TOWARDS QUANTITATIVE MODELLING OF BIOLOGICAL AND COMPLEX SYSTEMS USING POLARIZABLE FORCE FIELDS.

J.-P. Piquemal
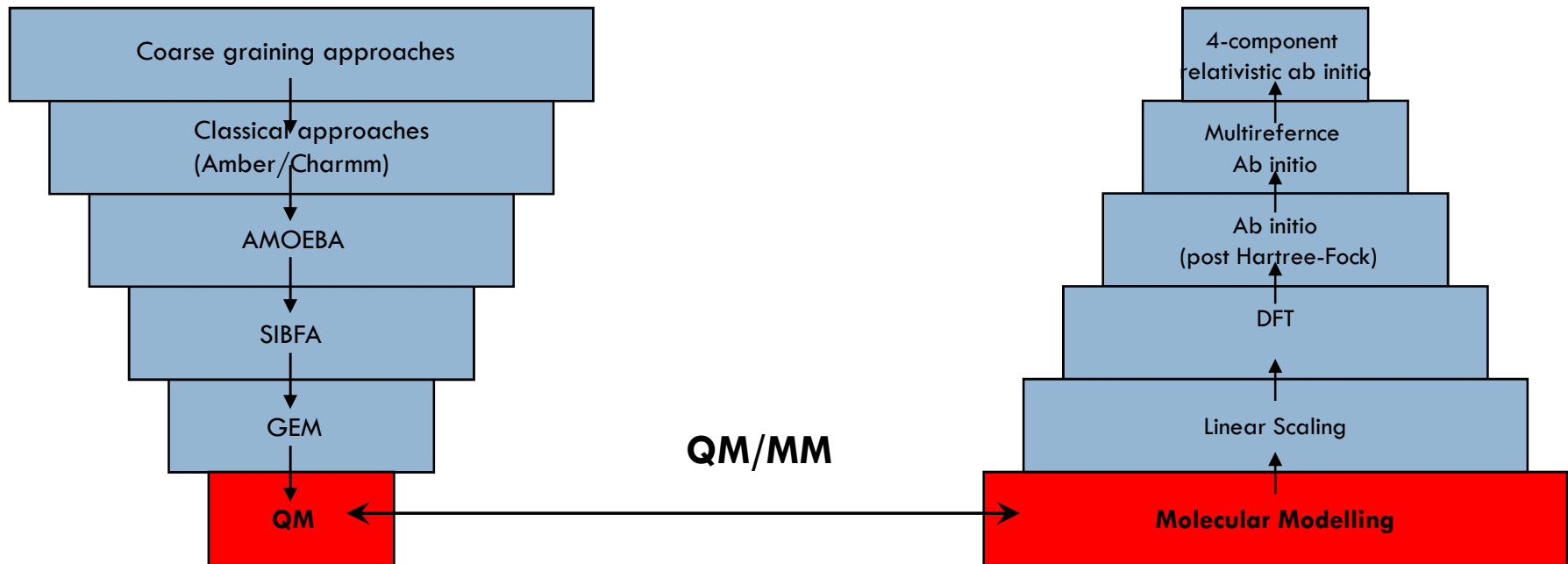
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10/16/2009

Ab Initio 2009, Nice, France.

Potential energy surfaces (PES):

MM (non reactive)

QM (access to chemical reactivity)

Unfortunatly…our interests are:
metalloproteins, transition/heavy metal cations in solution, weak interactions…

Philosophy

Force fields advantages: fast evaluation of PES

Possible treatment of large molecules (million atomes) directly or through QM/MM

-structure

-dynamique

-interaction (docking)

-IR spectrum

$$V_T = \sum_{1,2pairs} 0.5\ K_b\ (b - b_0)^2$$
$$+ \sum_{bond\ angles} 0.5\ K_\theta\ (\theta - \theta_0)^2$$
$$+ \sum_{dihedral\ angles} K_\phi\ [\ 1 + cos(n\phi - \delta)\ ]$$

$$+ \sum_{i,j} 4\varepsilon_{ij}\ [\ (\sigma_{ij}/r)^{12} - (\sigma_{ij}/r)^6\ ]$$
$$+ q_i q_j / \varepsilon r$$

The link with QM is broken...
Next generation "polarizable" force fields are needed.

Philosophy

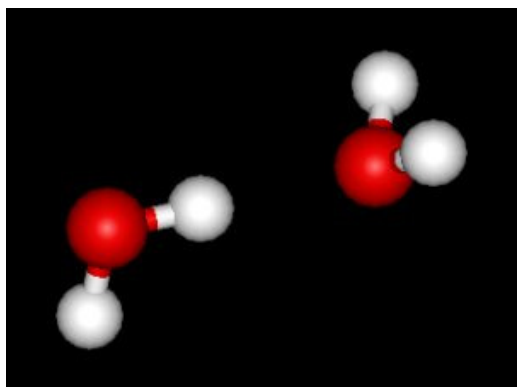Unravelling physics at place in a complex (large) system:

The right tool for the right problem
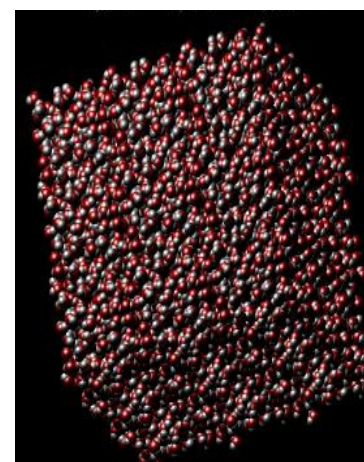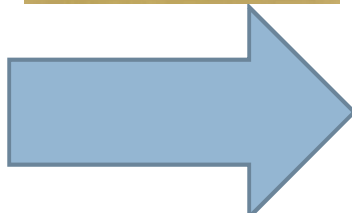
IMPORTANCE OF QM INTERPRETATIVES TECHNIQUES

-density partition schemes

-energy decomposition analysis

Beyond QM capabilities: insights from advanced polarizable MM methods

« Bottom-up » approch for quantitative results (general MM equations)

QM

MM or QM/MM

QM interpretative techniques

Electron Localization Function (ELF)

ELF : built upon the probability of finding an electron of a given spin in the vicinity of another same spin electron. $0 < ELF < 1$.

➢ Mesure of Pauli exclusion principle associated to a local excess of kinetic energy.

➢ When ELF → 1: high probability of opposite-spin pairs
➢ Maximal probability site are called attractors

Theory of dynamical systems:
bassins and separatrix
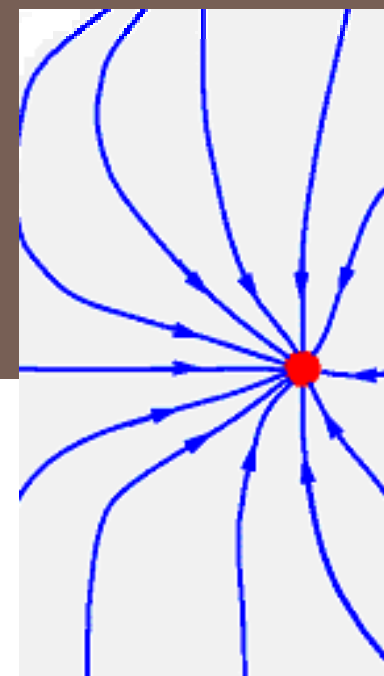
* A.D. Becke, K.E. Edgecombe, *J. Chem. Phys. 92*, 5397, **1990**

** B. Silvi, A. Savin, *Nature 371*, 683, **1994**

QM interpretative techniques

3D partition of the molecular space (3D grid) into chemically intuitive bassins:

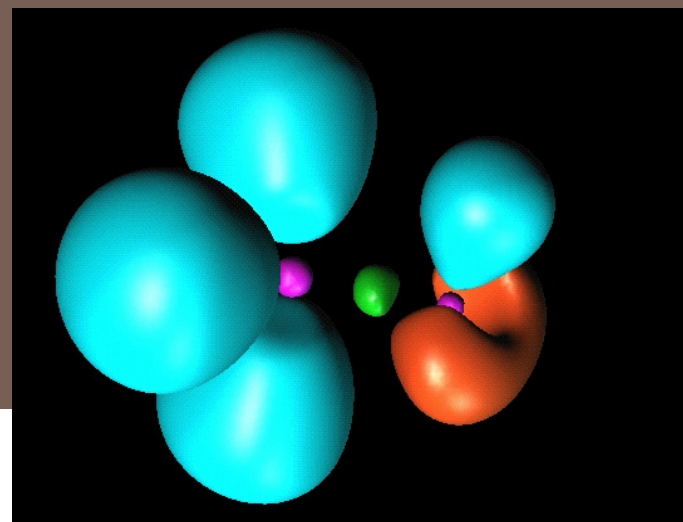Access to non atomic bassins: lone pairs, π systems etc...

Several type of bassins exist:

Core (violet)

Disynaptic (green) : covalent bond

Protonated Disynaptic (blue) : C-H bond

Monosynaptic (red) : Lewis-type lone pair

Valence Shell Electron Pair Repulsion (VSEPR) from Gillespie.

QM interpretative techniques

Distributed Electrostatic Moments from ELF partition (DEMEP)

Beyond traditional charge analysis: computation of local electrostatic properties onatomic and non atomic centers.
Introduction of the M_1 (dipole) and M_2 (quadrupole) quantities

$$M_0(\Omega) = -\int_\Omega \rho(\mathbf{r})d\tau$$

$$M_{1,x}(\Omega) = -\int_\Omega (x - X_c)\rho(\mathbf{r})d\tau$$

$$M_{1,y}(\Omega) = -\int_\Omega (y - Y_c)\rho(\mathbf{r})d\tau$$

$$M_{1,z}(\Omega) = -\int_\Omega (z - Z_c)\rho(\mathbf{r})d\tau$$

$$M_{2,zz}(\Omega) = -\frac{1}{2}\int_\Omega \left(3(z - Z_c)^2 - \mathbf{r}^2\right)\rho(\mathbf{r})d\tau$$

$$M_{2,x^2-y^2}(\Omega) = -\frac{\sqrt{3}}{2}\int_\Omega \left[(x - X_c)^2 - (y - Y_c)^2\right]\rho(\mathbf{r})d\tau$$

$$M_{2,xy}(\Omega) = -\sqrt{3}\int_\Omega (x - X_c)(y - Y_c)\rho(\mathbf{r})d\tau$$

$$M_{2,xz}(\Omega) = -\sqrt{3}\int_\Omega (x - X_c)(z - Z_c)\rho(\mathbf{r})d\tau$$

$$M_{2,yz}(\Omega) = -\sqrt{3}\int_\Omega (y - Y_c)(z - Z_c)\rho(\mathbf{r})d\tau$$

