Introduction to Numerical Simulations and High Performance Computing: From Materials Science to Biochemistry

UNIVERSITÉ DE STRASBOURG

Mauro Boero

EQUIP@MESO

IPCMS

Institut de Physique et Chimie des Matériaux de Strasbourg

University of Strasbourg - CNRS, F-67034 Strasbourg, France

Computational Materials Science Initiative

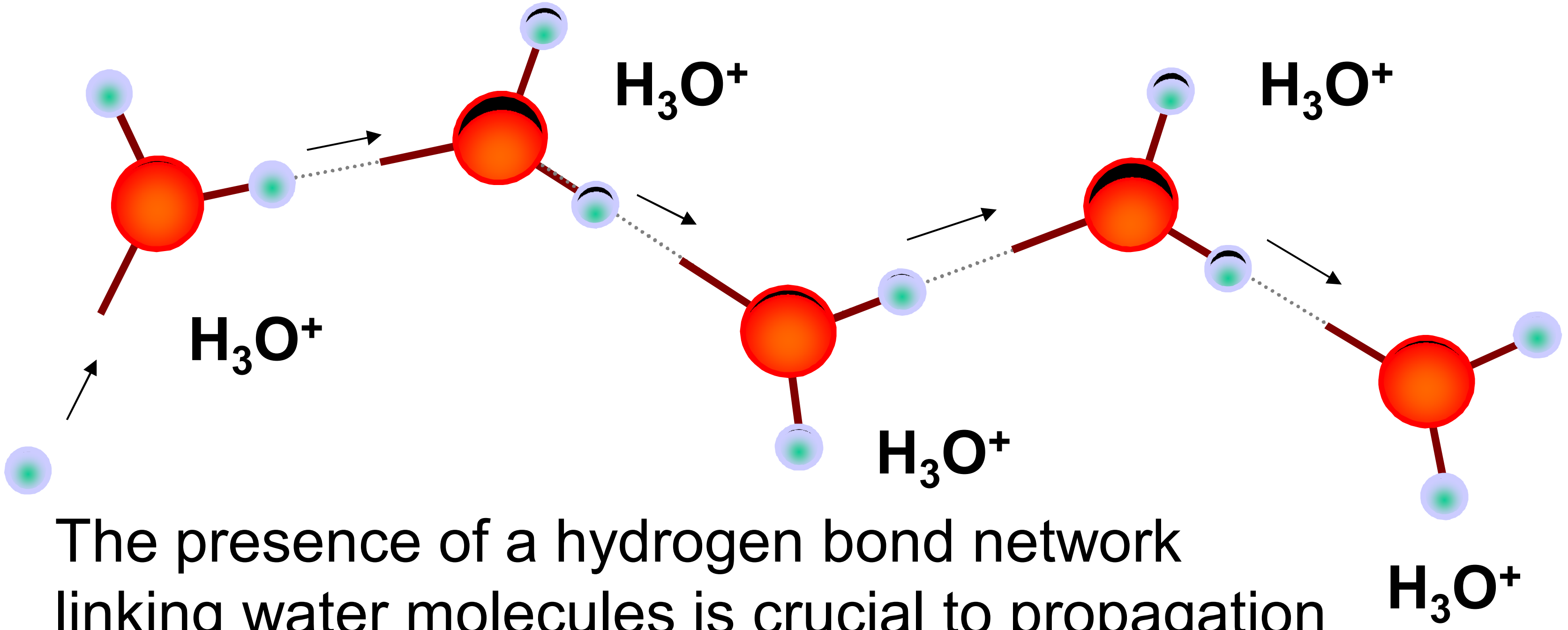
計算物質科学イニシアティブ

東京大学
THE UNIVERSITY OF TOKYO

@ Dept. of Applied Physics, The University of Tokyo,
7-3-1 Hongo, Tokyo 113-8656, Japan

Part 4:
Advanced Methods I
Reactive schemes

An example of dynamical ***chemical*** bond breaking and formation: first principles MD of the diffusion of protons in water (electronic structure becomes important…)



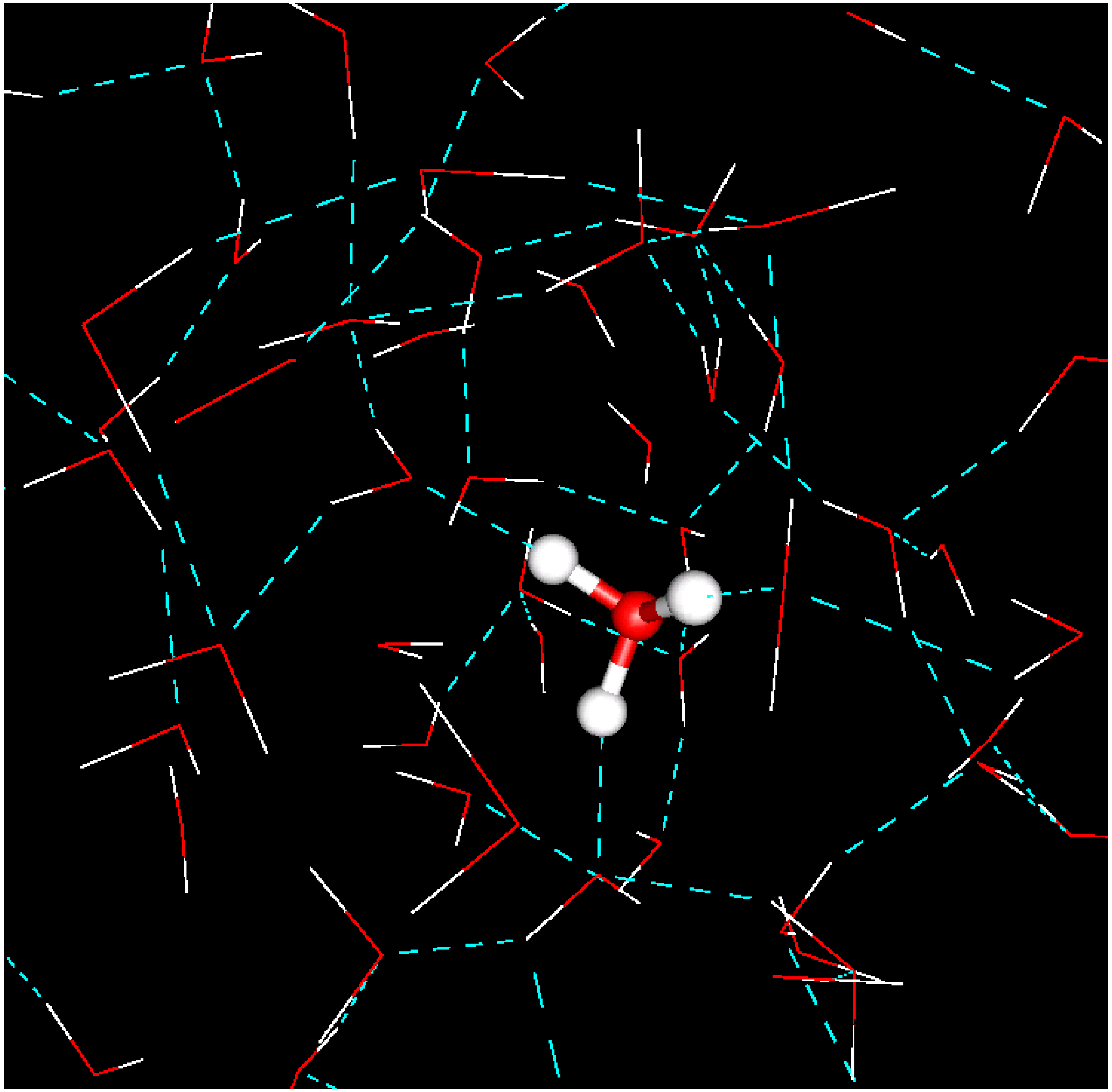
The presence of a hydrogen bond network linking water molecules is crucial to propagation

R. Pomès and B. Roux, *J. Phys. Chem.* **100**, 2519 (1996)

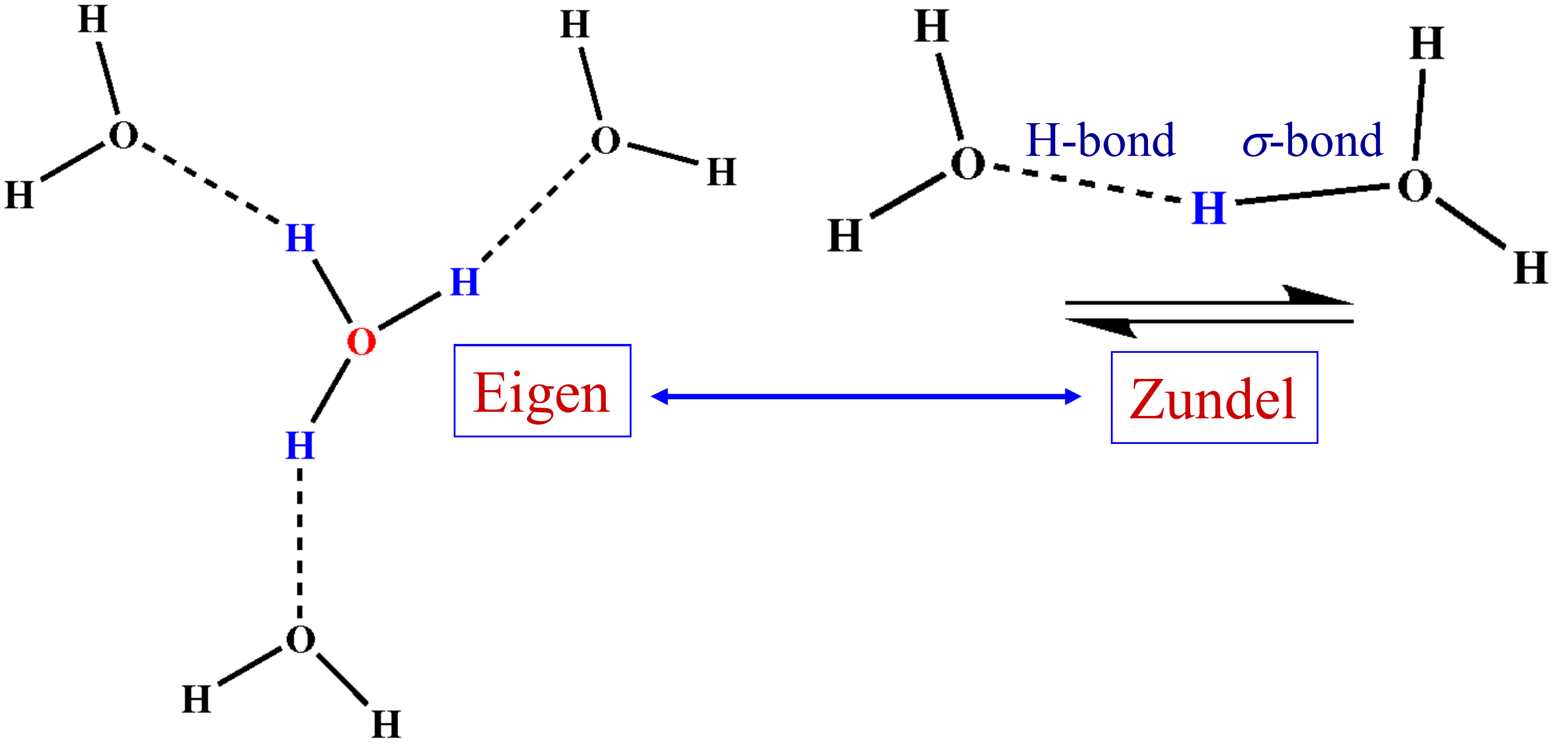
A proton in
normal liquid
water:
$\rho = 1.0\ \mathrm{g/cm^3}$
$T = 300\ \mathrm{K}$

simulation time
displayed: 0.6 ps

total simulation
time: 19.1 ps



The excess proton makes a continuous switch between Eigen $H_9O_4^+$ complex and Zundel $H_5O_2^+$ shared proton structure, ***forming and breaking bonds***



Proton diffusion: a couple of observations

- A simple first principles MD seems to be able to simulate the basic chemistry process for a proton diffusion: the Grotthus switching from a σ bond (O-H) to a hydrogen bond (H-bond)
- It seems than that if we can control in some way the temperature of the water, we can speed up (heating) or slow down (cooling) such a process

[Note: *this is the idea behind the use of supercritial water*]

- Indeed, for simple chemical reactions that occur with little (few $k_B T$) or no energy barrier, thermal fluctuations are enough to activate the process
- Yet, $k_B T$ = 26 meV = 0.60 kcal/mol at T = 300 K

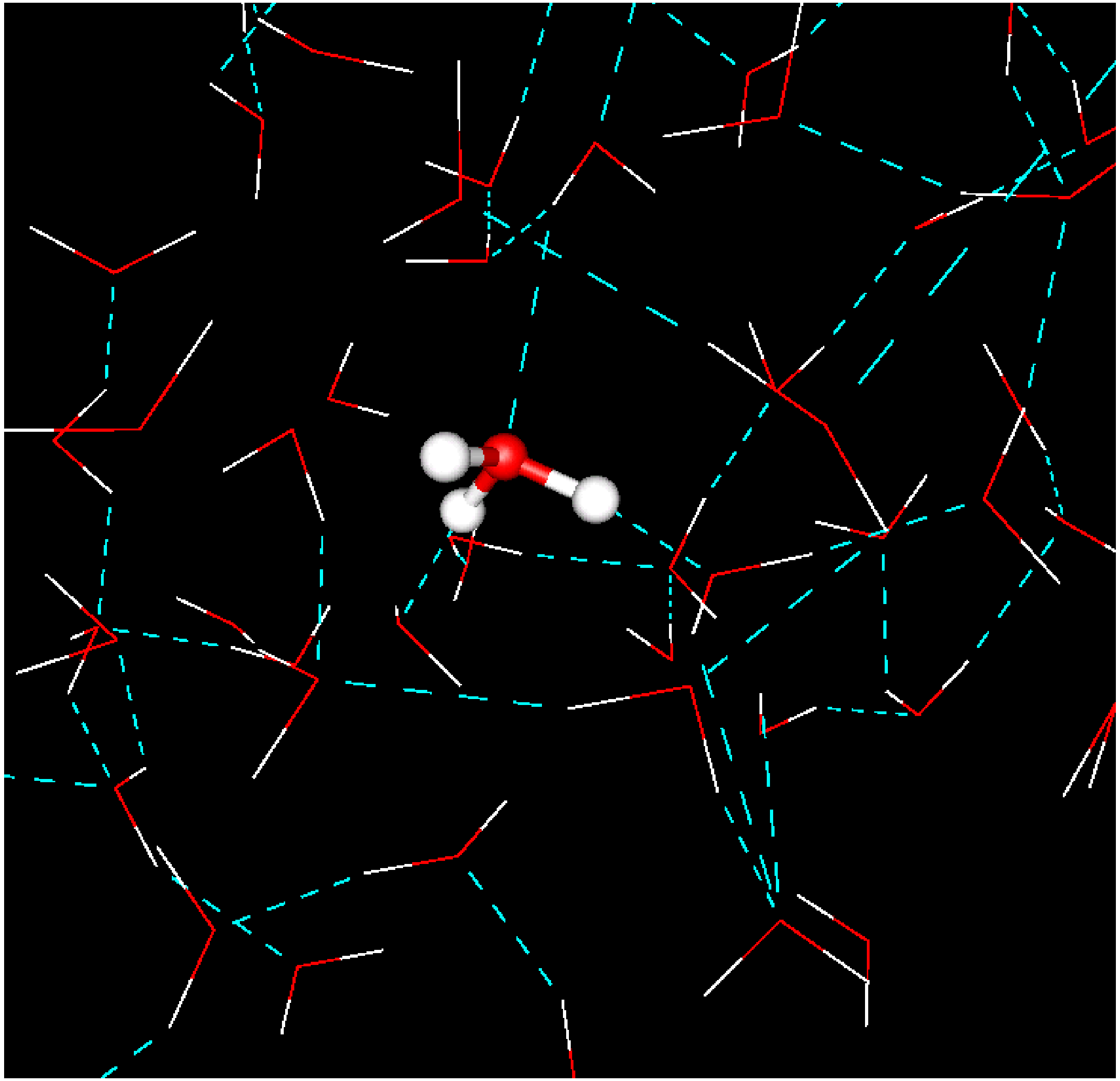
…so let's try to heat up our system from 300 K to 673 K*

**** Typical supercritical temperature***

High temperature:
$\rho = 1.0\ \mathrm{g/cm^3}$
$T = 673\ \mathrm{K}$

simulation time displayed: 0.6 ps
(total simulation time: 20.0 ps)

the H^+ diffusion becomes faster



Theoretical diffusion coefficients computed from the velocity-velocity autocorrelation function. ***D*** and from the mean square displacement, D^{MSD}. The experimental proton diffusion coefficient is D_{exp}, diffusion and D^{self} is the water self-diffusion coefficient.

ρ (g cm^{-3})	T (K)	D (cm^2/s)	D^{MSD} (cm^2/s)	D_{exp} (cm^2/s)	D^{self} (cm^2/s)
1.0	300	13.0×10^{-5}	15.0×10^{-5}	9.3×10^{-5} [a]	2.5×10^{-5}
1.0	673	70.0×10^{-5}	62.0×10^{-5}		33.0×10^{-5}

[a] R. A. Robinson and R. H. Stokes, *Electrolyte Solutions*, Butterworths, London, **1959**.

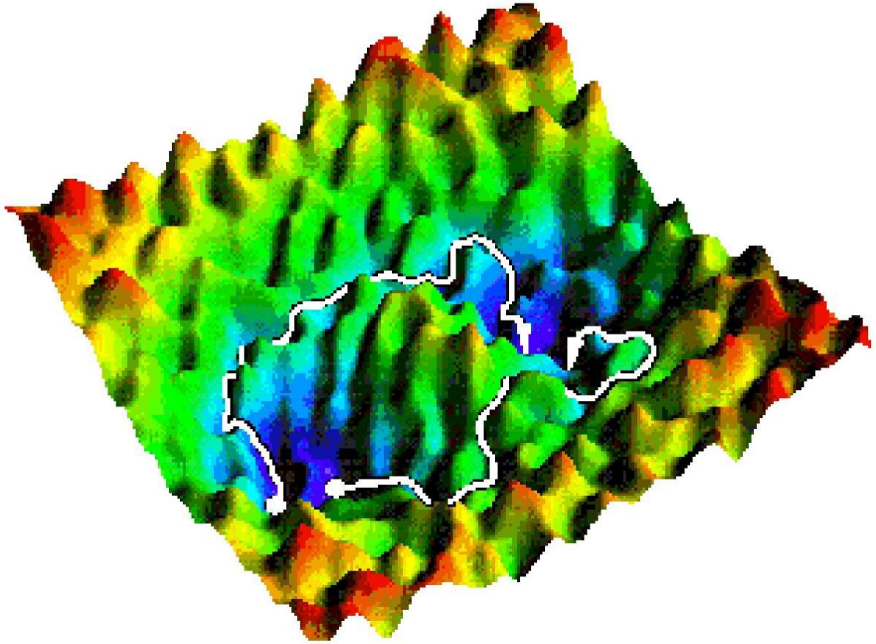
However this is just a lucky case… in general a chemical reaction requires the overcoming of a much higher energy barrier.

In general, can we use first principles or classical MD to explore long range (*time*, *space*) phenomena ?

- Unfortunately the general answer is NO !
- Classical MD or $O(N)$ method can help in extending the length scale
- …but classical (~10 ns) and quantum (~10 ps) MD are insufficient for most of the phenomena
- …and longer length scale often goes together with longer time scale (*we see very little in few ps simulations of billions of atoms* – P. Vashishta, CSW 2005)
- Most of the relevant phenomena occur on a long time scale and involve extended portions of the system under study: chemical reactions, diffusions, phase transitions, folding, nucleation, etc…

Unsolved Problems in Total Energy Surface Approaches

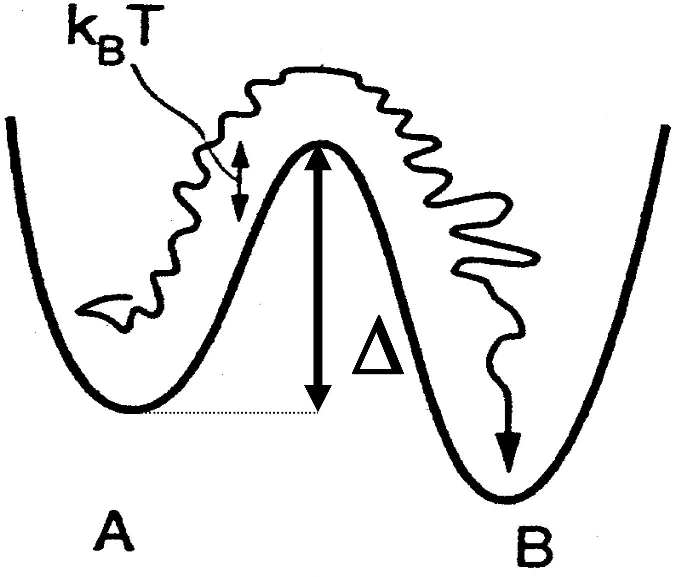
- •Intermediate states at equivalent saddle points
- •Complex and rough energy surface
- •Multiple equivalent minima
- •Equivalent reaction paths
- •Unforeseen reaction products



© by David Chandler

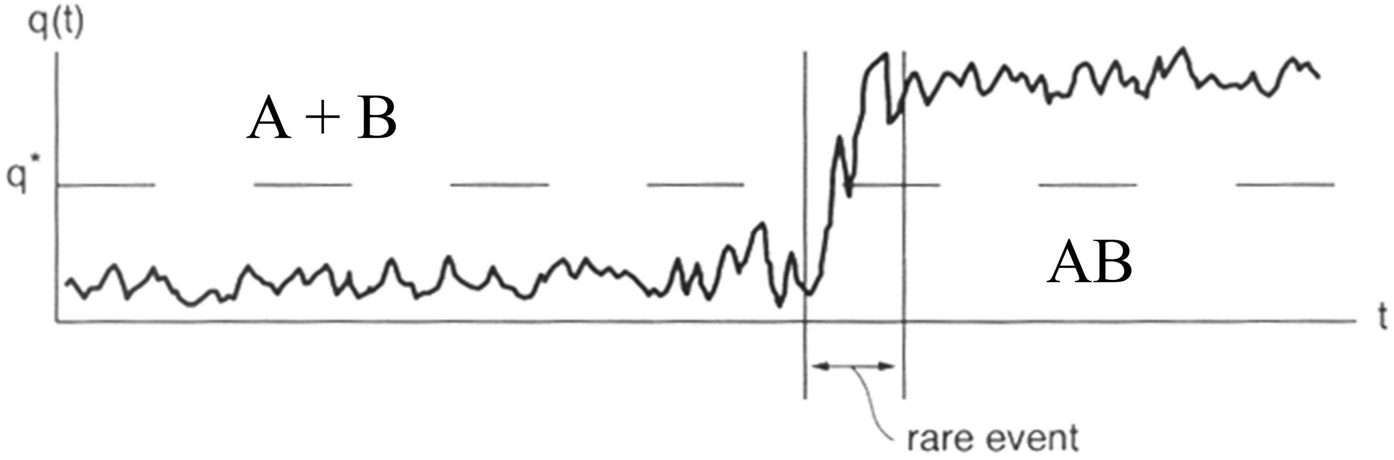
From reactants A to products B: we have to climb the mountain minimizing the time

- A general chemical reaction starts from reactants A and goes into products B
- The system spends most of the time in A and/or in B
- …but in between, for a short time, a barrier is overcome and **atomic** and **electronic** modifications occur
- Time scale: $\tau \sim \tau_{mol} e^{\frac{F^*}{k_B T}}$



$F^* \sim \Delta$

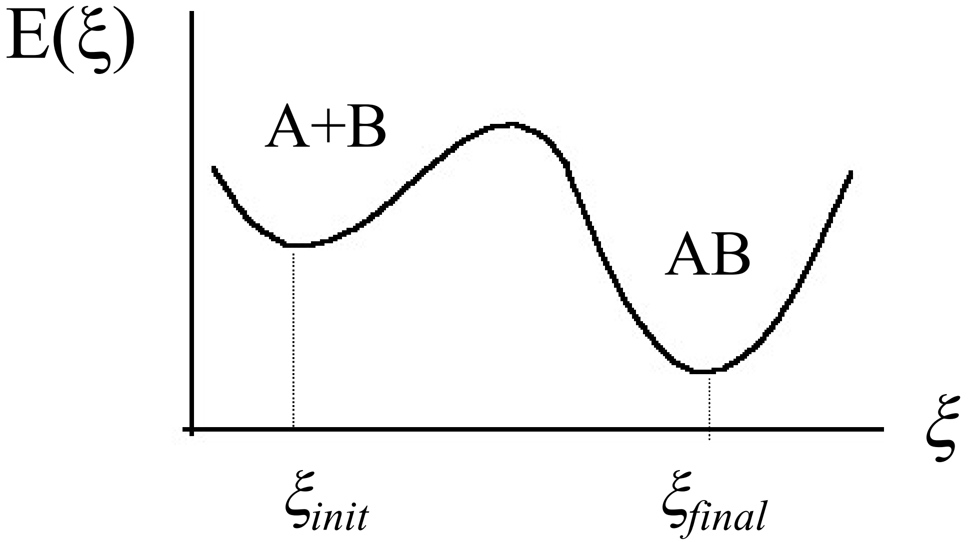
How to simulate a chemical reaction ?



