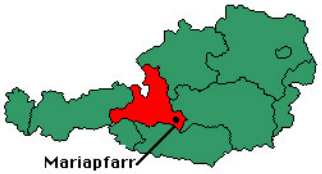
The Modelling of Environment Effects in Quantum Chemistry

QM/continuum models: from solvated systems to more complex environments (I)

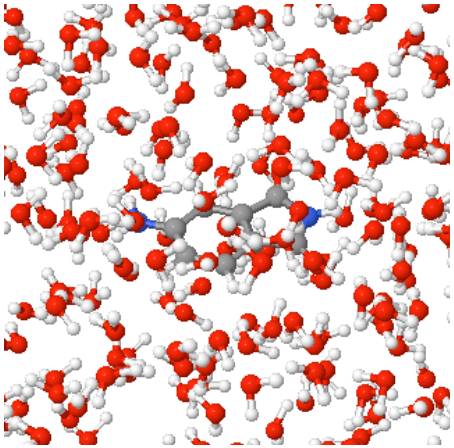
Benedetta Mennucci



Mariapfarr, Salzburg, Österreich

MOLECOLAB MODELLING LIGHT AND ENVIRONMENT IN COMPLEX SYSTEMS PISA

Which environment?

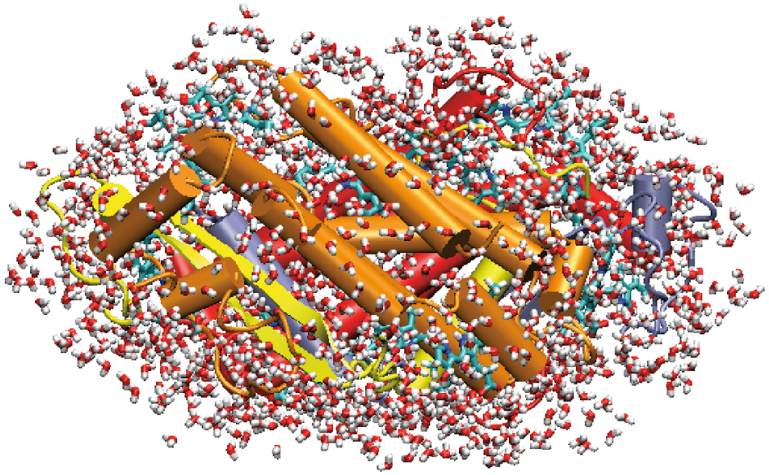


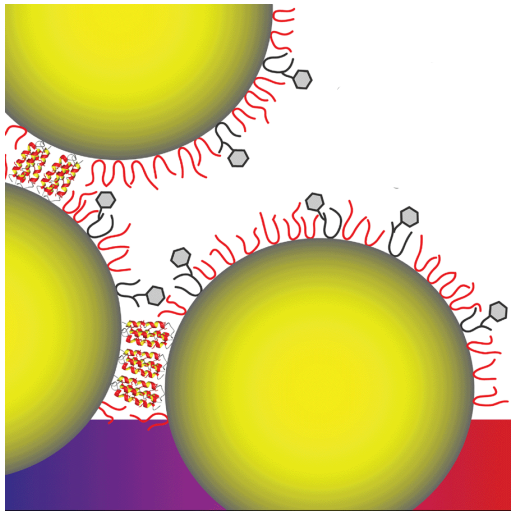
Solvated systems:

a (supra)molecular system within an environment which is "almost" homogeneous & isotropic

Embedded systems:

a (supra)molecular system within an environment which is heterogeneous & anisotropic



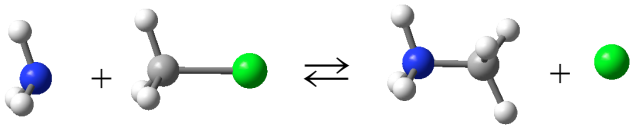


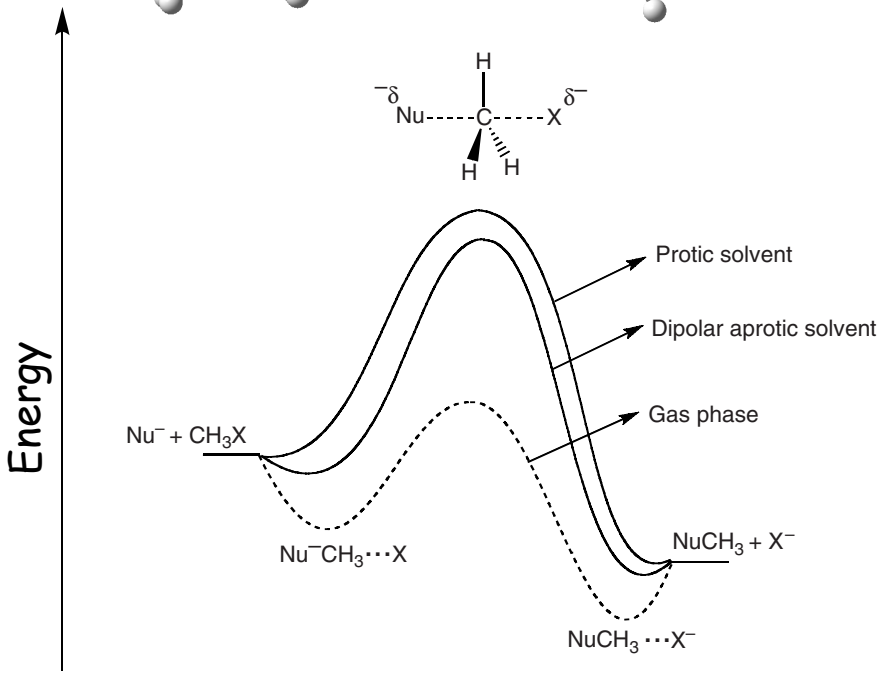
Composite systems:

a (supra)molecular system within an the environment containing surfaces/nanoparticles

Which environment effects?

A simple example: solvent & chemical reactions



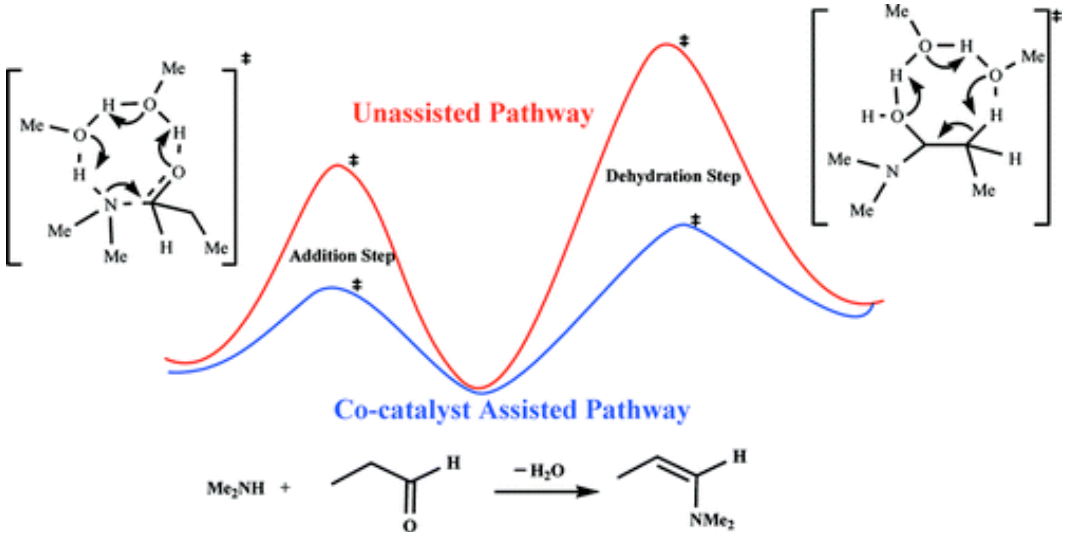


Solvent can change the energetics and the kinetics by changing the relative energy & geometry of the involved species

direct & indirect effects

Solvent can explicitly enter into the mechanism of the reaction

Specific effects
(first solvation shell effects)



Which environment effects?

