DE LA RECHERCHE À L'INDUSTRIE

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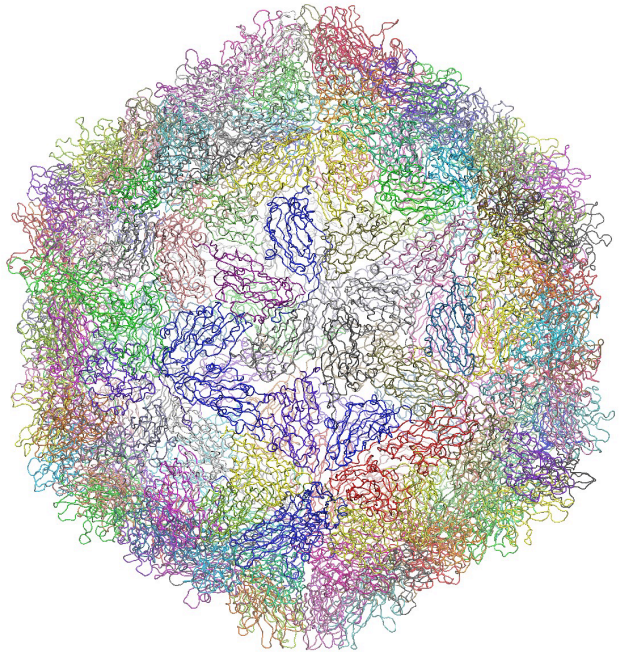
AN *O(N)* MULTI-SCALE *N*-BODY APPROACH FOR SIMULATING POLARIZABLE MICROSCOPIC SYSTEMS



Workshop Maths/Industry | Michel Masella | Life Science Division

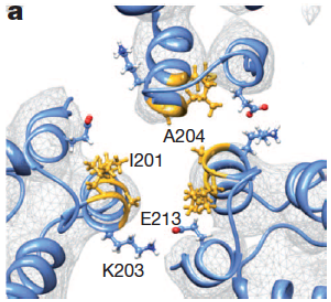
28 APRIL 2017

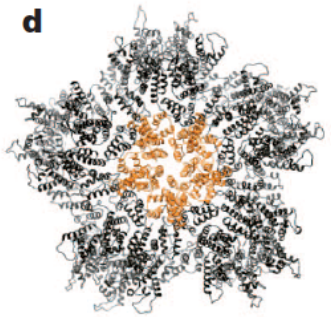
MOLECULAR MODELLING VS QUANTUM CHEMISTRY

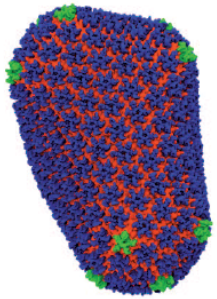
Why to use a classical formalism and empirical potentials to model protein systems in solution: efficiency

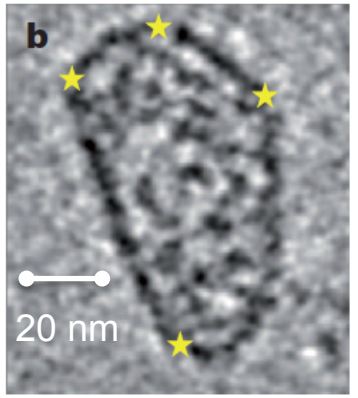
- Much faster computations compared to quantum approaches (DFT, MP2…)
- Large systems (thousands up to millions of atoms)
- Long simulations (from the ns up to the µs scale)

Example : simulating the mature HIV-1 capsid structure









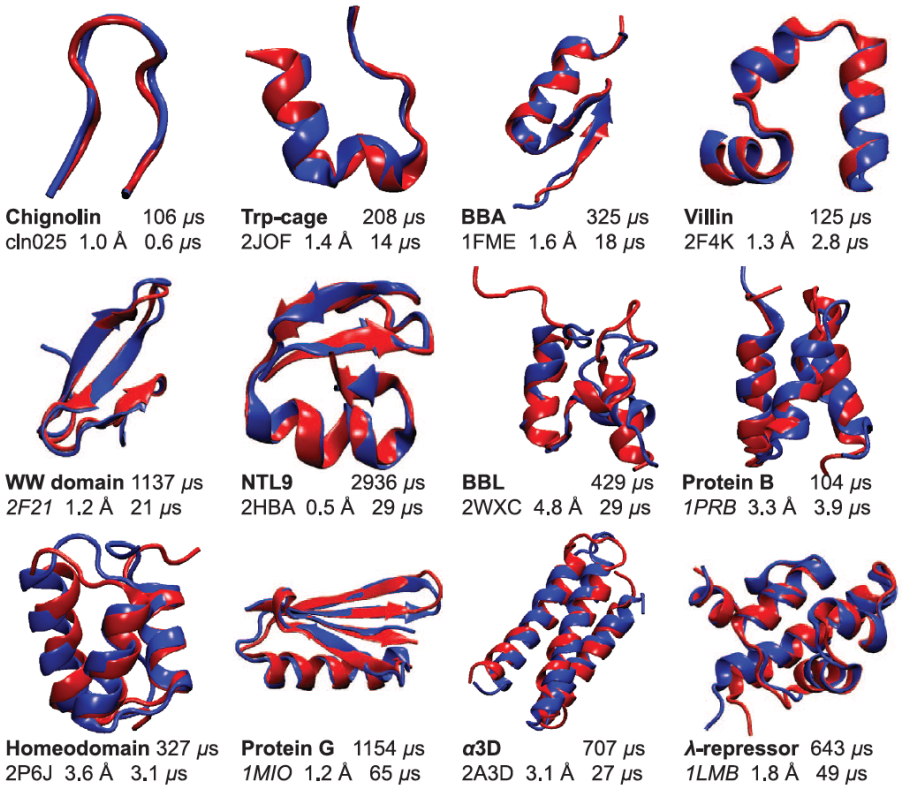
128 000 cores of the Cray “Blue Waters”, 300 ns, about 60.10^6 atoms (50.10^6 = water)

*Zhao et al, Nature, **497** (2013) 643*

THE ANTON MACHINE

Anton, a special-purpose machine for molecular dynamics simulation

Shaw et al, ACM SIGARCH, 35 (2007) 1-12



How fast folding proteins fold

*Lindorff-Larssen et al, Science, **334** (2011) 517*

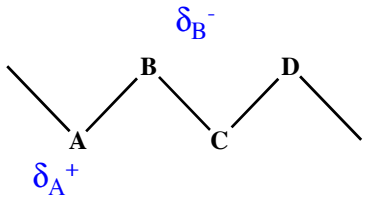
STANDARD MM APPROACHES: ACCURACY ?

The main drawback of MM approach: accuracy

Common force-fields are based on additive potentials (CHARMM, AMBER, OPLS …)

1 - The model parameters are constant along an MD trajectory

2 – Reliability of such an approach when mimicking microscopic electrostatic interactions



➔ $U_{Coulombic} = \sum_{i<j} \frac{\delta_i \delta_j}{r_{ij}}$ ➔ δ_i are static charges

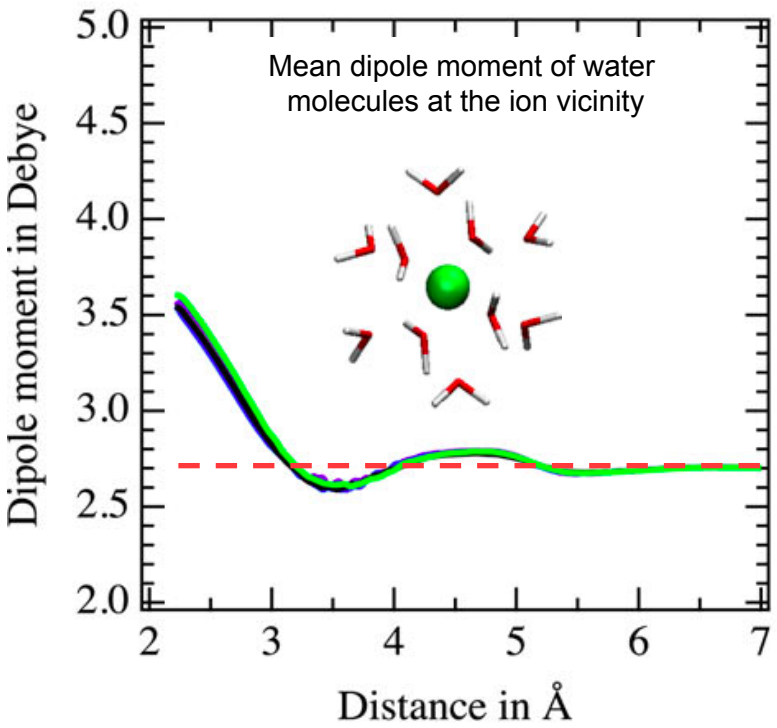
3 – Experimental results are commonly used for assigning/refining parameters, transferability ?

