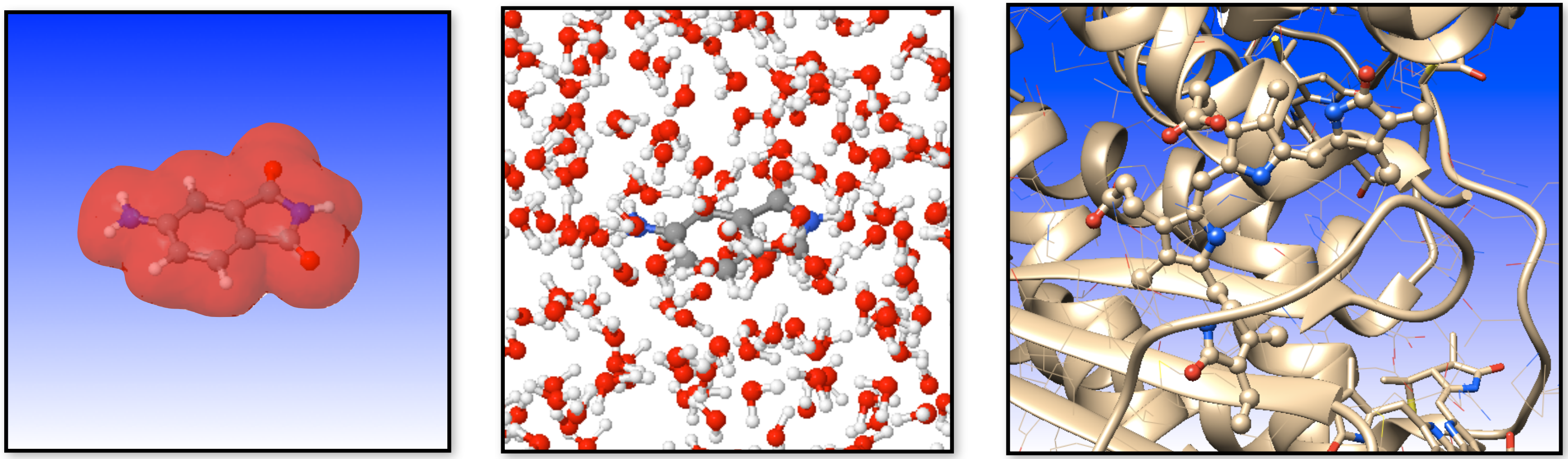
Dipartimento di Chimica e Chimica Industriale
University of Pisa

Hybrid QM/classical models in chemistry



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MOLECOLAB PISA
MODELLING LIGHT AND ENVIRONMENT IN COMPLEX SYSTEMS

http://molecolab.dcci.unipi.it

Outline

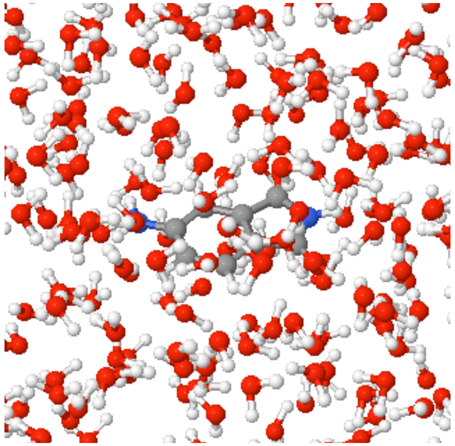
- **Methodological aspects**
    - Introduction
    - Continuum models
    - Atomistic models
    - Self Consistent reaction field

1st part

- **Molecular Properties of Solvated Systems**
    - Energy Derivatives
    - Direct vs. indirect effects
    - Bulk vs. specific solvation
    - Some examples

- **Excited states in solvated systems**
    - Nonequilibrium
    - State specific vs. linear response formulations
    - Examples

The systems of interest

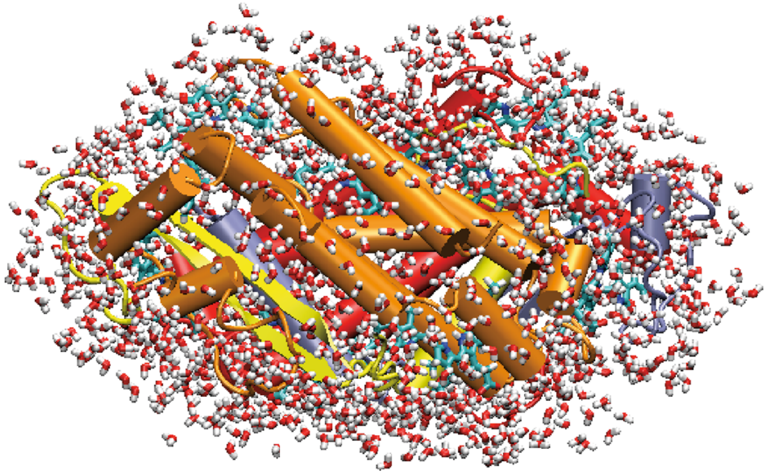


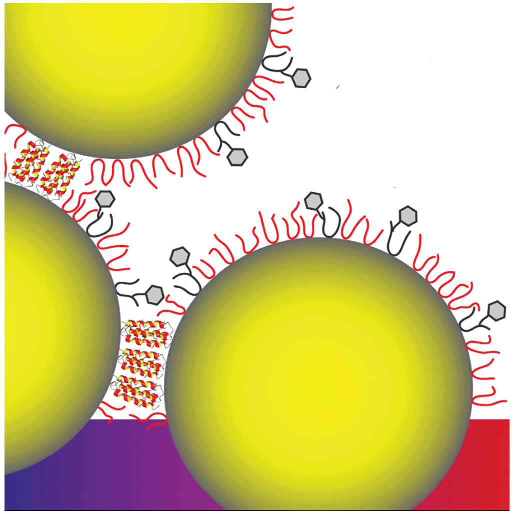
Solvated systems:

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 which is composed by parts with different macromolecular characteristics

Modeling complex systems:
two main problems to face

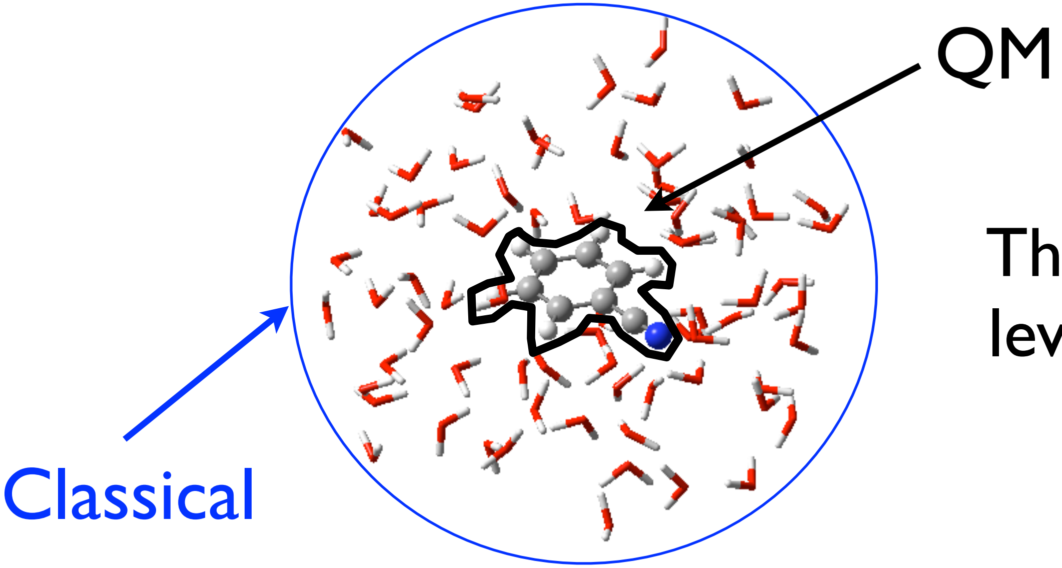
How to deal with the large dimension of the system?

How to achieve a statistically correct description?

A possible strategy:

the focused approach

The system is hierarchically partitioned in two parts:
the part of interest (the "solute") and the rest (the "environment")

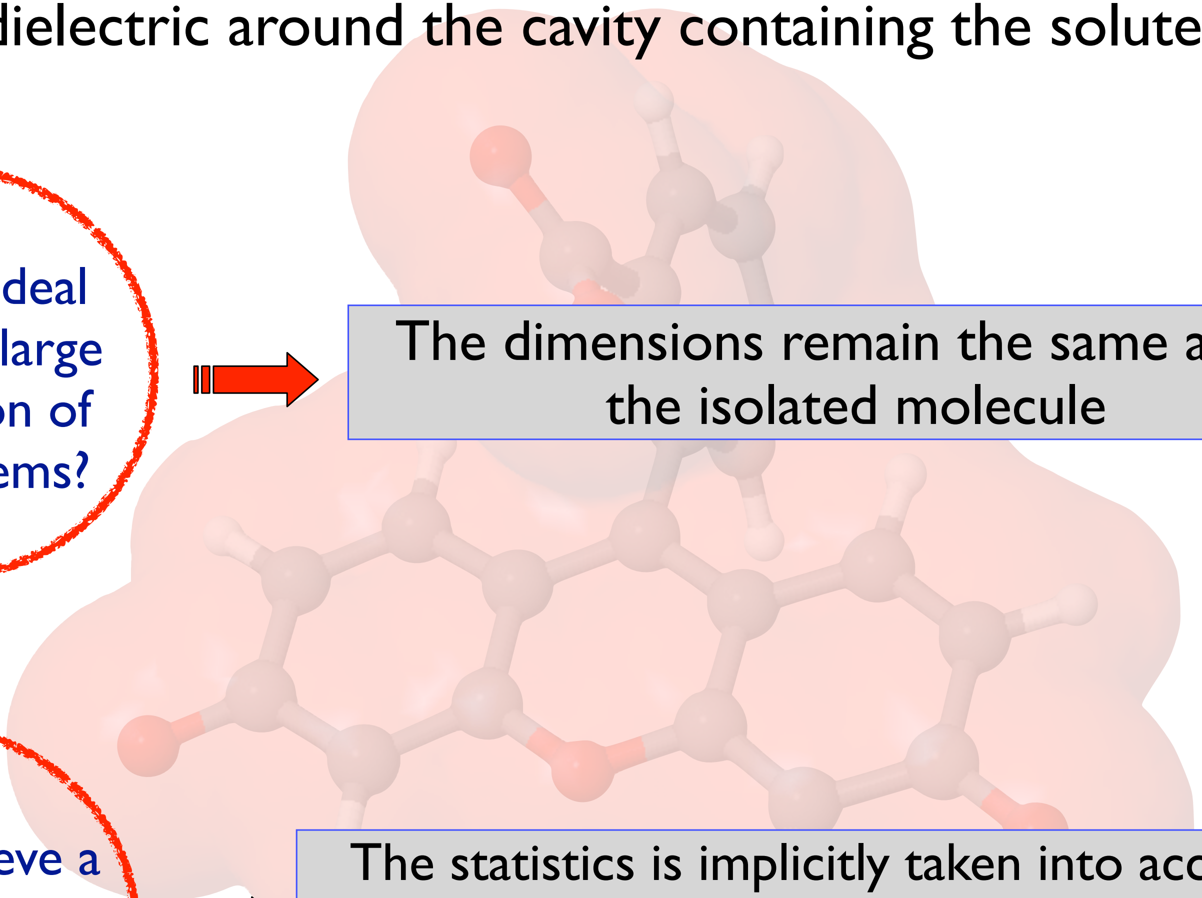


The solute is described at a high level (QM) and the environment at lower level (classical).