- The reaction A+B → AB passes across a rare event (transition state) that is difficult to see
- CP molecular dynamics time scale is of the order of some tens of ps and classical simulations are of the order of few ns, but still insufficient… ***we cannot wait forever***…

Blue Moon ensemble theory

(M. Sprik and G. Ciccotti *J. Chem. Phys*. **109**, 7737 (1998))



- Select the reaction coordinate ξ to be sampled, e.g. the interatomic distance $\xi = |\mathbf{R}_A - \mathbf{R}_B|$
- Add to the CP lagrangean L^{CP} the holonomic constraint
  $L^{CP} \rightarrow L^{CP} + \lambda_\xi (\xi - \xi_0)$ (λ_ξ = Lagrange multiplier)
- Compute the ensemble (time) average $< \lambda_\xi > \longrightarrow$ why ?

Blue Moon ensemble theory

From the standard definition of free energy

$$F = -k_B T \ln <\exp\{-[\mathrm{H}^{\mathrm{CP}} + \lambda_\xi(\xi-\xi_0)]/k_B T\}>$$

using $\exp(x) \sim 1+x+O(x^2)$ and $\ln(1+x) \sim x - O(x^2)$ we get

$$\delta F \cong -k_B T \delta \ln\left\langle 1 - \mathrm{H}^{CP}/k_B T - \lambda_\xi(\xi-\xi_0)/k_B T\right\rangle$$

$$= -k_B T \delta\left\langle -\mathrm{H}^{CP} - \lambda_\xi(\xi-\xi_0)\right\rangle / k_B T = \delta\left\langle \mathrm{H}^{CP} + \lambda_\xi(\xi-\xi_0)\right\rangle$$

$$= \delta\left\langle \mathrm{H}^{CP}\right\rangle + \delta\lambda_\xi\left\langle \xi-\xi_0\right\rangle + \left\langle \lambda_\xi\right\rangle \delta(\xi-\xi_0)$$

but $\delta\left\langle \mathrm{H}^{CP}\right\rangle = 0$ because H^{CP} is a constant of motion

and $\left\langle \xi-\xi_0\right\rangle = \left\langle \xi\right\rangle - \xi_0 = \xi_0 - \xi_0 = 0$, $\delta\left(\xi-\xi_0\right) = \delta\xi$

because ξ_0 is the average value of ξ (and a constant !)

Blue Moon ensemble theory

- …so the variation of the free energy become simply

$$\delta F = \frac{\partial F}{\partial \xi}\delta\xi = \left\langle \lambda_{\xi} \right\rangle \delta\xi$$

- If we now integrate the average constraint force along the sampled reaction path between ξ_{init} and ξ_{final} , we finally arrive at the following expression for the free energy difference between initial (reactant) and final (product) states

$$\Delta F = \int_{\xi_{init}}^{\xi_{final}} \langle \lambda_{\xi} \rangle d\xi$$

Blue Moon ensemble theory

The general evaluation of the average of the Lagrange multiplier is given by

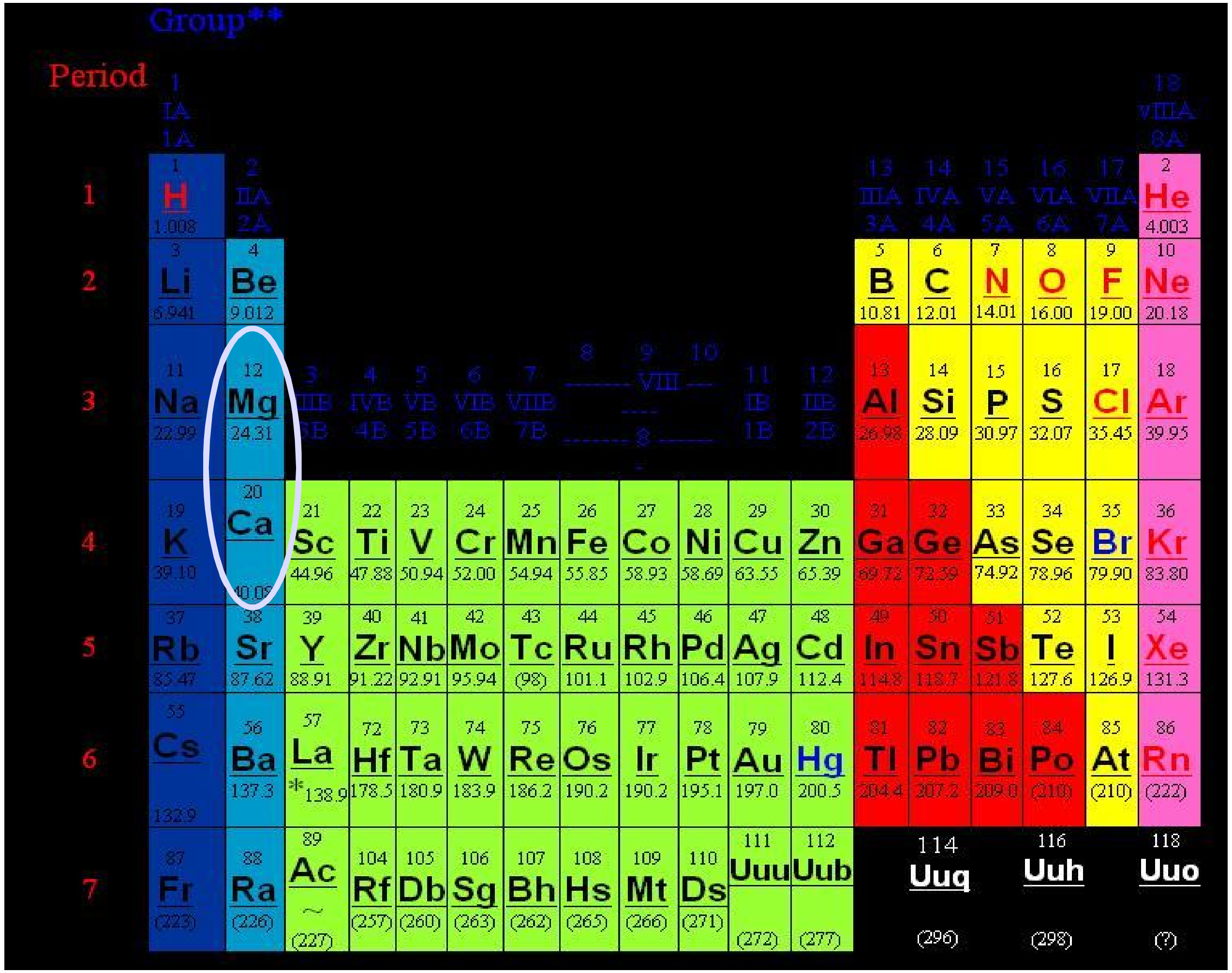
$$Z = \sum_i \frac{1}{m_i} \left(\frac{\partial \xi}{\partial \mathbf{r}_i} \right)^2 \qquad G = \frac{1}{Z^2} \sum_{i,j} \frac{1}{m_i m_j} \frac{\partial \xi}{\partial \mathbf{r}_i} \frac{\partial^2 \xi}{\partial \mathbf{r}_i \partial \mathbf{r}_j} \frac{\partial \xi}{\partial \mathbf{r}_j}$$

hence

$$\frac{\partial F}{\partial \xi'} = \left\langle \lambda_{\xi'} \right\rangle = f_{\xi'} = \frac{\langle Z^{-1/2} [\lambda - kTG] \rangle_{\xi'}}{\langle Z^{-1/2} \rangle_{\xi'}}$$

$$F(\xi_1) - F(\xi_0) = -\int_{\xi_0}^{\xi_1} f_{\xi'} \, d\xi'$$

Example 1: Divalent alkali metal cations in water – Mg^{2+}, Ca^{2+}

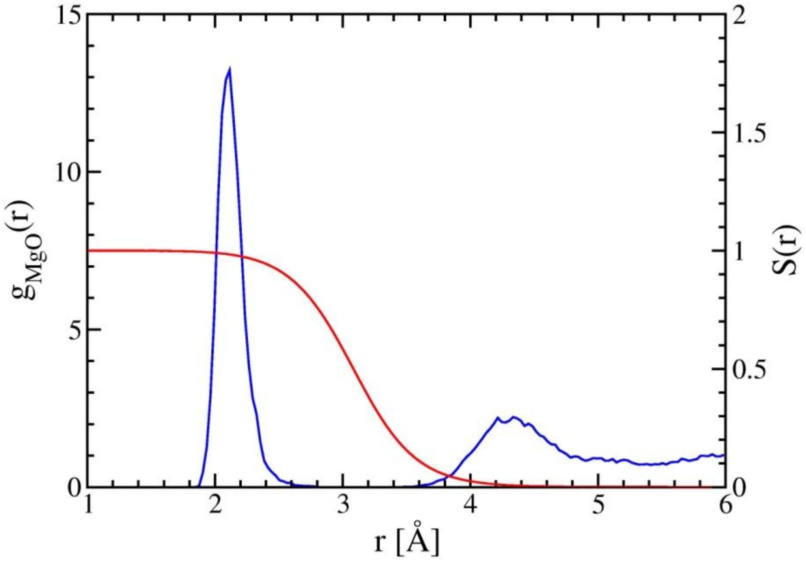


Group**

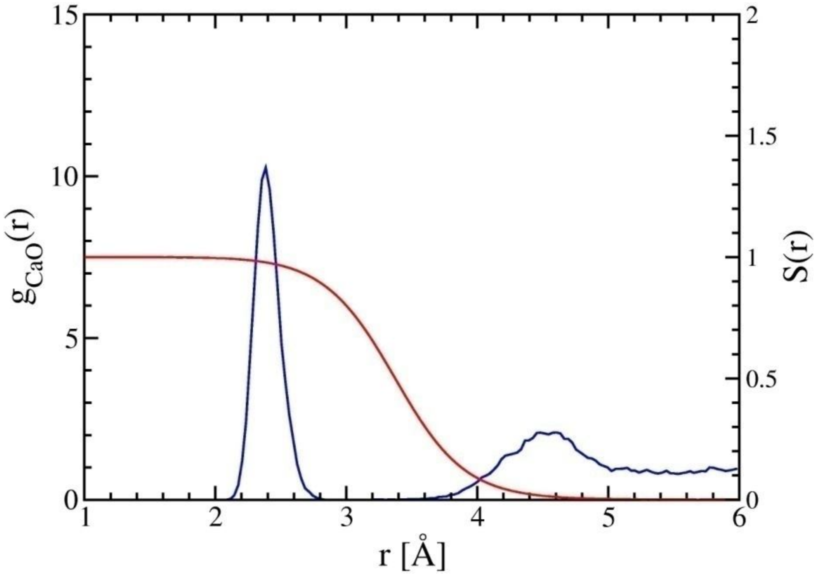
Period	1 IA 1A	2 IIA 2A	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8	9 VIII 8	10	11 IB 1B	12 IIB 2B	13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	18 VIIIA 8A
1	1 H 1.008																	2 He 4.003
2	3 Li 6.941	4 Be 9.012											5 B 10.81	6 C 12.01	7 N 14.01	8 O 16.00	9 F 19.00	10 Ne 20.18
3	11 Na 22.99	12 Mg 24.31											13 Al 26.98	14 Si 28.09	15 P 30.97	16 S 32.07	17 Cl 35.45	18 Ar 39.95
4	19 K 39.10	20 Ca 40.08	21 Sc 44.96	22 Ti 47.88	23 V 50.94	24 Cr 52.00	25 Mn 54.94	26 Fe 55.85	27 Co 58.93	28 Ni 58.69	29 Cu 63.55	30 Zn 65.39	31 Ga 69.72	32 Ge 72.59	33 As 74.92	34 Se 78.96	35 Br 79.90	36 Kr 83.80
5	37 Rb 85.47	38 Sr 87.62	39 Y 88.91	40 Zr 91.22	41 Nb 92.91	42 Mo 95.94	43 Tc (98)	44 Ru 101.1	45 Rh 102.9	46 Pd 106.4	47 Ag 107.9	48 Cd 112.4	49 In 114.8	50 Sn 118.7	51 Sb 121.8	52 Te 127.6	53 I 126.9	54 Xe 131.3
6	55 Cs 132.9	56 Ba 137.3	57 La *138.9	72 Hf 178.5	73 Ta 180.9	74 W 183.9	75 Re 186.2	76 Os 190.2	77 Ir 190.2	78 Pt 195.1	79 Au 197.0	80 Hg 200.5	81 Tl 204.4	82 Pb 207.2	83 Bi 209.0	84 Po (210)	85 At (210)	86 Rn (222)
7	87 Fr (223)	88 Ra (226)	89 Ac ~ (227)	104 Rf (257)	105 Db (260)	106 Sg (263)	107 Bh (262)	108 Hs (265)	109 Mt (266)	110 Ds (271)	111 Uuu (272)	112 Uub (277)		114 Uuq (296)		116 Uuh (298)		118 Uuo (?)

Blue Moon constraint = Coordination number of cation

$$\xi = N_{\text{coord}} = \sum_{j=1}^{N_{\text{O}}} S\left(\left|\mathbf{r}_{\text{O}_j} - \mathbf{r}_{\text{M}_i}\right|\right) \qquad S(r) = \frac{1-(r/r_c)^n}{1-(r/r_c)^{n+m}}$$



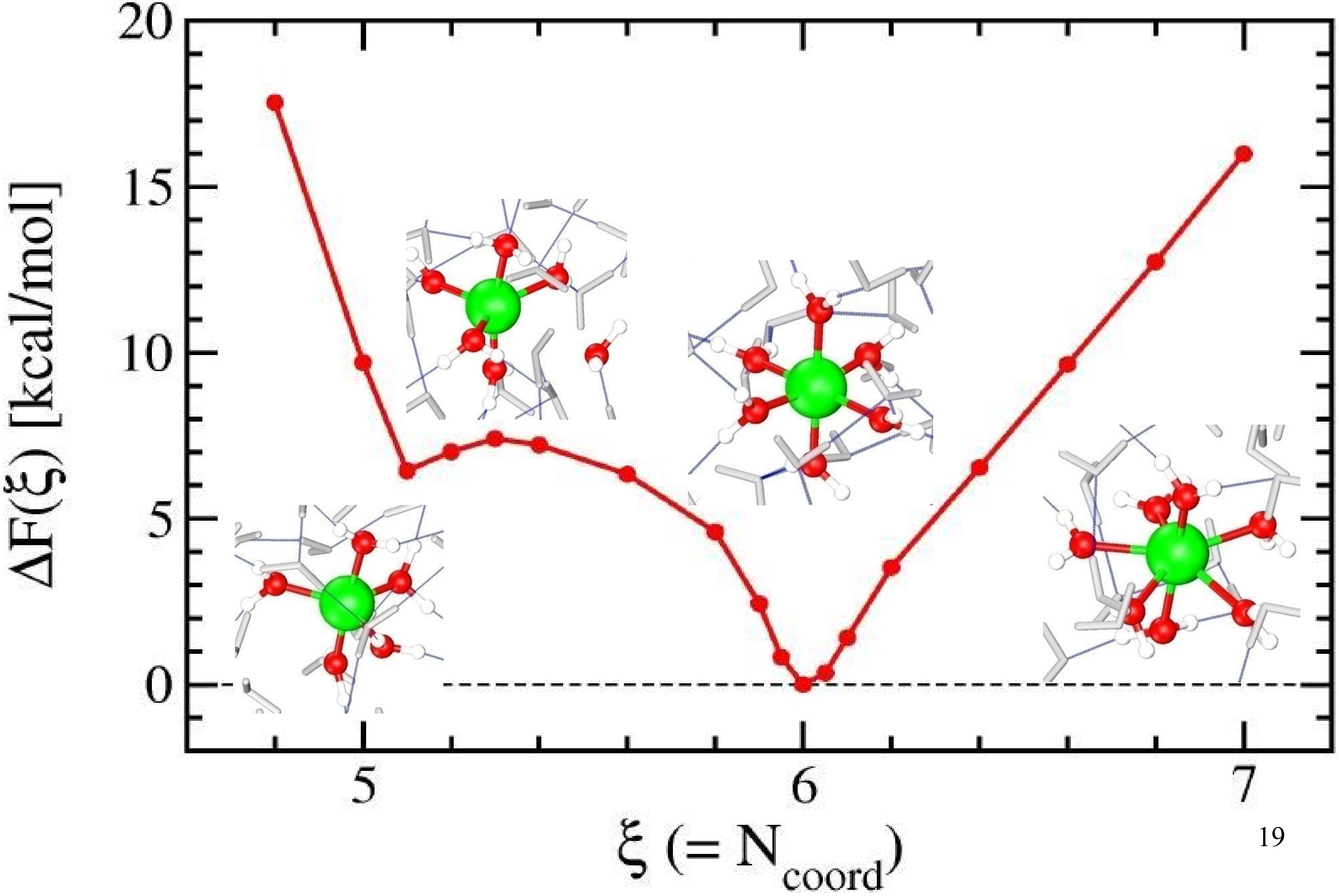
Mg: Radial distribution function and related coordination number $S(r)$



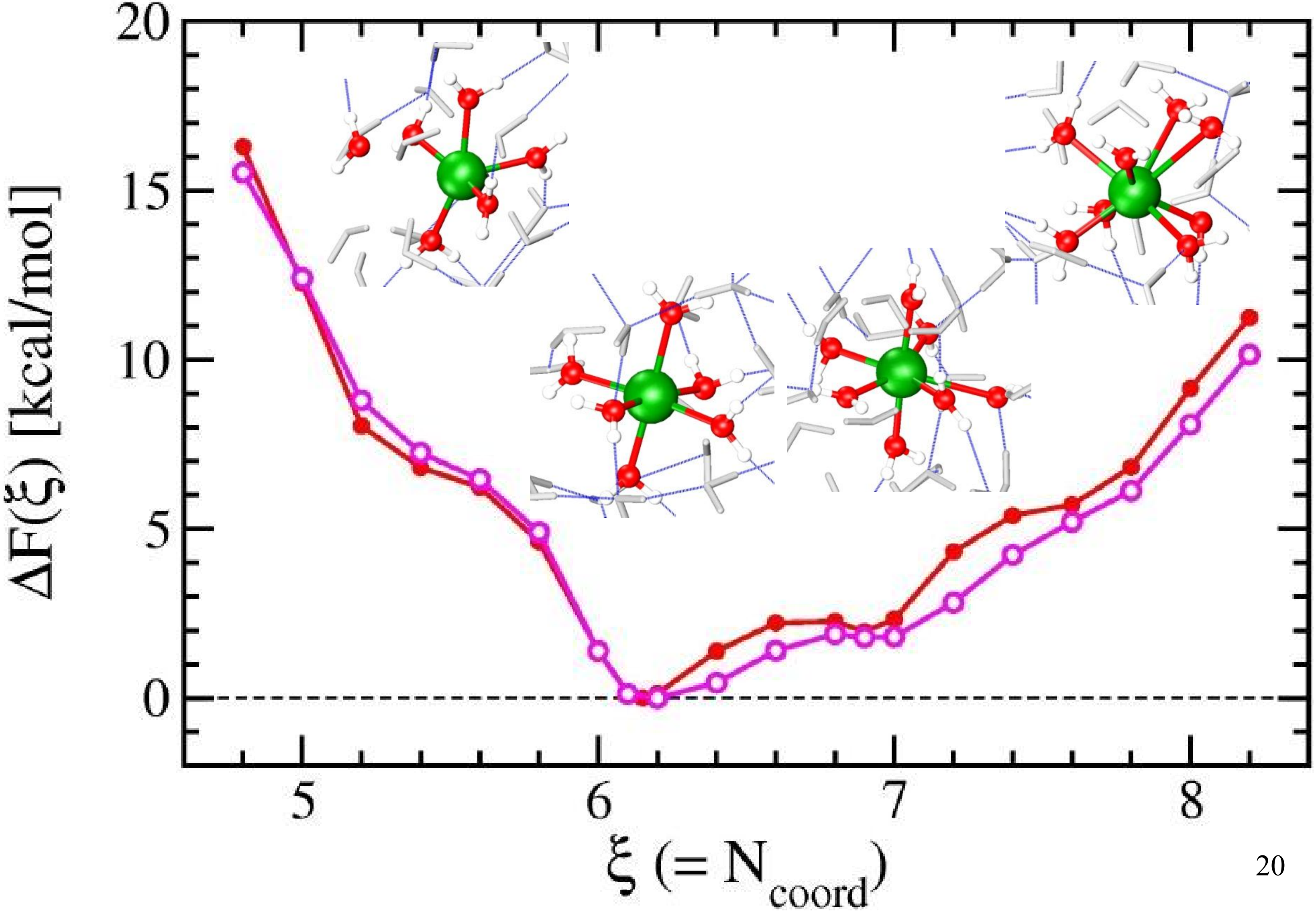
Ca: Radial distribution function and related coordination number $S(r)$

$n = 10$, $m = 16$ in both cases

Mg^{2+} free energy profile and main solvation structures

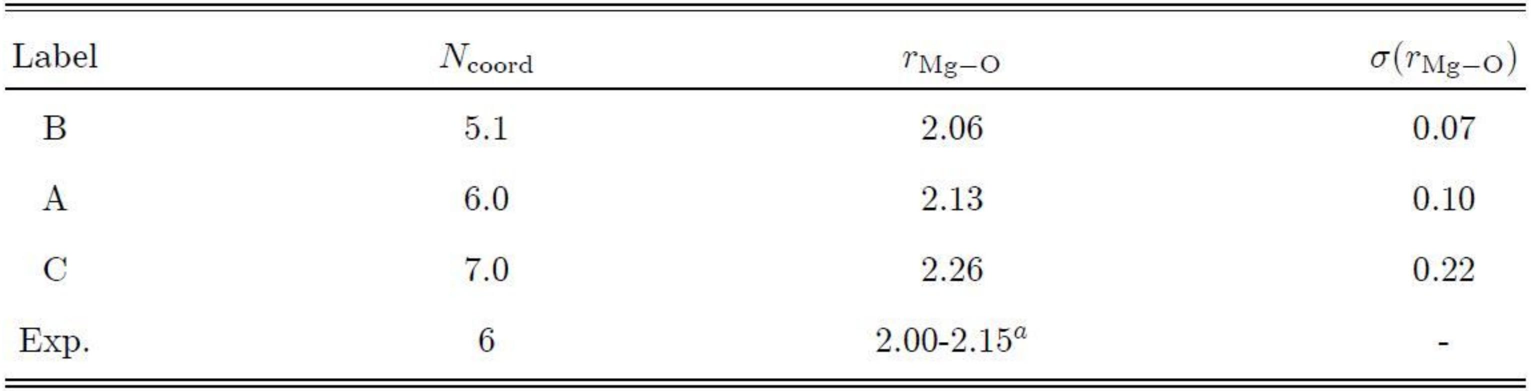


Ca^{2+} free energy profile and main solvation structures



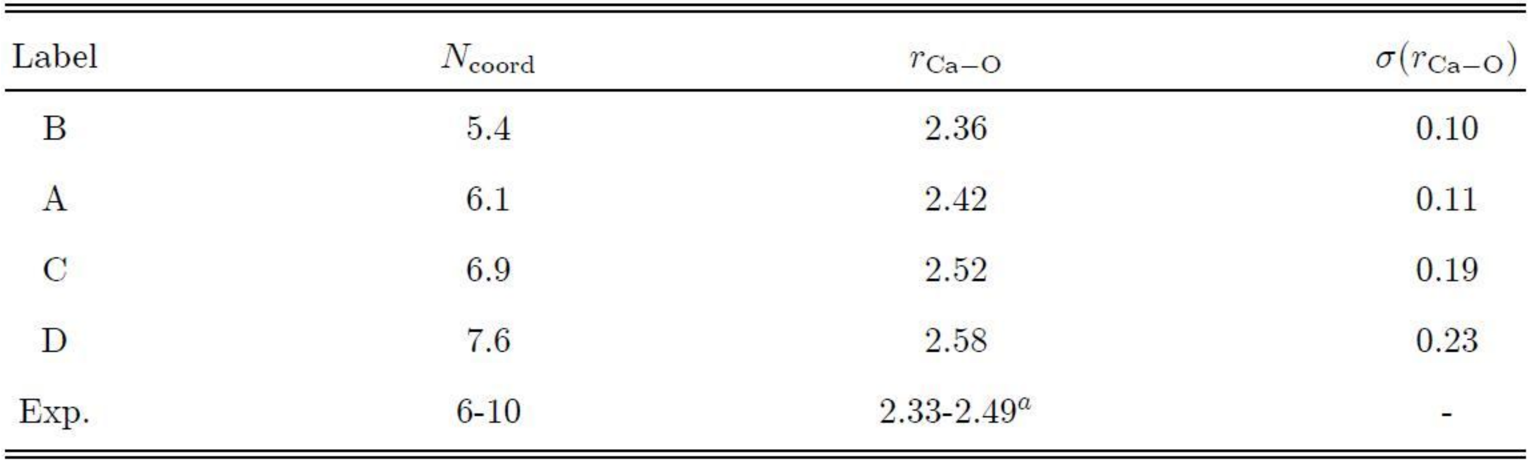
Comparison of the simulations results with experiments

Mg^{2+}



Label	N_{coord}	$r_{\mathrm{Mg-O}}$	$\sigma(r_{\mathrm{Mg-O}})$
B	5.1	2.06	0.07
A	6.0	2.13	0.10
C	7.0	2.26	0.22
Exp.	6	2.00-2.15[a]	-

Ca^{2+}



Label	N_{coord}	$r_{\mathrm{Ca-O}}$	$\sigma(r_{\mathrm{Ca-O}})$
B	5.4	2.36	0.10
A	6.1	2.42	0.11
C	6.9	2.52	0.19
D	7.6	2.58	0.23
Exp.	6-10	2.33-2.49[a]	-

[a] Experiments from H. Ohtaki and T. Radnai, *Chem. Rev.* **93**, 1157 (1993) – X-ray
N. A. Hewish *et al*. *Nature* **297**, 138 (1982) – isotopic substitution