4 - Ok, you may say that for a homogeneous and isotropic system, you are using a mean field approach…

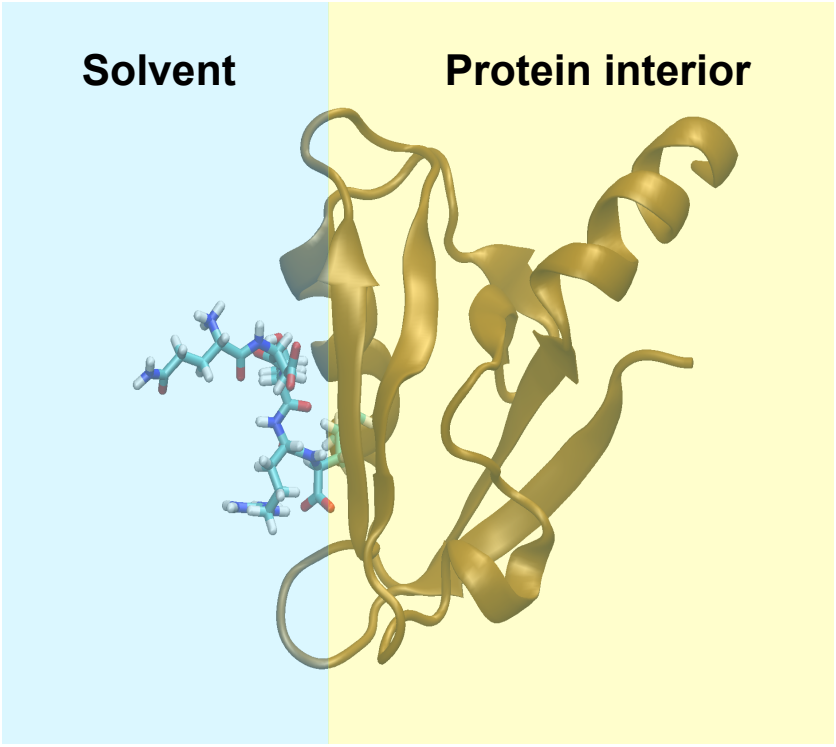
However, what about interfaces ?

POLARIZATION EFFECTS AND INTERFACES

The case of Cm(III) interacting with water



All protein/ligand interactions correspond to an interface problem



These phenomena can not be accounted for using static charges to model the molecular electronic cloud properties

POLARIZABLE FORCE-FIELDS

They allow to account for environmental effects on electrostatic molecular properties considered in classical molecular dynamics

Many approaches have been proposed :

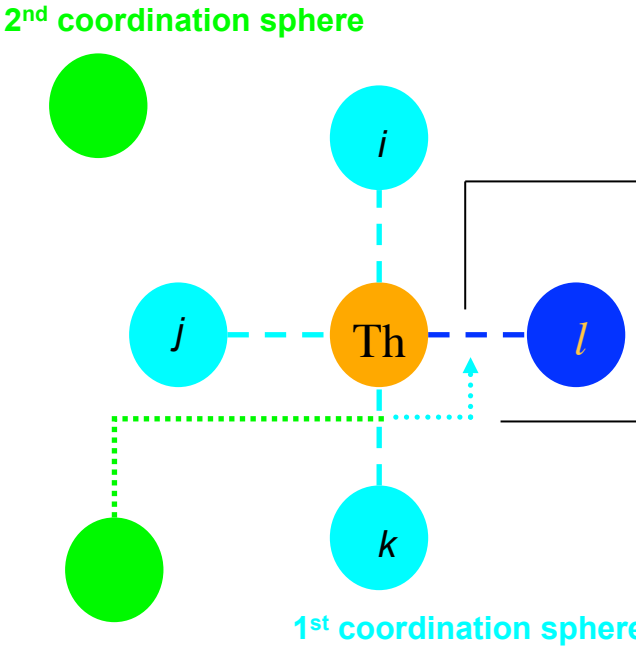
- Fluctuating charge approaches: the “static” δ_i charges are allowed to fluctuate
- Drude oscillators: “extra” atomic charges are introduced
- **Induced dipole moments: new degrees of freedom are introduced**

$$\boldsymbol{\mu}_i = \alpha_i \left(\boldsymbol{E}_i - \sum_{i=1, i \neq j}^{N} \mathbf{T}\left|\boldsymbol{r}_j - \boldsymbol{r}_i\right| \boldsymbol{\mu}_j \right) \Rightarrow \text{ to be solved iteratively, } O(N^2)$$

T is the dipolar tensor and α_i is the center *i* polarizability, usually isotropic
$\mathbf{E}_i$ is the electric field acting on center *i*
$\boldsymbol{\mu}_i$ is the induced dipole moment on center *i*

BEYOND POLARIZATION : CHARGE TRANSFER

Accounting for inter atomic interactions with a weak covalent character



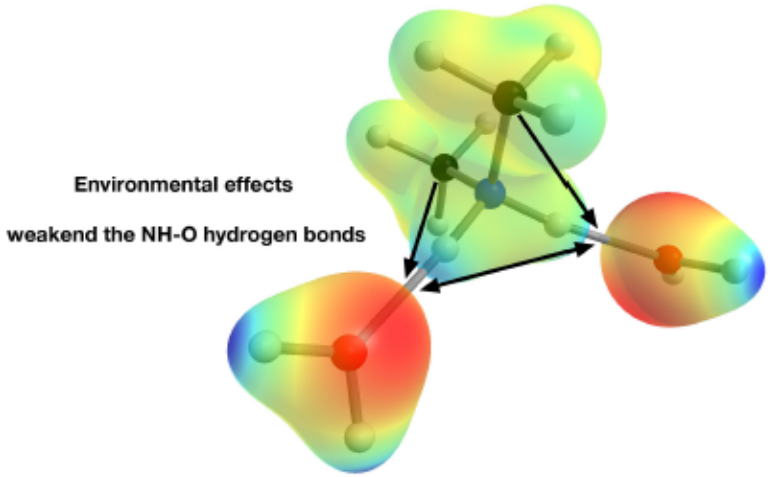
$$U_{ct} = \sum_{l \in water} D_e^c \exp(-\beta \cdot r_{Th-l})$$

$$D_e^c = D_e \left[1 - \xi \sum_{i \in water, i \neq l} \exp\left(-(r_{Th-i} - r_e)^2 / \gamma_r \right) \right]$$

Seems computationally demanding, however scales as *O(N)*

AB INITIO FORCE-FIELDS

Benchmark binding energies of ammonium and alkyl-ammonium ions interacting with water. Are ammonium-water hydrogen bonds strong?

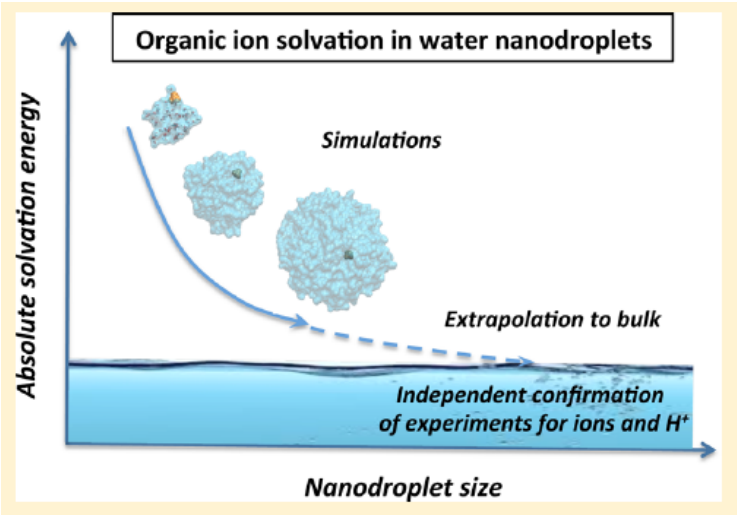


V. Vallet and M. Masella, CPL, 618 (2015) 168

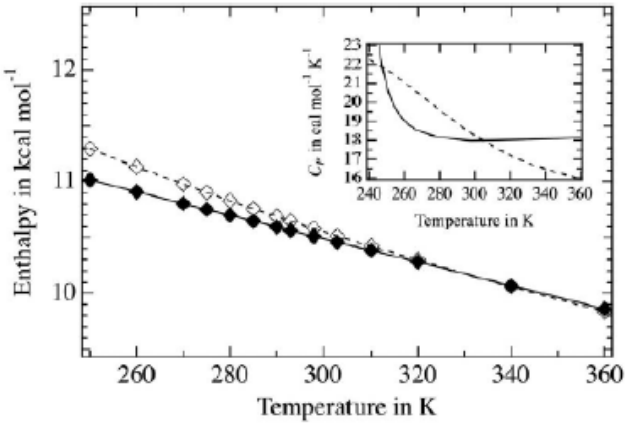
THE JOURNAL OF PHYSICAL CHEMISTRY B
Article
pubs.acs.org/JPCB