Which classical model?

The continuum approach

The environment is replaced by an infinite continuum dielectric around the cavity containing the solute



How to deal with the large dimension of the systems?

The dimensions remain the same as for the isolated molecule

How to achieve a statistically correct description?

The statistics is implicitly taken into account by the use of macroscopic solvent properties (dielectric constant, refractive index, etc)

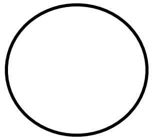
Solvated molecules: continuum approach

Which ingredients?

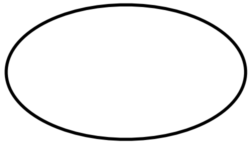
- The definition of the boundary between solute & solvent
- The definition of the interactions between the two parts
- The model used to represent the interactions

The boundary

Simple models



Sphere



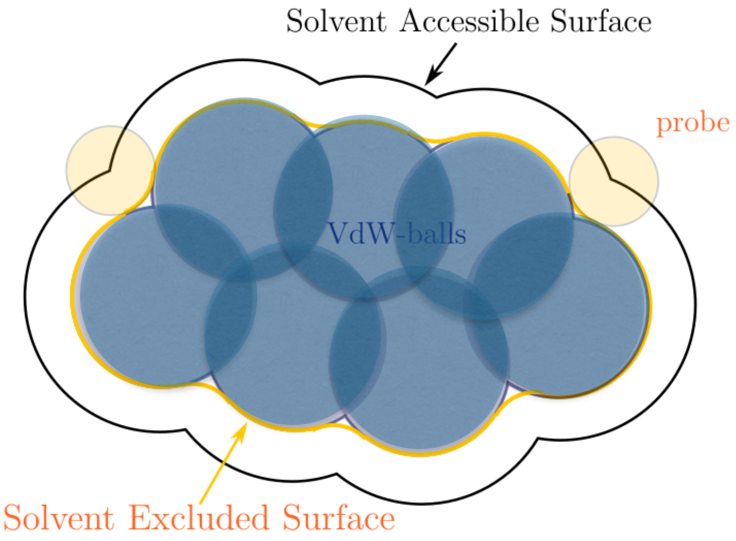
Ellipsoid

NOT ENOUGH!

We need molecular models

1. van der Waals Surface (VWS):

is constructed from the overlapping vdW spheres of the atoms



But we have to consider the dimension of the solvent:

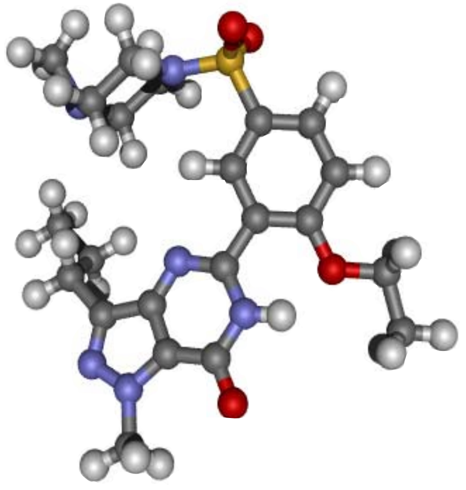
2. Solvent Accessible Surface (SAS):

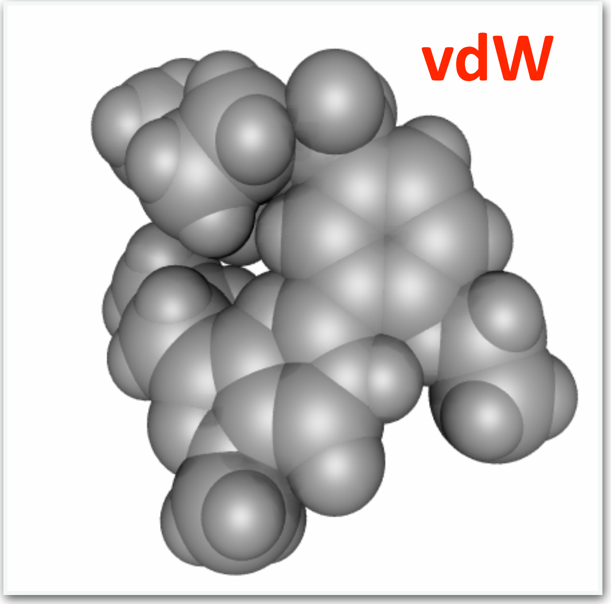
is the surface traced by the center of the probe sphere (the solvent).

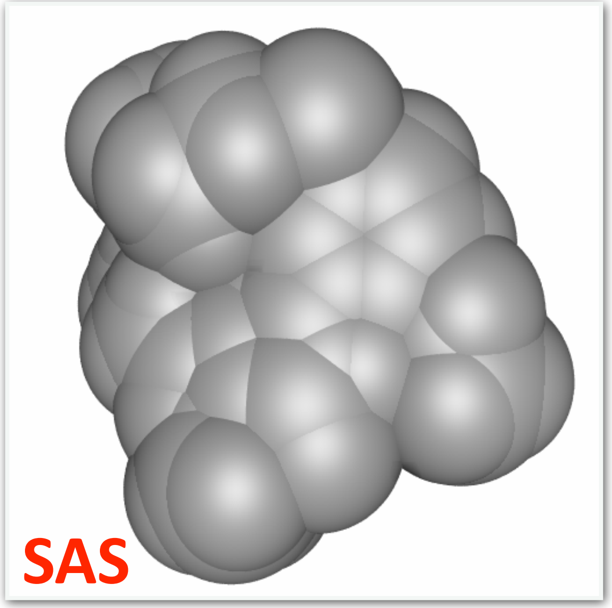
3. Solvent excluded Surface (SES or Connolly):

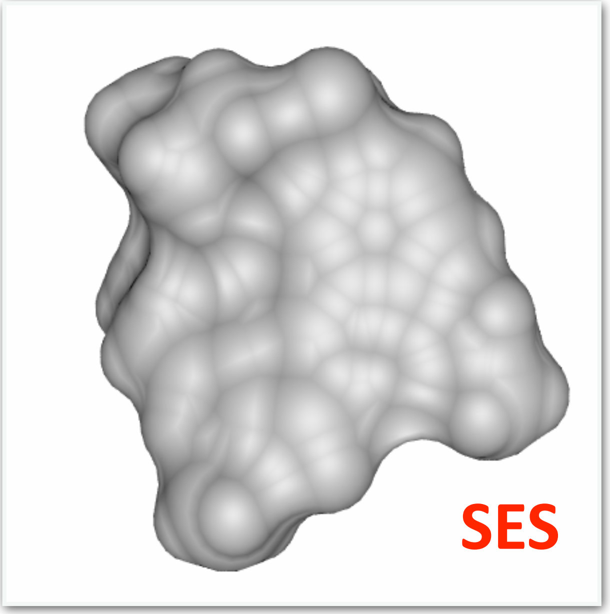
is traced by the inward-facing part of the probe sphere as it rolls on the vdW surface.

An example



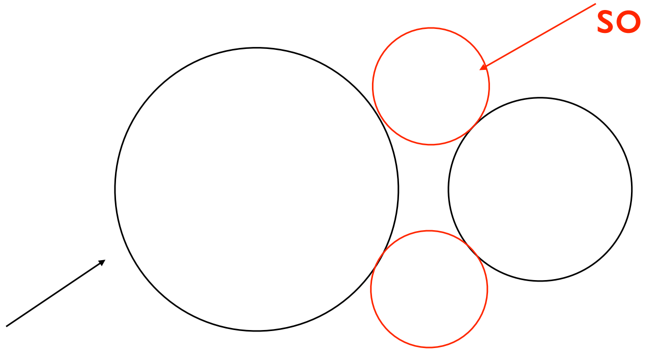






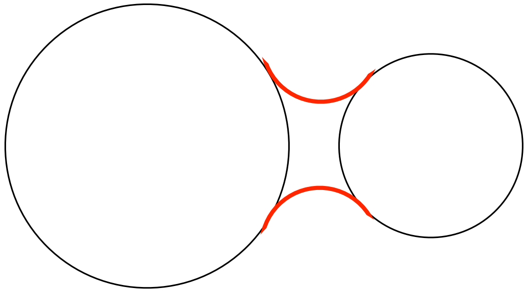
Solvent-excluded surface (SES): a simpler definition

Connolly (1983):



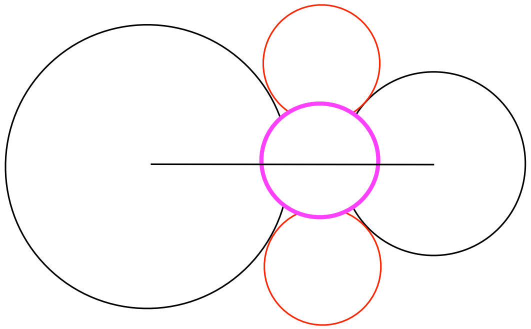
Probe sphere representing the solvent

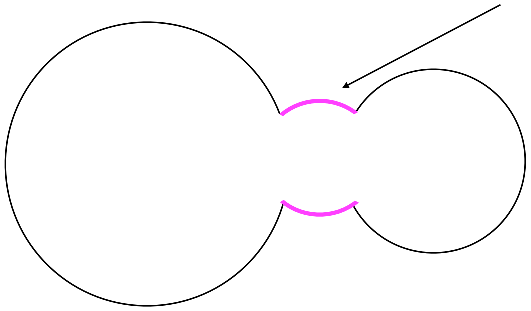
Spheres centered on solute atoms



Reentrant (concave) surface

Alternative approach: GePol (Pascual-Ahuir 1994)





Added sphere not centered on atoms

Convex surface

Easier to implement!

The interactions:
the definition of the energy

Let's consider a solvated molecule

$\Delta G_{sol} \Rightarrow$ the free energy change to transfer a molecule from vacuum to an infinite isotropic solution.

$$\Delta G_{sol} = W(\mathrm{M/S}) + \Delta G_{mm}$$

work necessary to "build up" the solute M in the solvent S, also called the coupling work of M with S.

molecular motion correction:
it results from changes in molecular motions on going from gas to solution phase

The coupling work W

We introduce a partition in terms of different interactions

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

Cavitation term: work required to create the cavity

Electrostatic term

van der Waals term: dispersion & repulsion

Non electrostatic Contributions

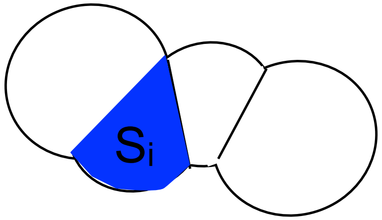
An “imaginary” process

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

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

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

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

The effects of an applied field

Electric Field → Induced dipole

Microscopically
(atoms & molecules)

$$\vec{E} \Rightarrow \vec{\mu} = \alpha \vec{E}$$

Electric Field → Polarization

Macroscopically

$$\vec{E} \Rightarrow \vec{P} = \chi \vec{E}$$

electric susceptibility

$$\chi = \frac{\varepsilon - 1}{4\pi}$$

dielectric constant or permittivity

Solute-solvent Electrostatic interactions

Historically, two are the milestones:

- Born Model (1920)

- Onsager Model (1936)

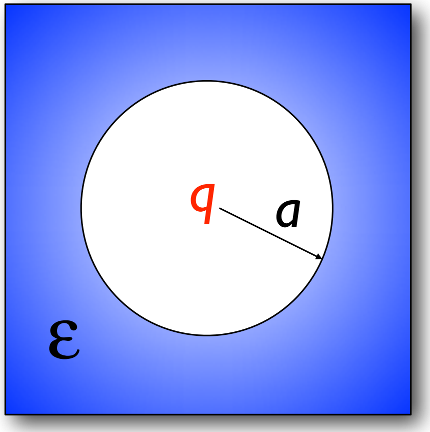
Born model

Electrostatic component of the free energy of solvation for placing a point charge (*q*) in a spherical cavity inside the dielectric.

