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

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Université Pierre et Marie Curie
Potential energy surfaces (PES):

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

From QM computations to condensed phase molecular dynamics

Force fields advantages: fast evaluation of PES
Possible treatment of large molecules (million atoms) directly or through QM/MM
- structure
- dynamique
- interaction (docking)
- IR spectrum

\[ V_T = \sum_{1,2 \text{pairs}} 0.5 K_b (b - b_0)^2 \]
\[ + \sum_{\text{bond angles}} 0.5 K_\theta (\theta - \theta_0)^2 \]
\[ + \sum_{\text{dihedral angles}} K_\phi [ 1 + \cos(n\phi - \delta) ] \]
\[ + \sum_{i,j} 4\epsilon_{ij} \left[ \left( \frac{\sigma_{ij}}{r} \right)^{12} - \left( \frac{\sigma_{ij}}{r} \right)^6 \right] \]
\[ + q_i q_j / \varepsilon r \]

The link with QM is broken...
Next generation “polarizable” force fields are needed.
Philosophy

From QM computations to condensed phase molecular dynamics

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 » approach for quantitative results (general MM equations)
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. $0<\text{ELF}<1$.

- Measure of Pauli exclusion principle associated to a local excess of kinetic energy.
- When ELF $\rightarrow 1$: high probability of opposite-spin pairs
- Maximal probability site are called attractors

Theory of dynamical systems:
- bassins and separatrix


QM interpretative techniques

ELF Topological Analysis

3D partition of the molecular space (3D grid) into chemically intuitive bassins:
Access to non atomic bassins: lone pairs, \( \pi \) 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 on atomic and non-atomic centers. Introduction of the $M_1$ (dipole) and $M_2$ (quadrupole) quantities.

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

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

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

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

\[
M_{2,xx}(\Omega) = -\frac{1}{2} \int_{\Omega} (3(z - Z_c)^2 - r^2) \rho(\mathbf{r}) d\tau
\]

\[
M_{2,yy}(\Omega) = -\frac{1}{2} \int_{\Omega} (3(y - Y_c)^2 - (y - Y_c)^2) \rho(\mathbf{r}) d\tau
\]

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

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

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

\[
|M(\Omega)| = \sqrt{\sum_{i} M_i(\Omega)^2}
\]

QM interpretative techniques

Applications of DEMEP (1)

Intermolecular Interactions

Intramolecular Interactions.

<table>
<thead>
<tr>
<th>Acide</th>
<th>Aminé</th>
<th>V(C₁, O₁)</th>
<th>V(C₁, O₂)</th>
<th>V(C₂, N)</th>
<th>V(N)</th>
<th>V(O²)</th>
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<tr>
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<td>0.052</td>
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<tr>
<td>Tyrosinea</td>
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<td>1.210</td>
<td>0.059</td>
<td>0.268</td>
<td>0.177</td>
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</table>
QM interpretative techniques

Applications of DEMEP (2)
QM interpretative techniques

Energy Decomposition Analysis (EDA)

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

\[ E_{\text{induction}} \]

\[ \Delta E: \text{Interaction Energy between Fragments.} \]
EDA (1)

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

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

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

- Reference computation for first order contributions and dispersion (*).
- Bad convergence of induction (metal etc...). Requires 3rd order corrections (tests on water dimer ***).


<table>
<thead>
<tr>
<th>n</th>
<th>SCFlike(2)</th>
<th>SCFlike,r(2)</th>
<th>SCFlike(3)</th>
<th>SCFlike,r(3)</th>
<th>ΔE(HF)</th>
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<tr>
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<tr>
<td>4</td>
<td>2.11</td>
<td>2.24</td>
<td>2.84</td>
<td>2.97</td>
<td>2.62</td>
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<tr>
<td>5</td>
<td>2.02</td>
<td>2.14</td>
<td>2.62</td>
<td>2.73</td>
<td>2.44</td>
</tr>
<tr>
<td>6</td>
<td>2.06</td>
<td>2.16</td>
<td>2.60</td>
<td>2.71</td>
<td>2.44</td>
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<td>7</td>
<td>1.80</td>
<td>1.85</td>
<td>2.23</td>
<td>2.29</td>
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<tr>
<td>8</td>
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<td>0.68</td>
<td>1.79</td>
<td>1.81</td>
<td>0.71</td>
</tr>
<tr>
<td>9</td>
<td>1.72</td>
<td>1.78</td>
<td>2.25</td>
<td>2.31</td>
<td>2.00</td>
</tr>
<tr>
<td>10</td>
<td>1.39</td>
<td>1.43</td>
<td>1.69</td>
<td>1.73</td>
<td>1.53</td>
</tr>
</tbody>
</table>