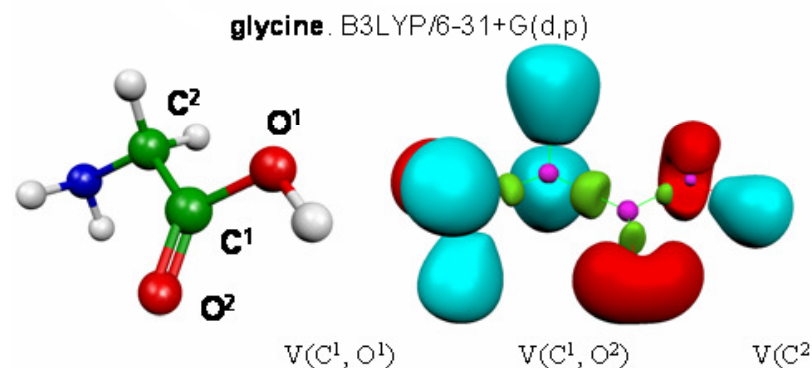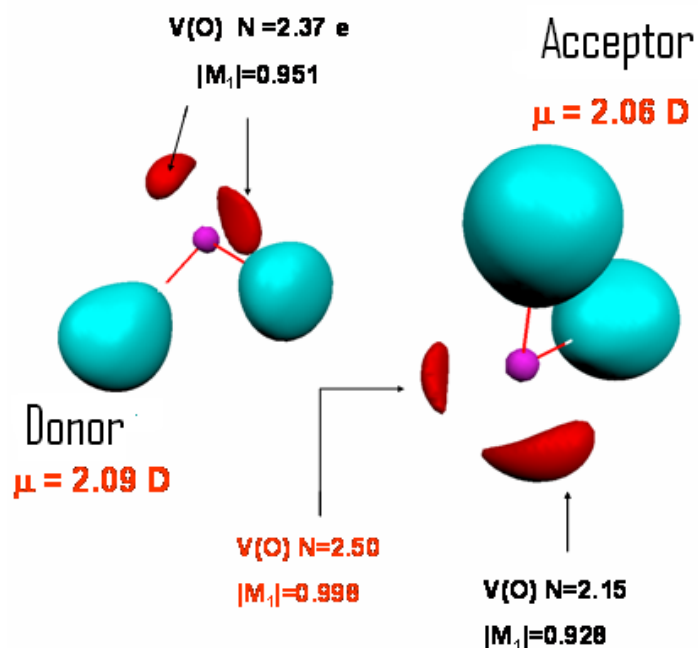$$|\mathbf{M}(\Omega)| = \sqrt{\sum_i M_i(\Omega)^2}$$

J. Pilmé, J-P. Piquemal, *J. Comput. Chem.* **29**, 1440, **2008**

QM interpretative techniques

Applications of DEMEP (1)

Intermolecular Interactions

Intramolecular Interactions.

glycine. B3LYP/6-31+G(d,p)

| Acide Aminé	V(C^1, O^1)		V(C^1, O^2)		V(C^2, N)		V(N)			V(O^2)	
	$|M_1|$	$|M_2|$	$|M_1|$	$|M_2|$	$|M_1|$	$|M_2|$	$|M_1|$	$|M_2|$	$|\mu|$	$|M_1|$	$|M_2|$
Glycine[ab]	0.255	1.249	0.052	0.257	0.183	0.166	0.952	0.125	11.6	3.308	2.446
Valine[a]	0.281	1.241	0.059	0.256	0.177	0.173	0.931	0.167	11.5	3.296	2.417
Tyrosine[a]	0.270	1.210	0.059	0.268	0.177	0.172	0.929	0.161	11,5	3.286	2.454

QM interpretative techniques
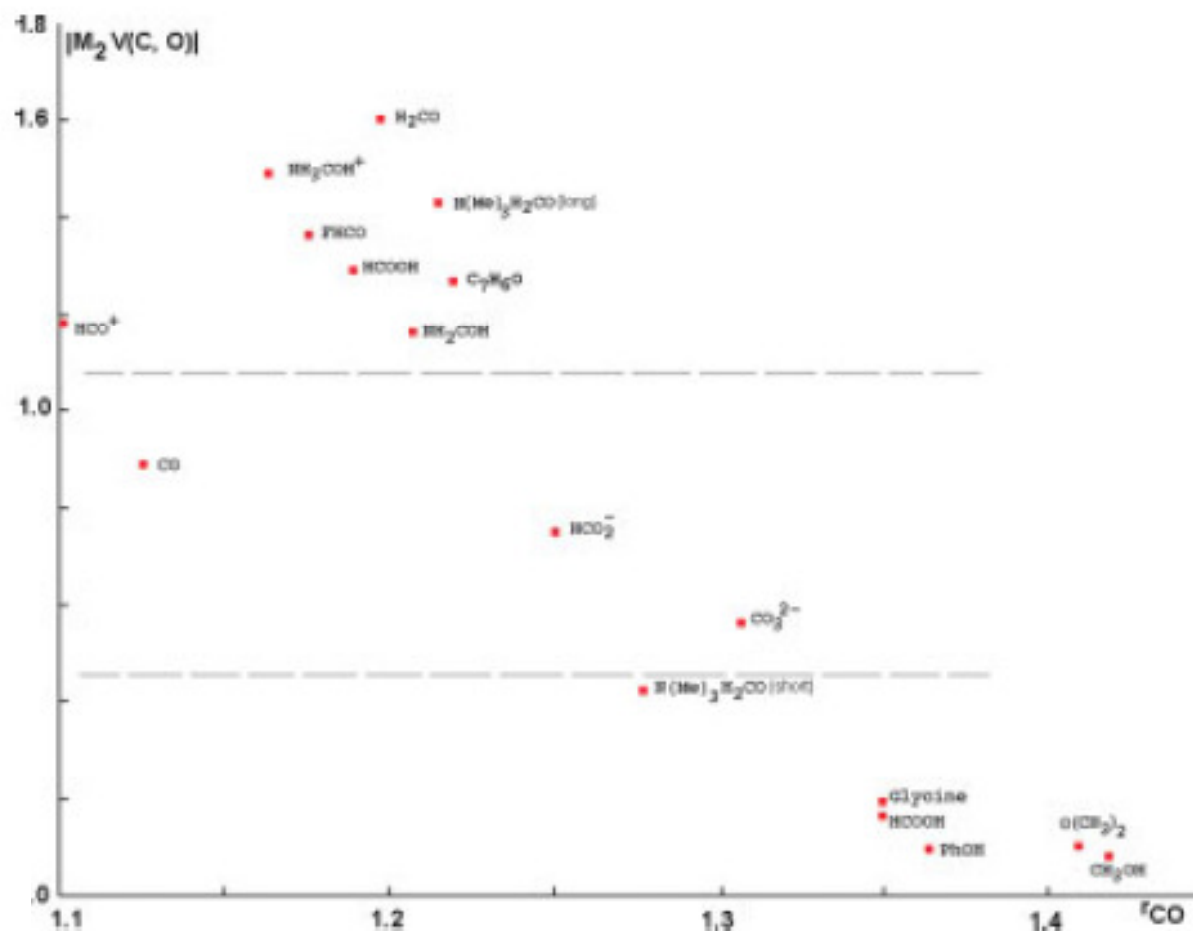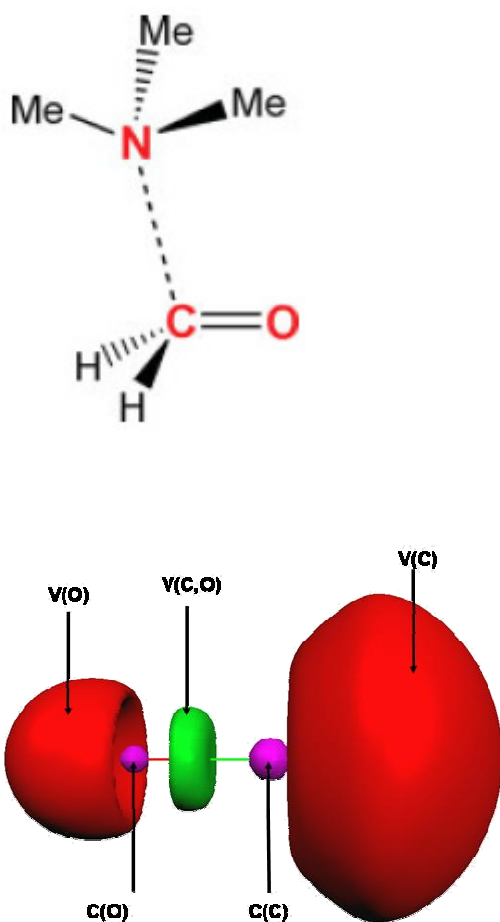
QM interpretative techniques

Energy Decomposition Analysis (EDA)

$$\Delta E = E_c + E_{exch\text{-}rep} + E_{pol} + E_{CT} + E_{disp}$$

$$E_{induction}$$

ΔE: Interaction Energy between Fragments.
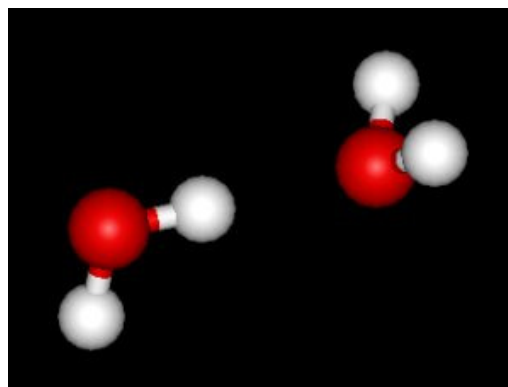
QM interpretative techniques

Perturbative techniques: high level QM (CCSD), non orthogonal orbitals.

$$\Delta E = E_c + E_{exch\text{-}rep} + \underbrace{E_{pol} + E_{CT}}_{E_{induction}} + E_{disp}$$

Symmetry Adapted Perturbation Theory (SAPT): K. Szalewicz et al.

- Reference computation for first order contributions and dispersion(*)

- Bad convergence of induction (métal etc…). Requires 3rd order corrections (tests on water dimer ***).

(*)Piquemal, Cisneros, Gresh, Reinhardt, Darden, J Chem. Phys. 124, 104101, **2006**.

(**) P. Reinhardt., J-P. Piquemal, Int. J. Quant. Chem. *Chem.* 29, 1440, **2009**
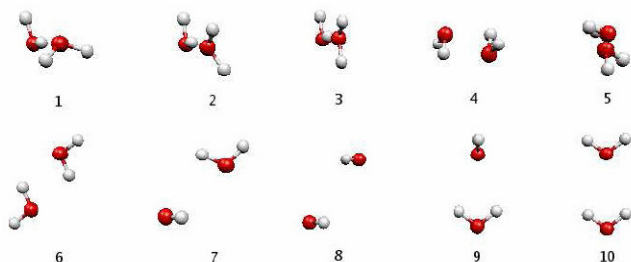
n	SCFlike(2)	SCFlike,r(2)	SCFlike(3)	SCFlike,r(3)	ΔE(HF)
1	2.43	2.63	3.71	3.91	3.53
2	2.25	2.43	3.32	3.50	3.16
3	2.31	2.48	3.34	3.51	3.18
4	2.11	2.24	2.84	2.97	2.62
5	2.02	2.14	2.62	2.73	2.44
6	2.06	2.16	2.60	2.71	2.44
7	1.80	1.85	2.23	2.29	2.04
8	0.66	0.68	1.79	1.81	0.71
9	1.72	1.78	2.25	2.31	2.00
10	1.39	1.43	1.69	1.73	1.53

\# SCFlike(2)   = E100pol + E100ex + E200Ind   + E200ExInd
\# SCFlike,r(2) = E100pol + E100ex + E200Ind,r + E200ExInd,r
\# SCFlike(3)   = E100pol + E100ex + E200Ind   + E200ExInd   + E300Ind(1+E200ExInd/E200Ind)
\# SCFlike,r(3) = E100pol + E100ex + E200Ind,r + E200ExInd,r + E300Ind(1+E200ExInd/E200Ind)

Method/system	1	2	3	4	5	6	7	8	9	10
LMP2	-4.46	-3.95	-3.90	-3.75	-3.75	-3.49	-2.82	-1.05	-2.59	-1.84
F12-MP2	-4.87	-4.38	-4.35	-4.16	-3.94	-3.92	-3.10	-1.16	-2.89	-2.06
F12-CCSD	-4.62	-4.15	-4.13	-3.92	-3.69	-3.67	-3.02	-1.18	-2.83	-2.06
F12-CCSD(T)	-4.84	-4.33	-4.30	-4.13	-3.89	-3.86	-3.19	-1.28	-2.97	-2.15
SAPT (hybrid)	-4.85	-4.39	-4.37	-4.11	-3.91	-3.90	-3.17	-1.28	-3.02	-2.22
SAPT (Paris)	-5.23	-4.72	-4.70	-4.46	-4.21	-4.17	-3.41	-1.37	-3.34	-2.42

