General vs. geometrical reaction coordinates on QM and QM/MM surfaces

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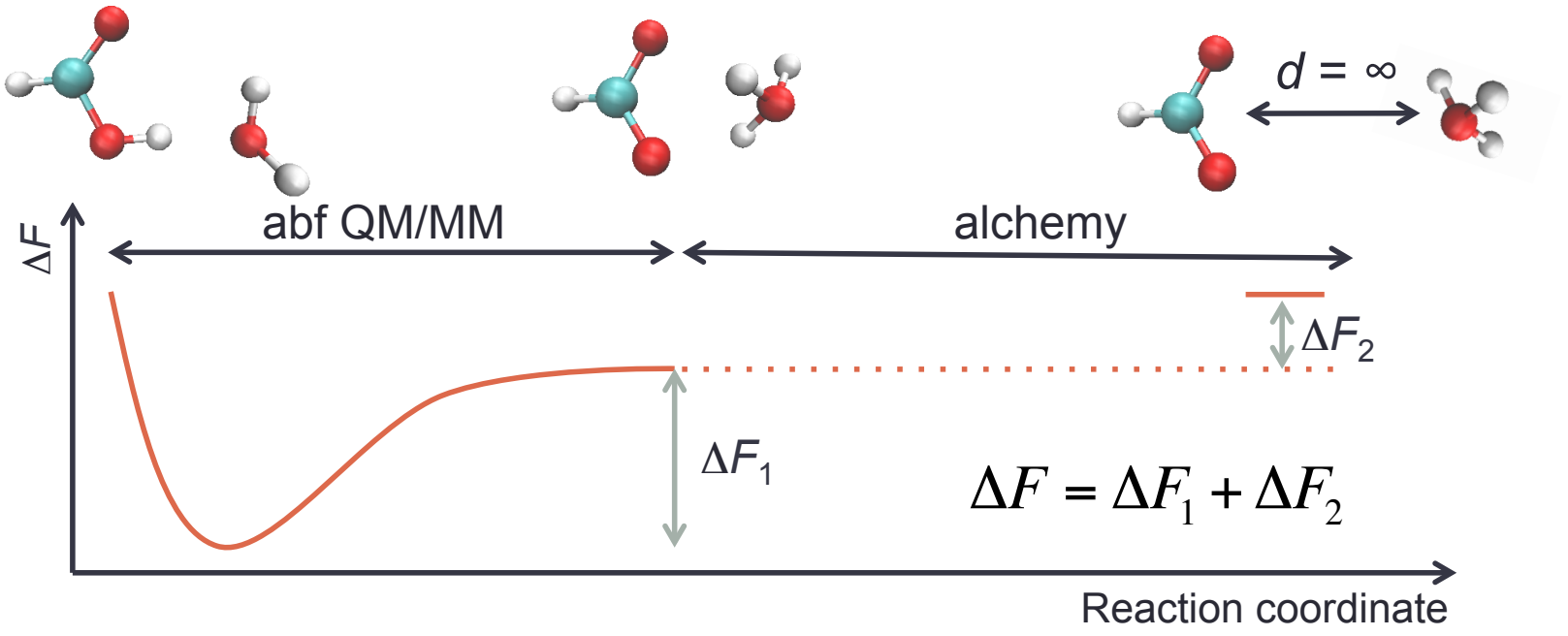
Preliminaries

- pK_a calculation of weak acids in:
  - water solution
  - enzymatic environment
- strategy:
  - adaptive buffered-force QM/MM
  - classical alchemical transformation

$$pK_a = \frac{\Delta F}{RT \ln 10}$$



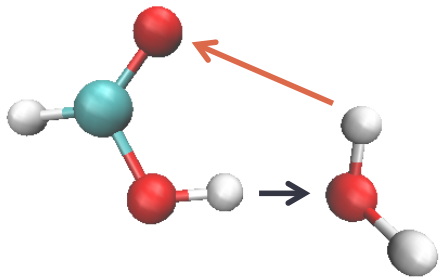
What should be the reaction coordinate?

