Metadynamics & *CPMD*

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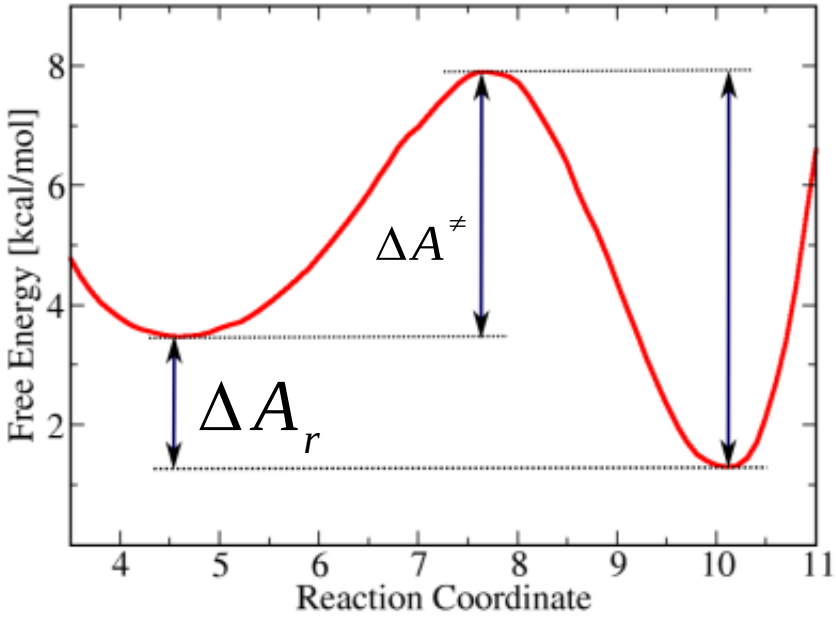
Free Energy Calculations

Free Energy

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

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

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



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

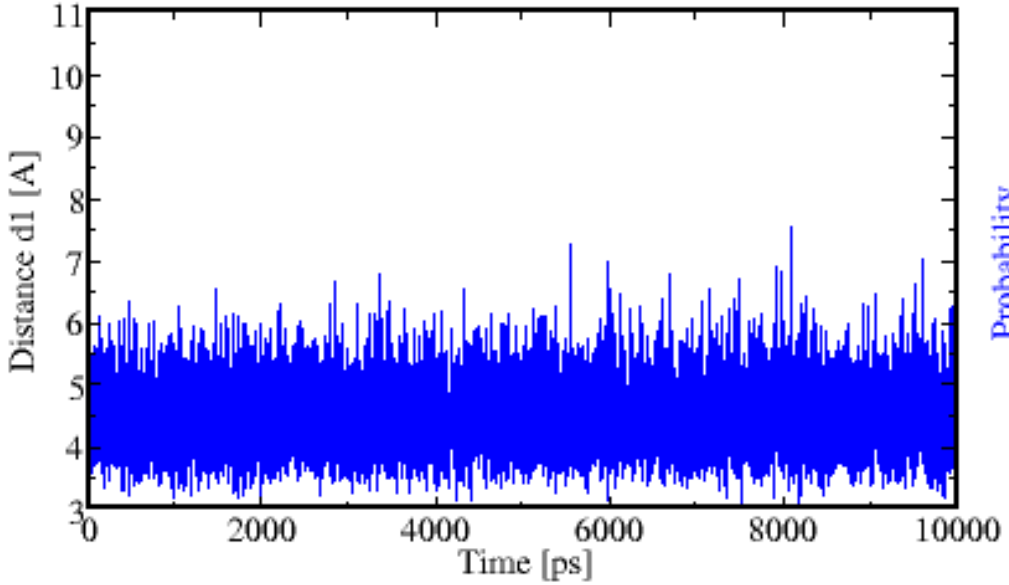
$$\Delta A_{1\to 2} = -RT \ln \frac{\sigma_2}{\sigma_1}$$

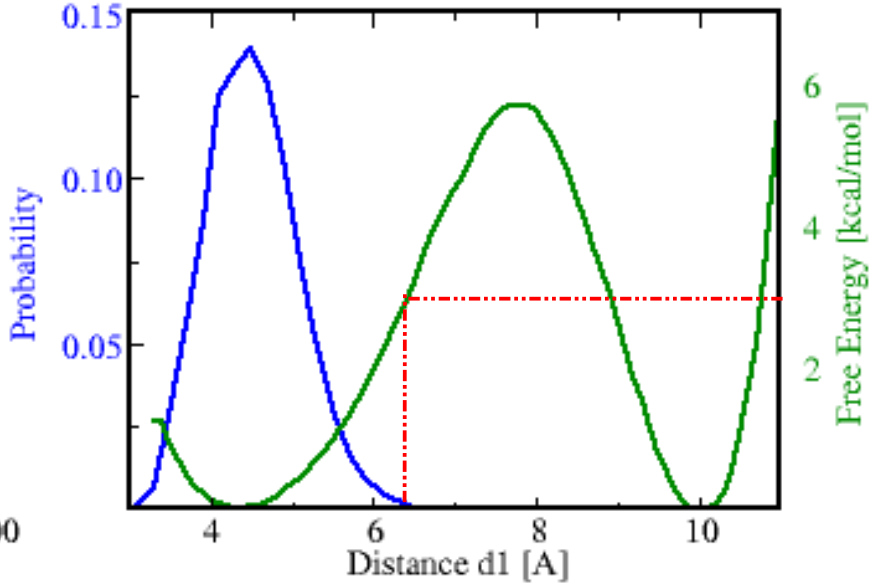
Density of state (probability)
It can be calculated from molecular dynamics or Monte Carlo simulations, **but …**