QM interpretative techniques

$$\Delta E = E_c + E_{exch\text{-}rep} + E_{pol} + E_{CT}$$

• Variational approaches (orthogonal orbitals) :

Constrained Space Orbital Variations (CSOV) (Bagus et al. 1984)

- correlation through DFT (*)or MCSCF (open-shell)
- correct induction (including exchange effects); charge transfer separation betwen donation-backdonation (*)- charge transfer increases at the DFT level !!!!
- Application to transition and heavy metals via pseudopotentials (**)
- Error bars on induction : improved charge transfer/polarization separation(***)

- Beyond 2 molecules: Localized DFT approach. (****)

(*)   Piquemal Marquez, Parisel, Giessner Prettre, J. Comput. Chem. 26, 1052, **2005.**

(**) Gourlaouen Piquemal, Saue, Parisel, J. Comput. Chem., 27, 142, **2006.**

(***) Piquemal, Bagus, **2009.**

(****) P. Reinhardt., J-P. Piquemal, A. Savin, J. Chem. Theo. Comput. *4, 2020,* **2008**

For constructing intrinsically localized DFT molecular orbitals, we take up an old idea,[15] further developed and published by Daudey[16] and still cited recently,[2,17,18] without the need to have delocalized canonical orbitals. The central point is that in Hartree−Fock theory a CI of singly excited Slater determinants lowers the total energy toward a set of Hartree−Fock orbitals, reaching convergence when satisfying Brillouin's theorem: interactions between occupied and virtual orbitals via the Fock matrix vanish. The singles-CI matrix is locally concentrated, as excitations on fragments with large spatial separation are much less important than those within close neighborhood. That permits the local correction of the monomer orbitals, disregarding the actual extent of the complete system. No canonical (completely delocalized) molecular orbitals are created or needed.

instance reference [19]).The scheme starts from a set of given (guess) orbitals and solves iteratively the Hartree-Fock equations via the steps:

1. Symmetric (Löwdin) orthogonalization of the orbitals via $S^{-1/2}$
2. Construction of the Fock matrix
3. Calculation of the total energy
4. Construction and search for the lowest eigenvalue of an approximate Singles-CI matrix
5. Use in first order of the CI coefficients to correct the occupied and virtual molecular orbitals
6. Return to step 1

In step 3, a criterion of convergence may be introduced to terminate the iterations. Two other points should be mentioned: instead of taking the correct Singles-CI matrix, we may resort to a simpler one, omitting single bi-electronic integrals and using only Fock-matrix elements as:

$$\langle \Phi_i^a | H | \Phi_i^b \rangle \approx F_{ab}\delta_{ij} - F_{ij}\delta_{ab} \tag{2}$$

functional	E_{es}	$E_{exch-rep}$	E_{FC}	$E_{OI+BSSE}$	total interaction
HF (5D)	−8.26	6.88	−1.38	−2.16	−3.55
HF (6D)	−8.27	6.91	−1.36 (−1.37)	−2.18 (−2.19)	−3.55
B-LYP	−8.00	7.42	−0.58	−3.28	−3.86
B-LYP (6D)	−8.03	7.48	−0.55 (−0.61)	−3.30 (−3.26)	−3.86
PW91	−7.91	6.22	−1.69	−3.30	−4.99
PW91 (6D)	−7.93	6.27	−1.66 (−1.50)	−3.33 (−3.48)	−4.99
B3LYP	−8.05	6.67	−1.38	−2.97	−4.35
B3LYP (6D)	−8.07	6.71	−1.36 (−1.45)	−2.99 (−2.95)	−4.35 (4.40)
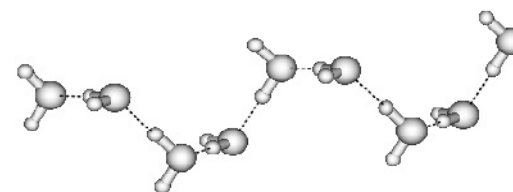
New generation force fields.

Sum of Interactions Between Fragments Ab initio computed
(SIBFA)

Full QM based Bottom up approach

-Energetic scheme based on simplified QM.
- Efficient reproduction of EDA schemes.
- Anisotropy of the potential through non atomic centers.

Unified treatment of inter- and intra-molecular interactions.

New generation force fields.

$$\Delta E = E_c + E_{exch-rep} + E_{pol} + E_{CT} + E_{disp}$$

Fully separable/anisotropic energy function.
QM references: CSOV (or RVS), SAPT

- E_c: Multipoles up to quadrupoles (atoms+bond midpoints)
+ short-range electrostatics (penetration correction) (*)
- Simplified LMO scheme for Exchange-Repulsion (Murrel, 1964)
  $S^2/R + S^2/R^2$ (**) (bond-bond+bond-LP+LP-LP)

(*) Piquemal , Gresh, Giessner-Prettre, J. Phys. Chem A, Comput. Chem. 107, 10353, **2003.**

(**) Piquemal, Chevreau, Gresh, J. Chem. Theo. Comput., 3, 824, **2007.**
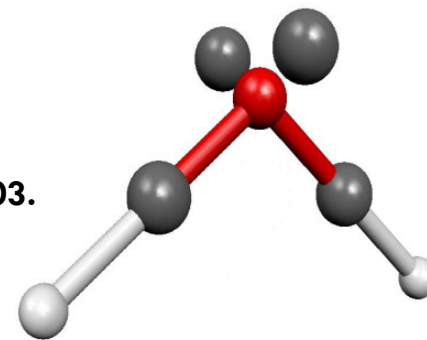
New generation force fields.

$$\Delta E = E_c + E_{exch-rep} + E_{pol} + E_{CT} + E_{disp}$$

- Polarization using ab initio polarizabilities on each LMO (Garmer-Stevens)+ short range correction for exchange.
- Quadrupolar polarizabilities on metals (Cu(I), Cu(II)…)
- SIBFA includes charge transfer (Murrel et al., 1966)
- Dispersion (C_6, C_8, C_{10}) + exchange-dispersion
- Effective Hamiltonian for open shell complexes: inclusion of ligand field effects
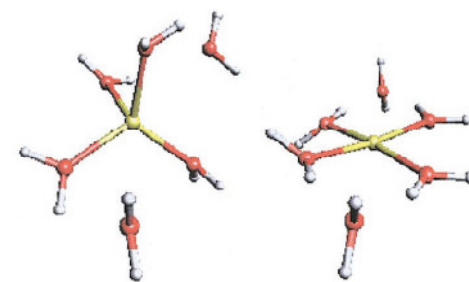
A
SIBFA

B
SIBFA-LF

(*) Gresh, Cisneros, Darden, Piquemal, J. Chem. Theo. Comput. 3, 1960, **2007**.

(**) Piquemal, Gresh, Deeth, Giessner-Prettre, J. Comput. Chem. 24, 1963, **2003.**

New generation force fields.
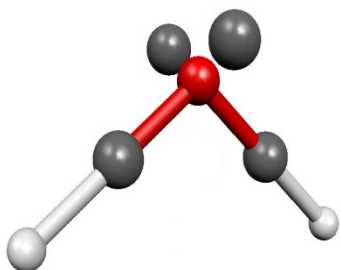
SIBFA vs. CPE (Chemical Potential Equalization) vs. RVS
Can SIBFA be a quantitative approach?
(To do that, it would need to reproduce both QM energies and QM average dipole moment/per molecule.)
→ It does thanks to its inclusion of polarizable lone pairs: importance of electron localization.
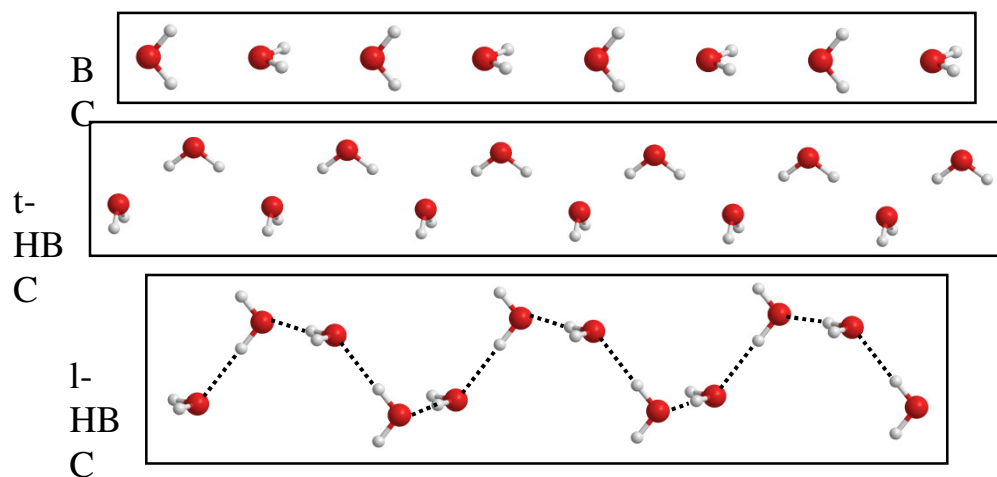
B C

t-HB C

l-HB C

Piquemal et al., J. Phys. Chem. A111, 8170, **2007**.
Piquemal et al., J. Chem. Theo. Comput. 3, 824, **2007**.
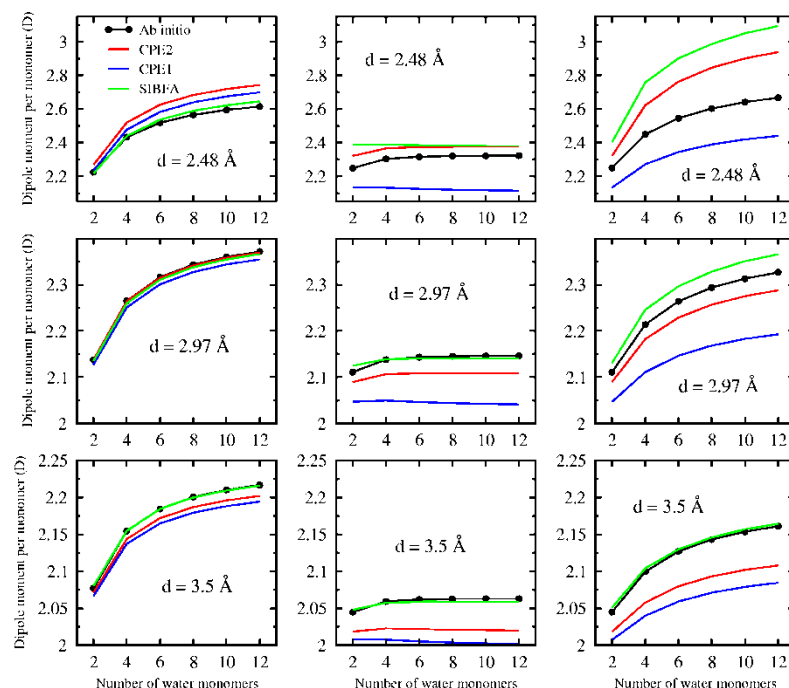
New generation force fields.
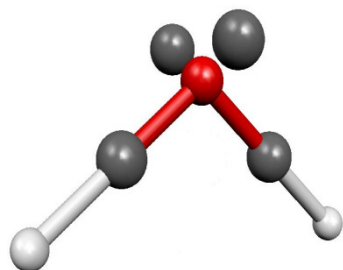
SIBFA vs. CPE (Chemical Potential Equalization)

energies (kcal/mol)	E_c	E_{exch}	E_1	E_{pol}	E_{ct}	E_2	ΔE
HBC SIBFA	−81.6	54.0	−27.6	−18.2 (−14.0)	−9.5	−27.7	−55.4
HBC RVS	−81.2	54.3	−26.8	−17.3 (−14.5)	−9.8	−24.3	−53.1
t-HBC SIBFA	−58.8	29.9	−28.8	−9.0 (−7.2)	−3.6	−12.6	−41.4
t-HBC RVS	−53.5	27.3	−26.3	−9.8 (−8.2)	−3.5		−39.2
I-HBC SIBFA	−60.9	54.0	−6.9	−3.9 (−3.6)	−7.5	−11.4	−18.3
I-HBC RVS	−60.5	55.1	−5.4	−5.5 (−4.7)	−7.7		−17.8

