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

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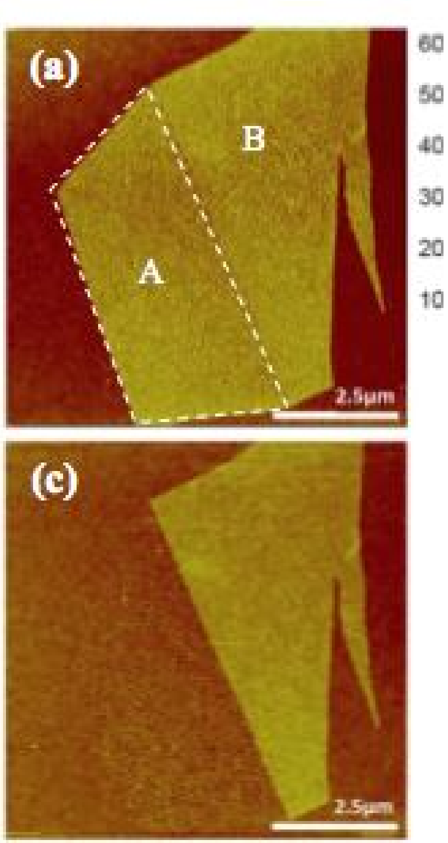
Part 5:
(Just a few) Examples of applications

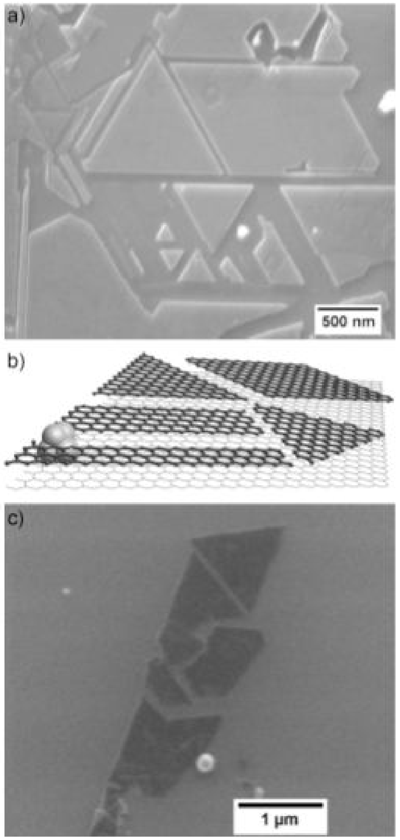
Example 1: Oxygen plasma etching of graphene to fabricate nano-scale devices

Oxygen plasma etching: a crucial step in the fabrication of carbon-based Nanodevices. *Nanolett*. **8**, 1965 (2008); *Science* **324**, 1530 (2009)



Layer-by-layer control

TEM images



Shape control @ atomic-scale

Optical emission spectroscopy

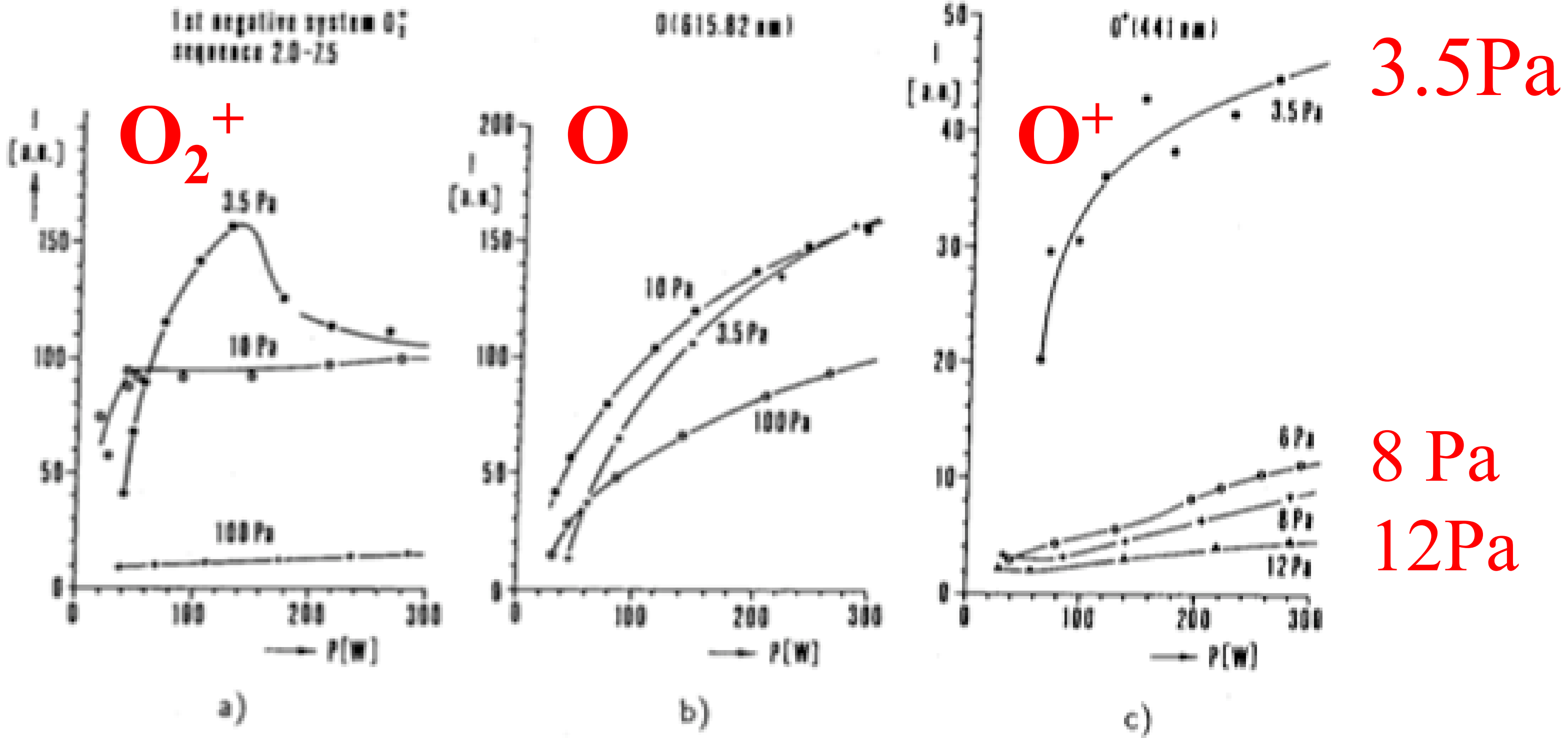
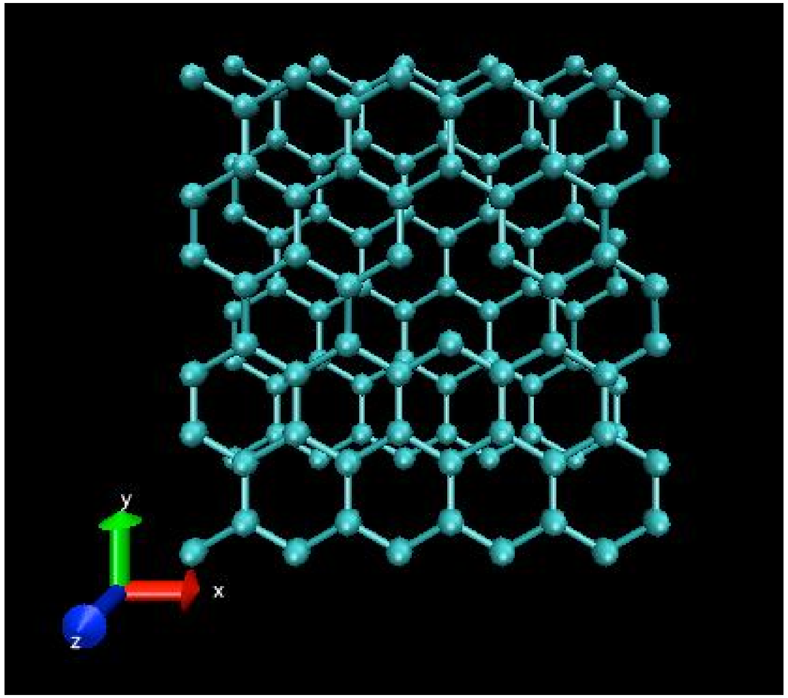


Fig. 5. Intensities of emission lines from molecular oxygen ion O_2^+, atomic oxygen O and atomic ion O^+ as a function of microwave power $P = P_i - P_r$ measured at three values of oxygen pressure $p_1 = 3.5$ Pa, 10 Pa and 100 Pa.

Main components of O plasma → Atomic O and charged molecular O

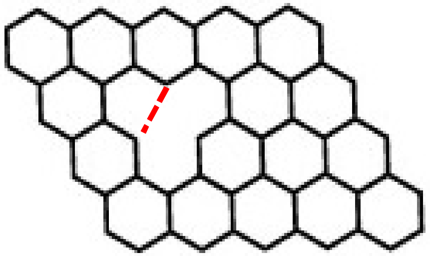
Simulated system: bilayer defect-free & vacancies



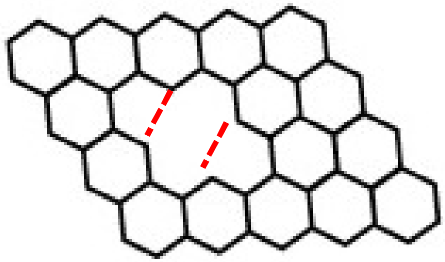
Spin-polarized PBE + Grimme’s D2
or WFC vdWcorrection

Box size: 12.3x12.75x15.0 Å^3

Inter-layer distance:
1.68 Å (minimum according to
van der Waals corrections)

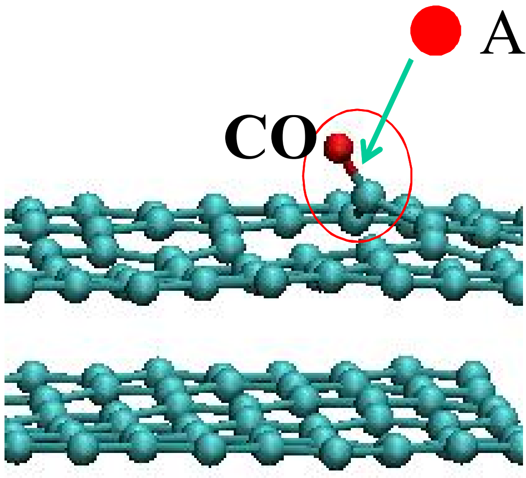


Mono-vacancy V_1
Two C rebounded
One dangling bond



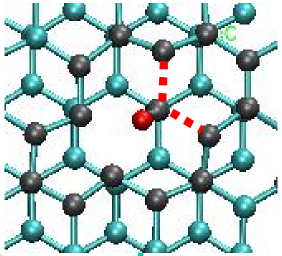
Di-vacancy V_2
Four C rebounded
No dangling bonds

Attack of atomic oxygen (O) to dangling bond and free energy barrier for CO desorption

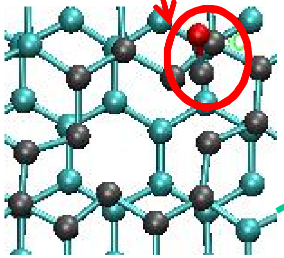


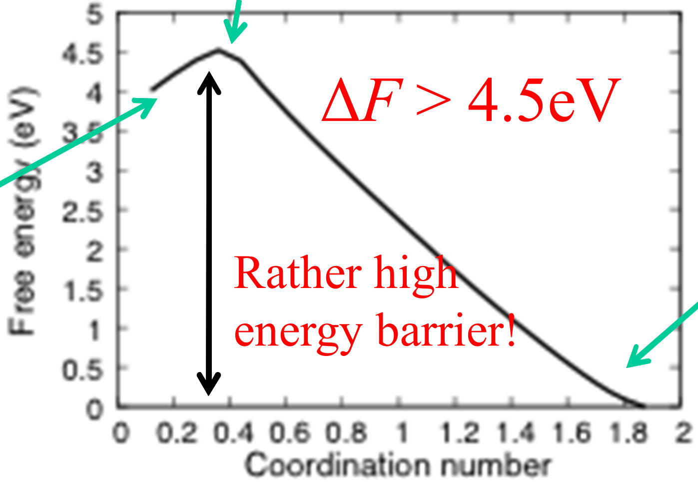
Atomic O attacks the DB @ mono-vacancy spontaneously.
This reaction generates a CO moiety

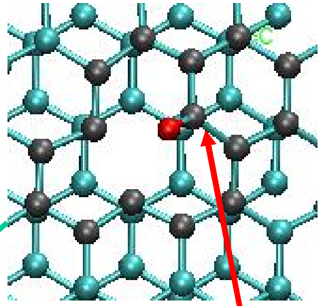
Blue-moon simulations:
activation barrier = 4.5 eV for the release of CO (*forbidden pathway*?)