A (simplified) classification

Always

Direct effects:

environment-induced changes in the electronic charge distribution

Indirect effects:

environment induced changes in the molecular geometry and/or in the relative energies of conformers

In particular cases

Specific effects:

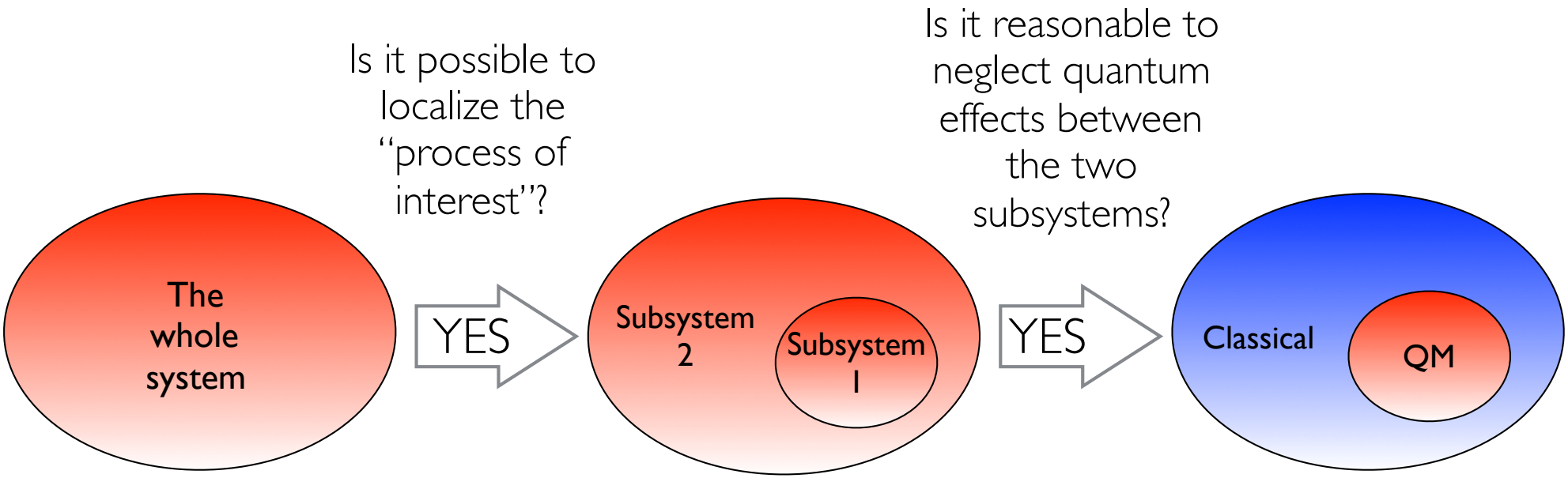
"first solvation shell" effects

Dynamic effects:

environment relaxation effects

... and many others

The multiscale strategy

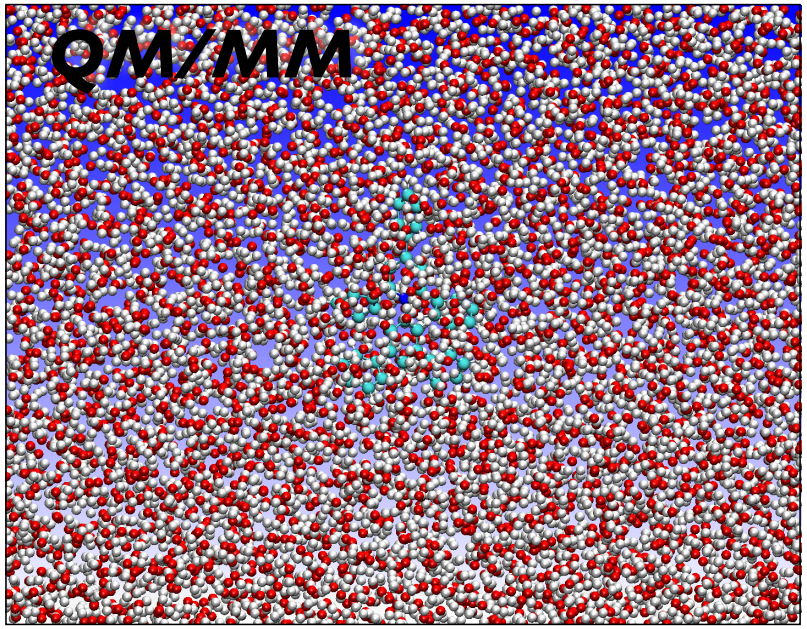


$$\hat{H}_{QM} \Rightarrow \hat{H}_{QM} + \hat{H}_{QM-class}$$

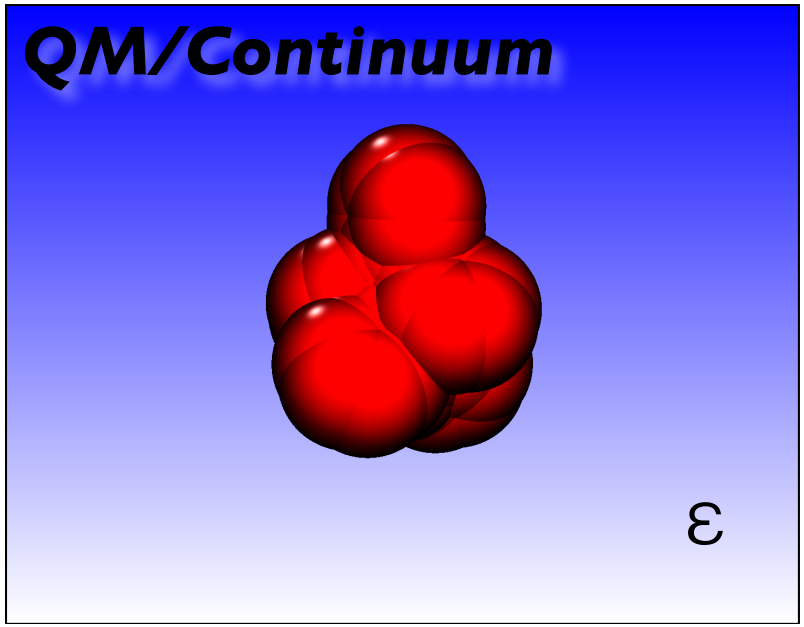
Which classical embedding?