Outcome of the simulations

- The **structural properties** of **Mg^{2+}** and **Ca^{2+}** aqueous solutions are **well described by our simple model**.
- First principles simulations successfully capture the **different hydration behavior** as observed in experiments.
- The solvation shell of **Mg^{2+}** is pretty **stable** in a 6-fold structure, whereas Ca^{2+} is characterized by a **higher flexibility** accounting for the experimental evidence

Related Publications:

M.B., T. Ikeda, E. Ito, K. Terakura, *J. Am. Chem. Soc*. **128**, 16798 (2006)
T. Ikeda, M. B., K. Terakura, *J. Chem. Phys*. **126**, 034501 (2007)
T. Ikeda, M. B., K. Terakura, *J. Chem. Phys*. **127**, 074503 (2007)
M. B., J. M. Park, T. Hagiwara, M.Tateno, *J. Phys. Cond. Mat.* **19**, 365217 (2007)

Example 2: catalysis of ethylene.. how polyethylene is produced

- The Ziegler-Natta (ZN) catalysis is the most important industrial process in the production of polyolefins with high degree of stereoselectivity
- The reaction occurs at room temperature with a very high reaction rate and low amount of catalyst
- Experimental probes fail in recovering the microscopic picture due to the very fast reaction and the low percentage of active sites
- Quantum dynamical simulations can be a viable tool to study active sites and reaction pathways

- **Annual Worldwide Production** (2008)[1] : 45 million tons
- Share of consumption by region (2007)[2] :

China — 23%	North America — 18%
Western Europe — 18%	Asia/Pacific — 16%
Middle East/Africa — 9%	Japan — 11%
Central/South America — 5%	

- Key Products: Packaging, textiles, fibers, automotive components, cups, cutlery, housewares, appliances, electronic components, carpeting, photo and graphic arts products.
- Top 10 world producers by 2008 market share (in descending order)[3] : LyondellBasell, Sinopec Group, Saudi Basic Industries Corp. (SABIC), PetroChina Group, Reliance Industries, ExxonMobil, Borealis, Total PC, Ineos, Formosa Plastics

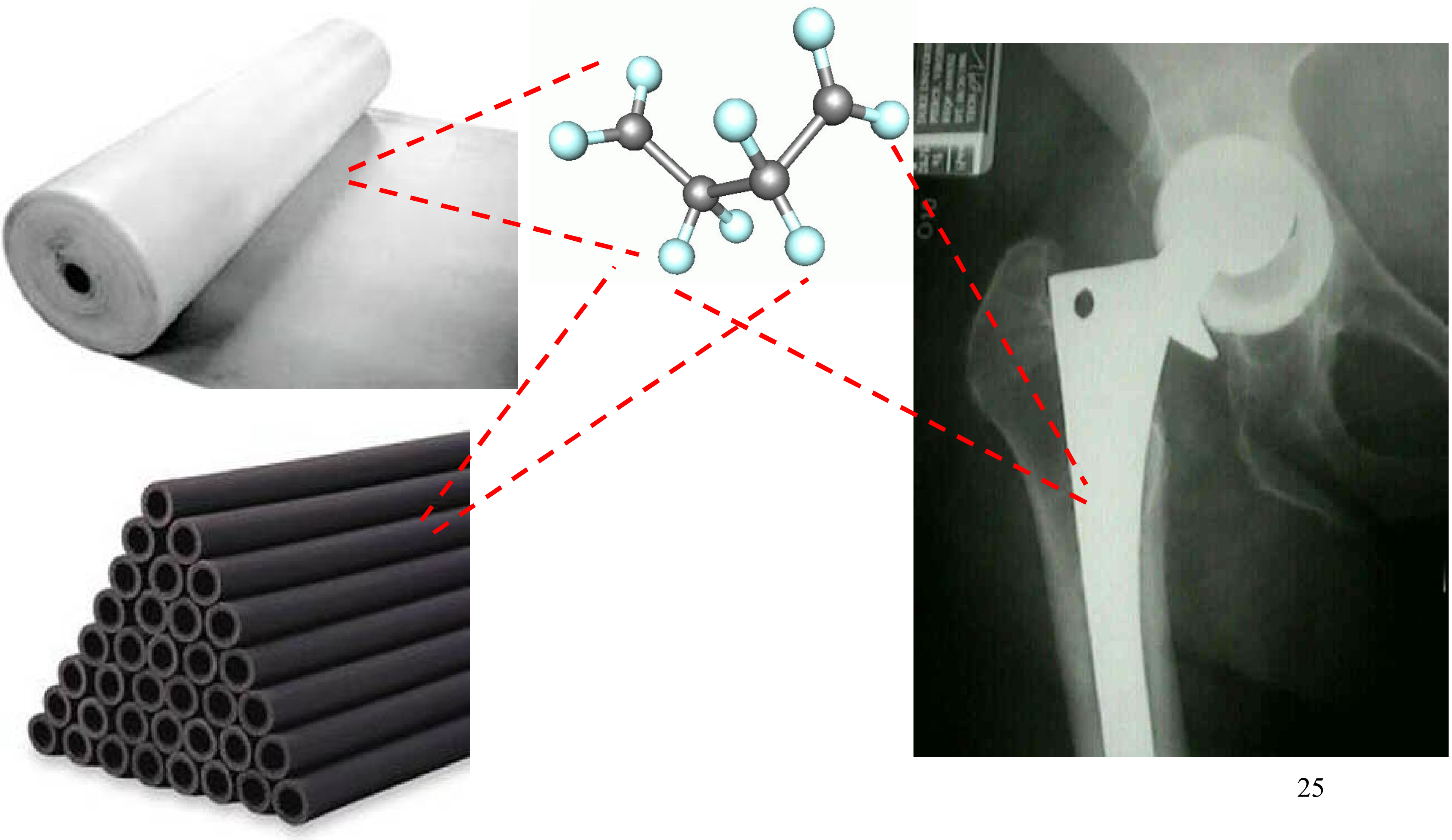
---

[1] Source: ChemSystems

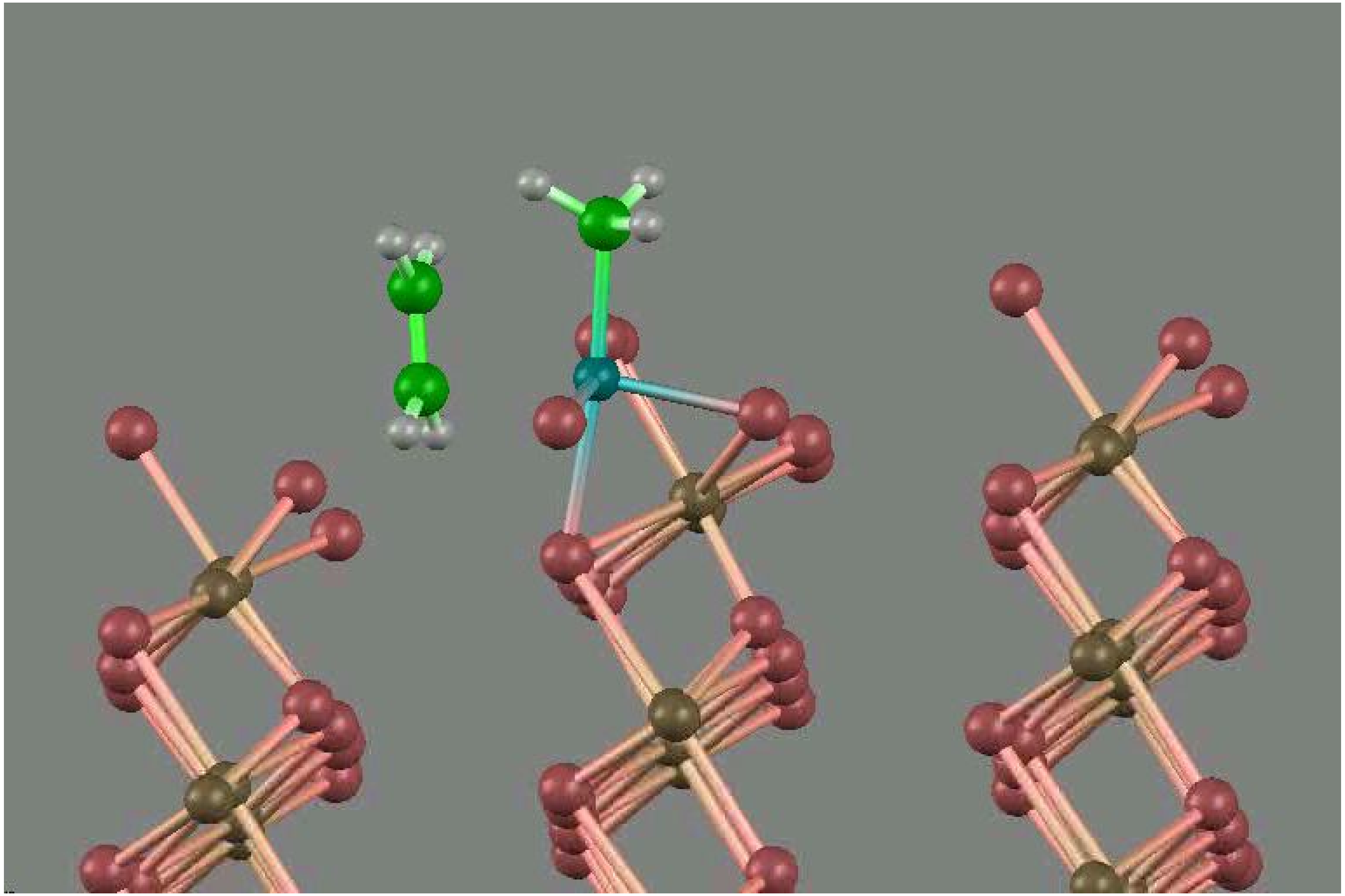
[2] Source: Townsend Solutions

[3] Source: Chemical Market Associates, Inc. (CMAI)

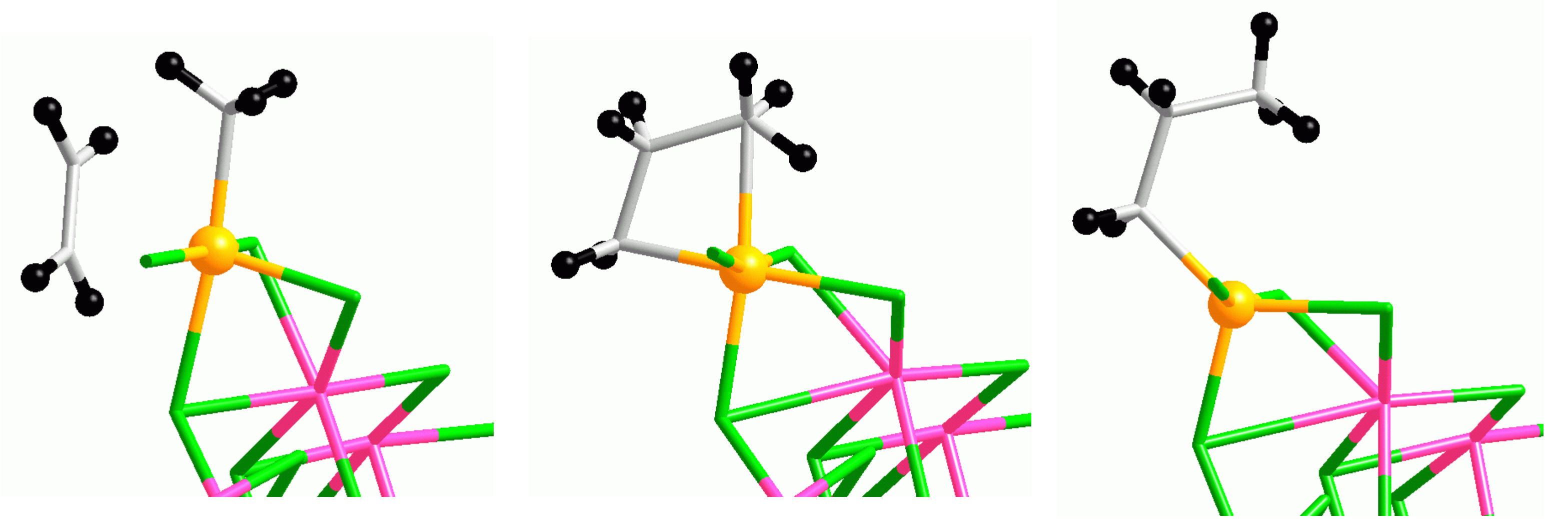
Polyolefins items produced routinely in industries and laboratories



First insertion of ethylene

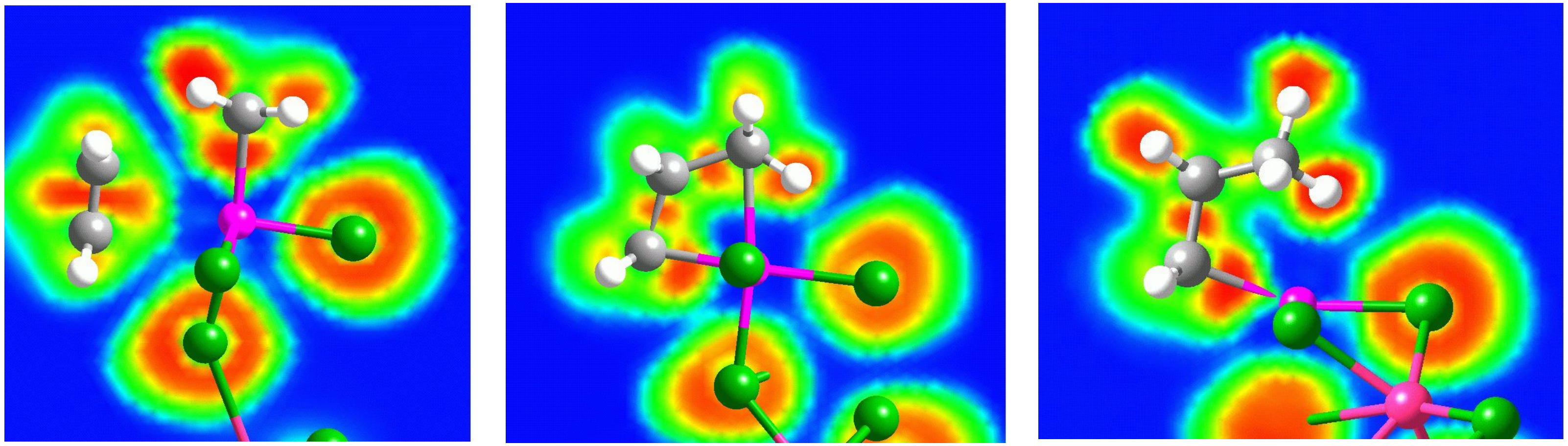


Main phases of the insertion



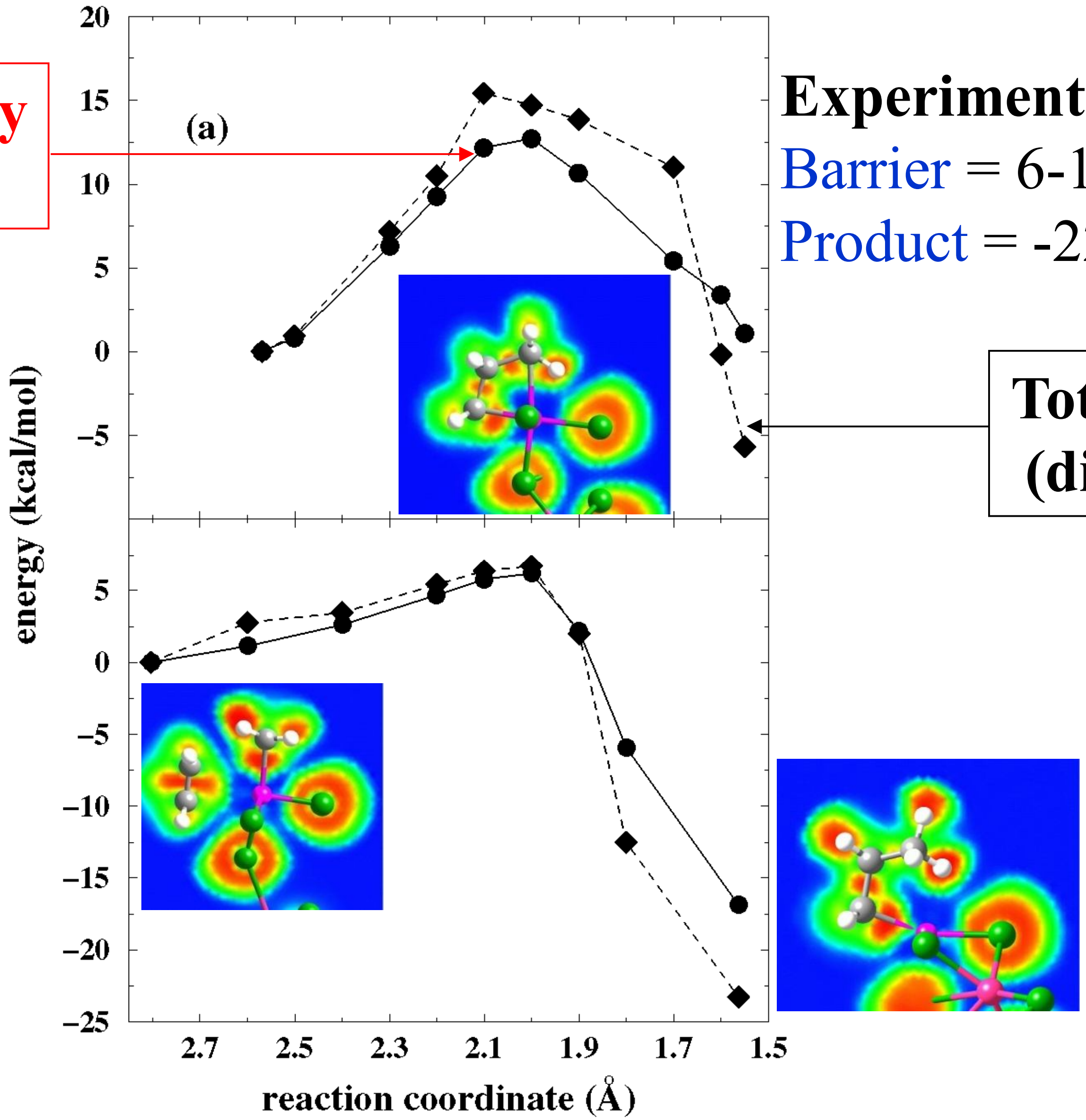
- The π-complex (left), the transition state (center) and the final product (right)
- Reaction coordinate: $\xi = |C_1 - C_\alpha|$
- The reaction is α-agostic assisted

Ethylene polymerization from mononuclear Ti



- ELF of the main steps of the ethylene insertion: the π-complex (right), the transition state (center) and the final product (right). ELF=0: **blue**, ELF=1: **red**
- ELF is projected on the plane containing the C_1 and C_2 carbon atoms (grey) of the ethylene and Ti (purple).

Catalysis of polyethylene: energetics



Free energy (balls)

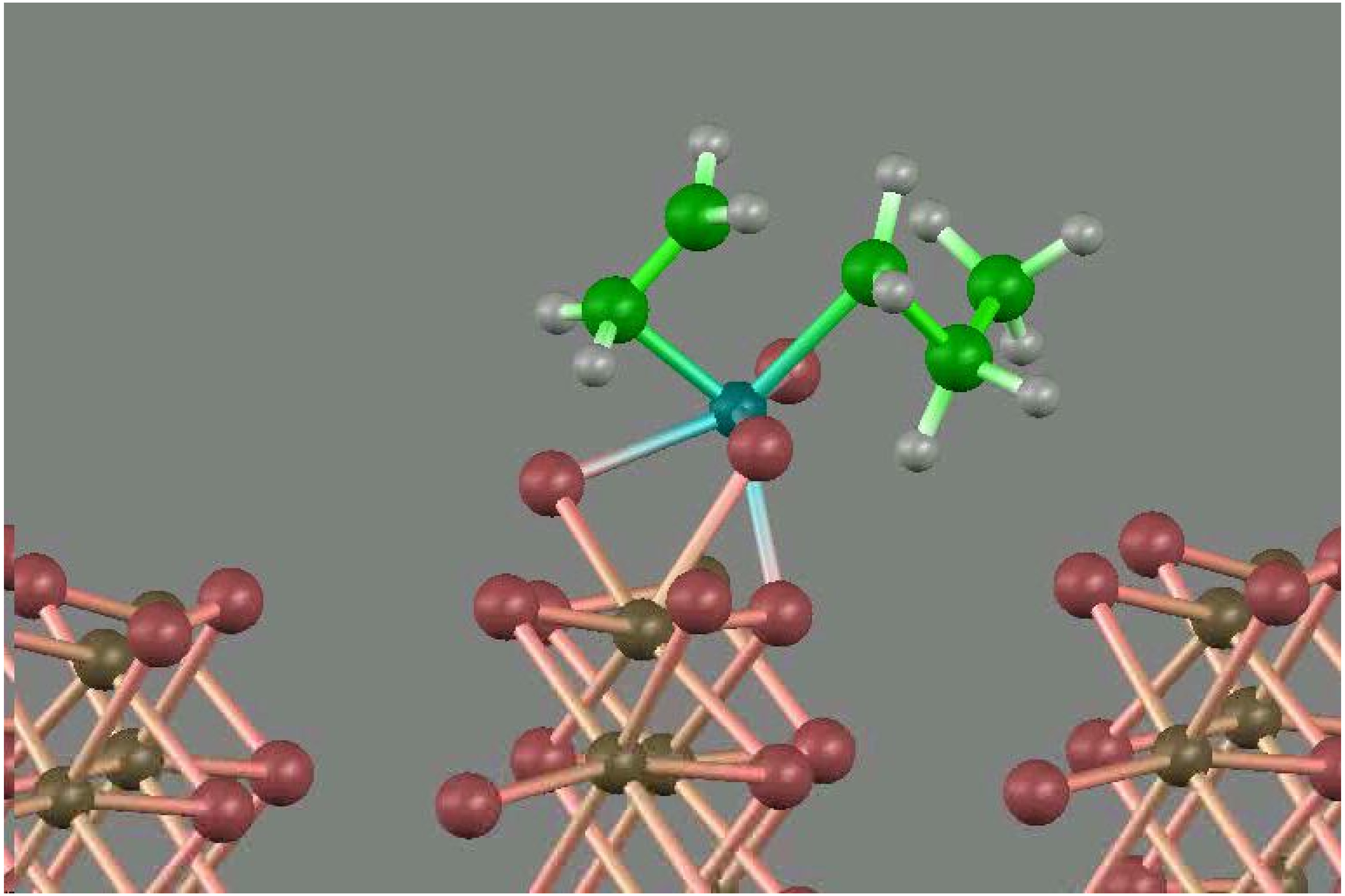
Total energy (diamonds)

Experiment:

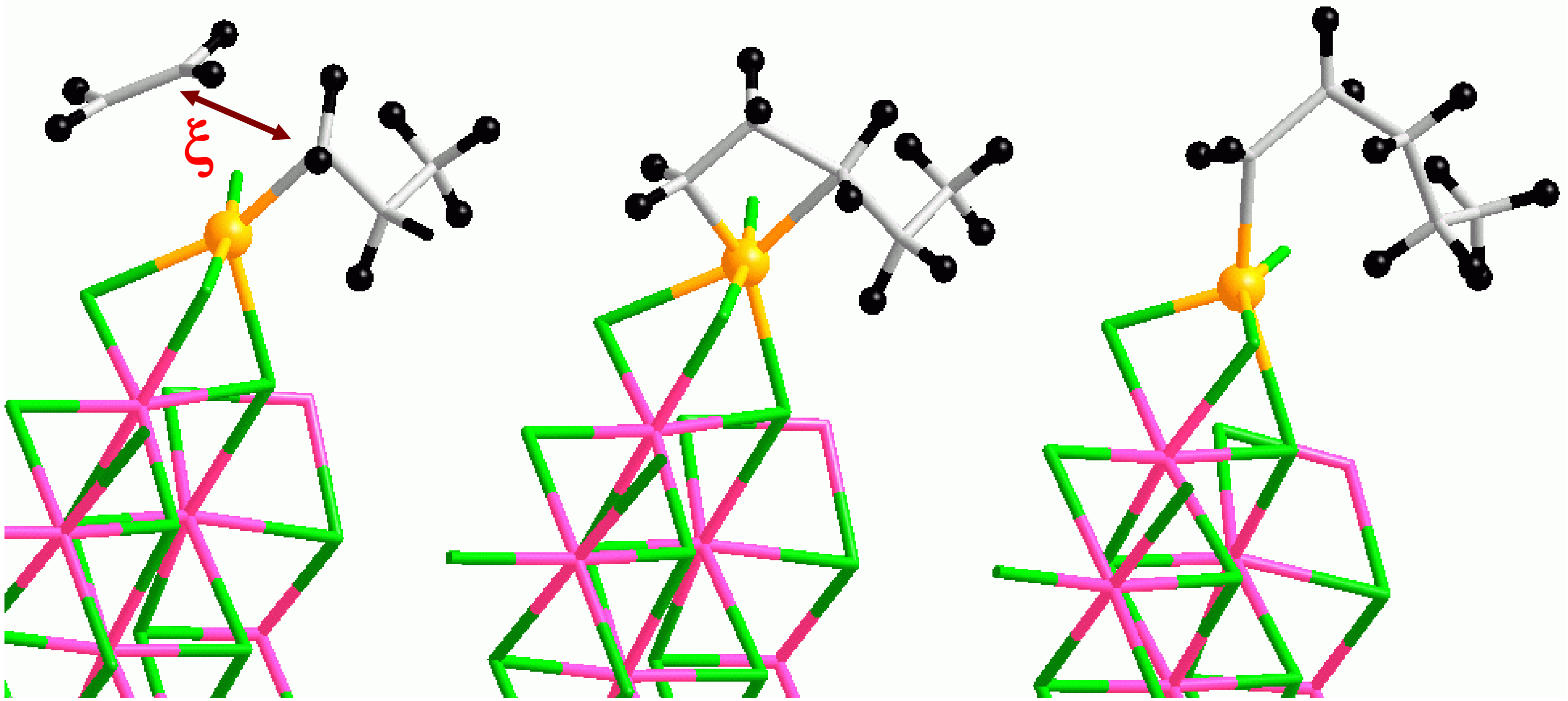
Barrier = 6-12 kcal/mol

Product = -22 kcal/mol

…how a polymer chain is produced



An example of application: catalysis of ethylene.. how polyethylene is produced



Formation of a complex on Ti catalytic site

Transition state at $\Delta F = 8$ kcal/mol

Final product: insertion of a new monomer

Outcome of the simulations

- Role and relative importance of the $MgCl_2$ active surface (substrate)
- Interaction of Ti species with the support
- The polymerization reaction pathway
- Energetic and efficiency of the reaction

Related publications:

M.B., K. Terakura and M. Parinello, *J. Am. Chem. Soc*. **120**, 2746 (1998)

M.B., M. Parrinello, S. Hüffer and H. Weiss, *J. Am. Chem. Soc*. **122**, 501 (2000)

M.B., M. Parrinello, H. Weiss and S. Hüffer, *J. Phys. Chem. A* **105**, 5096 (2001)

Sampling the reaction path via metadynamics

1) The atomic and electronic configuration of our initial system is given by a set of variables

$$\{\mathbf{R}_1,\ldots,\mathbf{R}_N\}_{t=0}\oplus\{\psi_1,\ldots,\psi_M\}$$

2) …and we assume that some known functions of a subset of them (collective variables) are necessary and sufficient to describe the process we are interested in

$$s_\alpha(\mathbf{R}_I;\psi_i)\qquad \alpha=1,\ldots,n<N,M$$

3) …so that the FES is a function of these changing variables

$$F(\mathbf{s})\qquad \mathbf{s}\equiv\mathbf{s}(t)=\{s_\alpha(t)\}_{\alpha=1,\ldots,n}$$

Collective variable(s) ?