Desorption of CO





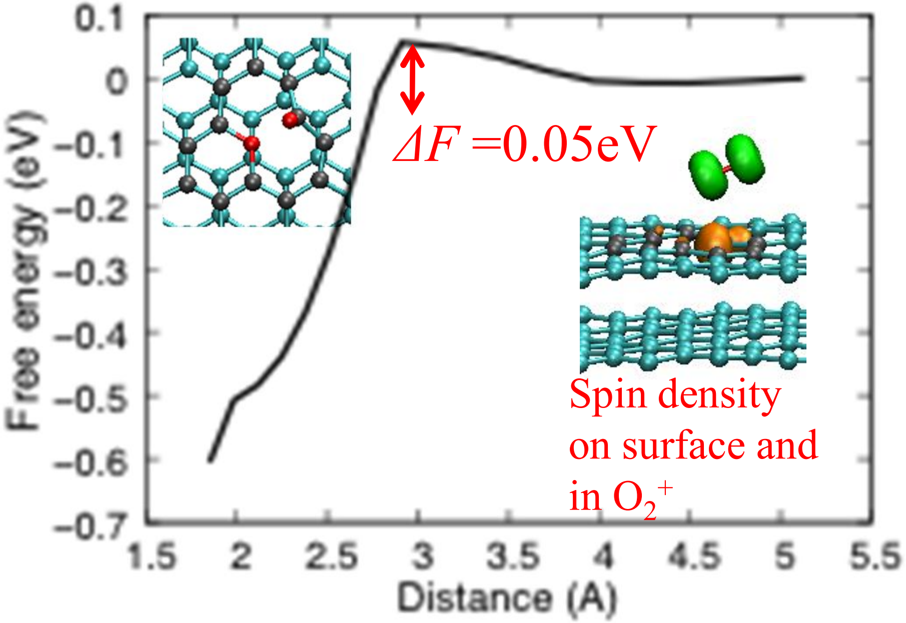


Two strong C-C bonds

Attacks of charged molecular oxygen (O_2^+) to mono-vacancy and di-vacancy

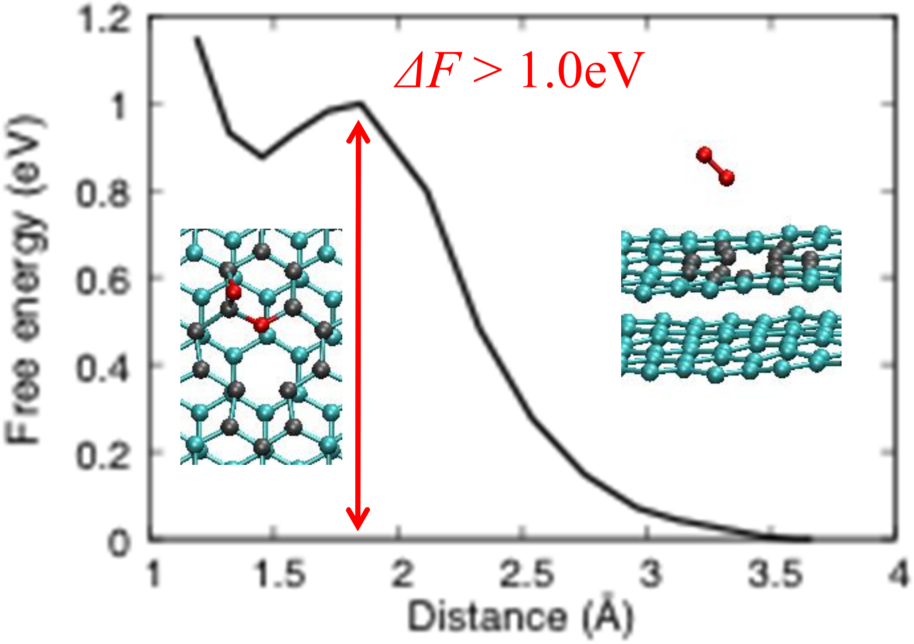
Mono-vacancy: one DB (spin density)

Di-vacancy: No DBs

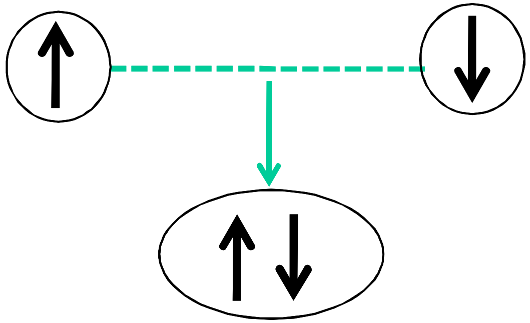


$\Delta F = 0.05\text{eV}$

Spin density on surface and in O_2^+



$\Delta F > 1.0\text{eV}$

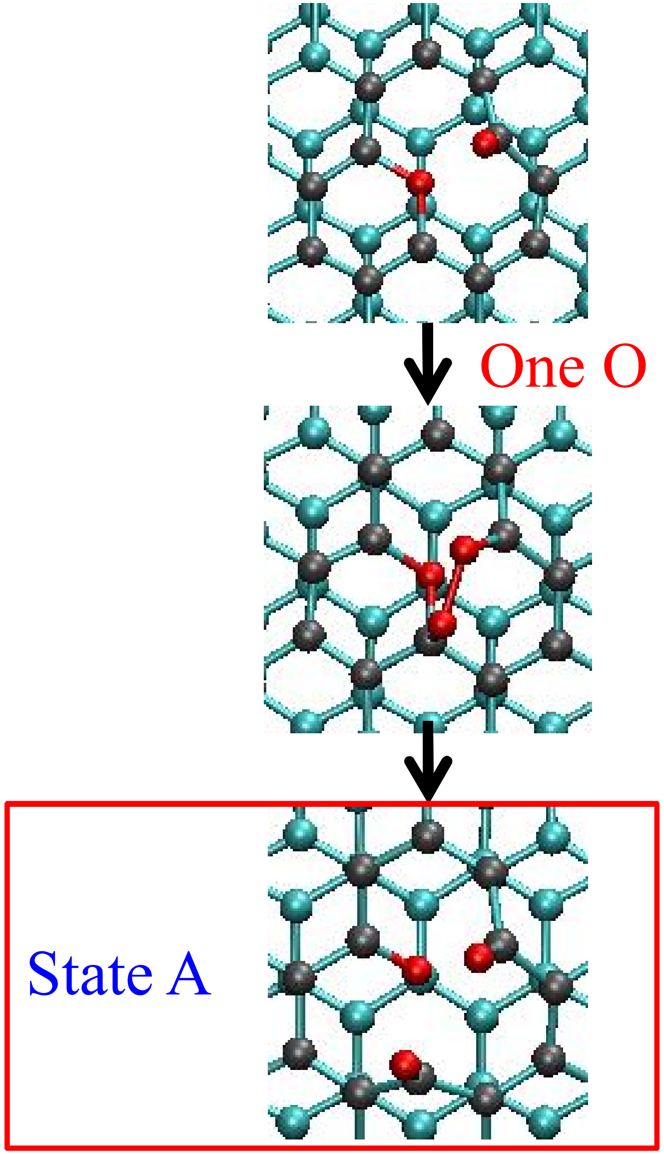


Up + down spins = chemical bond

A mono-vacancy adsorbs more favorably $\mathbf{O_2^+}$

Sequential addition of atomic oxygen (O)

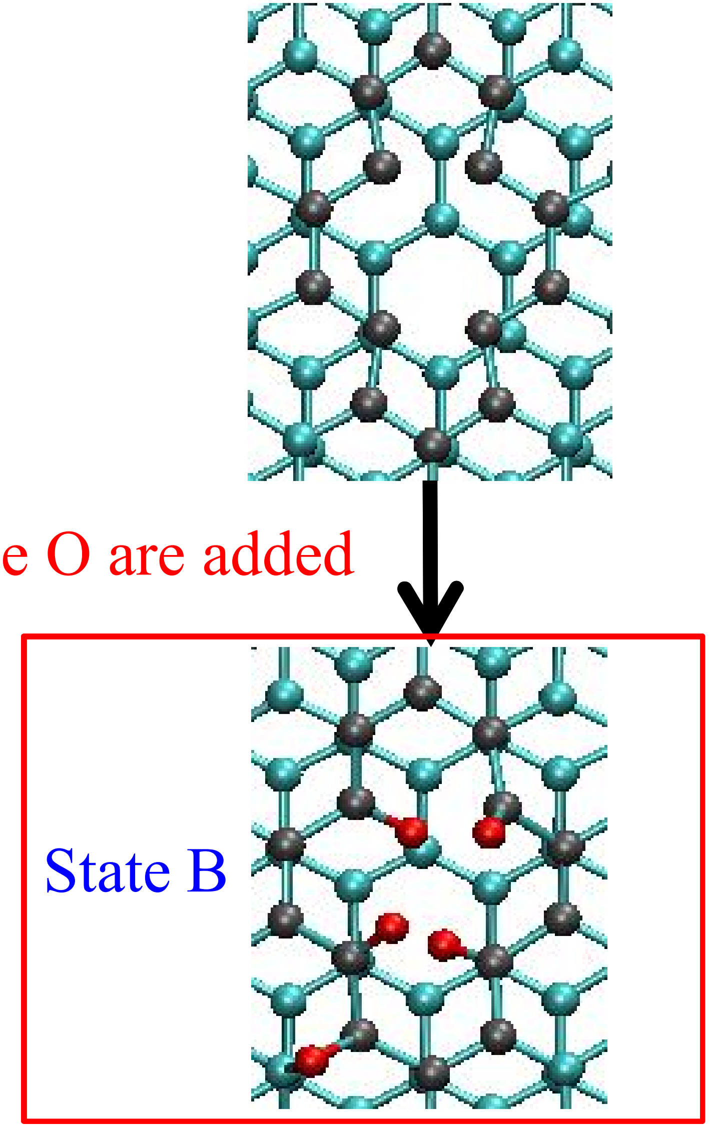
Mono-vacancy with O_2^+



One O is added

State A

Di-vacancy

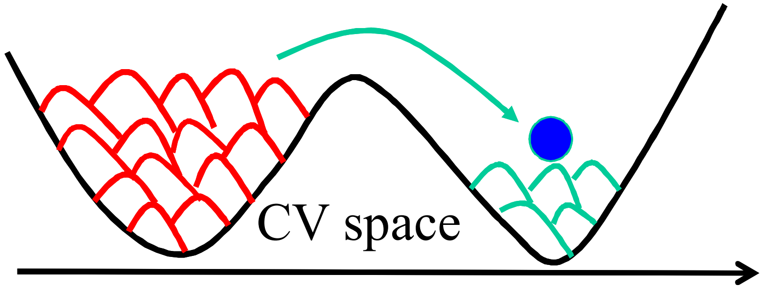


Five O are added

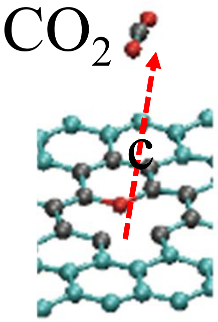
State B

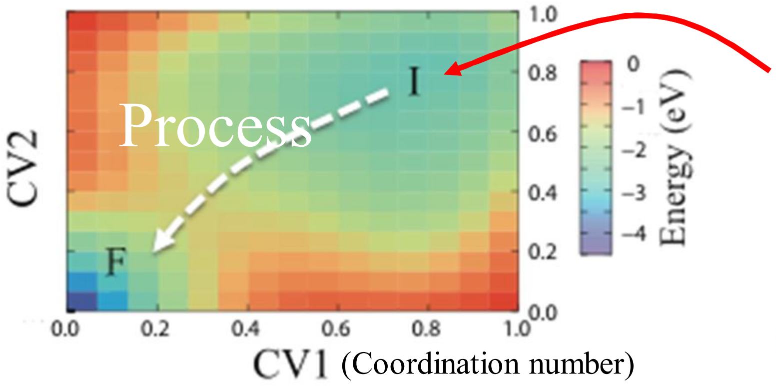
Final CO_2 desorption processes: Metadynamics free energy landscape)

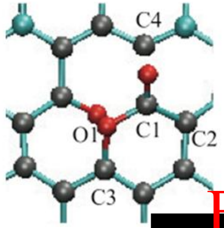
Collective variables (CVs)
Coordination number of C1 to C2
Coordination number of O1 to C3



Free energy barriers for desorption of CO_2 molecules: 1.5eV



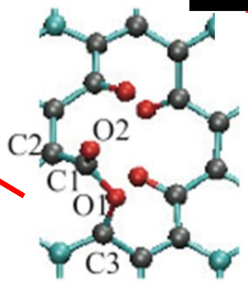




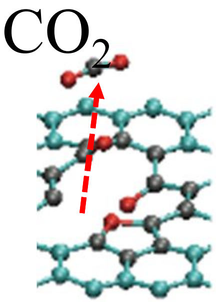
Mono-vacancy

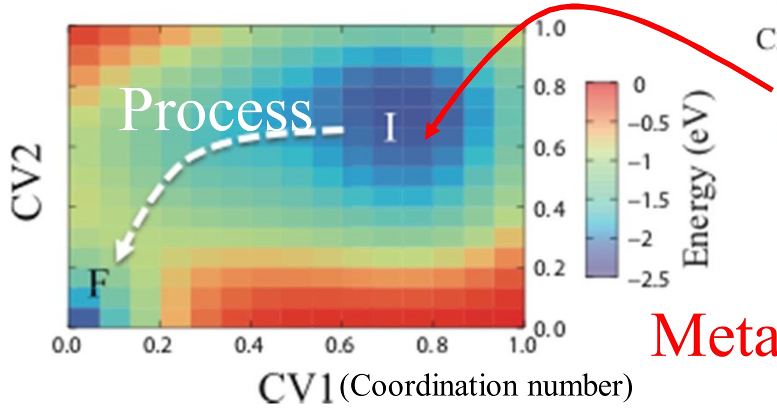
[redacted]