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

Sphere radius a

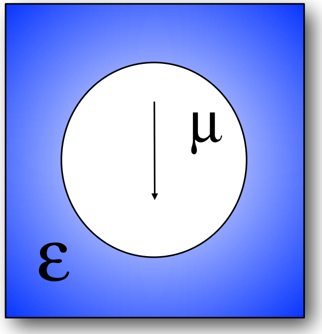
Dielectric constant of the solvent



Onsager model

When a molecule with a permanent dipole μ is surrounded by a solvent, the electric field produced by the permanent dipole polarizes it.

A possible model:
a dipole at the center of a spherical cavity inside a dielectric.



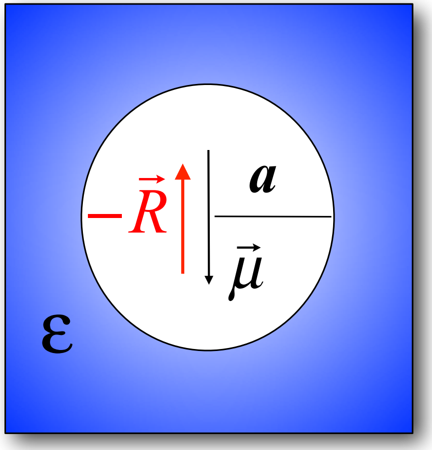
The field of the dipole polarizes the dielectric, and the resulting polarization gives rise to a field at the dipole: **the reaction field R**

$$\vec{R} = f\,\vec{\mu}$$

f is the reaction field factor

Onsager, L. Electric Moments of Molecules in Liquids. *J Am Chem Soc* **58**, 1486–1493 (1936).

Onsager model



$$\phi_{in} = \frac{\vec{\mu}\cdot\vec{r}}{r^3} - \vec{R}\cdot\vec{r}$$

Electrostatic potential inside the cavity

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

Reaction field of the solvent

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

Boundary conditions

$$\left(\phi_{in}\right)_{r=a} = \left(\phi_{out}\right)_{r=a}$$

$$\left(\frac{d}{dr}\phi_{in}\right)_{r=a} = \varepsilon\left(\frac{d}{dr}\phi_{out}\right)_{r=a}$$

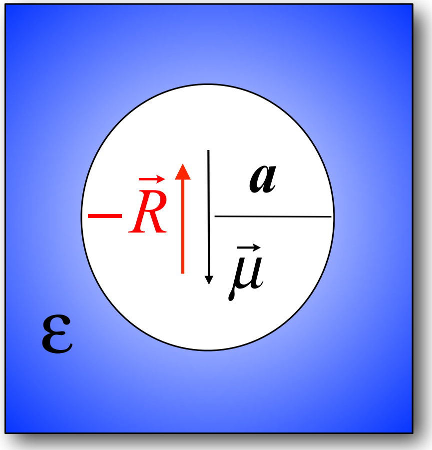
$$\phi_{out} = \frac{\vec{\mu}^*\cdot\vec{r}}{\varepsilon r^3}$$

Electrostatic potential outside the cavity

$$\vec{\mu}^* = \frac{3\varepsilon}{2\varepsilon+1}\vec{\mu}$$

External dipole moment

The Reaction field



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

Reaction field of the solvent

Work done in assembling the dipole μ within the dielectric

$$\frac{1}{2}\vec{R}\cdot\vec{\mu}$$

Electrostatic free energy of solvation

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

A more general strategy

Some electrostatics

In the linear response regime

Electric Field $\vec{E}$ → Polarization $\vec{P} = \chi \vec{E}$

↳ Displacement $\vec{D} = \vec{E} + 4\pi \vec{P} = \varepsilon \vec{E}$

1. Gauss' law: the integral of the displacement flux over a closed surface (Γ) equals the enclosed charge

$$\oint_{\Gamma} \vec{D} \cdot \vec{n}\, d\vec{s} = 4\pi \int_{V} \rho\, dv$$

2. Divergence theorem: the integral of a flux over a closed surface equals the enclosed divergence

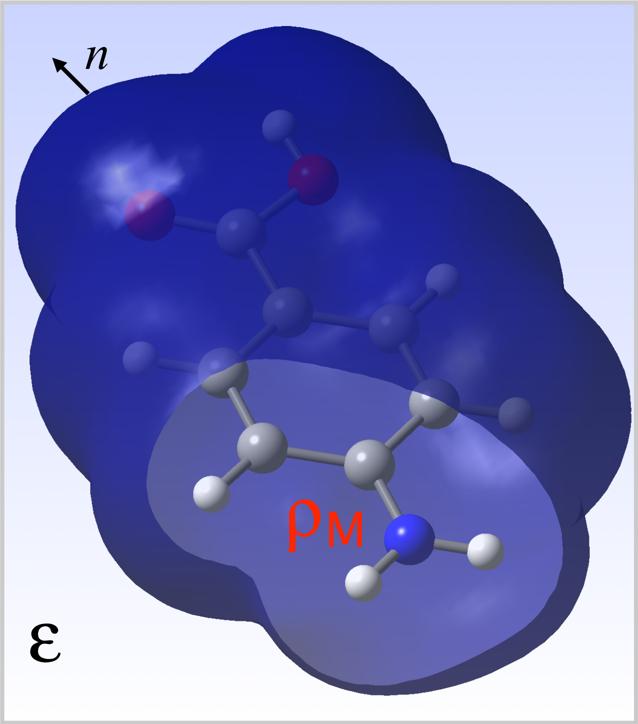
$$\oint_{\Gamma} \vec{D} \cdot \vec{n}\, d\vec{s} = \int_{V} \vec{\nabla} \cdot \vec{D}\, dv$$

1 + 2 :

$$\vec{\nabla} \cdot \vec{D}(\vec{r}) = \vec{\nabla} \cdot \left[\varepsilon(\vec{r}) \vec{E}(\vec{r}) \right] = 4\pi\rho(\vec{r})$$

The molecular problem

A charge density ρ_M (the molecular solute) inside a cavity within a continuum dielectric described by its permittivity ε (the solvent)



The electrostatic potential *V* has to satisfy Poisson and Laplace equations inside and outside the cavity (together with the proper boundary conditions)

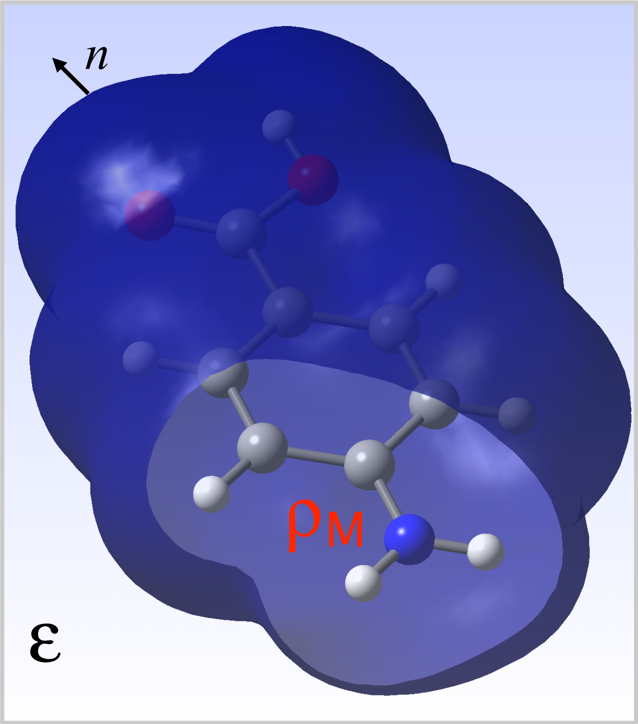
$$\begin{cases} -\nabla^2 V = 4\pi\rho_M & \text{inside the cavity: } \varepsilon=1 \\ -\varepsilon\nabla^2 V = 0 & \text{outside the cavity: } \rho_M=0 \end{cases}$$

$+$

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 solution



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:

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

Which form for the reaction potential V_R ?

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

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

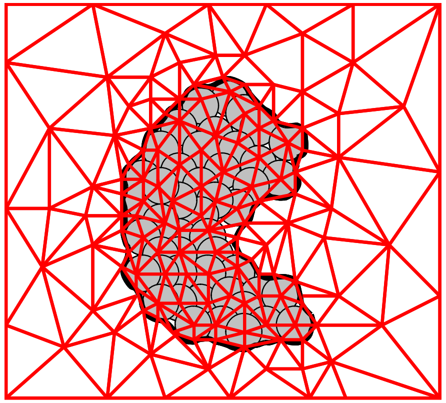
Partial Differential Equations

The Boundary Element Method

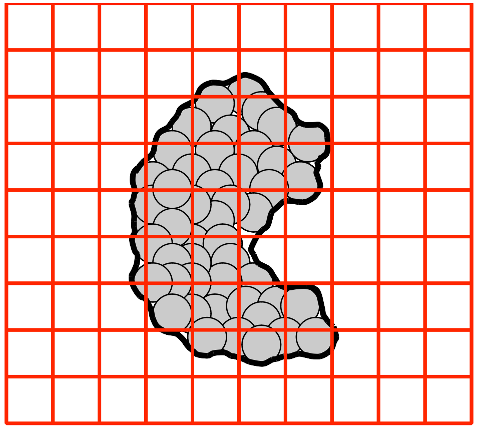
The boundary element method (BEM) is derived through the discretization of an integral equation that is mathematically equivalent to the original partial differential equation (PDE).

The advantages in the boundary element method arises from the fact that only the boundary (or boundaries) of the domain of the PDE requires sub-division.

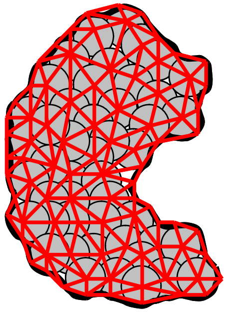
In the finite element method (FEM) or finite difference method (FDM) the whole domain of the PDE requires discretization.