- Distances
- Angles (bending, torsion, out-of-plane, etc.)
- Coordination numbers
- Spin density
- Local electric fields
- number of n-fold rings
- Lattice vectors
- Energy
- etc…

Metadynamics in few words:

- ***Artificial*** dynamics in the space of a few collective variables [1]
- The CPMD dynamics is biased by a history-dependent potential constructed as a sum of Gaussians [2].
- The history dependent potential compensates, step after step, the underlying free energy surface [3,4].

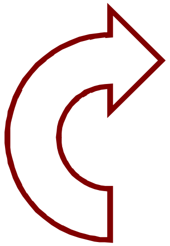
[1] I. Kevrekidis et al., *Comput. Chem. Eng.* (2002)
[2] T. Huber et al., *J. Comput.* (1994)
[3] F. Wang and D. Landau, *Phys. Rev. Lett.* (2001)
[4] E. Darve and A. Pohorille, *J. Chem. Phys.* (2001)

What is it used for ?

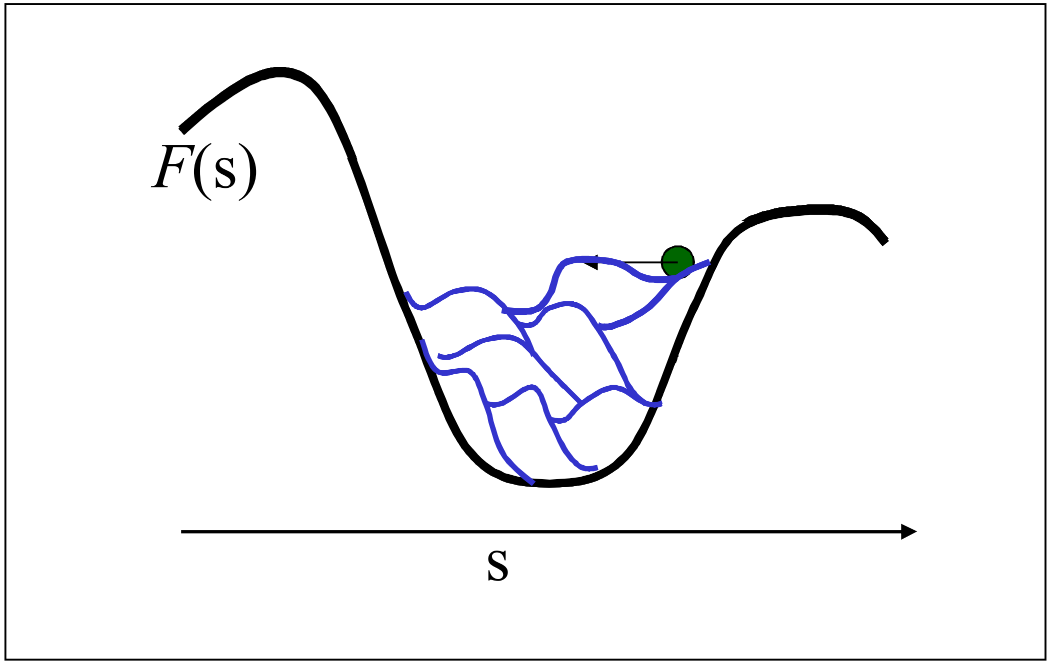
- For reconstructing $F(\mathbf{s})$ in many dimensions as a function of one or more collective variables.
- Used as a tool for escaping local (free energy) minima, i.e. accelerating rare events, reconstructing the free energy in the selected interval of reaction coordinates (***not*** everywhere !).

[1] A. Laio, A. and M. Parrinello, *Proc. Nat. Acad. Sci. USA* **99**, 12562 (2002)
[2] M. Iannuzzi, A. Laio, M. Parrinello, *Phys. Rev. Lett*. **90**, 238302 (2003)

Metadynamics: how does it work ?

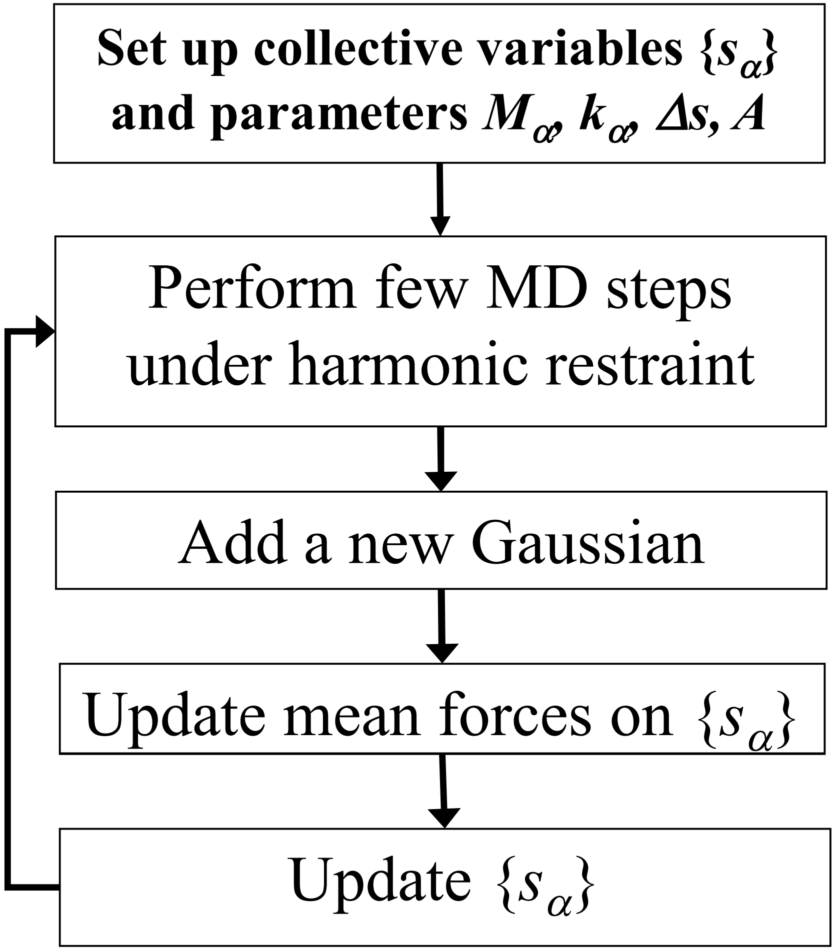


- Put a "small" Gaussian
- The dynamics brings you to the closest local minimum of *F*(s) plus the sum of all the Gaussians



Summarizing:

- In the one dimensional example shown, the system freely moves in a potential well (driven by MD).
- Adding a penalty potential in the region that has been already explored forces the system to move out of that region,
- …but always choosing the minimum energy path, i.e. the most natural path that brings it out of the well.
- Providing a properly shaped penalty potential, the dynamics is guaranteed to be smooth
- Therefore the systems explores the whole well, until it finds the lowest barrier to escape.



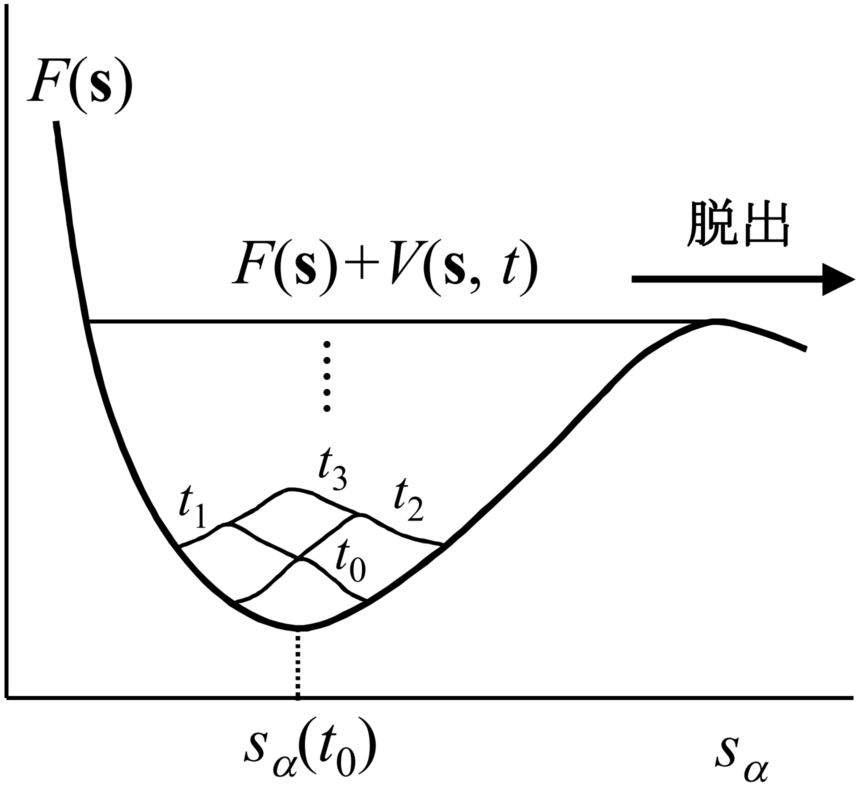
Set up collective variables $\{s_\alpha\}$ and parameters M_α, k_α, Δs, A

Perform few MD steps under harmonic restraint

Add a new Gaussian

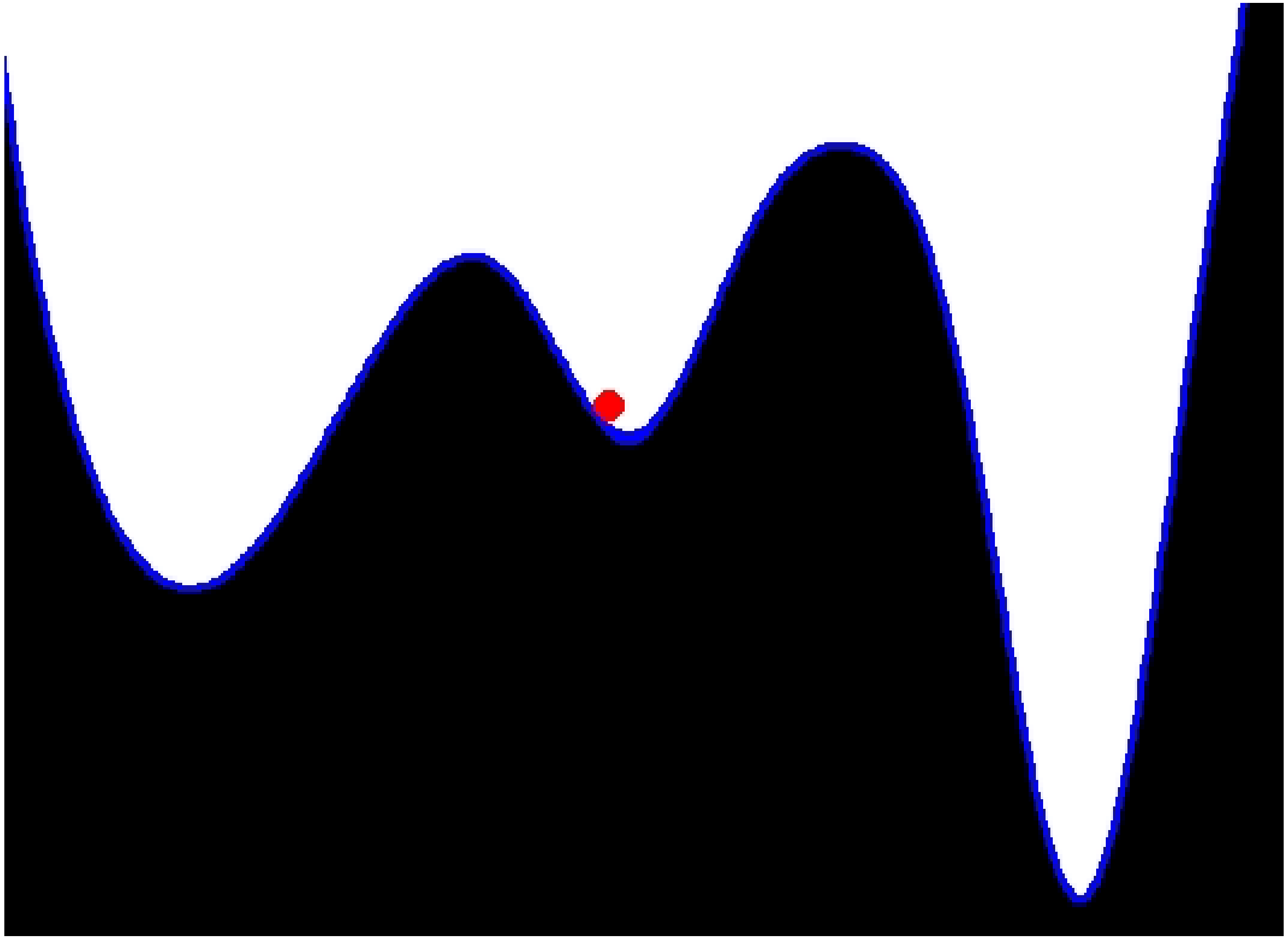
Update mean forces on $\{s_\alpha\}$

Update $\{s_\alpha\}$



The component of the force coming from the gaussians *subtracts* from the “true” force the *probability* to visit again the same place

A simple example: single collective variable (one *walker*)



How to plug all this in CPMD ?

We simply write a (further) extended Lagrangean including the new degrees of freedom

Fictitious kinetic energy

$$\mathcal{L} = \mathcal{L}_{CP} + \sum_{\alpha} \frac{1}{2} M_\alpha \dot{s}_\alpha^2 - \sum_{\alpha} \frac{1}{2} k_\alpha \left(S_\alpha(\mathbf{R}) - s_\alpha \right)^2 - V(\mathbf{s}, t)$$

Restrain potential: coupling fast and slow variables

$\sqrt{(k_\alpha/M_\alpha)} \ll \omega_I$

$$\frac{\partial \mathcal{F}}{\partial s_\alpha} \simeq \langle k_\alpha (S_\alpha(\mathbf{R}) - s_\alpha) \rangle$$

History-dependent potential

Equations of motion for the collective variables

We use (again) the velocity Verlet algorithm to solve the EOM

$$s_\alpha(t+\delta t) = 2s_\alpha(t) - s_\alpha(t-\delta t) + \frac{1}{2}\delta t^2 \frac{f_\alpha(t)}{M_\alpha}$$

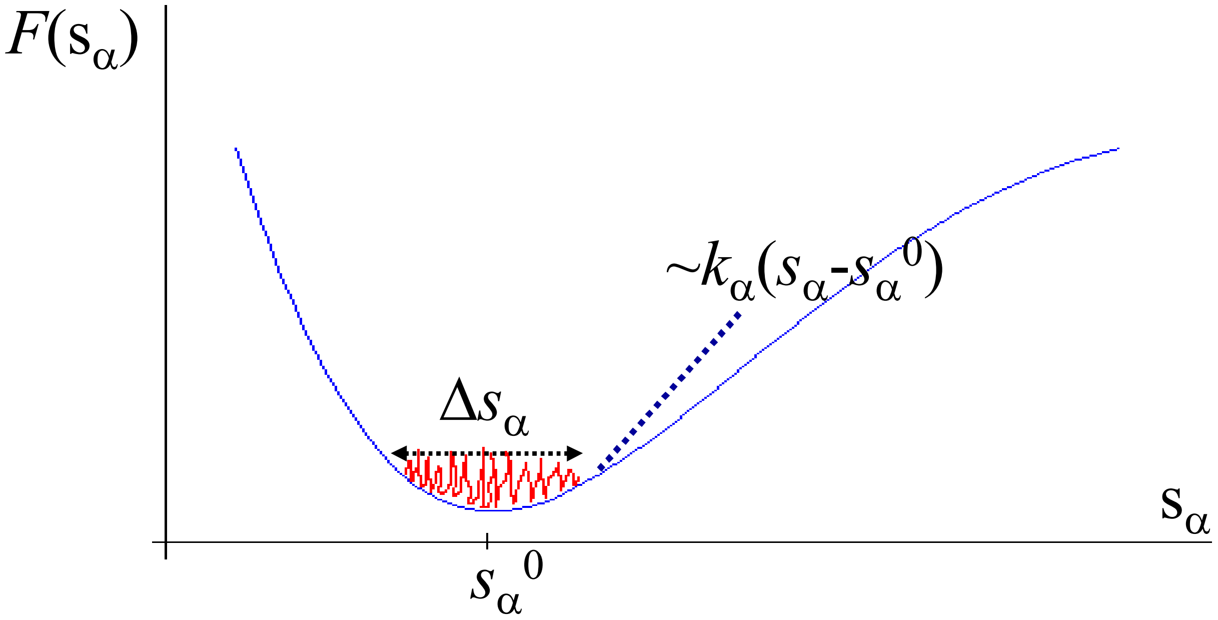
and we have ***two*** new contributions to the force

$$f_\alpha(t) = k_\alpha(S_\alpha(\mathbf{R},t) - s_\alpha(t)) + \frac{\partial V(t,\mathbf{s})}{\partial s_\alpha(t)}$$

- The fictitious kinetic energy $\frac{1}{2} M_\alpha \dot{s}_\alpha^2$ represents the collective variables evolution (*find the next Gaussian center*)
- If we initially set $V(s_\alpha, t)=0$, we get a harmonic oscillator

$$M_\alpha \ddot{s}_\alpha(t) = k_\alpha [s_\alpha(t) - s_\alpha^0]$$

that makes the system wandering around the minimum of $F(s_\alpha)$ without escaping. This gives us an idea of the range (and shape) of the local minimum



The dynamics of the s_α variables is driven by the force

$$f_\alpha(t) = k_\beta \left[s_\alpha(t) - s_\alpha^0 \right] - \frac{\partial}{\partial s_\alpha} V(s_\alpha, t)$$

We want *continuous* (integrable) lagrangean variables, in the spirit of the Car-Parrinello dynamics. Thus $V(s_\alpha,t)$ is chosen as

$$V(\mathbf{s},t) = \int_0^t dt' \left|\dot{\mathbf{s}}(t')\right| W(t') \exp\left[-\tfrac{1}{2} \frac{(\mathbf{s} - \mathbf{s}(t'))^2}{(\Delta s^\perp)^2} \right] \delta\left(\frac{\dot{\mathbf{s}}(t')}{\left|\dot{\mathbf{s}}(t')\right|} \left(\mathbf{s} - \mathbf{s}(t')\right) \right)$$

The prefactor $W(t')$ has the dimensions of an energy and must be chosen carefully in order to adapt $V(\mathbf{s},t)$ to the FES

The discrete form of $V(\mathbf{s},t)$ implemented in CPMD is

$$V\left(\mathbf{s},t\right)=\sum_{t_i<t} W_i \exp\left(-\tfrac{1}{2}\frac{\left(\mathbf{s}-\mathbf{s}_i\right)^2}{(\Delta s^{\perp})^2}\right)\exp\left[-\tfrac{1}{2}\frac{\left((\mathbf{s}_{i+1}-\mathbf{s}_i)\cdot(\mathbf{s}-\mathbf{s}_i)\right)^2}{(\Delta s_i^{\parallel})^4}\right]$$

where the Dirac δ has been expressed in the approximate Gaussian form

$$\delta\left(x\right)\approx\frac{1}{\beta\sqrt{2\pi}}\exp\left(-\frac{1}{2}\frac{x^2}{\beta^2}\right) \qquad \beta=\left|\dot{\mathbf{s}}(t)\right|\Delta t$$

and the discrete time step Δt must be such that

CPMD time step

$$\Delta t^{CPMD} << \Delta t << \omega_{\vec{s}_\alpha}^{-1}$$

Highest oscillation frequency of s_α

About the history dependent penalty potential

The N_s dimensional Gaussian :

$$V(t,\mathbf{s}) = \int_0^t dt'|\dot{\mathbf{s}}(t')|W(t')\exp\left\{-\frac{(\mathbf{s}-\mathbf{s}(t'))^2}{2(\Delta s^{\perp})^2}\right\}$$
$$\delta\left(\frac{\dot{\mathbf{s}}(t')}{|\dot{\mathbf{s}}(t')|}\cdot(\mathbf{s}-\mathbf{s}(t'))\right)$$

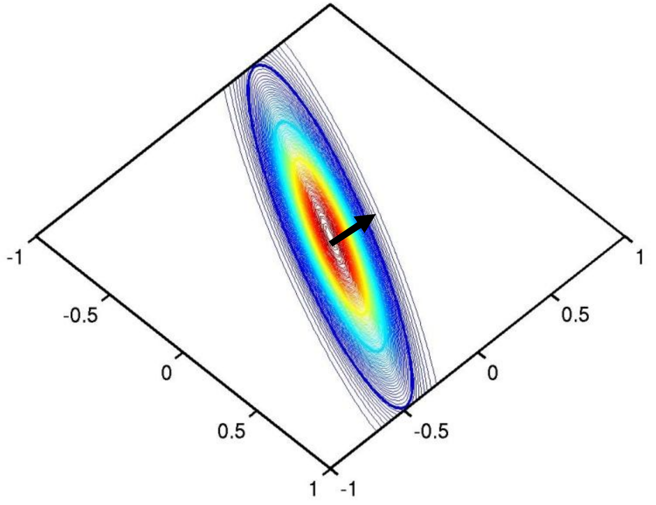
Localized on

Adaptive to the

Continuous trajectories in Σ

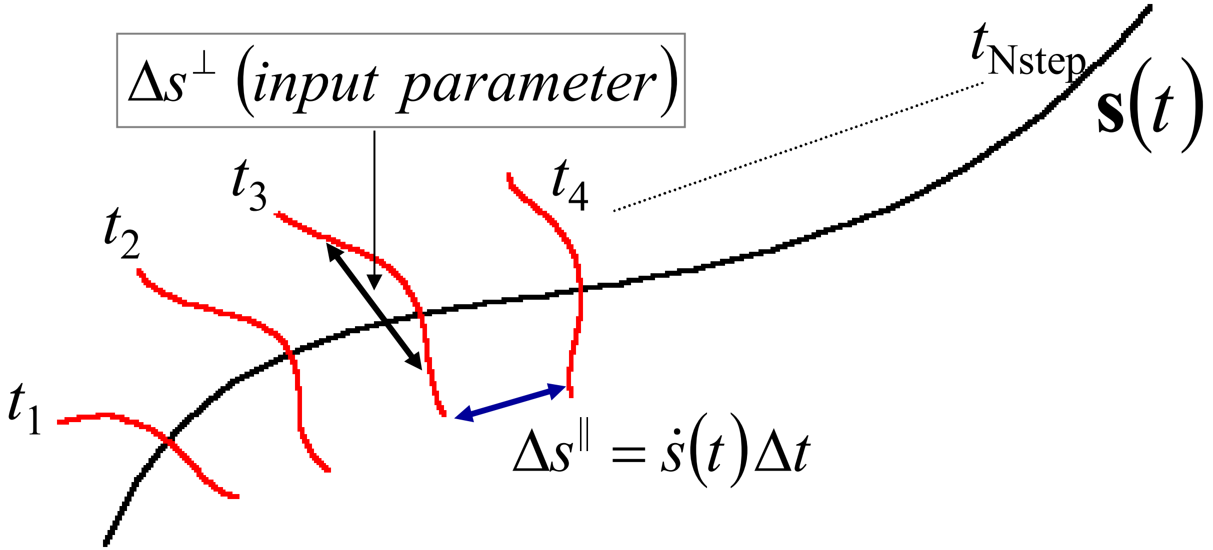
$$i \simeq \int_{t_i}^{t_i+\Delta t} dt'|\dot{\mathbf{s}}(t')|$$

Orthogonal to the trajectory



What is the meaning of all this ?