From metastable state
to CO_2 desorption



Di-vacancy

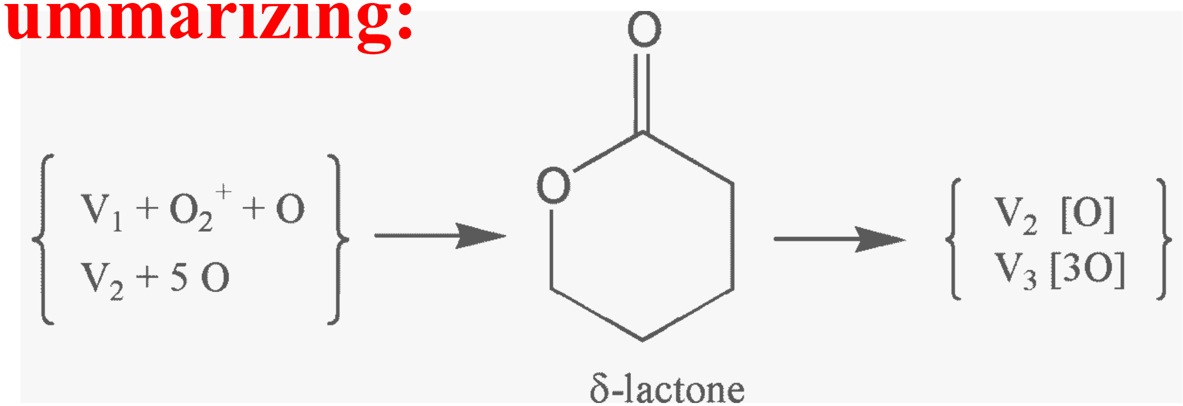




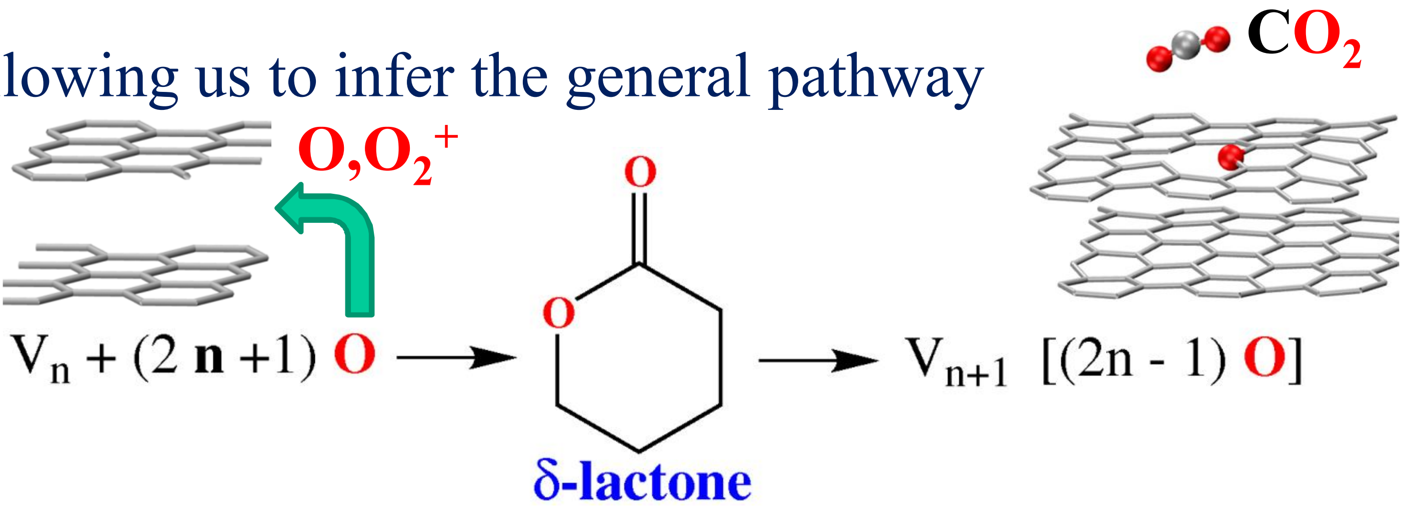
Two-step mechanism

Metastable state → CO_2desorption

Summarizing:



allowing us to infer the general pathway



for a vacancy V_n (n = number of missing C atoms)

K. Koizumi, M.B., Y. Shigeta, A. Oshiyama, *J. Phys. Chem. Lett.* **4**, 1592 (2013)

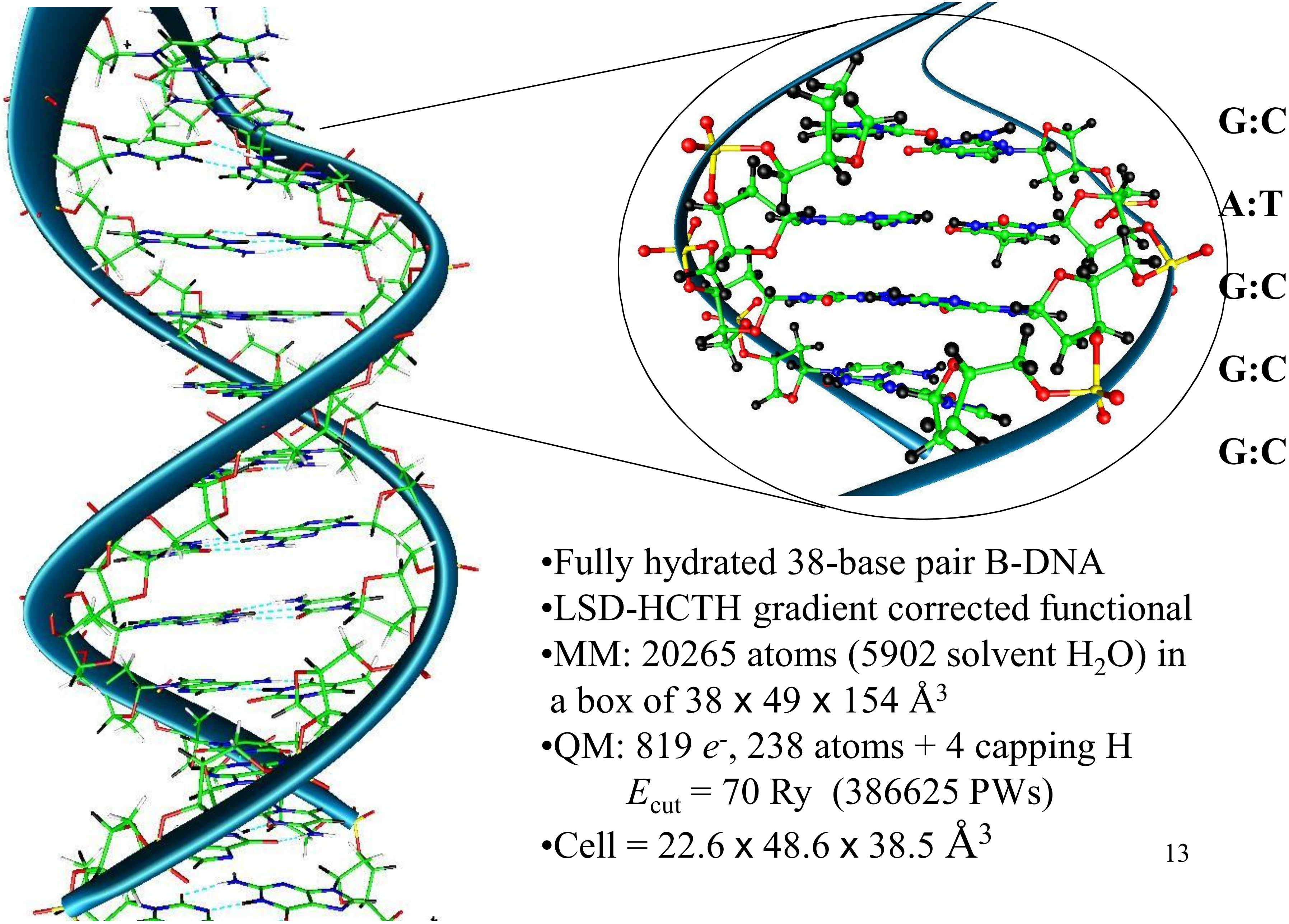
Conclusions

- The atom-scale mechanisms of graphene etching has been clarified by combined first principles molecular dynamics and free energy sampling methods
- Atomic O, one of the main plasma components, etches graphene from vacant sites either with or without dangling bonds.
- an efficient plasma for graphene etching is the one in which atomic O is the major component, providing a useful guideline in designing and optimizing graphene etching processes.
- The processes of graphene etching is a two-step mechanism always passing across lactone formation
- CO_2 desorption occurs, whereas CO is unlikely to desorb
- A layer-by-layer mechanism occurs: Underneath graphene layer are never attacked by O at whatever stage of the reaction

Example 2: Charge localization and transport in DNA

- Is the spin (and the charge) *moving along the DNA* coupled to the proton transfer process (proton coupled electron transfer) as proposed by B. Giese at al., *Chem. Comm.* 2108 (2001); *Nature* **412** 318 (2001) [Basel Universität] ?
- Or is it rather a polaron: charge *coupled to the tilting* of the G-bases (as suggested by P. T. Henderson et al. *Proc. Natl. Acad. Sci. USA* **96**, 8353 (1999) [Georgia Inst. of Technology] and J. Rudnick at al. *Phys. Rev. Lett.* **85**, 4393 (2000) [UCLA] ?
- Or are the two events occurring *simultaneously* in a concerted way. i.e. the bases tilt and in doing so they favor the proton transfer that, in turn, induces the spin localization and the charge transfer ?

QM/MM Double Stranded Hydrated B-DNA system

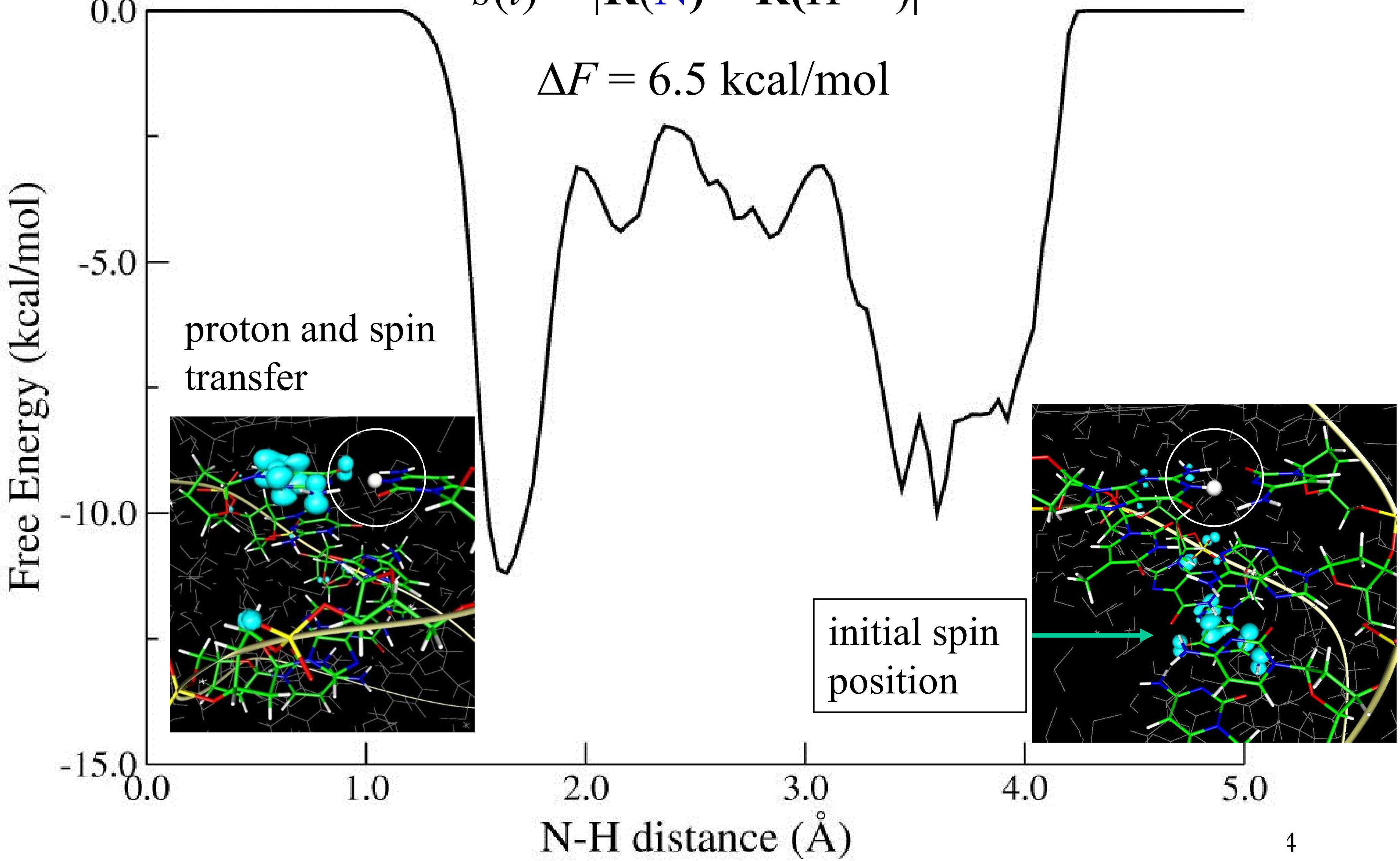


- Fully hydrated 38-base pair B-DNA
- LSD-HCTH gradient corrected functional
- MM: 20265 atoms (5902 solvent H_2O) in a box of $38 \times 49 \times 154$ Å^3
- QM: 819 e^-, 238 atoms + 4 capping H
  $E_{\mathrm{cut}} = 70$ Ry (386625 PWs)
- Cell = $22.6 \times 48.6 \times 38.5$ Å^3

