx V_{\max} - \frac{1}{2} \omega_{\max}^2 (x - x_{\max})^2$

$$J \int_{x_{\min}}^{x_*} e^{V(x)/k_B T} = J e^{V_{\max}/k_B T} \sqrt{\frac{2\pi k_B T}{\omega_{\max}^2}}$$

Combining the two pieces gives the rate over the barrier as:

$$J = \frac{\omega_{\max}}{\gamma} \frac{\omega_{\min}}{2\pi} e^{-V_{\max}/k_B T}$$

-----

*kappa*
*TST rate*

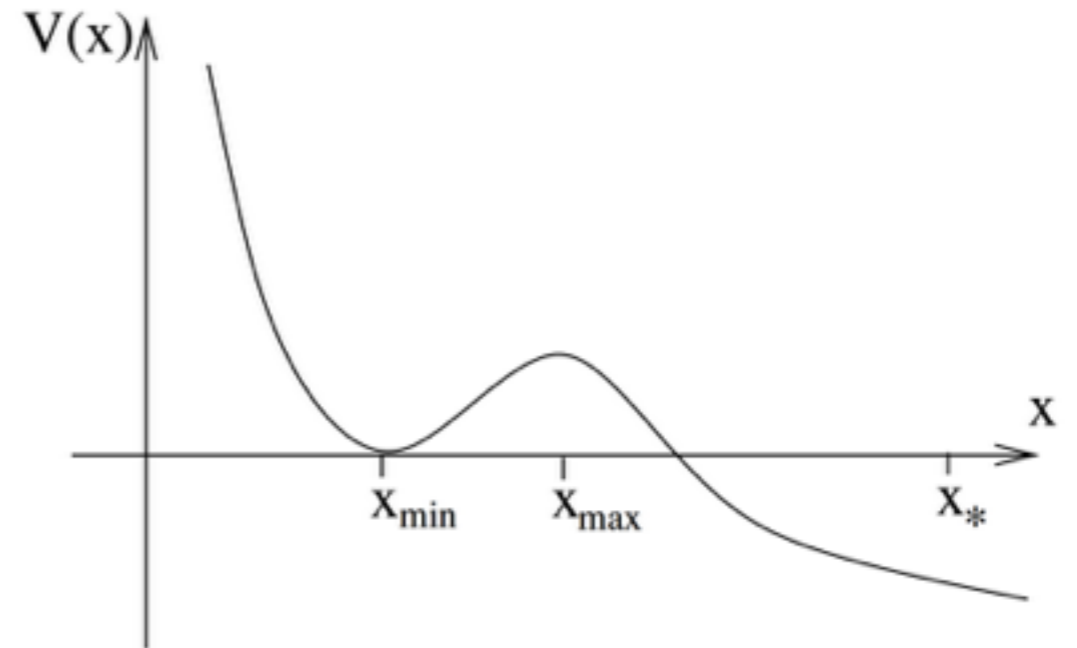
- *Kramers results for the reaction rate for strong friction! (no inertial motion;  $m=0$ )*
- *transmission coefficient:  $\kappa = \omega_{\max}/\gamma$*

# Escape over a barrier

Kramers rate equation:

Strong friction (over-damped) limit

$$k = \frac{\omega_{\max}}{\gamma} \frac{\omega_{\min}}{2\pi} e^{-V_{\max}/k_B T}$$



Including inertial motion ( $m > 0$ ):

$$k = \frac{1}{\omega_{\max}} \left( -\frac{\gamma}{2} + \sqrt{\frac{\gamma^2}{4} + \omega_{\max}^2} \right) \frac{\omega_{\min}}{2\pi} e^{-V_{\max}/k_B T}$$

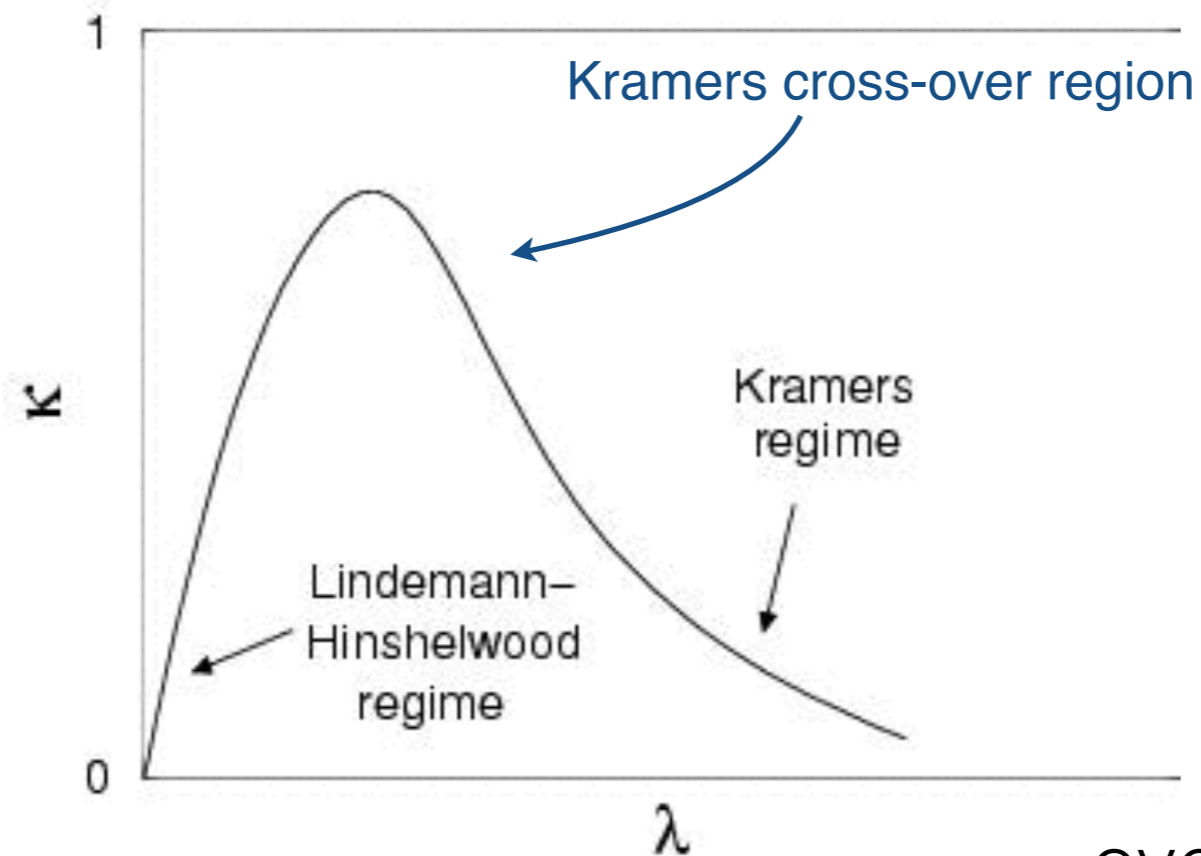
|  $\kappa$  (correction to transition state theory rate) |
TST rate

Weak friction limit:

$$k = p\gamma \frac{I(E_{\max})}{k_B T} \frac{\omega_{\min}}{2\pi} e^{-V_{\max}/k_B T}$$

# Escape over a barrier

Transmission coefficient as a function of the reactant-solvent coupling



weak coupling:

$$k = p\gamma \frac{I(E_{\max})}{k_B T} \frac{\omega_{\min}}{2\pi} e^{-V_{\max}/k_B T}$$

$$\kappa \sim \gamma$$

if  $\gamma \rightarrow 0$  then  $\kappa \rightarrow 0$

over-damped coupling:

$$k = \frac{\omega_{\max}}{\gamma} \frac{\omega_{\min}}{2\pi} e^{-V_{\max}/k_B T}$$

$$\kappa \sim \gamma^{-1}$$

if  $\gamma \rightarrow \infty$  then  $\kappa \rightarrow 0$



# Langevin dynamics in 2D barrier crossing

```
% Octave script for velocity Verlet algorithm + Langevin for
% dynamics in the 2D Muller-Brown potential
% Langevin dynamics using PRE 75, 056707 (2007) Bussi & Parrinello
clear; clf;
```

```
Nsteps=2000;      % number of steps
h=0.01;          % timestep
pos=[0.5 0.0];   % initial position
vel=[10.0 0.0];  % initial velocity
force=[0.0 0.0]; % initial force
friction=2.0;    % langevin friction
temp=30.0;
mass=1.0;
c1 = exp(-0.5*friction*h)
c2 = sqrt( (1-c1*c1) * temp * mass )
```

```
% initiate force
```

```
[Vpot(1), force] = Muller_potential(pos);
Ekin(1)=0.5*norm(vel)^2;
Etot(1)=Ekin(1) + Vpot(1);
t(1)=1;
```