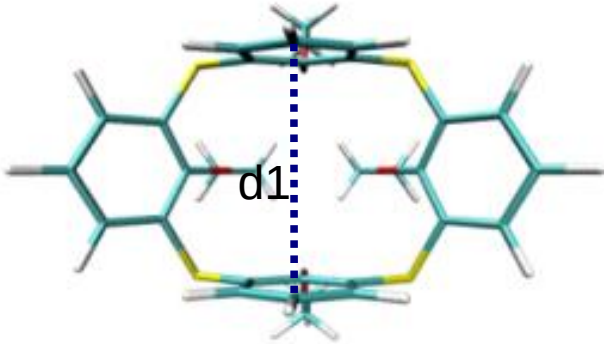
$$A(\xi) = -RT \ln \sigma(\xi) + A_0$$

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

Implemented in CPMD

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

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

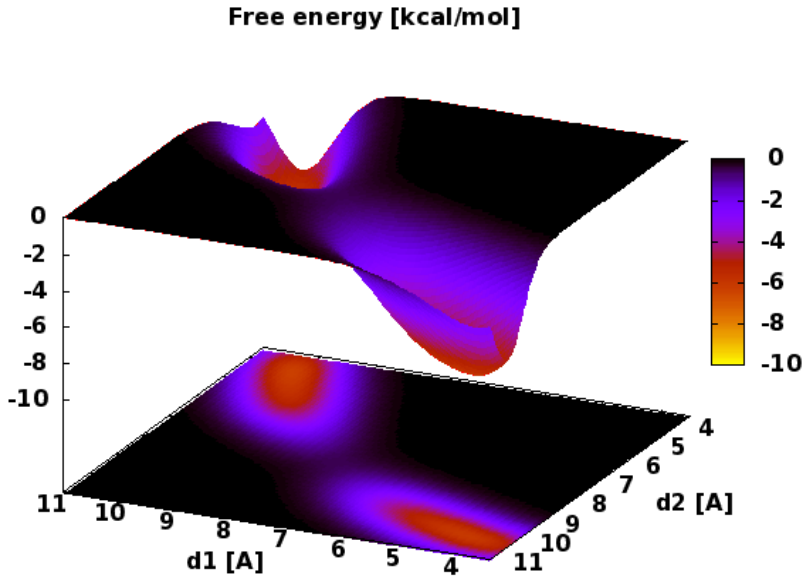
Equations of MTD motion (direct approach)

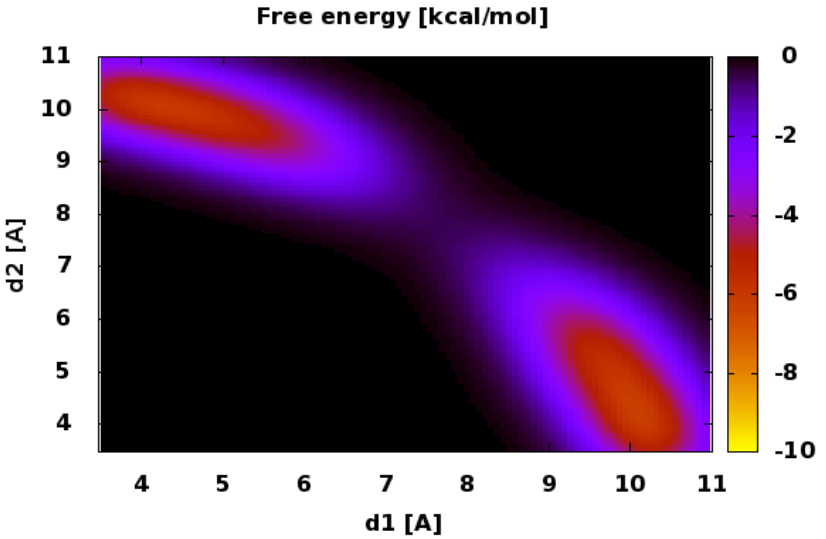
$$m_i \frac{d^2 x_i(t)}{dt^2} = -\frac{\partial}{\partial x_i}\{V(x) + V_h(x,i)\}$$

History-dependent term converges to FES

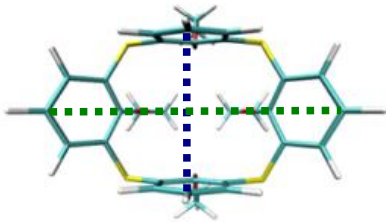
$$A(s) = \lim_{i \to \infty} -V_h(i,s)$$

