Metadynamics of Paths

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Sampling the Boltzmann distribution

Given a system of interacting particles described by a potential energy $U(\boldsymbol{R})$, equilibrium properties can be computed sampling configurations from the Boltzmann distribution:

$$p(\boldsymbol{R}) = \frac{e^{-\beta U(\boldsymbol{R})}}{\int e^{-\beta U(\boldsymbol{R})} \mathrm{d}R}$$

Hamilton's equations:

$$\dot{\boldsymbol{P}} = -\nabla_{\boldsymbol{R}} U(\boldsymbol{R}) = \boldsymbol{F}(\boldsymbol{R})$$
$$\dot{\boldsymbol{R}} = \frac{\boldsymbol{P}}{m}$$

Standard Molecular Dynamics:

$$\boldsymbol{R}^{n+1} = \boldsymbol{R}^n + \dot{\boldsymbol{R}}^n \Delta t + \frac{1}{2}\boldsymbol{F}^n \Delta t^2$$
$$\dot{\boldsymbol{R}}^{n+1} = \dot{\boldsymbol{R}}^n + \frac{\boldsymbol{F}^n + \boldsymbol{F}^{n+1}}{2m}\Delta t$$

+ thermostat

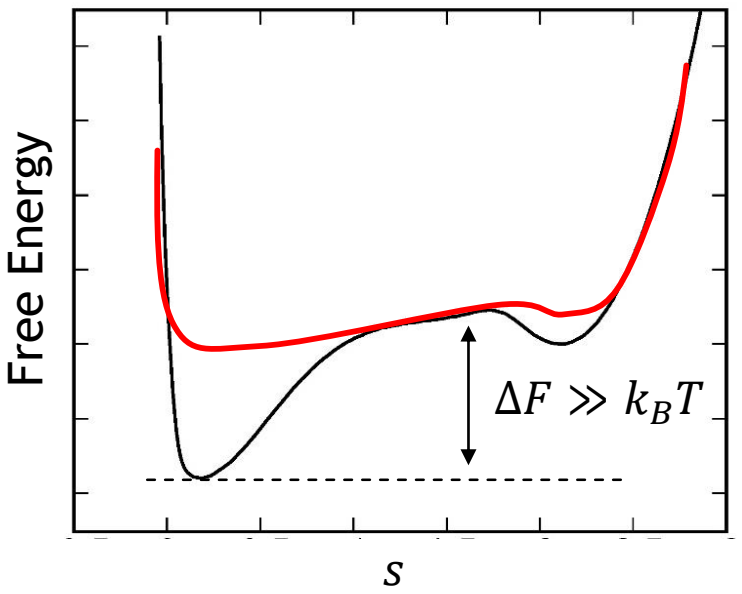
Ergodic assumption:

Static properties: $\langle O \rangle = \frac{1}{Z}\int O(\boldsymbol{R}) e^{-\beta U(\boldsymbol{R})} \mathrm{d}R \approx \frac{1}{N}\sum_{n=1}^{N} O(\boldsymbol{R}^n)$

Dynamical properties: $C_{O_1 O_2}(\tau) \approx \frac{1}{N}\sum_{n=1}^{N-p} O_1(\boldsymbol{R}^n) O_2\left(\boldsymbol{R}^{n+k}\right),\ \tau = k\Delta t$

Sampling the Boltzmann distribution

Rare event scenario



Hamilton's equations:

$$\dot{\boldsymbol{P}} = -\nabla_{\boldsymbol{R}}(U(\boldsymbol{R}) + V_{\text{bias}}(s(\boldsymbol{R}))) = \boldsymbol{F}_{\text{biased}}(\boldsymbol{R})$$

$$\dot{\boldsymbol{R}} = \frac{\boldsymbol{P}}{m}$$

Biased MD Simulations

$$\boldsymbol{R}^{n+1} = \boldsymbol{R}^n + \dot{\boldsymbol{R}}^n \Delta t + \frac{1}{2}\boldsymbol{F}^n_{\text{biased}} \Delta t^2$$

+ thermostat

$$\dot{\boldsymbol{R}}^{n+1} = \dot{\boldsymbol{R}}^n + \frac{\boldsymbol{F}^n_{\text{biased}} + \boldsymbol{F}^{n+1}_{\text{biased}}}{2m} \Delta t$$

Static properties can be computed via reweighted averages:

$$\langle O \rangle = \frac{1}{Z} \int O(\boldsymbol{R}) e^{-\beta U(\boldsymbol{R})} \mathrm{d}R \approx \frac{\sum_{n=1}^{N} w_n \, O(\boldsymbol{R}^n)}{\sum_{n=1}^{N} w_n} \qquad w_n = e^{\beta V_{\text{bias}}(\boldsymbol{s}(\boldsymbol{R}^n))}$$

The bias introduces unphysical forces: dynamical information is generally lost.

Sampling the path distribution

The probability of observing a trajectory $R(t)$ is given by:

$$P[R(t)] \propto e^{-S[R(t)]}$$

where the Onsager-Machlup (OM) action is defined as:

$$S[R(t)] = \int_0^\tau \frac{1}{2\sigma^2}\left(\dot{R}(t) - \frac{F(t)}{mv}\right)^2 \mathrm{d}t\,, \qquad \sigma^2 = 2k_B T/mv$$

One can sample trajectories by drawing them from $\mathrm{P[R(t)]} \propto \mathrm{e}^{-\mathrm{S[R(t)]}}$

Onsager L., Machlup S., *Phys. Rev.* **91**, 1505 (1953)

Sampling the path distribution

We consider a molecular system of M atoms, $\boldsymbol{R} = \{\boldsymbol{r}_j\}_{j=1,M}$

$$\boldsymbol{R}(t) \Longrightarrow \{\boldsymbol{R}^0 \to \boldsymbol{R}^1 \to \cdots \to \boldsymbol{R}^N\}$$

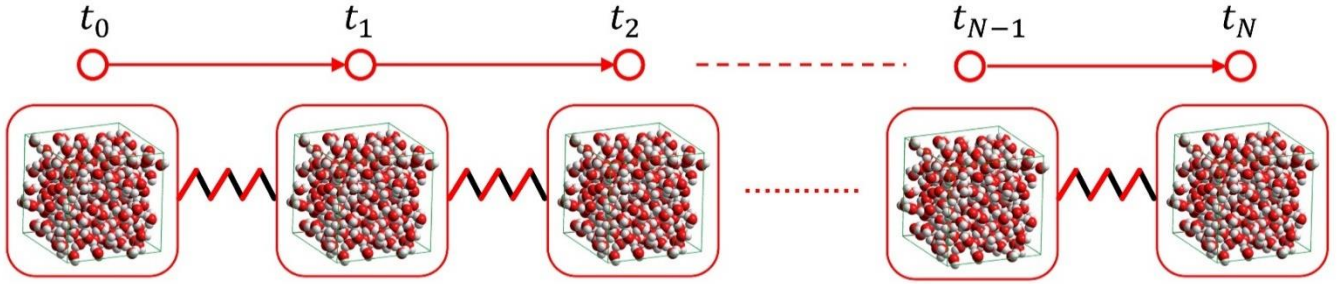
$\boldsymbol{R}^n$ = configuration at time $t_n = (n-1)\Delta t$

$$S(\boldsymbol{R}^0, \boldsymbol{R}^1, \cdots, \boldsymbol{R}^N) = \sum_{n=1}^{N-1} \sum_{j=1}^{M} \frac{1}{2\sigma_j^2} \left(\frac{\boldsymbol{r}_j^{n+1} - \boldsymbol{r}_j^n}{\Delta t} - \frac{\boldsymbol{F}_j^n}{m_j \upsilon} \right)^2 \Delta t$$