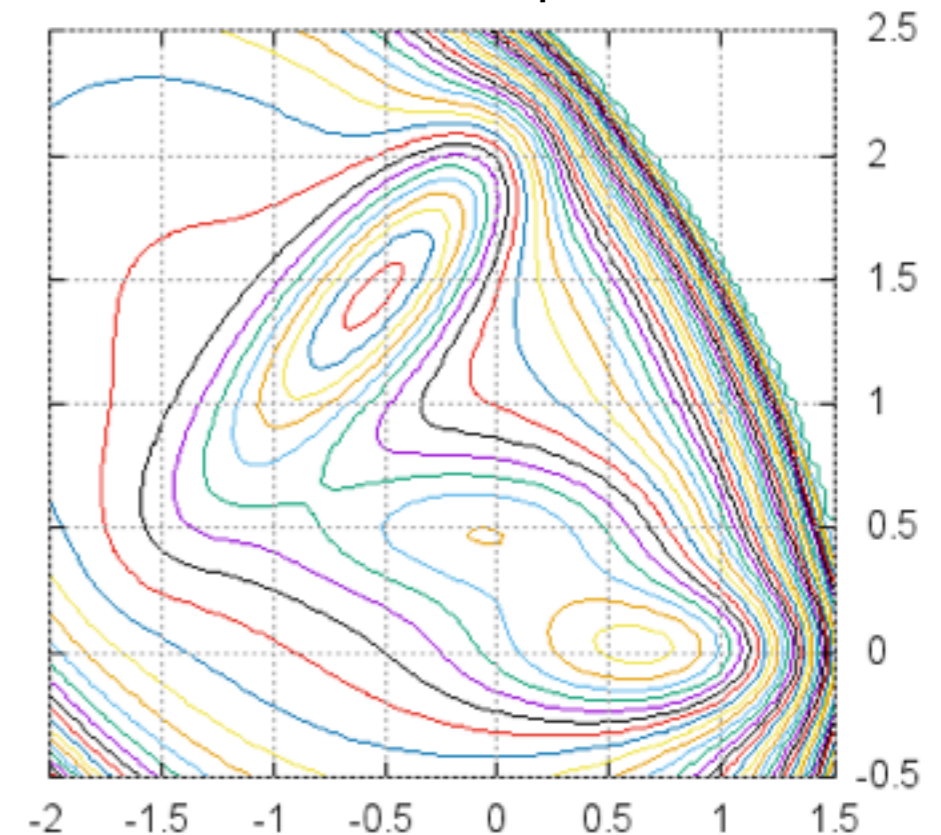
```
% main loop
```

```
for i=1:Nsteps
    t(i)=i;
    x(i)=pos(1);
    y(i)=pos(2);
```

```
% plot trajectory and energy
```

```
figure(1);
plot(x,y,'b-', 'linewidth',2, pos(1),pos(2), 'ko', 0,0, 'ro')
title(num2str(i*h))
axis equal;
axis([-2 1.5 -0.5 2.5]);
grid on;
figure(2);
plot(Etot,'g-'), hold on;
plot(Vpot,'r-'), hold on;
plot(Ekin,'b-');
title("Total energy");
```

Muller-Brown potential



```
% velocity verlet half step for velocities and positions
vel = c1*vel + c2*randn;
vel += 0.5*force*h;
pos += vel*h;
```

```
% force calculation
```

```
[Vpot(i), force] = Muller_potential(pos);
```

```
% velocity verlet second half step for velocities
```

```
vel += 0.5*force*h;
vel = c1*vel + c2*randn;
```

```
% compute energies
```

```
Ekin(i)=0.5*norm(vel)^2;
Etot(i)=Ekin(i) + Vpot(i);
```

```
end
```

# Rare event simulation

Macroscopic phenomenological theory

Chemical reaction:  $A \leftrightarrow B$

$$\frac{dc_A(t)}{dt} = -k_{A \rightarrow B}c_A(t) + k_{B \rightarrow A}c_B(t)$$

$$\frac{dc_B(t)}{dt} = +k_{A \rightarrow B}c_A(t) - k_{B \rightarrow A}c_B(t)$$

Total number of molecules:

$$\frac{d[c_A(t) + c_B(t)]}{dt} = 0$$

Equilibrium:

$$\frac{dc_A(t)}{dt} = \frac{dc_B(t)}{dt} = 0 \quad \frac{\langle c_A \rangle}{\langle c_B \rangle} = \frac{k_{B \rightarrow A}}{k_{A \rightarrow B}}$$

# Rare event simulation

## Macroscopic phenomenological theory

Make a small perturbation:

$$c_A(t) = \langle c_A \rangle + \Delta c_A(t) \quad c_B(t) = \langle c_B \rangle + \Delta c_B(t)$$

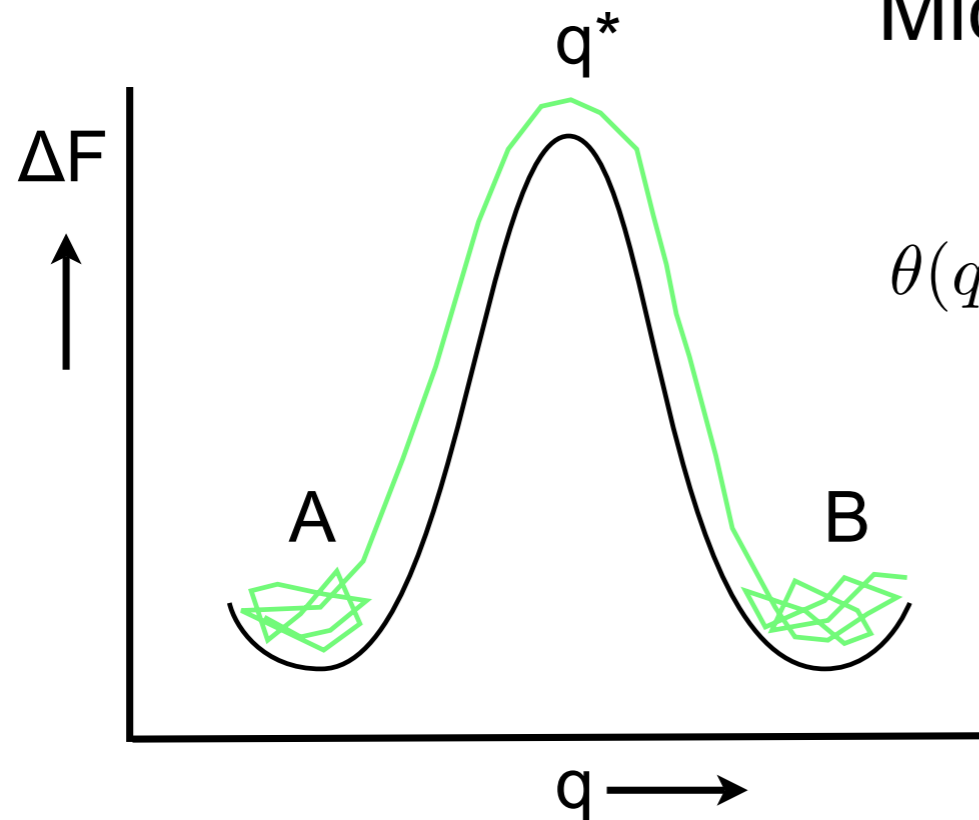
$$\frac{d\Delta c_A(t)}{dt} = -k_{A \rightarrow B} \Delta c_A(t) - k_{B \rightarrow A} \Delta c_B(t)$$

$$\begin{aligned} \Delta c_A(t) &= \Delta c_A(0) \exp[-(k_{A \rightarrow B} + k_{B \rightarrow A})t] \\ &= \Delta c_A(0) \exp[-t/\tau] \end{aligned}$$

$$\begin{aligned} \tau &= (k_{A \rightarrow B} + k_{B \rightarrow A})^{-1} \\ &= k_{A \rightarrow B}^{-1} (1 + \langle c_A \rangle / \langle c_B \rangle)^{-1} = \frac{\langle c_B \rangle}{k_{A \rightarrow B}} \end{aligned}$$

# Rare event simulation

Microscopic linear response theory



$$\theta(q - q^*) = \begin{cases} 0 & \text{if } q - q^* < 0 \quad (\text{Reactant A}) \\ 1 & \text{if } q - q^* > 0 \quad (\text{Product B}) \end{cases}$$