FEM



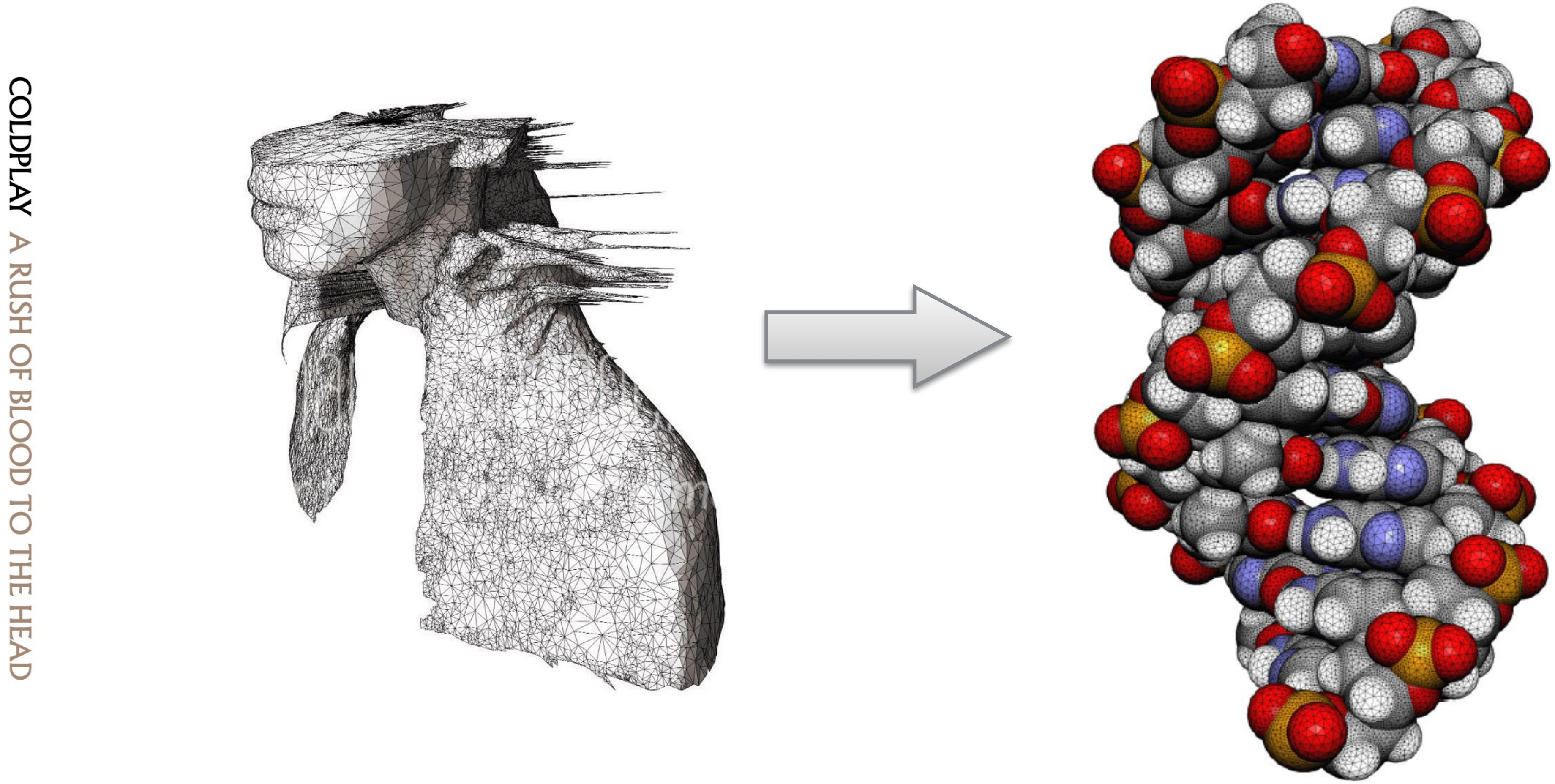
FDM



BEM

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

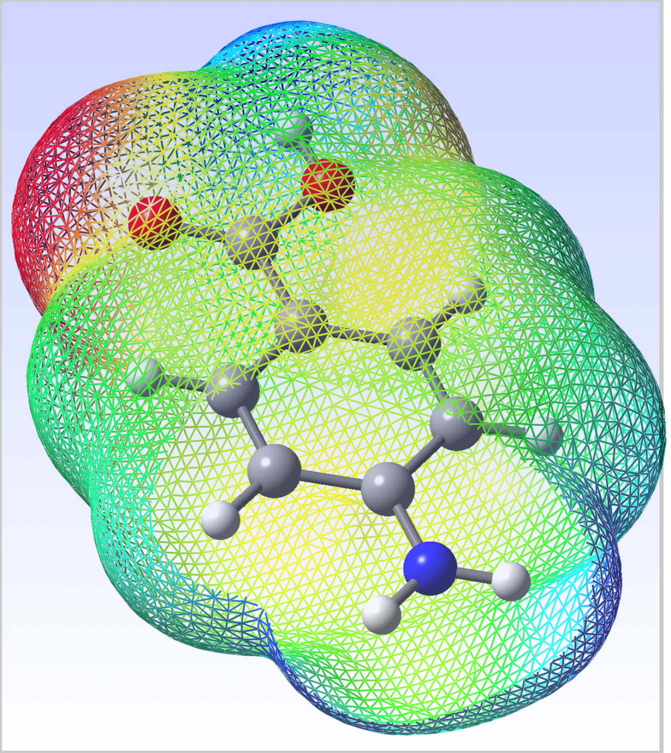
Boundary element method:
The mesh



The BEM strategy

The Apparent Surface Charge

1. Construction of the molecular cavity
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

$$q^{ASC}\left(\vec{s}_i\right)=a_i\sigma^{ASC}\left(\vec{s}_i\right)$$

The BEM strategy
The Apparent Surface Charge

Apparent surface charges

$$q^{ASC}\left(\vec{s}_i\right)=a_i\sigma^{ASC}\left(\vec{s}_i\right)$$

Reaction potential

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

Electrostatic interaction

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

Apparent surface charges

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

Which **σ**?

The original formulation: DPCM

Solvent polarization vector is:

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

At the boundary of two regions *i* and *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)

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

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

The Conductor-like Screening Model (COSMO)

A conductor (infinite permittivity, ε =∞) 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 S

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

Conductor
apparent charge

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

$$\sigma^{CPCM} = \frac{\varepsilon - 1}{\varepsilon + 0.5}\sigma^C$$

The conductor-like model is the DPCM limit for ε→∞

i.e. **very polar solvents**: practically, it is a good approximation for ε ≥ 5

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

Integral Equation Formalism: IEFPCM

Linear differential operator

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

inside the cavity: ε=1

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

outside the cavity: ρ_M=0

Green Functions

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

Linear
differential
operator

$$L_x u(x) = f(x)$$

The Green function associated to the operator L_x is (by definition)

$$L_x\, G(x,y) \;=\; \delta(x-y)$$

The solution can be written as:

$$u(x) \;=\; \int_{-\infty}^{+\infty} G(x,y)\; f(y)\; dy$$

in fact:

$$\begin{aligned} L_x\, u(x) \;&=\; \int_{-\infty}^{+\infty} L_x[G(x,y)]\; f(y)\; dy \\ &=\; \int_{-\infty}^{+\infty} \delta(x-y)\; f(y)\; dy \;=\; f(x) \end{aligned}$$

Integral Equation Formalism: IEFPCM

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

inside the cavity: ε=1

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

outside the cavity: ρ_M=0

⬇

$$L_{in} \Leftrightarrow G_{in}(x,y) = \frac{1}{4\pi\,|x-y|}$$

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

Green Functions

IEFPCM: a very general formulation

Potential operator
$$\hat{S}_{in/out} f(x) = \int_\Gamma G_{in/out}(x,y) f(y)\, dy$$

Normal field operator
$$\hat{D}_{in/out} f(x) = \int_\Gamma \left[\varepsilon_{in/out} \nabla G_{in/out}(x,y)\cdot n(y)\right] f(y)\, dy$$

$$\hat{D}^*_{in/out} f(x) = \int_\Gamma \left[\varepsilon_{in/out} \nabla G_{in/out}(x,y)\cdot n(x)\right] f(y)\, dy$$

G$_{in/out}$:
Green Functions

$$\boxed{\hat{A}\sigma^{IEFPCM} = -\hat{R}V_M}$$

$$\hat{A} = \left(2\pi\hat{I} - \hat{D}_{out}\right)\cdot \hat{S}_{in} + \hat{S}_{out}\cdot\left(2\pi\hat{I} + \hat{D}^*_{in}\right)$$

$$\hat{R} = \left[\left(2\pi\hat{I} - \hat{D}_{out}\right) - \hat{S}_{out}\hat{S}_{in}^{-1}\left(2\pi\hat{I} - \hat{D}_{in}\right)\right]$$

It can be applied to different environments:

we have only to change the function G_{out} (outside the cavity)

IEFPCM: a very general formulation

- **Ionic solutions: Linearized PB equation**

$$-\vec{\nabla}\cdot\left(\varepsilon\vec{\nabla}V(\vec{r})\right)+\kappa^2 V(\vec{r})=4\pi\rho(\vec{r})$$

$$\kappa^2=\frac{8\pi e^2 I}{\varepsilon kT}$$

ionic strength

$$I=\frac{1}{2}\sum_i z_i^2 c_i$$

$$G_{out}(x,y)=\frac{\exp\left(-\kappa|x-y|\right)}{4\pi\varepsilon|x-y|}$$

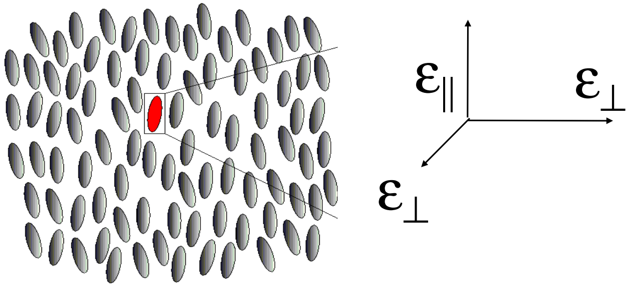
- **Anisotropic dielectric**:

