

C7790 Introduction to Molecular Modelling

TSM Modelling Molecular Structures

Lesson 27 Various (Molecular Dynamics II)

PS/2020 Distant Form of Teaching: Rev1

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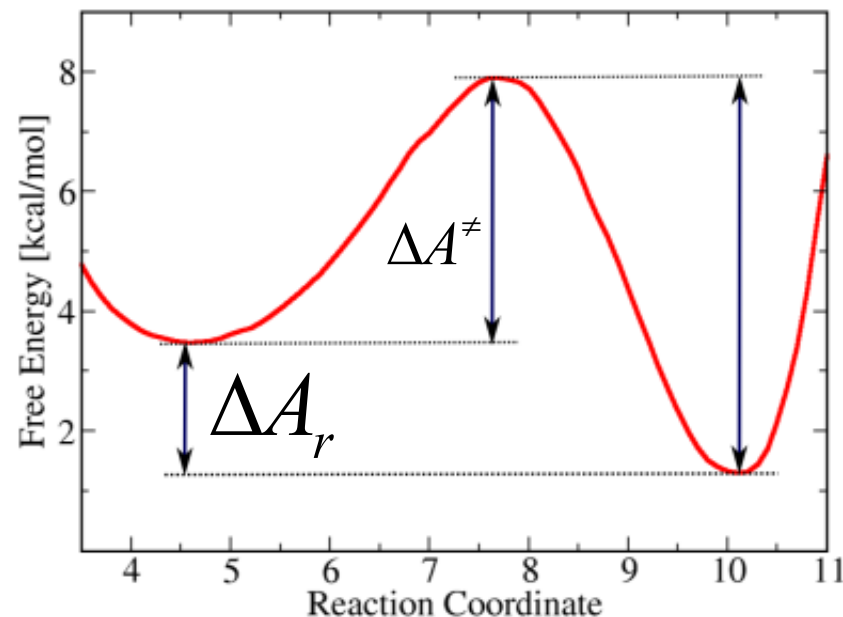
Free Energy Calculations

Free Energy

Free energy is related to **equilibrium** and **rate constants**.

$$\Delta A_r = -RT \ln K$$

$$k_1 = \kappa \frac{k_B T}{h} e^{-\frac{\Delta A^\ddagger}{RT}}$$



The free energy forms a bridge between a theory and an experiment.

Knowledge of **free energy** allows to quantify:

- chemical reactivity (e.g. enzymatic activities)
- thermodynamics (e.g. binding affinities)

Free Energy Calculations

$$\Delta A_{1 \rightarrow 2} = -RT \ln \frac{\sigma_2}{\sigma_1}$$

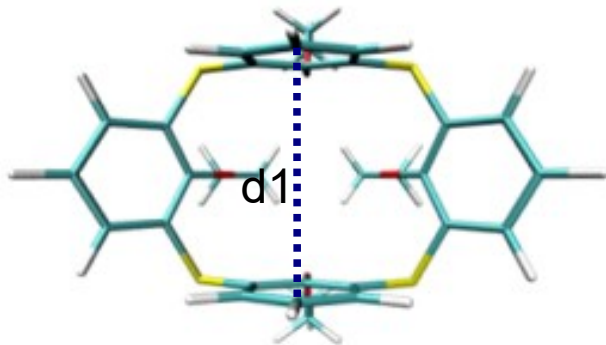
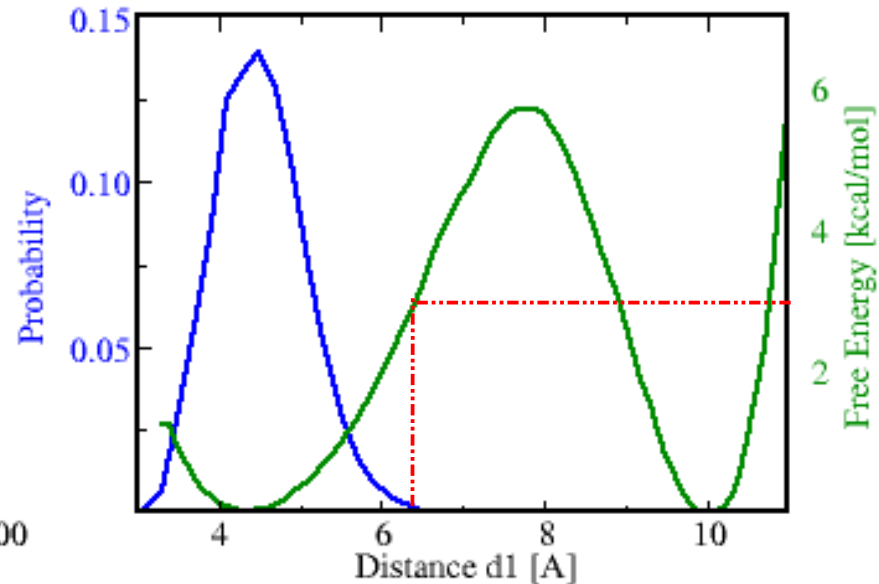
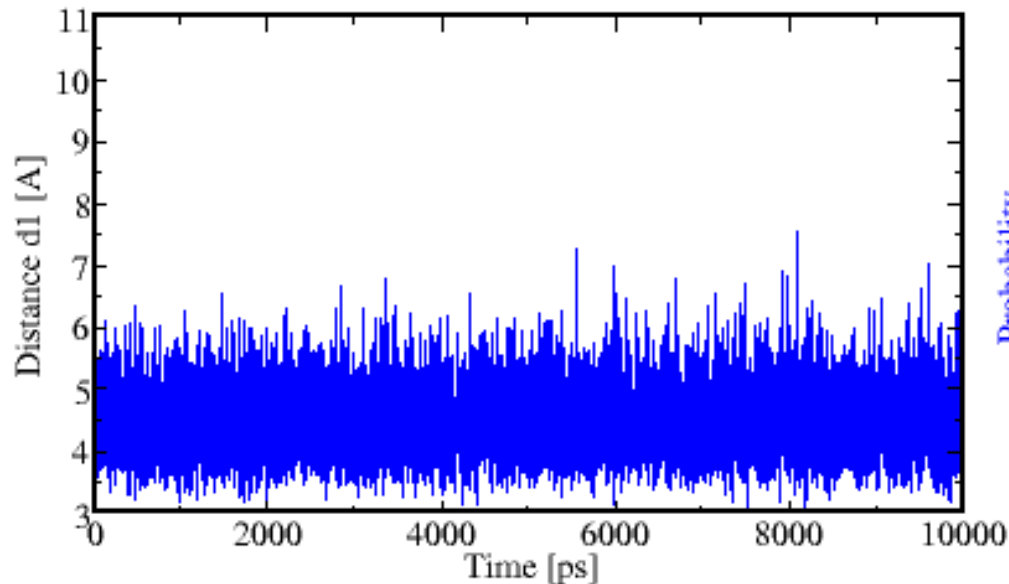
Density of state (probability)