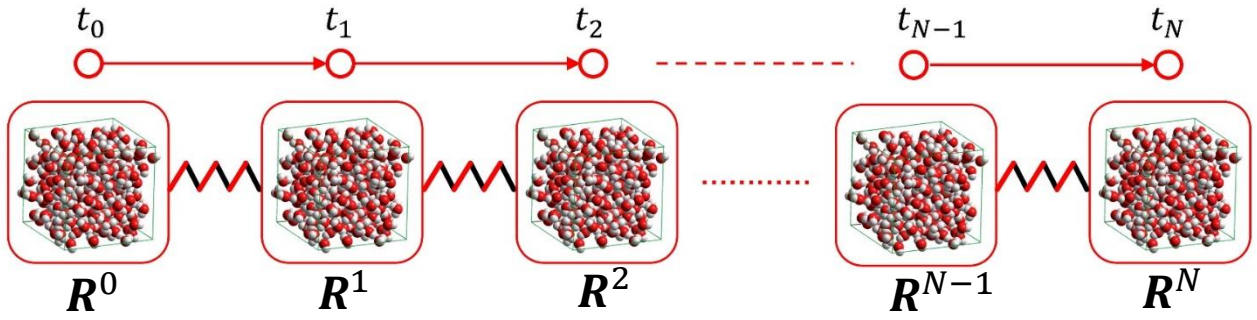
Probability of observing a discretized trajectory:

$$P(\boldsymbol{R}^0, \boldsymbol{R}^1, \cdots, \boldsymbol{R}^N) \propto e^{-\beta V_{\text{eff}}(\boldsymbol{R}^0, \boldsymbol{R}^1, \cdots, \boldsymbol{R}^N)}$$

$$V_{\text{eff}} = U(\boldsymbol{R}^0) + \sum_{n=0}^{N-1} \sum_{j=1}^{M} \frac{K_j}{2} \left(\boldsymbol{r}_j^{n+1} - \boldsymbol{r}_j^n - \boldsymbol{L}_j^n \right)^2, \qquad K_j = \frac{m_j \upsilon}{2\Delta t}, \qquad \boldsymbol{L}_j^n = \frac{\Delta t}{m_j \upsilon} \boldsymbol{F}_j^n$$



Molecular dynamics in trajectory space



$$P(\boldsymbol{R}^0, \boldsymbol{R}^2, \cdots, \boldsymbol{R}^N) \propto e^{-\beta V_{\text{eff}}(\boldsymbol{R}^0, \boldsymbol{R}^2, \cdots, \boldsymbol{R}^N)}$$

We have mapped the original dynamical problem into a static polymer problem.

We can sample $P(\boldsymbol{R}^0, \boldsymbol{R}^1, \cdots, \boldsymbol{R}^N)$ using standard MD:

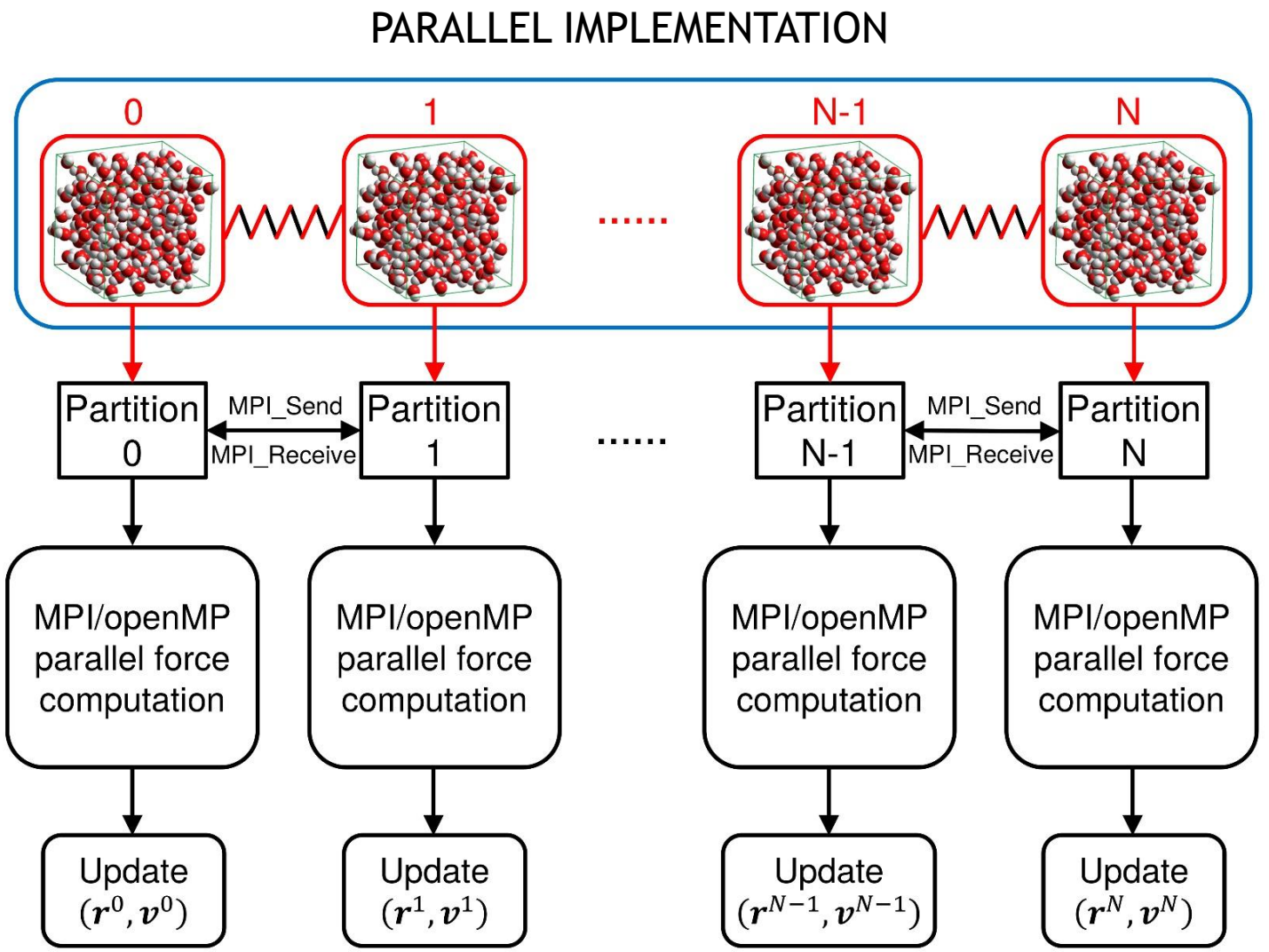
$$\dot{\boldsymbol{p}}_j^n = -\nabla_{\boldsymbol{r}_j^n} V_{\text{eff}}$$

$$\dot{\boldsymbol{r}}_j^n = \frac{\boldsymbol{p}_j^n}{\mathrm{M}_j}$$

+thermostat

- At each time step we obtain a new polymer configuration, which corresponds to a new discretized trajectory of N steps of the original system;