From atomistic to continuum descriptions

Both subsystems are treated atomistically



A "coarser grained" description is used for the "external" subsystem



✅ **Automatically Included**

Environment inhomogeneities & anisotropies

⚠️ **To be added (only of some kind)**

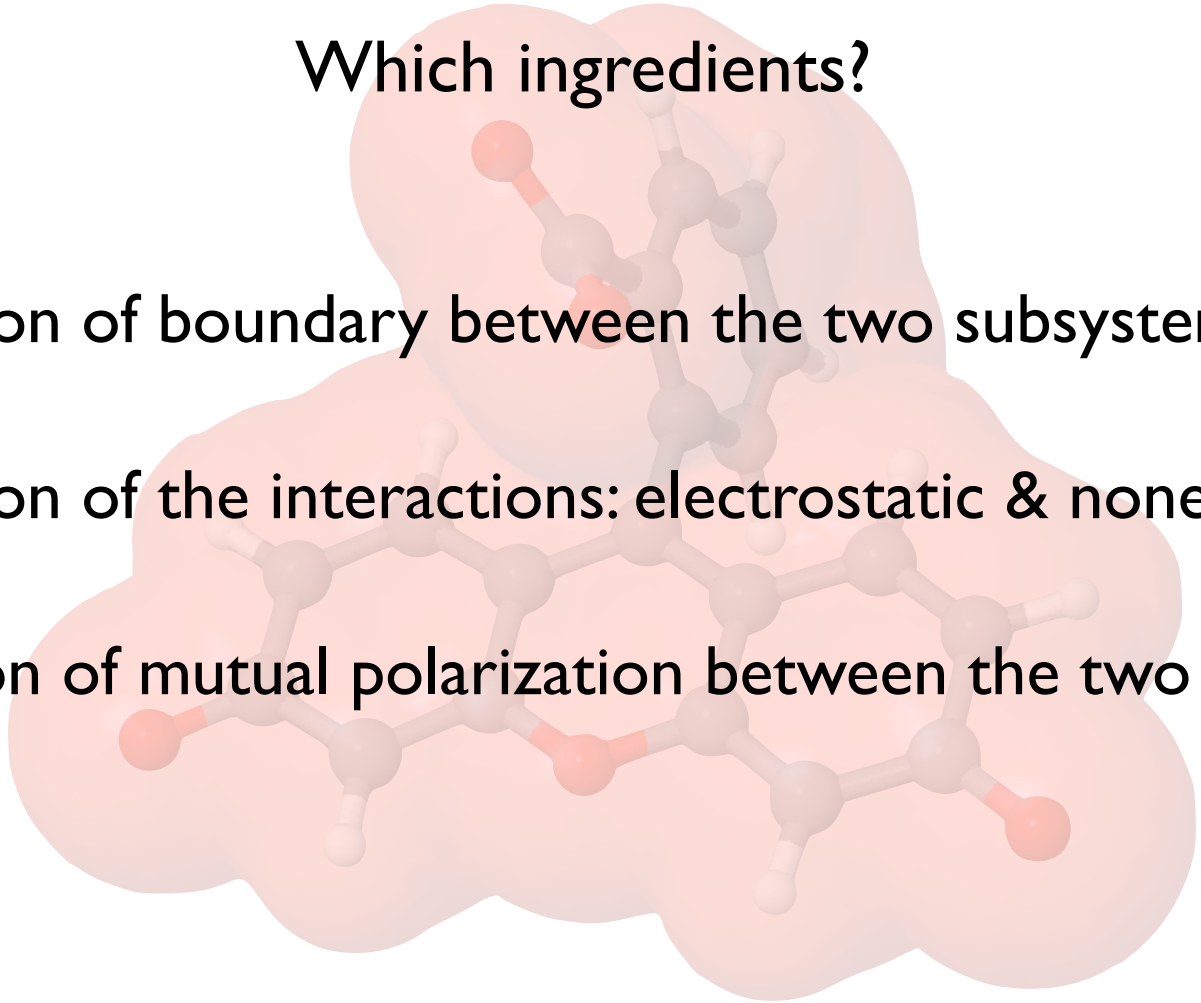
⚠️ **To be explicitly "added"**

Sampling of the environment configurational space

✅ **(Implicitly) included**

The continuum approach

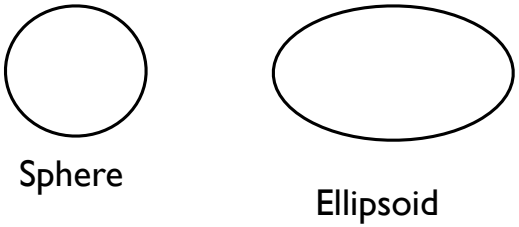
Which ingredients?



- The definition of boundary between the two subsystems
- The definition of the interactions: electrostatic & nonelectrostatic
- The inclusion of mutual polarization between the two subsystems

The boundary

Simple models

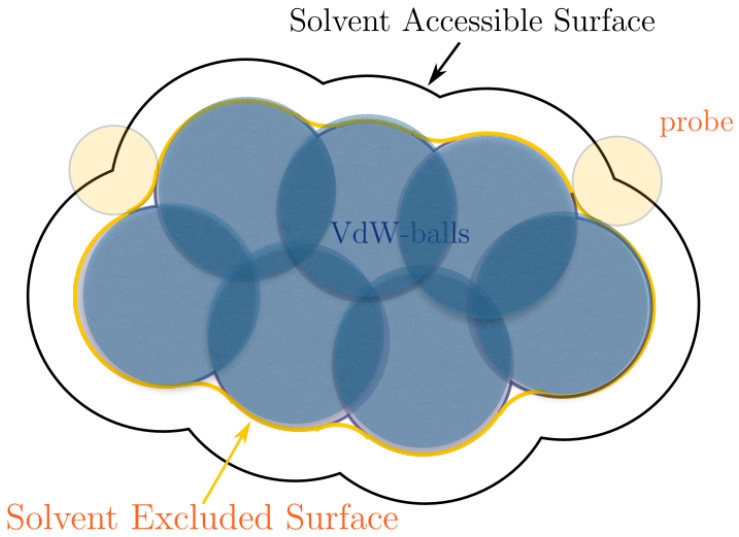


NOT ENOUGH!

We need molecular models

1. van der Waals Surface (VWS):

is constructed from the overlapping vdW spheres of the atoms



But if we want to account for the dimension of the solvent:

2. Solvent Accessible Surface (SAS):

is the surface traced by the center of the probe sphere (the solvent).

3. Solvent excluded Surface (SES or Connolly):

is traced by the inward-facing part of the probe sphere as it rolls on the vdW surface.