Piquemal et al., J. Phys. Chem. A111, 8170, **2007**.
Piquemal et al., J. Chem. Theo. Comput. 3, 824, **2007.**

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)
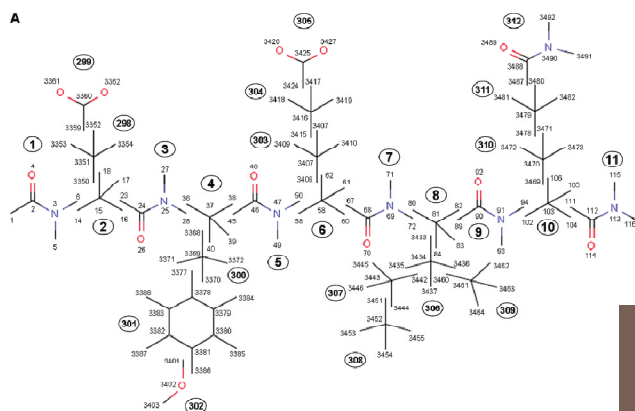
Macromolecules built upon using fragment libraries.
Multipoles & polarizabilities redistribution.
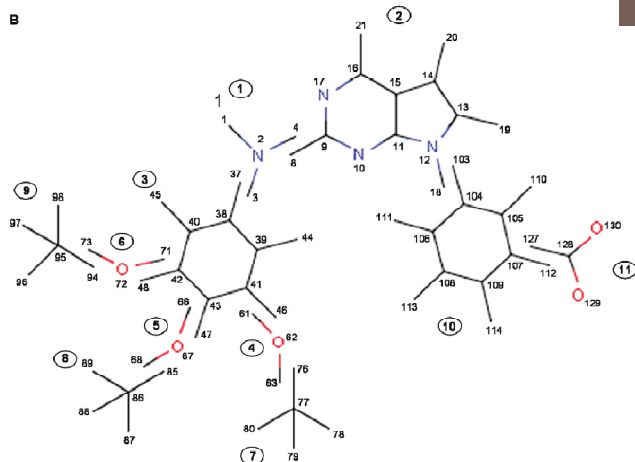
New generation force fields.

Experimental collaboration: Ettore Appella
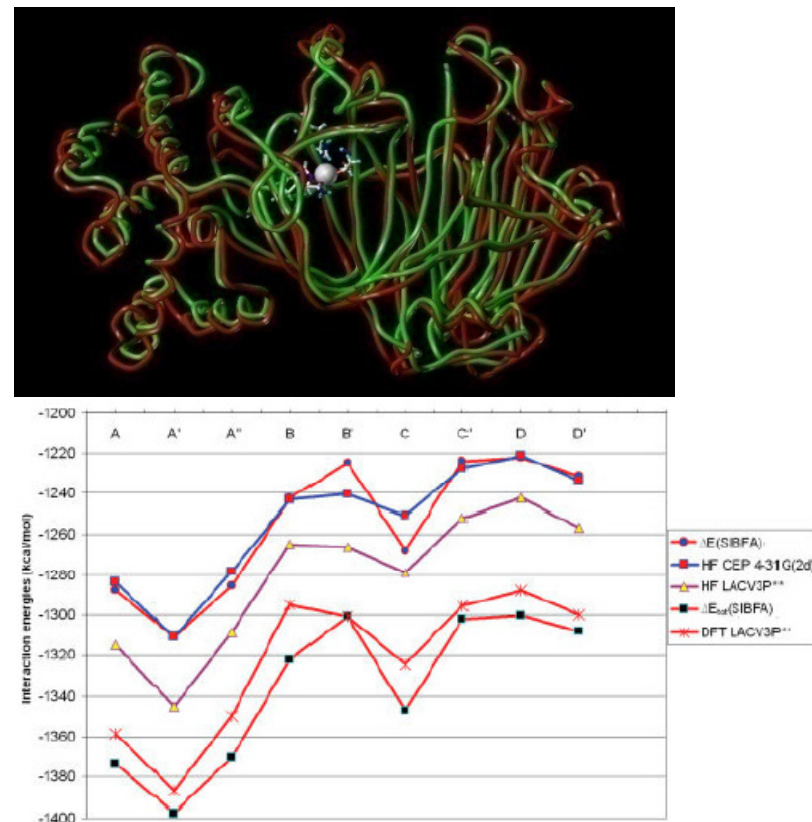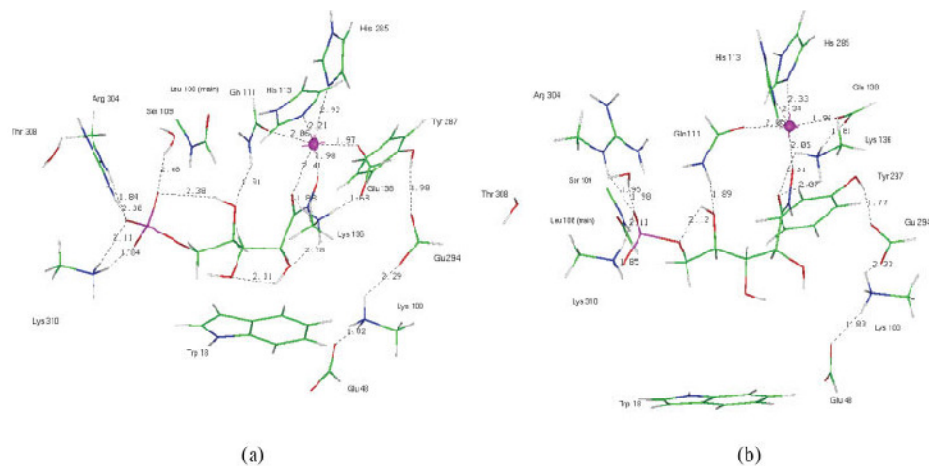NIH Immunology group (Bethesda, MA, USA)
Phase II molecule (Thioester)
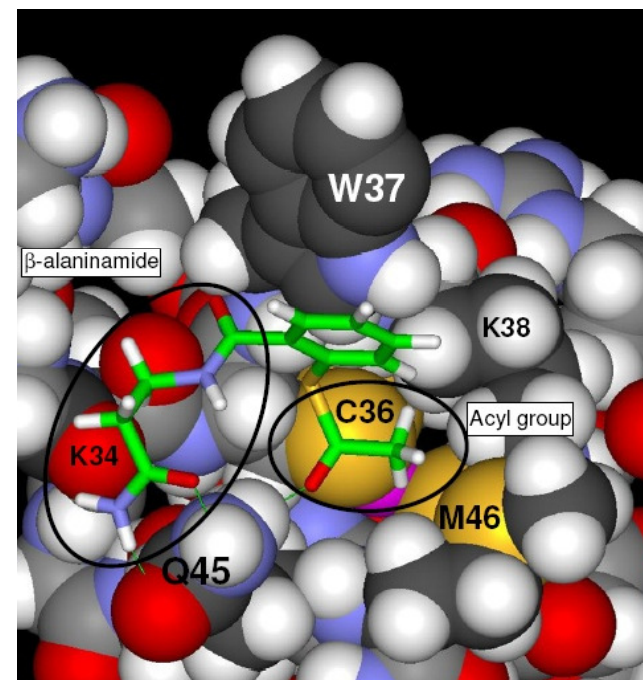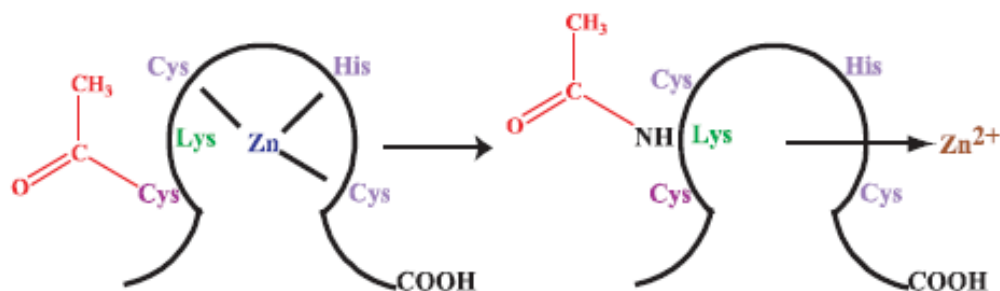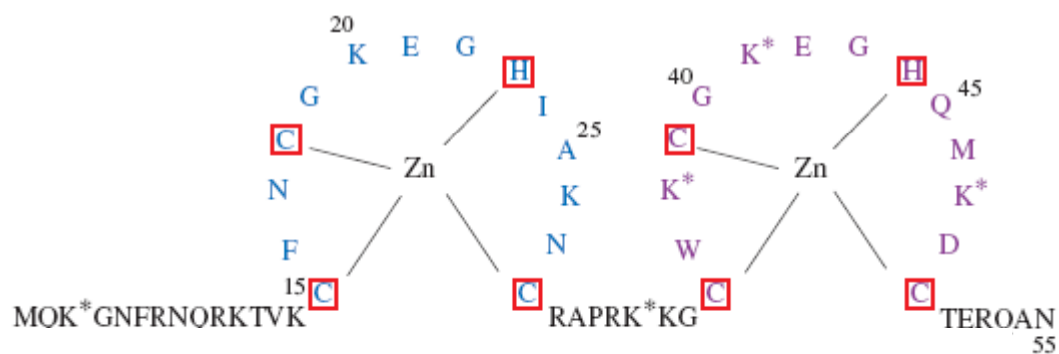
Miller Jenkins, Hara, Durell, Hayashi, Inman, Piquemal, Gresh, Appella, J. Am. Chem. Soc.129, 11067, **2007.**

New generation force fields.

Experimental collaboration:
L. Salmon, ICCMO, Orsay (France).
Phosphomannose Isomerase (PMI)
164 residues.

(a)   (b)

C. Roux, N. Gresh, L. Perera, J-P Piquemal and L. Salmon, J. Comput. Chem. 28, 938, **2007.**
J. Foret, B. de Courcy, N. Gresh, J-P. Piquemal, L. Salmon, **2009**, Bioorg. Med. Chem., online.
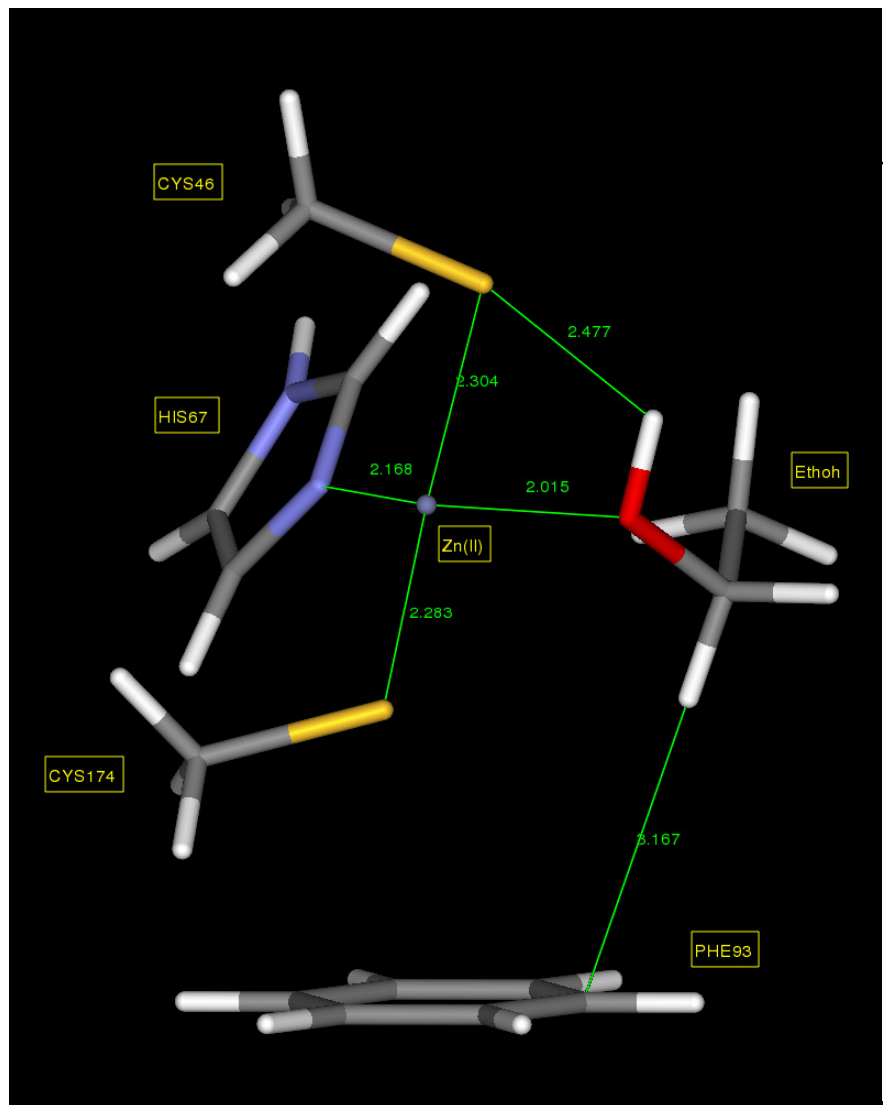
New generation force fields.