Metadynamics, example



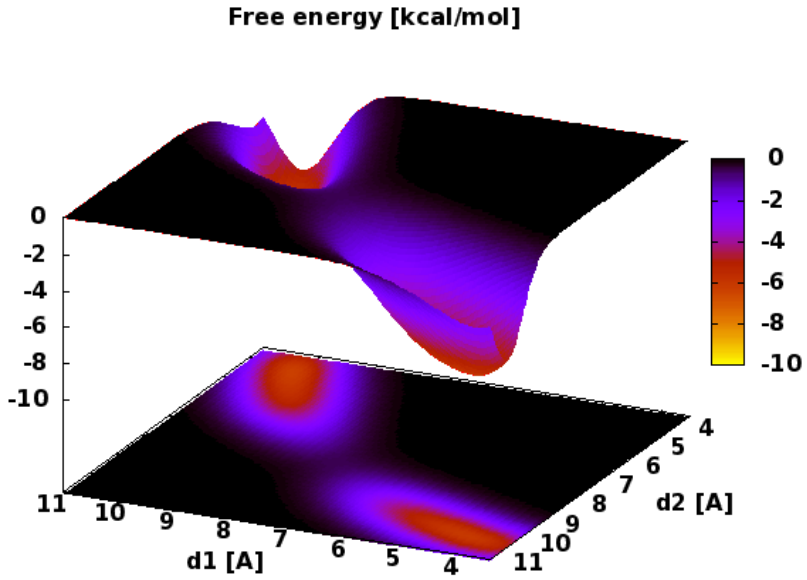


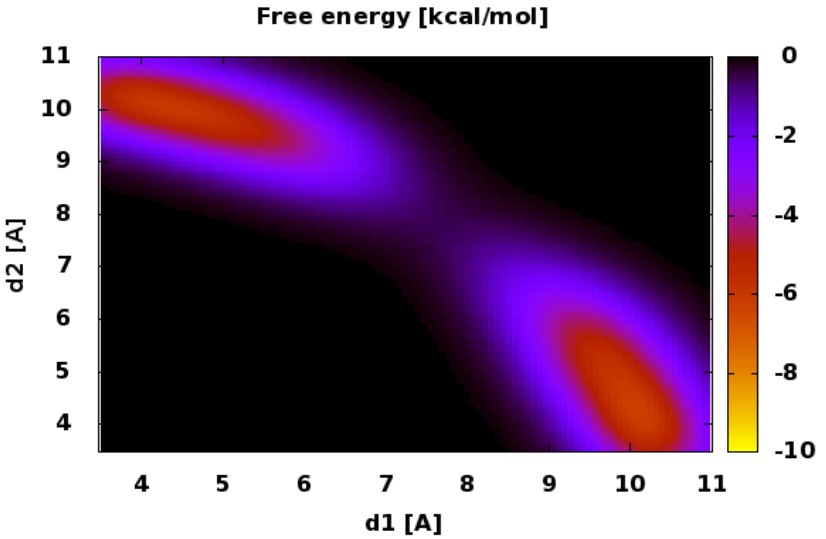
hill height 0.01 kcal/mol, width 0.5 x 0.5 Å
MTD frequency 500 fs
2 ns long simulation
300 K, vacuum, GAFF force field, time step 0.5 fs



DIS (distance)

Metadynamics, example





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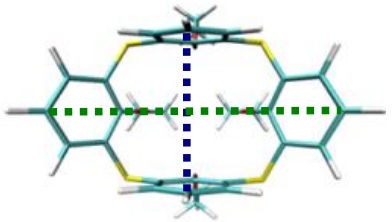


DIS (distance)

Constrained Dynamics

Implemented in CPMD

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

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

method of Lagrange multipliers

Equations of constrained motion

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

λ_k = Lagrange multipliers

Constrained Dynamics, theory

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

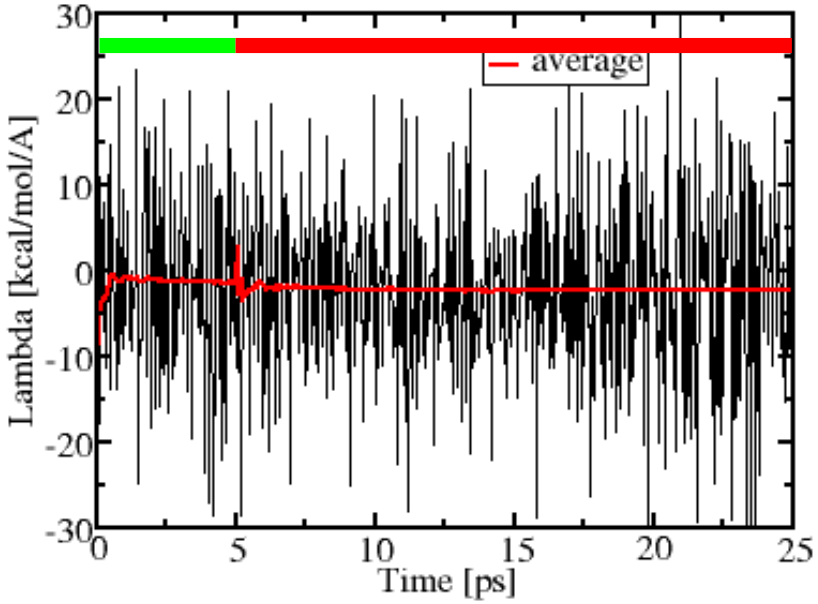
$$\frac{dA^{uc}(\xi)}{d\xi} = \frac{dA^{c}(\xi)}{d\xi} + \frac{dA^{c\to uc}(\xi)}{d\xi} = \left\langle -\lambda \right\rangle_{\xi_0} - RT\,\frac{d}{d\xi}\ln\left\langle Z^{-1/2}\right\rangle_{\xi_0}$$