QM/MM + Metadynamics for N-H distance

$s(t) = |\mathbf{R}(\mathbf{N}) - \mathbf{R}(\mathrm{H}^{\mathrm{Gua}})|$

$\Delta F = 6.5$ kcal/mol

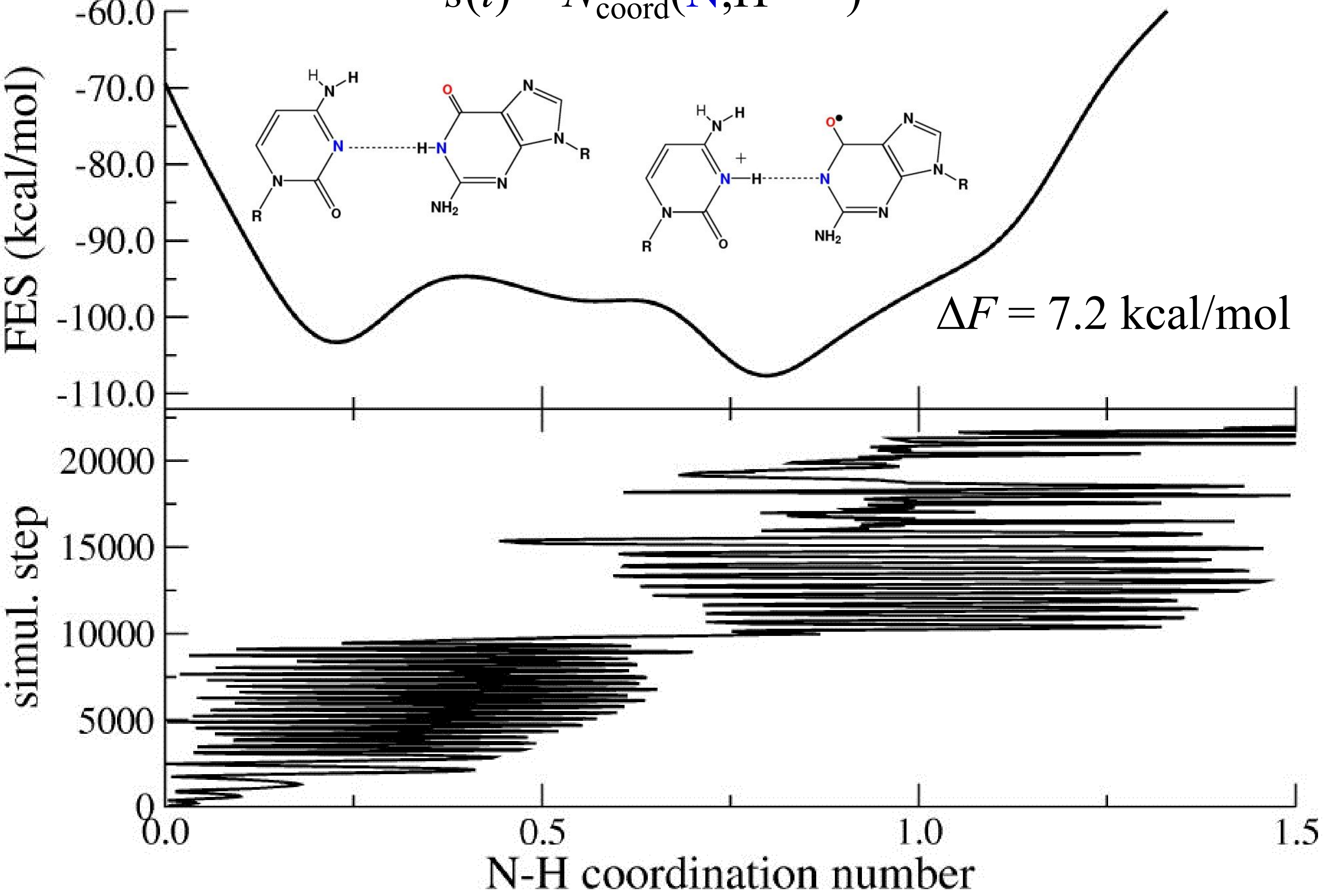


proton and spin transfer

initial spin position

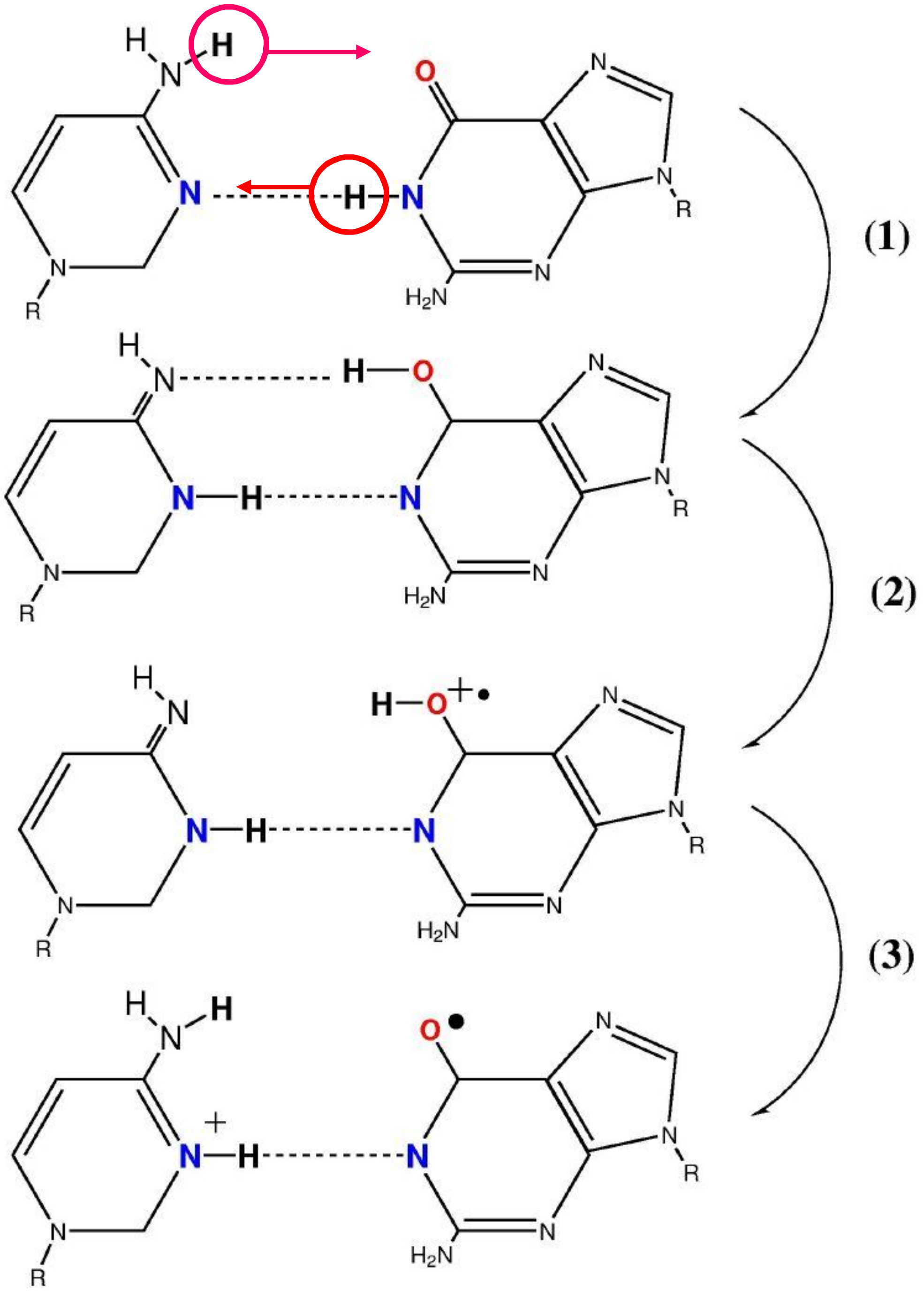
QM/MM + Metadynamics for N-H coordination number

$$s(t) = N_{\mathrm{coord}}(\mathbf{N},\mathrm{H}^{\mathrm{solute}})$$



Double proton shift: *Acidification* of G-base

- The deprotonation is triggered by a transfer to G of a proton belonging to C
- G (contrary to $G^{+\cdot}$) is not acidic, making the single proton exchange highly unfavorable
- A ***double proton exchange*** makes the final state energetically more favorable



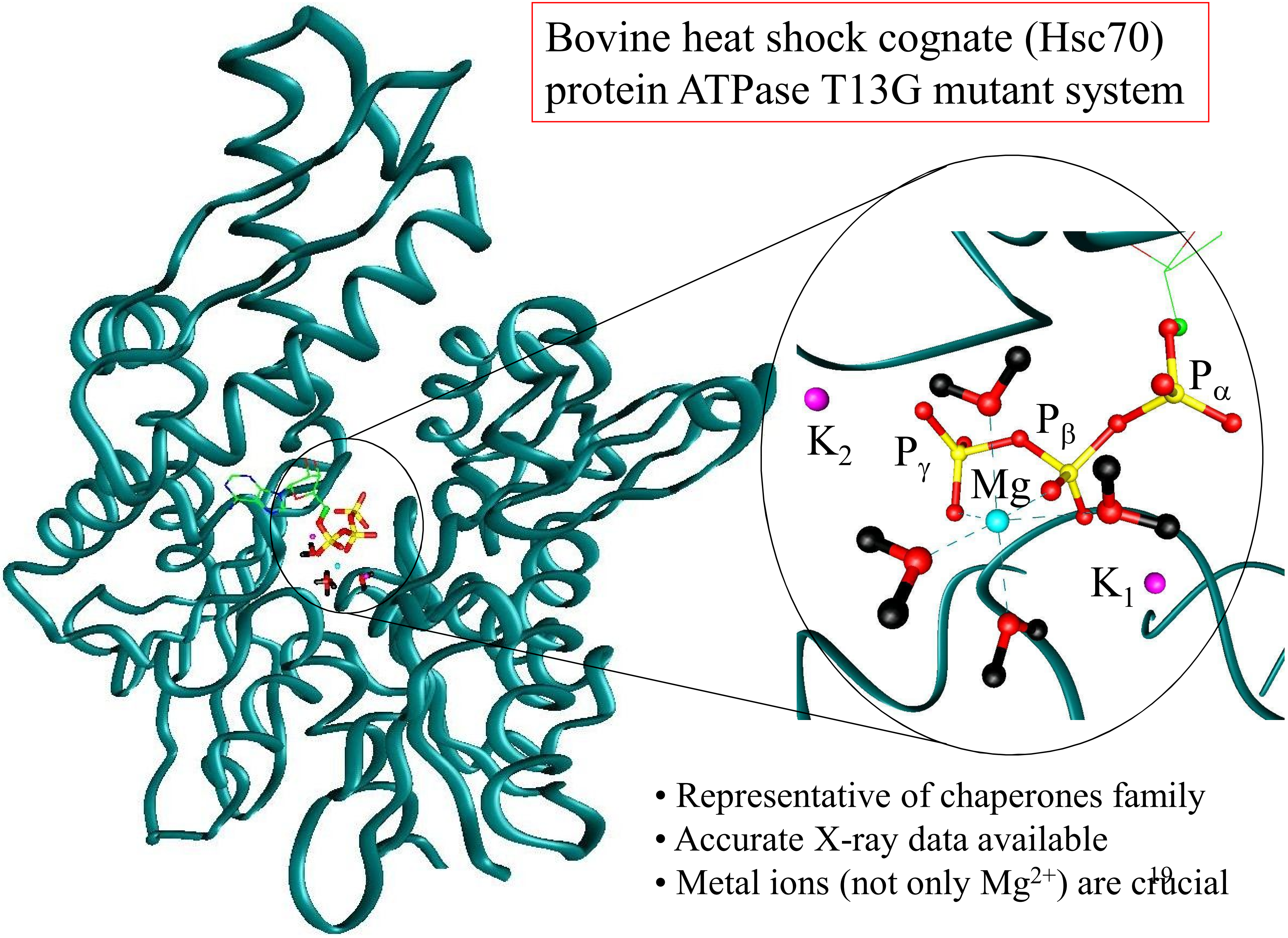
Conclusions about the DNA system:

1. The proton is transferred from the initial G base to the nearby paired C base and, in turn, this ***H^+ shift induces a charge transfer from the starting GGG site to this deprotonated G base***.
2. This provides a clear indication that the deprotonation is essential and not accessory to the charge transfer along DNA and is ***triggered by a transfer to G of a proton belonging to C***.
3. The double proton exchange makes the final state energetically more favorable than a single proton transfer ***since G is not acidic***.
4. The charge displacement occurs via a flow that passes across the backbone.
5. The free energy profile in the same figure shows that an activation barrier of 6-7 kcal/mol has to be overcome in order to complete the charge transfer and this agrees rather well with the known experimental outcome.
6. Yet, experiments are not capable of catching the intimate details of the reaction and in this respect these results represent the first attempt ever to unravel the proposed mechanism.

Example 3: ATP to ADP conversion

- **ATP synthase:** ATPase, short acronym for ATP synthase, is a reaction used by living organisms in a wealth of processes (see e.g. S. M. Wilbanks and D. B. McKay, *Biochemistry* **37**, 7456 (1988)).
- It is the "gasoline" of molecular motors: converting chemical energy of Adenosin-triphosphate (ATP) into mechanical motion *with metal ions* (Mg^{2+}/Ca^{2+}, K^{+}) *playing a still unclear role* (W.D. Frash, *Biochim. Biophys. Acta* **1458**, 310 (2000)).
- This process is ubiquitous in nature and is used by all living systems: "*The principal net chemical reaction occurring in the whole world* " (P. D. Boyer, *Nobel Lecture in Chemistry*, World Scientific Ed., Singapore, 2003)
- Appealing applications as molecular machines and nanoscale batteries are now at a (very) pioneering stage.

Bovine heat shock cognate (Hsc70) protein ATPase T13G mutant system



- Representative of chaperones family
- Accurate X-ray data available
- Metal ions (not only Mg^{2+}) are crucial

Bovine heat shock cognate (Hsc70) protein ATPase:
why is it interesting ?