It is a N_s-dimensional gaussian *tube* having the $s_\alpha(t)$ trajectory as an axis and around which we accumulate gaussians



In $V(\mathbf{s},t)$ the slices from t_1 to t_{Nstep} are accumulated as a sum of gaussian functions and the slices have a thickness $\Delta s^{\|}$

FES reconstruction: what $V(\mathbf{s},t)$ is used for

When the (meta)dynamics is over and the walker has explored all the portion of the $\{\mathbf{s}\}$ phase space available, we have completed our job (at large t) and filled all the local minima, then the shape of $V(\mathbf{s},t)$ is similar to the FES apart from a sign and an arbitrary additive constant

$$\lim_{t\to\infty} V(\mathbf{s},t) = -F(\mathbf{s}) + const.$$

In practice: the number of gaussians required to fill a minimum is proportional to $(1/\delta\sigma)^n$ (n = dimensionality of the problem) and

$$W / \delta\sigma\, e^{-1/2} = \gamma \left\langle f_\alpha^2 \right\rangle^{1/2} \qquad \gamma \approx 0.5$$

FES reconstruction: Convergence issues

- The underlying potential $V(s_\alpha, t)$ does not converge actually to the free energy (+ constant) , but oscillates around it. This has two consequences.

1) The bias potential overfills the underlying FES and pushes the system toward high energy regions of the CVs space.
2) It is not trivial to decide when to stop a simulation.

•Thumb rule: Metadynamics can be stopped as soon as the system exits from the (initial) minimum. If one is interested in reconstructing an FES, it should be stopped when the motion of the CVs becomes diffusive in the region of interest.

Warning: Identifying a set of CVs appropriate for describing

•complex processes is far from trivial.

FES reconstruction: Convergence issues

- The FES estimation by continuing the simulation to allow the system to pursue its (meta)dynamics for a few passages back and forth from the reactants side to the products one is a practical way of smoothing the $V(s_\alpha,t)$ oscillations
- When all the minima of the FES are saturated, the system can diffuse in a nearly free manner from reactants to product. Then

$$F(\mathbf{s}) = -\frac{1}{t_{simul} - t_{diff}} \int_{t_{diff}}^{t_{simul}} V(\mathbf{s},t)\,dt$$

FES reconstruction: Convergence issues

- Another workaround to cure the $V(s_\alpha,t)$ oscillations is the so called *well-tempered metadynamics*
- The bias deposition rate decreases over simulation time by the use of the expression

$$V(\mathbf{s},t) = k_B \Delta T \cdot \ln\left[1 + \frac{\omega \cdot N(\mathbf{s},t)}{k_B \Delta T}\right]$$

where $\omega = W/\tau_g$, ΔT is an input parameter having temperature dimensions and $N(\mathbf{s},t)$ is the histogram of **s** collected during the simulation. (τ_g=deposition stride of Gaussians)

FES reconstruction: Convergence issues

- In practice, the Gaussian amplitude W is rescaled as

$$W = \omega \cdot \tau_g \cdot \exp\left[-\frac{V(\mathbf{s},t)}{k_B \Delta T} \right]$$

and the bias deposition rate decreases as $1/t$

- The bias potential converges then to

$$\lim_{t\to\infty} V(\mathbf{s},t) = -\frac{\Delta T}{T+\Delta T} F(\mathbf{s}) + \text{constant}$$

- $\Delta T \rightarrow 0$: Standard MD $\quad \Delta T \rightarrow \infty$: Standard metadynamics

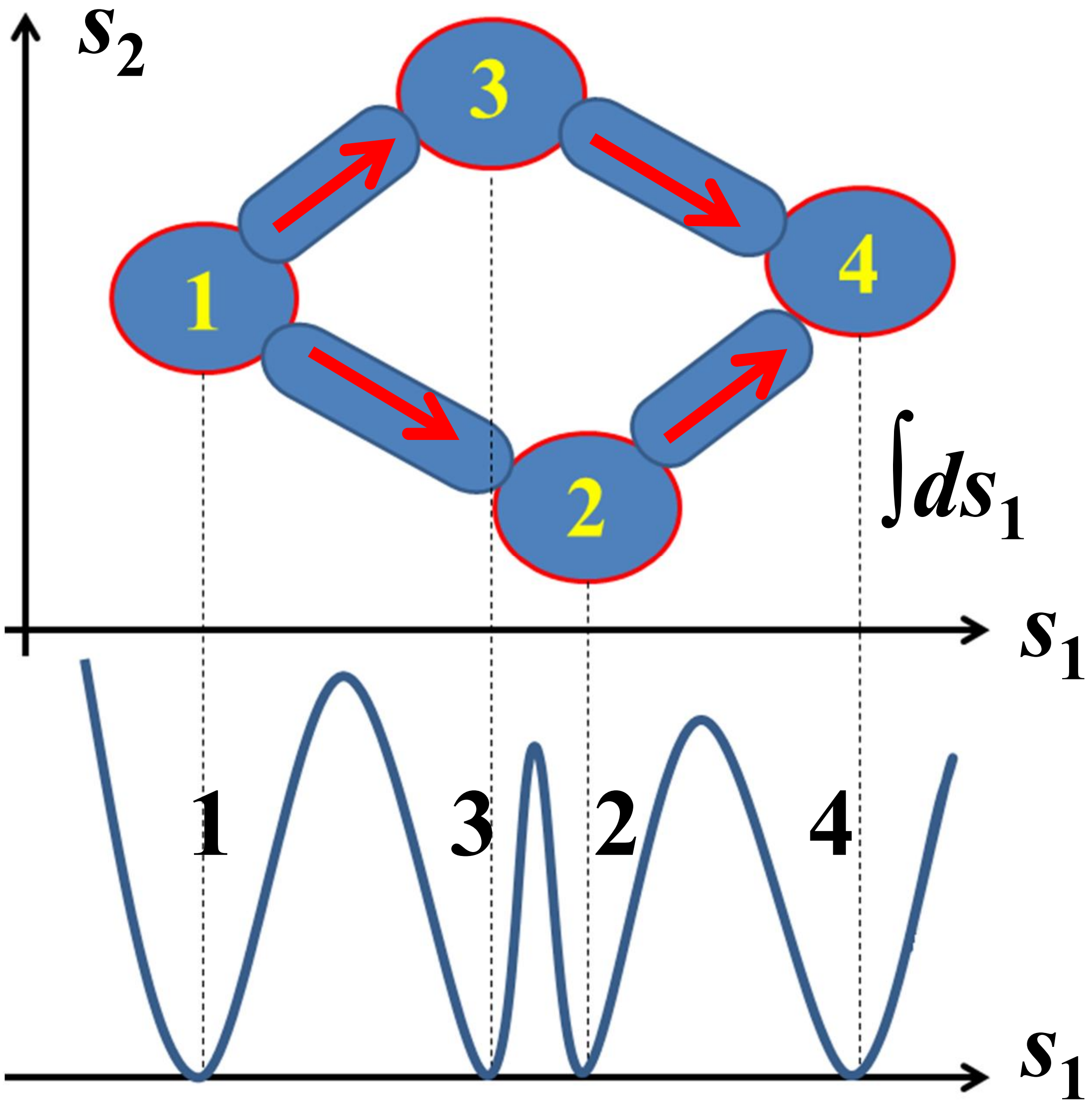
(Ref: WIREs vol. **1**, p. 826-843 (2011))

FES reconstruction: Focusing on relevant CVs

- In some (many) cases several $s_\alpha(t)$ can be selected, even redundant ones.
- This is not hindering or jeopardizing the FES exploration, provided that in the set $\{s_\alpha(t)\}$ the relevant CVs exist
- Once that $F(s_1,\ldots,s_N)$ has been obtained, the non-relevant CVs can be integrated out as

$$F\left(s_1,\ldots,s_{n<N}\right) = -k_B T \log \frac{\int \exp\left[-F\left(s_{n+1},\ldots,s_N\right)/k_B T\right] ds_{n+1}\ldots ds_N}{\int ds_{n+1}\ldots ds_N}$$

FES reconstruction: Focusing on relevant CVs … but with a warning



- Minima Topology
- Energy barriers
- Connectivity

can turn out wrong if a non-redundant CV is missing

Note that:

1. The parameter ***t*** in $s_\alpha(t)$ is not a *real* time, but rather an index labeling the configurations that explore the FES
2. $\Delta s_\alpha^{\|} = s_\alpha(t+\delta t) - s_\alpha(t)$ can be arbitrarily large (coarse-grained *meta*dynamics) and gives the accuracy in the sampling of the FES along the trajectory described by the $s_\alpha(t)$ variables
3. The dynamics at each fixed s_α is a *true* dynamics used to explore the local portion of FES
4. The FES is smoother than the PES, being dependent on a reduced number of variables

Some warnings:

- Parameters are system dependent
- The collective variables s_α must be identified by the *user*
- …and must be able to discriminate between initial and final state
- …and must keep into account all the *slow* degrees of freedom
- Although the trajectory generated describes the most probable reaction pathway, it is not the true dynamics

Note: connection between metadynamics and Blue Moon

In the case of a single collective variable (reaction coordinate), $\alpha = 1$

$$\mathcal{L} \quad = \quad \mathcal{L}_{CP} + \frac{1}{2} M \dot{s}^2 - \frac{1}{2} k \big(s(\mathbf{R}_I) - s\big)^2 - V(s,t)$$

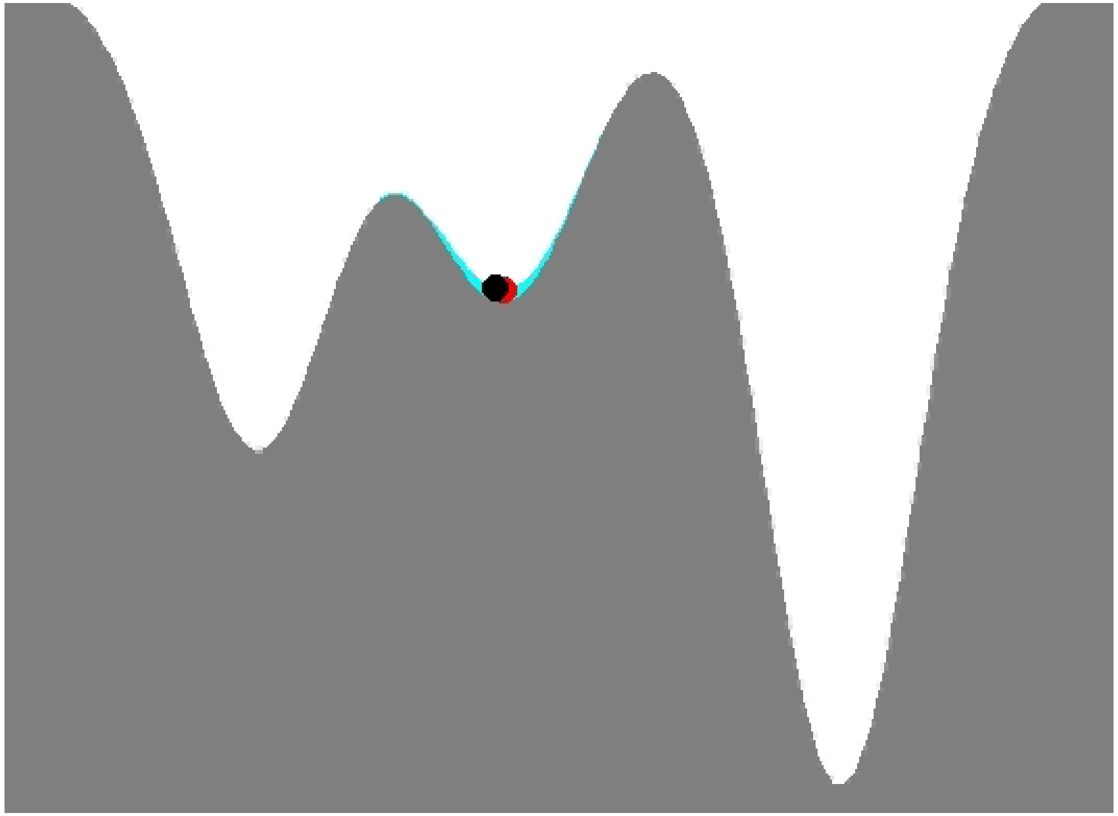
$$\left.\begin{array}{l} \text{• Do not update the Gaussians: } \quad V(s,t) \to 0 \\[1em] \text{• Do not move dynamically } s(t)\text{: } \quad \dot{s} = 0 \end{array}\right\} \text{ update } \textit{manually}$$

$$\mathcal{L} \quad = \quad \mathcal{L}_{CP} - \lambda \big(s(\mathbf{R}_I) - s\big)^2$$

where $\lambda = k/2$.

…Then we are back to a Blue Moon formulation.

Multiple walkers



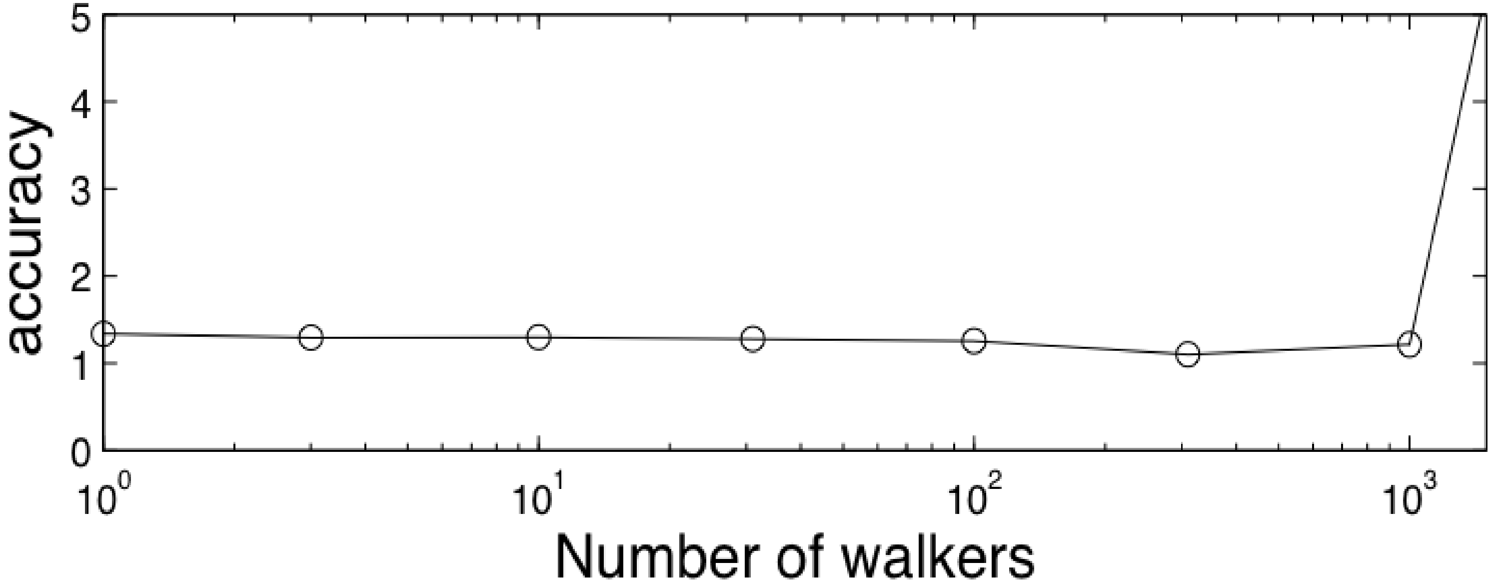
Parallel efficiency: the processors share only the position of the Gaussians

The accuracy is independent on the number of walkers

(but the simulation time decreases ***linearly***)

Unlimited speed up? No way !

There’s an upper limit defined by the ***system properties*** and the ***metadynamics parameters***



$$N_W \ll \frac{D}{S^2}\tau_G \frac{\beta F^2}{w}\left(\frac{S}{\delta s}\right)^d \frac{1}{c_d^2}$$

Example of Metadynamics application: NaCl in water

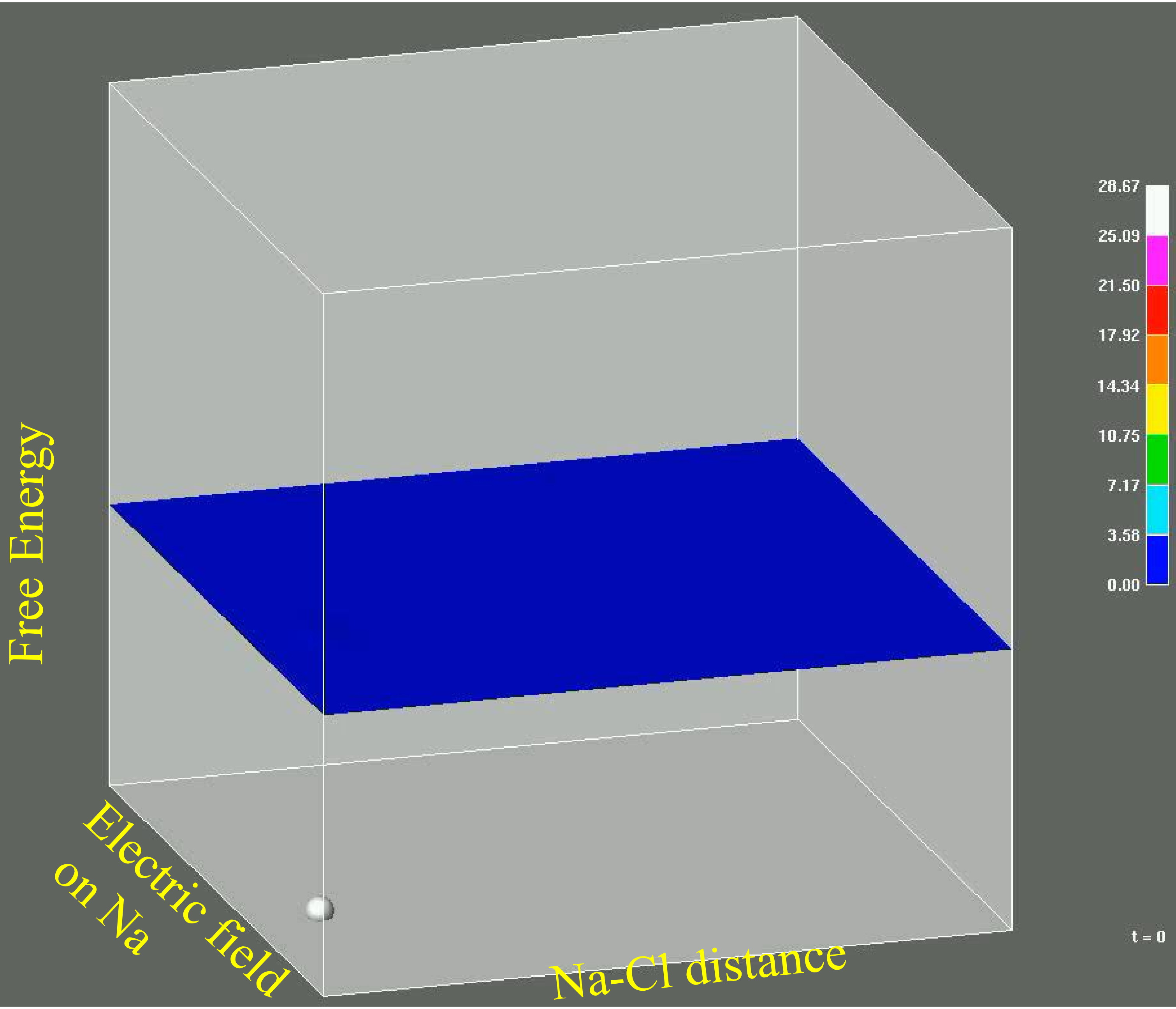
Two minima: Contact ion pair (metastable)

Dissociated

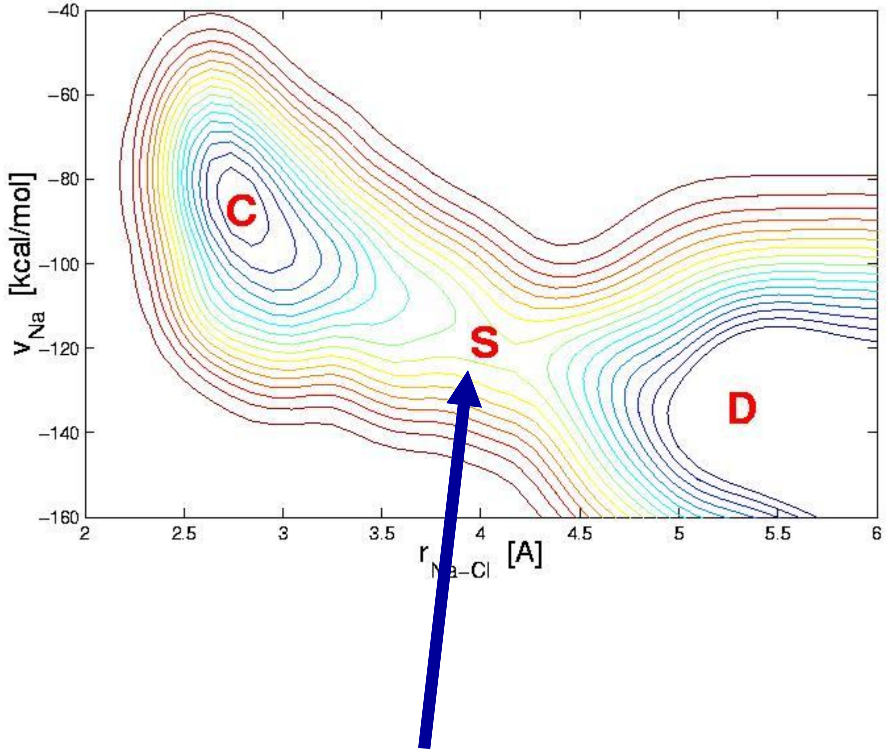
Collective variables: Electric field on Na^+

Electric field on Cl^-

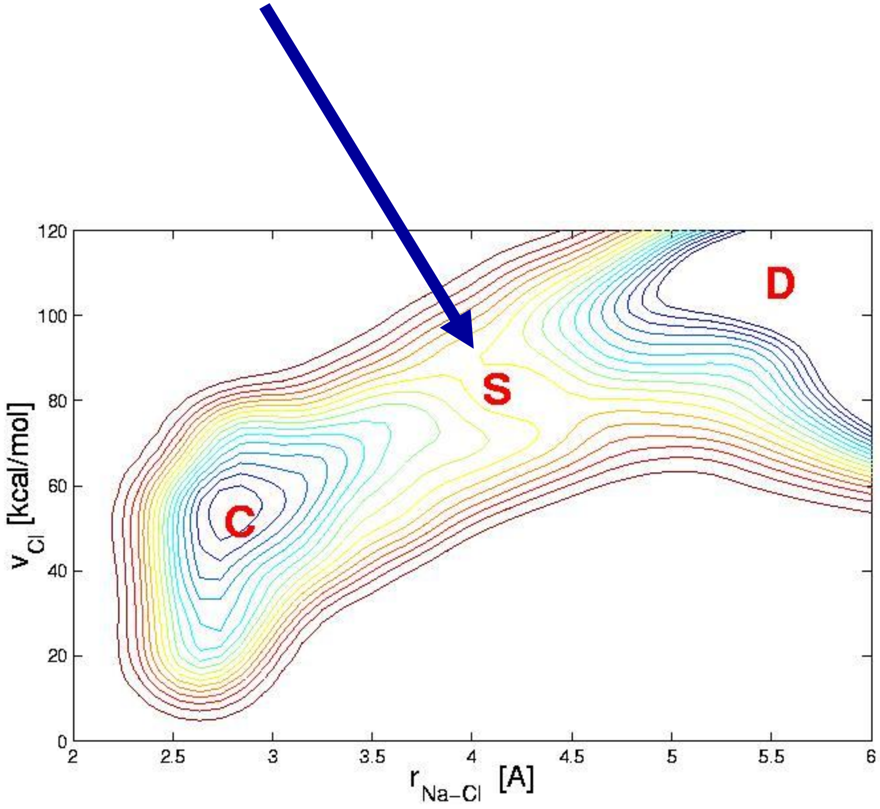
Distance Na^+ Cl^-


Free Energy
Electric field on Na
Na-Cl distance
28.67
25.09
21.50
17.92
14.34
10.75
7.17
3.58
0.00
t = 0