second derivatives are not required

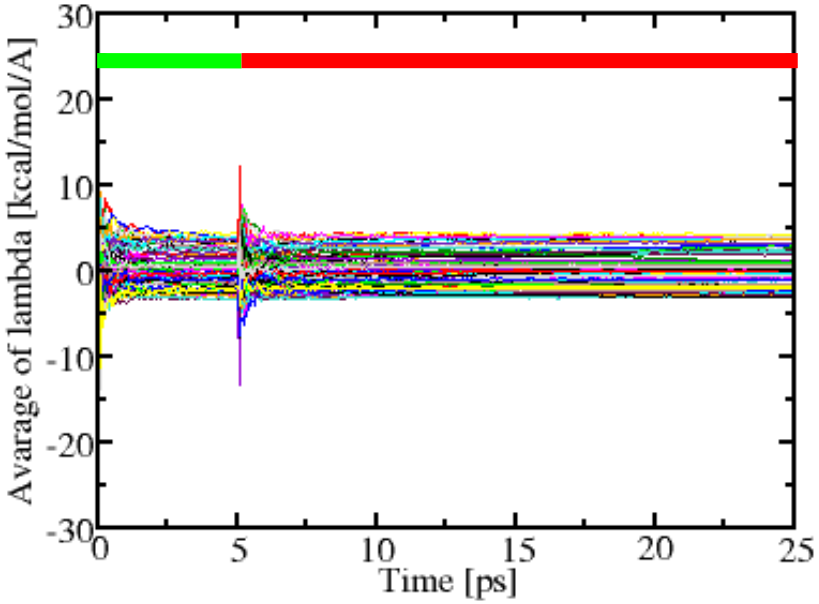
Final free energy is obtained by numerical **integration**:

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

Constrained Dynamics, example

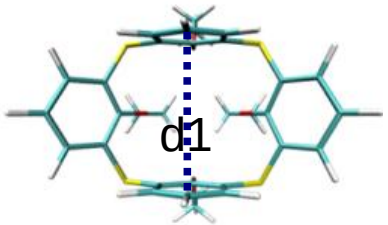


70 points



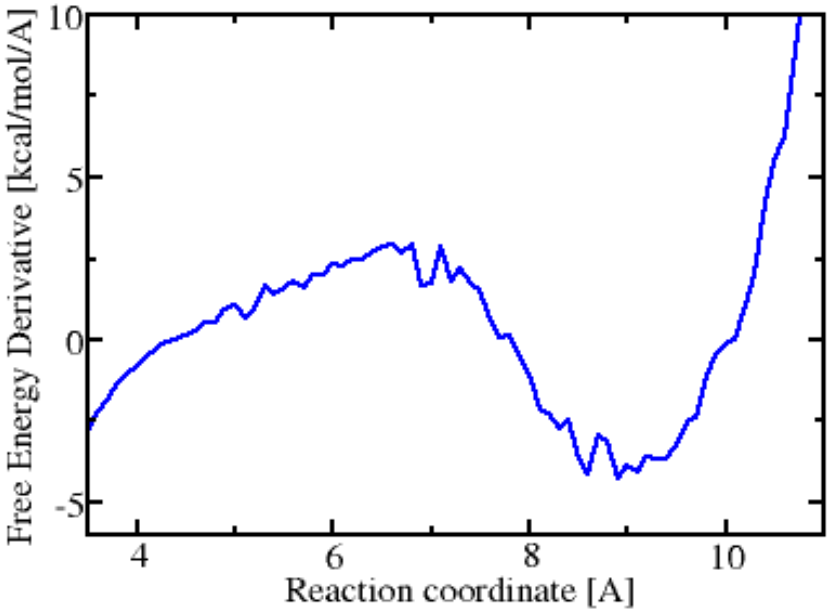
Small numbers are calculated by averaging big numbers.

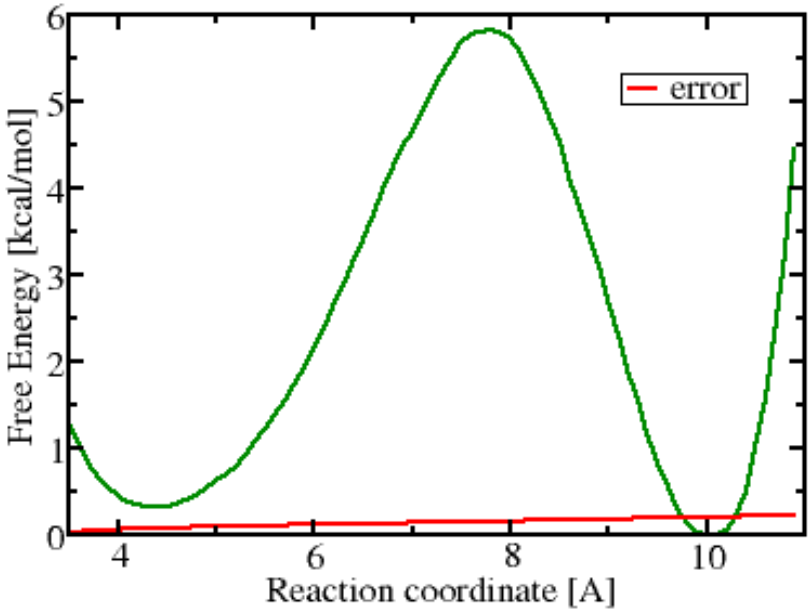
77 points, $\Delta\xi$ 0.1 Å
Method B: 5 ps shift, 5 ps equilibration, 20 ps production
300 K, vacuum, GAFF force field, time step 1 fs / 0.5 fs