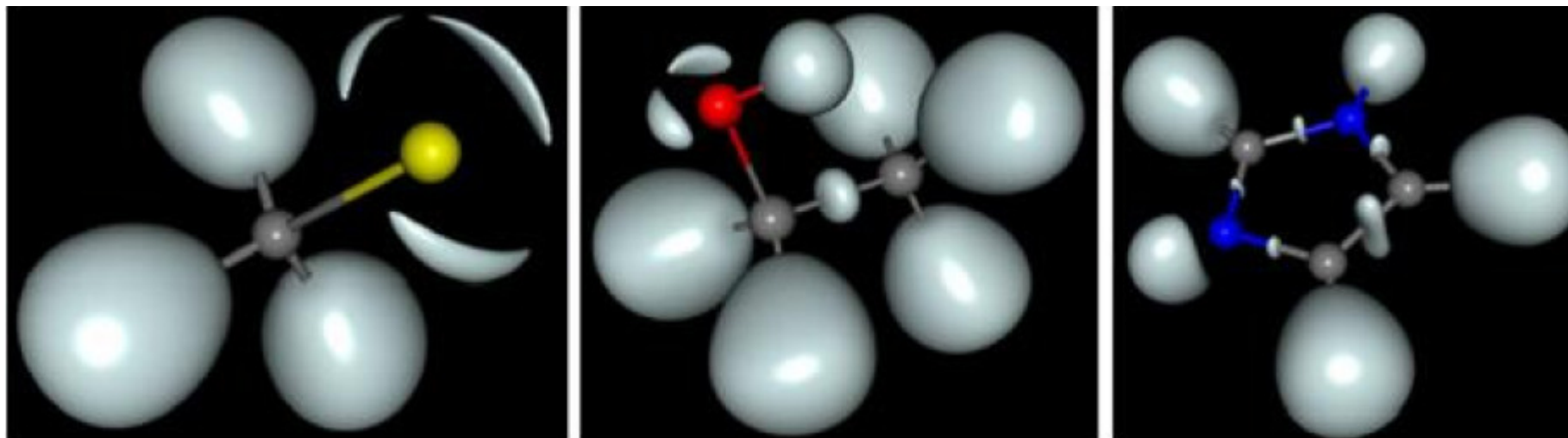Sum of Interactions Between Fragments Ab initio computed (SIBFA)

Focal Adhesion Kinase (FAK)

R 550

mu = 2.62 D

D 564

mu = 3.08 D

mu = 3.00 D

mu = 3.52 D

Ligand

mu = 2.93 D

E 471

K 454
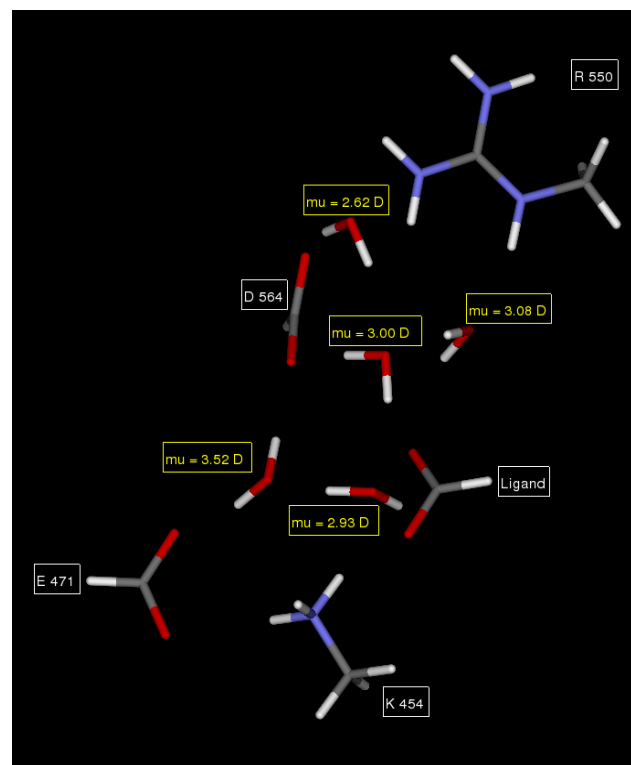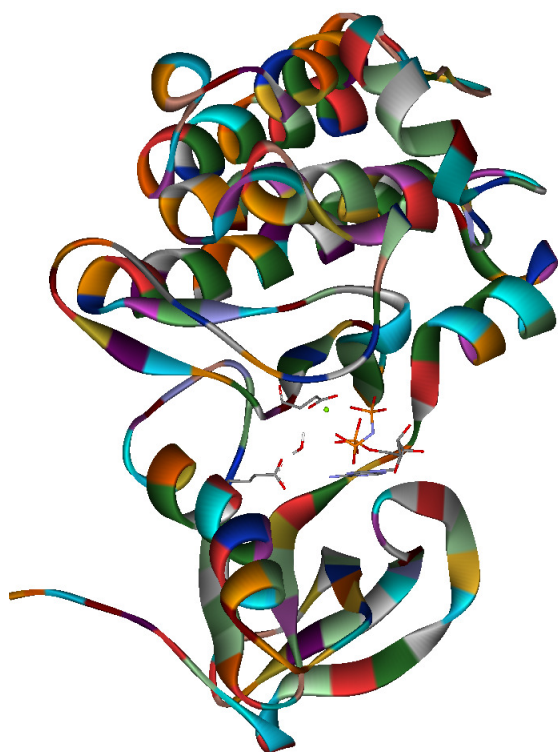
EXPLICIT SOLVATION REQUIRED!!!

*De Courcy, Piquemal*, Garbay, Gresh*, to appear in J. Am. Chem. Soc.,* **2009**

	Complex *a*		Complex *b*	
	Ab initio	**SIBFA**	**Ab initio**	**SIBFA**
$E_{Coul.}$ / E_{MTP}	-661,6	-657,9	-664,4	-662,4
$E_{exch.}$ / E_{rep}	177,4	168,9	180,2	173,5
E_1	-484,2	-489,0	-484,2	-488,9
$E_{pol}(HF)$ / E_{pol}	-85,5	-94,4	-84,5	-93,0
$E_{pol}(RVS)$ / E_{pol*}	-113,2	-121,6	-111,8	-120,0
$E_{ct}(RVS)$	-48,5		-48,6	
BSSE	-5,1		-5,6	
E_{ct*} / E_{ct}	-43,4	-41,3	-43,0	-41,3
E_2	-156,6	-162,9	-154,8	-161,3
ΔE	**-618,2**	**-624,7**	**-617,3**	**-623,2**
$\delta E(MP2)$ / E_{disp}	-48,4	-65,9	-57,8	-70,5
ΔE_tot	**-666,6**	**-690,6**	**-675,1**	**-693,7**

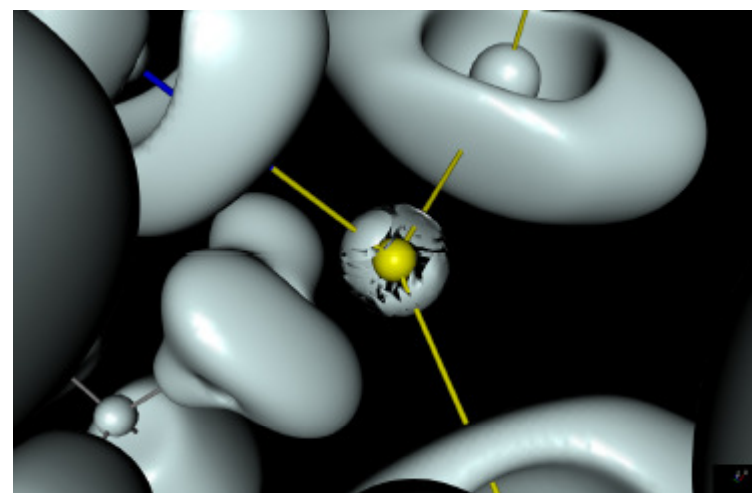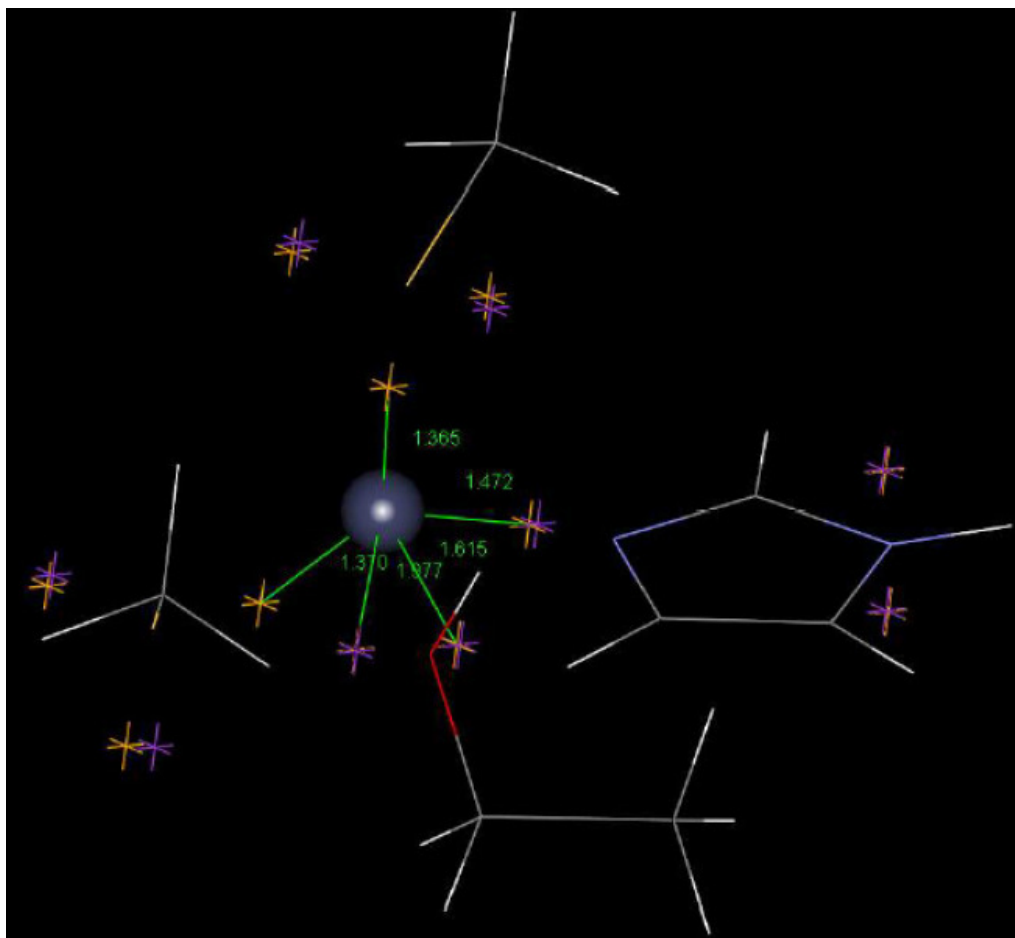de Courcy, Piquemal*, Gresh, J. Chem. Theo. Comput, 2008, 4, 1659