## Perturbation

add bias to increase concentration  $c_A$

$$H = H_0 - \epsilon g_A(q - q^*)$$

$$g_A(q - q^*) = 1 - \theta(q - q^*) = \theta(q^* - q)$$

$$\Delta c_A = \langle c_A \rangle_\epsilon - \langle c_A \rangle_0$$

$$\Delta c_A = \langle g_A \rangle_\epsilon - \langle g_A \rangle_0$$

$\langle g_A \rangle \rightarrow$  probability to be in state A

## Linear response theory: static

$$\langle \Delta A \rangle = \langle A \rangle - \langle A \rangle_0 \quad H = H_0 - \epsilon B$$

$$\langle A \rangle_0 = \frac{\int d\Gamma A \exp[-\beta(H_0)]}{\int d\Gamma \exp[-\beta(H_0)]} \quad \langle A \rangle = \frac{\int d\Gamma A \exp[-\beta(H_0 - \epsilon B)]}{\int d\Gamma \exp[-\beta(H_0 - \epsilon B)]}$$

$$\begin{aligned} \left\langle \frac{\partial \Delta A}{\partial \epsilon} \right\rangle &= \frac{\int d\Gamma \beta AB \exp[-\beta(H_0 - \epsilon B)] \int d\Gamma \exp[-\beta(H_0 - \epsilon B)]}{\left\{ \int d\Gamma \exp[-\beta(H_0 - \epsilon B)] \right\}^2} \\ &- \frac{\int d\Gamma A \exp[-\beta(H_0 - \epsilon B)] \int d\Gamma \beta B \exp[-\beta(H_0 - \epsilon B)]}{\left\{ \int d\Gamma \exp[-\beta(H_0 - \epsilon B)] \right\}^2} \\ &= \beta \{ \langle AB \rangle_0 - \langle A \rangle_0 \langle B \rangle_0 \} \end{aligned}$$

Very small perturbation: linear response theory

$$\Delta c_A = \langle g_A \rangle_\epsilon - \langle g_A \rangle_0 \quad H = H_0 - \epsilon g_A(q - q^*)$$

How does the response ( $\Delta c$ ) depend on the perturbation ( $\Delta \epsilon$ )?

$$\begin{aligned} \frac{d\Delta c_A}{d\epsilon} &= \beta \left( \langle (g_A)^2 \rangle_0 - \langle g_A \rangle_0^2 \right) \\ &= \beta \left( \langle g_A \rangle_0 \left( 1 - \langle g_A \rangle_0 \right) \right) \\ &= \beta \left( \langle c_A \rangle_0 \left( 1 - \langle c_A \rangle_0 \right) \right) = \beta \langle c_A \rangle_0 \langle c_B \rangle_0 \end{aligned}$$

Outside the barrier

$$g_A = 0 \text{ or } 1$$

$$g_A(x)g_A(x) = g_A(x)$$

Switch of the perturbation: dynamic linear response

$$\begin{aligned} \Delta c_A(t) &= \Delta c_A(0) \frac{\Delta g_A(0) \Delta g_A(t)}{\langle c_A \rangle \langle c_B \rangle} \\ &= \Delta c_A(0) \exp[-t/\tau] \end{aligned}$$

holds for sufficiently long times

$$\exp[-t/\tau] = \frac{\langle \Delta g_A(0) \Delta g_A(t) \rangle}{\langle c_A \rangle \langle c_B \rangle}$$

Derivative

$$-\frac{1}{\tau} \exp[-t/\tau] = \frac{\langle g_A(0) \dot{g}_A(t) \rangle}{\langle c_A \rangle \langle c_B \rangle} = \frac{\langle \dot{g}_A(0) g_A(t) \rangle}{\langle c_A \rangle \langle c_B \rangle}$$

$\Delta$  has disappeared  
because of derivative

For sufficiently short  $t$

$$k_{A \rightarrow B}(t) = \frac{\langle \dot{g}_A(0) g_A(t) \rangle}{\langle c_A \rangle}$$

$$\dot{g}_A(q - q^*) = \dot{q} \frac{\partial g_A(q - q^*)}{\partial q} = -\dot{q} \frac{\partial g_B(q - q^*)}{\partial q}$$

$$k_{a \rightarrow B}(t) = \frac{\left\langle \dot{q}(0) \frac{\partial g_B(q(0) - q^*)}{\partial q} g_B(t) \right\rangle}{\langle c_A \rangle}$$

Stationary

$$\frac{d}{dt} \langle A(t)B(t+t') \rangle = 0$$

$$\langle A(t)\dot{B}(t+t') \rangle + \langle \dot{A}(t)B(t+t') \rangle = 0$$

$$\langle A(t)\dot{B}(t+t') \rangle = -\langle \dot{A}(t)B(t+t') \rangle$$



# Eyring's transition state theory

$$\begin{aligned}k_{a \rightarrow B}(t) &= \frac{\left\langle \dot{q}(0) \frac{\partial g_B(q(0) - q^*)}{\partial q} g_B(t) \right\rangle}{\langle c_A \rangle} \\ &= \frac{\langle \dot{q}(0) \delta(q(0) - q^*) \theta(q(t) - q^*) \rangle}{\langle \theta(q^* - q) \rangle}\end{aligned}$$

Correlation between velocity of states that are at the top of the barrier at  $t=0$  and in the product state B some time  $t$  later.

Let us consider the limit  $t \rightarrow 0^+$  :

$$\begin{aligned}\lim_{t \rightarrow 0^+} &= \theta(q(t) - q^*) = \theta(\dot{q}(t)) \\ k_{a \rightarrow B}^{\text{TST}}(t) &= \frac{\langle \dot{q}(0) \delta(q(0) - q^*) \theta(\dot{q}) \rangle}{\langle \theta(q^* - q) \rangle}\end{aligned}$$

# Bennett-Chandler approach

(or Reactive flux method)

$$k_{a \rightarrow B}(t) = \frac{\langle \dot{q}(0) \delta(q(0) - q^*) \theta(q(t) - q^*) \rangle}{\langle \theta(q^* - q) \rangle}$$

$$k_{a \rightarrow B}(t) = \frac{\langle \dot{q}(0) \delta(q(0) - q^*) \theta(q(t) - q^*) \rangle}{\langle \delta(q(0) - q^*) \rangle} \times \frac{\delta(q(0) - q^*)}{\theta(q^* - q)}$$

Conditional average:  $\dot{q}(0) \theta(q(t) - q^*)$   
given that we start on top of barrier

Probability to find  $q$   
on barrier top

## Computational scheme:

- Determine the probability with free energy calculation
- Compute conditional average from “shooting” trajectories from barrier top

# Free energy methods

It is very (very) difficult to compute (or measure) absolute thermodynamic properties, such as free energy and entropy, that depend on the size of the phase space.

But we can compute relative free energies, in particular free energy differences between thermodynamic states.

Reaction equilibrium constants  $A \longleftrightarrow B$

$$K = \frac{[B]}{[A]} = \frac{p_B}{p_A} = \exp[-\beta(G_B - G_A)]$$

Examples:

- Chemical reactions, catalysis, isomerization, etc...
- Protein folding, ligand binding affinity, protein-protein association
- Phase diagrams, coexistence lines, critical points, transitions

# Free energy perturbation

$$\Delta\beta F = -\ln(Q_B/Q_A) = -\ln\left(\frac{\int ds^N \exp(-\beta U_B)}{\int ds^N \exp(-\beta U_A)}\right)$$

$$\begin{aligned}\Delta F &= -k_B T \ln\left(\frac{\int ds^N \exp(-\beta U_A) \exp(-\beta \Delta U)}{\int ds^N \exp(-\beta U_A)}\right) \\ &= -k_B T \ln \langle \exp(-\beta \Delta U) \rangle_A\end{aligned}$$

$$\Delta F = -k_B T \ln \langle \exp(-\beta \Delta U) \rangle_A = -k_B T \ln \langle \exp(\beta \Delta U) \rangle_B$$

Sampling problems may lead to hysteresis between the two samples

# Umbrella Sampling

Bias the sampling along an order parameter  $q$

Add and subtract bias potential  $w(q)$ :

$$P(q) = \frac{\int d\mathbf{r}^N \delta(q'(\mathbf{r}^N) - q) \exp[-\beta(U(\mathbf{r}^N) + w(q') - w(q))]}{\int d\mathbf{r}^N \exp[-\beta(U(\mathbf{r}^N) + w(q') - w(q))]}$$

$$P(q) = \frac{\int d\mathbf{r}^N \delta(q'(\mathbf{r}^N) - q) \exp[-\beta(U(\mathbf{r}^N) + w(q'))] \exp(\beta w(q))}{\int d\mathbf{r}^N \exp[-\beta(U(\mathbf{r}^N) + w(q'))] \exp(\beta w(q))}$$

$$P(q) = \frac{\langle \delta(q'(\mathbf{r}^N) - q) \exp(\beta w(q')) \rangle_{\text{biased}}}{\langle \exp(\beta w(q')) \rangle_{\text{biased}}}$$

$$P(q) = \frac{\exp(\beta w(q))}{\langle \exp(\beta w(q')) \rangle_{\text{biased}}} P_{\text{biased}}(q)$$

- Let  $w(q)$  be a good guess of minus the free energy  $F(q)$ , or
- Choose  $w(q)$  to confine sampling to a specific window along  $q$ .
- Or do both.

$$F(q) = k_B T \ln P(q) = -k_B T \ln P_{\text{biased}}(q) - w(q) + \text{const}$$

# Constrained MD

The derivative of the free energy  $F(\lambda)$  with respect to  $\lambda$  can be written as an ensemble average.

$$\begin{aligned}\left(\frac{\partial F(\lambda)}{\partial \lambda}\right)_{\text{NVT}} &= \frac{\int d\mathbf{r}^N (\partial U(\lambda)/\partial \lambda) \exp[-\beta U(\lambda)]}{\int d\mathbf{r}^N \exp[-\beta U(\lambda)]} \\ &= \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda}\end{aligned}$$

The free energy difference between states A and B can then be obtained by thermodynamic integration

$$F(\lambda_B) - F(\lambda_A) = \int_{\lambda_A}^{\lambda_B} d\lambda \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda}$$

In the case “hard” constraints are used, additional corrections are needed to unbiased for sampling in a constraint ensemble (instead of the actual NVT ensemble)

# Steered MD

Mechanical work to bring the system from state A to state B

$$W_{A \rightarrow B} \geq \Delta F_{A \rightarrow B}$$

Jarzynski's equality

$$\langle \exp[-\beta W_{A \rightarrow B}] \rangle_A = \exp[-\beta \Delta F_{A \rightarrow B}]$$

Surprisingly, we can obtain the equilibrium free energy difference from a non-equilibrium simulation, in which we force the system in a finite time to move from A to B.