Molecular dynamics in trajectory space



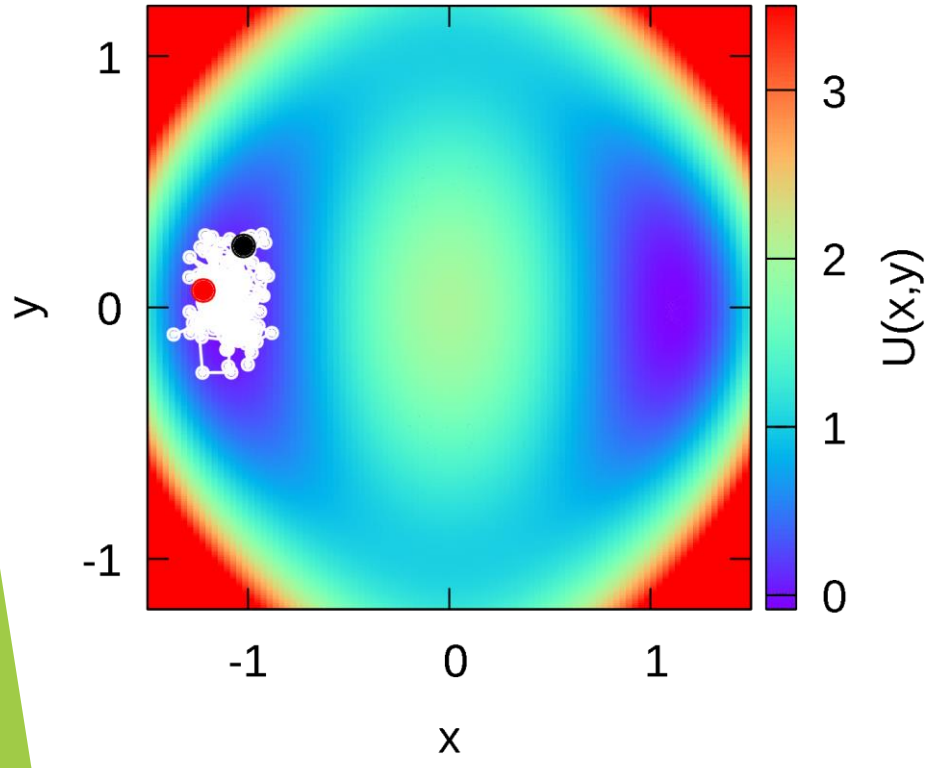
The method realizes parallelization at the level of time.

Calhoun *et al.*, *Chem. Phys. Lett.* **262**, 415 (1996)

Metadynamics in trajectory space

Temperature $k_B T \ll \Delta E$.

UNBIASED



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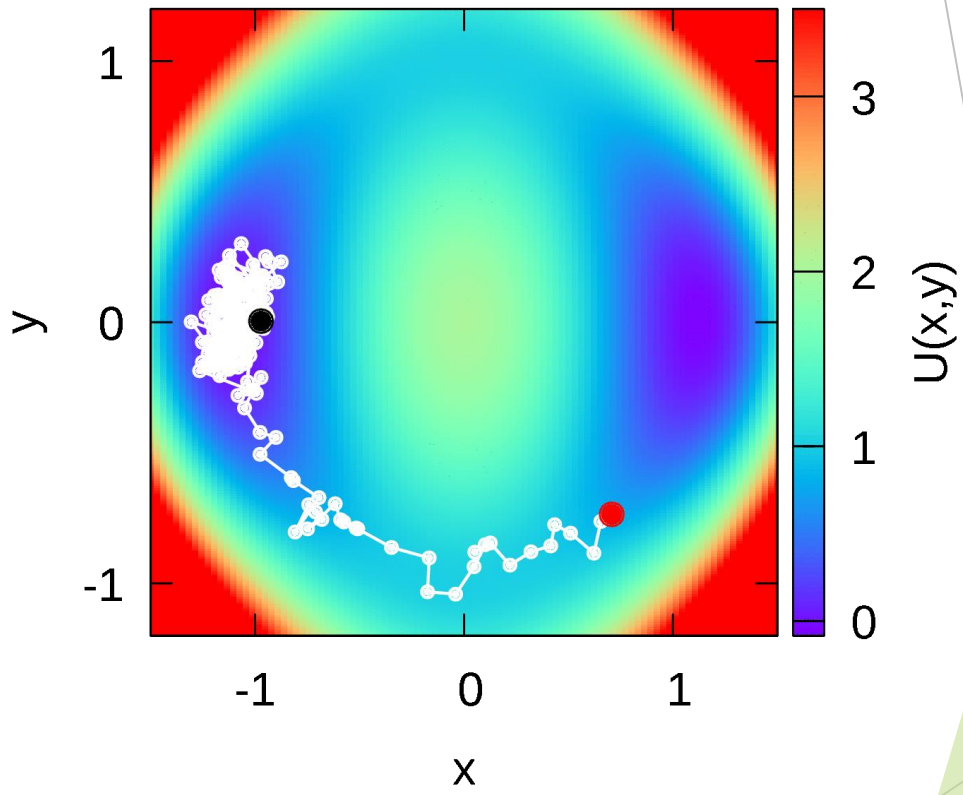
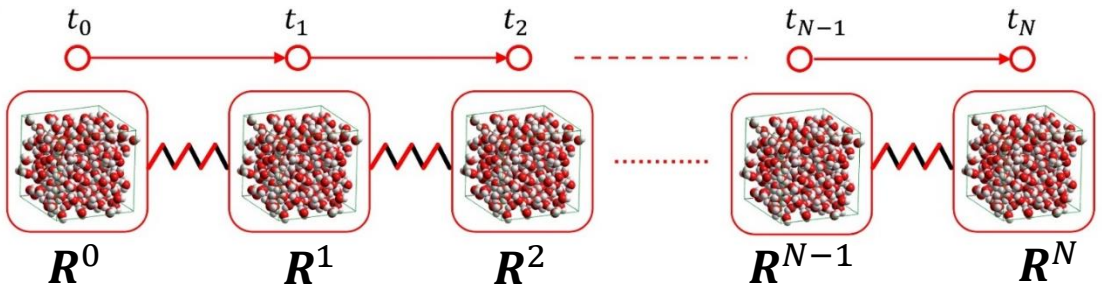


● First replica, $\boldsymbol{R}^1$
● Last replica, $\boldsymbol{R}^N$

CV: $d_{\mathrm{e2e}} = |\boldsymbol{R}^N - \boldsymbol{R}^1|$

Unconstrained exploration of multiple reaction routes.