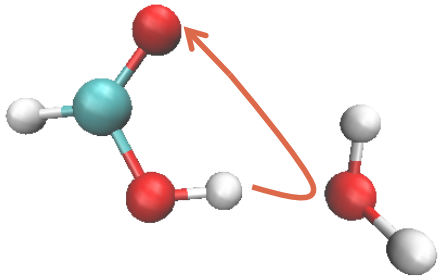
- geometrical coordinates:
  - distance
  - distance difference
  - coordination number

- problems with geometrical coordinates:

  general problem:
  - very few degrees of freedom of the reactants
  - hidden important effects are not taken into account
  - indication of TS is wrong
  - energetics (free energy profile) is also wrong

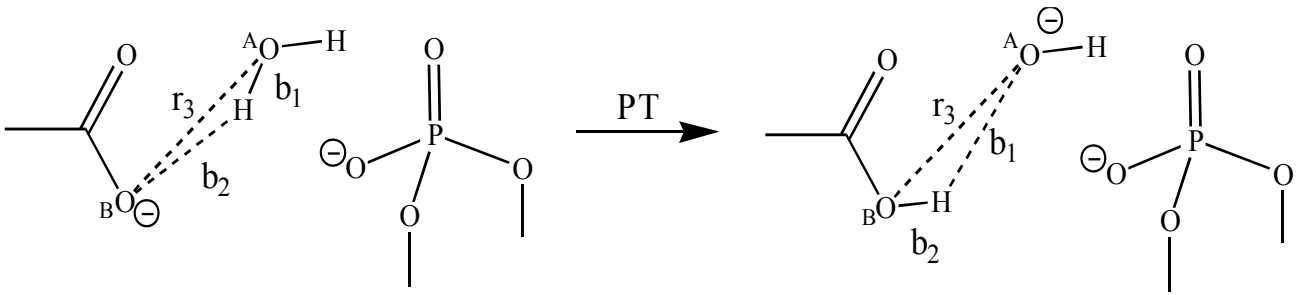
  specific problem:
  - permutation problem
  - several possible equivalent states
  - restraints/constraints lead to unrealistic geometry/profile





General reaction coordinate on classical surfaces: Egap

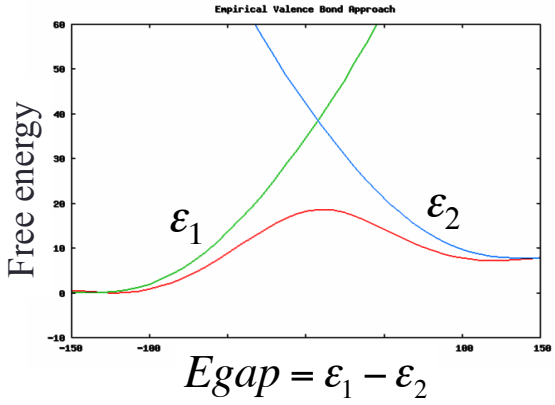
Original idea: EVB method *A. Warshel and R. M. Weiss, (1981) Ann. N Y Acad. Sci. **367**: 370*



1. resonance state ε_1 2. resonance state ε_2

$$\varepsilon_i(\mathbf{x}) = \sum_{q=1}^{N_q} D_q^i \left(1 - e^{-a_q^i (r_q - r_{0,q}^i)}\right)^2 + \sum_{j=1}^{N_k} U_{bond,j}^i + \sum_{j=1}^{N_{sz}} U_{angle,j}^i + \sum_{j=1}^{N_t} U_{torsion,j}^i + \sum_{k,l=1}^{N_{nk}} U_{nonbonded,kl}^i$$

Energy gap: $Egap(\mathbf{x}) = \varepsilon_1(\mathbf{x}) - \varepsilon_2(\mathbf{x})$



Extension of use of Egap for QM/MM surfaces

- Direct implementation of Egap:

Dynamics on QM/MM representation

$f_{QM}, f_{QM/MM}, f_{MM}$

coordinates →

← f_{bias}

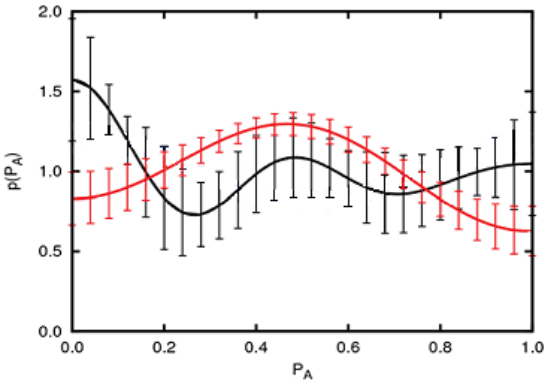
PMF(Egap) calculation on classical representation