The coupling work

work necessary to "build up" the solute M in the solvent S

We introduce a partition in terms of different interactions

$$W(\mathrm{M/S}) = \mathrm{G_{cav}} + \mathrm{G_{elec}} + \mathrm{G_{vdW}}$$

Cavitation term: work required to create the cavity

Electrostatic term

nonelectrostatic: dispersion & repulsion

Non electrostatic contributions: an effective strategy

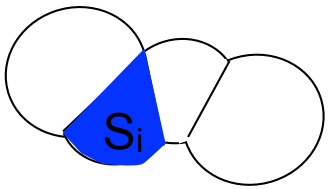
An "imaginary" process

- Create an empty cavity: a positive contribution to the solvation free energy
- Switch on the nonelectrostatic solute-solvent interactions: positive & negative contributions to the solvation free energy

We can simplify the process by merging all contributions through an empirical expression:

$$G_{non\text{-}el} = G_{\mathrm{cav}} + G_{\mathrm{vdW}} = \Sigma_i \xi_i S_i$$

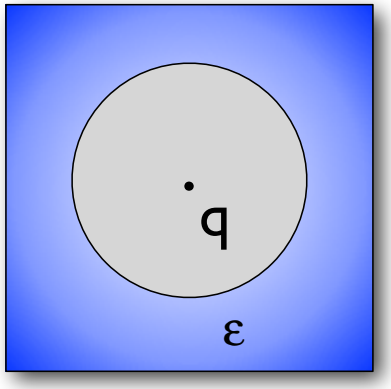
ξ_i is an empirically determined parameter for the *i*-th atom and S_i is the part of the *solvent* accessible surface for the *i*-th atom



Electrostatics & Polarization

Two milestones

- **Born Model (1920)**



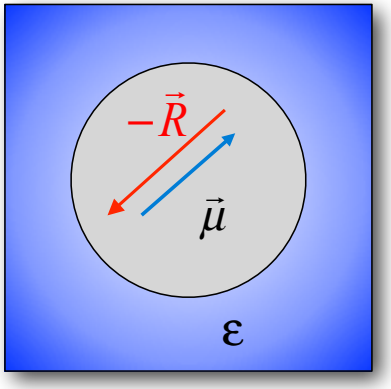
electrostatic component of solvation free energy

- A point charge (q) in a spherical cavity of radius a inside the dielectric

$$\Delta G_{elec} = -\frac{q^2}{2a}\left(1-\frac{1}{\varepsilon}\right)$$

dielectric constant

- **Onsager Model (1936)**



- A dipole at the center of a spherical cavity inside a dielectric.

Reaction field of the solvent

$$\vec{R} = \frac{1}{a^3}\frac{2(\varepsilon-1)}{2\varepsilon+1}\vec{\mu} = f\vec{\mu}$$

$$\Delta G_{elec} = -\frac{1}{2}\vec{R}\cdot\vec{\mu} = -\frac{(\varepsilon-1)\mu^2}{(2\varepsilon+1)a^3}$$

"It measures the electric field which acts upon the dipole as a result of the electric displacement induced by its own presence"

Electrostatics & Polarization

- Born Model (1920)

→ The modern extension: Generalized Born (GB)

Several charges inside an arbitrary cavity: each one with its own "effective" Born radius.

$$\Delta G_{el} = \sum_{i=1}^{N} \Delta G_i^{self} + 2\sum_{i=1}^{N}\sum_{j>i}^{N} \Delta G_{ij}^{pair}$$

$$\Delta G_i^{self} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\frac{q_i^2}{a_i}$$

$$\Delta G_{ij}^{pair} = -\frac{1}{2}\left(1-\frac{1}{\varepsilon}\right)\frac{q_i q_j}{\sqrt{r_{ij}^2 + a_i a_j \exp\left(-\frac{r_{ij}^2}{4 a_i a_j}\right)}}$$

effective Born radii

Different GB-models:

- The Still model (Still, 1990, 1997)
- SMx (Cramer & Truhlar, 1996-today): extended to QM
- ACE: Analytical Continuum Electrostatics (Schaefer & Karplus, 1996)
- GBMV (GB Molecular Volume, Brooks 2003)

Electrostatics & Polarization

- Onsager Model (1936)

⇒ The modern extension: the multipole expansion (MPE)

The solute enclosed in a spherical cavity is represented in terms of a multipolar expansion

Solute-solvent interaction energy

$$W_{MS} = \sum_l \sum_m M_l^m R_l^m$$

M_l^m is the m component of the spherical multipole moment of order l corresponding to the solute charge distribution

Generalized Reaction field term

$$R_l^m = f_l M_l^m \qquad f_l = \frac{1}{a^{2l+1}} \frac{(l+1)(\varepsilon - 1)}{(l+1)\varepsilon + l}$$

Generalized reaction field factors

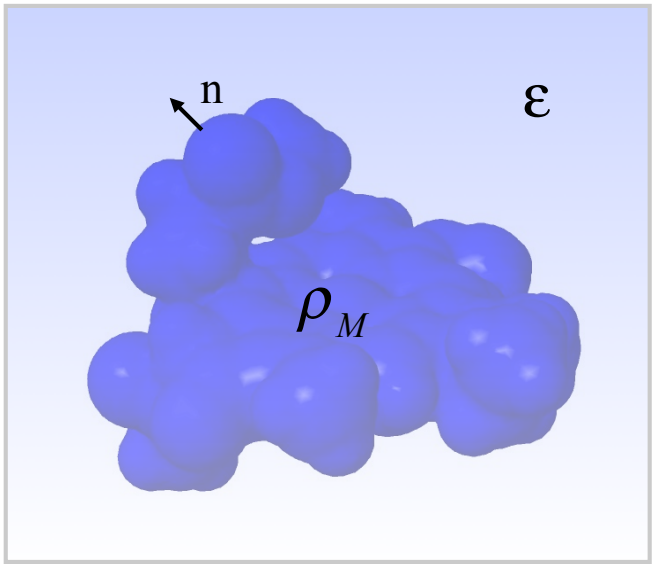
Different MPE-models (both extended to QM):

- Nancy model (Rivail & Rinaldi, 1973-today)
- Mikkelsen model (Mikkelsen et al., 1988-today)

A more general strategy

The electrostatic problem

A "general" charge density ρ_M inside a cavity of any shape within a n homogeneous & isotropic continuum dielectric



Generalized Poisson equation

$$\vec{\nabla}\cdot\left(\varepsilon(\vec{r})\vec{E}(\vec{r})\right)=4\pi\rho_M(\vec{r})$$

$$\varepsilon\vec{\nabla}\cdot\vec{E}(\vec{r})=-\varepsilon\vec{\nabla}\cdot\left[\vec{\nabla}V(\vec{r})\right]=-\varepsilon\nabla^2V$$

In terms of the electrostatic potential *V*

$$\begin{cases} -\nabla^2V=4\pi\rho_M & \text{inside the cavity: } \varepsilon=1 \\ -\varepsilon\nabla^2V=0 & \text{outside the cavity: } \rho_M=0 \end{cases}$$

Boundary conditions

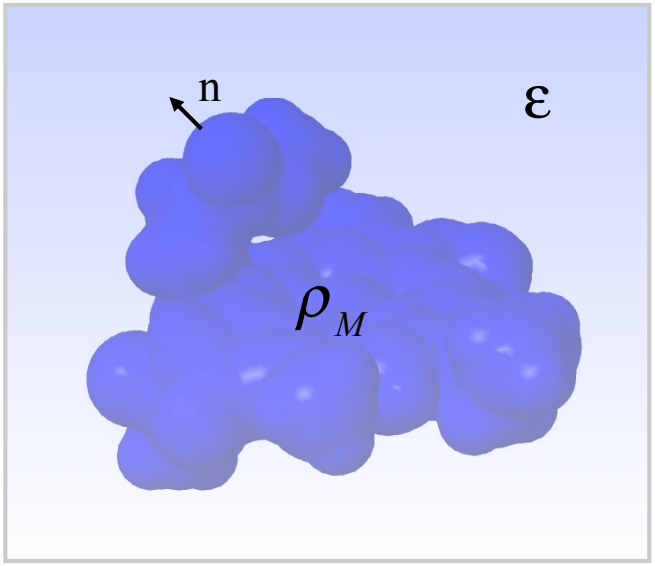
$$+\begin{cases} \left[\vec{\nabla}V\cdot\vec{n}\right]_{in}=\left[\varepsilon\vec{\nabla}V\cdot\vec{n}\right]_{out} \\ V_{in}=V_{out} \end{cases}$$

The Apparent Surface Charge

Which electrostatic potential V ?