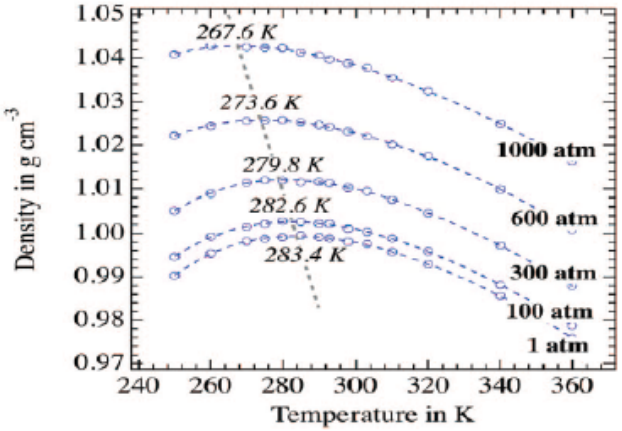
Simulated Solvation of Organic Ions: Protonated Methylamines in Water Nanodroplets. Convergence toward Bulk Properties and the Absolute Proton Solvation Enthalpy

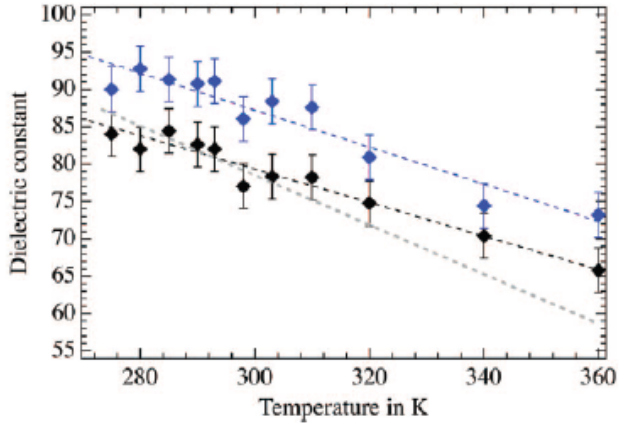
Céline Houriez,*[,†] Michael Meot-Ner (Mautner),[‡,§] and Michel Masella[∥]



AB INITIO FORCE-FIELDS: LIQUID WATER

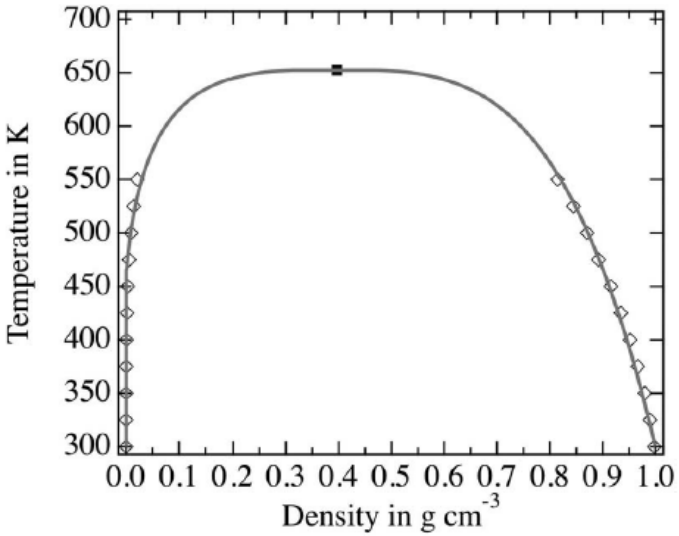






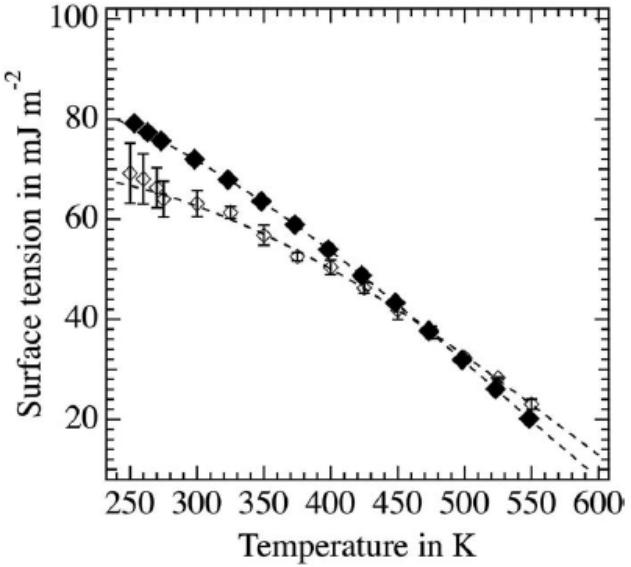
THE WATER CRITICAL POINT

Water critical point



$$\rho_{\pm} = \rho_c + b_0|\mathrm{T} - \mathrm{T}_c| \pm \left(b_1|\mathrm{T} - \mathrm{T}_c|^{\beta_e} + b_2|\mathrm{T} - \mathrm{T}_c|^{\beta_e+1/2}\right),$$