Tensorial permittivity

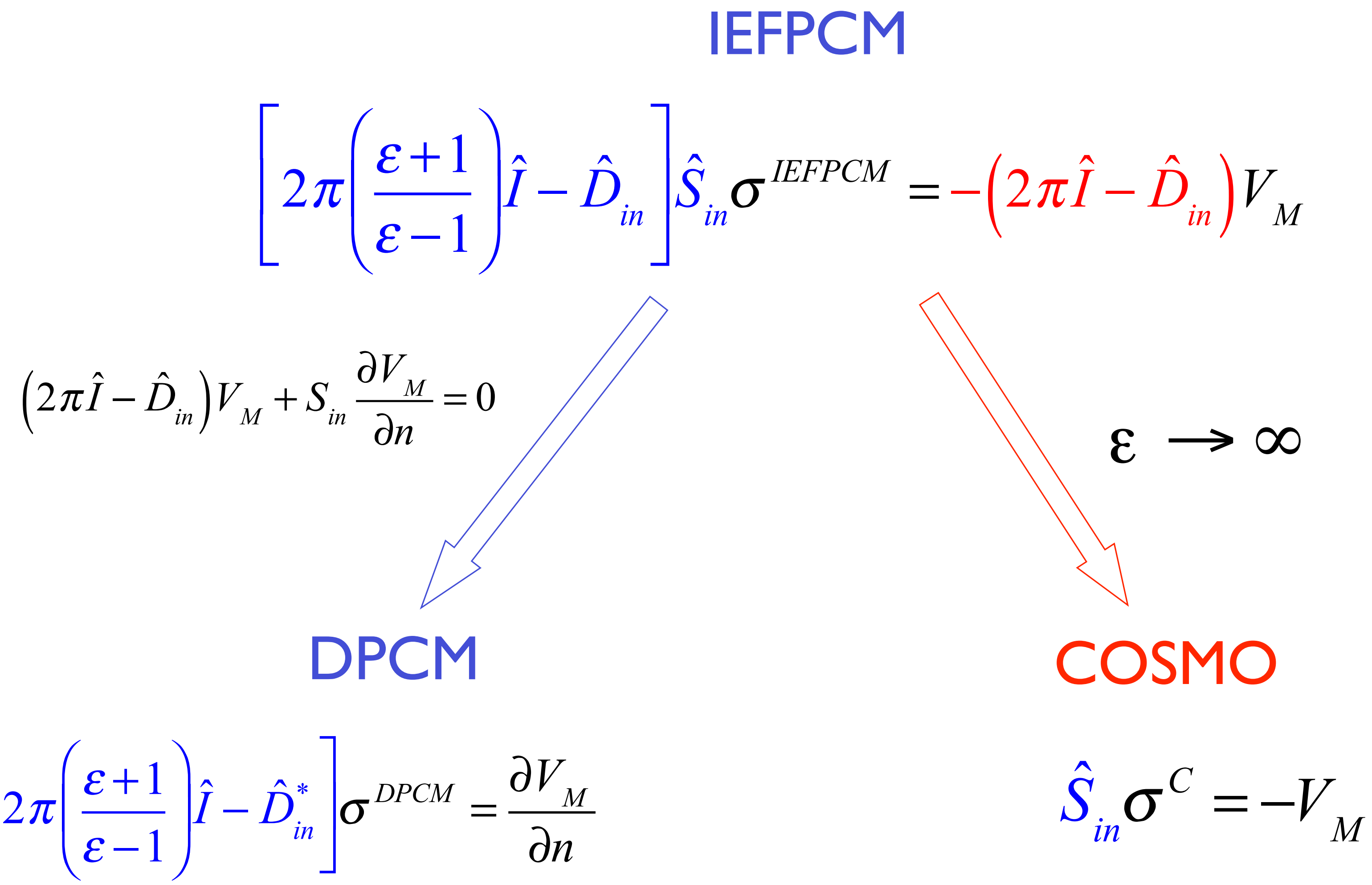
$$\boldsymbol{\varepsilon}=\begin{pmatrix}\varepsilon_{xx} & 0 & 0\\ 0 & \varepsilon_{yy} & 0\\ 0 & 0 & \varepsilon_{zz}\end{pmatrix}$$

$$G_{out}(x,y)=\frac{1}{4\pi\sqrt{\det[\boldsymbol{\varepsilon}]}\sqrt{\left[\boldsymbol{\varepsilon}^{-1}(x-y)\right]\cdot(x-y)}}$$

For example: a nematic liquid crystal



The relations between the ASC models



IEFPCM

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

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

$$\varepsilon \longrightarrow \infty$$

DPCM

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

COSMO

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

Discretization of the surface charge

$$\hat{T}(\varepsilon)\sigma^{ASC} = -\hat{R}\begin{cases} \vec{E}_M \cdot \vec{n} & \text{DPCM (R=1)} \\ V_M & \text{COSMO (R=1) \& IEFPCM} \end{cases} \quad \Longleftrightarrow \quad q^{ASC}\left(\vec{s}_i\right) = a_i\sigma\left(\vec{s}_i\right)$$

$$\mathbf{T}(\varepsilon)\mathbf{q}^{ASC} = -\mathbf{R}\mathbf{f}_M$$

Collects electrostatic potential (or field) produced by the solute on the surface elements:

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

There are basically two strategies to solve the system:

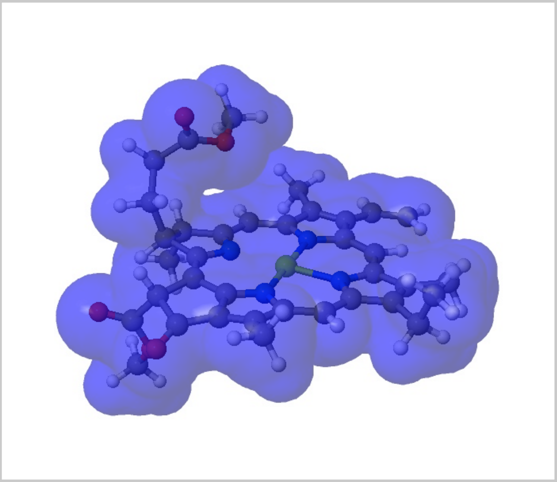
- Inverting **T** by a direct method

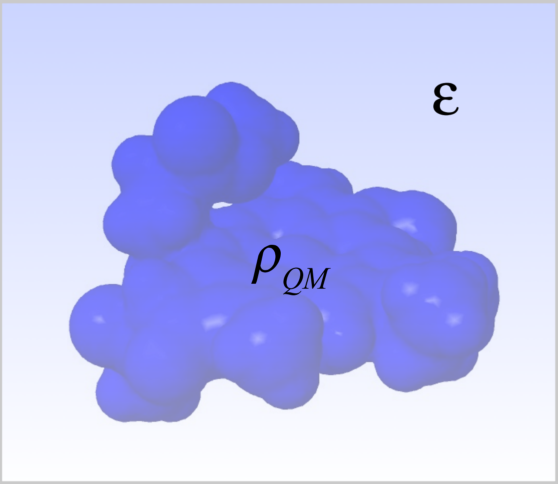
$$\mathbf{q}^{ASC} = -\mathbf{T}(\varepsilon)^{-1}\mathbf{R}\mathbf{f}_M = \mathbf{Q}\mathbf{f}_M$$

- By an iterative method

QM/continuum: a step by step strategy

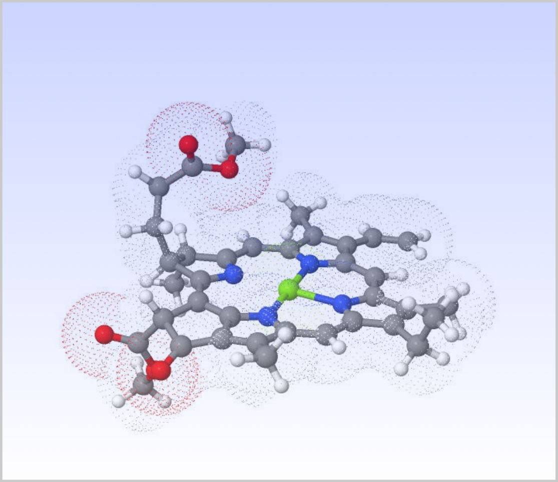
1) The definition of the boundary: the molecular cavity

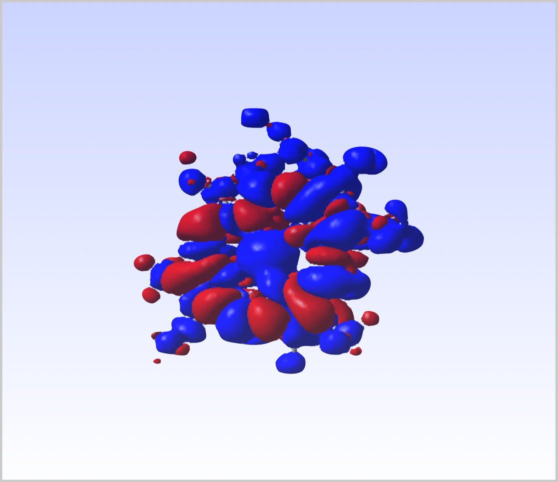




2) The electrostatic problem: the Poisson equation

3) The numerical solution: the surface mesh





4) The QM problem

The QM/continuum approach

The Self-Consistent Reaction Field (SCRF) method

The effective Hamiltonian

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

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

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

Solute electrostatic potential on the surface cavity:

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

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

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

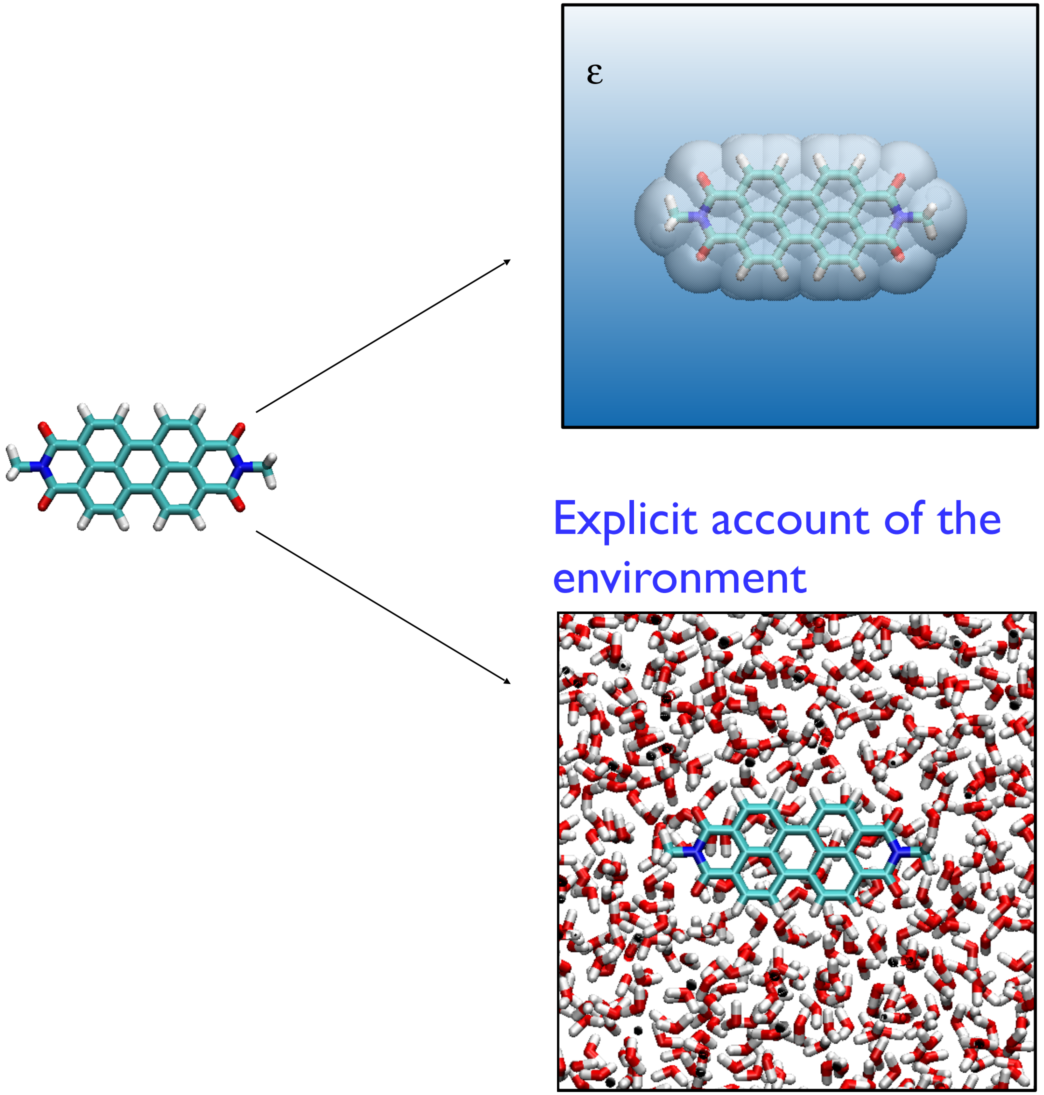
solvent
operator

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

$$\mathbf{q}^{ASC} = \mathbf{QV}(\rho) \quad \Rightarrow \quad \hat{X}^{ASC}(\rho) = \sum_{i} q_{i}^{ASC}(\rho)\hat{V}_{i}$$

It changes at
each iteration of
the SCF cycle

An alternative to continuum models



Continuum solvation models

Explicit account of the environment

The atomistic approach

All molecules are treated explicitly

Can we maintain a physical realism together with a computationally feasible description?