# 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)

<table>
<thead>
<tr>
<th>Method/system</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tbody>
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<td>-3.90</td>
<td>-3.75</td>
<td>-3.75</td>
<td>-3.49</td>
<td>-2.82</td>
<td>-1.05</td>
<td>-2.59</td>
<td>-1.84</td>
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<td>F12-MP2</td>
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<td>-4.35</td>
<td>-4.16</td>
<td>-3.94</td>
<td>-3.92</td>
<td>-3.10</td>
<td>-1.16</td>
<td>-2.89</td>
<td>-2.06</td>
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<tr>
<td>F12-CCSD(T)</td>
<td>-4.84</td>
<td>-4.33</td>
<td>-4.30</td>
<td>-4.13</td>
<td>-3.89</td>
<td>-3.86</td>
<td>-3.19</td>
<td>-1.28</td>
<td>-2.97</td>
<td>-2.15</td>
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<td>-4.85</td>
<td>-4.39</td>
<td>-4.37</td>
<td>-4.11</td>
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<td>-3.90</td>
<td>-3.17</td>
<td>-1.28</td>
<td>-3.02</td>
<td>-2.22</td>
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<tr>
<td>SAPT (Paris)</td>
<td>-5.23</td>
<td>-4.72</td>
<td>-4.70</td>
<td>-4.46</td>
<td>-4.21</td>
<td>-4.17</td>
<td>-3.41</td>
<td>-1.37</td>
<td>-3.34</td>
<td>-2.42</td>
</tr>
</tbody>
</table>
QM interpretative techniques

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 between 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, Bagus, 2009.

\[ \Delta E = E_c + E_{\text{exch-rep}} + E_{\text{pol}} + E_{\text{CT}} \]
For constructing intrinsically localized DFT molecular orbitals, we take up an old idea,\textsuperscript{15} further developed and published by Daudey\textsuperscript{16} and still cited recently,\textsuperscript{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.

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:

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

\(\text{Total Interaction}\)

<table>
<thead>
<tr>
<th>functional</th>
<th>$E_{ex}$</th>
<th>$E_{SHEP}$</th>
<th>$E_{FC}$</th>
<th>$E_{OLBSSPE}$</th>
<th>total interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF (5D)</td>
<td>-8.26</td>
<td>6.08</td>
<td>-1.30</td>
<td>-2.16</td>
<td>-3.55</td>
</tr>
<tr>
<td>HF (6D)</td>
<td>-8.27</td>
<td>6.91</td>
<td>-1.36 (-1.37)</td>
<td>-2.18 (-2.19)</td>
<td>-3.55</td>
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<tr>
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<td>7.42</td>
<td>-0.58</td>
<td>-3.28</td>
<td>-3.86</td>
</tr>
<tr>
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<td>7.48</td>
<td>-0.55 (-0.61)</td>
<td>-3.30 (-3.26)</td>
<td>-3.86</td>
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<tr>
<td>PW91</td>
<td>-7.91</td>
<td>6.22</td>
<td>-1.69</td>
<td>-3.30</td>
<td>-4.99</td>
</tr>
<tr>
<td>PW91 (6D)</td>
<td>-7.93</td>
<td>6.97</td>
<td>-1.66 (-1.50)</td>
<td>-3.33 (-3.48)</td>
<td>-4.99</td>
</tr>
<tr>
<td>B3LYP</td>
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<td>6.67</td>
<td>-1.38</td>
<td>-2.97</td>
<td>-4.35</td>
</tr>
<tr>
<td>B3LYP (6D)</td>
<td>-8.07</td>
<td>6.71</td>
<td>-1.36 (-1.45)</td>
<td>-2.99 (-2.95)</td>
<td>-4.35 (4.40)</td>
</tr>
</tbody>
</table>

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

- 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.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

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

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)

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

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

- 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

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

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.