Water surface tension

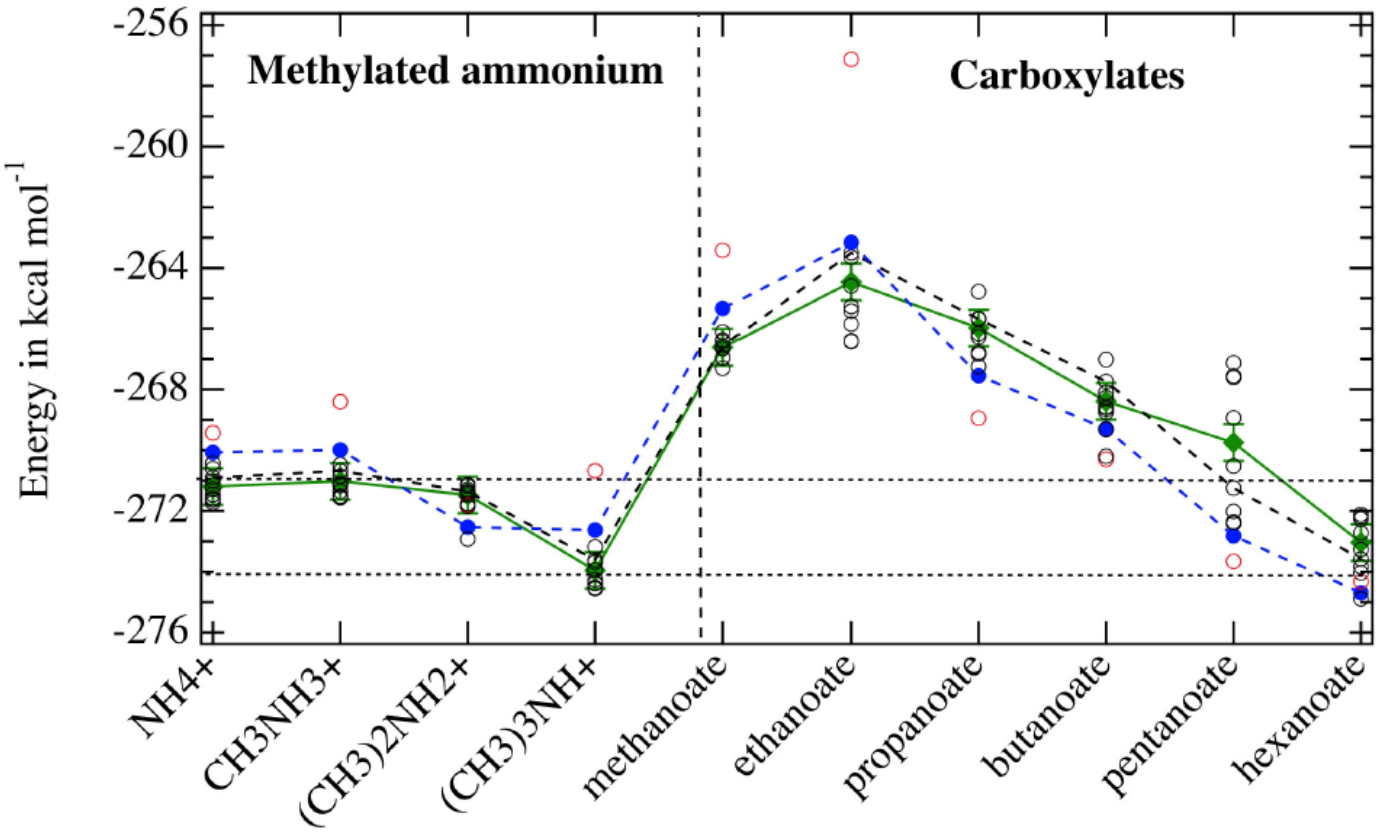


$$\gamma(\mathrm{T}) = a_\gamma(\mathrm{T}_c - \mathrm{T})^{5/4} + b_\gamma(\mathrm{T}_c - \mathrm{T})^{9/4},$$

Real et al, J Chem Phys, 2013

ACCURACY OF AB INITIO FORCE-FIELDS

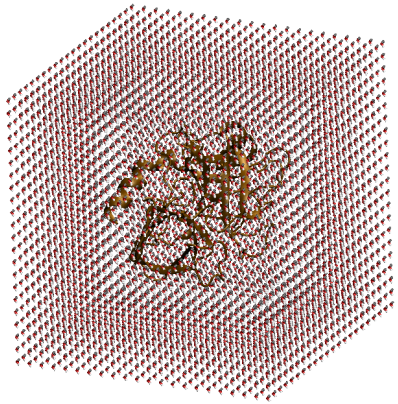
$$\Delta H_{solv}(\mathrm{H}^+) = \Delta H_{g\to aq}(\mathrm{PH}) - \Delta H_{g\to aq}(\mathrm{P}) + \Delta H_g^{prot}(\mathrm{P}) + \Delta H^0_{aq,\mathrm{dissociation}}(\mathrm{PH})$$

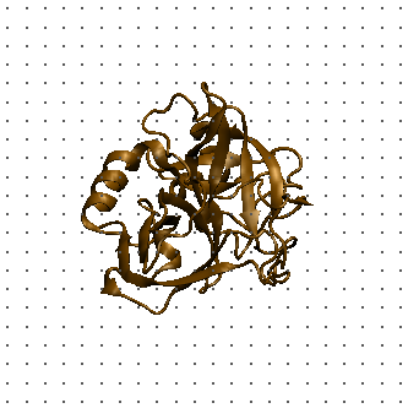


A multiscale solvent coarse grained approach

A SOLVENT COARSE GRAINED APPROACH

Explicit solvent approach, need of FFT !





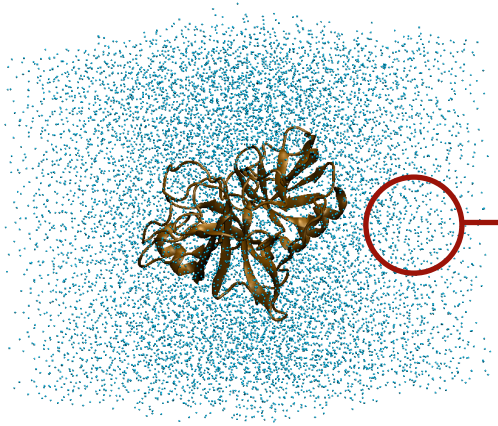
Implicit solvent approaches

Poisson-Boltzman

Warshell's grid approach

Coarse grained approach

Efficiency and microscopic solvation properties



$$\alpha_S = \frac{1}{4\pi}\left(1 - \frac{1}{\varepsilon_s}\right) \times \frac{1}{\rho_s}$$

i.e. $\alpha_s \propto \Delta v_s$

$$F_P[\mathbf{P}] = \frac{1}{2}\int \frac{\varepsilon(\mathbf{r})\mathbf{P}(\mathbf{r})^2}{\chi(\mathbf{r})} dv - \int \mathbf{P}(\mathbf{r}) \cdot \mathbf{E}_S(\mathbf{r}) dv$$

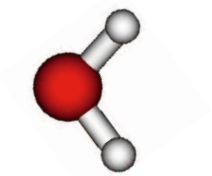
$$\mathbf{P}(\mathbf{r}) = \frac{\chi(\mathbf{r})}{\varepsilon(\mathbf{r})}\mathbf{E}_S(\mathbf{r}) \longrightarrow \mathbf{p}_k^s = \Delta v \mathbf{P}(\mathbf{r}) = \frac{\mathbf{P}(\mathbf{r})}{\rho_s}$$

*Haduong et al, J. Chem. Phys., **117** (2002) 541*

*Masella et al, J. Comput. Chem., **29** (2008) 1707*

ORIGIN OF COARSE-GRAINED APPROACH EFFICIENCY

In the case of water, number of solvent atoms divided by 3



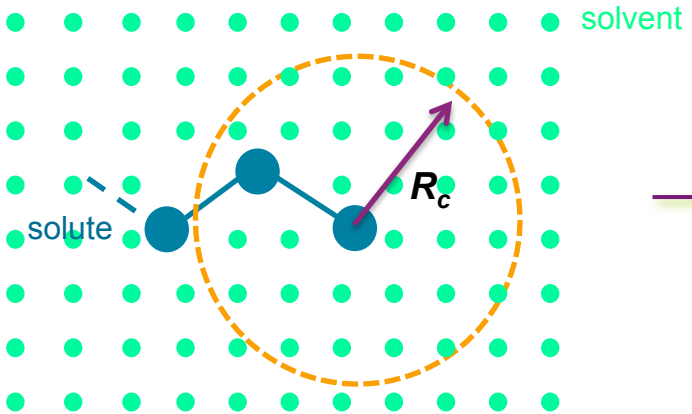
An explicit water molecule

A nonpolar polarizable particule
= a water molecule

What about the liquid water hydrogen bond network ?