DIS (distance)

Constrained Dynamics, example





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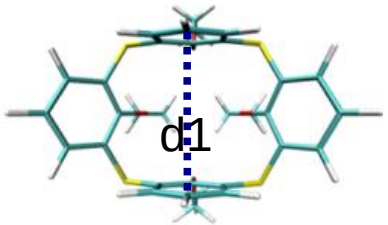
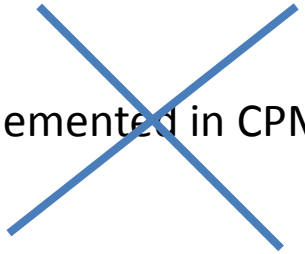


DIS (distance)

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:

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

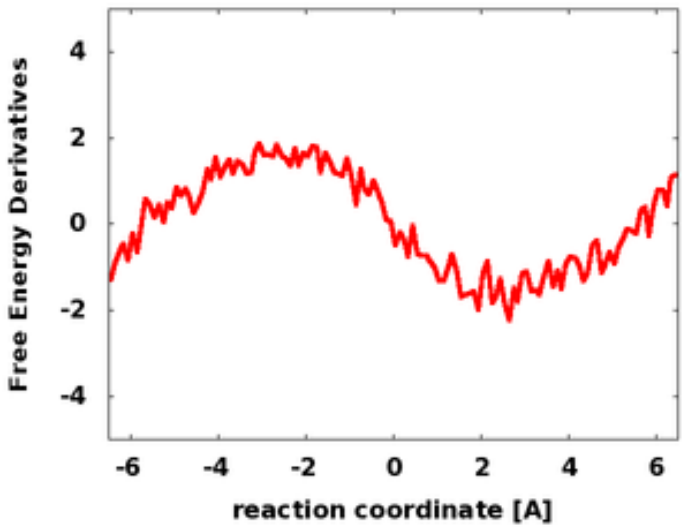
it contains the second derivatives of reaction coordinate if treated analytically

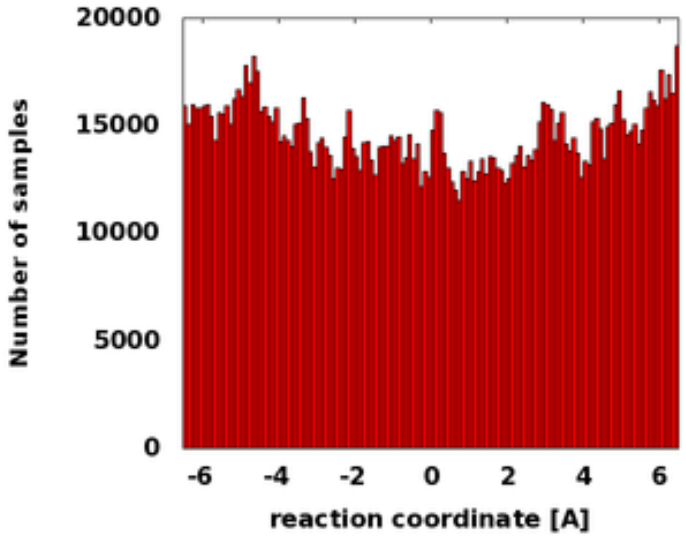
equation is solved **numerically**

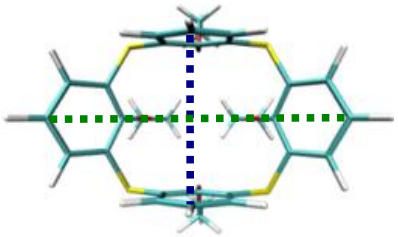
Procedure:

- 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

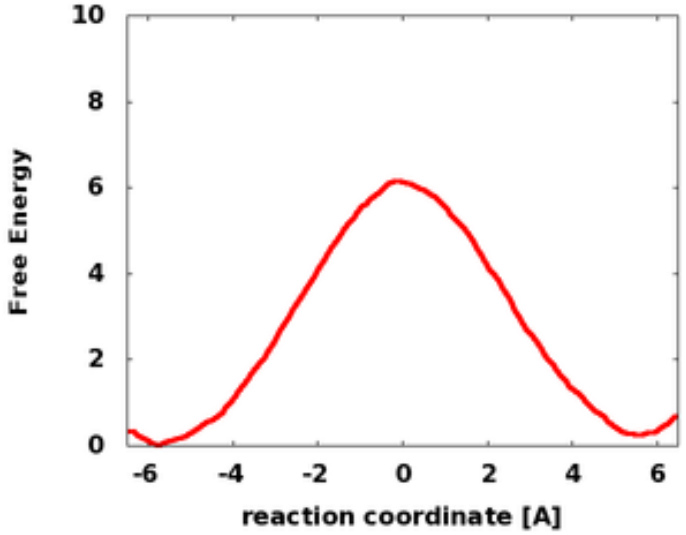
ABF, example







DD
(difference of distances)