Although, this may sound as a *free lunch* method, note that it requires sampling an exponential distribution of the work. For infinitely slow switching from A to B, the system is always in equilibrium so that a single simulation gives  $\Delta F$ . But the faster the switching the more rare are the important low-work contributions to the average, so that many steered simulations are required for convergence.

# Metadynamics

*Escaping free-energy minima,*  
Laio and Parrinello, PNAS (2002)

$$V(t, s) = \sum_{t' < t} H_{t'} \prod_{\alpha} \exp \left[ \frac{-(s_{\alpha} - s_{\alpha}^{t'})^2}{2\delta_{\alpha}^2 W^2} \right]$$

- The metadynamics biasing potential “grows” with time, by adding relatively small repulsive Gaussian potentials.
- The potentials placed at visited points in the space of order parameters (collective variables) enhance sampling of unexplored regions.
- The Gaussian “hills” accumulate in the free energy minima, until the counter-balance the basins and allow the system to escape to product states, where the process repeats
- The biasing potential is an estimator of the free energy.

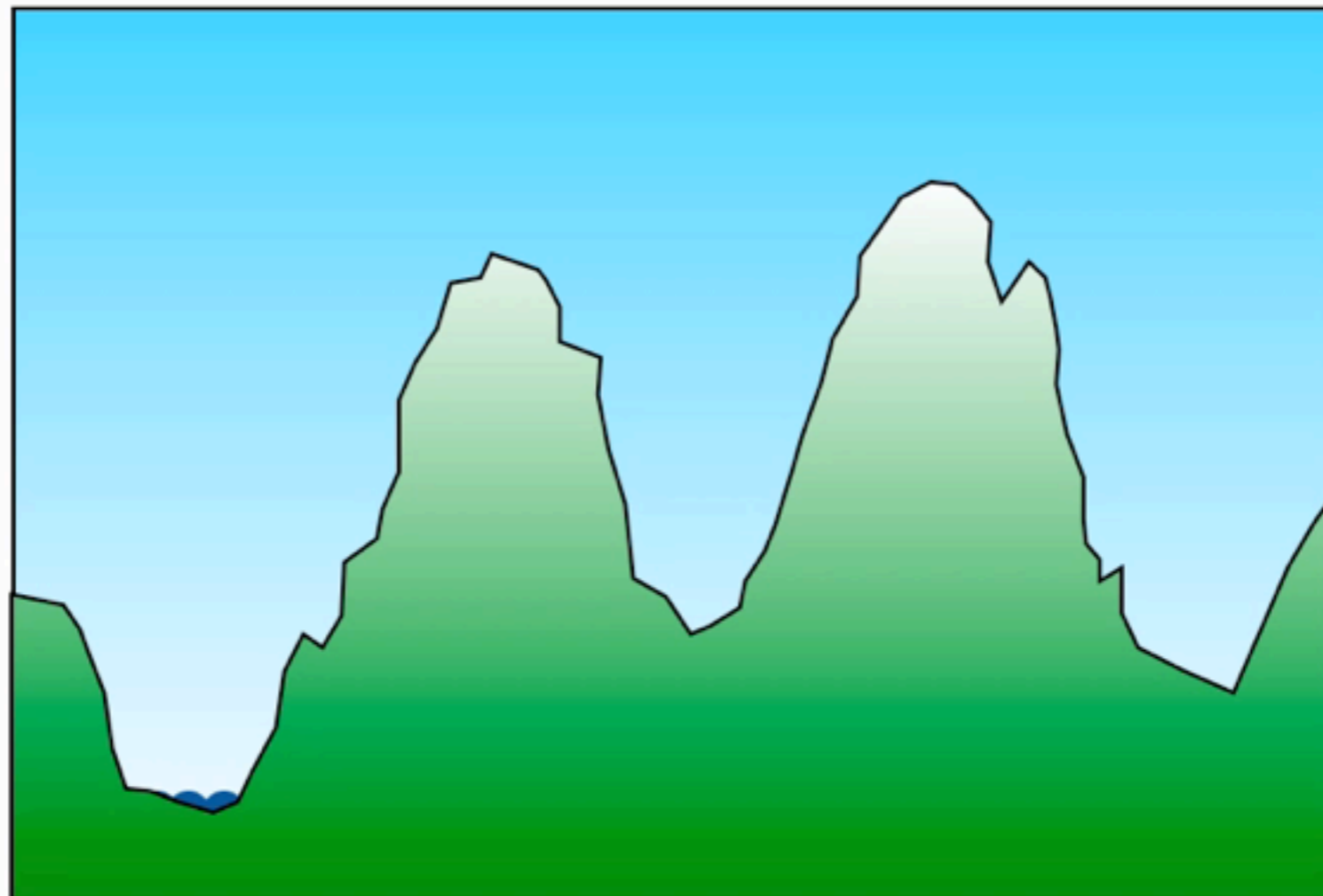
The error depends on the height, width, and time interval of the added Gaussians, and on the diffusion, temperature and order parameter space of the system.

$$\epsilon = C_d \sqrt{\frac{HWS}{D\Delta\tau\beta}}$$



# A Dutch perspective on escaping free energy minima

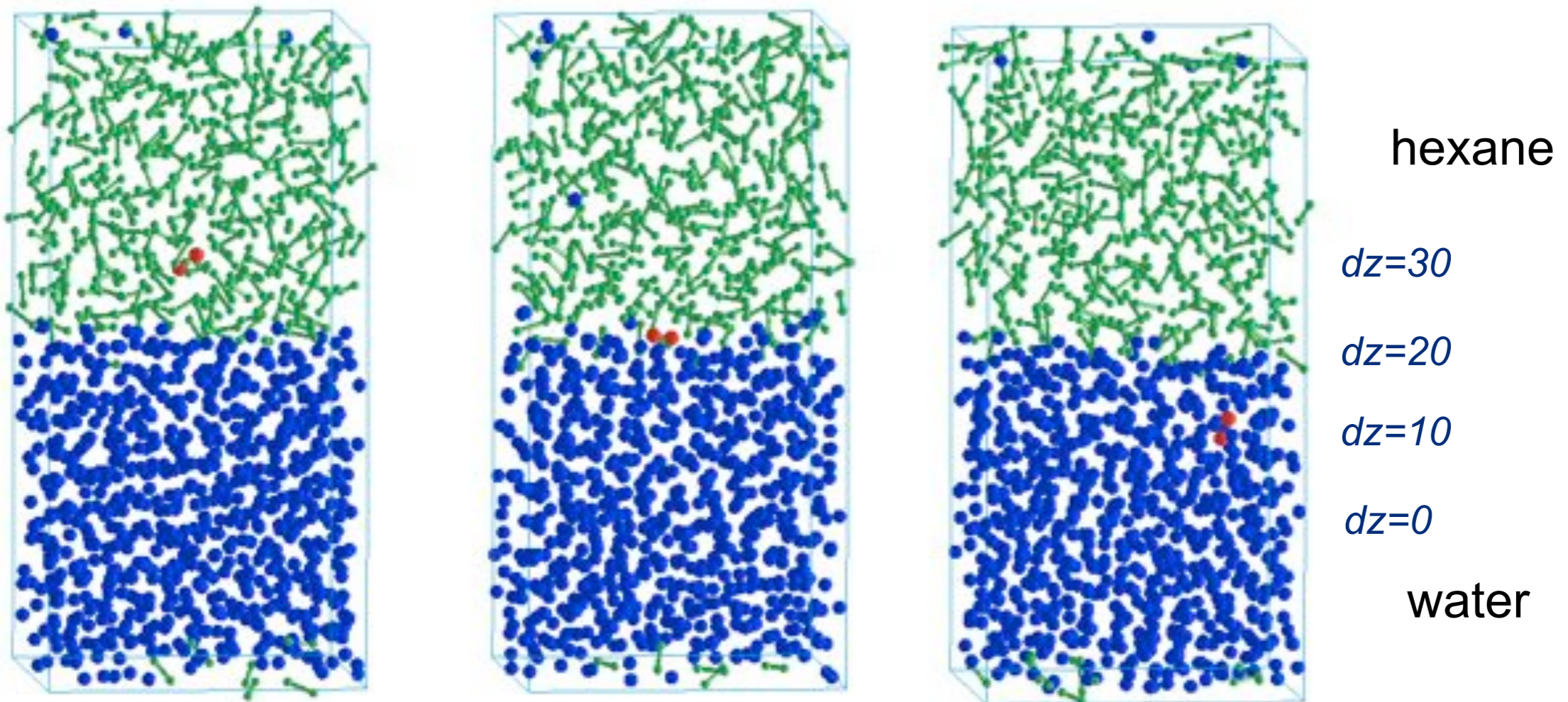
Metadynamics, Laio and Parrinello, PNAS (2002)