De Courcy, Gresh, Piquemal*, Interdiscip Sci Comput Life Sci (2009) 1, 55
DOI: 10.1007/s12539-008-0027-0
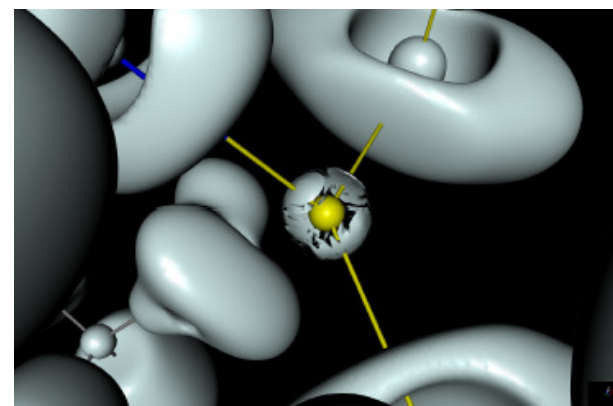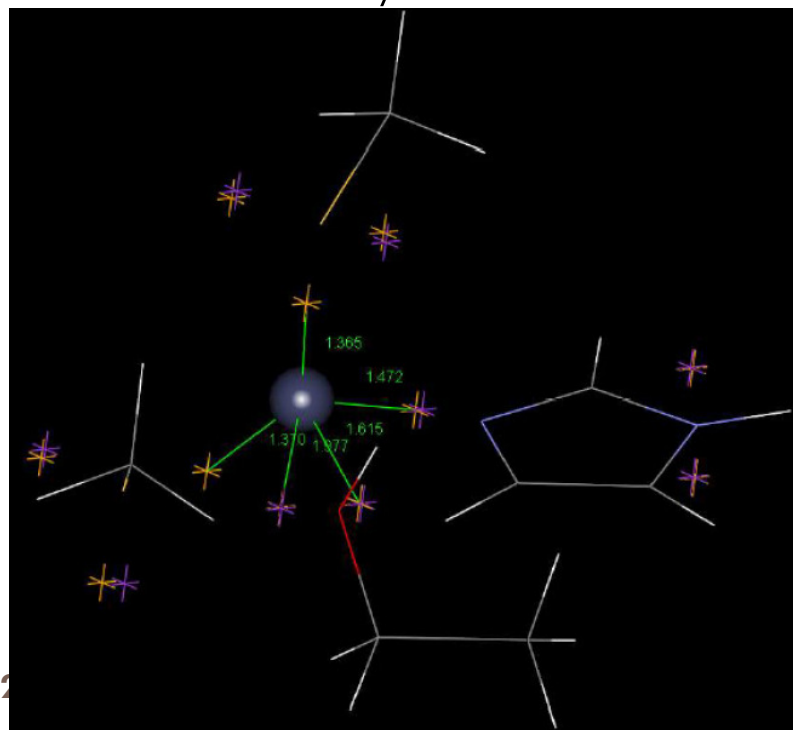
	$E_1 / \Delta E$	$E_2 / \Delta E$
Cy^- 46/ Zn(II)	66,8%	33,2%
Imh / Zn(II)	44,1%	55,9%
Cy^- 174/ Zn(II)	67,1%	32,9%
EtOH / Zn(II)	39,7%	60,3%

	$E_1 / \Delta E$	$E_2 / \Delta E$
Cy⁻ 46/ Zn(II)	66,8%	33,2%
Imh / Zn(II)	44,1%	55,9%
Cy⁻ 174/ Zn(II)	67,1%	32,9%
EtOH / Zn(II)	39,7%	60,3%

Next generation force field.

•Beyond multipoles: Gaussian Electrostatics Model.(*).

Density Fitting

A fundamental calculation of the energy surface for the system of three hydrogen atoms
S F Boys and I Shavitt, University of Wisconsin, Report WIS-AF-13 (1959) NTIS AD212985

"In this method, each two-center charge distribution is expanded by least-squares as a sum of single-centre charge distributions centered on various points on the line passing through the two centres. . ."

$$\tilde{\rho} = \sum_{k=1}^{N} x_k k(r) \approx \rho = \sum_{\mu\nu} P_{\mu\nu} \phi_\mu(r) \phi_v^*(r)$$

$$E_{coulomb} = \frac{Z_A Z_B}{r_{AB}} - \int \frac{Z_A \tilde{\rho}^B(r_B)}{r_{AB}} dr - \int \frac{Z_B \tilde{\rho}^A(r_A)}{r_{AB}} dr + \int \frac{\tilde{\rho}^A(r_A)\tilde{\rho}^B(r_B)}{r_{AB}} dr$$

(*)   Cisneros, Piquemal, Darden, J. Chem. Phys. 123, 055109, **2005**

Piquemal, Marquez, Parisel, Giessner-Prettre, J. Comput. Chem., 26, 1052, **2005**..

Next generation force field.
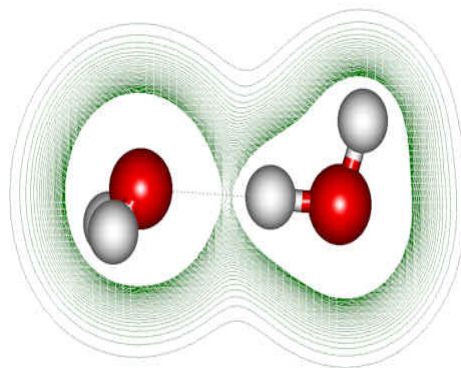
$$\Delta E = E_c + E_{\text{éch-rép}} + E_{pol} + E_{TC} + E_{disp}$$

Frozen density of a rigid fragment
Hermite gaussians
(recursions using PME –fourier space nlog(n)

Piquemal, Cisneros, Reinhardt, Gresh, Darden, J. Chem. Phys.124, 104101, **2006**
Cisneros, Piquemal, Darden, J. Chem. Phys. 125, 184101, **2006**
Cisneros, Piquemal, Darden, J. Phys. Chem. B. 110, 13682, **2006**
Cisneros, Elking, Piquemal, Darden, J. Phys. Chem.A 111, 12049, **2007**
Gresh, Cisneros, Darden, Piquemal, J. Chem. Theo. Comp.3, 1960, **2007**

Next generation force field.

Auxiliary Coefficients → Integrales → $E_{coul} + E_{exch-rep}$

Electrostatic attraction
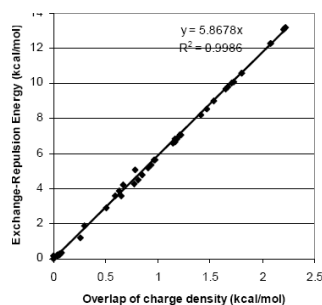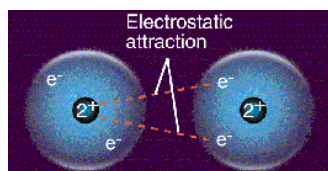
$$E_{coulomb} = \frac{Z_A Z_B}{r_{AB}} - \int \frac{Z_A \tilde{\rho}^B(r_B)}{r_{AB}} dr - \int \frac{Z_B \tilde{\rho}^A(r_A)}{r_{AB}} dr + \int \frac{\tilde{\rho}^A(r_A)\tilde{\rho}^B(r_B)}{r_{AB}} dr$$

$$S\rho = \int \rho_a(r)\rho_b(r)dr \approx \int \tilde{\rho}_a(r)\tilde{\rho}_b(r)dr$$

$E_{exch/rep} \approx KS\rho$ *(Wheatley and Price)*

Electrostatic Potentials & Field from frozen densities

Polarization + Charge transfer

$$-0.5 * \sum_j^{xyz} \Delta\mu(i)*(\gamma E_0(j))$$

$$E_{ct} = -2 \sum_\alpha \sum_{\beta*} \frac{(I_{\alpha\beta*})^2}{\Delta E_{\alpha\beta*}}$$

(Garmer et Stevens) *(Gresh, Claverie et Pullman)*

# Next generation force field.
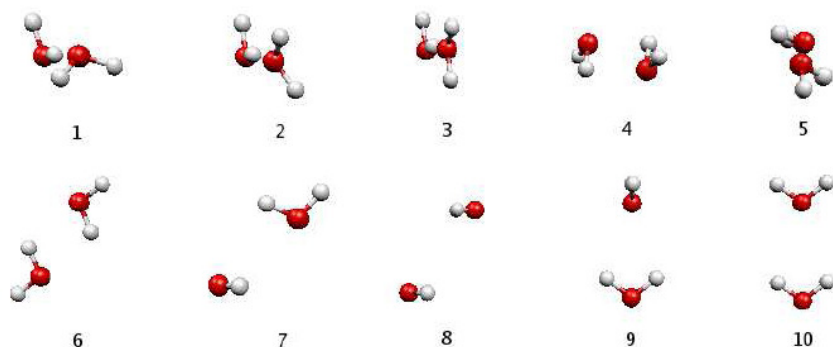
Chemical precision?

Average errors on total interaction energies:
< O.1 kcal/mol .
Errors < 0.1 kcal on each of the components.