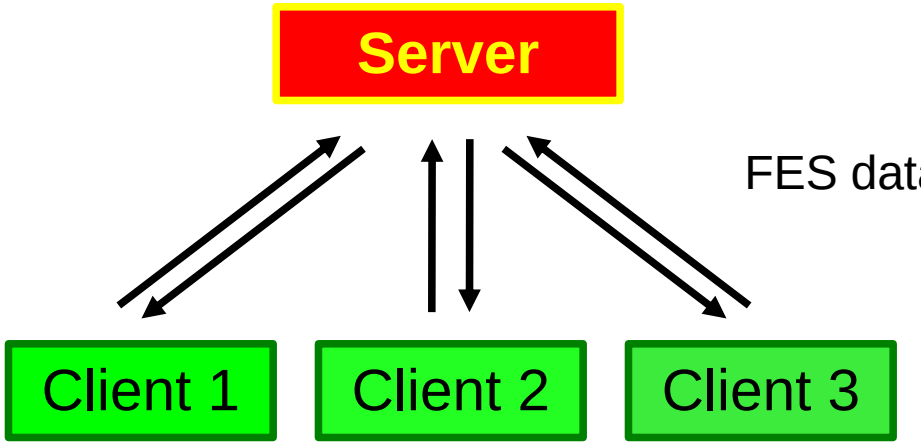


Show movie?

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



FES data are exchanged every $\mathbf{N_{update}}$ MD steps

N_{update} ~ 500-1000 steps

Applicable to:

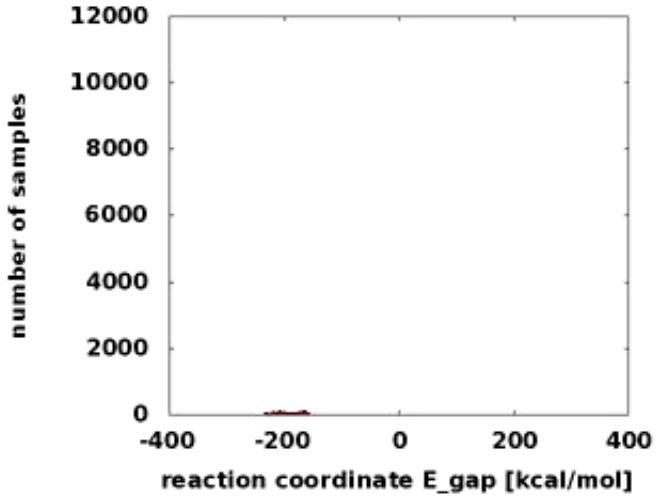
- Metadynamics
- Adaptive biasing force

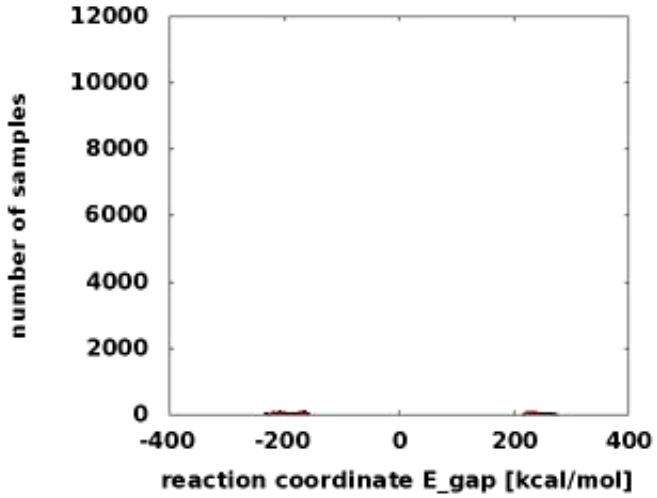
Advantages:

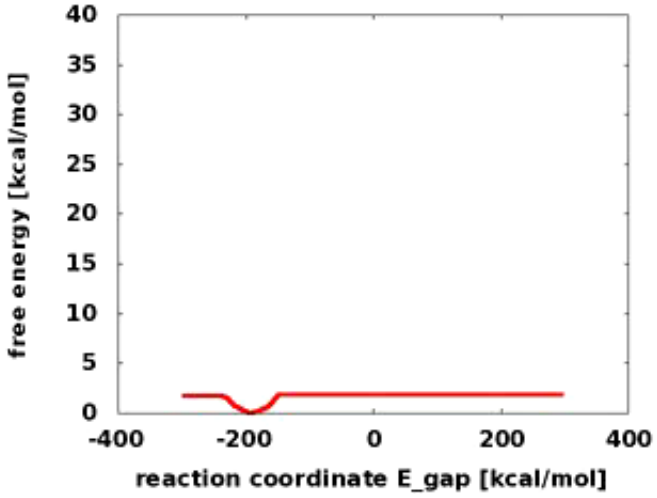
- Faster convergence
- Easy to implement
- Parallel scaling is almost linear

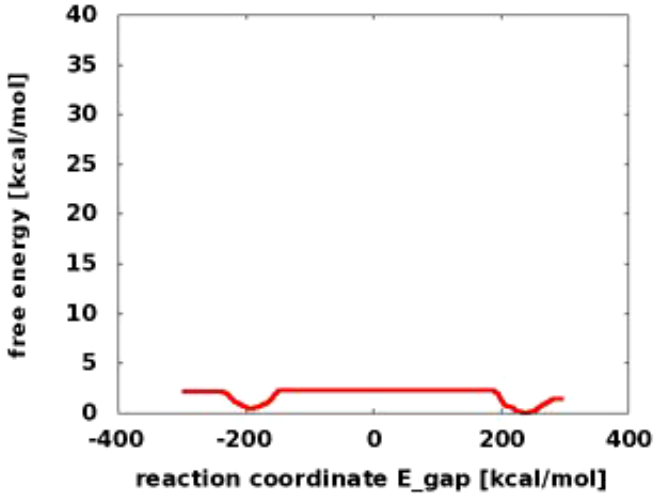
Multiple Walkers Approach

Nucleophilic substitution reaction (test case)