$\varepsilon_1, \varepsilon_2, Egap = \varepsilon_1 - \varepsilon_2$

$$f_i = -\frac{\partial}{\partial r_i}\left[H^{QM/MM}(\mathbf{r},\Psi) + V_{bias}^{MM}\left(Egap(\mathbf{r}),t\right)\right]$$

- Egap works much better even on higher level surface:

Egap
DD



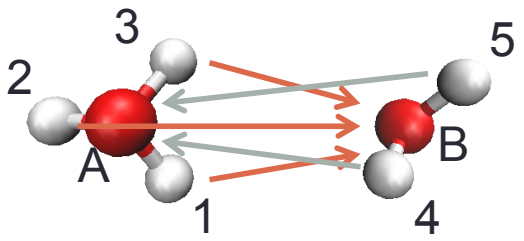
- good TS indication
- faster convergence

*L. Mones P. Kulhanek, I. Simon, A. Laio and M. Fuxreiter (2009) J. Phys. Chem. B **113**: 7867*

Model system for investigating multiple state reactions

- Reaction: $H_3O_A^+ + H_2O_B \rightarrow H_2O_A + H_3O_B^+$

  10 states 10 states



- Potential energy surface: QM(PM3-PDDG)/MM

  QM: reactants

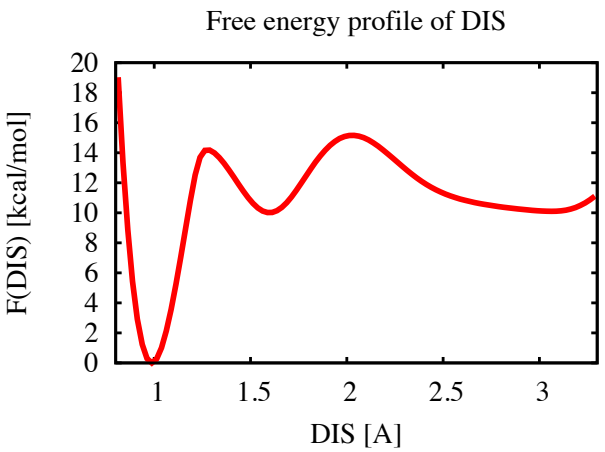
  MM: flexible TIP3P

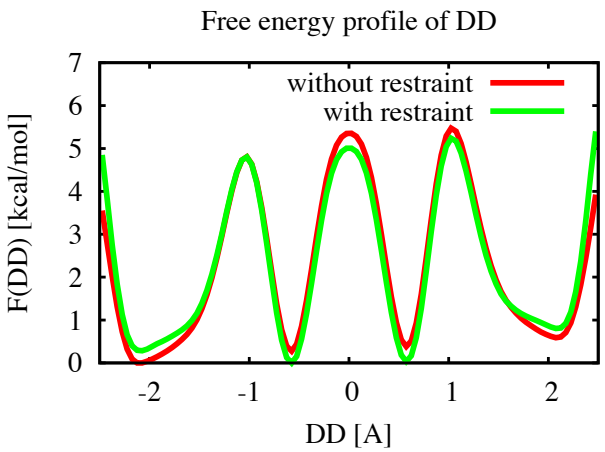
- Program: Amber9 + XdynBP/PMFlib

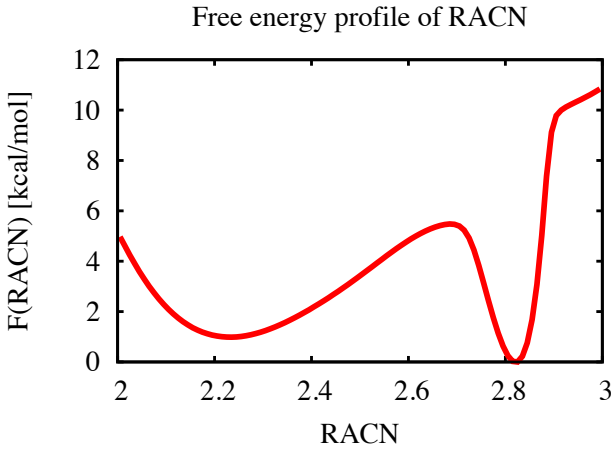
- Sampling: adaptive biasing force accelerated by multiple walker method