Free energy surface

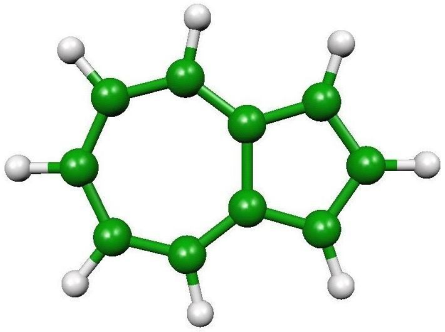


Transition state

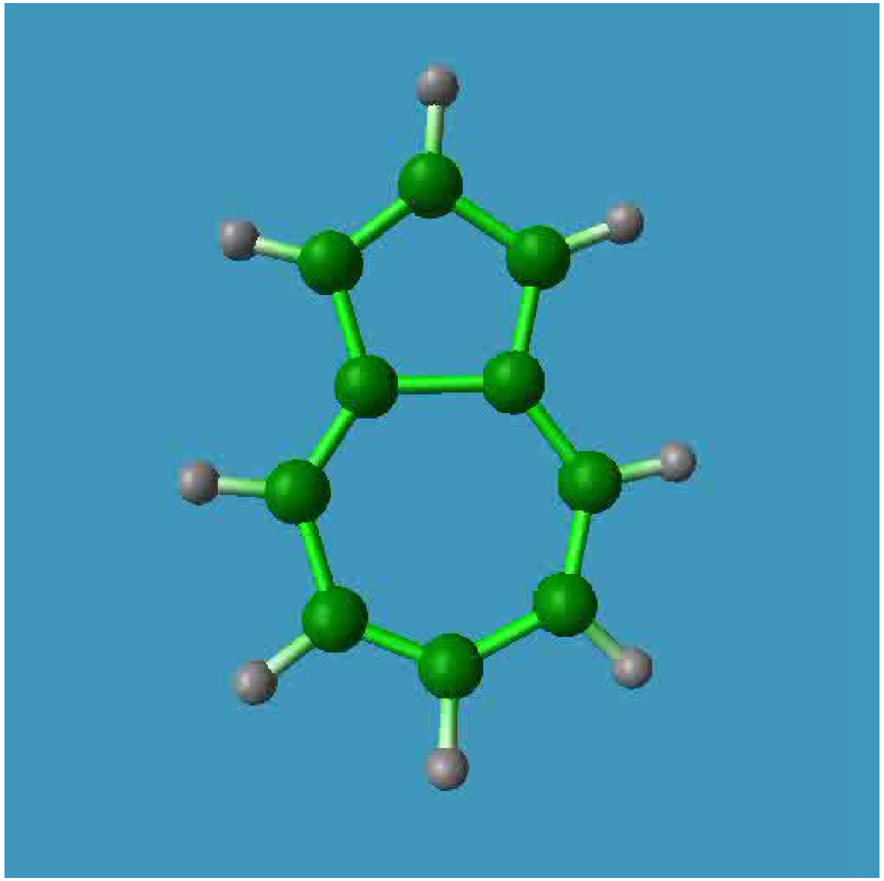


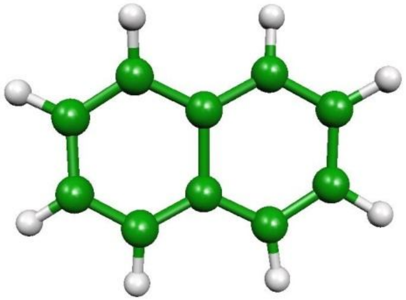
Transition state

CPMD metdynamics: an example of application



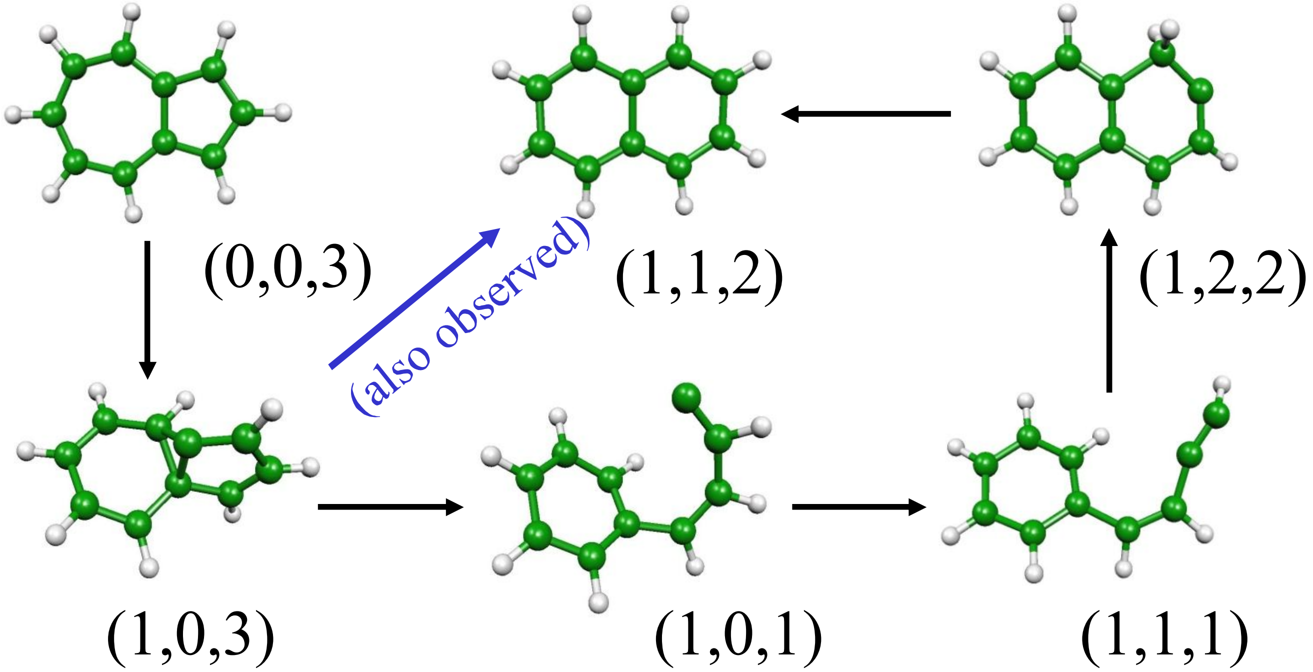
Azulene

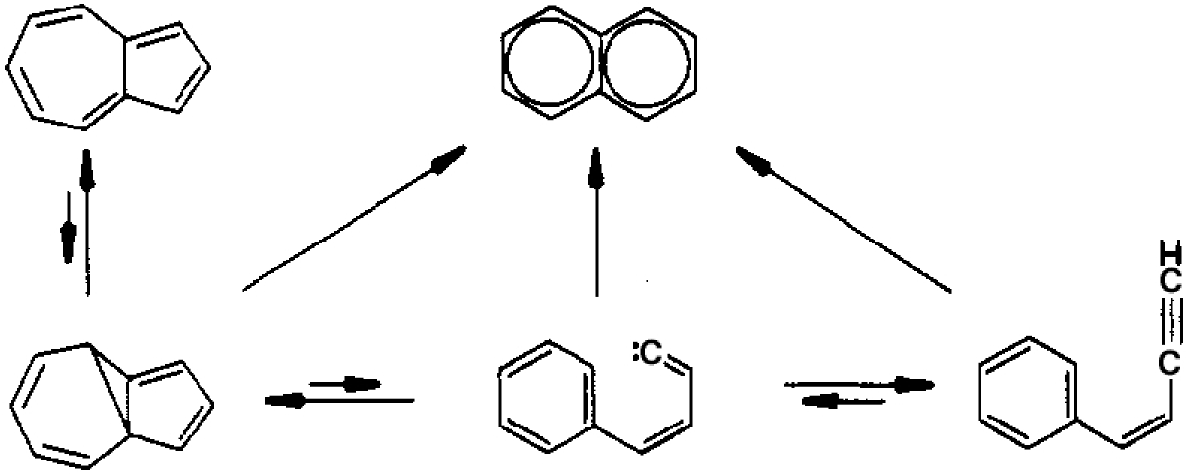




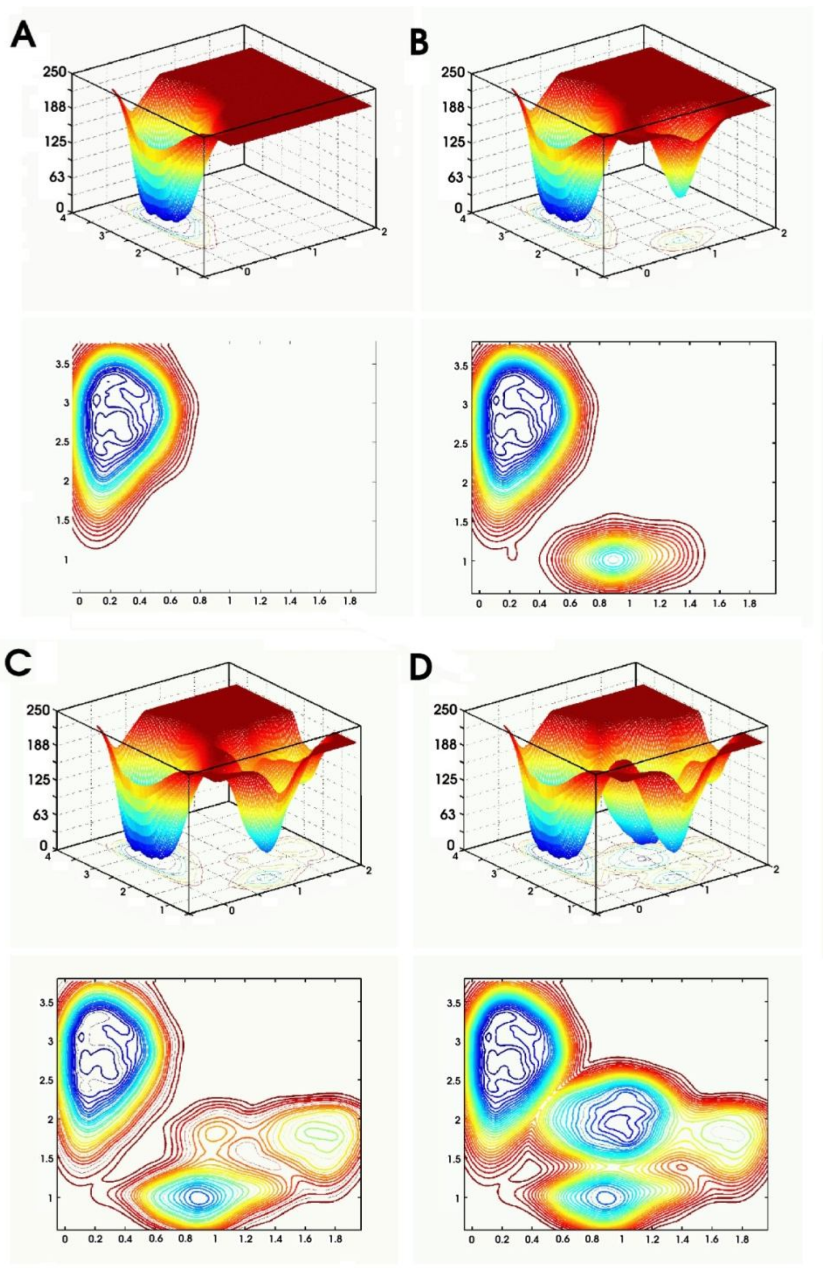
Naphthalene

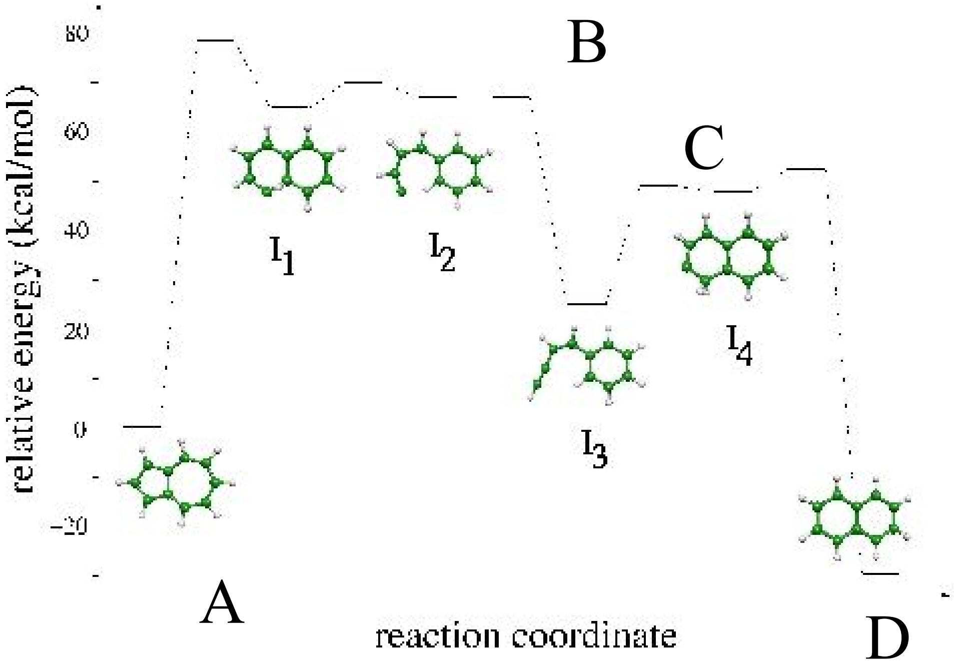
Clearing a barrier > **70 kcal/mole**





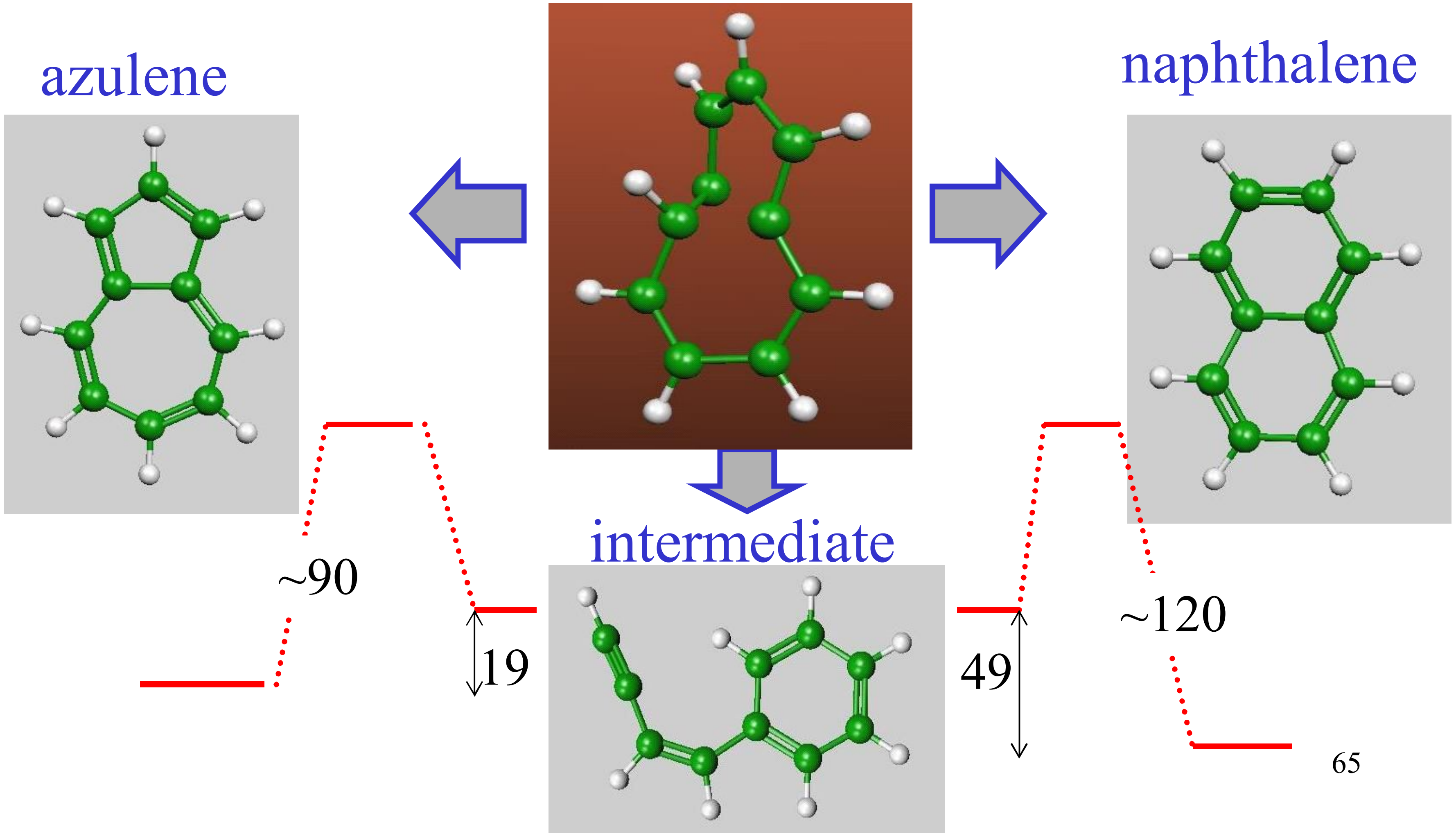
L.T. Scott, Acc.Chem.Res., **52** p 15 (1982)


A
B
C
D
250
188
125
63
0
4
3
2
1
0
1
2
3.5
3
2.5
2
1.5
1
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8


relative energy (kcal/mol)
80
60
40
20
0
-20
B
C
I_1
I_2
I_3
I_4
A
D
reaction coordinate

The Dynamic Transition State

Shooting with random velocities & free MD



azulene

naphthalene

intermediate

~90

19

49

~120

Summarizing

- The method is useful for adiabatic processes (we stay always on the same PES)
- The collective variables describing the process are known exactly and they must be able to distinguish the reactants from the products
- It is applicable in the microcanonical ensemble and it makes use of an underlying (faster) dynamics (e.g. CPMD)
- It requires an approximate knowledge of the FES, but does not require any knowledge about the products
- It does not require unaffordable long simulation times

An alternative to biasing methods: Path searching methods

- Nudged elastic band (H. Jonsson et al, 1998)
- Path search (M. Karplus et al., 1997)
- Path sampling/annealing (D. Chandler et al., 1998)
- Action derived MD (D. Passerone and M. Parrinello (2001))
- String method in collective variables (CVs) L. Maragliano *et al*., J. Chem. Phys. **125**, 024106 (2006)
- Free energy path A-to-B (M. Parrinello et al., *J. Chem. Phys*. **126**, 054103 (2007))

No one of those methods is able to give the real dynamical path chosen by the reactants to transform into the products and requires previous knowledge of both the reactant and the product

See e.g. D. Chandler et al. *J. Chem. Phys*. **108**, 1964 (1998)
J. Phys. Chem. B **103**, 3706 (1999)

What we do need to know:

1) The atomic configuration at the starting point

$$q_A = q(0) = \left\{ \vec{R}_1, \ldots, \vec{R}_N \right\}_{t=0}$$

2) The atomic configuration at the end of the reaction

$$q_B = q(\tau) = \left\{ \vec{R}_1, \ldots, \vec{R}_N \right\}_{t=\tau}$$

3) The equations of motion or the lagrangean

$$L(q, \dot{q}) = \frac{1}{2} \dot{q}^2 - V(q)$$

Path minimization

However, in many cases, we simply want to know the barrier height and its location for a known reactant and product pair.

String method in collective variables (CVs) proposed by L. Maragliano *et al*., J. Chem. Phys. **125**, 024106 (2006).

String method + biased sampling method → Minimum free energy paths (MFEPs) in some selected CVs space

Blue moon ensemble :

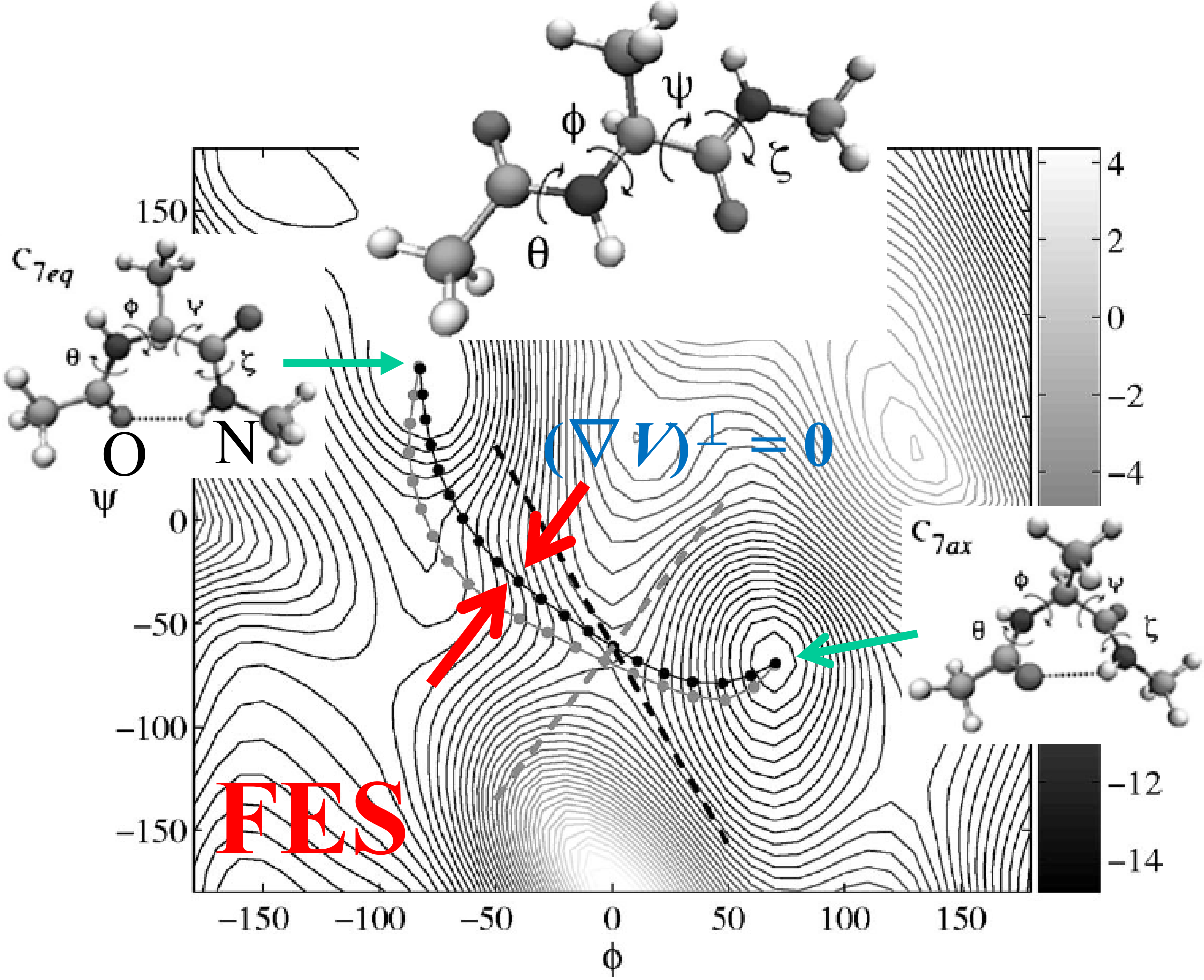
- Applicable to reactions of unknown products
- In practice 1 CV only
- Very time-consuming

Path minimization:

- Require *a priori* knowledge of products
- Applicable to more than 2 CVs
- Not time but ***resource*** consuming

Minimum free energy paths

Minimum energy path → $(\nabla V)^{\perp} = 0$ for any point along the path



E.g. minimum free energy paths for conformers of alanine depeptide molecule

String method ?