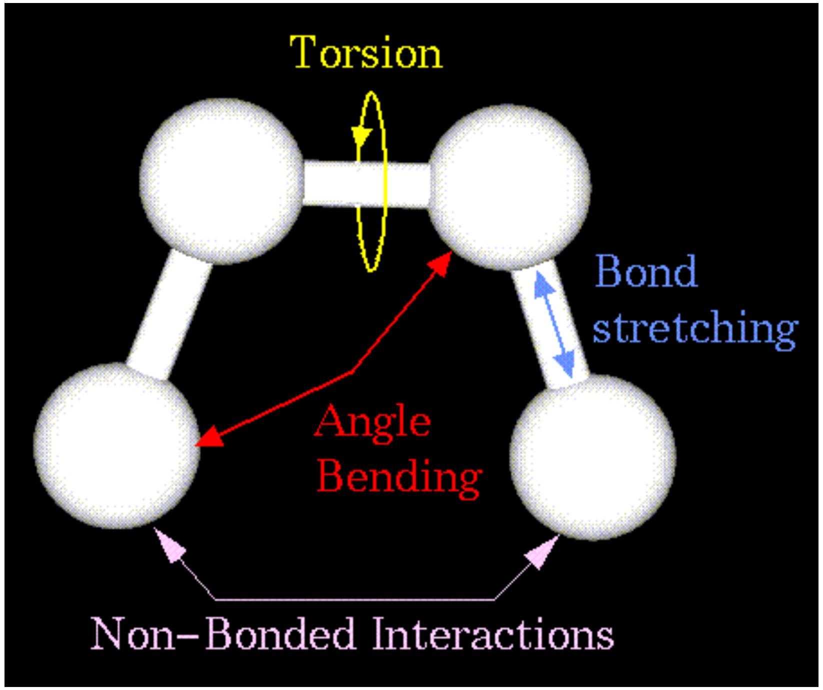
YES!

Through Molecular Mechanics (MM)

Molecular Mechanics

Atoms as spheres and bonds as springs, interactions between particles in terms of mathematical functions derived from classical mechanics.

Energy = Bonding terms + Non-Bonded Interaction Energy

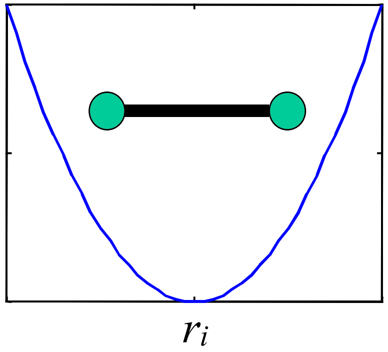


The energy function together with the data (parameters) required to describe the behavior of different kinds of atoms & bonds, are called a force-field.

Energy functions for bonding terms

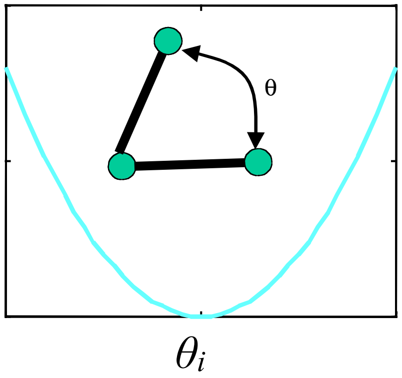
Stretching

$$\frac{1}{2}k_i^b(r_i - r_{i0})^2$$



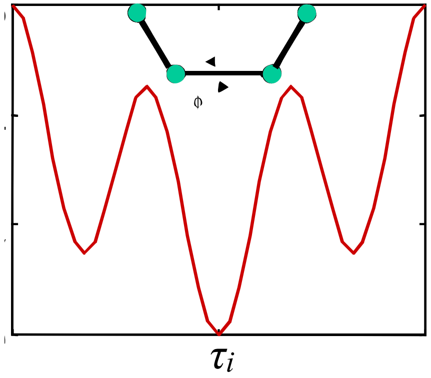
Bending

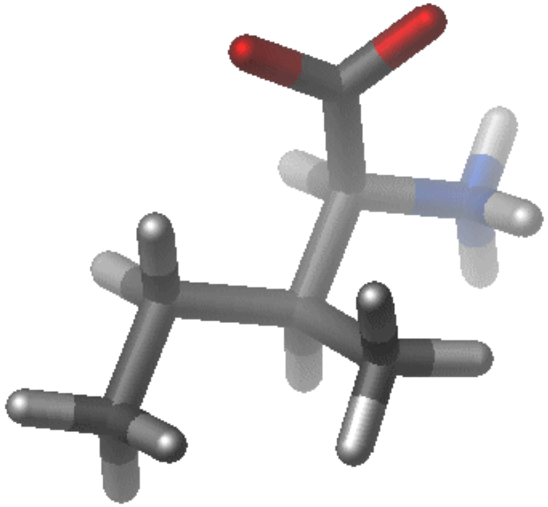
$$\frac{1}{2}k_i^a(\theta_i - \theta_{i0})^2$$



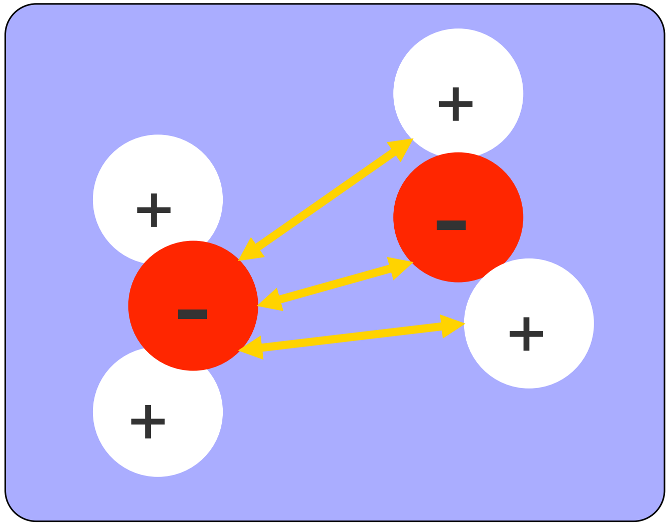
Torsion

$$\frac{1}{2}\sum_j A_j[1+(-1)^{j+1}\cos(j\tau_i+\phi)]$$





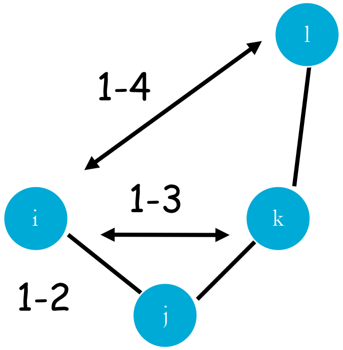
Non bonded terms: electrostatic interactions



Atoms as point-charges

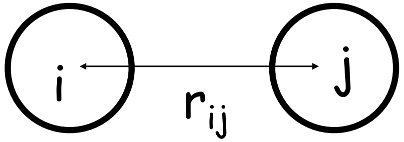
$$E_{es} = \sum_{i>j} \frac{q_i q_j}{\varepsilon_{ij} R_{ij}}$$

$$\varepsilon_{ij} = \begin{cases} \infty & \text{if i and j are bonded (1,2) or bonded to the same atom (1,3)} \\ 3.0 & \text{if i and j are separated by three bonds (1,4)} \\ 1.5 & \text{otherwise} \end{cases}$$



van der Waals interactions: repulsion & dispersion

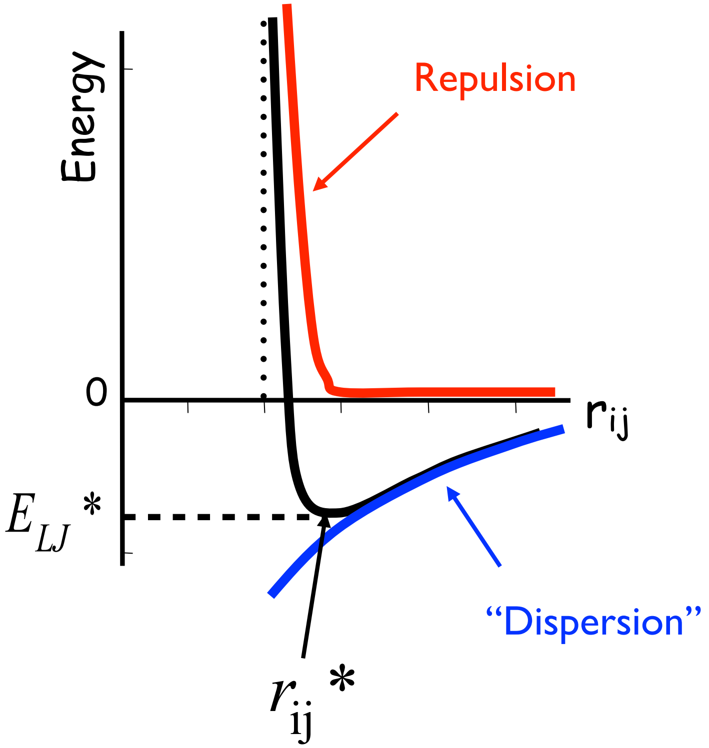
Lennard-Jones Potential



$$E_{LJ} = \sum_{i<j} 4\varepsilon_{ij}\left(\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right)$$

repulsion

dispersion



$$\frac{dE_{LJ}}{dr_{ij}} = 0 \quad \Rightarrow \quad \begin{aligned} r_{ij}^* &= 2^{1/6}\sigma_{ij} \\ E_{LJ}^* &= -\varepsilon_{ij} \end{aligned}$$

Ingredients of the force field

- **“atom type“**

The concept of "atom type" substitutes that of “atom” and allows the Force Field to correctly reproduce molecular behaviors & properties and to be transferable.

