Applications of quantum mechanical continuum solvation models to the study of molecular properties and spectroscopic features of molecular solutes

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The QM description of solvent effects on molecular properties and spectroscopies

Physical issue:
the solvation model has to properly include the main physical interactions giving rise to solvent-induced change on the property/spectroscopic signal

Quantum-Mechanical issue:
the QM model has to properly describe the effects of solute-solvent mutual polarization at both electronic and structural level
The Quantum Mechanical issue

We need a proper definition of molecular properties

We have to start from a quantity which is the basic element of any QM description:

the Energy

The molecular property can be defined in terms of the change of the energy of the system with respect to a perturbation (an external electric, or magnetic field, a geometrical deformation …): this definition is still valid for a solvated system
The energy is expanded in a Taylor series in the perturbation strength $\lambda$

$$E(\lambda) = E(0) + \frac{\partial E}{\partial \lambda} \lambda + \frac{1}{2} \frac{\partial^2 E}{\partial \lambda^2} \lambda^2 + \frac{1}{6} \frac{\partial^3 E}{\partial \lambda^3} \lambda^3 + ...$$

The nth-order property is the nth-order derivative of the energy

For example, by considering four types of perturbations: external electric (F) or magnetic field (B), nuclear magnetic moment (nuclear spin, I) and a change in the nuclear geometry (R).

<table>
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<th>$n_F$</th>
<th>$n_B$</th>
<th>$n_I$</th>
<th>$n_R$</th>
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The Quantum Mechanical issue

IR spectra

NMR spectra
An example: the Hartree-Fock description

MO-LCAO
Finite basis approximation:
\[
\begin{align*}
\phi &= \chi C \\
C &= (c_1 \mid c_2 \mid \ldots \mid c_K \mid \ldots)
\end{align*}
\]

Density matrix:
\[
D = CC^\dagger = \sum_{K} c_K c_K^\dagger
\]

Orthonormality
\[
C^\dagger S C = 1 \quad S_{\alpha\beta} = \langle \chi_\alpha \mid \chi_\beta \rangle
\]

Fock matrix
\[
F = h + J(D) - K(D) = h + G(D)
\]
\[
h_{\alpha\beta} = \langle \chi_\alpha \mid h \mid \chi_\beta \rangle \quad G_{\alpha\beta} = \sum_{\sigma\delta} D_{\sigma\delta} \left( \langle \chi_\alpha \chi_\sigma \mid g \mid \chi_\beta \chi_\delta \rangle - \langle \chi_\alpha \chi_\sigma \mid g \mid \chi_\delta \chi_\beta \rangle \right)
\]

\[
FC = SC\varepsilon
\]

Energy
\[
E = tr\left( Dh \right) + \frac{1}{2} tr\left( DG(D) \right) + V_{NN}
\]
HF: First derivative

\[
\frac{\partial E}{\partial \lambda} = tr\left(Dh^{(\lambda)}\right) + \frac{1}{2} tr\left(DG^{(\lambda)}(D)\right) - trS^{(\lambda)}DFD + V_{NN}^{(\lambda)}
\]

Easy to calculate: only derivatives of integrals on the atomic basis

Example:

First-order algorithms for geometry optimizations

\[
\left.\frac{\partial E(x)}{\partial x}\right|_{\text{stationary}} = 0
\]
First derivative: geometry optimization in solution

\[ \frac{\partial E(x)}{\partial x} \bigg|_{\text{stationary}} = 0 \]

\[ \frac{\partial E}{\partial x} = \text{tr} \left( \mathbf{Dh}^{(x)} \right) + \frac{1}{2} \text{tr} \left( \mathbf{DG}^{(x)}(\mathbf{D}) \right) + \frac{1}{2} \text{tr} \left( \mathbf{DV}^{R(x)}(\mathbf{D}) \right) - \text{tr} \mathbf{S}^{(x)} \mathbf{D} \tilde{\mathbf{F}} \mathbf{D} + \mathbf{V}^{(x)}_{NN} + \frac{1}{2} U^{R(x)} \]