It can be calculated from molecular dynamics or Monte Carlo simulations, **but ...**

$$A(\xi) = -RT \ln \sigma(\xi) + A_0$$

reaction coordinate
collective variables

Sampling Problem



10 ns long simulation is able to discover free energy landscape with depth only about **3 kcal/mol**.

Free Energy Calculations

A system has to be **biased** achieving efficient sampling in the region of interest. We need to know how to obtain the **unbiased free energy** from such biased simulation.

Available methods:

➤ ***constrained dynamics***

system is biased by constraining reaction coordinate

➤ ***adaptive biasing force***

system is biased by force which is opposite to potential of mean force

➤ ***umbrella sampling***

system is biased by restraining reaction coordinate

➤ ***metadynamics***

system is biased by Gaussian hills, which fill free energy landscape

Free Energy Calculations

➤ Alchemical Transformation

one system is slowly changed to another one (changes are very often unrealistic, atoms are created and/or annihilated)

what: mostly *changes* in binding free energies:

how: thermodynamic integration (TI), free energy perturbation (FEP)

➤ Potential of Mean Force

system is changed along reaction coordinate

what: free energy of conformation changes, **reaction free energies**

how: constrained dynamics, adaptive biasing force, umbrella sampling, metadynamics, steered dynamics

➤ *End-points Methods*

free energy of every state is calculated independently

what: mostly binding free energies

how: MM/XXSA; XX=PB, GB, LRA

Metadynamics

Metadynamics, theory

Free energy landscape is filled by Gaussian hills.