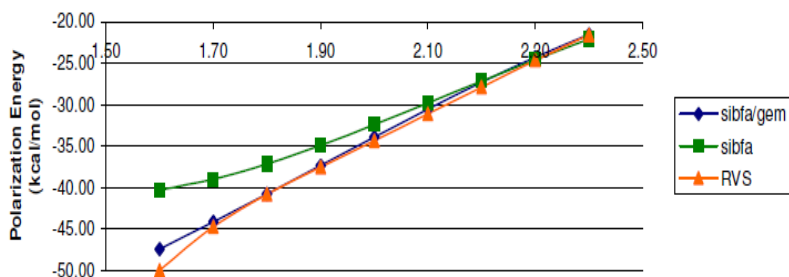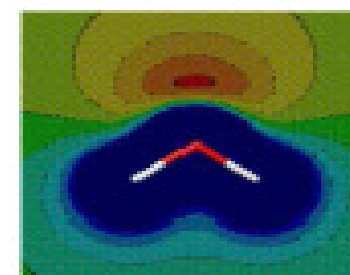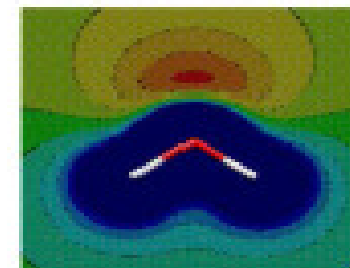| n	$E_{coulomb}$ GEM-0	$E_{coulomb}$ CSOV	$E_{coulomb}$ GEM-0 (BD)	$E_{exch-rep}$ GEM-0	$E_{exch-rep}$ CSOV
16	-186.842	-186.379 (-186.842)	-184.798	164.946	166.539 (166.549)
20	-309.380	-307.199 (-309.204)	-305.838	292.25	292.164 (292.190)
64	-449.519	-446.122 (-454.077)	-443.537	336.48	-
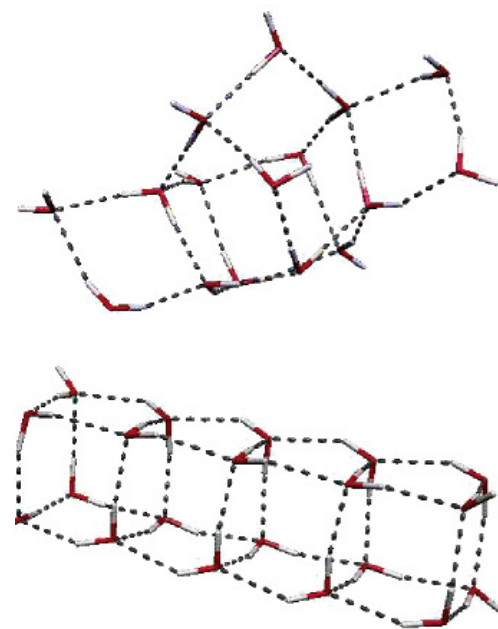
The Gaussian Electrostatic Model (GEM): QM/MM and MM'/MM
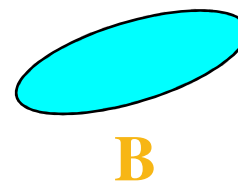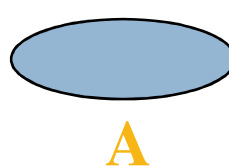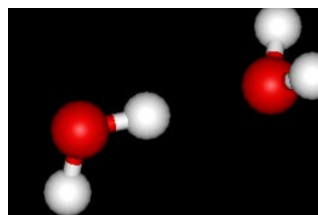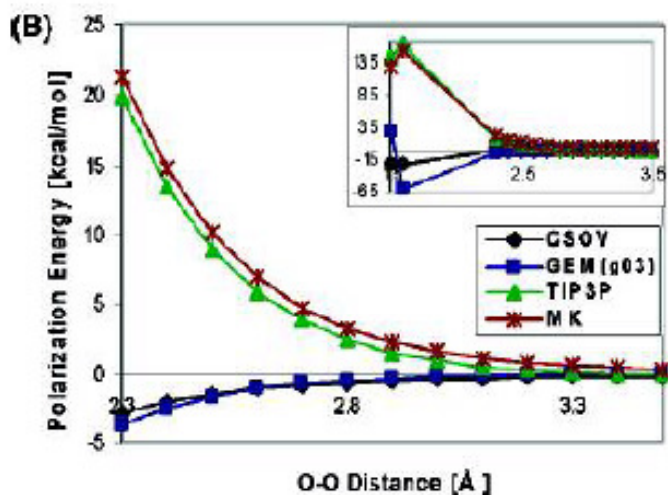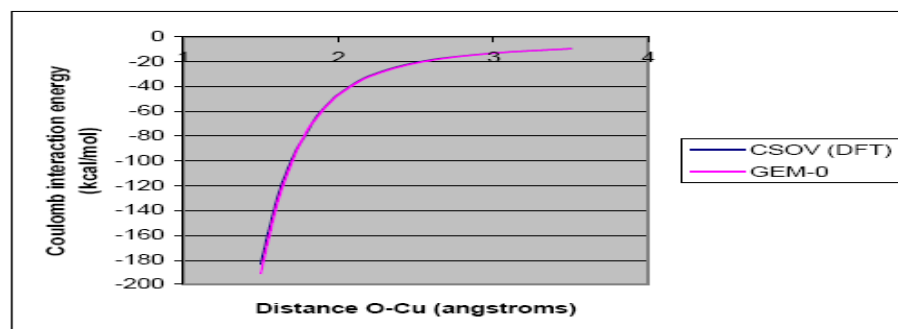

Molecule A (QM)   Molecule B (GEM)

$$H_A = H°_A + V_{AB}$$

SIBFA   GEM

Inclusion of scalar relativity via pseudopotentials: Hg(II) potential including quadrupolar polarisation & back-donation.

Cu(I)-H$_2$O Complex

Figure 2 : Intermolecular coulomb energy for the water-Cu(I) complex at various distances for GEM-0 and CSOV at the B3LYP/aug-cc-PVTZ level for the water and B3LYP/6-31G* for the cation. The water is immobile at the position of the molecule A of the dimer 1.
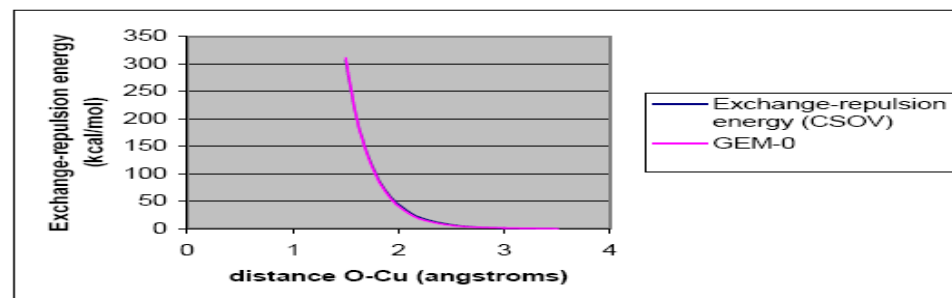
Figure 3 : Intermolecular exchange-repulsion energy for the water-Cu(I) complex at various distances for GEM-0 and CSOV at the B3LYP/aug-cc-PVTZ level for the water and B3LYP/6-31G* for the cation. The water is immobile at the position of the molecule A of the dimer 1. The K parameter is 2.8942 (R^2=0.9991).

Continuous Electrostatic Model

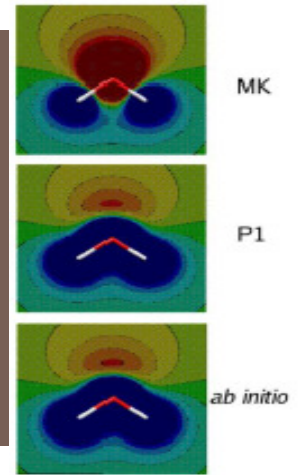$$\widetilde{\rho} = \sum_{k=1}^{N} x_k k(r) \approx \rho = \sum_{\mu\nu} P_{\mu\nu}\phi_\mu(r)\phi_\nu^*(r)$$

Efficient recursion for cartesians multipoles :
Cipriani et Silvi (1982) (L^4)

Hermites (gaussian derivative) : link to cartesian multipole.
Challacombe, Schwegler, Amlof (1995) (L^2)

MK

P1

ab initio

$$\Lambda_{tuv}(\mathbf{r}, \alpha, \mathbf{P}) = \left(\frac{\partial}{\partial P_x}\right)^t \left(\frac{\partial}{\partial P_y}\right)^u \left(\frac{\partial}{\partial P_z}\right)^v exp(-\alpha r_\mathbf{P}^2)$$

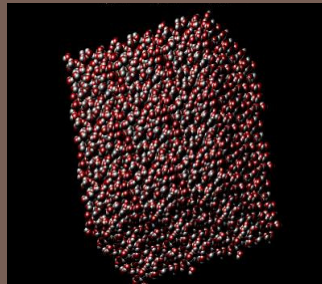Fast convergence of the multipole serie:
Quadrupole is enough!
+ efficient generalized McMurchie-Davidson recursion

How fast it is?

- It depends on the basis sets and can be improved by a dual density/ESP grid fitting neglecting the core.

4096 water molecules, single CPU 3.6 Ghz

A2 basis sets fitted on B3LYP 6-31G*

2.29 s

To be compared to 0.2 s for AMBER (TIP$_3$P)

It could be less using spherical harmonics/Slater-type expressions (JCTC, 2009, in press)

Rethinking Amoeba: metals and PBC

(Atomic Multipole Optimized Energetics for Biomolecular Applications)
Ren et Ponder, 2003

A « reasonable » first step towards precision (protein ready!)

Piquemal, Perera, Cisneros, Ren, Pedersen, Darden, J. Chem. Phys., **2006**, 125, 054511

AMOEBA: no universal Thole damping!!!

Atomic Multipoles (Stone)
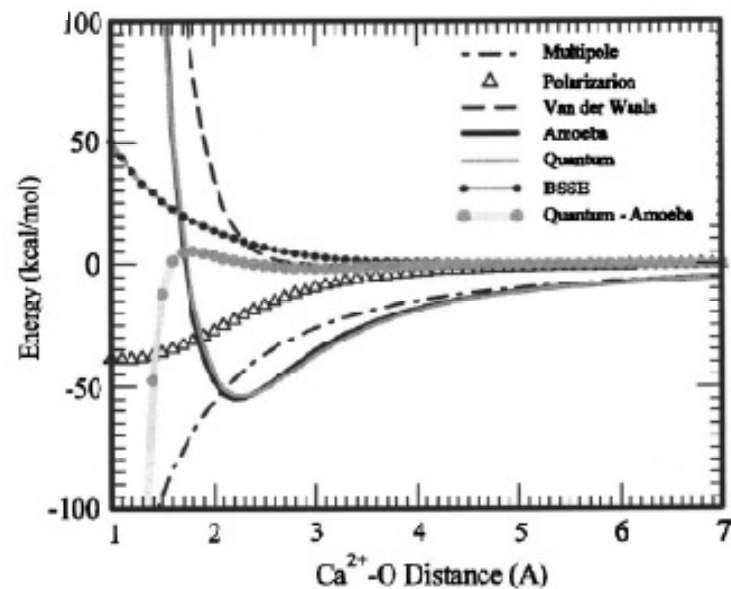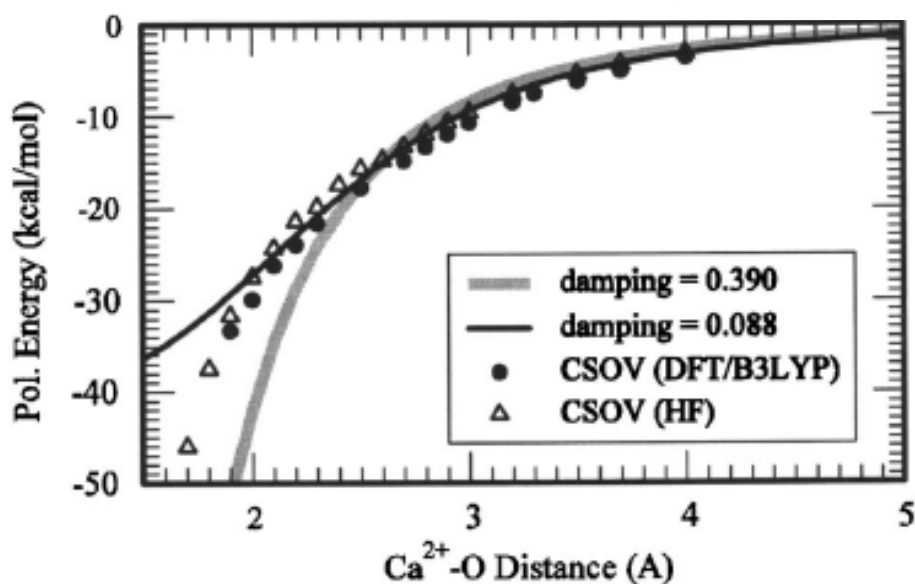Polarization: Applequist/Tholé
van der Waals: Halgren's function

$$E_{Halgren} (14\text{-}7) = E_{exc\text{-}rep} + E_{disp} + E_{TC}$$
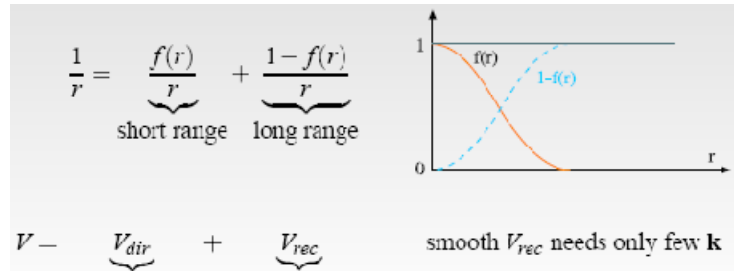$$= E_{Halgren} (direct) + E_{Halgren} (recip.)$$

$$E_{Halgren} = \Delta E_{tot}(\text{MP2BSSE corrected})$$
$$- E_{Coulomb}(\text{amoeba multipoles})$$
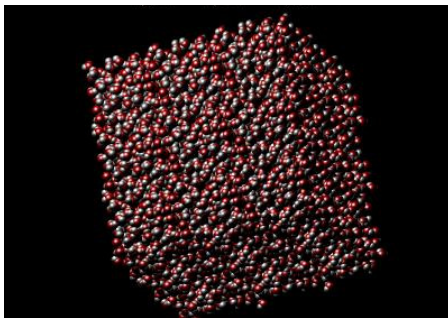$$- E_{polarization}(\text{amoeba}).$$