Effective Fock:

\[ \tilde{\mathbf{F}} = \mathbf{F}^{\text{vac}} + \mathbf{V}^{R} = \mathbf{F}^{\text{vac}} + \sum_{i} q_{i} \mathbf{V}_{i} \]

Differentiation of the reaction terms = derivatives of ASC charges

Derivatives of the geometrical parameters which define the cavity surface
HF: Second derivative

\[
\frac{\partial^2 E}{\partial \eta \partial \lambda} = \text{tr} \left( D h^{(\lambda, \eta)} \right) + \frac{1}{2} \text{tr} \left( D G^{(\lambda, \eta)} (D) \right) + V^{(\lambda, \eta)}_{NN} - \text{tr} S^{(\lambda, \eta)} W + \text{tr} \left( D^{(\eta)} h^{(\lambda)} \right) + \text{tr} \left( D^{(\eta)} G^{(\lambda)} (D) \right) - \text{tr} S^{(\lambda)} W^{(\eta)}
\]

\[
W^{(\eta)} = D^{(\eta)} F D + DF^{[\eta]} D + DG(D^{(\eta)}) D + DFD^{(\eta)}
\]

More difficult: we need to calculate derivatives of the density matrix

\[\begin{align*}
\text{Example:} \\
\text{IR Vibrational frequencies and intensities and NMR parameters}
\end{align*}\]

How to get \( D^{(\eta)} \) ?
Coupled perturbed HF

Hartree Fock stationary conditions

\[ \text{FD} - \text{DF} = 0 \]

\[ \text{DD} = (\text{CC}^\dagger)(\text{CC}^\dagger) = \text{C1C}^\dagger = \text{D} \]

Switching on the perturbation and expanding with respect to it:

First-order change in the Fock matrix

\[ F^{(1)} = h^{(1)} + G^{(1)}(D^{(0)}) + G^{(0)}(D^{(1)}) \]

First-order \textit{Coupled Perturbed Hartree-Fock} (CPHF):

\[ F^{(0)}D^{(1)} - D^{(1)}F^{(0)} + F^{(1)}D^{(0)} - D^{(0)}F^{(1)} = 0 \]

\[ D^{(0)}D^{(1)} + D^{(1)}D^{(0)} = D^{(1)} \]
And in solution?

Coupled perturbed equations in the presence of a polarizable dielectric

Effective Fock: \[ \tilde{F} = F^{vac} + V^R \]

ASC reaction charges \( q \): \[ V^R = \sum_k q_k (D) V_k \]

\[ \tilde{F}^{(1)} = h^{(1)} + G^{(1)} (D^{(0)}) + G^{(0)} (D^{(1)}) + V^{R(1)} (D^{(0)}) + V^{R(0)} (D^{(1)}) \]

\[ \tilde{F}^{(0)} D^{(1)} - D^{(1)} \tilde{F}^{(0)} + \tilde{F}^{(1)} D^{(0)} - D^{(0)} \tilde{F}^{(1)} = 0 \]

As a result the final density matrix (and the corresponding response properties) will be changed by the presence of the polarizable environment
The physical issue:
a tentative schematization of solvent effects

Indirect effects:
solvent induced changes in the solute geometry and/or in the relative energies of different conformers

Direct effects:
solvent induced changes in the solute electronic charge
Direct vs Indirect effects: an example

N-Methyl Acetylproline Amide (NAP) in water: a simple model for peptides

The conformation of NAP in polar, protic solvents, such as water or alcohols, is still controversial.

In particular, it has been recently demonstrated that the results obtained by using Amber MD simulations strongly depend on the force field exploited (ff99 vs. ff03).