Equations of motion

$$m_i \frac{d^2 x_i(t)}{dt^2} = - \frac{\partial V(x)}{\partial x_i}$$

MTD history potential

$$V_h(s, i) = \sum_{t=1}^i H_t \exp\left(-\frac{(s - s_t)^2}{2\sigma^2}\right)$$



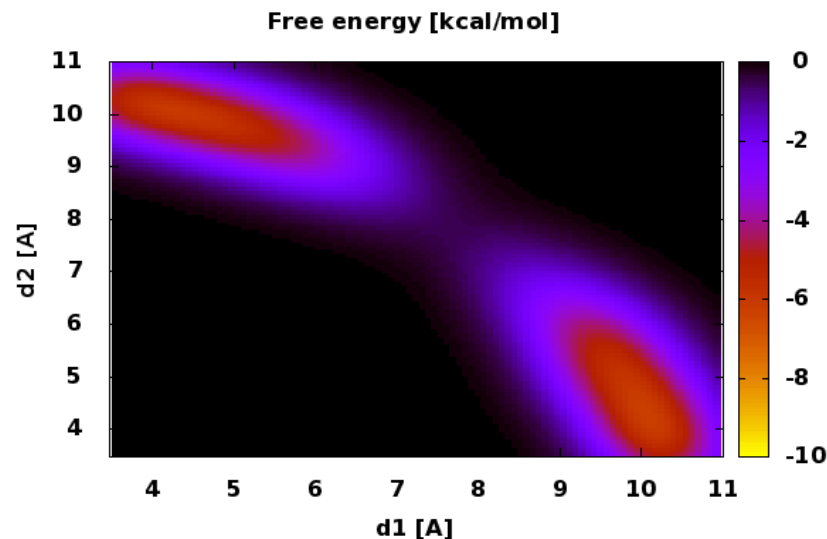
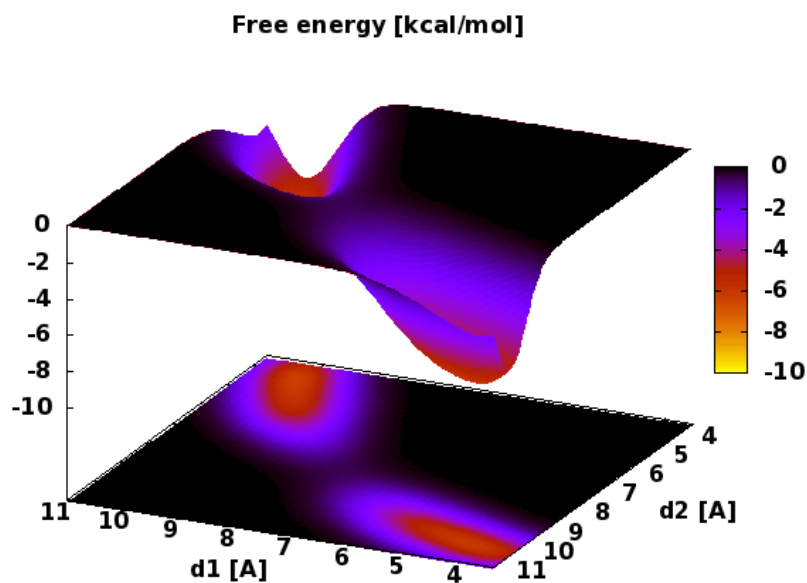
Equations of MTD motion (direct approach)

$$m_i \frac{d^2 x_i(t)}{dt^2} = - \frac{\partial}{\partial x_i} \{V(x) + V_h(x, i)\}$$

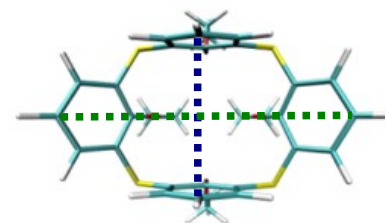
History-dependent term converges to FES

$$A(s) = \lim_{i \rightarrow \infty} -V_h(i, s)$$

Metadynamics, example



hill height 0.01 kcal/mol, width $0.5 \times 0.5 \text{ \AA}$
MTD frequency 500 fs
2 ns long simulation
300 K, vacuum, GAFF force field, time step 0.5 fs



DIS (distance)

Constrained Dynamics

Constrained Dynamics, theory

Reaction coordinate is fixed (constrained) at the value of interest.

Equations of motion

$$m_i \frac{d^2 x_i(t)}{dt^2} = - \frac{\partial V(x)}{\partial x_i}$$

Constraint condition

holonomic constraint

$$\sigma(x) = \xi(x) - \xi_0 = 0$$

Equations of constrained motion

$$m_i \frac{d^2 x_i(t)}{dt^2} = - \frac{\partial}{\partial x_i} \left\{ V(x) + \sum_k \lambda_k(t) \sigma_k(x) \right\}$$

method of Lagrange multipliers

λ_k = Lagrange multipliers

Constrained Dynamics, theory

Derivative of **unbiased free energy** is also given by (concise formulation):