One walker
(from reactants)

Two walkers
(from reactants and products)

PMFLib

A Toolkit for Free Energy Calculations

developed by
Petr Kulhánek

PMFLib, functionality

Implemented methods:

- Constrained dynamics (BM)
- Adaptive biasing force (ABF)
- Metadynamics (MTD)
- Umbrella sampling
- Multiple walker MTD
- Multiple walker ABF
- Replica Exchange Dynamics
- String Method

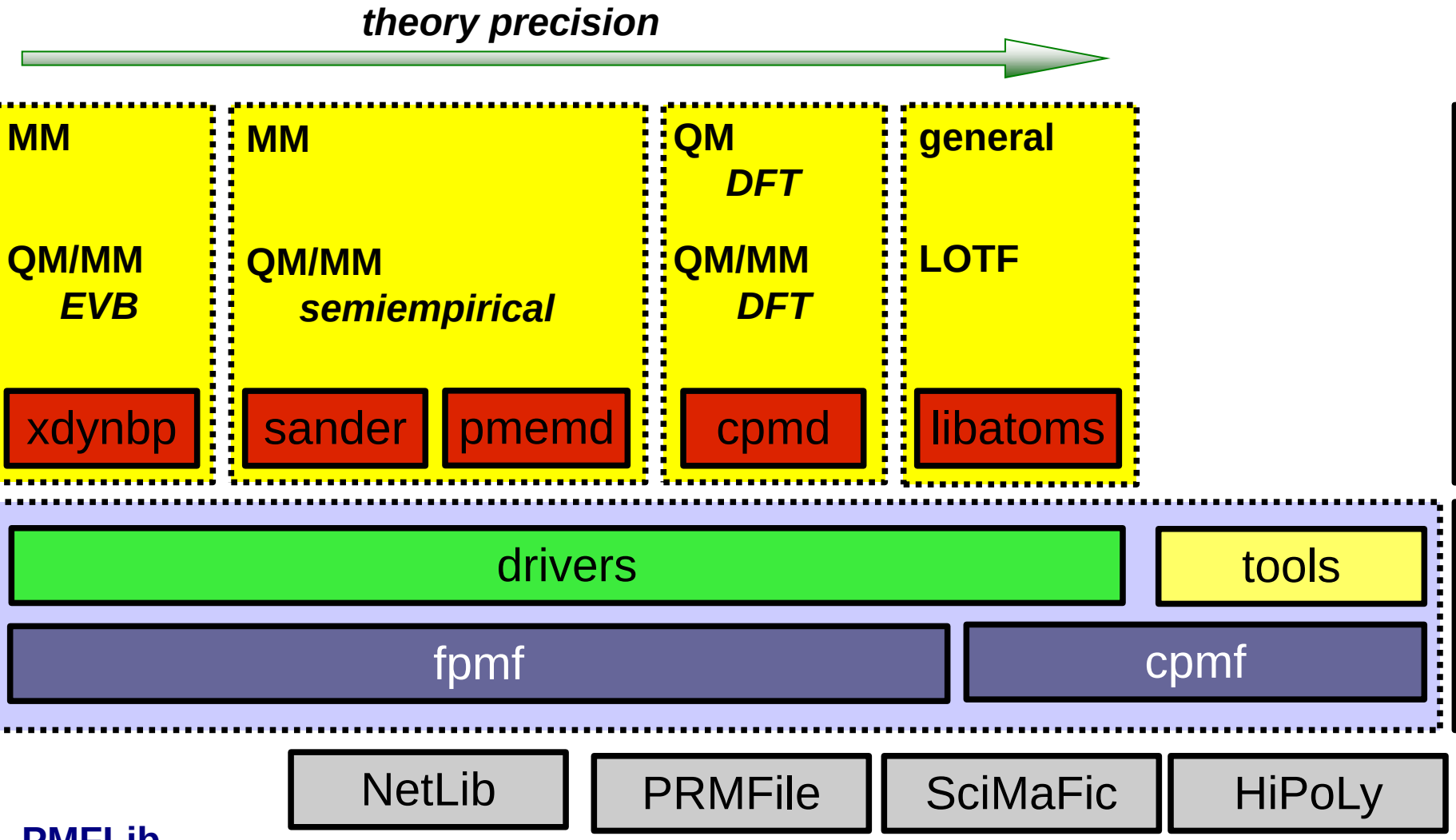
Reaction coordinates:

- DIS, DS
- DD, DDS
- ODISM, ODSM
- ANG, ANGM, CANG, CANGM
- DIH, DIHM
- AC, GC
- RGYR
- RMSDT, RMSDL
- EPOT, EGAP and variants

Tools:

- MTD energy
- BM integration
- ABF integration
- Multiple walker MTD – server and administration client
- Multiple walker ABF – server and administration client