PBC for Amoeba

$$\frac{1}{r} = \underbrace{\frac{f(r)}{r}}_{\text{short range}} + \underbrace{\frac{1-f(r)}{r}}_{\text{long range}}$$

$$V - \underbrace{V_{dir}}_{} + \underbrace{V_{rec}}_{} \quad \text{smooth } V_{rec} \text{ needs only few } \mathbf{k}$$

Particle Mesh Ewald
$N^2 \rightarrow N\log(N)$

Amber:
van der Waals are in reciprocal sum too!!!
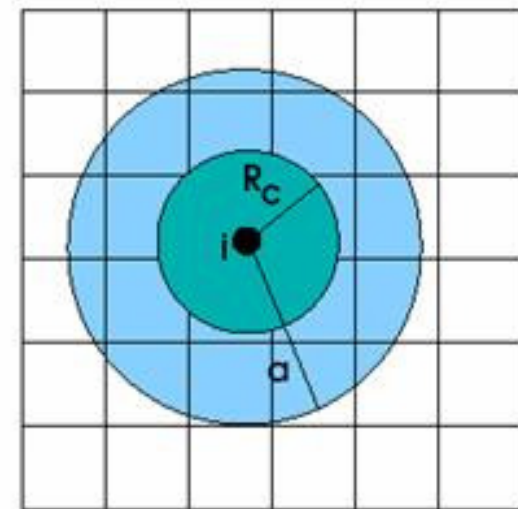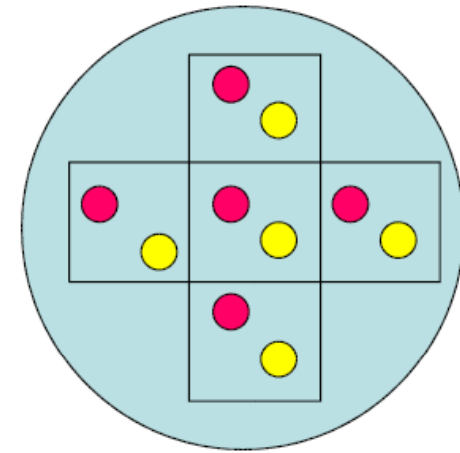
MD

-Intégration step:1fs
-Successive over relaxation (SOR)
-Direct sum: 6,7 Å cutoff (8 Å vdw)

CCl :
10-12 time Amber
but robust MD, Proteines ready

1 ns = 34 H (216 H_2O)
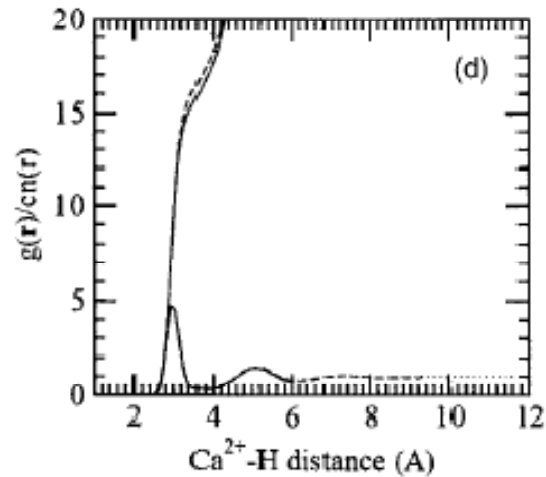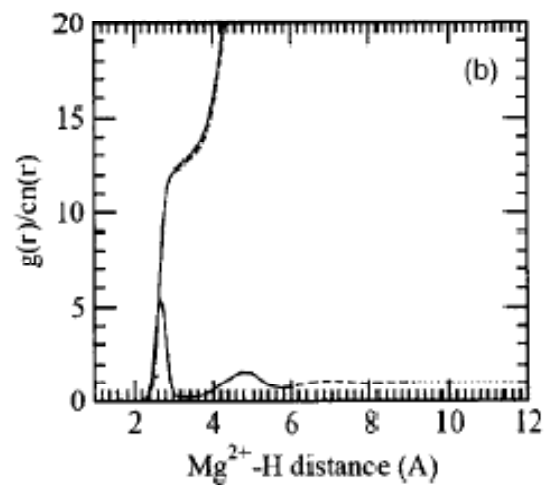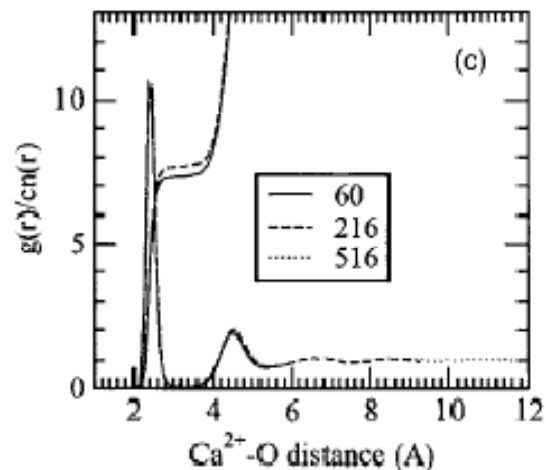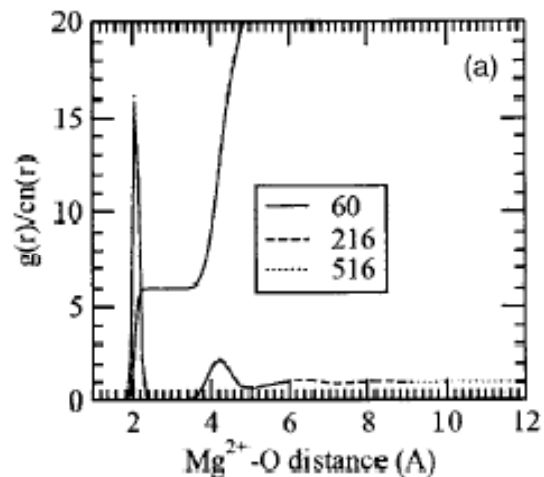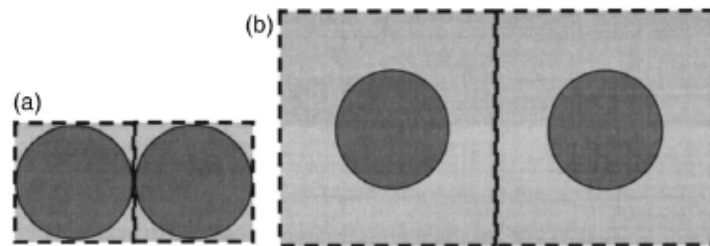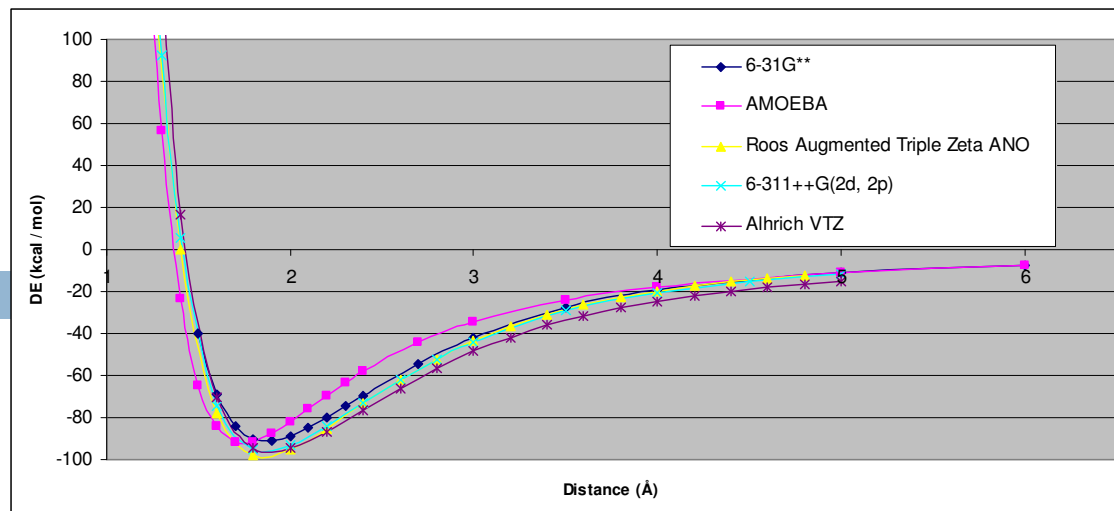   = 94 H (512 H_2O)

1.8 Ghz Opteron AMD

Piquemal, Perera, Cisneros, Ren, Pedersen, Darden, J. Chem. Phys., **2006**, 125, 054511

	$M=Ca^{2+}$			$M=Mg^{2+}$
Water coordination				
Experimental[a,b]	7.0–8.0			6.0
Car-Parrinello[c]	6.2–7, 7.2, 8–9			6.0
This work	7.7 (216 and 516 waters), 7.2 (60 waters)			6.0
First $M(II)$–O peak (Å)				
Experimental[d]	2.41–2.44; 2.437; 2.46			2.09
Car-Parrinello[e]	2.43–2.44			2.13
This work	2.42–2.46			2.08
First $M(II)$–H peak (Å)				
Experimental[a]	2.97–3.07			…
Car-Parrinello[f]	3.03–3.07			…
This work	3.01–3.05			2.63–2.73
Average first shell water tilt angle				
Experimental[g]	34.0–38.0; 39.7			…
Car-Parrinello[f]	40.1			…
This work	40.2–40.7			39.7–40.6
First shell water residence time (ps) for n water molecules	N	$t^*=0$ ps	$t^*=2$ ps	No exchange of water during the simulation time
	60	131	154	
	216	158	182	
	516	160	203	
Percentage coordination with n water molecules	$n=60$	$n=216$	$n=516$	
6	0.84	0	0.2	100.0
7	46.16	33.16	30.28	0.0
8	52.72	66.32	69.16	0.0
9	0.28	0.52	0.36	0.0

Chart legend:
- 6-31G**
- AMOEBA
- Roos Augmented Triple Zeta ANO
- 6-311++G(2d, 2p)
- Alhrich VTZ

Y-axis: DE (kcal / mol)
X-axis: Distance (Å)

Zn (II):

Free energy of solvation

Zn^{2+}	-457.01	-467.26 (Marcus)
Mg^{2+}	-431.1 (2.9)	-435.4 (Schmid)
Ca^{2+}	-354.9 (1.7)	-357.2 (Schmid)

Piquemal, Wu, Reinhardt, Chaudret, Ren, 2009, to appear, JPCB.

Incoming developments: Charge transfer/IR spectroscopy.

(Chaudret, Gresh, Darden, Piquemal)

Design of next generation polarizable force fields from ab initio computations: beyond point charges.

Cisneros, Darden, Gresh, Reinhardt, Parisel, Pilmé and Piquemal

in Multi-scale Quantum Models for Biocatalysis: Modern Techniques and Applications, for the Book Series: Challenges and Advances in Computational Chemistry and Physics , ed. D. M. York and T.-S. Lee, **2009**, 137-172, Springer Verlag

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Thomas Darden (Open Eyes Inc.)

Pengyu Ren (University of Texas, Austin)

Dennis Salahub (Calgary)

Michel Mons, Jean-Pierre Dognon (French Atomic Commission, CEA)