A solution from DPD

Systematic truncation of long tail electrostatic interactions



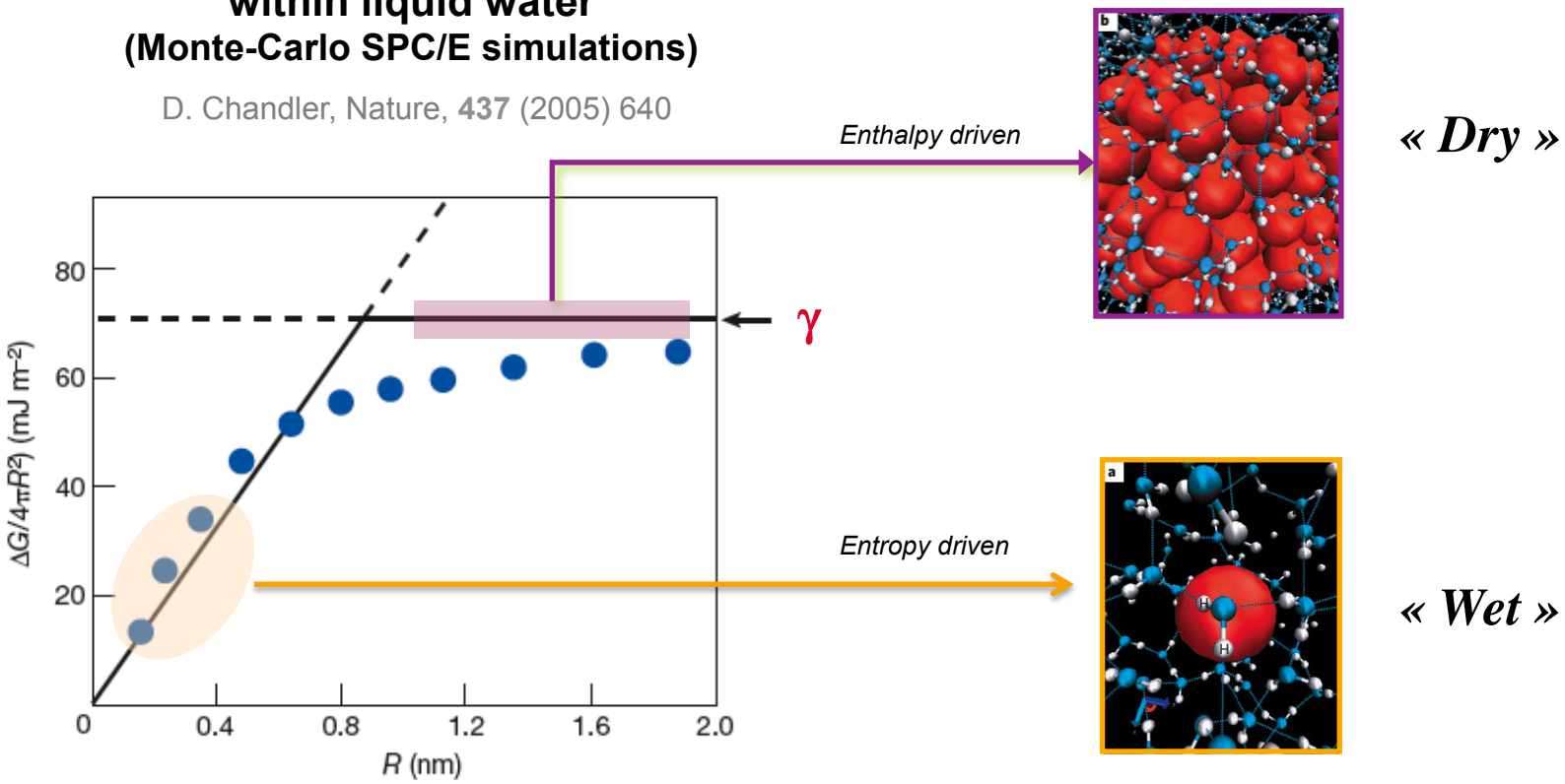
What about electrostatic long tail effects ?

with R_c = 12 Å, the solvent cost represents 10 to 30% of the total cpu time

HB NETWORK IN WATER AND HYDROPHOBIC EFFECTS

Free energy cost ΔG for creating a cavity within liquid water
(Monte-Carlo SPC/E simulations)

D. Chandler, Nature, **437** (2005) 640



Computing γ with VdW potentials : large cutoff (15 Å) for estimating it within 10%

Mecke *et al*, J. Chem. Phys, **107** (1997) 9264

HYDROPHOBIC EFFECTS

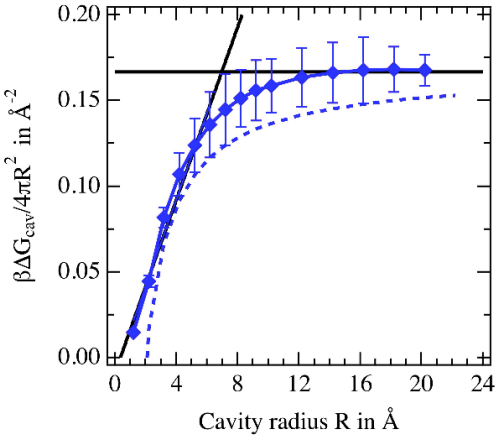
$$U_{pp}^{density} = \sum_{1 \le i \le N_s} \varepsilon_s^0 \left(n_i^0 - \bar{n}^0 \right)^2 + \varepsilon_s^1 \left(n_i^1 - \bar{n}^1 \right)^2$$

n_i : solvent local density at the vicinity of a particle

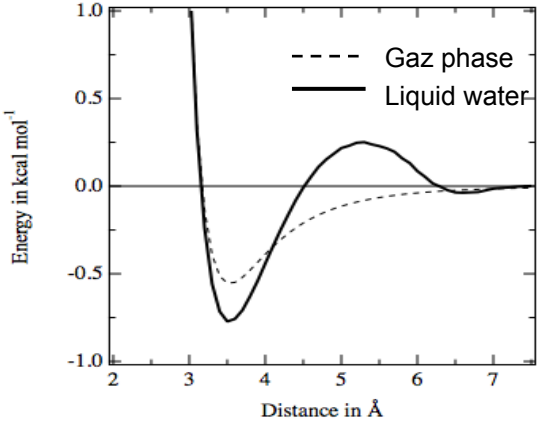
0 → 1st shell ; 1 → 2nd shell

➔ **solvent/solvent interaction truncation : 7 Å**

Masella et al, J. Comput Chem, 2011



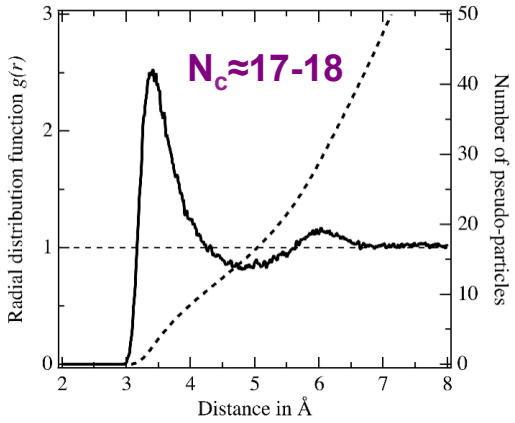
PMF of the methane dimer (300 K,1 atm)



Agreeing with the theory of the hydrophobic effect …

Pratt and Chandler, J. Chem. Phys., **67** (1977) 3683

Methane : solvent structure



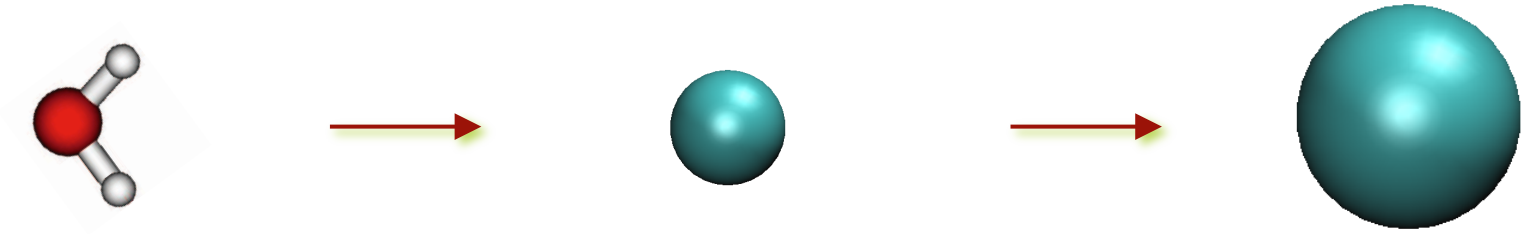
…and all atom simulations

Asthagari *et al*, J. Chem. Phys., **128** (2008) 244152

« MULTI-SCALING » THE COARSE GRAINED APPROACH

Particle polarizability proportional to their individual volume : $\alpha_s \propto \Delta v_s$

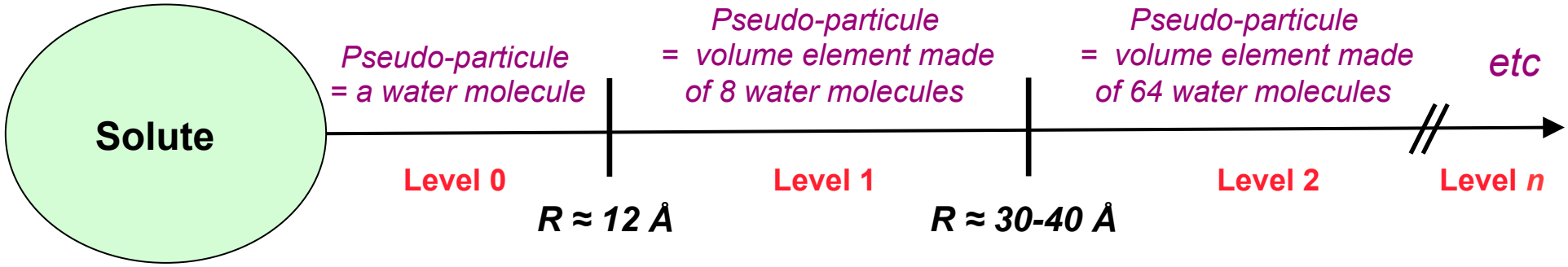
➔ **a multi-scale coarse grained approach to handle long tail bulk electrostatic**