New generation force fields.

### Sum of Interactions Between Fragments Ab initio computed (SIBFA)

**SIBFA vs. CPE (Chemical Potential Equalization)**

<table>
<thead>
<tr>
<th></th>
<th>$E_c$</th>
<th>$E_{\text{exch}}$</th>
<th>$E_1$</th>
<th>$E_{\text{pol}}$</th>
<th>$E_{\text{cl}}$</th>
<th>$E_2$</th>
<th>$\Delta E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBC SIBFA</td>
<td>−81.6</td>
<td>54.0</td>
<td>−27.6</td>
<td>−18.2 (−14.0)</td>
<td>−9.5</td>
<td>−27.7</td>
<td>−55.4</td>
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<tr>
<td>HBC RVS</td>
<td>−81.2</td>
<td>54.3</td>
<td>−26.8</td>
<td>−17.3 (−14.5)</td>
<td>−9.8</td>
<td>−24.3</td>
<td>−53.1</td>
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<tr>
<td>t HBC SIBFA</td>
<td>−58.9</td>
<td>29.0</td>
<td>−29.9</td>
<td>−9.0 (−7.2)</td>
<td>−9.6</td>
<td>−12.6</td>
<td>−41.1</td>
</tr>
<tr>
<td>t-HBC RVS</td>
<td>−53.5</td>
<td>27.3</td>
<td>−26.3</td>
<td>−9.8 (−8.2)</td>
<td>−3.5</td>
<td>−39.2</td>
<td>−41.4</td>
</tr>
<tr>
<td>l-HBC SIBFA</td>
<td>−60.9</td>
<td>54.0</td>
<td>−6.9</td>
<td>−3.9 (−3.6)</td>
<td>−7.5</td>
<td>−11.4</td>
<td>−18.3</td>
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<tr>
<td>l-HBC RVS</td>
<td>−60.5</td>
<td>55.1</td>
<td>−5.4</td>
<td>−5.5 (−4.7)</td>
<td>−7.7</td>
<td>−17.8</td>
<td>−17.8</td>
</tr>
</tbody>
</table>

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

New generation force fields.

Experimental collaboration: Ettore Appella
NIH Immunology group (Bethesda, MA, USA)
Phase II molecule (Thioester)

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

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

New generation force fields.

Sum of Interactions Between Fragments Ab initio computed (SIBFA)

Focal Adhesion Kinase (FAK)

EXPLICIT SOLVATION REQUIRED!!!

<table>
<thead>
<tr>
<th></th>
<th>Complex a</th>
<th>Complex b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ab initio</td>
<td>SIBFA</td>
</tr>
<tr>
<td>$E_{\text{coul}} / E_{\text{MTP}}$</td>
<td>-661,6</td>
<td>-657,9</td>
</tr>
<tr>
<td>$E_{\text{exch}} / E_{\text{rep}}$</td>
<td>177,4</td>
<td>168,9</td>
</tr>
<tr>
<td>$E_1$</td>
<td>-484,2</td>
<td>-489,0</td>
</tr>
<tr>
<td>$E_{\text{pol}}(\text{HF}) / E_{\text{pol}}^*$</td>
<td>-85,5</td>
<td>-94,4</td>
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<td>$E_{\text{pol}}(\text{RVS}) / E_{\text{pol}}^*$</td>
<td>-113,2</td>
<td>-121,6</td>
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<tr>
<td>$E_{\text{cl}}(\text{RVS})$</td>
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<td>-48,6</td>
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<td>$E_{\text{cl}} / E_{\text{cl}}$</td>
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<td>-41,3</td>
</tr>
<tr>
<td>$E_2$</td>
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<tr>
<td>$\Delta E$</td>
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<td>-624,7</td>
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<tr>
<td>$\delta E(\text{MP2}) / E_{\text{disp}}$</td>
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<td>-65,9</td>
</tr>
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<td>$\Delta E_{\text{tot}}$</td>
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<td>-690,6</td>
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DOI: 10.1007/s12539-008-0027-0