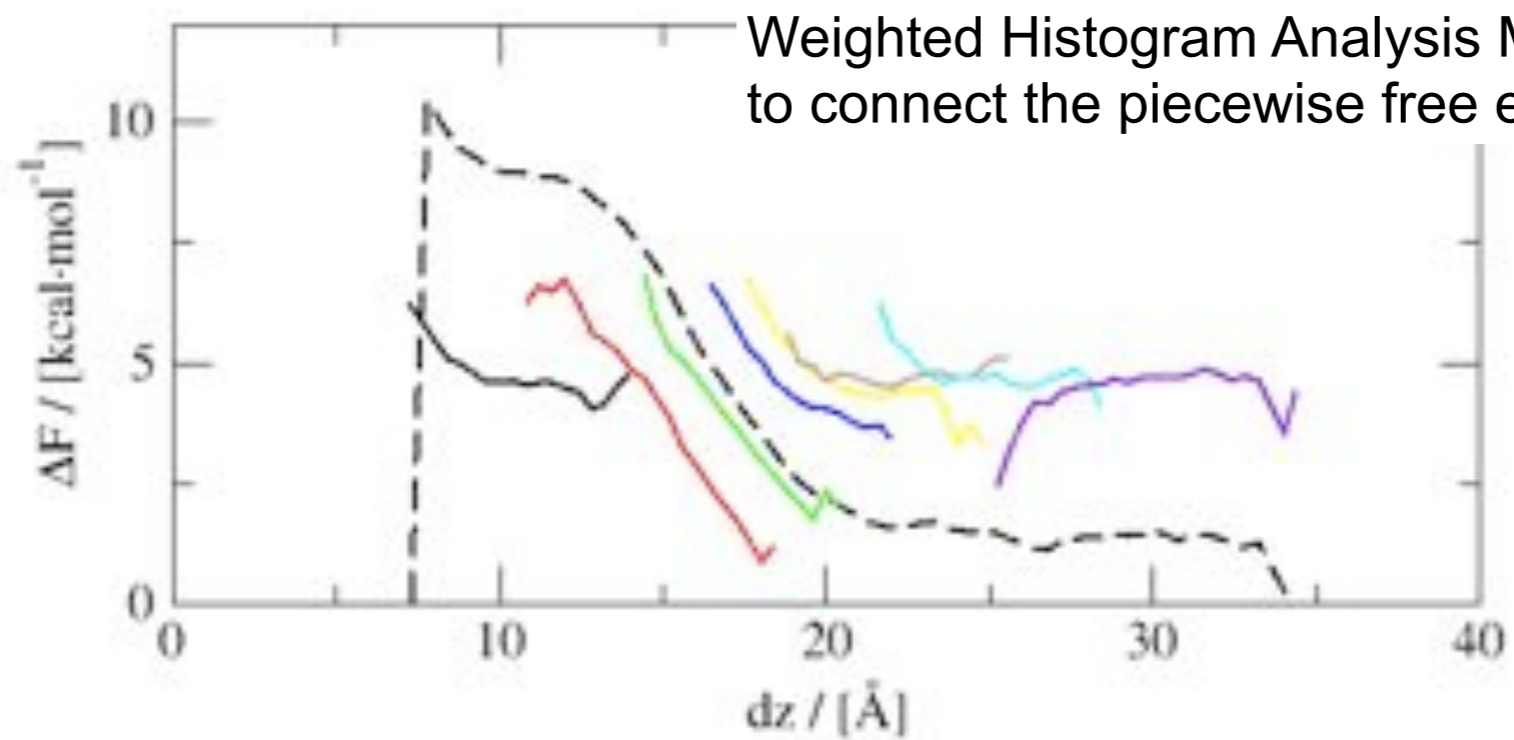
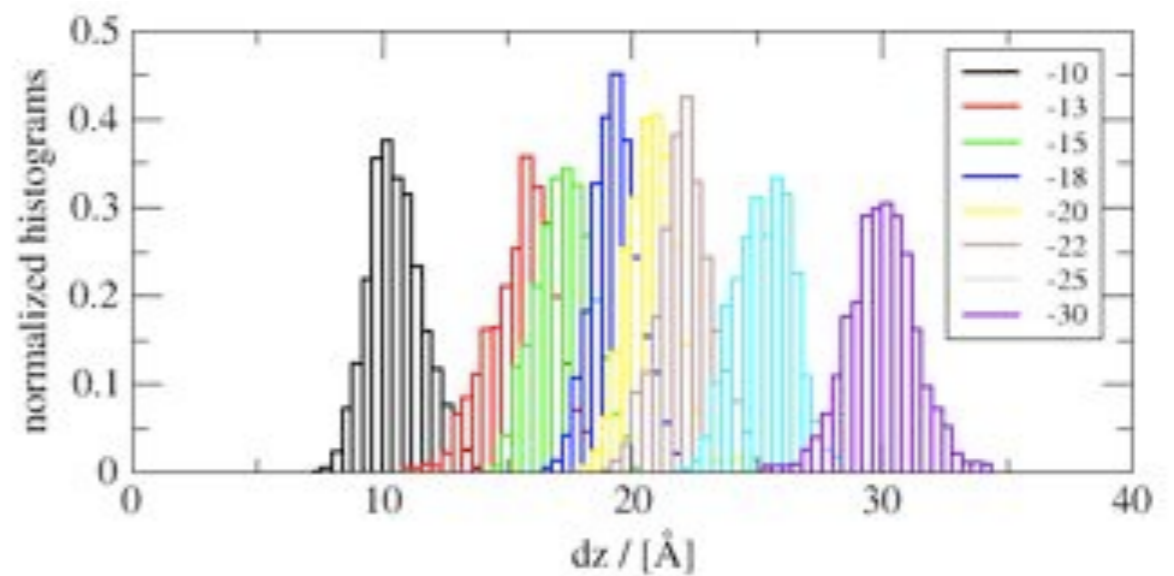
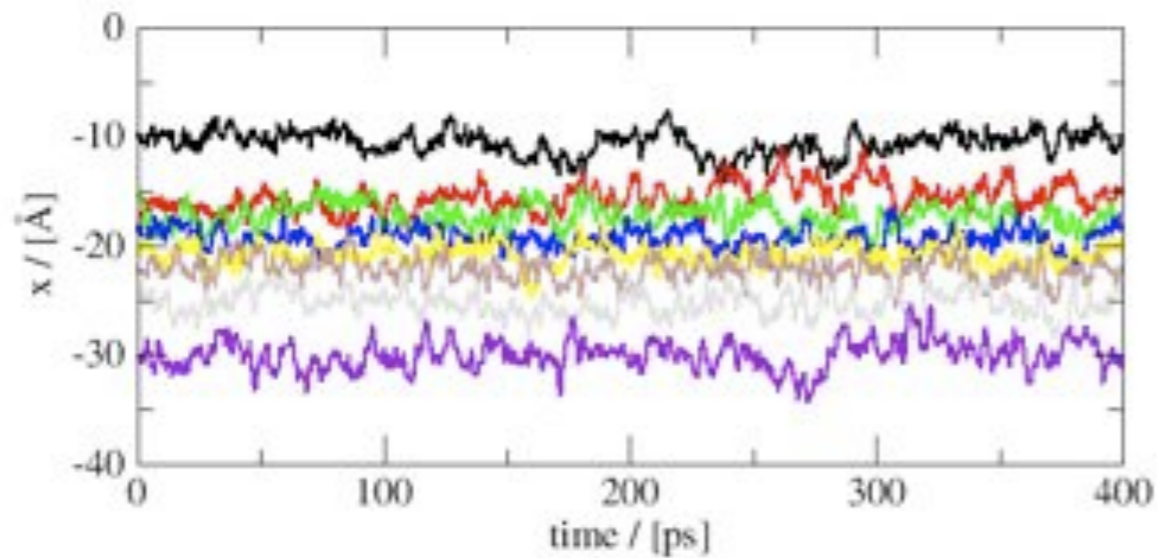
# Example

## Relative solvation free energy of hexane molecule

The solvation free energy free difference of a solute in different solvents is here used a target property to parameterized a coarse-grain forcefield.