An explicit water molecule

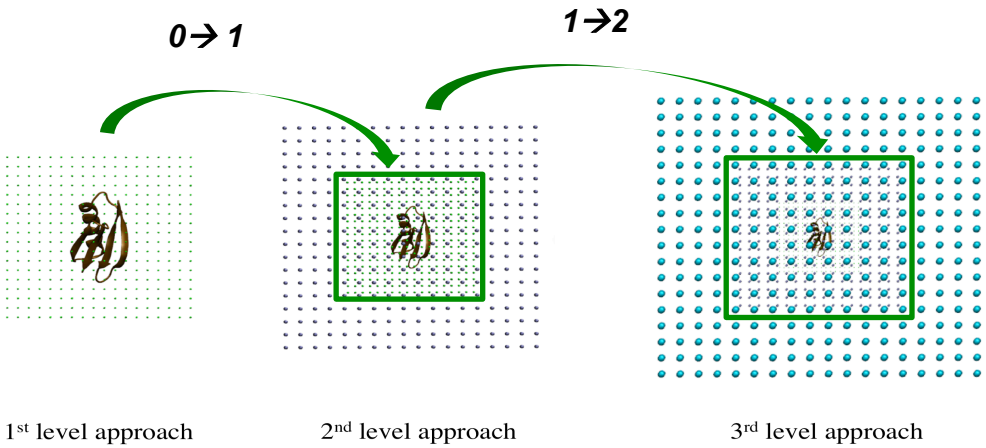
A polarizable pseudo-particule
= a water molecule

A larger polarizable pseudo-particule
= a volume element of liquid water

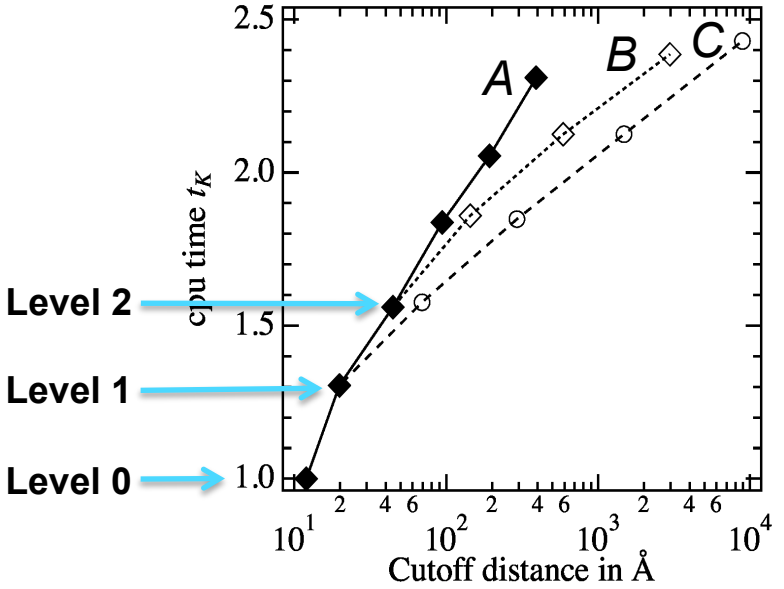


MULTI-SCALE APPROACH EFFICIENCY

*M. Masella et al, J. Comput Chem, **32** (2011) 2664; ibid, **34** (2013) 1112*



Particle size	8	64
Box	8 V_0	64 V_0



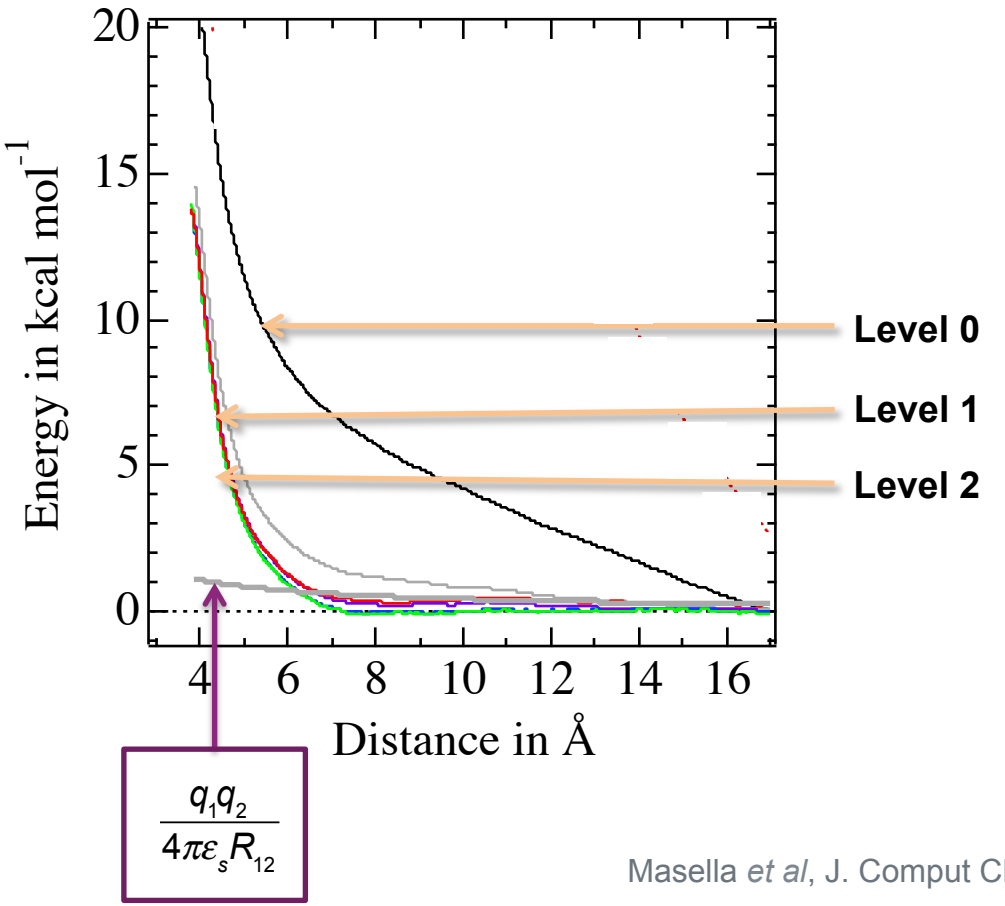
Boxes	0→1	1→2	2→3	3→4
A	x2	x2	x2	x2
B	x2	x2	x3	x4
C	x2	x3	x4	x5

Now, the bottleneck is handling the interactions within the solute…

« MULTI-SCALING » THE COARSE GRAINED APPROACH

Potential of mean force of Cl^-/Cl^- and the coarse grained approach level

(1ns simulation, solvent boxes made of 4096 particles, umbrella sampling, etc…)

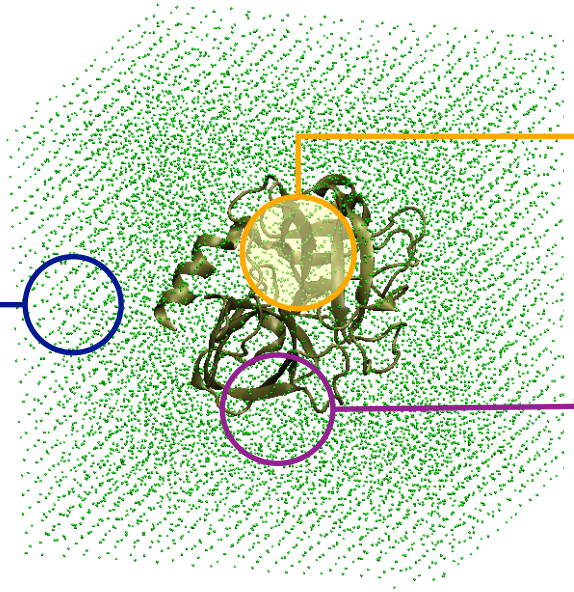


Masella *et al*, J. Comput Chem, 2013

THE CODE POLARIS(MD)

The code POLARIS(MD) © CEA/DSV

Masella, Mol. Phys., 2006 ; Masella *et al*, J. Comput Chem, 2008; *ibid*, 2011; *ibid*, 2013