Dynamical properties from static averages

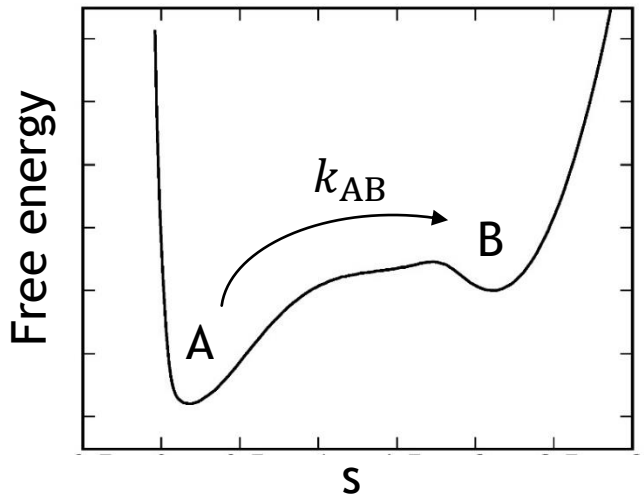


$$t_n = n\Delta t$$

Time correlation functions:

$$C(\tau) = \langle O(t=0)O(\tau)\rangle = \frac{\sum_{i=1}^{P} w_i O_i^0 O_i^n}{\sum_{i=1}^{P} w_i}, \qquad w_i = e^{\beta V_{\text{bias}}(s_i)}$$

$P = \#$ of samples, $\qquad O^n = O(\boldsymbol{R}^n) = O(n\Delta t)$

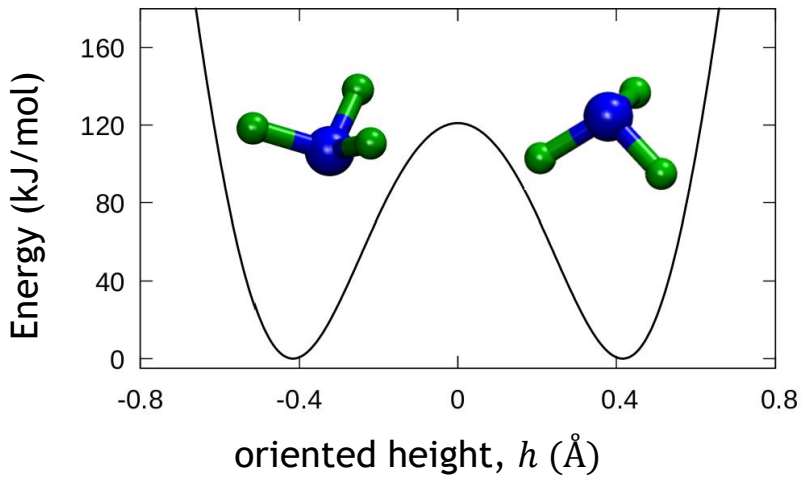


$$k_{AB} = \frac{\mathrm{dC(t)}}{\mathrm{d}t}, \qquad C(t) = \frac{\langle I_A(0) I_B(t)\rangle}{\langle I_A(0)\rangle}$$

$I_X(t) = 1$ if $R \in X$ at time t, and 0 otherwise.

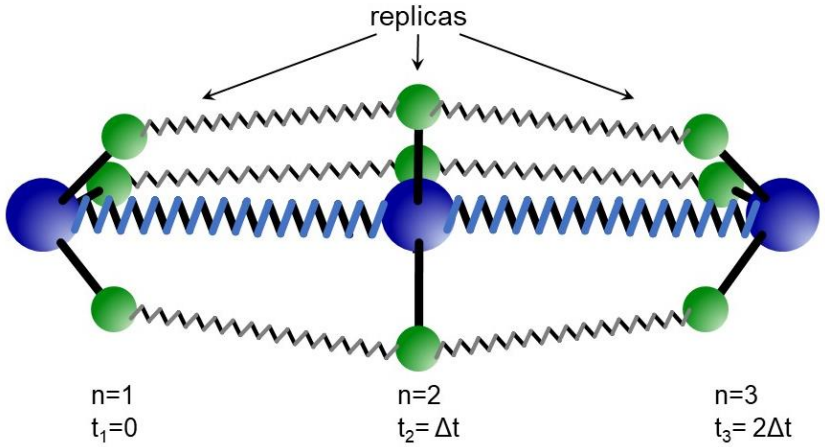
W. H. Miller, *J. Chem. Phys.* **61**, 1823 (1974)

Results: inversion of NH_3 in vacuum



$\Delta E \approx 120$ kJ/mol

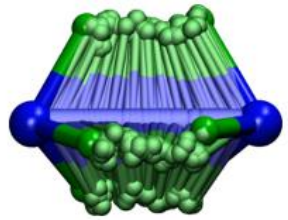
ReaxFF force field
[Weismiller *et al.*, *J. Phys. Chem. A* **114**, 5485 (2010)]



N up to 200 replicas.

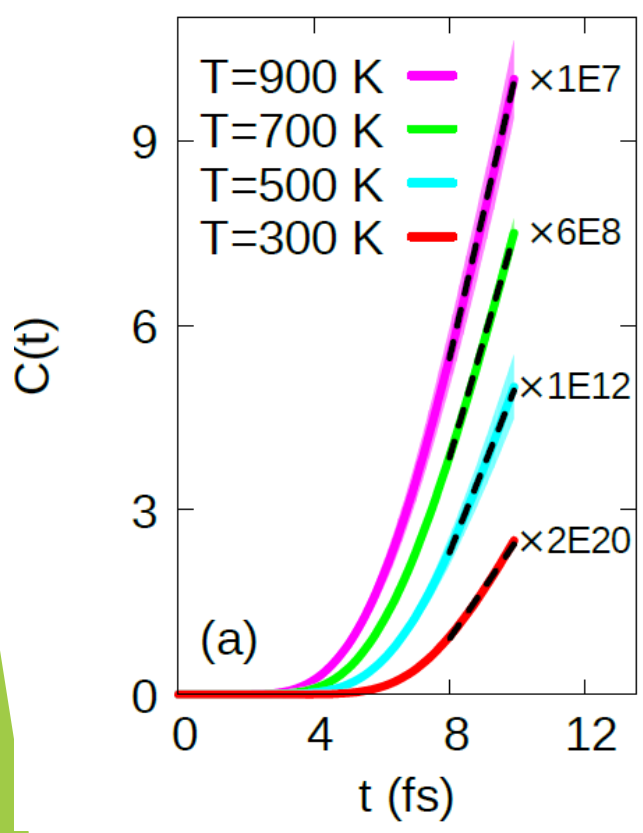
CV: $\Delta h_{e2e} = (h^N - h^1)$ as CV.