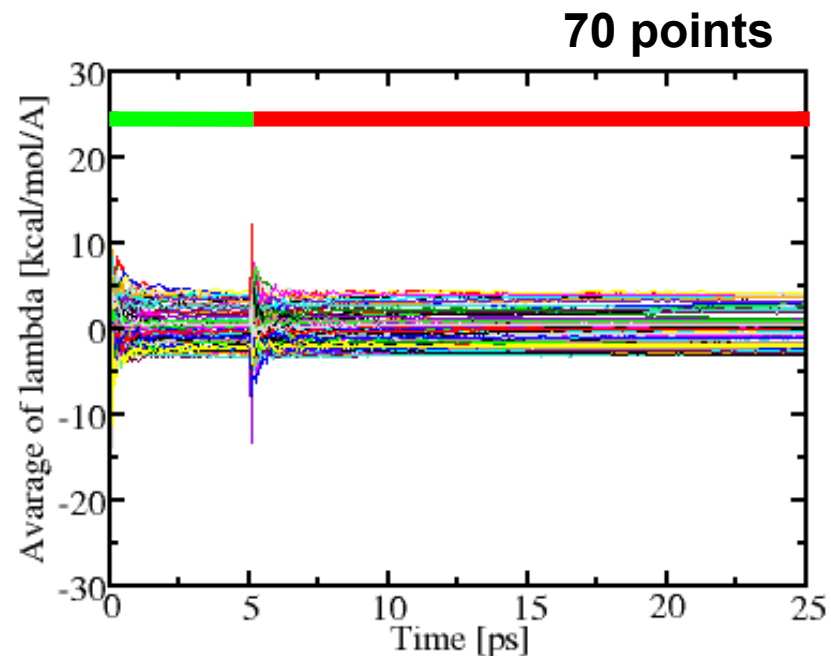
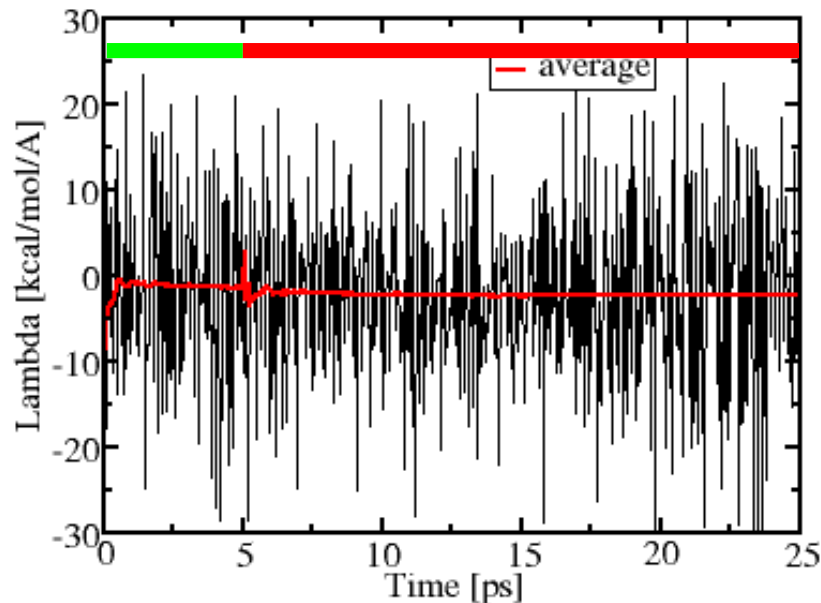
$$\frac{dA^{uc}(\xi)}{d\xi} = \frac{dA^c(\xi)}{d\xi} + \frac{dA^{c \rightarrow uc}(\xi)}{d\xi} = \langle -\lambda \rangle_{\xi_0} - RT \frac{d}{d\xi} \ln \langle Z^{-1/2} \rangle_{\xi_0}$$

second derivatives are not required

Final free energy is obtained by numerical **integration**:

$$\Delta G = \int_{\xi_1}^{\xi_2} \frac{dA^{uc}(\xi)}{d\xi} d\xi$$

Constrained Dynamics, example

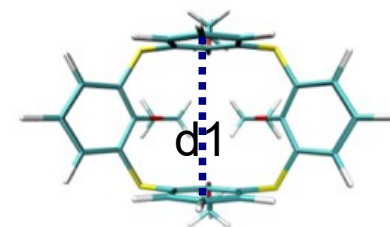


Small numbers are calculated by averaging big numbers.

77 points, $\Delta\xi$ 0.1 Å

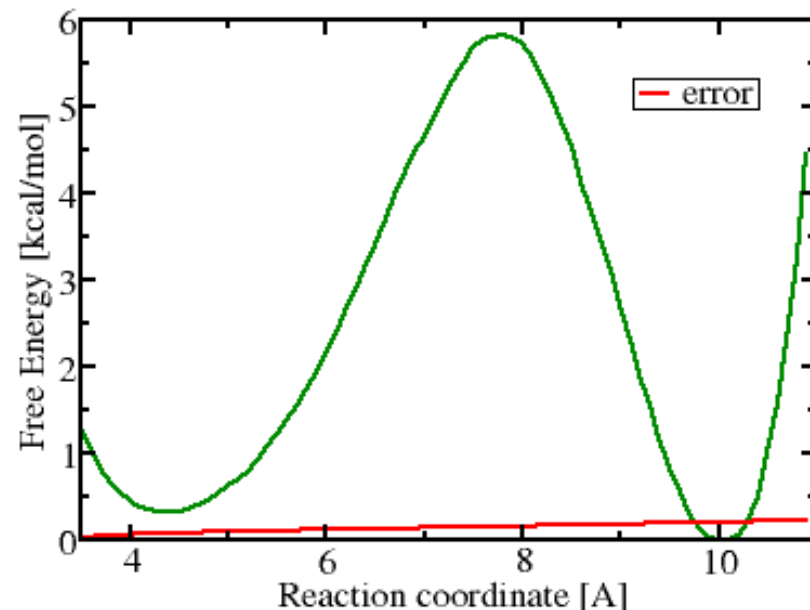
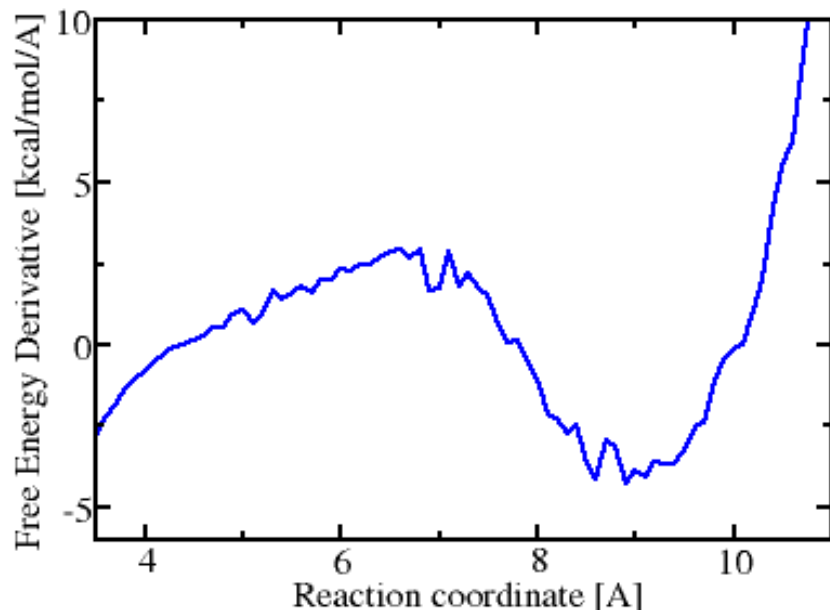
Method B: 5 ps shift, 5 ps equilibration, 20 ps production