- As a response to stress, cells produce a whole series of Heat Shock Proteins.
- They protects the cell against stress.
- Exert protein metabolism functions such as degradation, folding and synthesis
- Act as stress sensing and help the cell to adapt to stress and development
- Response to muscle disorders (atrophy, hypertropy) and injury
- Response to heat shock
- Response to ischemia
- Response to fatigue and exercise in skeletal muscle

See e.g. Y. Liu *et al*. *Frontiers in Bioscience* **11**, 2802-2827 (2006)

QM/MM hybrid 5 ps simulation

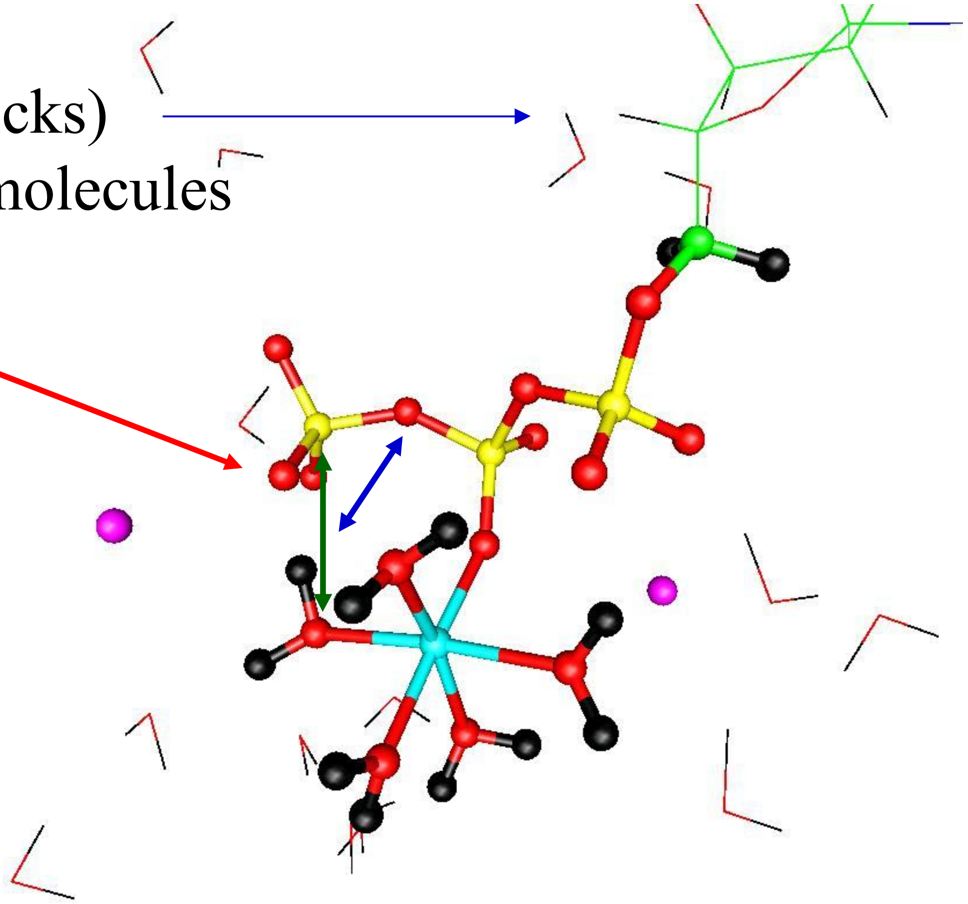
(started after AMBER equilibration)

System size: 50730 atoms (thin sticks)

5910 Hsc70 atoms + 14940 H_2O molecules

QM subsystem:

- 35 atoms (stick&balls)
- +1 H-capping link atom
- 142 electrons (LSD)
- DFT - HCTH functional
- PW basis set (194196 PWs)
- $E^{\text{cut-off}} = 80$ Ry
- Martins-Troullier PPs
- NLCC for Mg, semicore for K
- QM cell = 17 x 17 x 17 Å^3

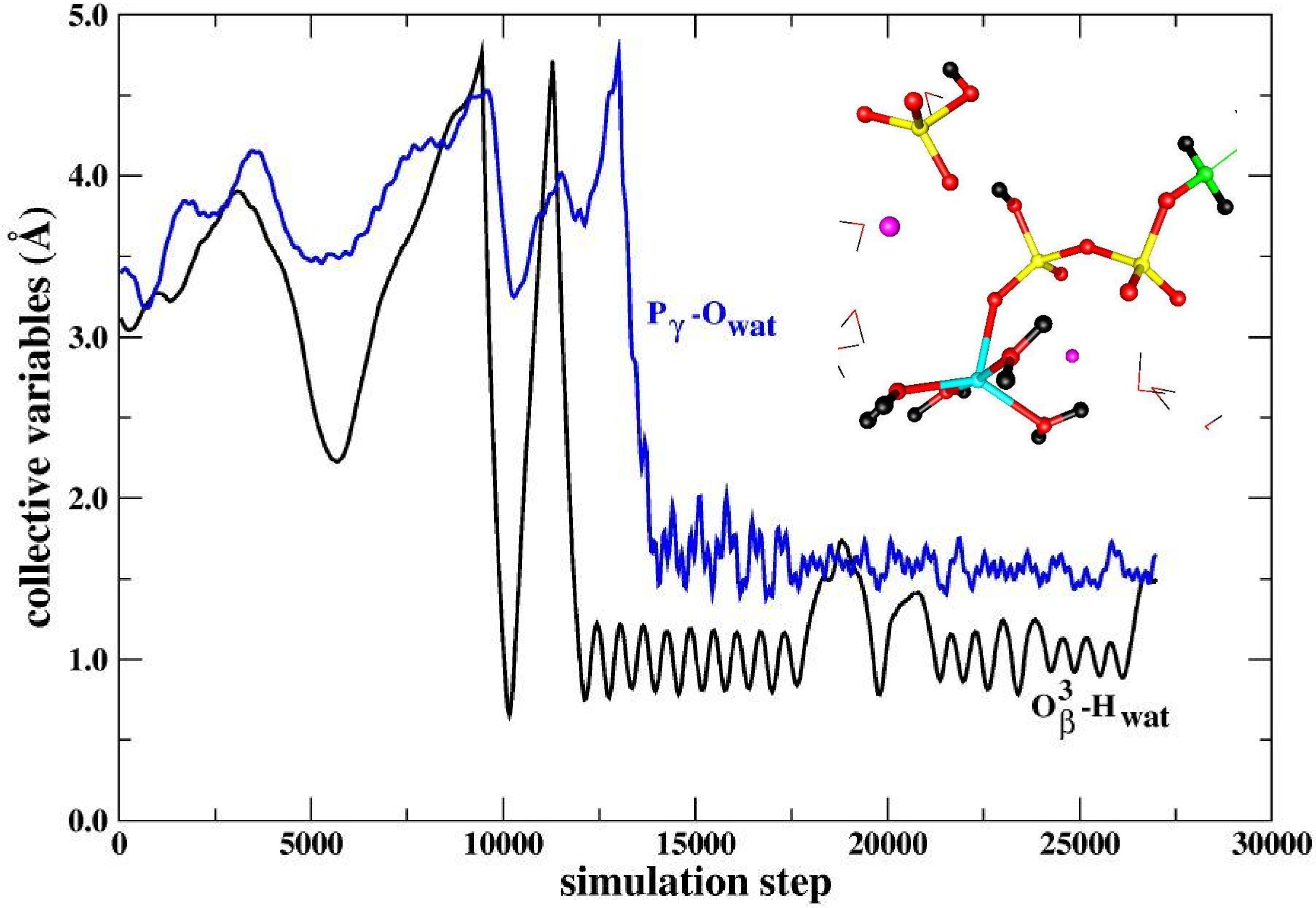


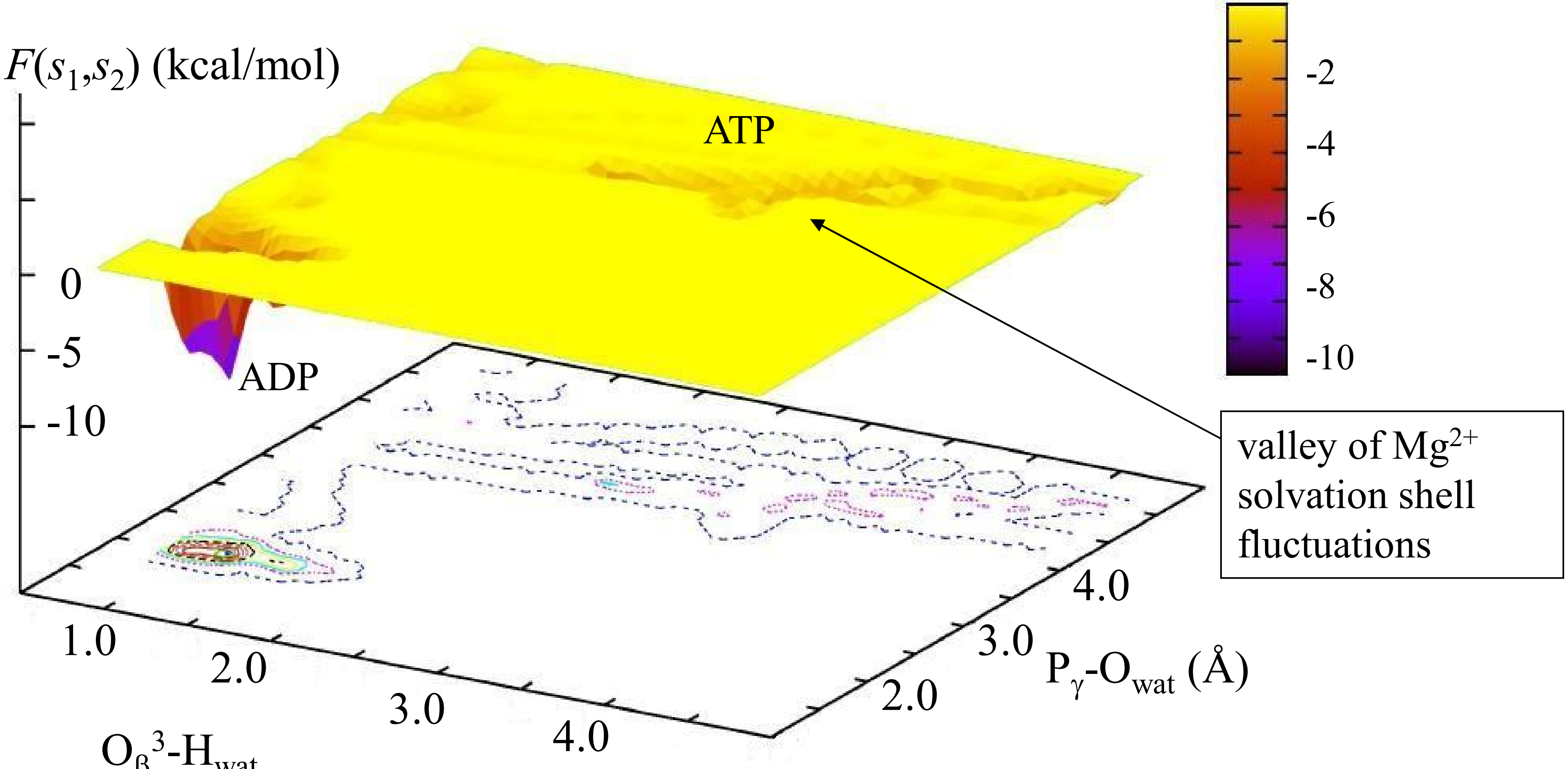
$s_1 = |P_\gamma - \mathbf{O}_{\text{water}}|$

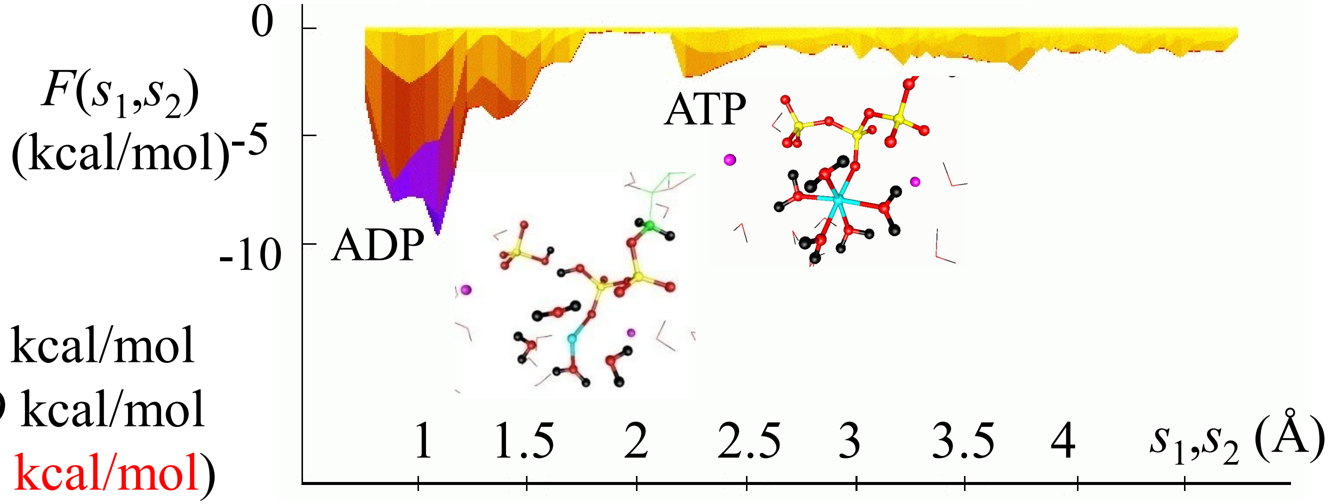
$s_2 = |O^3_\beta - H_{\text{water}}|$

Collective variables from metadynamics: breaking the P_γ-O^3_β bond upon H_2O dissociation