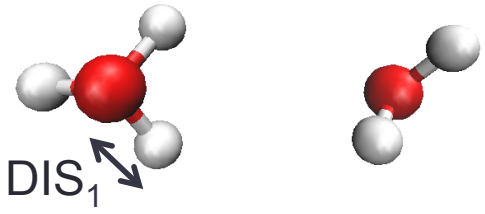
- Investigated collective variables:
  - Distance
  - Distance diff. with and without restraints
  - Rational coordination number
  - Egap variants

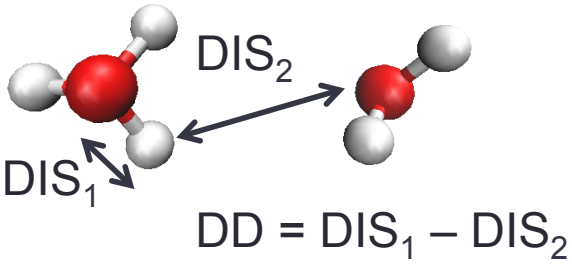
Free energy profiles of geometrical CVs

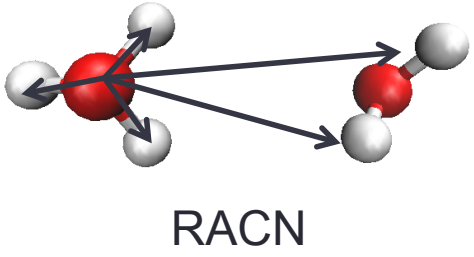