Polarizable force-field

Energetic of creating a cavity within liquid water

⇒ **Hydrophobic effects**

Polarizable Pseudo Particles

⇒**Macroscopic laws of electrostatic**

Supported by the Exascale Computing Research Laboratory

energie atomique • energies alternatives

UNIVERSITÉ DE VERSAILLES SAINT-QUENTIN-EN-YVELINES

CODE EFFICIENCY ON MODERN SUPERCOMPUTERS

Reference : Intel Sandy-Bridge octo-cores 2.7 Ghz (CURIE)

All atom simulations+ PME summation techniques

A water box of 1000 molecules ➔ **3.0 ns per day** (1 cpu)
4.5 ns per day (2 cpu)

Coarse grained simulations + solute interactions O(N^2)

6000 particles + solute = 900 atoms ➔ **15 ns per day** (level 0 + 1 cpu)
13 ns per day (level 1 + 1 cpu)
11.5 ns per day (level 2 + 1 cpu)
9.5 ns per day (level 3 + 1 cpu)

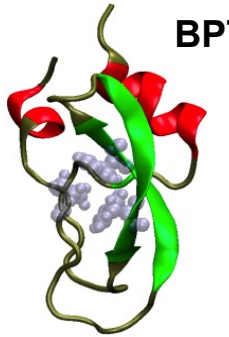
Largest system simulated :

8400 atoms solute + 51 000 particles, **850 ps per day** (level 0 + 1 cpu)

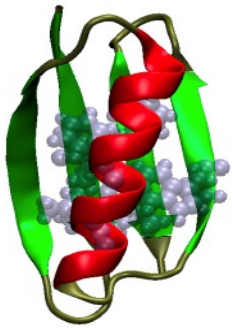
➔ Fast Multipole Method !!!

APPROACH ACCURACY : 3D STRUCTURES

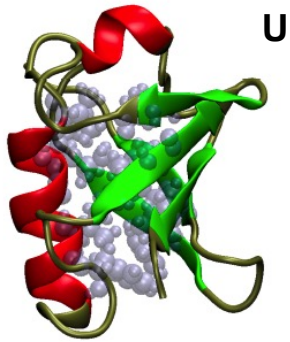
10x20 ns simulations of three small solvated proteins (240 SB cores/36 h)



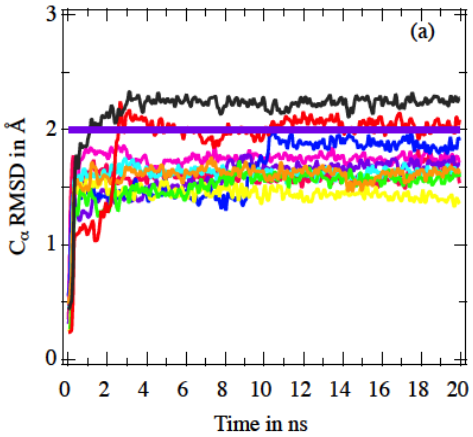
BPTI

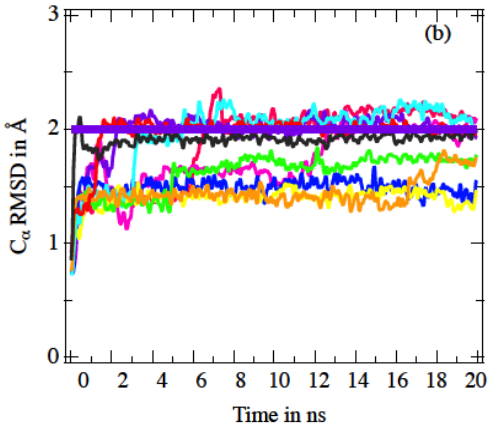


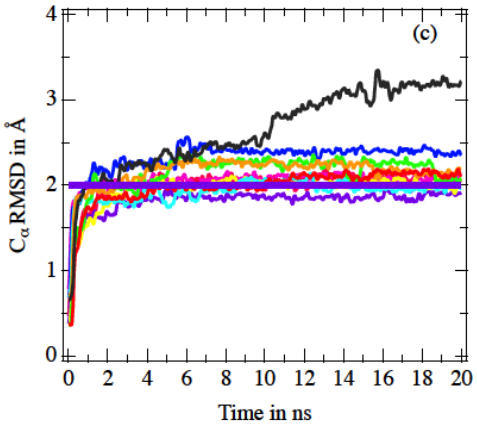
PGB



UBL







Masella et al, J. Comput Chem, 2011

No parameter assigned to reproduce protein structures

An *O(N)* multi-scale *N*-body approach for simulating polarizable microscopic systems

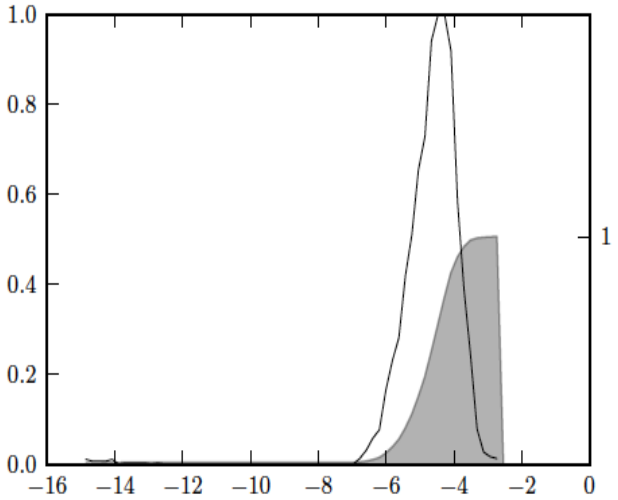
A O(N) FFM APPROACH

$$\phi(\boldsymbol{x}_b - \boldsymbol{x}_a) = \frac{q_a}{|\boldsymbol{x}_b - \boldsymbol{x}_a|}$$

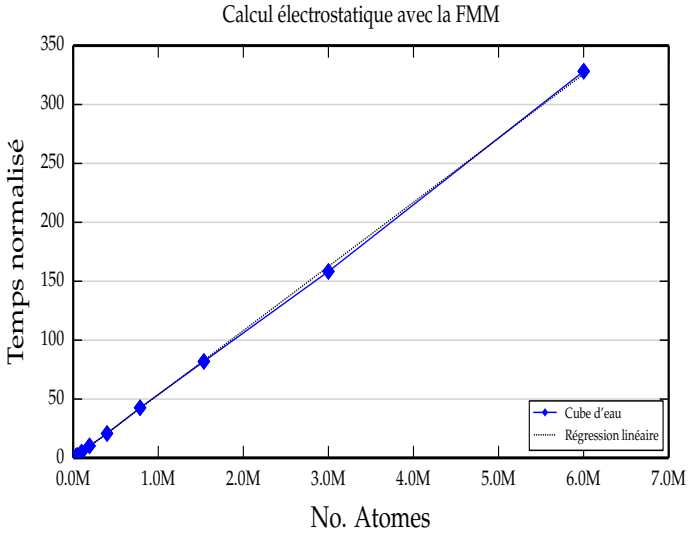
$$\rightarrow \quad \phi(\boldsymbol{x}_b - \boldsymbol{x}_a) \approx \sum_{|\mathbf{n}|\leq p} \sum_{|\mathbf{m}|\leq p-|\mathbf{n}|} \frac{(-1)^{|\mathbf{n}|}}{\mathbf{n}!\mathbf{m}!} r_b^{\mathbf{n}} r_a^{\mathbf{m}} \nabla^{\mathbf{n}+\mathbf{m}} \phi(z_B - z_A)$$

$$+ \quad \boldsymbol{\mu}_a = 2q_q^{\mu} \delta \boldsymbol{l}_a$$

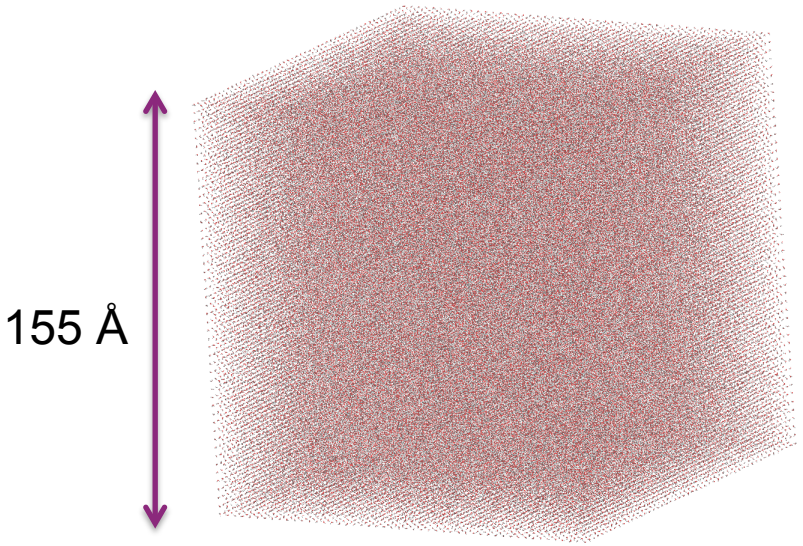
+ atoms organized via a kd-tree spatial decomposition