$s_1 = |\mathbf{P_\gamma - O_{water}}|$ & $s_2 = |\mathbf{O^3_\beta - H_{water}}|$







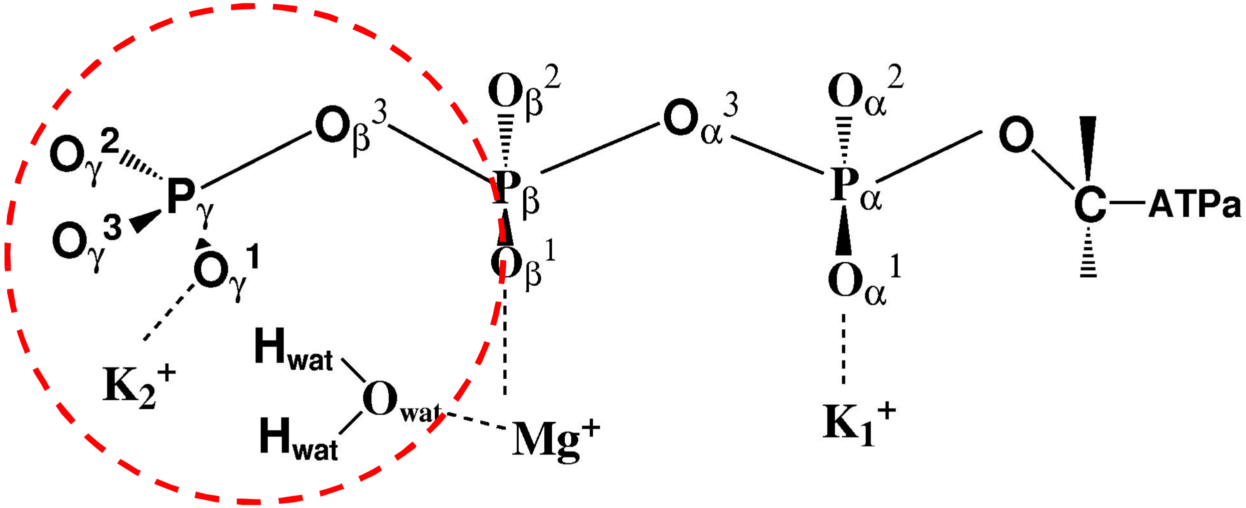
$\Delta F^{\#} = F^{ATP} - F^{TS} = 3.0$ kcal/mol

$\Delta F = F^{ATP} - F^{ADP} = 6.9$ kcal/mol

(exp. 7.1 kcal/mol)

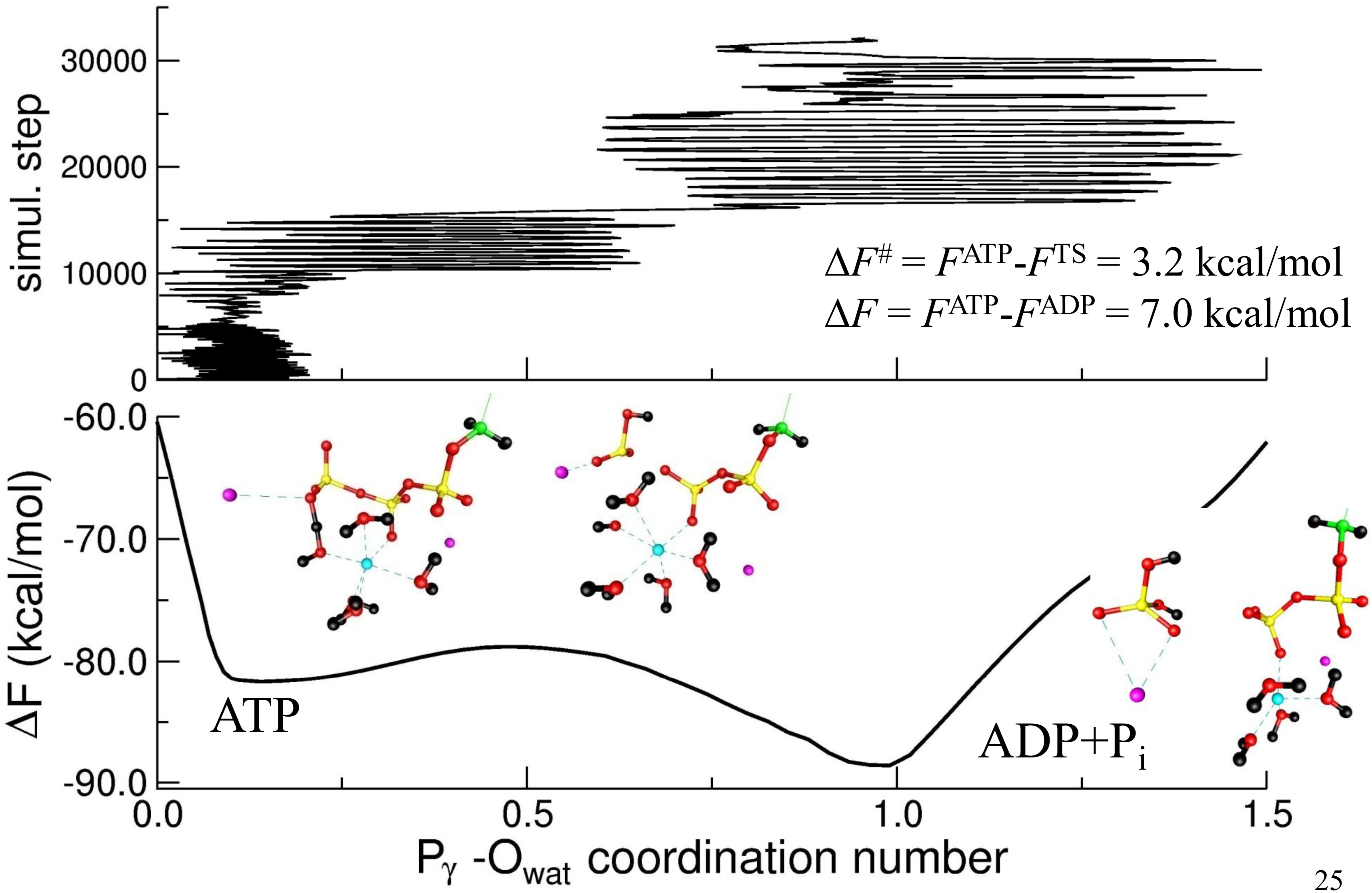
Collective variables for metadynamics simulations

Simulation using $s(t) = N_{\mathrm{coord}}(\mathbf{P}_{\gamma},\mathrm{O}_{\mathrm{wat}})$ coordination number of P_{γ} with **any** $\mathrm{O}_{\mathrm{wat}}$ of the solvent to check in an unbiased way which water molecule participate to the reaction



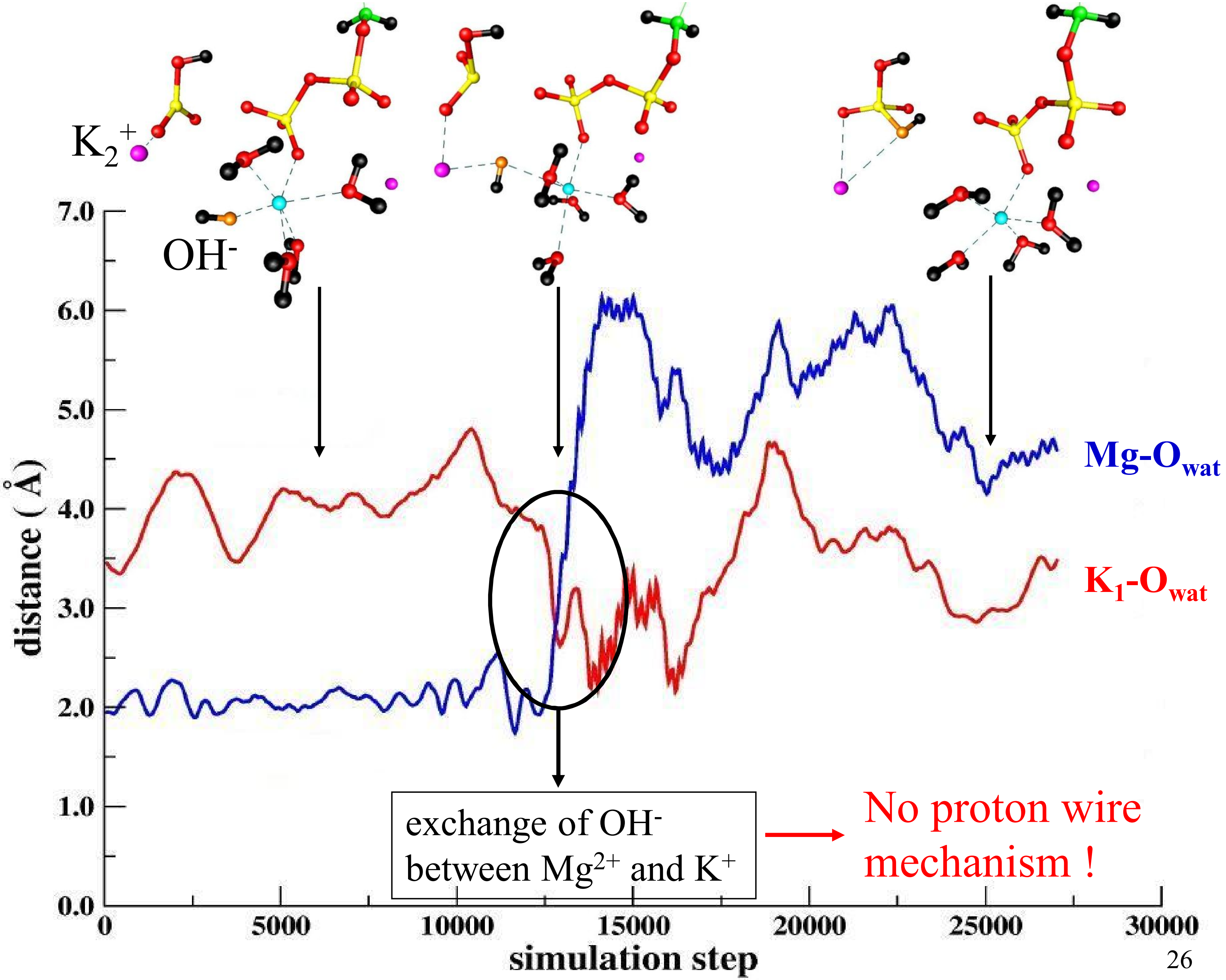
No constraint is imposed on $\mathrm{H}_{\mathrm{wat}}$ atoms

Simulation with $N_{coord}(P_\gamma\text{-}O_{wat})$



$\Delta F^{\#} = F^{ATP}\text{-}F^{TS} = 3.2$ kcal/mol

$\Delta F = F^{ATP}\text{-}F^{ADP} = 7.0$ kcal/mol



exchange of OH$^-$ between Mg^{2+} and K$^+$

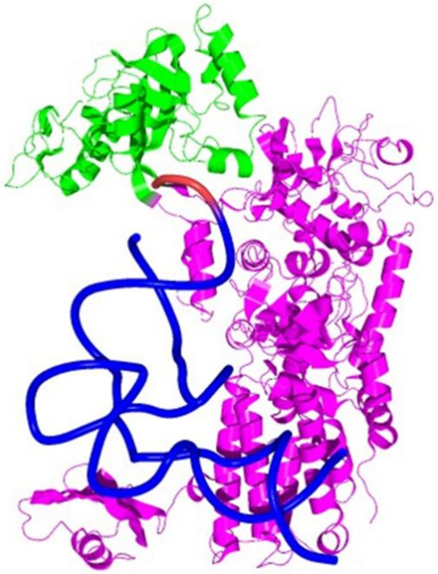
→ No proton wire mechanism !