300 K, vacuum, GAFF force field, time step 1 fs / 0.5 fs



DIS (distance)

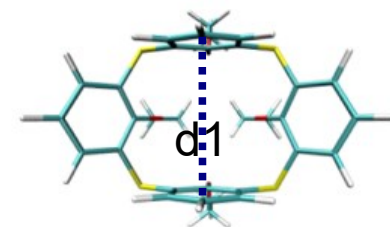
Constrained Dynamics, example



77 points, $\Delta\xi$ 0.1 Å

Method B: 5 ps shift, 5 ps equilibration, 20 ps production

300 K, vacuum, GAFF force field, time step 1 fs / 0.5 fs



DIS (distance)

Adaptive Biasing Force

ABF, theory

Movement along reaction coordinate is the subject of diffusion process.

Equations of motion

$$m_i \frac{d^2 x_i(t)}{dt^2} = - \frac{\partial V(x)}{\partial x_i}$$

Free energy and force along RC

$$F_{ABF}(x) = - \frac{dA(\xi)}{d\xi} \frac{d\xi}{dx}$$



force along reaction coordinate is subtracted from the system

Equations of ABF motion

$$m_i \frac{d^2 x_i(t)}{dt^2} = - \frac{\partial V(x)}{\partial x_i} + F_{ABF}(\xi)$$

ABF, theory

Free energy is given by:

$$\frac{\partial A}{\partial \xi} = - \left\langle \frac{d}{dt} \left(\frac{1}{Z_\xi} \frac{d\xi}{dt} \right) \right\rangle_{\xi}$$

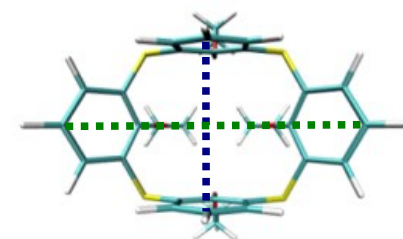
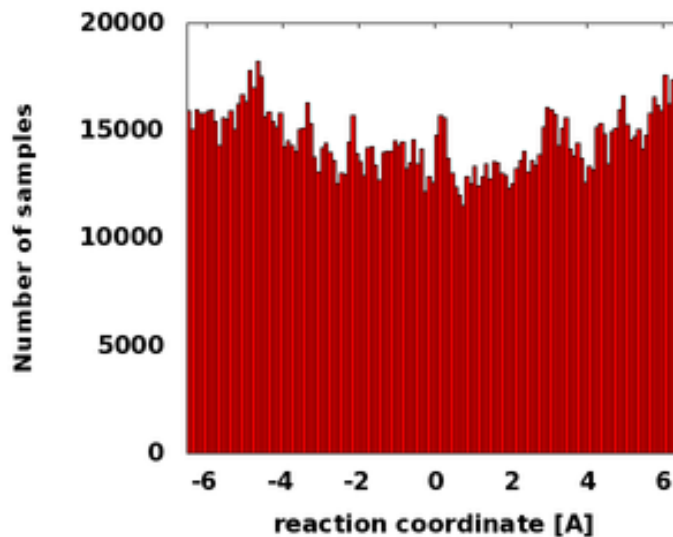
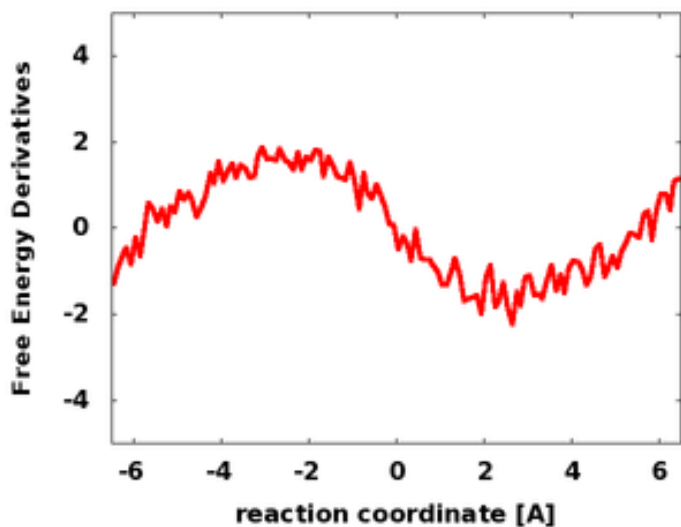
it contains the second derivatives of reaction coordinate if treated analytically