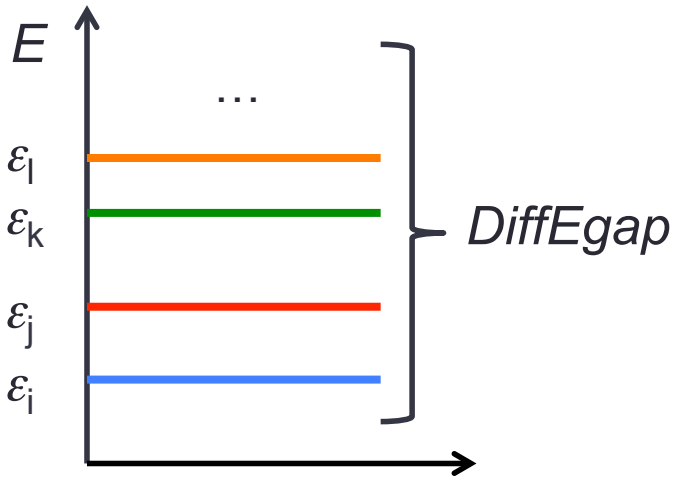


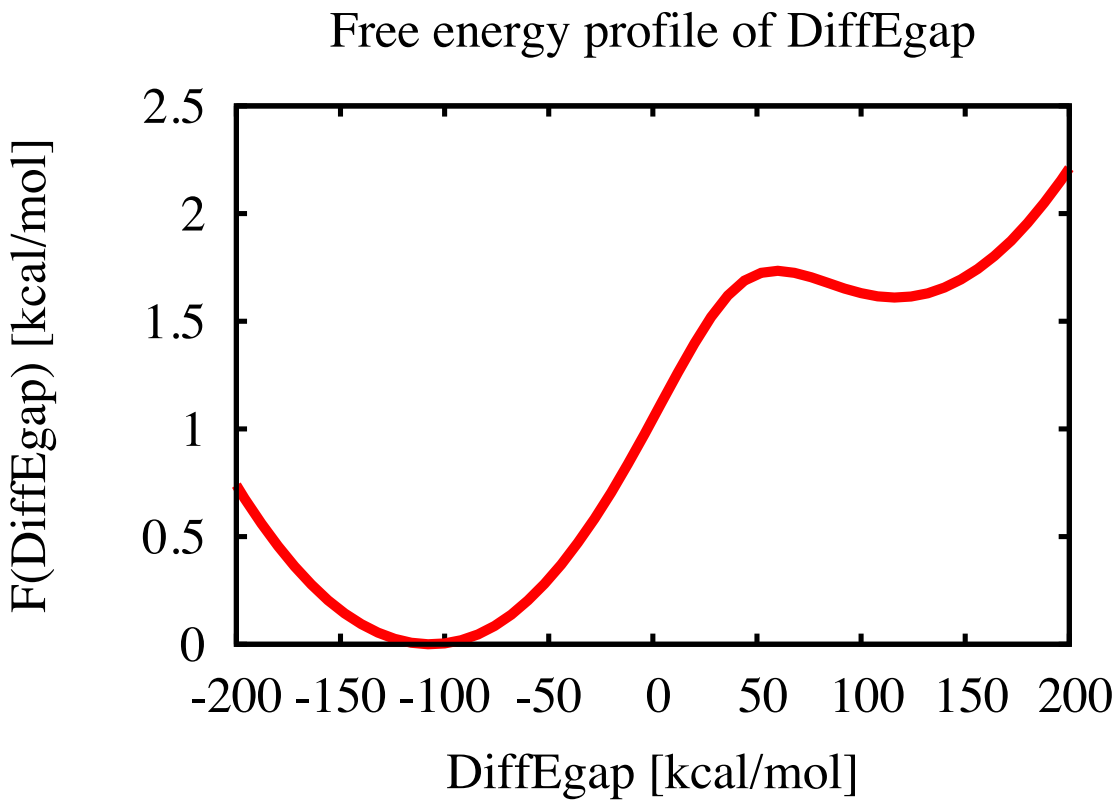




Free energy profile of DiffEgap

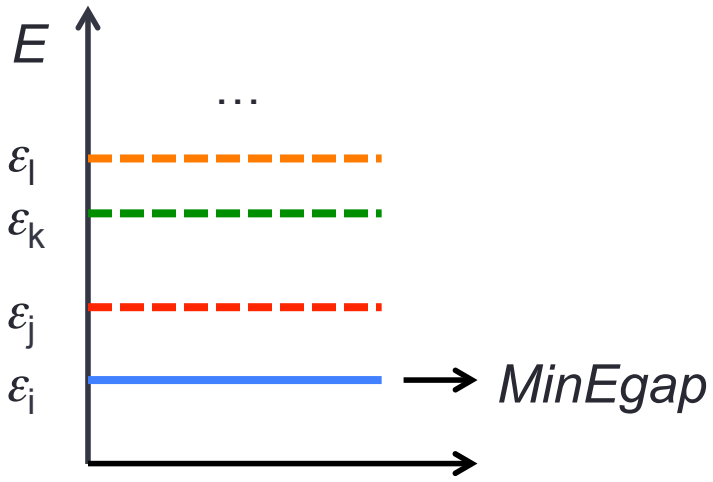
- natural extension of two-state Egap: $$DiffEgap = \frac{1}{n_R}\sum_i^{n_R} \varepsilon_i^R - \frac{1}{n_P}\sum_j^{n_P} \varepsilon_j^P$$