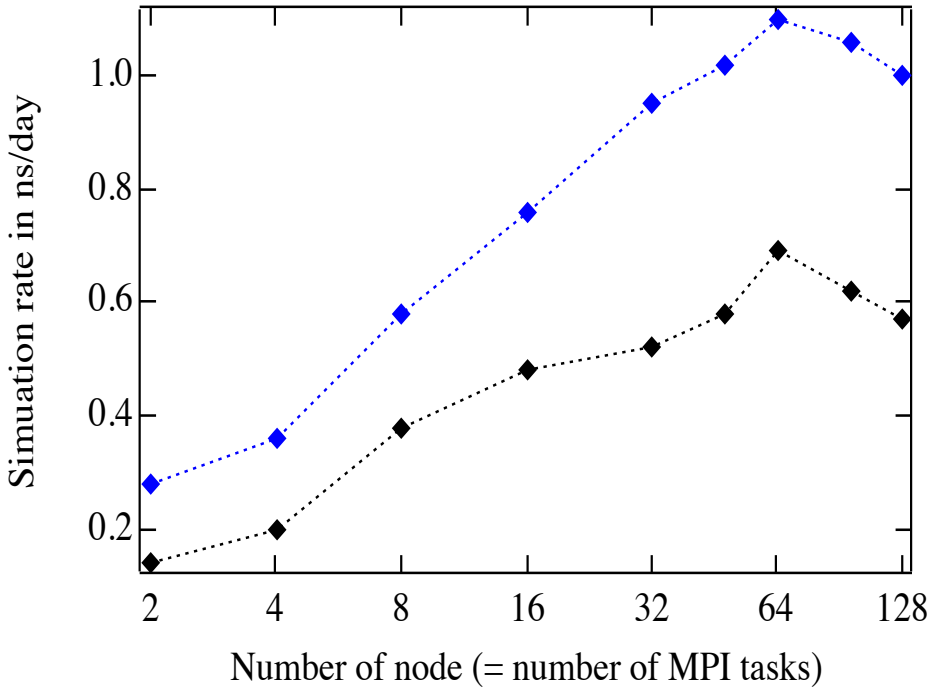


Mean error on the forces



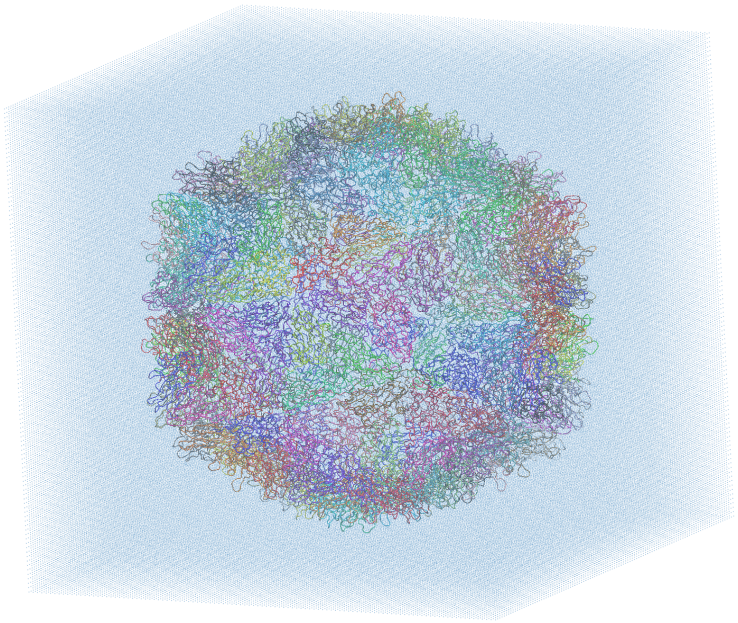
PARALLEL EFFICIENCY : A 125K ATOM SYSTEM

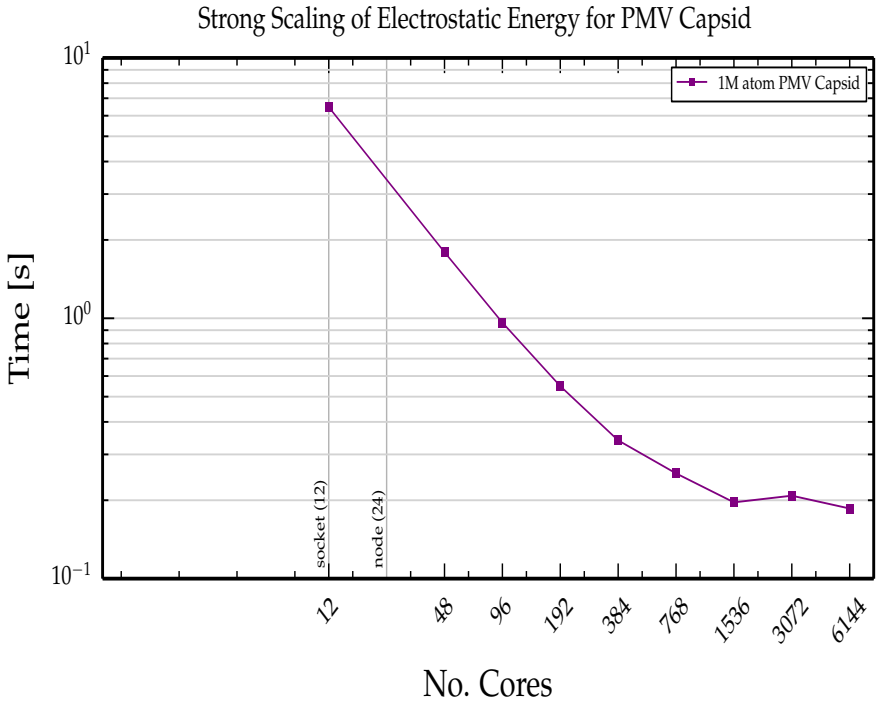




Dipoles solved iteratively; MTS (2f/4fs); black: CURIE@CEA (node = 16 cores); blue: OCCIGEN@CINES (1 node 24 cores)

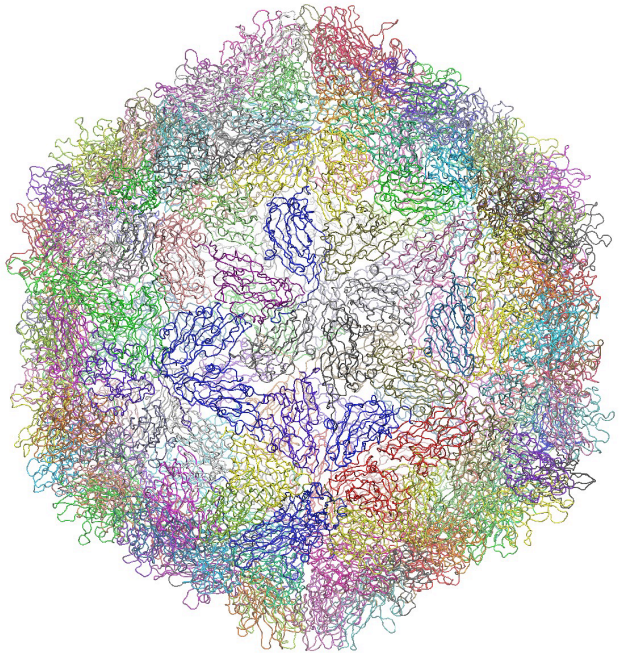
A SOLVATED VIRUS CAPSID





Mosaic Panicum virus capsid
0.6 M atoms + 1.8 M coarse grained solvent particules
Equivalent to a 6.5 M atom systems

Method scalabilty
Hazelhen supercomputing system
(HLRS, Stuttgard, Gemany)



29 MARCH 2016

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