More precisely,

$$0=\sum_{j,k=1}^{N}P_{ij}(\alpha)M_{jk}(z(\alpha))\frac{\partial F(z(\alpha))}{\partial z_k} \qquad (1)$$

where $P_{ij}(\alpha)$: projector on the plane perpendicular to the path at $z(\alpha)$

The string method constructs an *evolution equation for a parametrized curve* (string), which converges to a solution of Eq. (1) as time evolves.

$$\begin{cases} \dfrac{\partial z_i(\alpha,t)}{\partial t}=-\displaystyle\sum_{j,k=1}^{N}P_{ij}(\alpha,t)M_{jk}(z(\alpha,t))\frac{\partial F(z(\alpha,t))}{\partial z_k} \\ z(0,t)=z_a \quad \text{and} \quad z(1,t)=z_b \end{cases} \qquad (2)$$

Mean force calculation

The mean force $\nabla_z F(z)$ and the tensor $M_{ij}(z)$ are given in terms of a conditional average on $s(x) = z =$ constant. The key is to use the extended potential rather than the bare $V(x)$:

$$U_{k,z} = V(x) + \frac{k}{2}\sum_{j=1}^{N}\left(s_j(x) - z_j\right)^2 \tag{3}$$

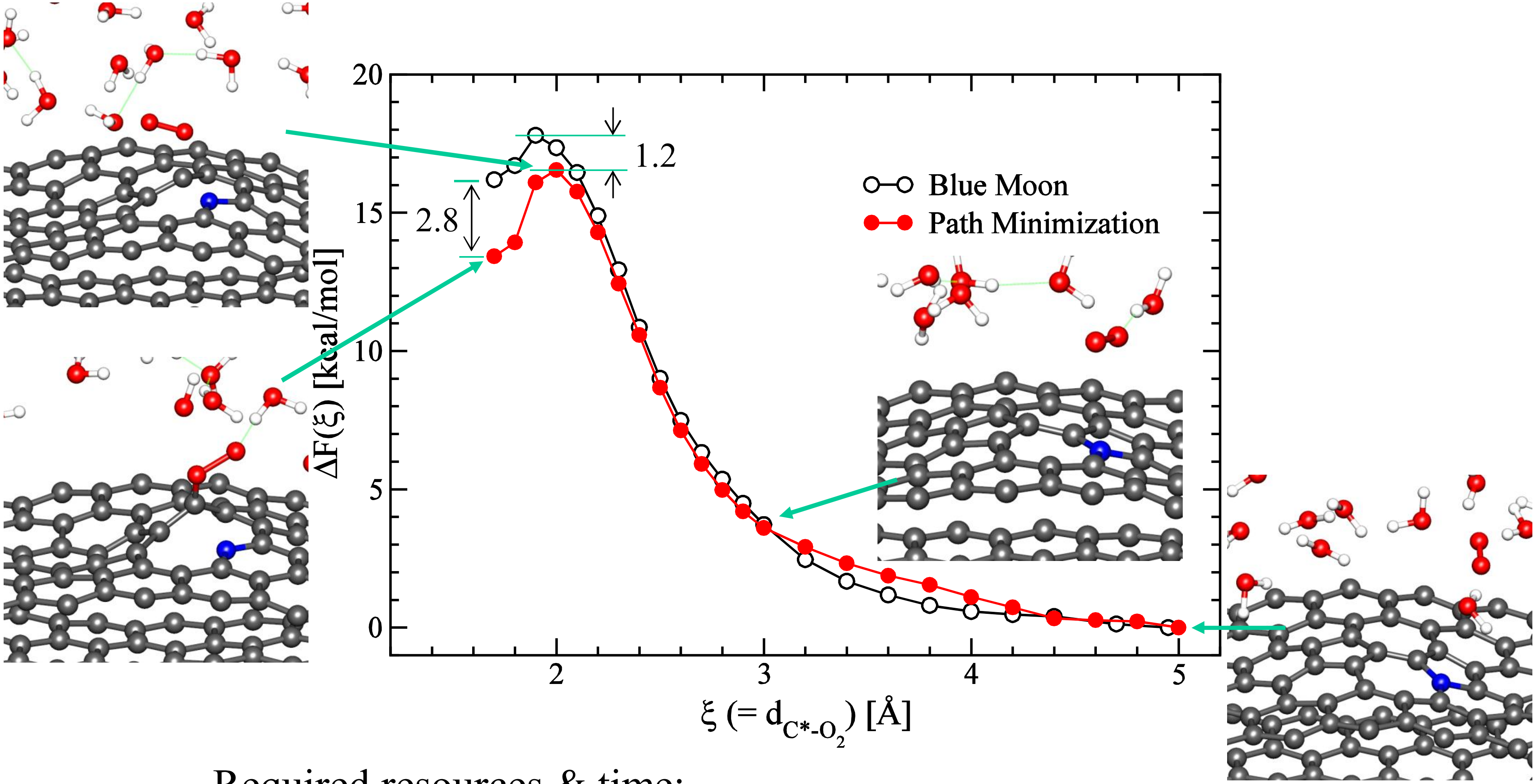
Then

$$\frac{k}{T}\int_0^T \left(z_j - s_j(x(t))\right)dt \approx \frac{\partial F(z)}{\partial z_j}, \quad \frac{1}{T}\int_0^T \frac{\partial s_i(x(t))}{\partial x_k}\frac{\partial s_j(x(t))}{\partial x_k}dt \approx M_{ij}(z)$$

Finally, the free energy difference along the string can be computed as

$$F(z(\alpha)) - F(z(0)) = \int_0^\alpha \sum_{i=1}^{N} \frac{dz_i(\alpha')}{d\alpha'}\frac{\partial F(z(\alpha'))}{\partial z_i} d\alpha' \tag{4}$$

An example: Stone-Wales defect



Required resources & time:

- 2 nodes x 24 replicas = 48 nodes in total
- 6 days (including waiting time) @TSUBAME (Japan)

Input for CPMD

```
&CPMD
  PATH MINIMIZATION
  MOLECULAR DYNAMICS
  RESTART LATEST ACCUMULATORS WAVEFUNCTION COORDINATES VELOCITIES
  MAXSTEP
   13500
  FILEPATH
  /home/usr0/10ITA059/CPMD/Work/shokucar/pmin
&END

&PATH
  REPLICA NUMBER
   24
  READ REPLICAS
   replica.inp
  OUTPUT GROUPS
  NLOOP
   1
  NEQUI
   300
  NPREVIOUS latest
   0
  PROJOUT
  CONVERGENCE
   1.0D-4
  COLLECTIVE VARIABLES
   1
   1
&END

&ATOMS
    ......
    ......
    ......
  CONSTRAINTS
   RESTRAINT
     25
     DIST  168  106  -999.  1.0
     RESPOS  140 -8.047591 10.368175 -5.172371  0.0  0.0035
     RESPOS  141 -8.023780  7.724259 -5.363423  0.0  0.0035
     ......
     ......
     ......
  END CONSTRAINTS
&END
```

pmin_1,
pmin_2, …

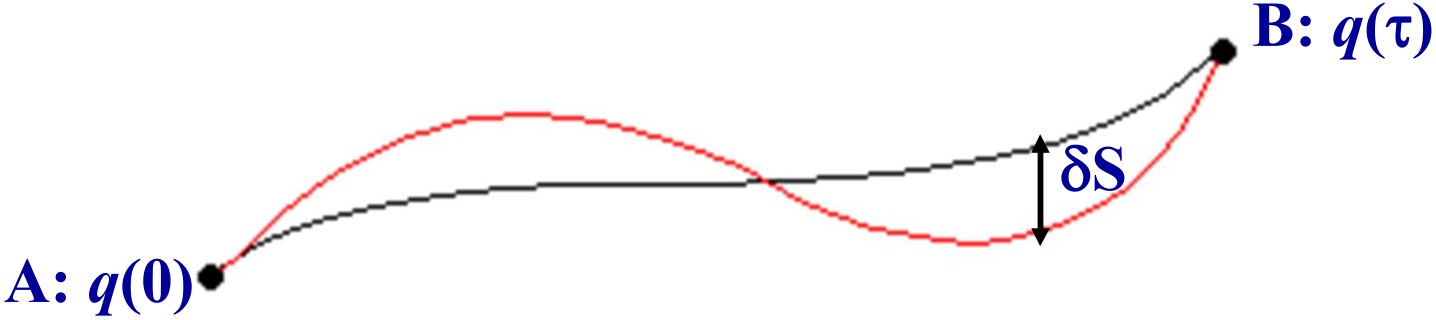
replica.i
np

STRING.0,
STRING.1, …

LATEST_STRING

Action-derived MD: Hamilton principle of stationary action at fixed boundaries

$$S = \int_0^{\tau} L(q(t), \dot{q}(t))\, dt$$



$$\delta S = \delta \int_0^{\tau} L(q(t), \dot{q}(t))\, dt = 0$$

…unfortunately, stationary does NOT mean minimum

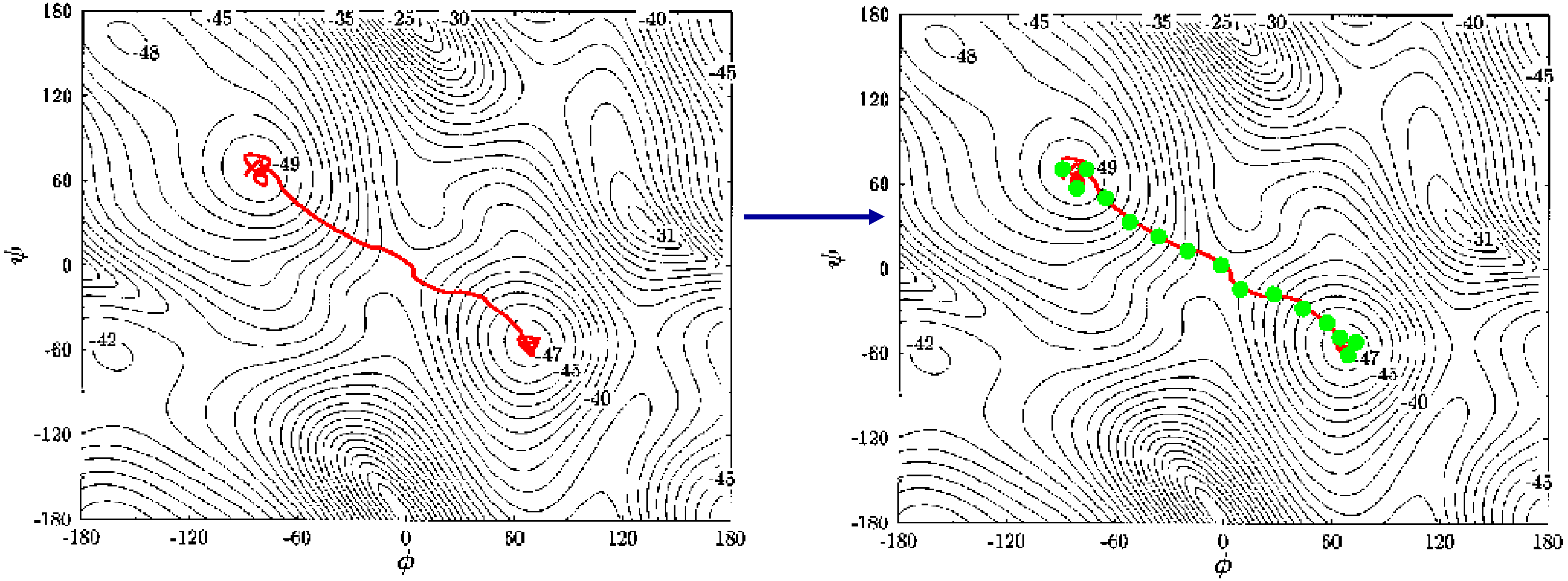
Adding some physics to bound the action: energy conservation as a constraint

$$\Theta(q,E) = \int_0^\tau L(q(t),\dot{q}(t))\,dt + \lambda \int_0^\tau (\widetilde{H} - E_0)^2\,dt$$

- The constraint is a quadratic form (i.e. positive) that sets a boundary to the action
- The parameter λ is a Lagrange multiplier which has the physical dimensions of 1/E
- The pseudo-*hamiltonian* $\widetilde{H} = \dot{q}^2(t)/2 + V(q)$ is not related to L by a linear transformation

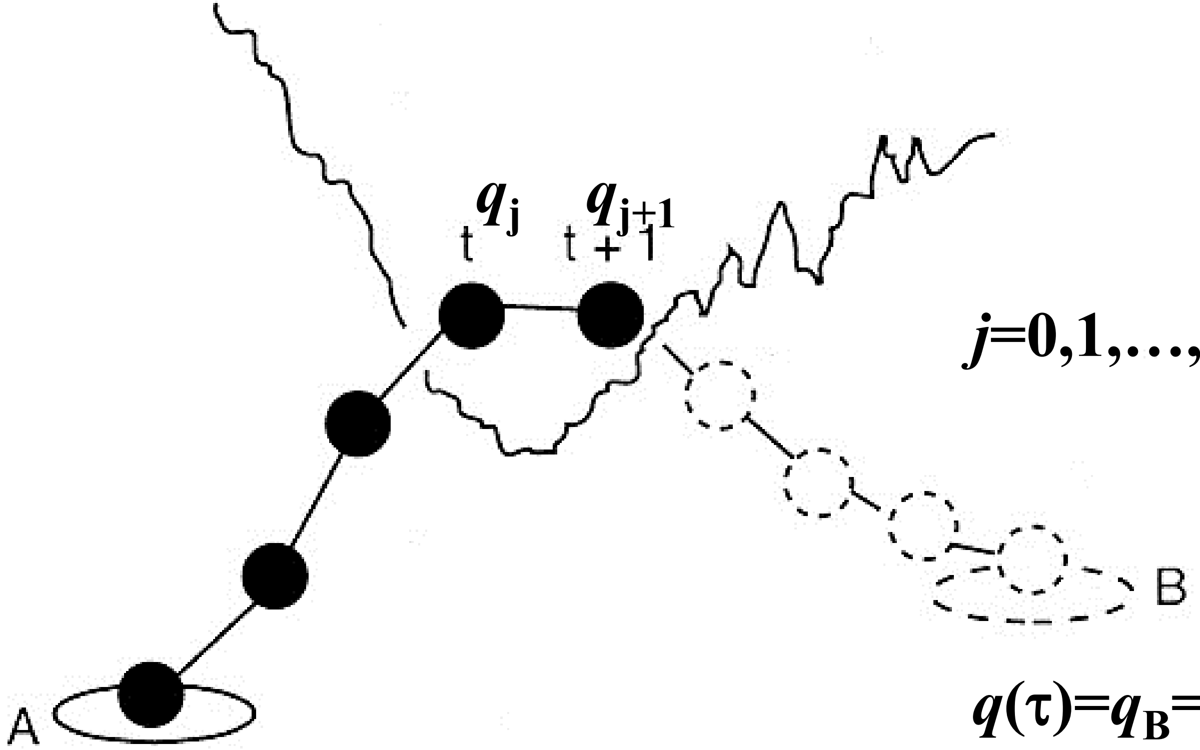
note that it is not a ***Legendre*** transformaton $\dot{q}(t) \Rightarrow p(t)$

Practical implementation:how to write the action in a discrete form



$$S \to \tilde{S} = \sum_{j=0}^{P} \Delta \left(m \frac{\left(\dot{\tilde{q}}_j\right)^2}{2} - V\left(q_j\right) \right) w_j \quad \left(P\Delta = \tau = t_B - t_A\right)$$

Practical implementation:how to write the action in a discrete form



$j=0,1,\ldots,P$

$q(\tau)=q_B=q_P$

$q(0)=q_A=q_0$

every physical trajectory conserves the energy, but ***not every trajectory that conserves energy is physical***

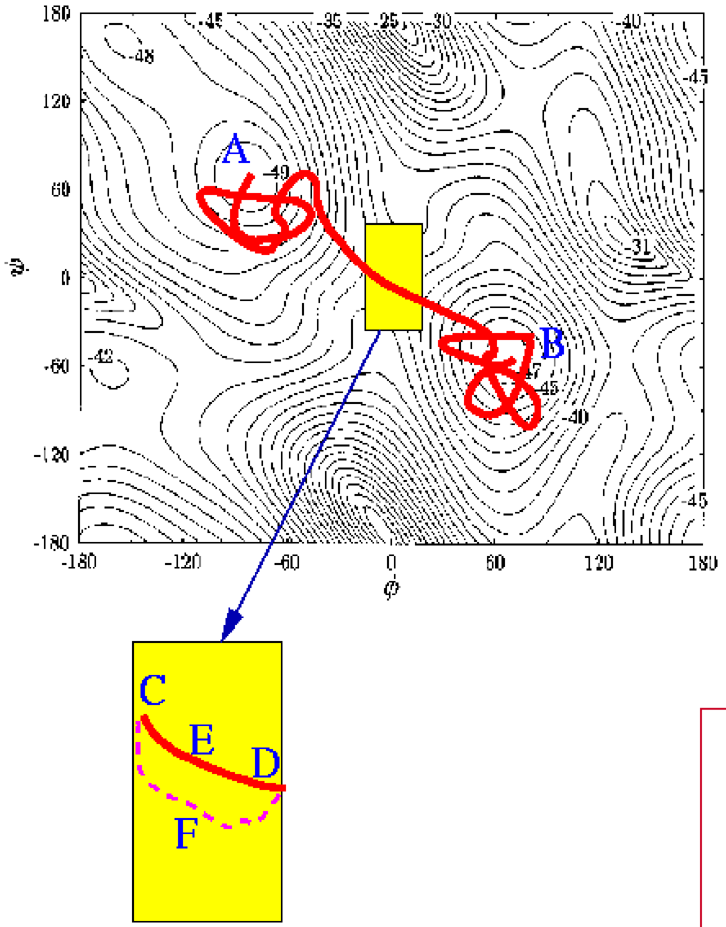
Practical implementation: discretize the action without the constraint

$$S = \sum_{j=0}^{P-1} \left[\frac{1}{2} \left(\frac{q_{j+1} - q_j}{\Delta} \right)^2 - V(q_j) \right] \cdot \Delta$$

where $\Delta = \tau / P$, P = number of discrete points that has been chosen to write the integral in terms of a sum

- The finite difference algorithm for the velocities can be refined (e.g. central differences)
- …but S is not bounded and searching for a stationary (minimum) point is challenging !

Maximum action?



- If the trajectory is **very short** (no inversion in the velocities), it can be proven that the stationary point **is** a minimum.
- Could it be a maximum? **NO**

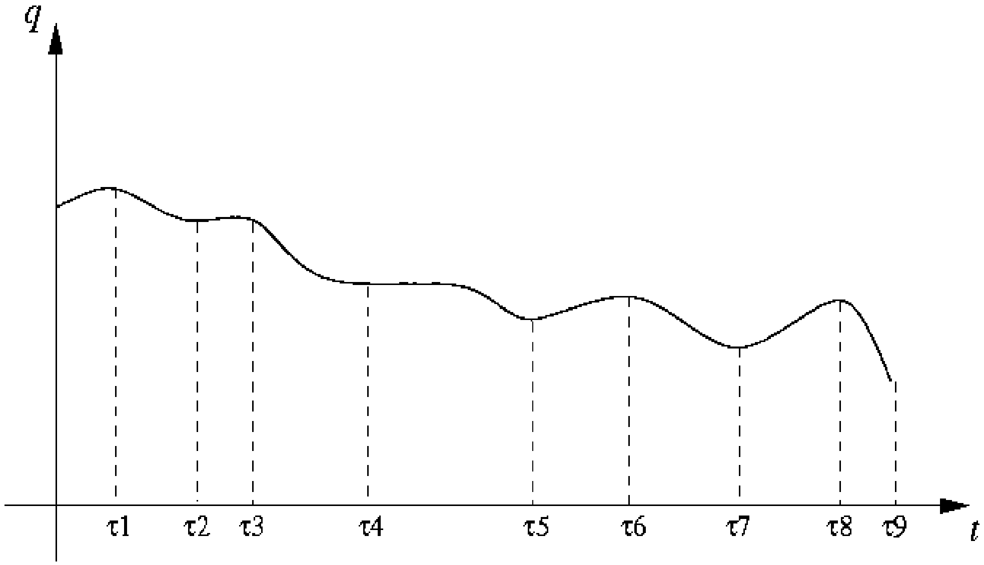
•If *AB* is a physical trajectory, $\delta S_{AB} = 0$

•A small portion of *AB* (with $\tau_{CD} < \tau_1$) makes *S* minimum

$$S_{AB} = S_{AC} + S_{CED} + S_{DB} < S_{AC} + S_{CFD} + S_{DB}$$

Saddle points

- For small enough times, the motion can always be approximated by the motion of a free particle. In this case the solution (straight line) is a minimum.
- Upon time increase, at given instants (*conjugate points*), negative eigenvalues may appear in the Hessian of S at the stationary point, and the minimum becomes a saddle point… and in long trajectory, several negative eigenvalues can occur:



Equations of motions by finite differences

$$\frac{\delta S}{\delta q} = 0 \Rightarrow \ddot{q}(t) + \frac{\partial V(q)}{\partial q(t)} = 0$$

$$-\frac{\partial S}{\partial q_j} \equiv F_j = 0 \Rightarrow -\frac{q_j - q_{j-1}}{\Delta^2} + \frac{q_{j+1} - q_j}{\Delta^2} + \frac{\partial V}{\partial q_j} = 0$$

$$\xrightarrow{\textbf{left}} \quad \boldsymbol{q_j} \quad \xleftarrow{\textbf{right}}$$

- The “force” F_j (left + right components) has to be set to zero on each point of the path chain

Practical implementation: which problems arise ?

$$\ddot{q}(t) = -\frac{\partial V(q)}{\partial q(t)} \Rightarrow q_{j+1} + q_{j-1} - 2q_j = -\Delta^2 \frac{\partial V}{\partial q_j}$$

- A set of (coupled) linear equations whose roots (solutions) depend on the choice of Δ
- Furthermore (as in every MD) we want to compute only first derivatives (=forces)
- …and we want the solution to be a minimum of S

Practical implementation: adding the energy constraint

$$\Theta\left(q_j, E_0\right) = S + \mu \sum_{j=0}^{P-1} \left(\widetilde{H}_{j+1,j} - E_0\right)^2$$

$$\widetilde{H}_{j+1,j} = \frac{(q_{j+1} - q_j)^2}{2\Delta^2} + V(q_j)$$

- The constraint (in discrete form) is added to impose the energy conservation
- The Lagrange multiplier μ (λΔ) determines how strict the energy conservation is

Practical implementation:
μ ? Quadratic constraint ?

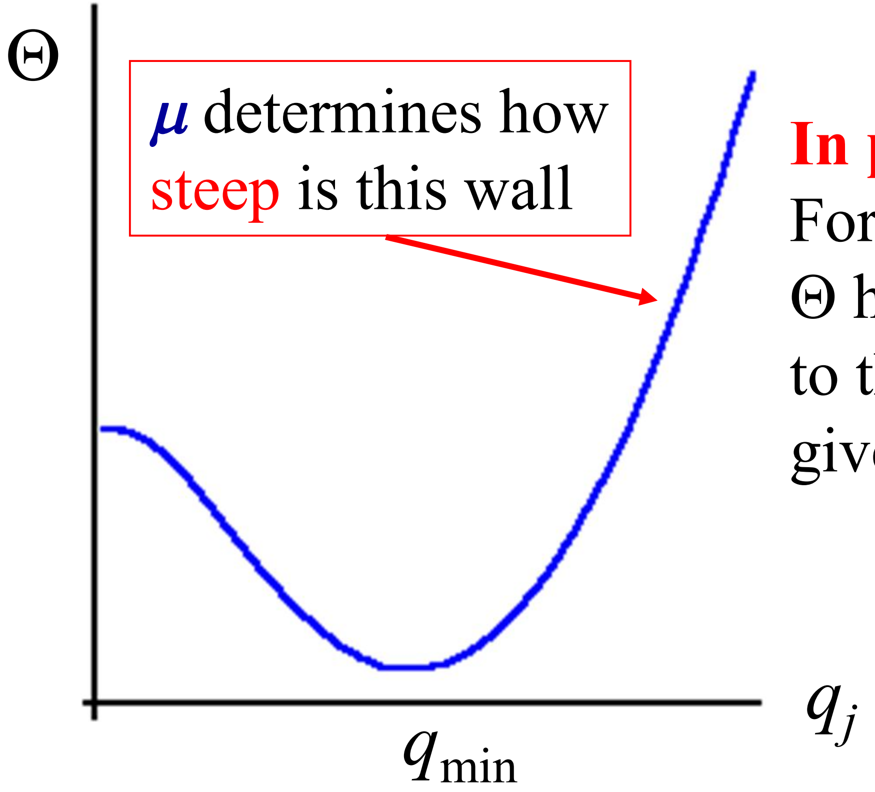
- Just to simplify, let's approximate $\Theta(q_j,E_0)$ as

$$\Theta(q_j,E_0)\approx const.+\sum_j\left(\frac{1}{2\Delta^2}q_j^{\,2}-\frac{1}{2}k\,q_j^{\,2}+\mu\,q_j^{\,4}\right)+\ldots$$

- $const.$ is $V(0)+E_0$+etc…, and $k=\left.\frac{\partial^2 V}{\partial q_j^{\,2}}\right|_0$
- For large μ, Θ is a quartic function of q_j with positive curvature: it has a minimum and the constraint dominates
- For small μ, Θ is practically S (stationary point =?)

Practical implementation: μ ? Quadratic constraint ?

- between $\mu \to 0$ and $\mu \to \infty$ there is a value μ^* separating the two regimes for which Θ behaves like



μ determines how steep is this wall

In practice:
For $\mu > \mu^*$ (do not overdo !)
Θ has a **minimum** very close to the MD Verlet trajectories given by S (Newtonian e.o.m.)

Practical implementation: minimization of the Θ functional

- The problem now is reduced to the minimization of the functional $\Theta(q_j,E_0)$ with respect to q_j (and E_0 if unknown)

$$\frac{\delta\,\Theta(q_j,E_0)}{\delta\,q_j}=0 \qquad \frac{\delta\,\Theta(q_j,E_0)}{\delta E_0}=0$$

- This sets E_0 to the physically relevant values
- But the variational q_j must not vary at $t=0$ (A) and $t=\tau$ (B) since we must satisfy the request of fixed boundaries

Practical implementation: from A to B without a map ? (M. Parrinello, 2001)

- If we do not know the road let's go straight first
  (and pray for the best)

$$\bar{q}_j = q_A + j\frac{\Delta}{\tau}\left(q_B - q_A\right)$$

This is not variational: everything is fixed and known, so let's add the variations δq_j and write

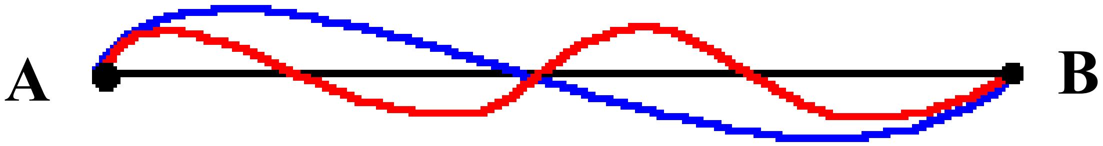
$$q_j = \bar{q}_j + \delta\, q_j$$

Practical implementation:
how to vary a path whose two ends are fixed

$$q_j = \overline{q}_j + \delta q_j$$

$$= q_A + j\frac{\Delta}{\tau}\left(q_B - q_A\right) + \sum_{l=1}^{P} a_l \cdot \sin\left(\pi\, l\, j \frac{\Delta}{\tau}\right)$$

What are we writing ?