V is the sum of the electrostatic potential V_M generated by the charge distribution ρ_M and of the reaction potential V_R generated by the polarization of the dielectric medium:

$$V(\vec{r}) = V_M(\vec{r}) + V_R(\vec{r})$$



Which form for the reaction potential V_R ?

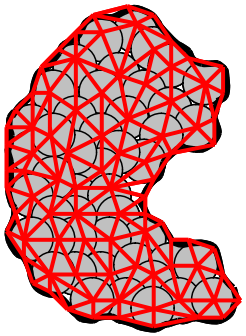
$$V_R(\vec{r}) \Rightarrow V_\sigma(\vec{r}) = \int_\Gamma \frac{\sigma(\vec{s})}{|\vec{r} - \vec{s}|} d^2 s$$

The reaction potential is defined by introducing an **apparent surface charge (ASC)** density (σ) on the cavity

Numerical methods for partial differential equations

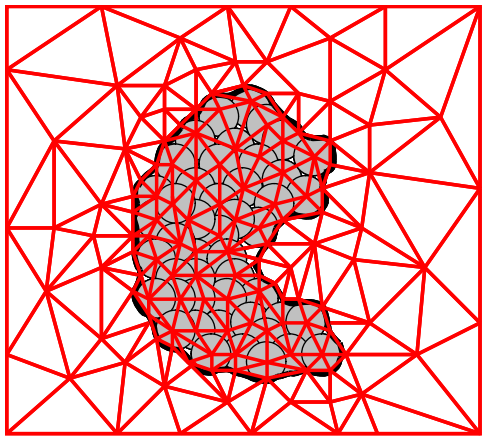
Boundary element method (BEM)

BEM is derived through the discretization of an integral equation that is mathematically equivalent to the original partial differential equation (PDE).

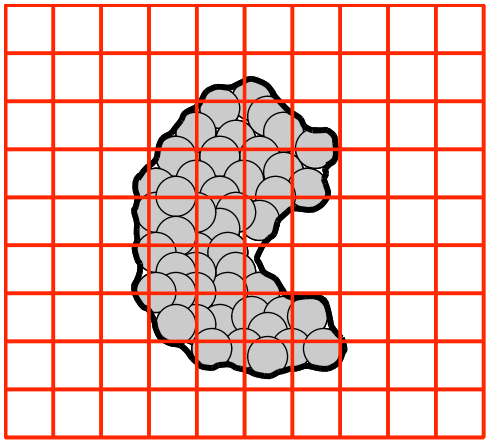


BEM

In applying the boundary element method, only a mesh of the surface is required.



FEM



FDM

Finite element method (FEM) or finite difference method (FDM): the whole domain of the PDE requires discretization.

The Apparent Surface Charge: the BEM solution

Reaction potential

$$V_R(\vec{r}) \Rightarrow V_\sigma(\vec{r}) = \int_\Gamma \frac{\sigma(\vec{s})}{|\vec{r}-\vec{s}|} d^2 s$$

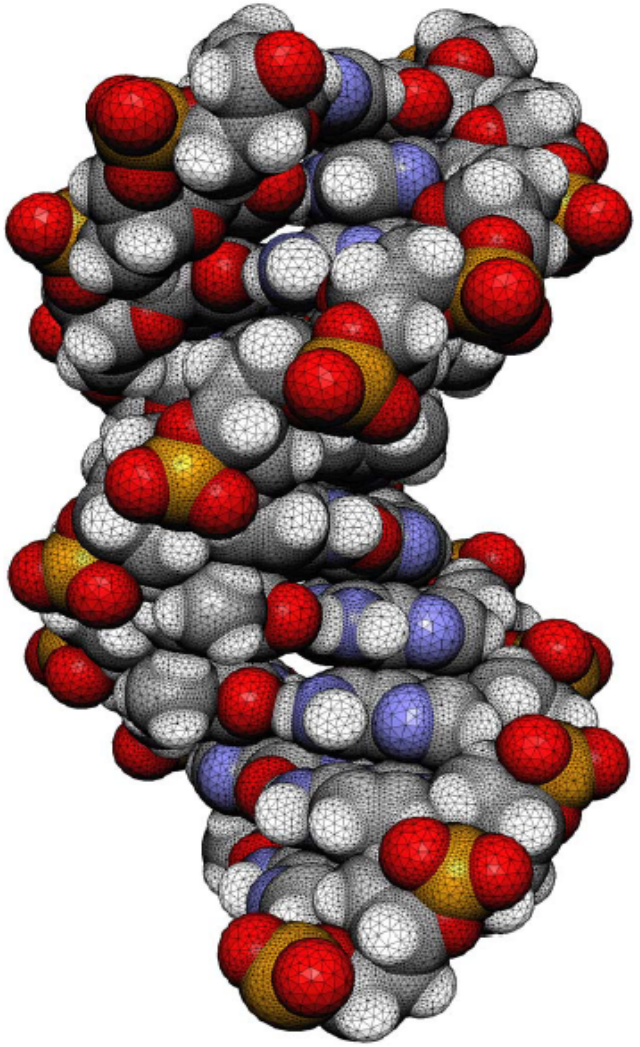
1. Construction of the molecular cavity in terms of interlocking spheres (centered on the solute atoms)

2. Partition of the cavity surface into *N* finite elements (tesserae)

3. Discretization of the apparent surface charge σ into *N* point-like charges **q**

we assume that σ is constant on each element of area a_i

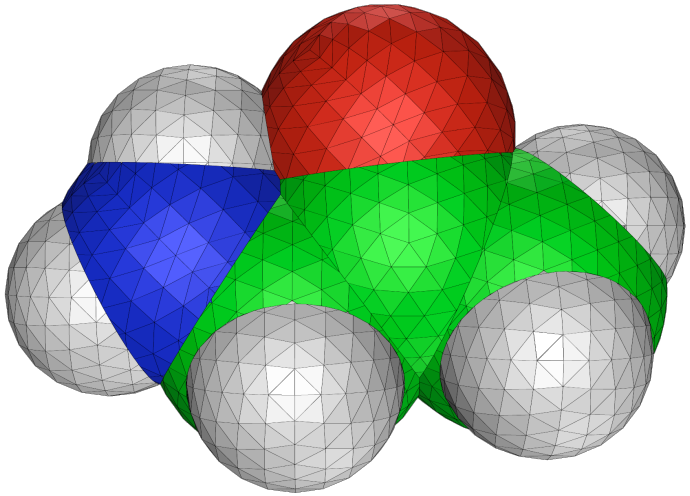
$$q(\vec{s}_i) = a_i \sigma(\vec{s}_i)$$