These are atoms similar enough in the physical and chemical sense for them to be the same in different molecules, allowing them to be treated as identical in a MM calculation

The atom types are defined according to:

- Ibridization
- Atomic charge
- Connectivity

Numerical parameters

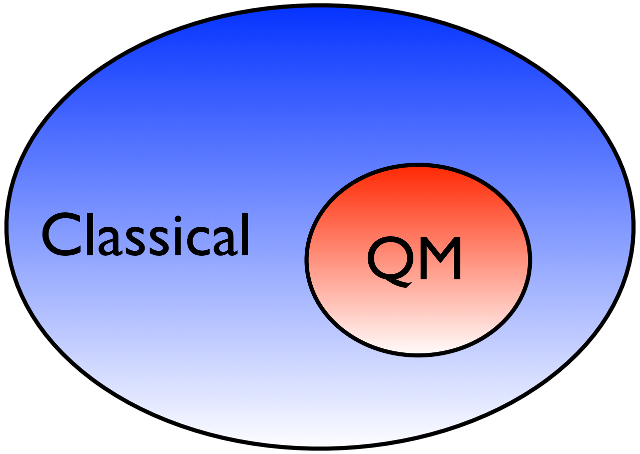
- **force constants**
- **Lennard-Jones parameters**
- **partial atomic charges**

QM/MM:

subtractive vs. additive models

- **subtractive**: several layers:
  double counting on the regions is subtracted

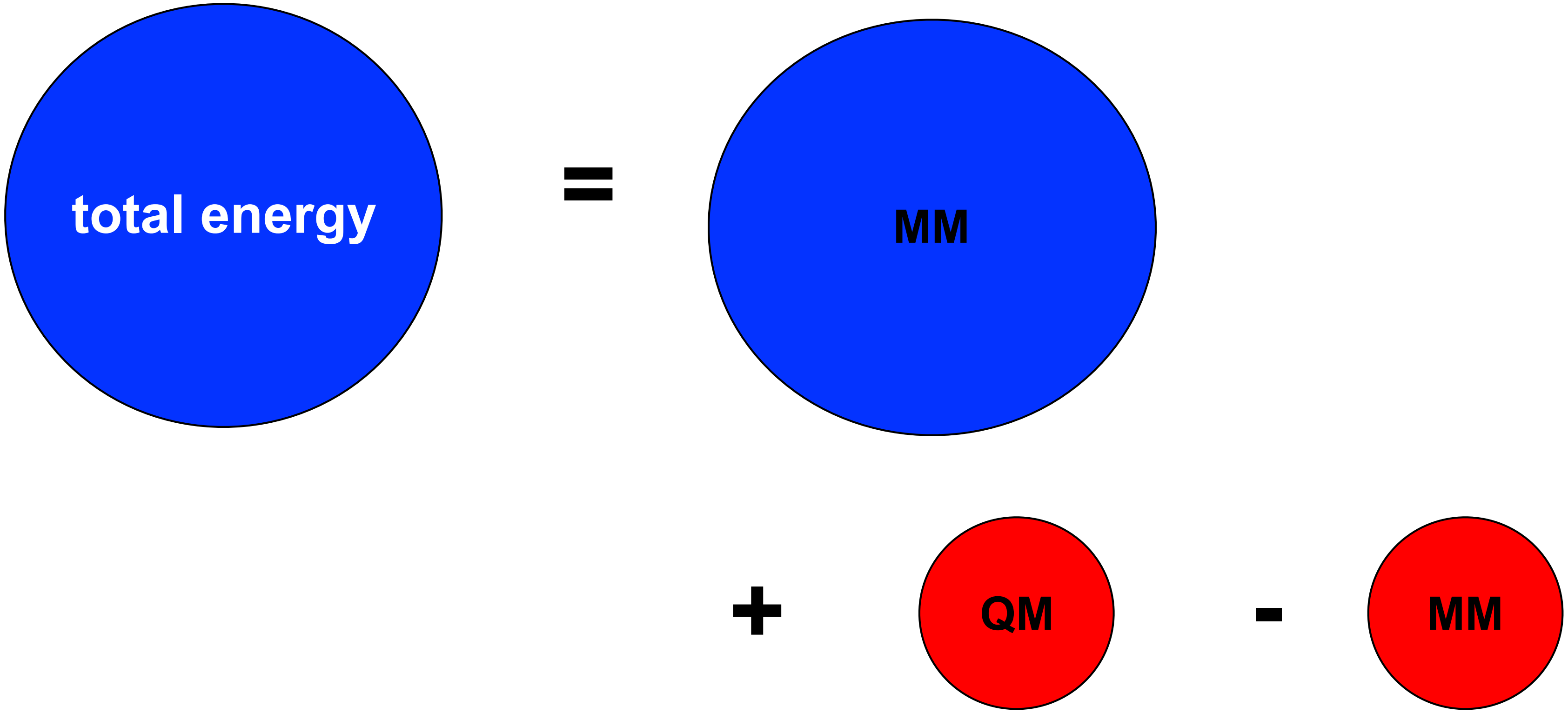
- **additive**: different methods in different regions +
  interaction between the regions



Subtractive QM/MM

Subtractive QM/MM schemes require

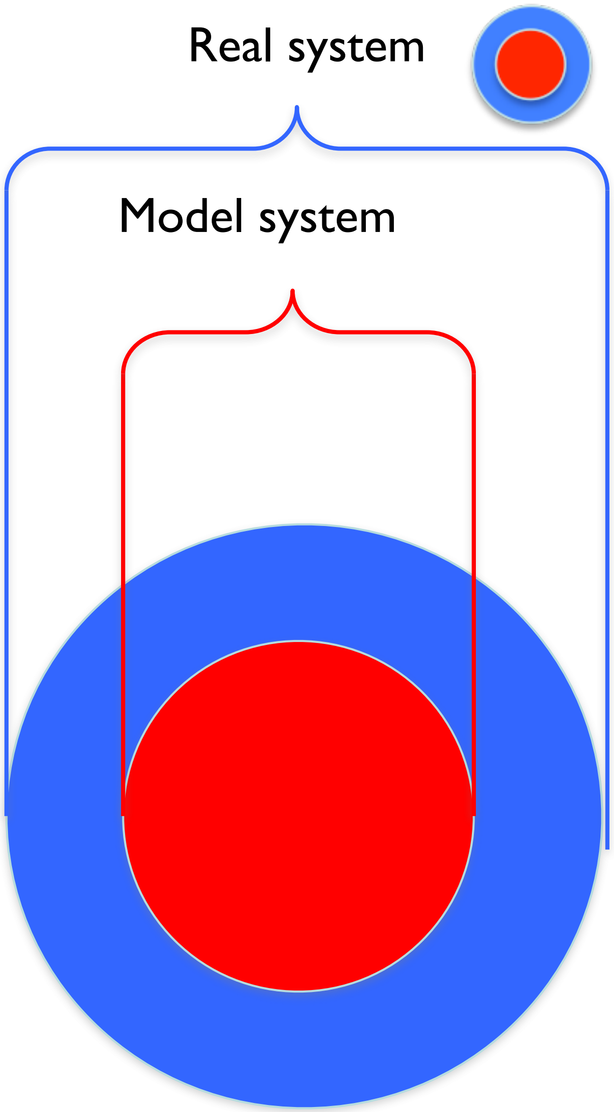
1) a MM calculation on the entire system;
2) a QM calculation on the inner subsystem;
3) a MM calculation on the inner subsystem.



No explicit QM–MM coupling terms are needed; the standard QM & MM procedures can be used without any modification.

The ONIOM Method

(Own N-layered Integrated Molecular Orbital and Molecular Mechanics)



Developed initially in the group of K. Morokuma.

First layer: the subsystem of interest (the QM part in additive QM/MM).
Use the High-level method