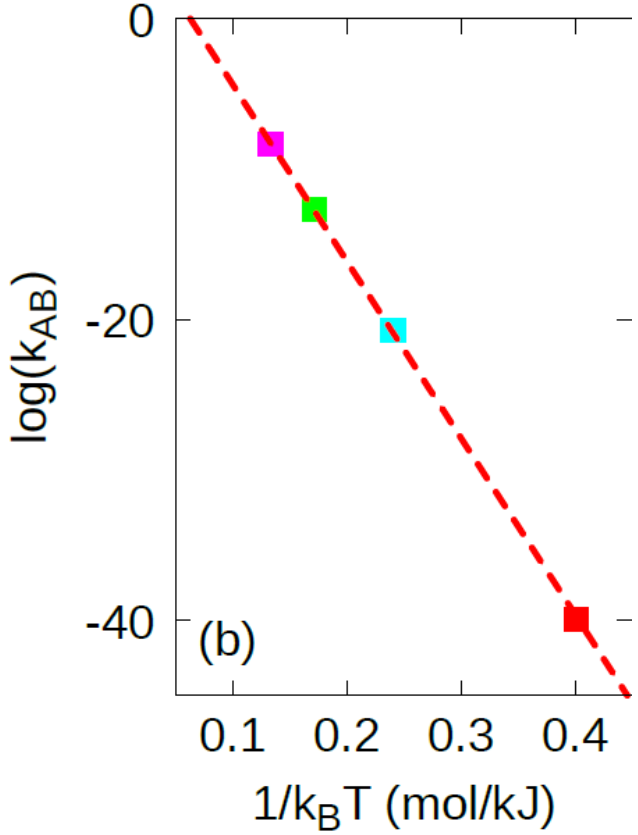
Biased MD simulations using OPES[1].



[1]Invernizzi M. and Parrinello M., *J. Phys. Chem. Lett.* **11**, 2731 (2020)

Results: inversion of NH_3 in vacuum





From the linear fit:

$\Delta E^{\mathrm{fit}} \approx 118 \pm 1$ kJ/mol

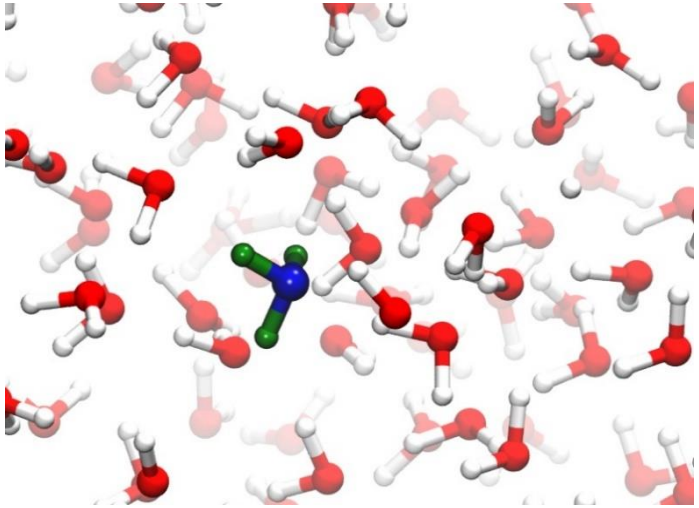
Exact value:

$\Delta E^{\mathrm{ReaxFF}} \approx 120$ kJ/mol

$$C(t) = \frac{\langle I_{\mathrm{A}}(0) I_{\mathrm{B}}(t) \rangle}{\langle I_{\mathrm{A}}(0) \rangle}$$

$$k_{\mathrm{AB}} = \frac{\mathrm{dC(t)}}{\mathrm{d}t}$$

Results: inversion of NH_3 in water



$NH_3 + 215H_2O$, tip3p water.

Cubic box $L \approx 19$ Å.

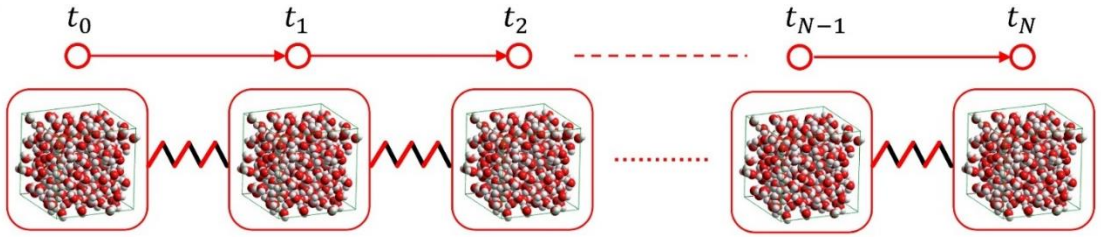
NH_3 force field: $\sum_{i=1}^{3}\left(D\left[1-e^{-\alpha(r_i-r_o)^2}\right]+K(\theta_i-\theta_0)^2\right)$

Long range vdW interactions, cutoff at 9 Å.

Long range electroctatic interactions using pppm.

Temperature *T*=300 K.