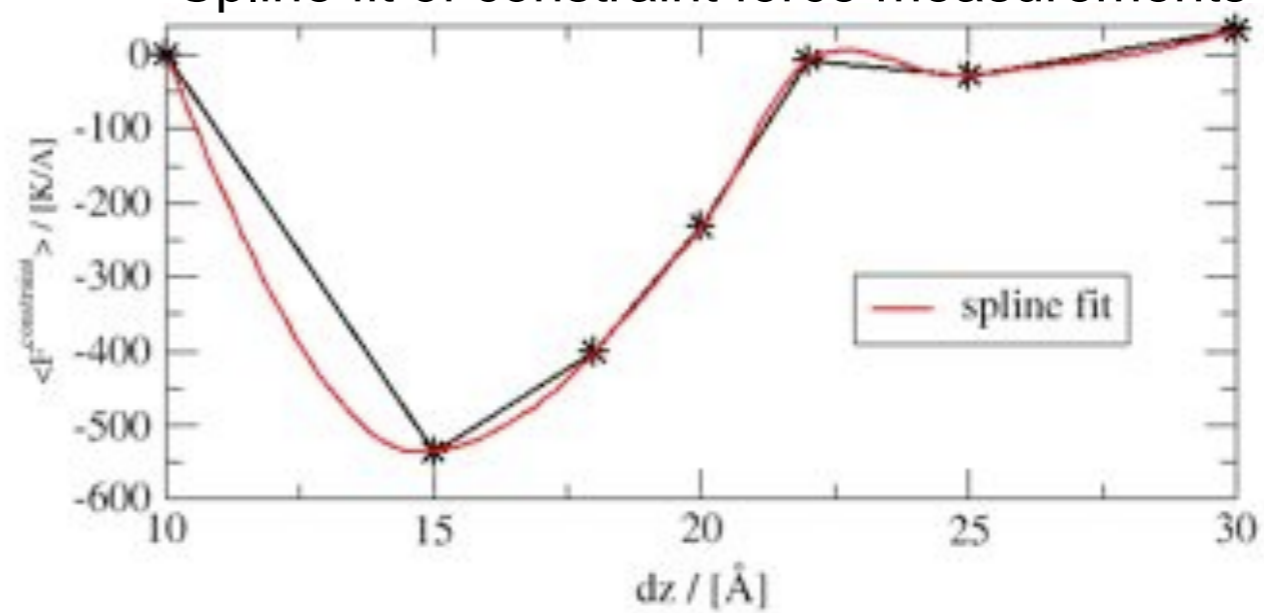
# Umbrella Sampling



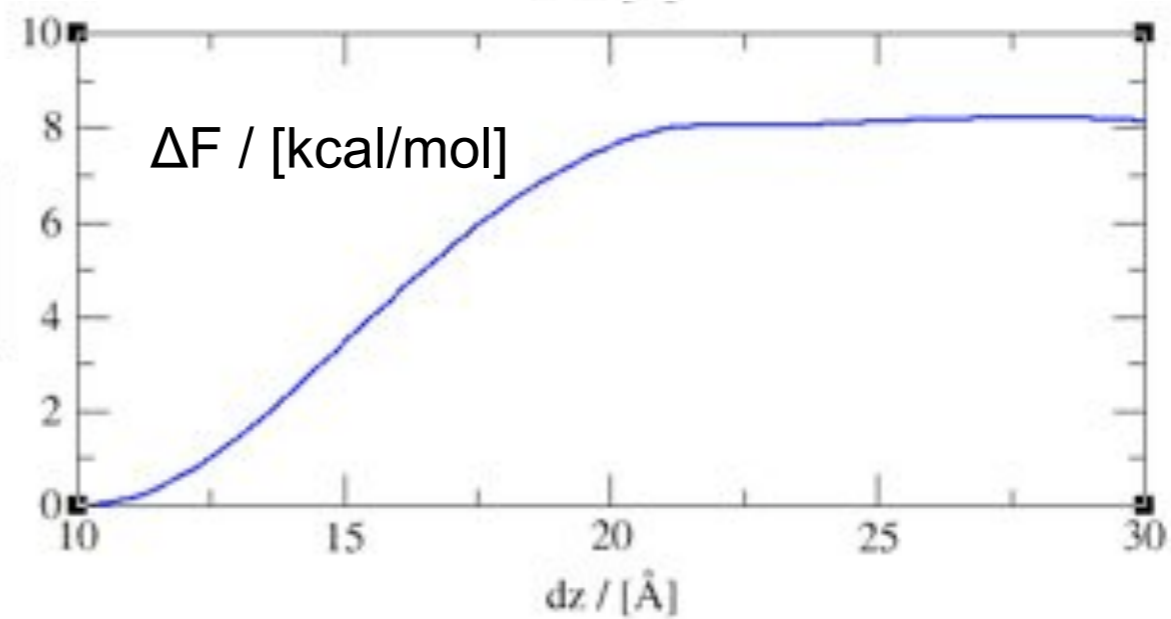
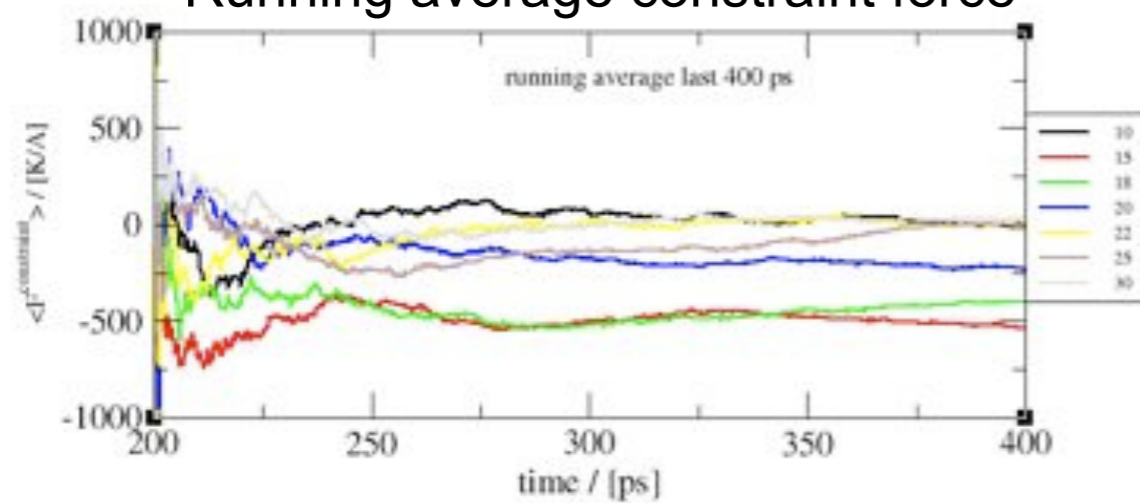
Weighted Histogram Analysis Method (WHAM)  
to connect the piecewise free energy curves