equation is solved **numerically**

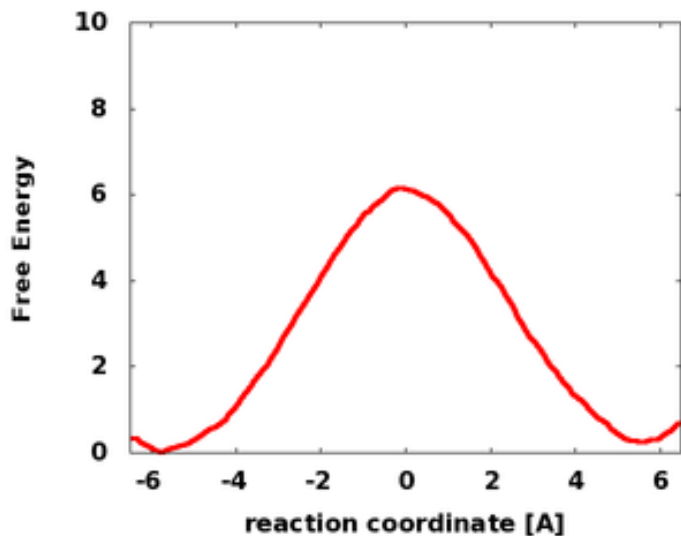
Procedure:

- range of reaction coordinate is divided into bins
- a value of reaction coordinate determine a bin
 - a contribution to the derivative of free energy is accumulated into a bin
 - ABF force calculated from accumulated free energy derivative is applied to the system
- accumulated free energy derivative very rapidly converges

ABF, example



DD
(difference of distances)

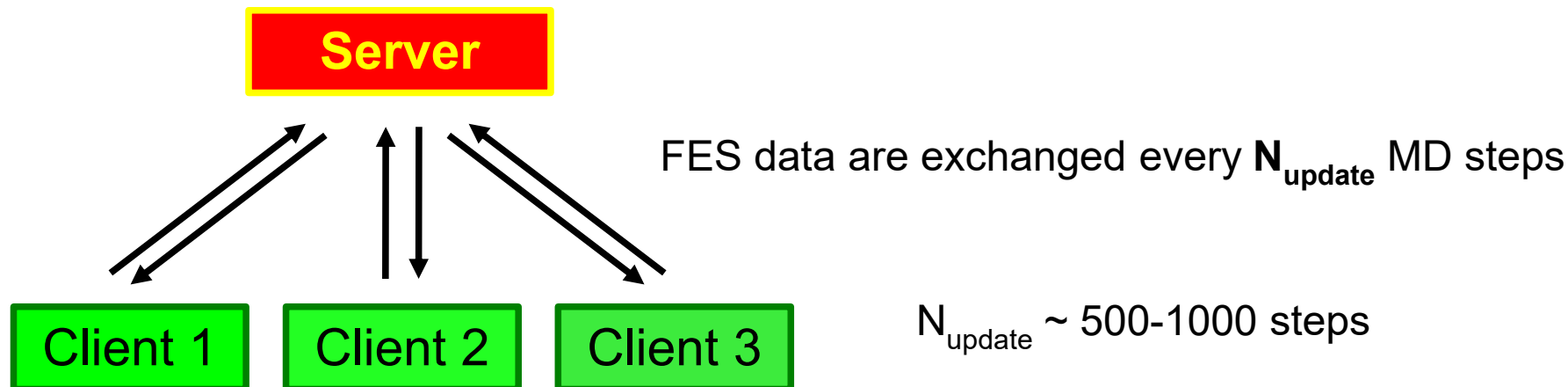


Show movie?