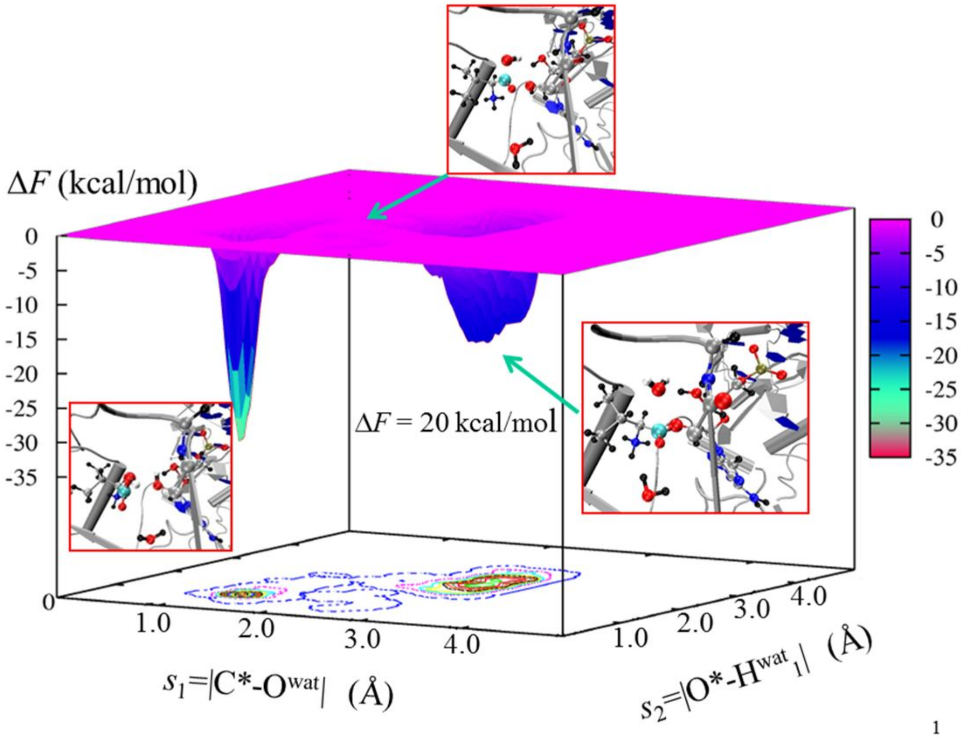
Conclusions on ATPase

- The presence of a putative catalytic water molecule stabilizes the solvation shell of Mg^{2+} and is essential in the ATPase of Hsc70 heat shock protein
- Dissociation of water is the first stage of the reaction, while the rate limiting step is the P_γ-$O_\beta{}^3$ bond cleavage and subsequent OH^- attack.
- The free energy landscape has been worked out, providing a detailed picture of the reaction mechanism and the energetically ordered processes occurring at the different stages (ΔF in good agreement with experiments)
- The cooperative role of K^+ and Mg^{2+} has been shown to be crucial in providing the OH^- hydroxyl anion to the leaving P_γ group. and ***replacing the proton wire mechanism of Actin*** (where only Mg and no K ions are present)

Example 4: editing reaction of RNA for the transmission of the genetic information (post-Genoma Project)

[M. B., *J. Chem Phys. B* **115**, 12276 (2011)]

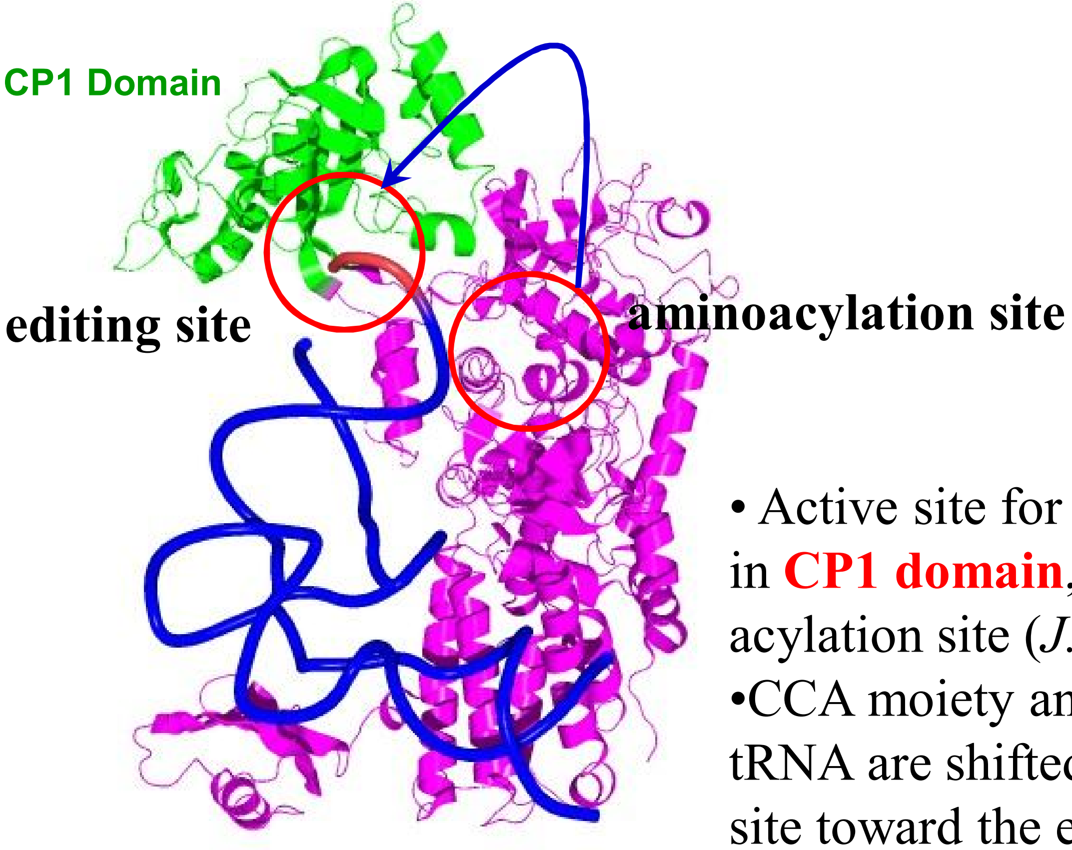




Simulations by hybrid QM/MM molecular dynamics coupled to free energy sampling techniques (Blue Moon & Metadynamics)

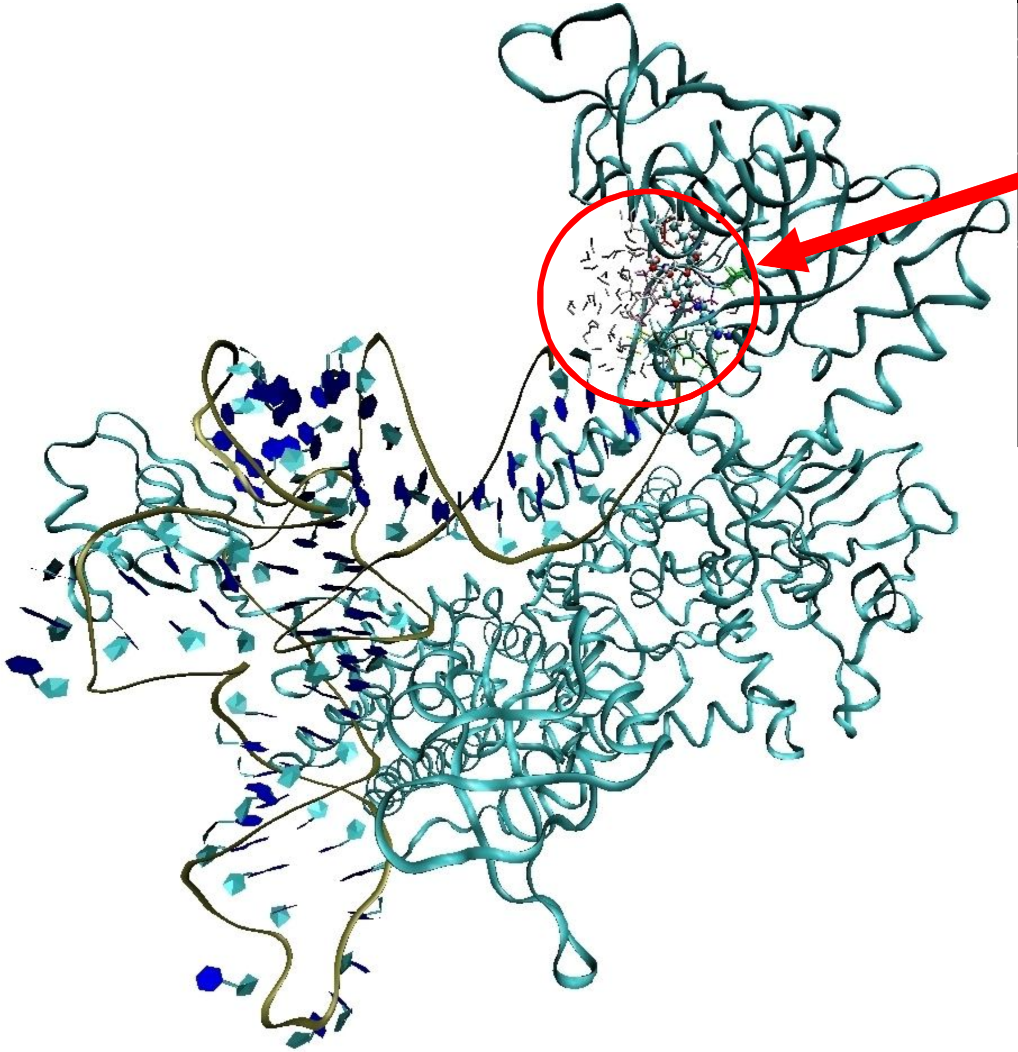
Leucyl-tRNA synthetase (LeuRS)

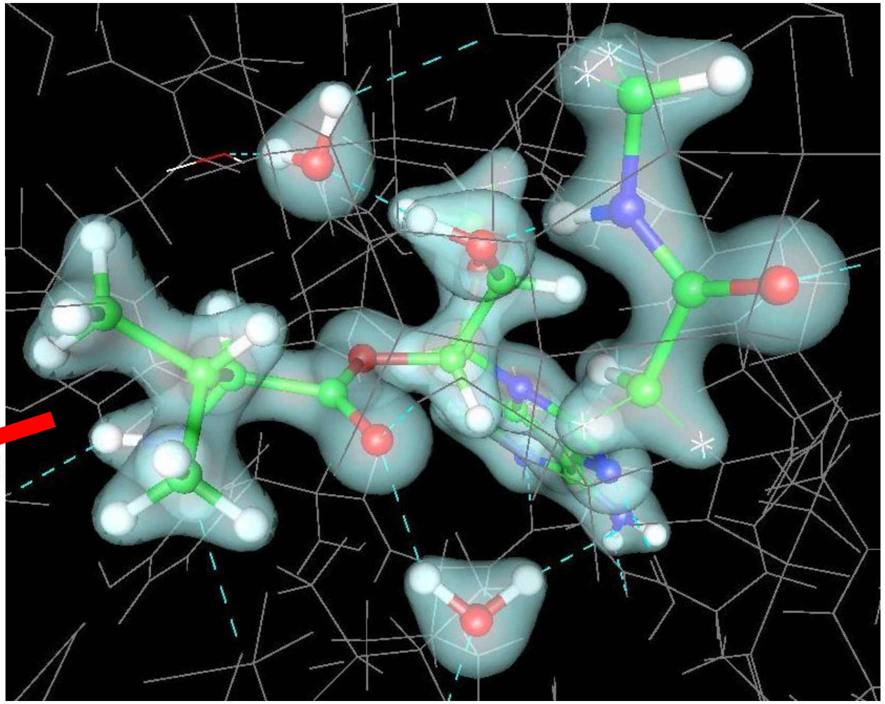
Hydrolyze the mischarged aminoacyl-tRNA's (editing reaction)



- Active site for the editing reaction located in **CP1 domain**, at ~35 Å from the amino acylation site (*J. Mol. Biol.* **346**, 57 (2005)).
- CCA moiety and the discriminator base of tRNA are shifted from the aminoacylation site toward the editing site.

QM/MM Simulation of the Complex of Leucine and its specific tRNA





System size analyzed:

MM: 165750 atoms

QM: 63 atoms + 5 capping H atoms

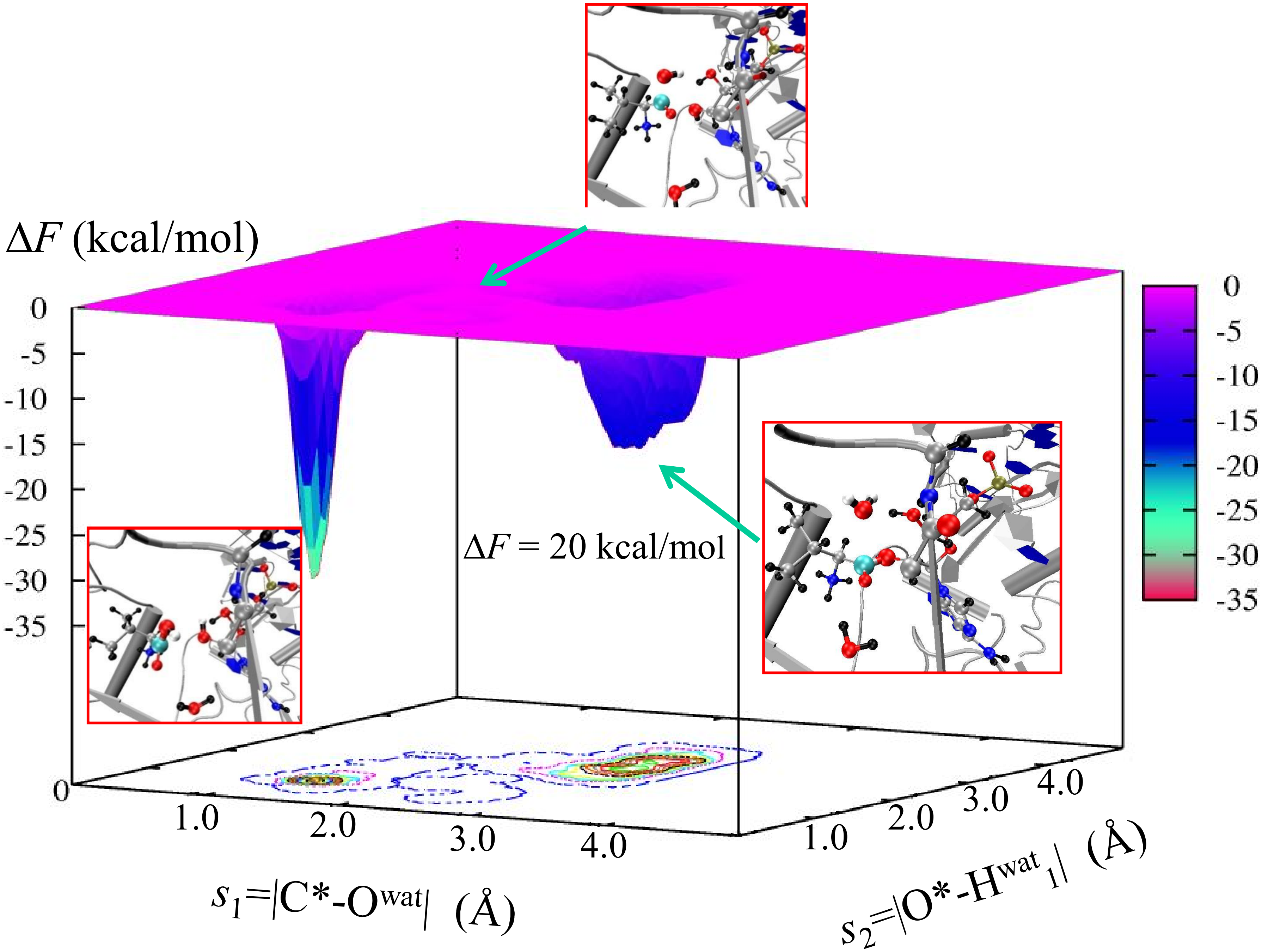
LSDA and HCTH functional

E^{cut}=70 Ry 176 e^- (Q = +1)