Polymer model

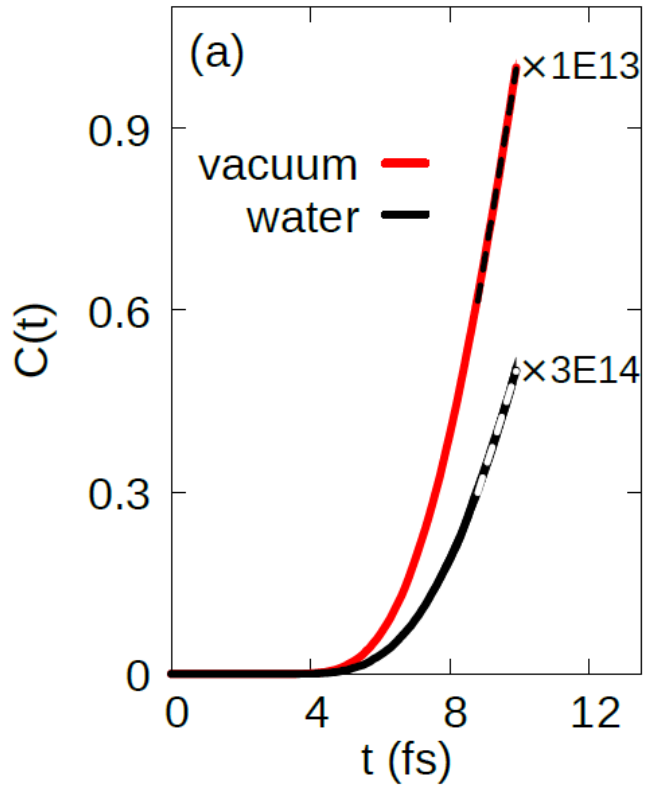


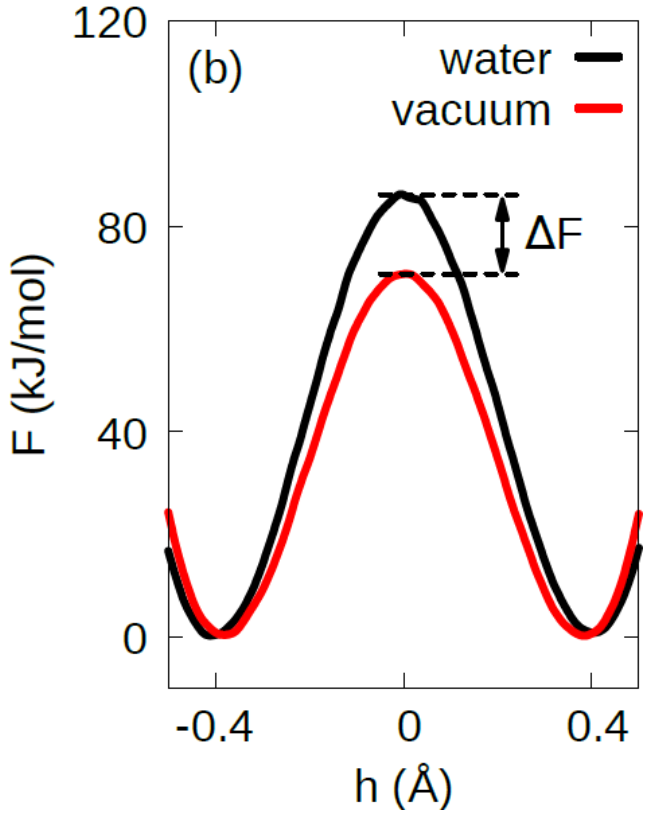
N up to 200 replicas.

Biased MD simulations using OPES.

CV: $\Delta h_{e2e} = (h^N - h^1)$.

Results: inversion of NH_3 in water





$k_{\mathrm{vac}} \approx 3 \times 10^{-11}\ \mathrm{ps}^{-1}$

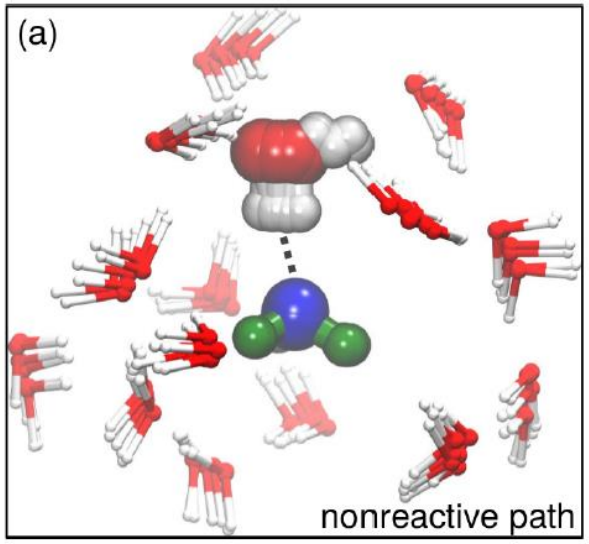
$k_{\mathrm{wat}} \approx 6 \times 10^{-14}\ \mathrm{ps}^{-1}$

Prediction from TST

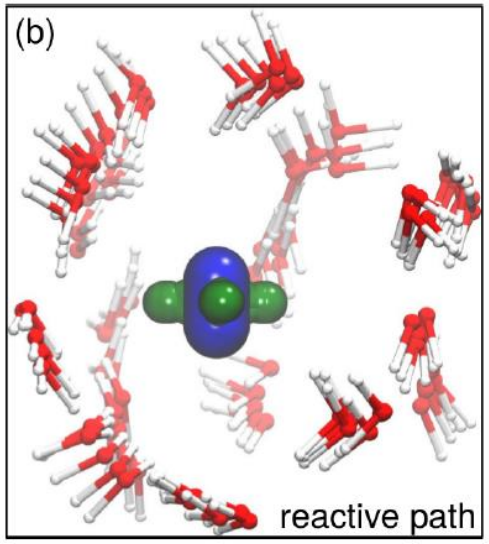
$k_{\mathrm{wat}}/k_{\mathrm{vac}} = e^{-\Delta F/k_B T} \approx 2.2 \times 10^{-3}$