ξ range from -6.5 to 6.5 Å, 130 bins
2 ns long simulation
300 K, vacuum, GAFF force field, time step 1 fs

Multiple Walkers Approach

server collects information about free energy surface (FES) and redistributes it among clients



Applicable to:

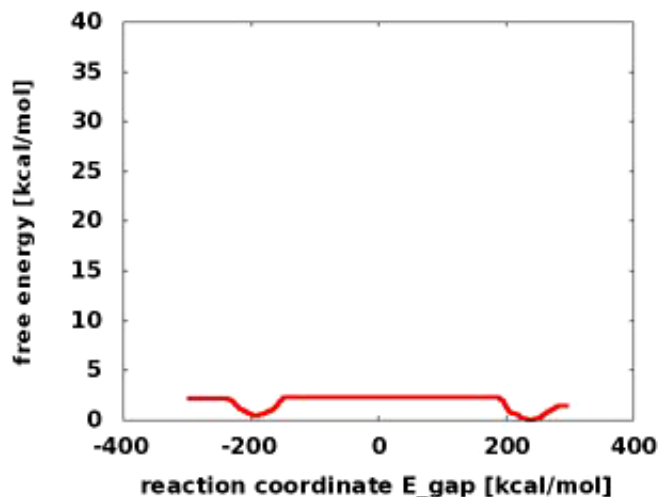
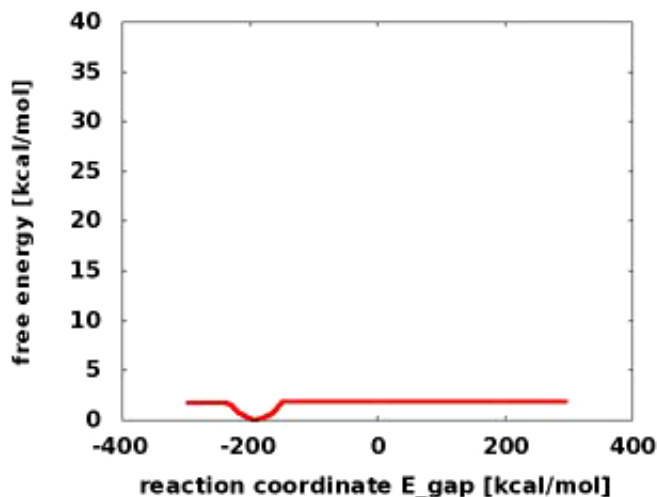
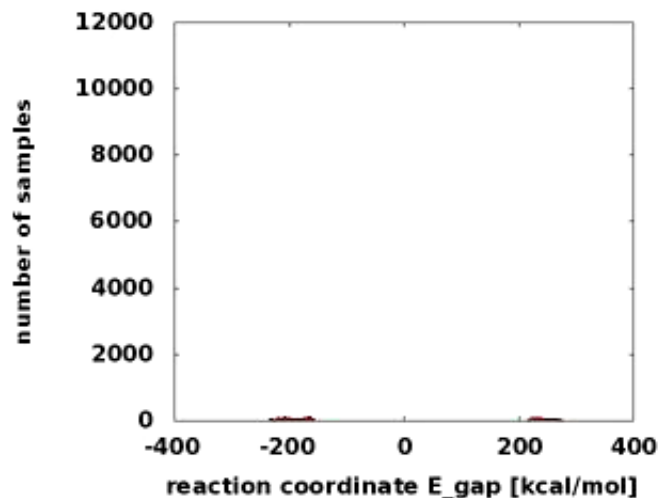
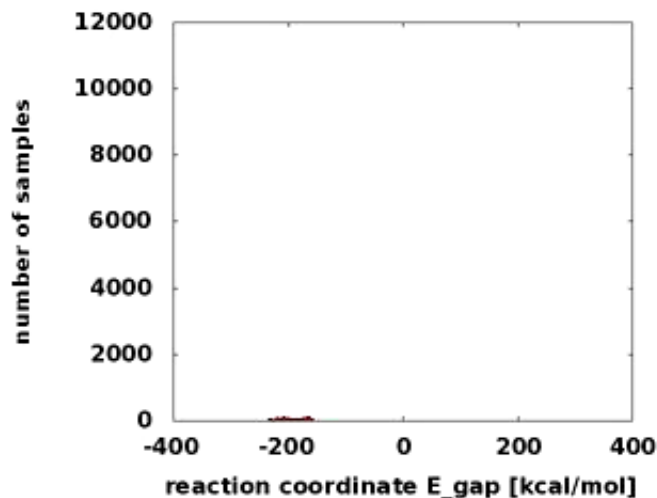
- Metadynamics
- Adaptive biasing force

Advantages:

- Faster convergence
- Easy to implement
- Parallel scaling is almost linear

Multiple Walkers Approach

Nucleophilic substitution reaction (test case)