PMFLib, design

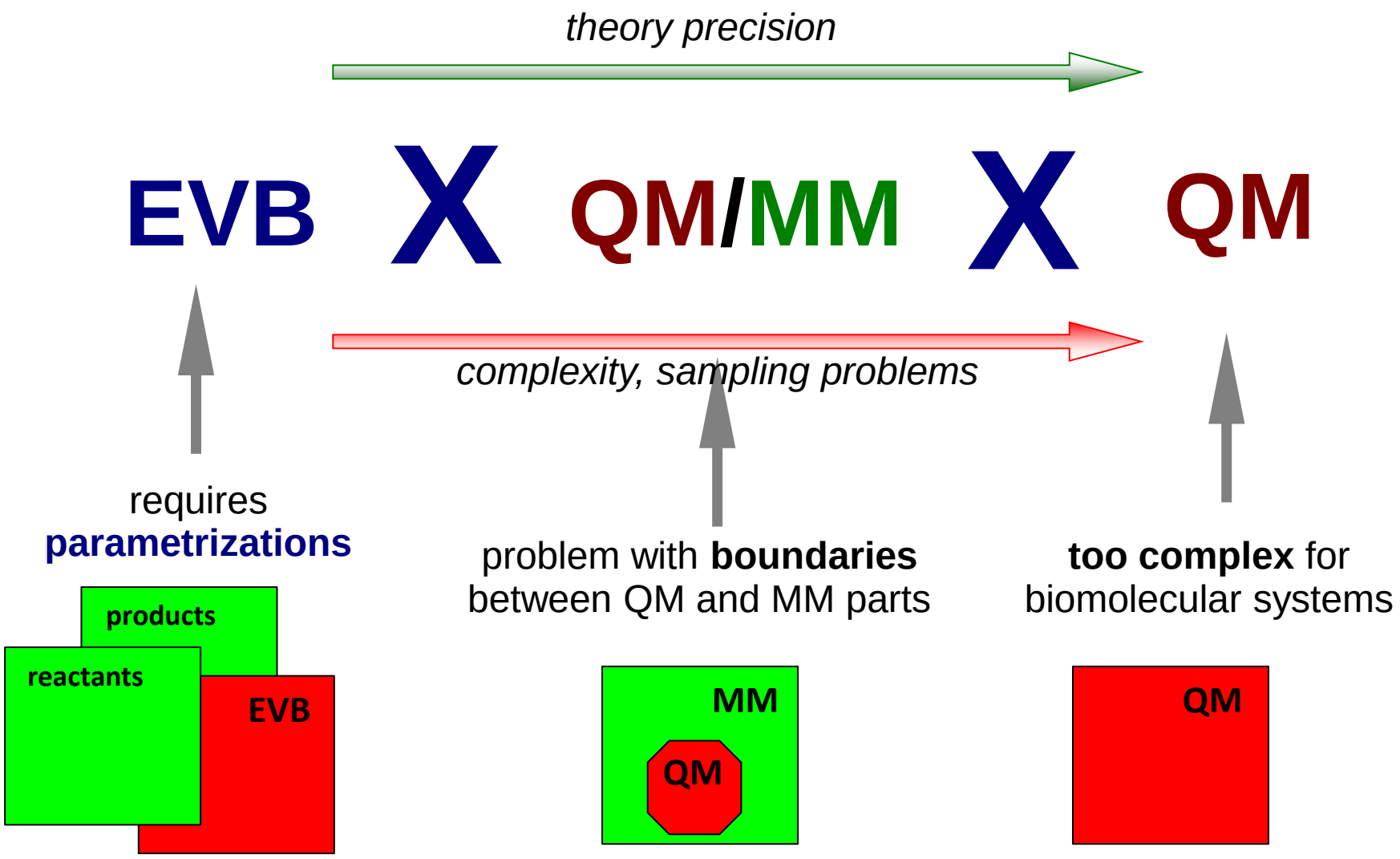


PMFLib

- Fortran 90 (162 files / ~25000 lines)
- C/C++ (178 files / ~24000 lines)

Molecular Dynamics and Reactions

Description of Chemical Reactions



CPMD
Car-Parrinello Molecular Dynamics

Method

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

Equations of motion:

$$M_I \ddot{\mathbf{R}}_I = -\frac{\partial E^{\mathrm{KS}}}{\partial \mathbf{R}_I} + \sum_{ij} \Lambda_{ij} \frac{\partial}{\partial \mathbf{R}_I} \langle \Phi_i \mid \Phi_j \rangle$$ ions

$$\mu \mid \ddot{\Phi}_i \rangle = -\frac{\delta E^{\mathrm{KS}}}{\delta \langle \Phi_i \mid} + \sum_j \Lambda_{ij} \mid \Phi_j \rangle$$ 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.)

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

- 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)

Practicals …

- read manual (it was very improved in the last version) !
- read two chapters from NIC books about CPMD (about 150 pages), freely downloadable
- be veeeery patient

Typical setup:

- time step 5 a.u.
- WF mass 600 a.u.
- pseudopotentials: Troulier-Martins normconserving
- WF cutoff: 70 Rydbergs
- charged/isolated systems (also in QM/MM calculations)
  - add 2-3A to box dimensions, molecule has to be centered!!!
  - Poission solver: Tuckerman
- heating: Berendsen thermostat
- production: Nose-Hoover thermostat
- ultrasoft Vanderbilt pseudopotential are problematic for Mg

Practicals in smaller group.

Acknowledgements

- Igor Tvaroška, Stanislav Kozmon
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