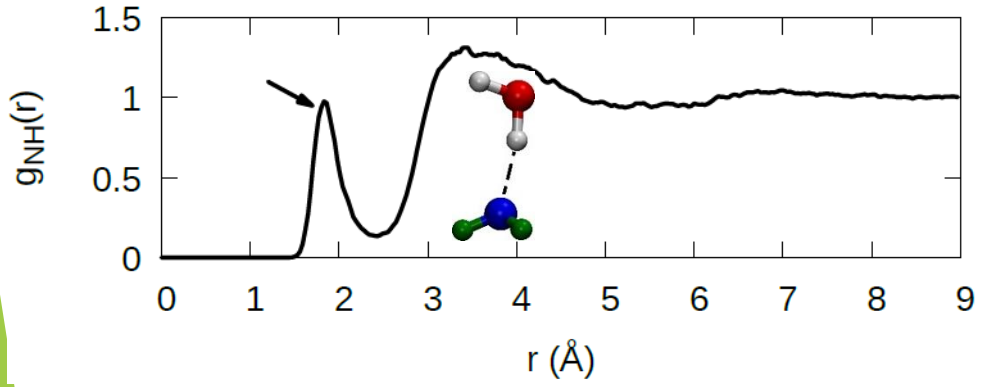
Results: NH_3-water correlations

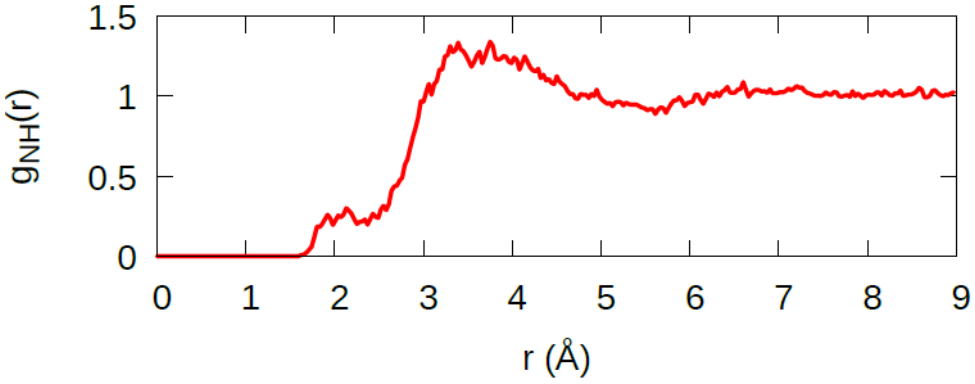
Non reactive trajectories



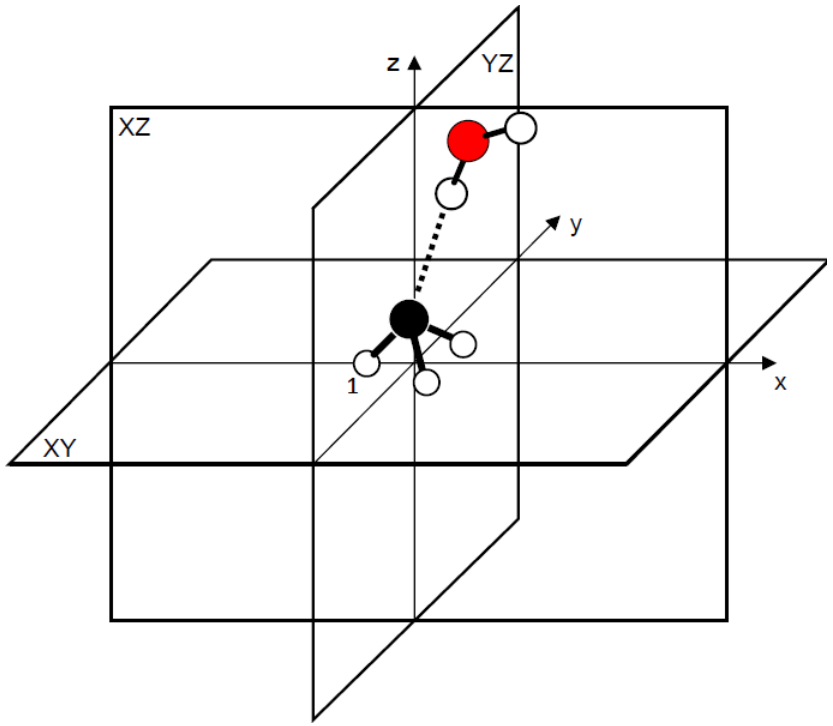
Reactive trajectories

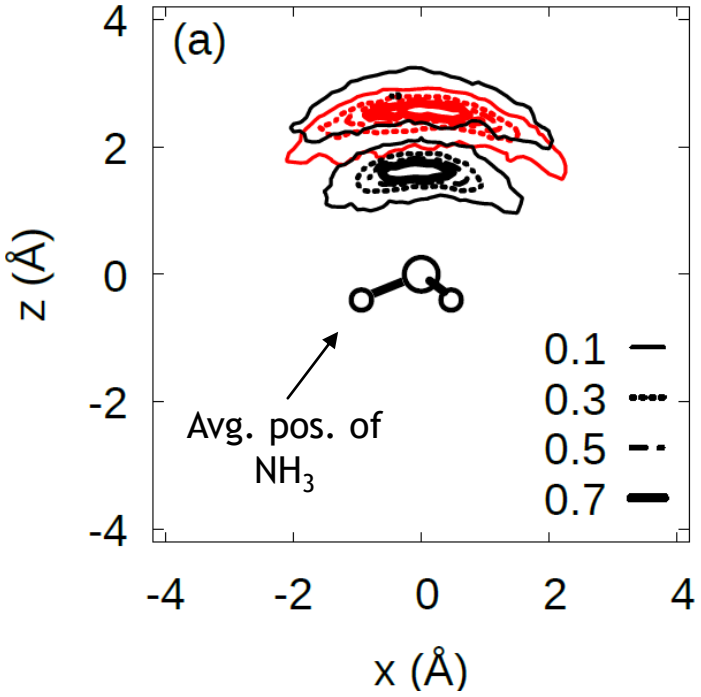






Results: hydration shell of NH_3





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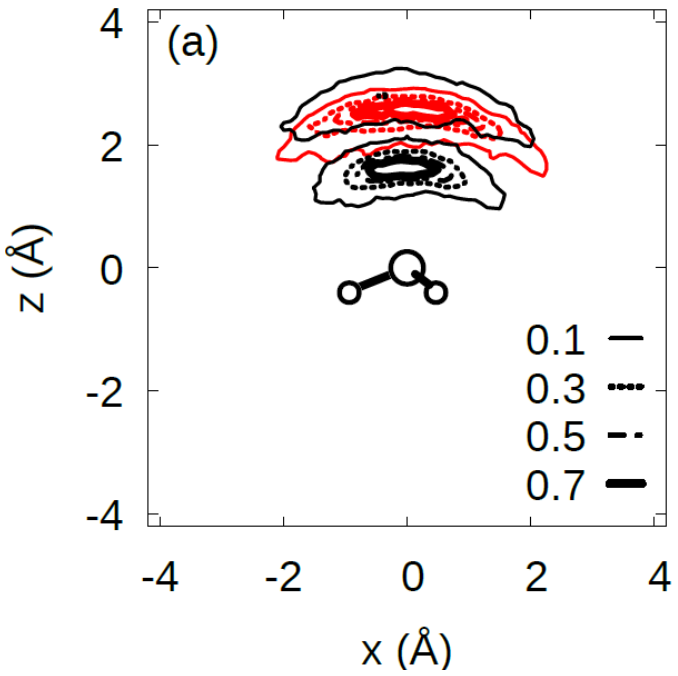
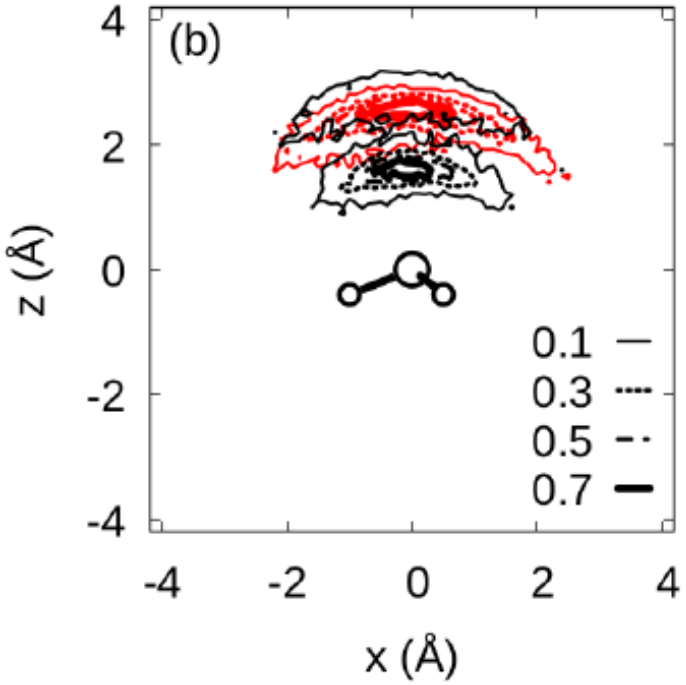
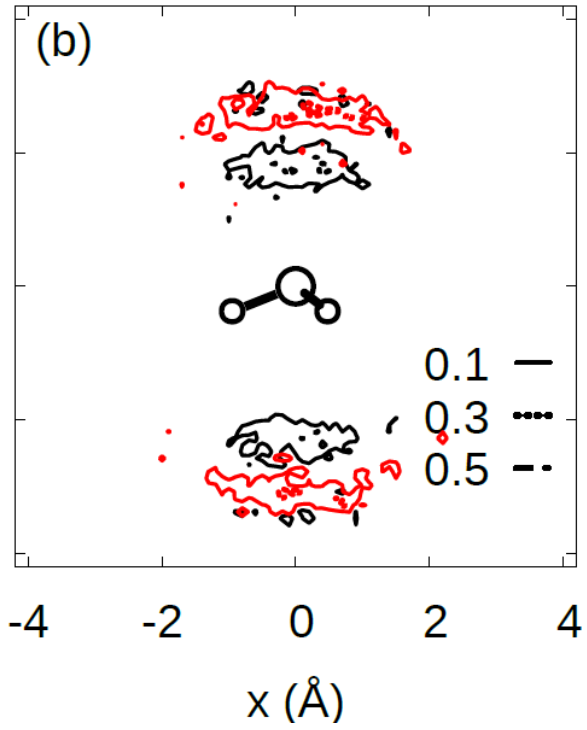