Conformational analysis: three stable conformers

*Boltzmann Populations (%)*

<table>
<thead>
<tr>
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<th>In gas-phase B3LYP/6-311++G**</th>
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</thead>
<tbody>
<tr>
<td>$C_7$</td>
<td>99</td>
</tr>
<tr>
<td>$3_{10}$ Helix I</td>
<td>1</td>
</tr>
<tr>
<td>$P_{II}$</td>
<td>-</td>
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</table>

The $C_7$ conformer dominates in gas-phase due to the presence of a stabilizing intra-molecular H-bond.

Conformational analysis: three stable conformers

In water the other two conformers become important: they present a better interaction with the solvent (polar groups are more exposed to the solvent)

<table>
<thead>
<tr>
<th></th>
<th>In gas-phase</th>
<th>In water</th>
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<tbody>
<tr>
<td></td>
<td>B3LYP/6-311++G**</td>
<td>PCM-B3LYP/6-311++G**</td>
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<tr>
<td>C7</td>
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<td>28</td>
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<tr>
<td>P_{II}</td>
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<td>68</td>
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Infrared and vibrational circular dichroism spectra of single conformers: direct effects

- **In gas-phase**
  - IR
    - Amide II
    - Amide I
  - VCD

- **In water**
  - PI
  - PII

Both position and intensity of peaks change passing from gas-phase to water.

B3LYP/6-311++G**
Averaged Infrared and vibrational circular dichroism spectra: direct vs indirect effects

The physical issue: a tentative schematization of solvent effects

Indirect effects:

solvent induced changes in the solute geometry and/or in the relative energies of different conformers

Direct effects:

solvent induced changes in the solute electronic charge
Bulk versus specific solvation

Bulk (averaged) effects

Local (specific) effects

Macro- and micro-solvation
To understand solvent effects at the molecular scale, some questions need to be addressed:

✔ How does solvation at the solute surface differ from that of bulk?
✔ Are there local rigid structures of solvent at the solute surface?
✔ What are the time scales for solvent dynamics at the solute surface?

No significant differences between surface and bulk: **continuum models**

Rigid and/or persistent solvent structures at the surface: ?
Solvent structures at the surface

**Supermolecule** = solute surrounded by some explicit solvent molecules

It properly accounts for short-range effects.

The different components of the supermolecule can be described at the same level (QM) or using an hybrid approach: a better level for the solute and a more approximated level for the solvent molecules (semiempirical or MM)
The Supermolecule

How many explicit solvent molecules are needed?

An example: N-methyl acetamide in water

From the chemical analysis of the system:
3 possible H-bonds: 2 on the O(C) and 1 on the H(N)

From MD simulations:

O-Hw RDF: On average, 2 hydrogen atoms of 2 water molecules hydrate the carbonyl group by means of hydrogen bonding.

(N)H-OW: The integration number up to the first minimum gives 1 water molecule H-bonded to the H(N).
The Supermolecule

Which configuration?

◊ **From QM geometry optimizations:** the most stable configuration

  Proper description for strongly interacting solute-solvent systems giving rise to stable clusters.

  The structure of strong H-bonded solute-solvent can be properly described with QM geometry optimizations

◊ **From MD simulations:**

  Better for weaker solute-solvent interactions described by a more dynamic situation.
From MD simulations: how does it work?

First we perform an analysis of the radial and spatial distribution functions so to obtain information on how solvent molecules pack in “shells” around some specific atoms in the solute.

Then we select solute-solvent clusters on the basis of a cutoff distance ($r_{\text{cut}}$): each cluster includes all solvent molecules inside the sphere of radius $= r_{\text{cut}}$.

The value used for $r_{\text{cut}}$ has to be chosen so the represent the first solvation shell.

Finally, in order to achieve a statistically meaningful description of the liquid, we introduce averages on many different clusters obtained with the same cutoff.
Clusters from MD simulations

Calculations of the property of interest have to be repeated for all the clusters so to obtain a correct average value

Advantage:

Proper description of weak solute-solvent specific interactions which cannot be represented by a single configuration obtained from a QM geometry optimization

Disadvantage:

Quite demanding from a computational point of view
How can we include long-range effects?