The oscillations, in a Fourier fashion, around the straight path where the amplitudes of the various frequencies a_l are our (global) variational variables

Advantages and disadvantages

- Advantages of a Fourier description with respect to a cartesian one are the **smoothness** and the possibility of extracting **different time scales**
- The disadvantage is that the **sparseness** of the linear system due to discretization of Stationary Principle is lost
- **Continuity and smoothness**: the velocity reads

$$\dot{q}_j = \frac{q_B - q_A}{\tau} - \sum_{l=1}^{P} a_l \frac{\pi l}{\tau} \cos\left(\pi l \frac{j\Delta}{\tau} \right)$$

Keeping only a few harmonics is a good starting point

Practical implementation: minimizing the Θ functional

$$\frac{\delta\,\Theta\left(a_l, E_0\right)}{\delta\,a_l} = 0$$

The $\boldsymbol{a_l}$ variables do not depend on index $\boldsymbol{j}$, hence each $\boldsymbol{q_j}$ can be computed in parallel (no recursion)

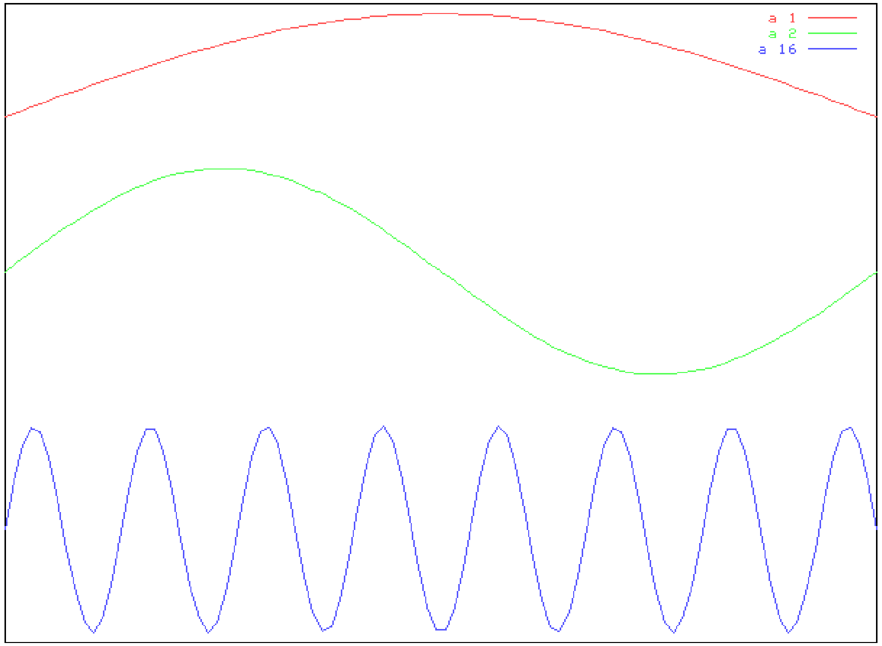
Using (e.g.) conjugate gradient algorithms only first derivatives (= forces) are required

⇓

The scaling is linear with $\boldsymbol{q} = \{\mathbf{R}_1,\ldots,\mathbf{R}_N\}$ (is quadratic with 2nd derivatives !)

Fourier expansion

- **Different timescales** for different Fourier components: the period is $\mathbf{2\tau/\mathit{l}}$



- Minimization of $\boldsymbol{\Theta}$ with $\boldsymbol{\mu = 0}$, keeping frozen the slowest harmonics, is possible: the Hessian of the action is positive definite in the subspace of the fastest harmonics.

How to extract the total time

- **Maupertuis' principle**: given a fixed total energy *E,* dynamical trajectories are those for which

$$\boxed{S_0 = \int_0^s \sum_{i=1}^{N} p_i \, \mathrm{d}q_i}$$

is *stationary*. ***s*** is a parameter, not the total time.

$$\boxed{S_0 = \int_0^s \sqrt{2(E-V)} \sqrt{\left(\sum_{i=1}^{N} m_i \, \mathrm{d}q_i \, \mathrm{d}q_i\right)}}$$

After finding the geometrical trajectory, the time intervals can be found as:

$$\boxed{t = \int_0^s \sqrt{\frac{\sum_{i=1}^{N} m_i \, \mathrm{d}q_i \, \mathrm{d}q_i}{2(E-V)}}.}$$

Minimization algorithms

Simulated annealing

- The Fourier components $\{a_l\}$ are given a fictitious mass and become dynamical variables in a Verlet integration scheme.
- An initial (CP)MD (on the $\{a_l\}$) on the PES of Θ is needed to equilibrate away from the initial trial trajectory
- During this equilibration step, the fictitious temperature of the Fourier components corresponds to an actual temperature of the atoms of a few thousand Kelvin.
- The fictitious dynamical system is then *cooled* through velocity scaling until the atoms temperature in the initial and final state is close the expected physical conditions. Since a rare event is not an equilibrium process, temperature is not a well defined thermodynamic quantity along the dynamic trajectory

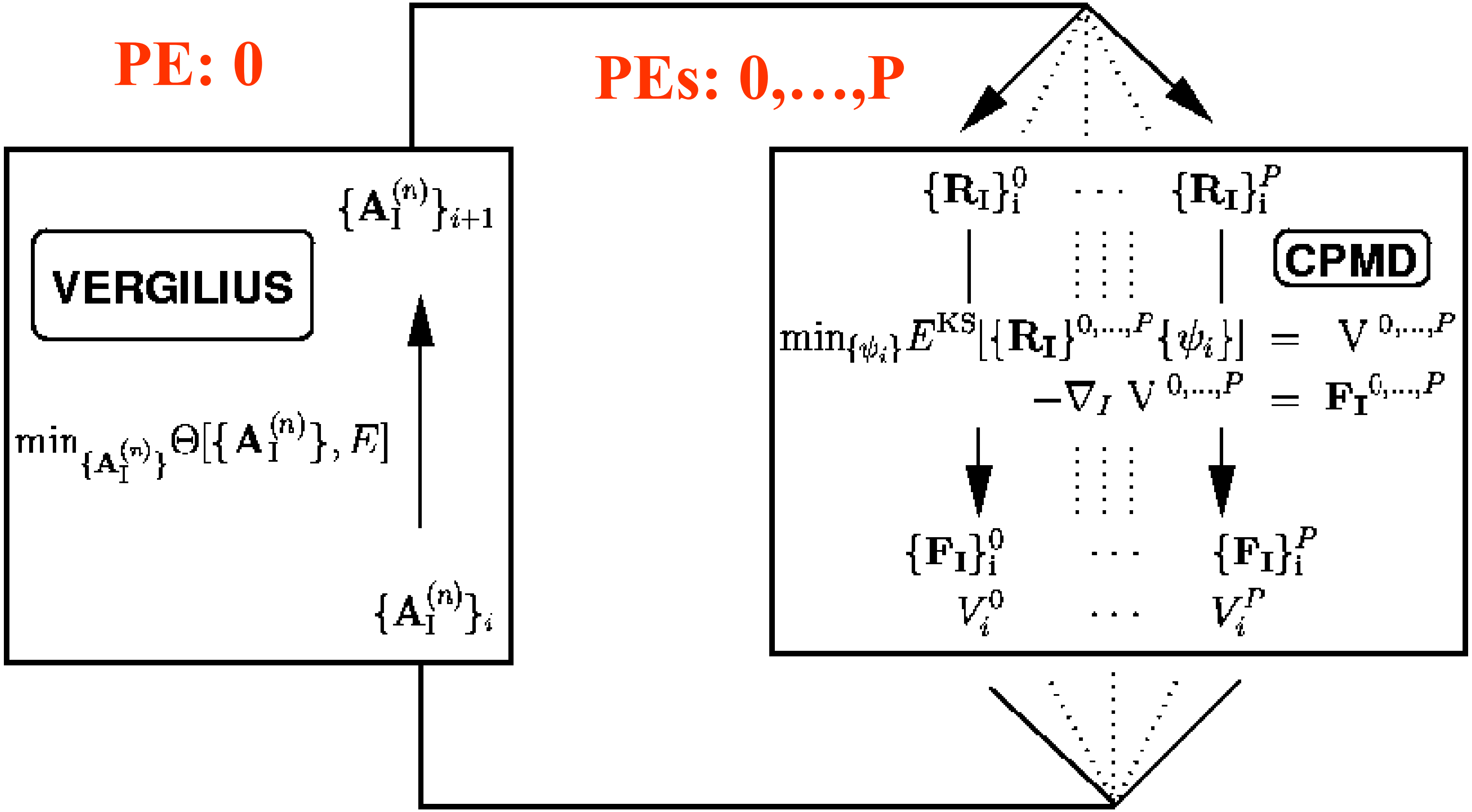
Minimization algorithms

- **Conjugate gradient**
  - Minimize the action $\Theta(a_l,E_0)$ with respect to $\{a_l\}$.
  - Only first derivatives (=forces) are needed.
  - **Preconditioning** is important. In a free particle case, the dependence of the action is of the kind $(l^* a_l)^2$.

    Minimization with respect to a_l/l can be used as a first efficient preconditioning scheme. Other preconditioning requires some components of the Hessian (computationally very expensive).
  - Powerful, but local: it reaches the nearest minimum, but it is often desirable to explore configurational space in a more effective way.

Computational scheme:

Flow chart of the calculation (Interface)



PE: 0

PEs: 0,…,P

VERGILIUS

$\{\mathbf{A}_{\mathrm{I}}^{(n)}\}_{i+1}$

$\min_{\{\mathbf{A}_{\mathrm{I}}^{(n)}\}} \Theta[\{\mathbf{A}_{\mathrm{I}}^{(n)}\}, E]$

$\{\mathbf{A}_{\mathrm{I}}^{(n)}\}_{i}$

CPMD

$\{\mathbf{R}_{\mathrm{I}}\}_{\mathrm{i}}^{0} \quad \cdots \quad \{\mathbf{R}_{\mathrm{I}}\}_{\mathrm{i}}^{P}$

$$\begin{aligned} \min_{\{\psi_i\}} E^{\mathrm{KS}}[\{\mathbf{R}_{\mathbf{I}}\}^{0,\ldots,P}\{\psi_i\}] &= \mathrm{V}^{\,0,\ldots,P} \\ -\nabla_I \, \mathrm{V}^{\,0,\ldots,P} &= \mathbf{F}_{\mathbf{I}}^{\,0,\ldots,P} \end{aligned}$$

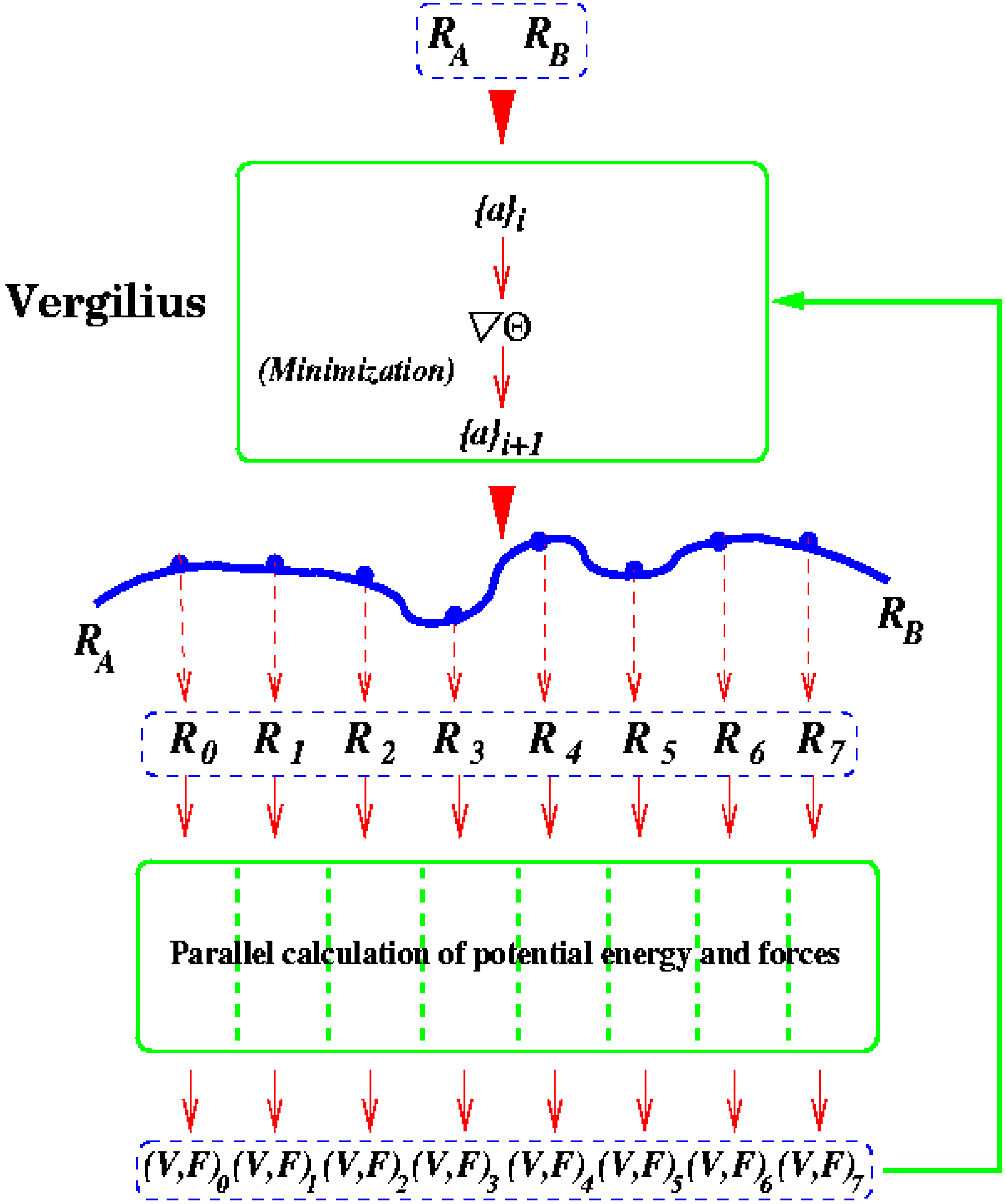
$\{\mathbf{F}_{\mathbf{I}}\}_{\mathrm{i}}^{0} \quad \cdots \quad \{\mathbf{F}_{\mathbf{I}}\}_{\mathrm{i}}^{P}$

$V_i^0 \quad \cdots \quad V_i^P$

Implementation in typical codes

- **Classical schemes for biological and biochemical systems:**
  - Interface with ORAC (using CHARMM force field)
  - Vergilius is inserted in the code, efficient implementation with FFT for calculating the Fourier components Communication between Orac and Vergilius is internal (not through the NFS)
- **Quantum Chemical calculations**
  - Interface with GAUSSIAN 98 (by D. Aktah @ CSCS)
  - Vergilius appended externally to Gaussian, communication through NFS
- **Density Functional calculation**
  - Interface with CPMD (Communication through NFS)

Classical MD



R_A R_B

Vergilius

$\{a\}_i$

$\nabla\Theta$

(Minimization)

$\{a\}_{i+1}$

R_A

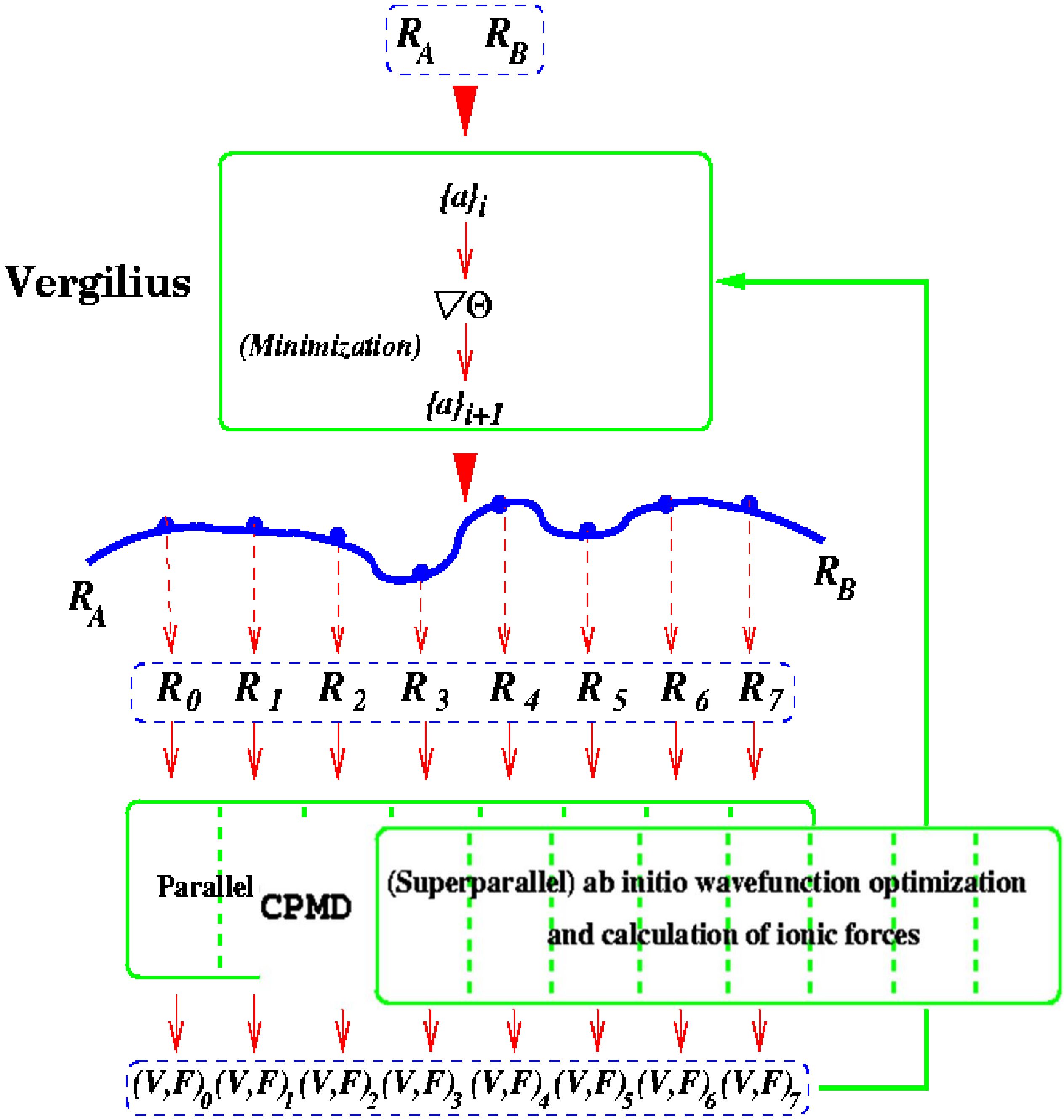
R_B

R_0 R_1 R_2 R_3 R_4 R_5 R_6 R_7

Parallel calculation of potential energy and forces

$(V,F)_0$ $(V,F)_1$ $(V,F)_2$ $(V,F)_3$ $(V,F)_4$ $(V,F)_5$ $(V,F)_6$ $(V,F)_7$

CPMD



R_A R_B

Vergilius

$\{a\}_i$

$\nabla\Theta$

(Minimization)

$\{a\}_{i+1}$

R_A R_B

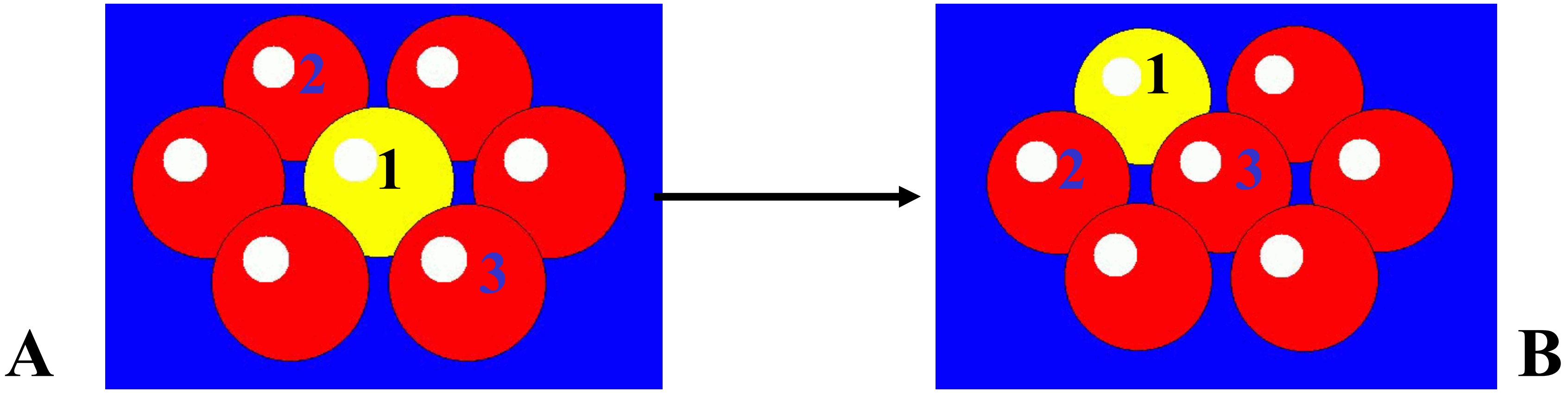
R_0 R_1 R_2 R_3 R_4 R_5 R_6 R_7

Parallel CPMD

(Superparallel) ab initio wavefunction optimization and calculation of ionic forces

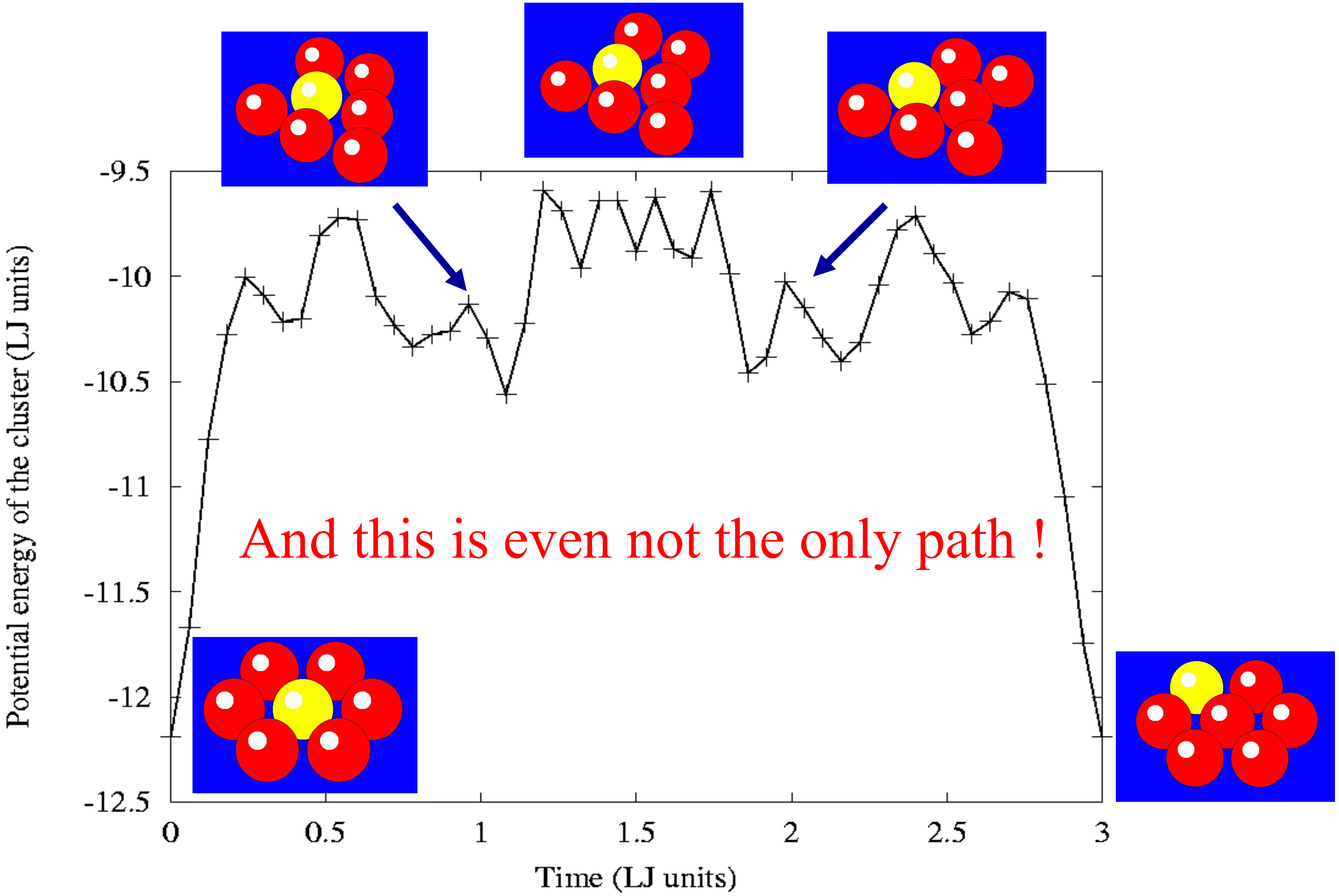
$(V,F)_0$ $(V,F)_1$ $(V,F)_2$ $(V,F)_3$ $(V,F)_4$ $(V,F)_5$ $(V,F)_6$ $(V,F)_7$

An example of application: changing the order of atoms in a cluster



- LJ 2-dimensional model: a simple example of isomerization in a classical context
- A and B are known *a priori*

…when the transition state is not unique and the PES is complicated…



And this is even not the only path !

Further readings:

- G. M. Torrie, J. P. Valleau, *J. Comput. Phys*. **23**, 187 (1977): Umbrella sampling
- M. Sprik, G. Ciccotti, *J. Chem. Phys*. **109**, 7737 (1998): Blue Moon method
- M. B. *et al*., *J. Chem. Phys*.**112**, 9549 (2000): limitations of Blue Moon
- M.B. *et al*., *J. Am. Chem. Soc*. **120**, 2746 (1998): Blue Moon application
- C. J. Geyger and A. Thompson, *J. Am. Stat. Assoc*. **90**, 909 (1995): Temperature enhanced sampling (parallel tempering)
- van Gunsteren et al. *J. Comput*. **8**, 695 (1994): Adaptive elevated potential
- H. Grubmüller *Phys. Rev. E* **52**, 2893 (1997): Flooding potential
- A. Laio and M. Parrinello, *Proc. Nat. Ac. Sci. USA* **99**, 12562 (2002): Coarse grained non-Markovian metadynamics
- M. Iannuzzi *et al*., *Phys. Rev. Lett*. **90**, 238302 (2003): CPMD metadynamics
- M. B. et al., *J. Chem. Theory Comput*. **1**, 925 (2005); CPMD metadynamics
- D. Chandler *et al*. *J. Chem. Phys*. **108**, 1964 (1988): Path sampling
- D. Passerone and M. Parrinello, *Phys. Rev. Lett*. **87**, 8302 (2001): Action derived reaction path
- D. Branduardi, F. Gervasio and M. Parrinello et al., *J. Chem. Phys*. **126**, 054103 (2007): Free energy derived reaction path