The Apparent Surface Charge: the BEM solution

NTS apparent surface charges

$$q(\vec{s}_i) = a_i \sigma(\vec{s}_i)$$



Reaction potential

$$V_R(\vec{r}) = \int_\Gamma \frac{\sigma(\vec{s})}{|\vec{r} - \vec{s}|} d^2 s \quad \Rightarrow \quad V_R(\vec{r}) = \sum_{i=1}^{NTS} \frac{q(\vec{s}_i)}{|\vec{r} - \vec{s}_i|}$$

Electrostatic interaction

$$W_{ele} = \int \rho^M(\vec{r}) V_R(\vec{r}) d\vec{r} \quad \Rightarrow \quad W_{ele} = \sum_{i=1}^{NTS} q(\vec{s}_i) V^M(\vec{s}_i)$$

Apparent surface charges

$$q(\vec{s}_i) = a_i \sigma(\vec{s}_i)$$

Which **σ**?

Apparent surface charges: the PCM family

Dielectric PCM: DPCM

S. Miertuš, E. Scrocco, J. Tomasi
Electrostatic interaction of a solute with a continuum. A direct utilization of ab initio molecular potentials for the prevision of solvent effects
Chem. Phys. 117-129, 55 (1981)

Integral Equation Formalism: IEFPCM

E. Cancès, B. Mennucci and J. Tomasi
A new integral equation formalism for the polarizable continuum model: Theoretical background and applications to isotropic & anisotropic dielectrics
J. Chem. Phys. 3032-3041 107 (1997)

Conductor-like Screening Model: COSMO

A. Klamt and G. Schüürmann,
COSMO: A New Approach to Dielectric Screening in Solvents with Explicit Expressions for the Screening Energy and its Gradient
J. Chem. Soc. Perkin Trans. II 799-805, 2 (1993).

A PCM-like reformulation of the COSMO model: CPCM

V. Barone, M. Cossi
Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model
J. Phys. Chem. A 1995-2001, 102 (1998)

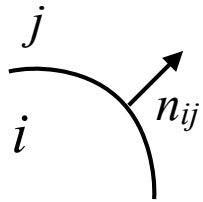
The original formulation: DPCM

S. Miertuš, E. Scrocco, J. Tomasi, Chem. Phys. 117-129, 55 (1981)

In the linear response approximation, the solvent polarization vector is:

$$\vec{P} = \frac{\varepsilon - 1}{4\pi}\vec{E}$$

At the boundary of two dielectrics, *i* & *j*, there is an apparent surface charge distribution given by



$$\sigma_{ij} = -\left(\vec{P}_i - \vec{P}_j\right)\cdot\vec{n}_{ij}$$

Taking into account that :

$\varepsilon_i = 1$ (inside the cavity there is no dielectric)

$\varepsilon_j > 1$ (outside the cavity there is the solvent)

$$\sigma^{DPCM} = -\frac{\varepsilon - 1}{4\pi\varepsilon}\left(\vec{E}_M + \vec{E}_\sigma\right)\cdot\vec{n}$$

Integral operator

$$\hat{D}^*\sigma(x) = \int_\Gamma \left[\nabla\left(1/|x-y|\right)\cdot n(x)\right]\sigma(y)\,dy$$

$$\left[2\pi\left(\frac{\varepsilon+1}{\varepsilon-1}\right)\hat{I} - \hat{D}^*\right]\sigma^{DPCM} = \frac{\partial V_M}{\partial n}$$

The Conductor-like formulation

A. Klamt and G. Schüürmann, *J. Chem. Soc. Perkin Trans. II* 799-805, 2 (1993).

A conductor (infinite permittivity, $\varepsilon = \infty$) instead of a dielectric: a new condition on the total potential

$$V_M(\vec{r}) + V_R(\vec{r}) = 0$$

$$V_R(\vec{r}) \rightarrow V_\sigma(\vec{r}) = \int \frac{\sigma^C(\vec{s})}{|\vec{r} - \vec{s}|} d\vec{s} = \hat{S}\sigma^C$$

Integral operator

$$V_M + \hat{S}\sigma^C = 0 \quad \Rightarrow \quad \sigma^C = -\hat{S}^{-1}V_M$$

Conductor apparent charge

We recover the true dielectric behavior by scaling the conductor charges using the real (finite) dielectric constant:

$$\sigma^{CPCM} = \frac{\varepsilon - 1}{\varepsilon + x}\sigma^C$$

the value of x should be set to 0.5 for neutral molecules and to 0.0 for ions

Integral Equation Formalism: IEFPCM

E. Cancès, B. Mennucci and J. Tomasi, J. Chem. Phys. 3032-3041 107 (1997)

$$L_{in}V = -\nabla^2 V = 4\pi\rho_M$$

inside the cavity: $\varepsilon = 1$

$$L_{out}V = -\varepsilon\nabla^2 V = 0$$

outside the cavity: $\rho_M = 0$

$$L_{in} \Leftrightarrow G_{in}(x,y) = \frac{1}{|x-y|}$$

$$L_{out} \Leftrightarrow G_{out}(x,y) = \frac{1}{\varepsilon|x-y|}$$

Green Functions

The ASC family & the connections

Integral operators

$$\hat{S}\sigma(x) = \int_\Gamma \frac{\sigma(y)}{|x-y|}dy$$

$$\hat{D}\sigma(x) = \int_\Gamma \left[\nabla\left(1/|x-y|\right)\cdot n(y)\right]\sigma(y)\,dy$$

$$\hat{D}^*\sigma(x) = \int_\Gamma \left[\nabla\left(1/|x-y|\right)\cdot n(x)\right]\sigma(y)\,dy$$

IEFPCM

$$\left[2\pi\left(\frac{\varepsilon+1}{\varepsilon-1}\right)\hat{I}-\hat{D}\right]\hat{S}\sigma^{IEFPCM} = -\left(2\pi\hat{I}-\hat{D}\right)V_M$$

$$\left(2\pi\hat{I}-\hat{D}\right)V_M + S\frac{\partial V_M}{\partial n} = 0$$

$\varepsilon \rightarrow \infty$

DPCM

$$\left[2\pi\left(\frac{\varepsilon+1}{\varepsilon-1}\right)\hat{I}-\hat{D}^*\right]\sigma^{DPCM} = \frac{\partial V_M}{\partial n}$$

COSMO (CPCM)

$$\hat{S}\sigma^C = -V_M$$

The discretization of the surface charge

$$\hat{T}(\varepsilon)\sigma = -\hat{R}\begin{cases} \vec{E}_M \cdot \vec{n} \\ V_M \end{cases} \quad \Longrightarrow \quad \mathbf{T}(\varepsilon)\mathbf{q} = -\mathbf{R}\mathbf{f}_M$$

Vector $\mathbf{f}_M$ collects electrostatic potential (or field) produced by the solute on the surface elements:

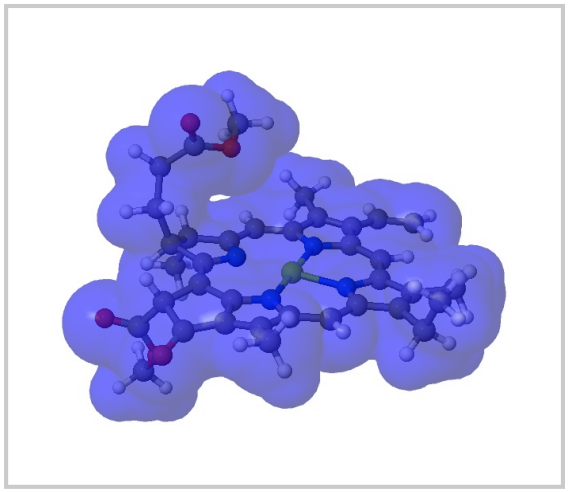
$$\left[\mathbf{f}_M\right]_j = \begin{cases} \vec{E}_M(\vec{s}_j)\cdot\vec{n}(\vec{s}_j) & \text{DPCM} \\ V_M(\vec{s}_j) & \text{CPCM \& IEFPCM} \end{cases}$$

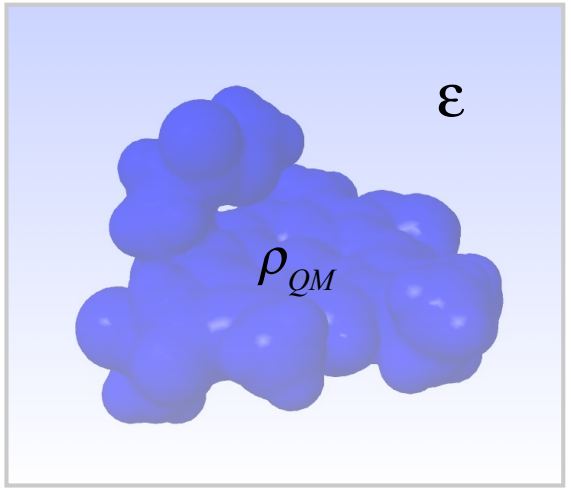
There are basically two strategies to solve the system:

- Inverting **T** by a direct method
- By an iterative method

QM/continuum: a step by step strategy

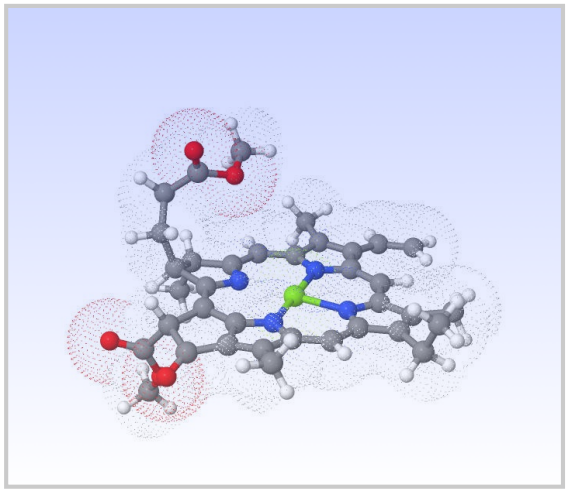
1) The definition of the boundary: the molecular cavity

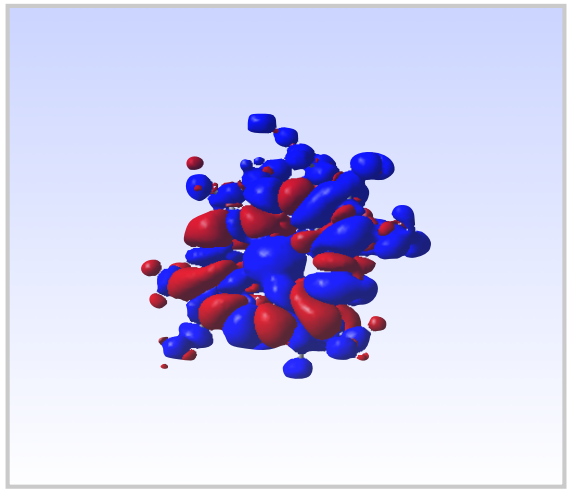




2) The electrostatic problem: the Poisson equation

3) The numerical solution: the surface mesh





4) The QM problem

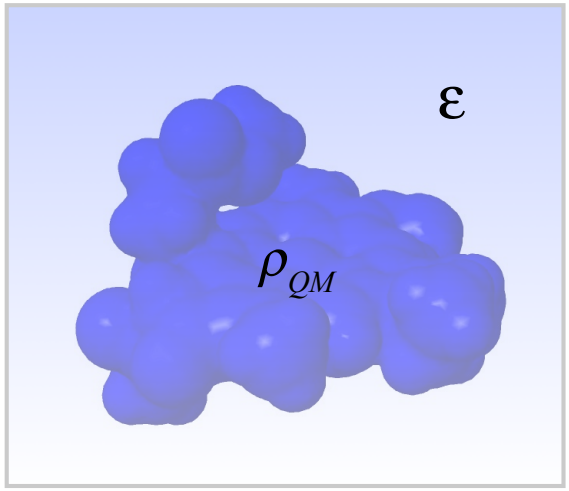
The QM/Continuum approach

The Self-Consistent Reaction Field (SCRF) method

Tomasi, J., Mennucci, B., & Cammi, R. (2005) 105, 2999

The outlying charge effect

The ASC model is formulated for an ideal charge density completely inside the cavity



$$\begin{cases} -\nabla^2 V = 4\pi\rho & \text{(in)} \\ -\varepsilon\nabla^2 V = 0 & \text{(out)} \\ \text{Boundary conditions} \end{cases}$$

Gauss Theorem

$$\int_\Gamma \sigma^{PCM}\, ds = -\frac{\varepsilon - 1}{4\pi\varepsilon}\int_\Gamma \vec{E}\cdot\vec{n}\, ds$$

$$\int_\Gamma \vec{E}\cdot\vec{n}\, ds = 4\pi\int_V \rho\, dv$$

$$\Rightarrow \quad \sum_i q_i = Q^{calc} = -\frac{\varepsilon - 1}{\varepsilon} Q_M$$

In the ideal world: the Gauss theorem is satisfied

In the "real" word: $Q^{calc} \neq -\frac{\varepsilon - 1}{\varepsilon} Q_M$

Within a QM description of the solute: the electronic charge necessarily spreads outside the cavity (escaped or **outlying charge**)

The outlying charge effect

In the presence of the escaped or **outlying charge**:

The polarization of the solvent should be expressed in terms of two apparent charge distributions:

σ

On the cavity surface

$$\beta = -\frac{\varepsilon - 1}{\varepsilon}\rho_M^{out}$$

In the outside (bulk) volume

β is easily computed once ρ is known, but its contribution to the reaction field involves an integration over the whole space outside the cavity !