# Constrained MD

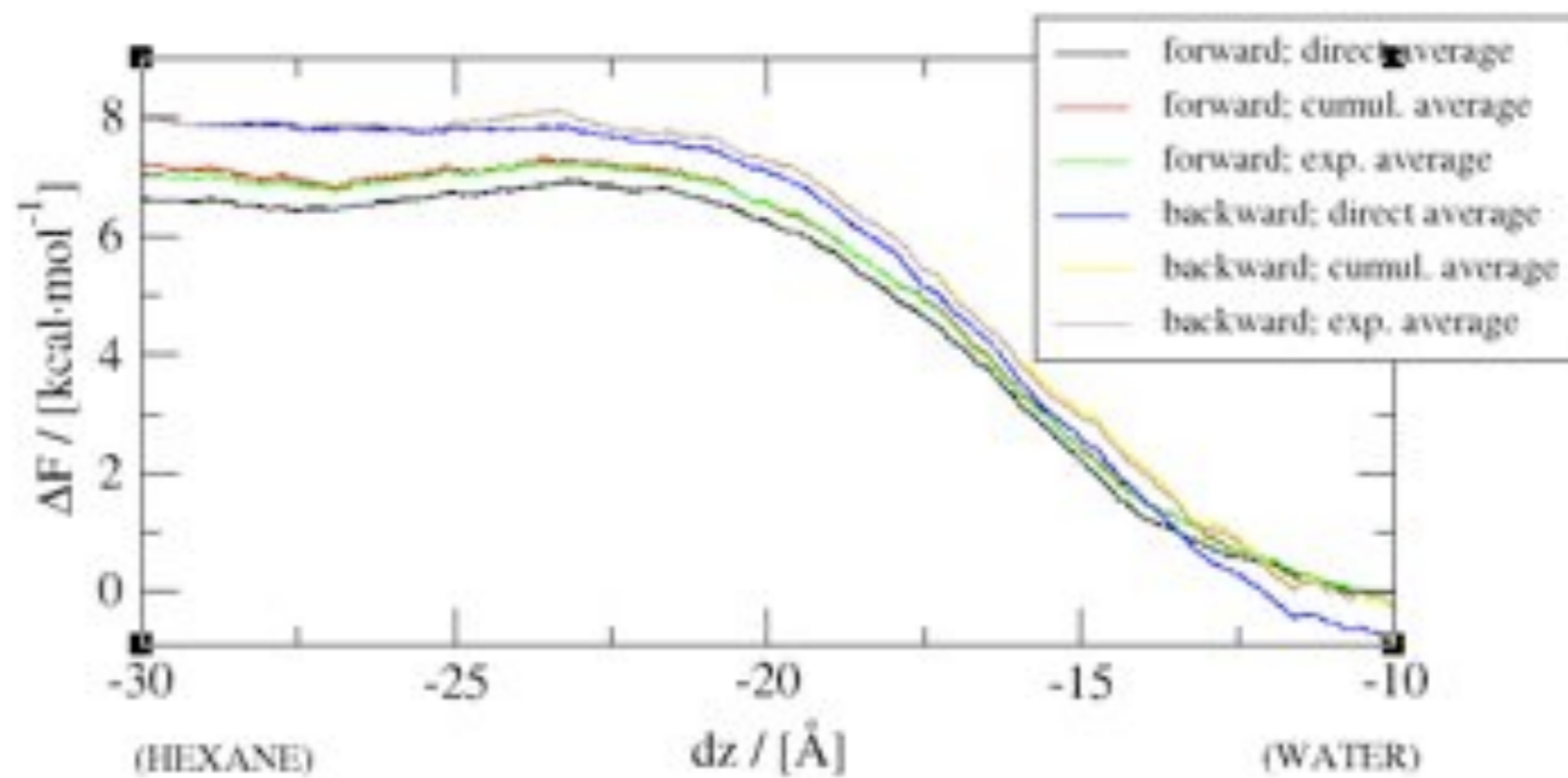
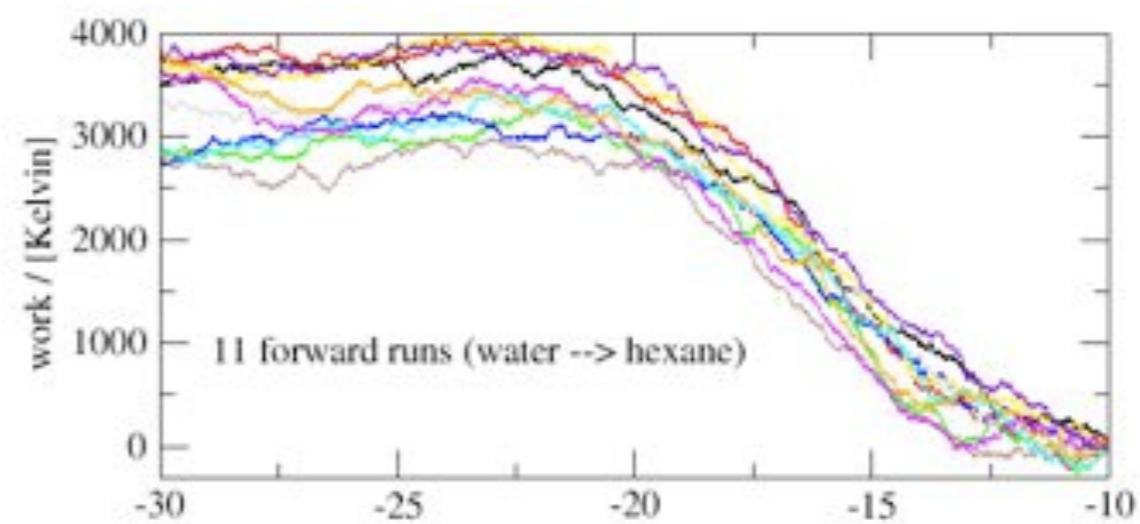
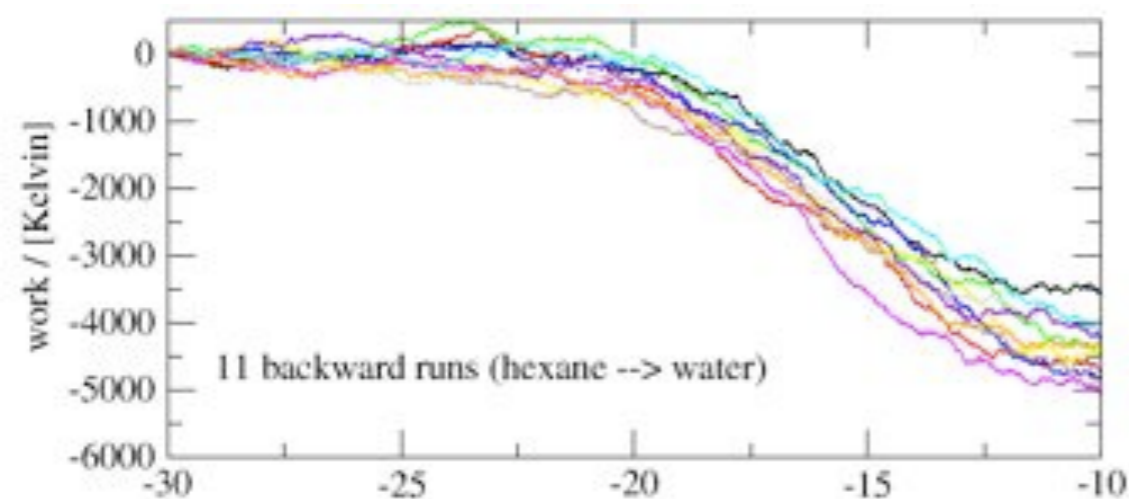
Spline fit of constraint force measurements