<table>
<thead>
<tr>
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<th>$E_1 / \Delta E$</th>
<th>$E_2 / \Delta E$</th>
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<tr>
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<td>66.8%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Imh / Zn(II)</td>
<td>44.1%</td>
<td>55.9%</td>
</tr>
<tr>
<td>Cy$^{-}$ 174/ Zn(II)</td>
<td>67.1%</td>
<td>32.9%</td>
</tr>
<tr>
<td>EtOH / Zn(II)</td>
<td>39.7%</td>
<td>60.3%</td>
</tr>
<tr>
<td>Compound</td>
<td>E₁ / ΔE</td>
<td>E₂ / ΔE</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Cy⁻ 46 / Zn(II)</td>
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<td>Imh / Zn(II)</td>
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<td>55.9%</td>
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<tr>
<td>Cy⁻ 174 / Zn(II)</td>
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<td>32.9%</td>
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<tr>
<td>EtOH / Zn(II)</td>
<td>39.7%</td>
<td>60.3%</td>
</tr>
</tbody>
</table>
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. . .”

\[
\tilde{\rho} = \sum_{k=1}^{N} x_{kk}(r) \approx \rho = \sum_{\mu \nu} P_{\mu \nu} \phi_{\mu}(r) \phi_{\nu}^*(r)
\]

\[
E_{\text{coulomb}} = \frac{Z_A Z_B}{r_{AB}} - \int \frac{Z_A \tilde{\rho}^B(r_B)}{r'_{AB}} dr - \int \frac{Z_B \tilde{\rho}^A(r_A)}{r'_{AB}} dr + \int \frac{\tilde{\rho}^A(r_A) \tilde{\rho}^B(r_B)}{r'_{AB}} dr
\]

Next generation force field.

GEM : what if MM=QM??

\[ \Delta E = E_c + E_{\text{éch-rép}} + E_{\text{pol}} + E_{\text{TC}} + E_{\text{disp}} \]

Frozen density of a rigid fragment

Hermite gaussians

(recursions using PME – fourier space nlog(n))

Next generation force field.

GEM: what if MM=QM??

Auxiliary Coefficients \rightarrow \text{Integrals} \rightarrow E_{\text{coul}} + E_{\text{exch-rep}}

$$E_{\text{coulomb}} = \sum_{A} Z_{A} Z_{B} \frac{\rho_{a}(r_{AB})}{r_{AB}} + \sum_{A} Z_{B} \frac{\rho_{b}(r_{AB})}{r_{AB}} + \sum_{A} Z_{A} \frac{\rho_{a}(r_{AB})}{r_{AB}}$$

$$S_{\rho} = \int \rho_{a}(r) \rho_{b}(r) dr \approx \int \bar{\rho}_{a}(r) \bar{\rho}_{b}(r) dr$$

$$E_{\text{exch/rep}} \approx K \rho \quad \text{(Wheatley and Price)}$$

Electrostatic Potentials & Field from frozen densities

Polarization + Charge transfer

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

(Garmer et Stevens) + (Gresh, Claverie et Pullman)
Next generation force field.

GEM: what if MM=QM?? Water clusters: aug-cc-pVTZ

Chemical precision?

Average errors on total interaction energies: < 0.1 kcal/mol.
Errors < 0.1 kcal on each of the components.
The Gaussian Electrostatic Model (GEM): QM/MM and MM'/MM

$H_A = H_A^0 + V_{AB}$

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

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

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

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

\[ \Lambda_{\mu \nu}(r, \alpha, P) = \left( \frac{\partial}{\partial P_x} \right)^i \left( \frac{\partial}{\partial P_y} \right)^u \left( \frac{\partial}{\partial P_z} \right)^v \exp(-\alpha r^2_p) \]

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 (TIP3P)

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

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

\[ E_{\text{Halgren}} = \Delta E_{\text{ext}}(\text{MP2BSSE corrected}) - E_{\text{Coulomb}}(\text{amoeba multipoles}) - E_{\text{polarization}}(\text{amoeba}). \]
PBC for Amoeba