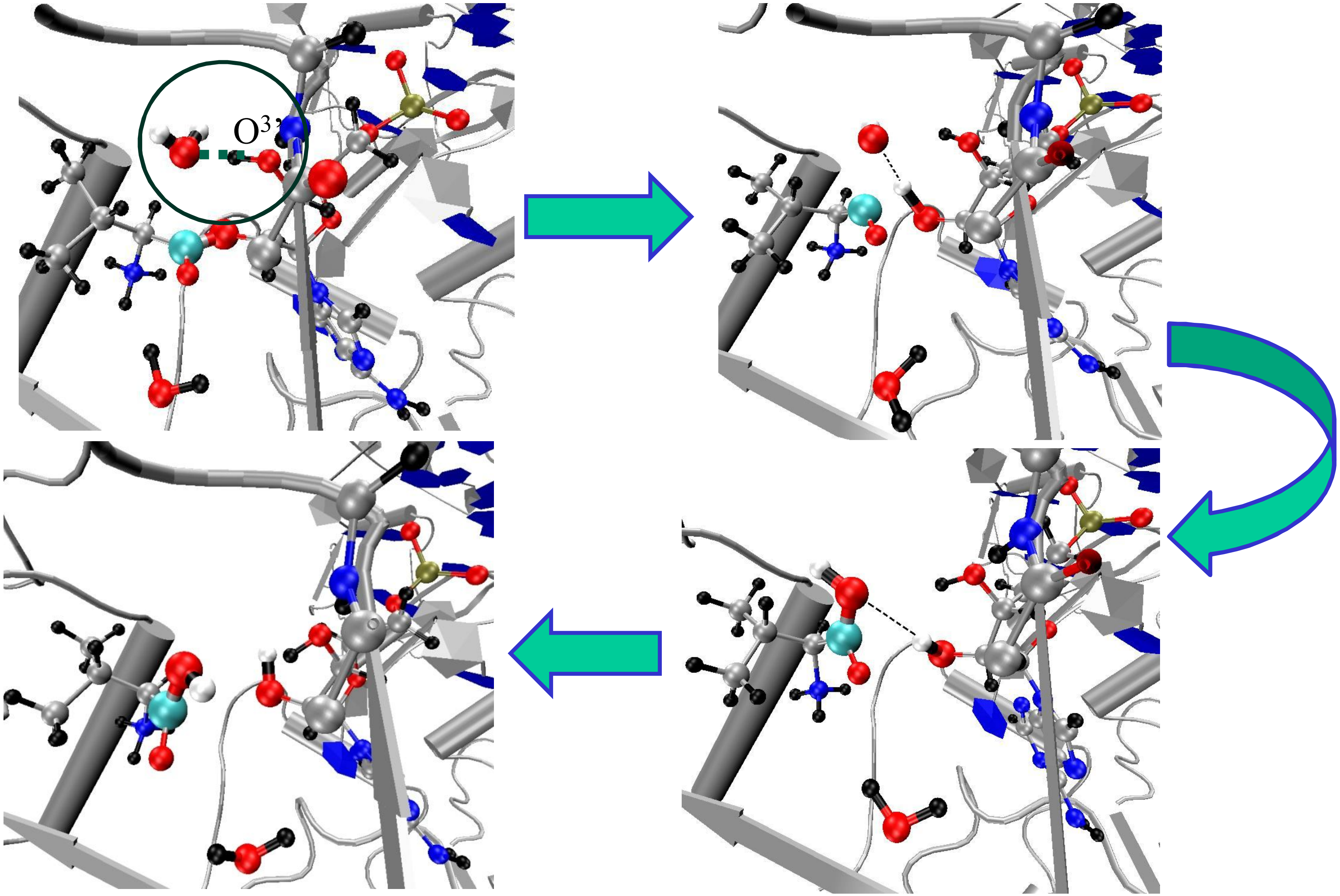
164759 PWs

QM Cell = $17 \times 15 \times 21$ Å^3

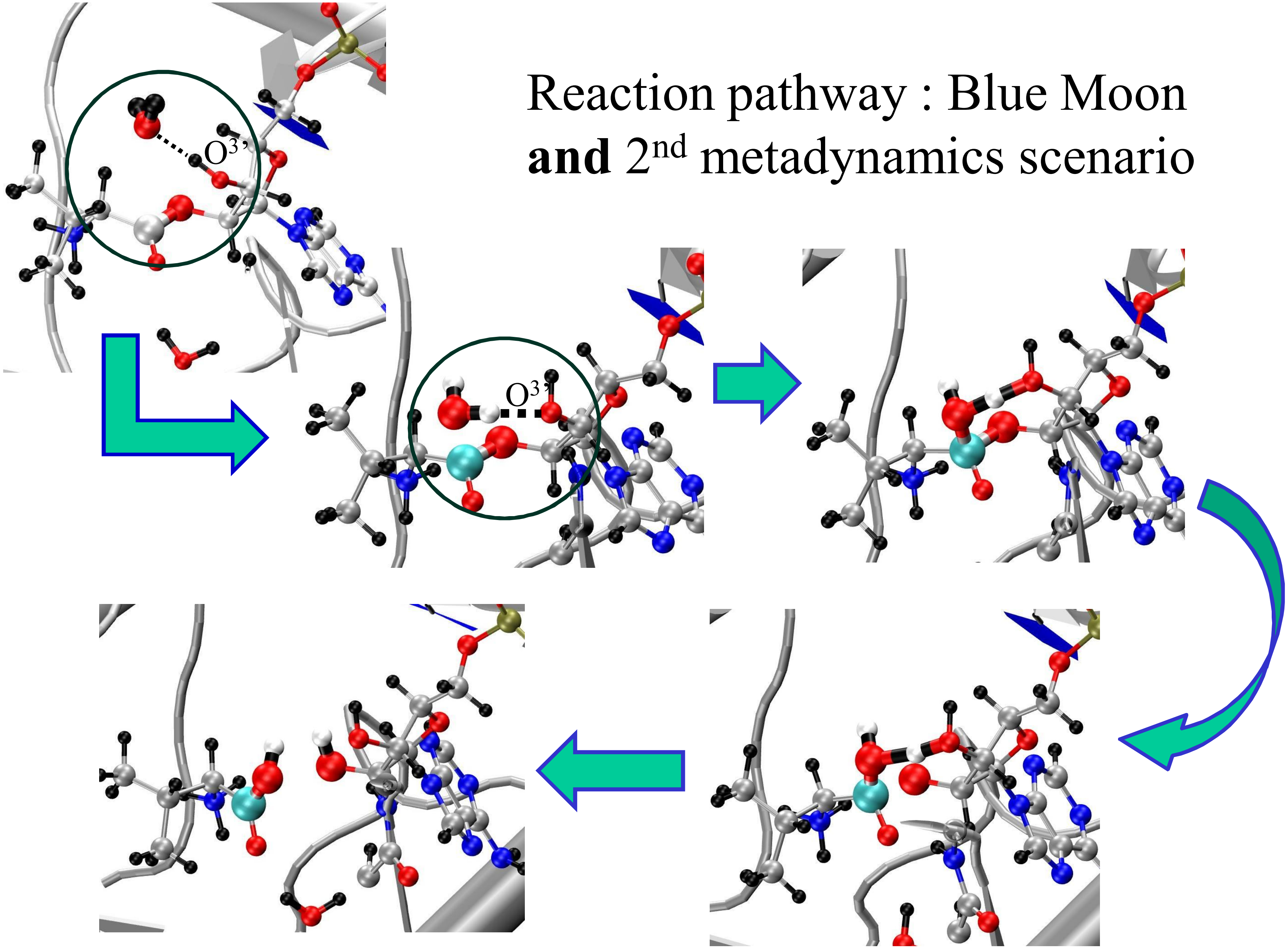
$N_x \times N_y \times N_z = 180 \times 144 \times 216$


ΔF (kcal/mol)
0
-5
-10
-15
-20
-25
-30
-35
0
ΔF = 20 kcal/mol
1.0
2.0
3.0
4.0
s_1=|C*-O^{wat}| (Å)
1.0
2.0
3.0
4.0
s_2=|O*-H$^{wat}{}_1$| (Å)
0
-5
-10
-15
-20
-25
-30
-35

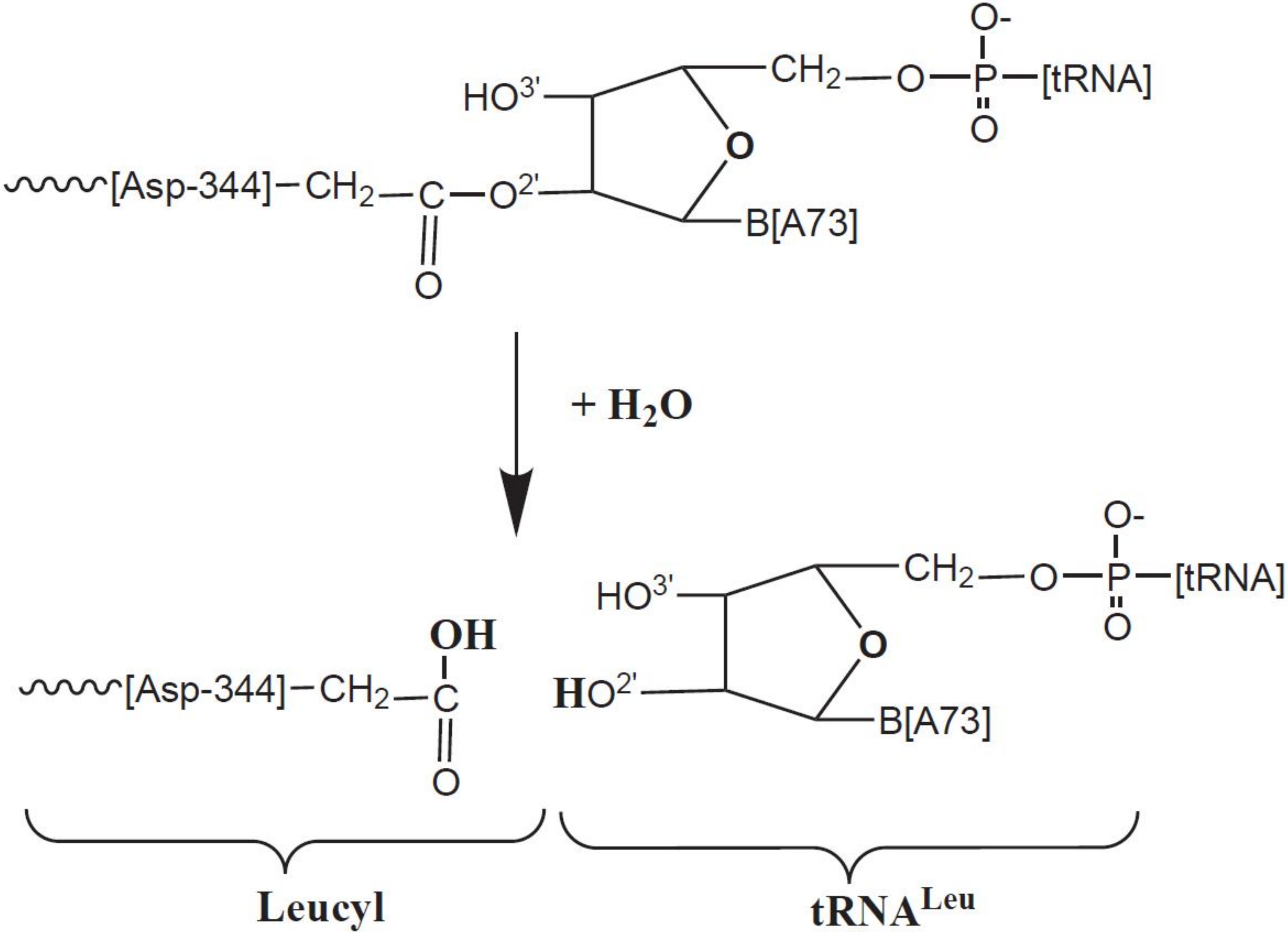
Reaction pathway from metadynamics:



Reaction pathway : Blue Moon **and** 2nd metadynamics scenario



Summarizing:



Conclusions

- An H-bond formed between [*t*RNA]–$O^{2'}$-H and an H_2O molecule is crucial in triggering the reaction
- Two alternative (energetically equivalent) reaction pathways:

(a) the 3’-OH’group of the cognate tRNA acts as a Lewis acid

(b) the 3’-OH group of the cognate tRNA drives, via H- bond, the catalytic H_2O molecule towards the unoccupied LUMO state at the active site

Perspectives

- Applications to proteins and nucleic acids for drug and enzyme (ribozymes) design
- Provide *in silico* atomic-scale insight to complement *in vitro* and *in vivo* biochemical experiments
- Transfer of know-how to bio-inspired materials

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