The electrostatic interaction between solute and solvent (solvent reaction field) should be computed by a double integration

$$\int_{surface} \frac{\sigma(\bar{s})}{|r-s|} d\bar{s} + \int \frac{\beta(\bar{r}')}{|r-r'|} d\bar{r}'$$

A solution for the outlying charge effect

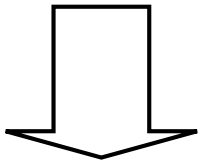
To have a more correct description of the solvent polarization we have to find a way to include the effects of the volume apparent charge β

These effects can be approximated by an additional surface charge.

$$\sigma' = \sigma_{ins} + \alpha_{out}$$

α_{out} can be defined so to generate *inside the cavity* the same electrostatic potential as that due to β:

$$\hat{S}\alpha = V_{\beta}$$



$$\sigma' \Leftrightarrow \sigma^{IEFPCM}$$

IEFPCM charges produce inside the cavity an exact reaction potential

D M Chipman, J Chem Phys, 112, 5558 (2000).

The effective Hamiltonian

$$\hat{H}_{eff}\Psi = \left(\hat{H}_{QM} + \hat{H}^{elec}_{QM/clas}\right)\Psi = E\Psi$$

$$\hat{V}_R = \sum_i q_i^{ASC}\hat{V}(\vec{s}_i)$$

ASC charges

$$\mathbf{T}(\varepsilon)\mathbf{q}^{ASC} = -\mathbf{R}\mathbf{V}_{QM}$$

Solute electrostatic potential on the surface cavity:

$$V_{QM}(\vec{s}_i) = \left\langle \Psi \middle| \hat{V}_i \middle| \Psi \right\rangle + V_i^N = -\left\langle \Psi \middle| \frac{1}{|\vec{r} - \vec{s}_i|} \middle| \Psi \right\rangle + \sum_K \frac{Z_k}{|\vec{R}_K - \vec{s}_i|}$$

The solute wavefuntion depends on the solvent operator & the solvent operator depends on the wavefunction!

A variational formulation

$$\hat{H}_{eff}\Psi = \left(\hat{H}_{QM} + \hat{V}_R\right)\Psi = E\Psi$$

non linear effective Hamiltonian

The variational principle can be applied but not in the standard form:
here the functional to be minimized does NOT correspond to the eigenvalue

Eigenvalue:
Internal energy

$$E^s = \left\langle \Psi \middle| \hat{H}^{eff} \middle| \Psi \right\rangle$$

Electrostatic Free energy functional

$$G = \left\langle \Psi \middle| \hat{H}^{eff} \middle| \Psi \right\rangle - \frac{1}{2}\left\langle \Psi \middle| \hat{V}_R \middle| \Psi \right\rangle = E_s - \frac{1}{2}E_{\text{int}}$$

In a thermodynamical language:
we have to add the work necessary to polarize the solvent which is opposite in sign and half in magnitude with respect to the interaction energy.

Self consistent reaction field (SCRF)

How do we introduce solvent effects?

we add a new solvent-dependent operator

Effective Fock (or Kohn-Sham) operator

$$\hat{F}^{eff} = \hat{F}^{0} + \hat{X}^{RF}$$

Reaction Field operator

$$\hat{X}^{RF} = \frac{1}{2}\frac{\partial E_{\text{int}}}{\partial \rho} = \frac{1}{2}\frac{\partial\left\{\mathbf{q}^{ASC}(\rho)\mathbf{V}(\rho)\right\}}{\partial \rho}$$

$$\mathbf{T}(\varepsilon)\mathbf{q}^{ASC} = -\mathbf{R}\mathbf{V}(\rho)$$

$$\Updownarrow$$

$$\mathbf{q}^{ASQ} = \left(-\mathbf{T}^{-1}\mathbf{R}\right)\mathbf{V}(\rho) = \mathbf{Q}\mathbf{V}(\rho)$$

$$\Rightarrow \quad \hat{X}^{RF}(\rho) = \sum_i q_i^{ASC}(\rho)\hat{V}_i$$

It changes at each iteration of the SCF cycle

Post-SCF methods & Polarization

The nonlinear solvent operator is easily nested in the standard Self-Consistent-Field approaches (Hartree-Fock, DFT):

no need of further iterative schemes

But difficulties appear in post-SCF calculations

An example:
inclusion of electronic correlation using
Moller Plesset perturbation theory

MP2 & Continuum Models

MP2 correction

$$E_2 = \frac{1}{4}\sum_{ij}^{occ}\sum_{ab}^{virt}\frac{\left(\langle ij|ab\rangle - \langle ia|jb\rangle\right)^2}{\varepsilon_i + \varepsilon_j - \varepsilon_a - \varepsilon_b}$$

When the molecule interacts with a solvent

Orbitals & orbital energies are obtained with a "solvated" Fock operator:

they account for the presence of the environment

Solvation effects change correlation but not viceversa

Can we include correlation effects in solvation?

MP2/ASC: the relaxed scheme

Solvated Hartree-Fock

$$\hat{F}^{eff} = \hat{F}^{0} + \hat{X}^{RF}$$

$$\hat{X}^{RF} \Leftrightarrow \mathbf{q}^{\mathrm{ASC}}(\mathbf{P}_{\mathrm{HF}})$$

Relaxed MP2 density

$$\mathbf{P}_{relax} = \mathbf{P}_{\mathrm{HF}} + \mathbf{P}^{(2)}$$

MP2 change in the density matrix: orbital relaxation

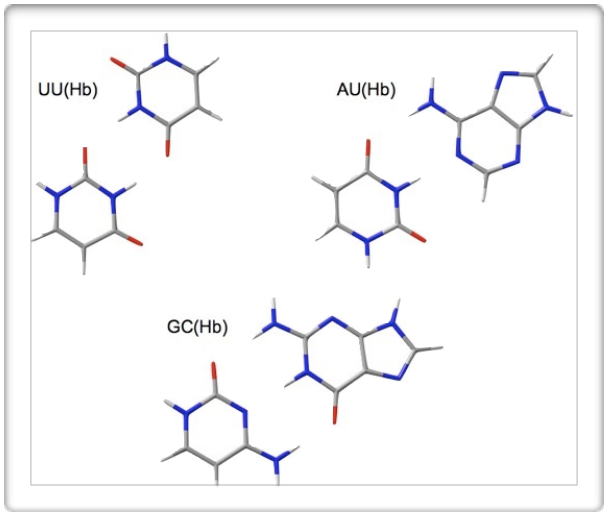
Relaxed ASC charges

$$\mathbf{q}^{\mathrm{ASC}}(\mathbf{P}_{relax}) = \mathbf{q}^{\mathrm{ASC}}(\mathbf{P}_{\mathrm{HF}}) + \mathbf{q}^{\mathrm{ASC}}(\mathbf{P}^{(2)})$$

Iteration until convergency

New reference state in the presence of new ASC charges

Unrelaxed & Relaxed solvation: Interaction energies



Hydrogen bonding interaction energies

	UnRelaxed	Relaxed	% variation
UU	-1,06	-2,23	-110
GC	-6,73	-9,97	-48
AU	-3,37	-4,65	-38

BSSE MP2/aug-cc-pVDZ; energies in kcal/mol

Stacking interaction energies

	UnRelaxed	Relaxed	% variation
CU	-4,58	-6,85	-50
UU	-4,54	-5,90	-30
GC	-4,92	-6,24	-27
AU	-6,53	-7,68	-18

BSSE MP2/aug-cc-pVDZ; energies in kcal/mol