Path MD:
non-reactive trajectories

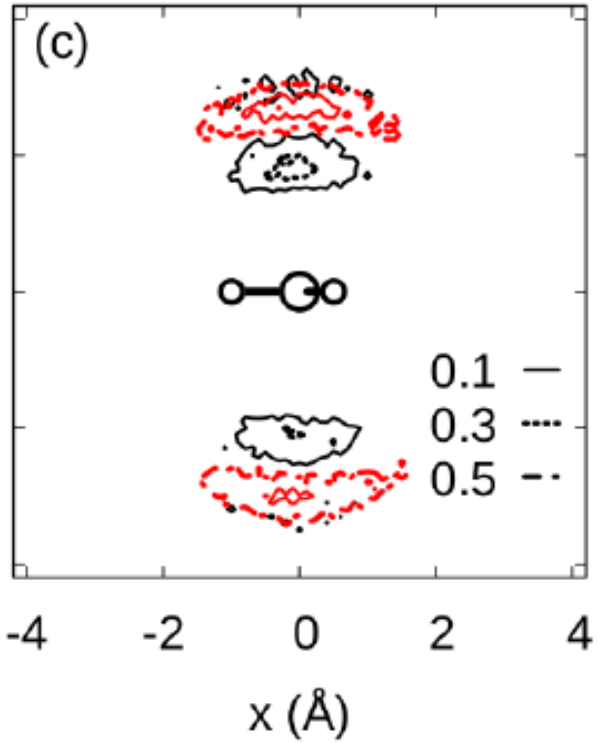


Standard equilibrium MD.

Results: hydration shell of NH_3



Path-MD:
Starting configurations
of reactive trajectories.



Transition state configurations sampled
via (constrained) standard MD.

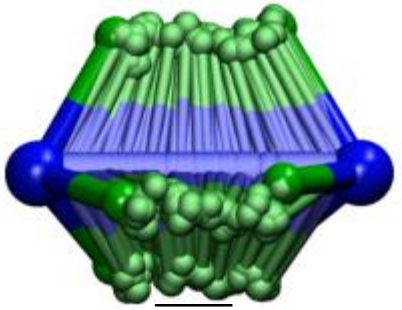
The change in solvation structure from asymmetric to symmetric lowers the transition state energy and promotes the reaction.

Results: transition states and reactive trajectories

$$V_{\text{eff}} = U(\boldsymbol{R}^1) + \sum_{n=1}^{N-1}\sum_{j=1}^{M}\frac{m_j v}{4\Delta t}\left(\boldsymbol{r}_j^{n+1} - \boldsymbol{r}_j^{n} - \frac{\Delta t}{m_j v}\boldsymbol{F}_j^{n}\right)^2$$

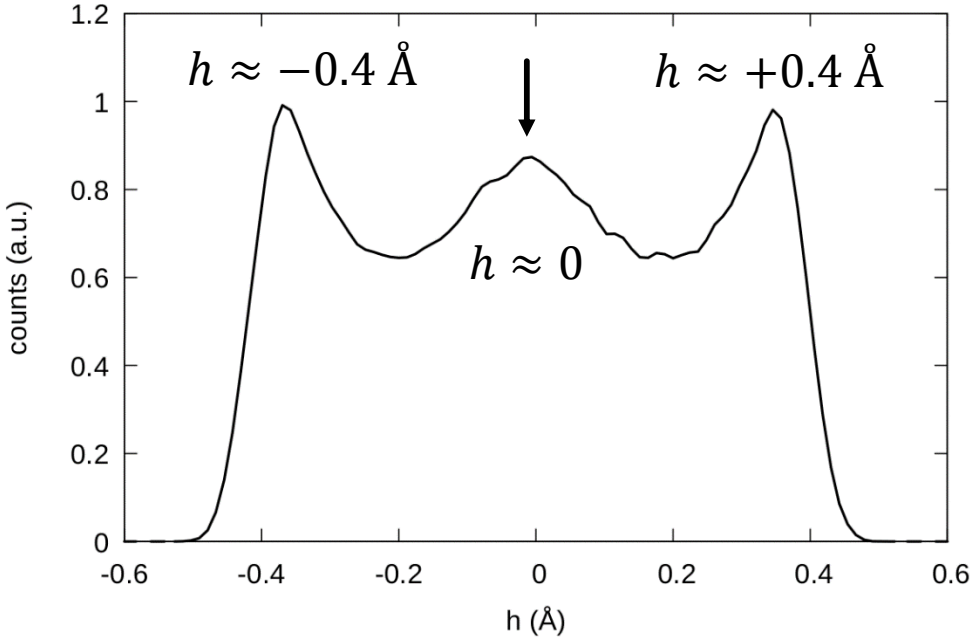
The equilibrium length of the spring is zero near stable and unstable equilibrium states: $\boldsymbol{F}_j^n \approx 0$.

Reactive trajectories

$h \approx -0.4$ Å  $h \approx +0.4$ Å

$h \approx 0$

Distribution of h in reactive paths.



Transition states correspond to peaks in the distribution of the reaction coordinate.

Conclusions

- We proposed a method to study rare events via enhanced-sampling MD simulations in trajectory space;
- The method allows unconstrained exploration of reactive routes;
- Time correlation functions can be computed as static (reweighted) averages;
- The method allows a parallel implementation that can take full advantage of modern massively parallel computer architectures;

Mandelli D., Hirshberg B., Parrinello M., *Phys. Rev. Lett.* **125**, 026001 (2020)