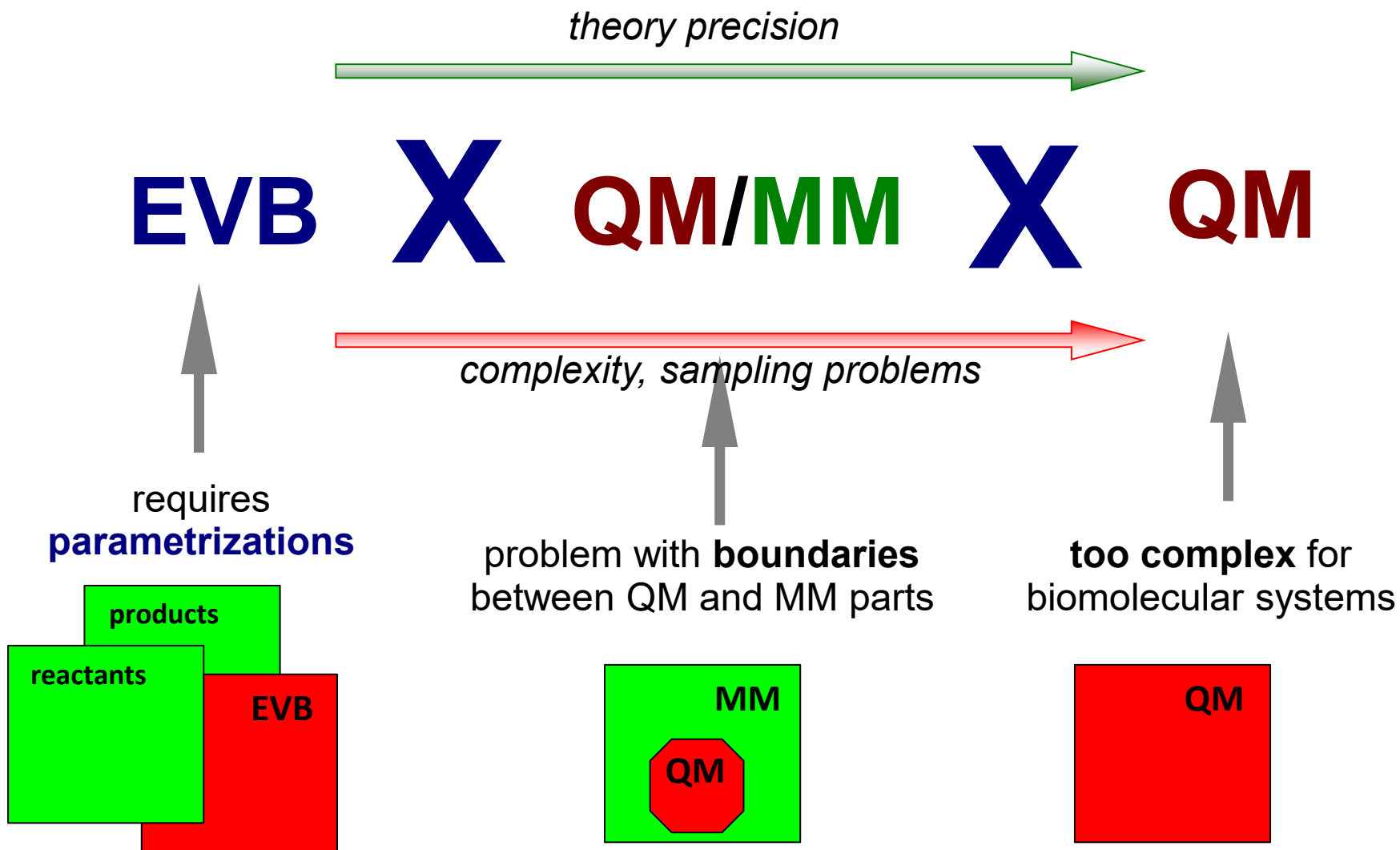


One walker
(from reactants)

Two walkers
(from reactants and products)

Molecular Dynamics and Reactions

Description of Chemical Reactions



CPMD

Car-Parrinello

Molecular Dynamics

Method

$$\mathcal{L}_{\text{CP}}[\mathbf{R}^N, \dot{\mathbf{R}}^N, \{\Phi_i\}, \{\dot{\Phi}_i\}] = \sum_I \frac{1}{2} M_I \dot{\mathbf{R}}_I^2 + \sum_i \mu \langle \dot{\Phi}_i | \dot{\Phi}_i \rangle - \mathcal{E}^{\text{KS}} [\{\Phi_i\}, \mathbf{R}^N]$$

Equations of motion:

$$M_I \ddot{\mathbf{R}}_I = -\frac{\partial E^{\text{KS}}}{\partial \mathbf{R}_I} + \sum_{ij} \Lambda_{ij} \frac{\partial}{\partial \mathbf{R}_I} \langle \Phi_i | \Phi_j \rangle \quad \text{ions}$$
$$\mu | \ddot{\Phi}_i \rangle = -\frac{\delta E^{\text{KS}}}{\delta \langle \Phi_i |} + \sum_j \Lambda_{ij} | \Phi_j \rangle \quad \text{wavefunction}$$

fictitious mass of wavefunction
(ca 300-700 a.u. , **typical value is about 600 a.u.**)

constraints due to
orthonormality of wavefunction

CPMD versus BOMD

CPMD

- no SCF procedure
- motion of ions in time
- motions of wavefunction in time
- time step ~ 0.1 fs (5 a.u.)

- DFT only (in CPMD)
- hybrid functional possible but very slow
- dispersion correction available

- planewaves wavefunction (periodicity!)
- wavefunction quality is determined by cutoff (single value)
- pseudopotentials required (core electrons)

BOMD

- SCF procedure
- motion of ions in time only
- wavefunction follows ions by SCF (BO)
- time step max ~ 1 fs
- gradients require very tight convergence of wavefunction optimization