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

Amber:
van der Waals are in reciprocal sum too!!!
- Integration step: 1 fs
- Successive over relaxation (SOR)
- Direct sum: 6,7 Å cutoff (8 Å vdw)

$\text{CCI} :$
10-12 time Amber
but robust MD, Proteines ready

$1 \text{ ns} = 34 \text{ H} (216 \text{ H}_2\text{O})$
$= 94 \text{ H} (512 \text{ H}_2\text{O})$

1.8 Ghz Opteron AMD

Piquemal, Perera, Cisneros, Ren, Pedersen, Darden, J. Chem. Phys., 2006, 125, 054511
<table>
<thead>
<tr>
<th></th>
<th>$M = \text{Ca}^{2+}$</th>
<th>$M = \text{Mg}^{2+}$</th>
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<tr>
<td><strong>Water coordination</strong></td>
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<tr>
<td>Experimental$^{ab}$</td>
<td>7.0–8.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Car-Parrinello$^c$</td>
<td>6.2–7, 7.2, 8–9</td>
<td>6.0</td>
</tr>
<tr>
<td>This work</td>
<td>7.7 (216 and 516 waters), 7.2 (60 waters)</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>First $\text{M(II)}-\text{O}$ peak (Å)</strong></td>
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<tr>
<td>Experimental$^d$</td>
<td>2.41–2.44; 2.437; 2.46</td>
<td>2.09</td>
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<tr>
<td>Car-Parrinello$^e$</td>
<td>2.43–2.44</td>
<td>2.13</td>
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<tr>
<td>This work</td>
<td>2.42–2.46</td>
<td>2.08</td>
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<td><strong>First $\text{M(II)}-\text{H}$ peak (Å)</strong></td>
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<tr>
<td>Experimental$^f$</td>
<td>2.97–3.07</td>
<td>...</td>
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<tr>
<td>Car-Parrinello$^f$</td>
<td>3.03–3.07</td>
<td>...</td>
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<tr>
<td>This work</td>
<td>3.01–3.05</td>
<td>2.63–2.73</td>
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<tr>
<td><strong>Average first shell water tilt angle</strong></td>
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<tr>
<td>Experimental$^g$</td>
<td>34.0–38.0; 39.7</td>
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<tr>
<td>Car-Parrinello$^f$</td>
<td>40.1</td>
<td>...</td>
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<td>40.2–40.7</td>
<td>39.7–40.6</td>
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<table>
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<tr>
<th>First shell water residence time (ps) for $n$ water molecules</th>
<th>$N$</th>
<th>$t^*=0$ ps</th>
<th>$t^*=2$ ps</th>
<th>No exchange of water during the simulation time</th>
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</thead>
<tbody>
<tr>
<td>60 water molecules</td>
<td>60</td>
<td>131</td>
<td>154</td>
<td></td>
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<tr>
<td>216 water molecules</td>
<td>216</td>
<td>158</td>
<td>182</td>
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<tr>
<td>516 water molecules</td>
<td>516</td>
<td>160</td>
<td>203</td>
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<table>
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<tr>
<th>Percentage coordination with $n$ water molecules</th>
<th>$n=60$</th>
<th>$n=216$</th>
<th>$n=516$</th>
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<tr>
<td>6</td>
<td>0.84</td>
<td>0</td>
<td>0.2</td>
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<td>7</td>
<td>46.16</td>
<td>33.16</td>
<td>30.28</td>
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<td>8</td>
<td>52.72</td>
<td>66.32</td>
<td>69.16</td>
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<tr>
<td>9</td>
<td>0.28</td>
<td>0.52</td>
<td>0.36</td>
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Zn (II):

Free energy of solvation

<table>
<thead>
<tr>
<th>Ion</th>
<th>DE (kcal/mol)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Zn$^{2+}$</td>
<td>-457.01</td>
<td>-467.26 (Marcus)</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>-431.1 (2.9)</td>
<td>-435.4 (Schmid)</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>-354.9 (1.7)</td>
<td>-357.2 (Schmid)</td>
</tr>
</tbody>
</table>

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.

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