Running average constraint force



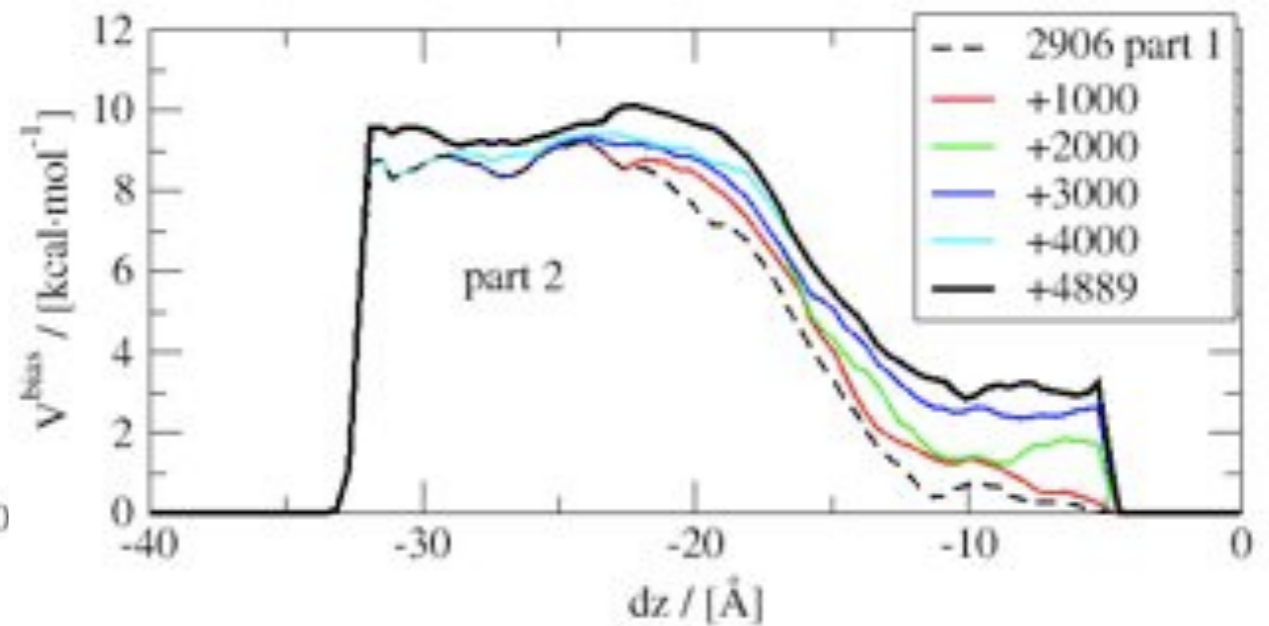
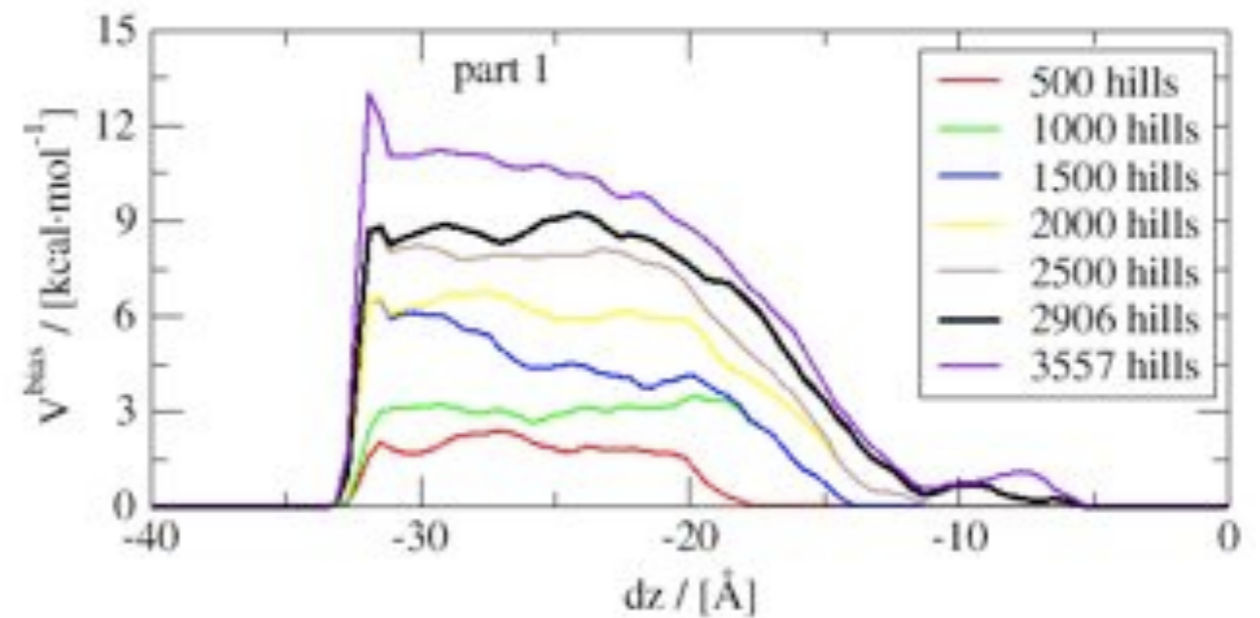
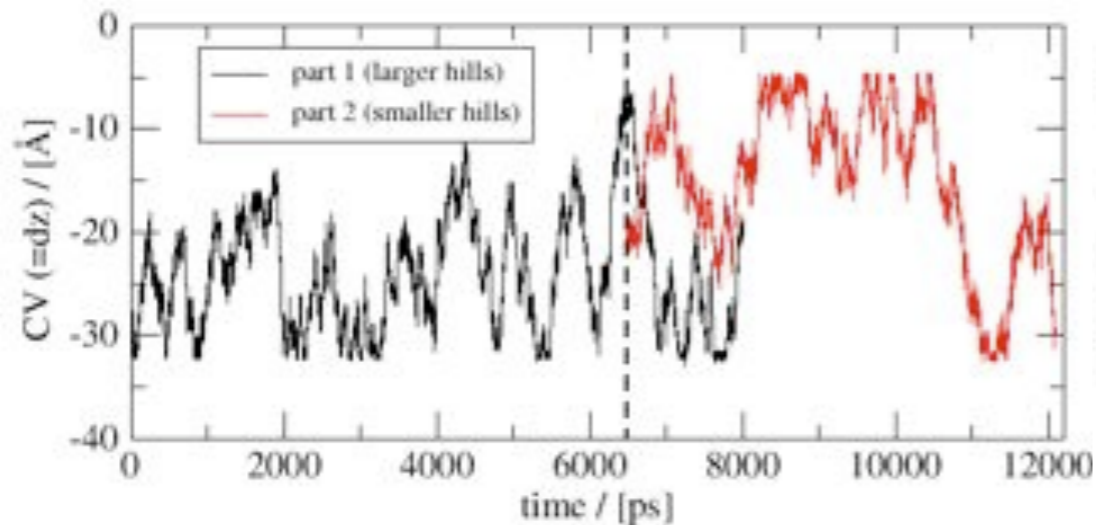
# Steered MD



# Metadynamics

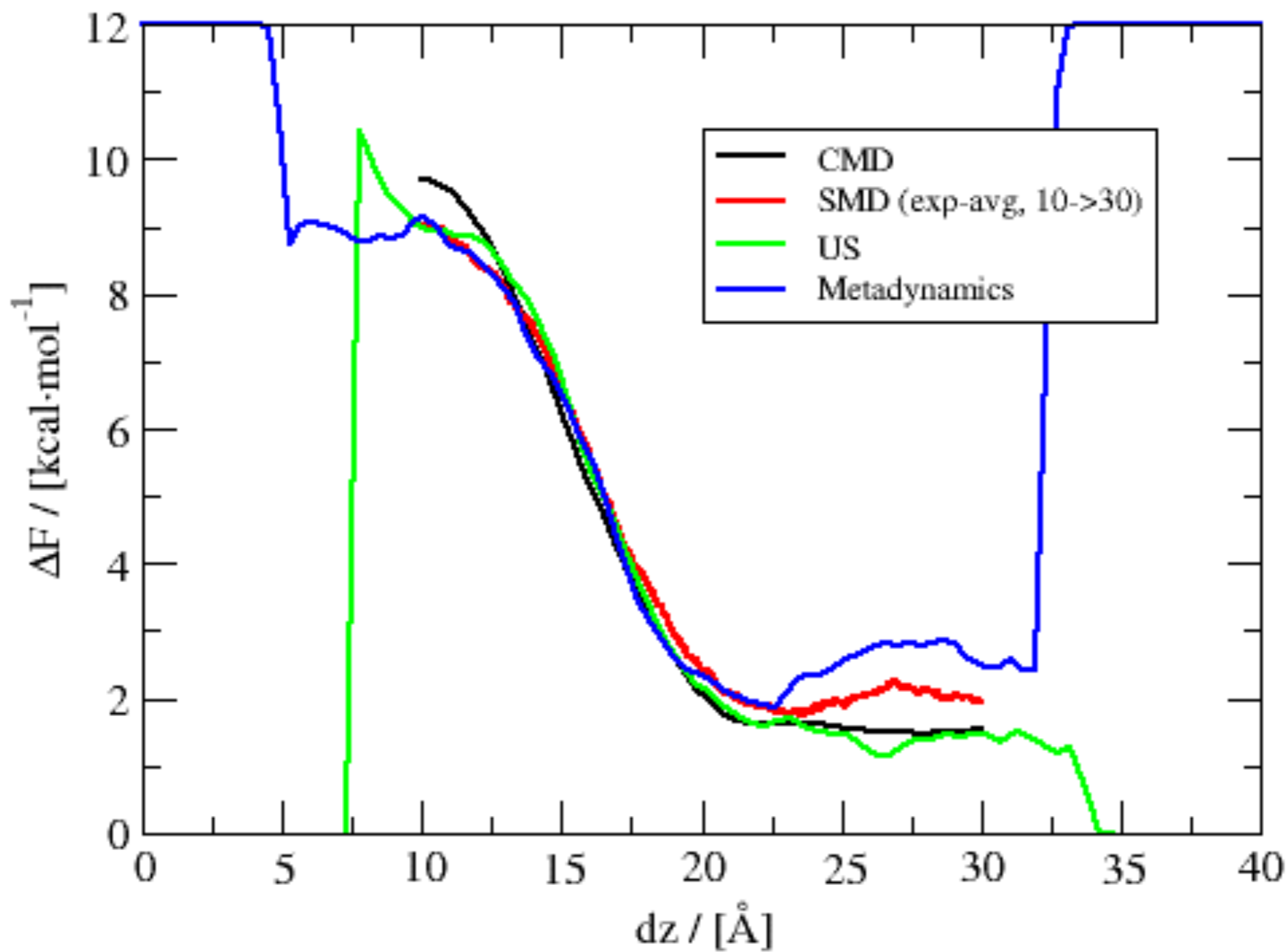
Simulation in two parts with different size of the Gaussian “hills”:

- Part 1:  $H=0.25$  K,  $W=0.4$  Å
- Part 2:  $H=0.10$  K,  $W=0.2$  Å



# Free energy simulations

hexane molecule in hexane-water interface



# Summary

- Intro Kramers theory
- Transition State Theory
- The Langevin equation
- The Fokker-Planck equation
- Kramers reaction kinetics
- high-friction vs low-friction limit
- memory, Grote-Hynes theory
  
- Bennet-Chandler approach
- Reactive Flux
- Transmission coefficient calculation
- Free energy methods
- Summary
- Bibliography



# Bibliography

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- Kinetic Theory, University of Cambridge Graduate Course, David Tong, Cambridge 2012 (<http://www.damtp.cam.ac.uk/user/tong/kinetic.html>)
- Reaction-rate theory: fifty years after Kramers, P. Hänggi, P. Talkner, and M. Borkovec, *Rev. Mod. Phys.* 62, 215 (1990)
- A Short Account of RRKM Theory of Unimolecular Reactions and of Marcus Theory of Electron Transfer in a Historical Perspective, F. Di Giacomo, *J. Chem. Educ.* 92, 476 (2015)
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- Accurate sampling using Langevin dynamics, G. Bussi and M. Parrinello, *Phys. Rev. E* 75, 056707 (2007)