- Enlarging the dimension of the supermolecule:

Problems:

1. By increasing the dimensions, the accuracy of the QM level has to be largely reduced, or an hybrid QM/MM has to be introduced
2. The problem of statistical representativity becomes very difficult: increasing the dimension of the cluster we need more and more clusters so to get a correct picture of the liquid
The main problems disappear:

1. The dimensions do not increase, we do not need to reduce the accuracy of the QM level, or to shift to an hybrid QM/MM method
2. The statistical representativity is automatically satisfied by using the continuum description in terms of the solvent bulk properties.
An example of bulk versus specific effects: Nuclear Magnetic Resonance (NMR) spectra

The resonance frequency for a particular nucleus depends on its molecular environment. This is why NMR is such a useful tool for structure determination... and solvent effects.

\[ \nu_L = \gamma B_{\text{loc}}/2\pi = (1 - \sigma) \gamma B_0/2\pi \]

- Electron density around the nucleus studied
- Neighboring chemical groups in the molecule studied
- Shielding constant: \( \sigma = \sigma(\text{local}) + \sigma(\text{neighbour}) + \sigma(\text{solvent}) \)
- Solvent molecules around the nucleus studied
An example of bulk versus specific effects: Nuclear Magnetic Resonance (NMR) spectra

$^{15}\text{N}$ nuclear shieldings of diazines in various solvents

Different electronic distributions: different interactions with a solvent
$^{15}$N nuclear shieldings of diazines in solution

A continuum-only approach

In water the calculated values are smaller than what observed: a part of the solvent effect is missing.

Specific effects are now correctly accounted for but only with inclusion of bulk effects (PCM clusters) the observed solvent effect is reproduced.
A more difficult case: N-Methyl-acetamide in acetone

Nuclear shieldings: $^{17}\text{O}$ (red) and $^{15}\text{N}$ (blue)

Why a so different accuracy for the two nuclei?

Weak but persistent interactions

From MD simulation:

An homogeneous sphere-like distribution of methyl groups is found around the NMA oxygen.

Methyl groups create a cage which prevents the polar part of the acetone molecules to be in close contact with NMA oxygen.

Bulk effects introduced by the PCM leads to an excessive polarization on NMA oxygen.

A more difficult case: N-Methylacetamide in acetone

Nuclear shieldings: $^{17}\text{O}$ (red) and $^{15}\text{N}$ (blue)

$\langle\text{MD}\rangle + \text{PCM}$:
- averages on MD clusters + continuum

$\text{PCM}$:
- Only continuum

Error (ppm) with respect to exp

Only averages on clusters extracted from MD snapshots correctly reproduce the solvation on oxygen

Some conclusive remarks
Solvent effects on molecular properties: Global versus local

Solvent effects are difficult to define: they act differently on different quantities

✓ Solvation free energies are generally “globally sensitive”: they are properly described by a continuum model even when specific effects are present

✓ Molecular response properties are generally “locally sensitive”: they cannot be properly described by a continuum model when specific effects are present
Persistent versus Labile

A useful simplification for “locally sensitive” properties: distinction between persistent and labile interactions, based on their characteristic residence time.

► persistent interactions:

QM optimized supermolecules can be used and the effects of outer-shell molecules can be included with the continuum model.

► labile interactions:

QM optimized supermolecules are not representative of the real situation; structures extracted from MD simulations are to be preferred.

Necessity of a double average on the solvent molecules:

➢ for the first shell: average on different MD clusters
➢ for the outer shells: an implicit average through the continuum
Solvation is an intrinsically dynamic and long-range phenomenon: statistical treatments involving averaging and fluctuations from averages are important.

Which Theoretical Model?

Not a unique answer!

The choice has to be preceded by an analysis on:

(i) the chemical system,
(ii) the properties of interest,
(iii) the required accuracy,
(iv) the computational cost