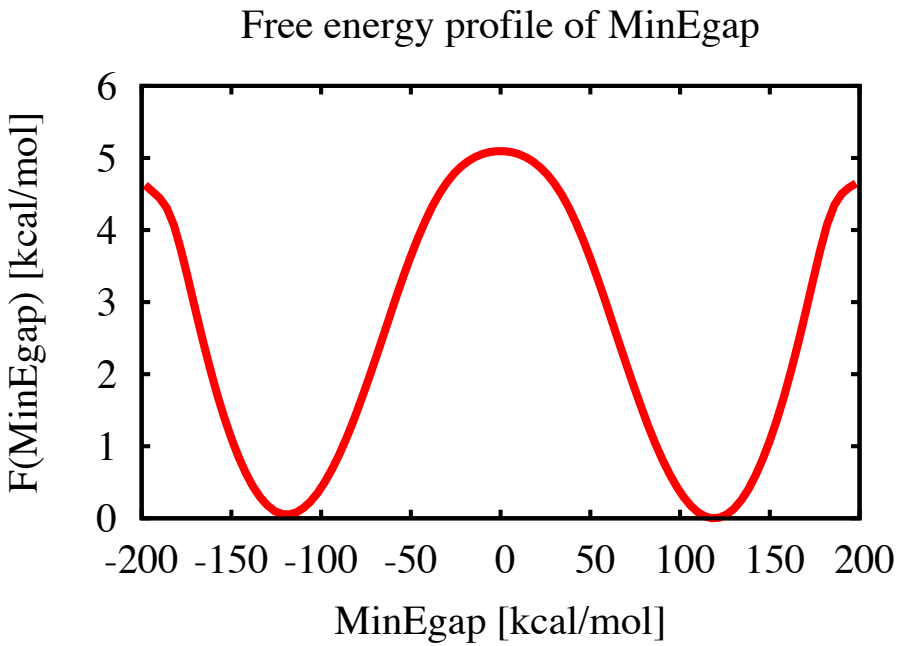




Selecting the corresponding states: MinEgap and EwEgap

- select the state with lowest energy $MinEgap = \min\left\{\varepsilon_i^R\right\}_i^{n_R} - \min\left\{\varepsilon_j^P\right\}_j^{n_P}$





- "continuous" version:

$$EwEgap = \frac{\sum_i^{n_R} e^{-\beta\varepsilon_i^R}\varepsilon_i^R}{\sum_k^{n_R} e^{-\beta\varepsilon_k^R}} - \frac{\sum_j^{n_P} e^{-\beta\varepsilon_j^P}\varepsilon_j^P}{\sum_l^{n_P} e^{-\beta\varepsilon_l^P}}$$

$$\lim_{\beta\to 0}\left(EwEgap\right) = DiffEgap$$

$$\lim_{\beta\to \infty}\left(EwEgap\right) = MinEgap$$

How good is the TS indication?

1. Reaction coordinate $\xi(\mathbf{r})$

MD — Sampling method

2. Free energy profile and indication of TS $\xi(\mathbf{r}) = \xi^{\ddagger}$

Constraint MD $\xi(\mathbf{r}) = \xi^{\ddagger}$

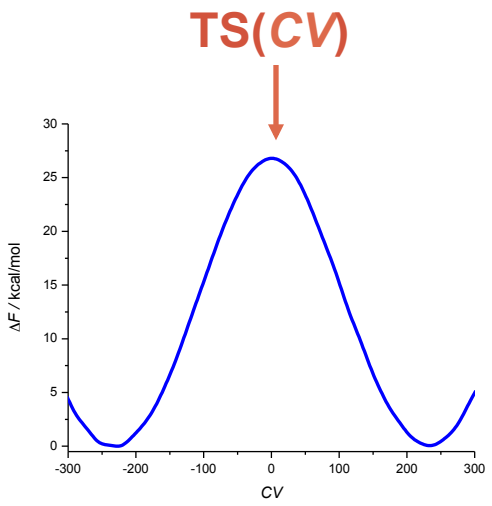
3. Configurations at the indicated TS

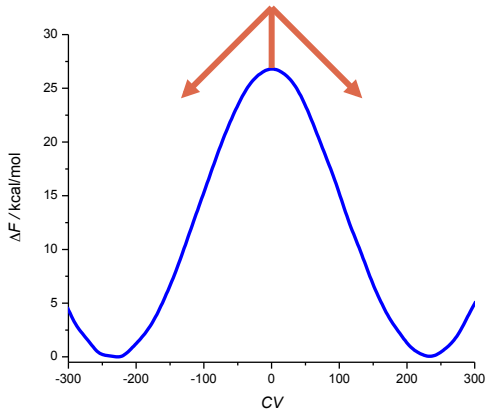
K_1 K_2 K_3 K_4 K_5 … K_n

Short MD trajectories — random velocities according to Maxweel-Boltzmann distr.

4. Sliding into the minima

K_1 K_2 K_3 K_4 K_5 … K_n





Results of committor analysis