Second layer: the rest.
Use the Low-level method

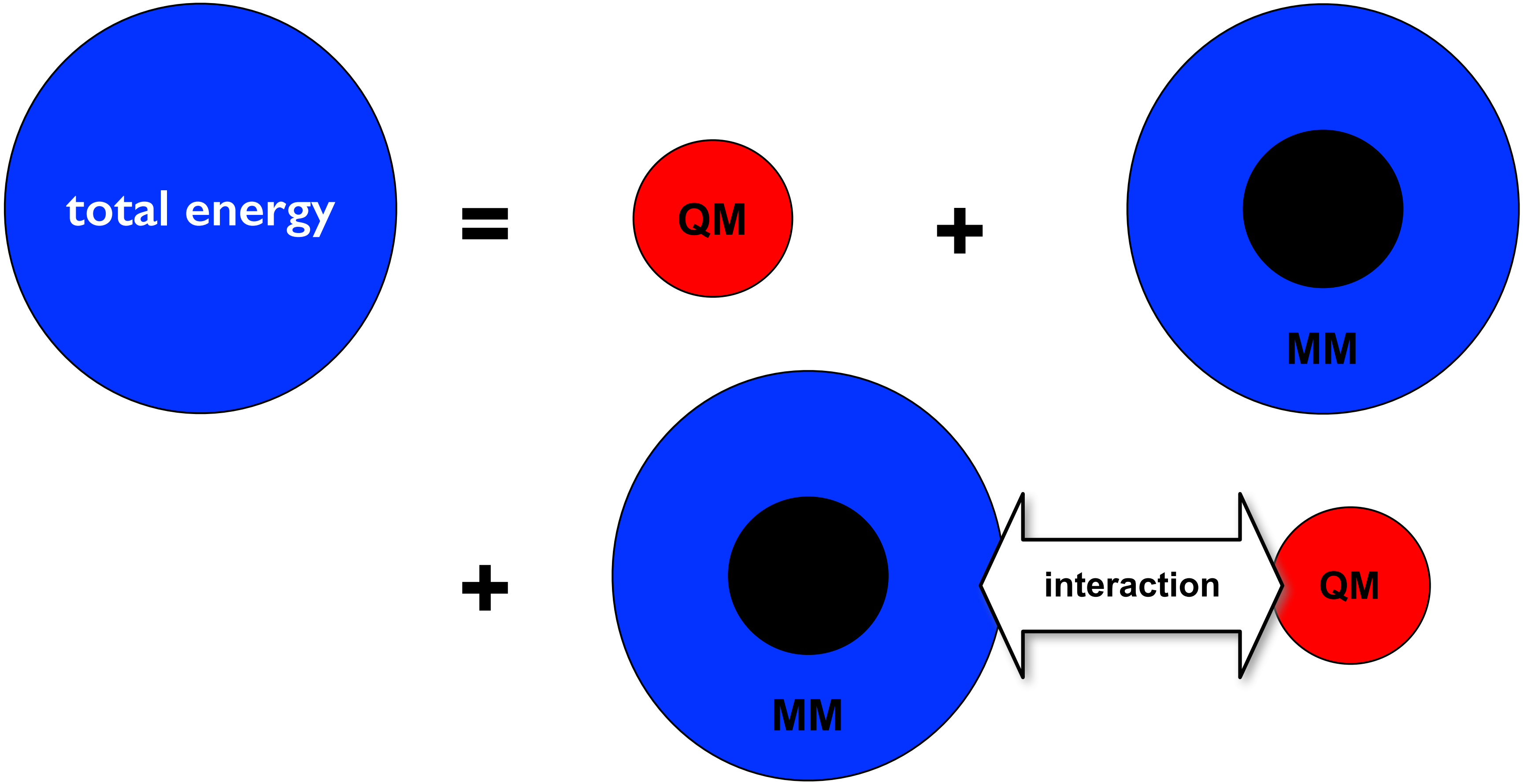
ONIOM energy

$$E_{ONIOM} = E_{real}^{low} - E_{model}^{low} + E_{model}^{high}$$

Additive QM/MM

The total Hamiltonian

$$H_{eff} = H_{QM} + H_{MM} + H_{QM/MM}^{\text{int}}$$



The interaction term

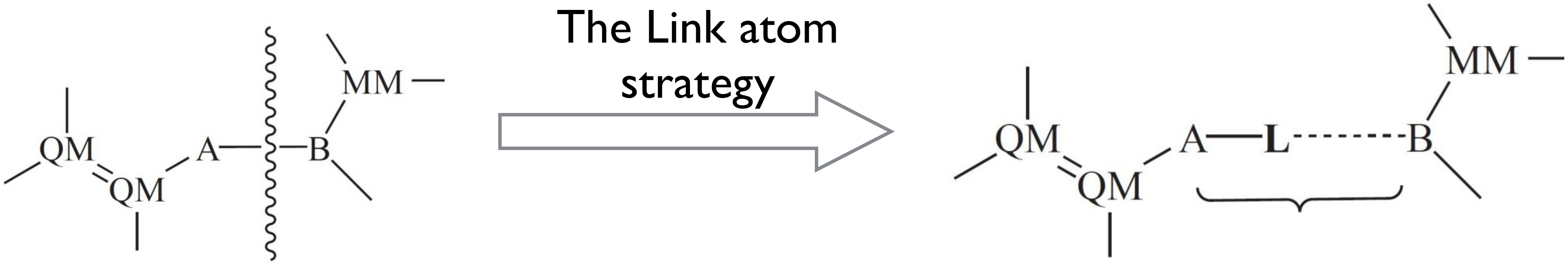
Nonbonding:

- Electrostatics
- VdW

$$\hat{H}_{QM/MM} = \hat{H}^{elec}_{QM/MM} + \hat{H}^{vdW}_{QM/MM} + \hat{H}^{bond}_{QM/MM}$$

Bonding

Covalent Bonds across QM & MM Regions

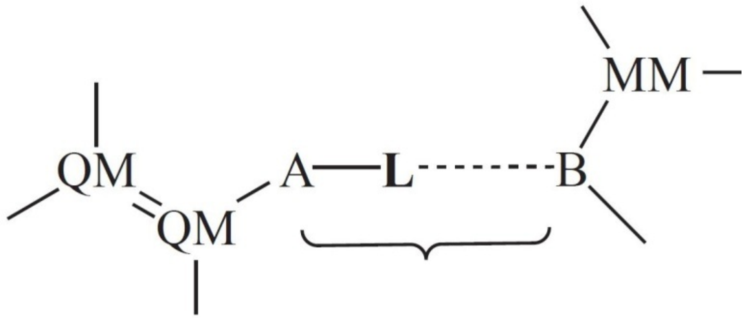

The Link atom strategy

An additional atomic center L that is not part of the real system is introduced. It is covalently bound to the QM atom A and saturates its free valence.

This link atom L is in most cases a hydrogen atom, but any monovalent atom or group might be used.

QM calculations are performed on an electronically saturated system consisting of the inner subsystem and the link atom(s).
The bond A-B is described at the MM level.

Link atoms



Problem 1:

Each link atom generates three artificial structural degrees of freedom not present in the real system.

Common solution

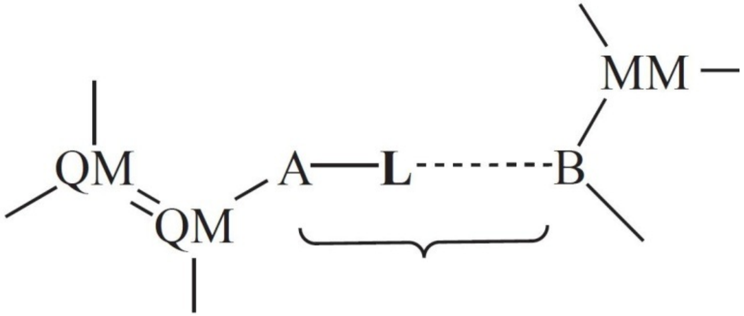
The position of the link atom becomes a function of the positions of A & B.

The link atom L is placed along A–B, and the distance A–L is related to the distance A–B by a scaling factor. Exactly three degrees of freedom are removed.

The link atoms appear only in the internal description of the QM/MM coupling scheme, and they are transparent to geometry-optimization or MD algorithms, which only handle the set of independent variables.

The link atoms become force-free; their coordinates in the next geometry or time step are fully determined by the positioning rule, rather than being propagated according to forces acting on them.

Link atoms

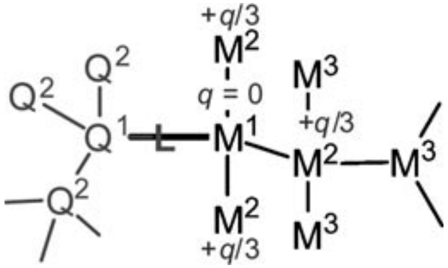


Problem 2:

The link atom is spatially very close to the MM frontier atom B: the point charge on B will tend to overpolarize the QM density in the case of electrostatic or polarized embedding.

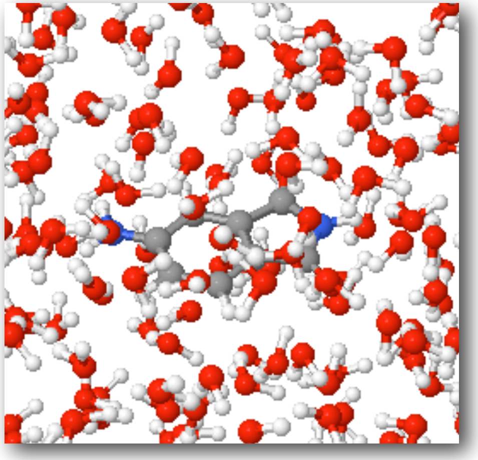
Possible solutions

1)Deletion of the one-electron integrals associated with the link atoms.
2)Deletion of MM point charges in the link region from the Hamiltonian.
3)Shifting/redistribution of the point charges in the link region

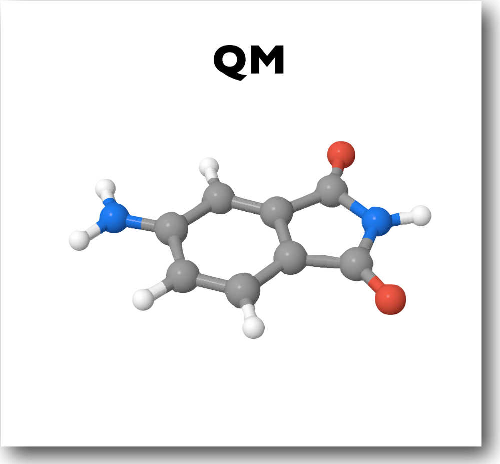


4)“Smearing” the charges close to the QM region by replacing them by (e.g. , Gaussian) charge distributions.

Non bonding terms



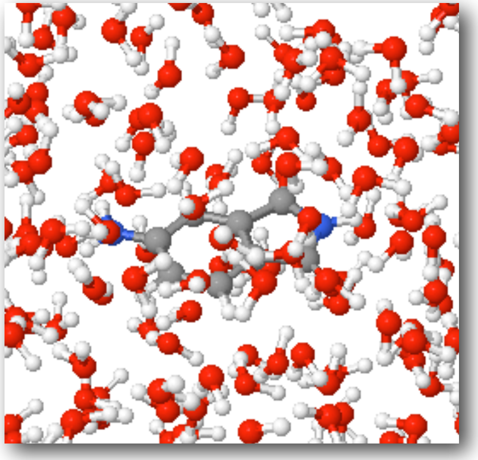
1) Mechanical embedding



- The QM calculation is done in the absence of the MM part.
- The vdW interactions are calculated at MM level
- The electrostatic interactions between the QM and the MM regions are described at MM level: the QM part of the system is replaced with a set of classical charges.

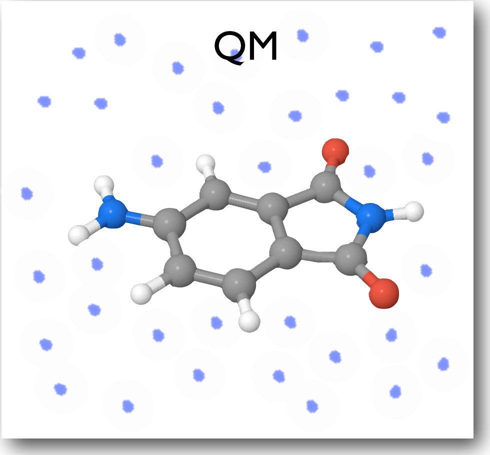
Inaccurate model

Non bonding terms



2) Electrostatic embedding

$$\hat{H}_{QM/MM} = \sum_i q_i \hat{V}_{QM}(r_i) + \sum_{\alpha,M} \left\{ \frac{A_{\alpha M}}{R_{\alpha M}^{12}} - \frac{B_{\alpha M}}{R_{\alpha M}^{6}} \right\}$$

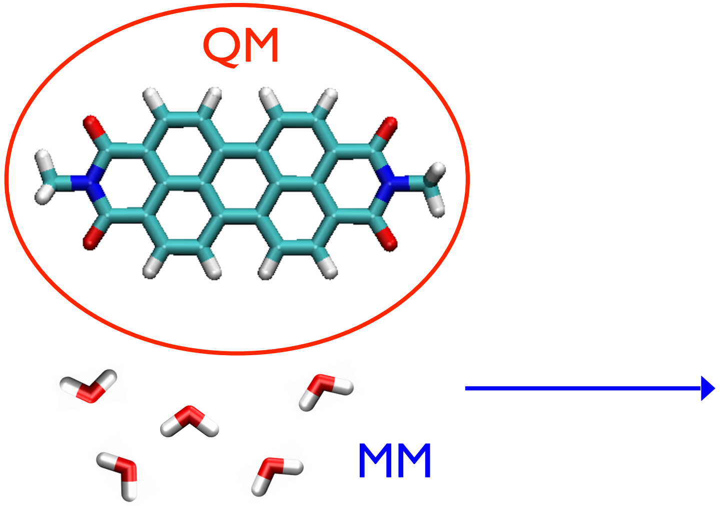


- The vdW interactions are calculated at MM level
- The QM calculation is done in the presence of the MM part: the QM part "feels" the MM part as a distribution of point charges or a multipolar expansion (according to the selected force field)
- The QM part is polarized by the MM part.

More accurate model

Polarizable embedding:

a possible strategy based on induced dipoles



MM atoms represented with point charges & (isotropic) polarizabilities

$$\vec{\mu}_i^{ind} = \alpha_i \vec{E}(r_i) = \alpha_i \left(\vec{E}_{QM}(r_i) + \vec{E}_{MM}(r_i) \right)$$

The induced dipoles

Electric field produced by the QM density & the MM charges

$$\mu_p = \alpha_p \left[\mathrm{E}_p \boxed{- \sum_{q \neq p}^{N} \mathrm{T}_{pq} \mu_q} \right]$$

Electric field produced by all dipoles

$$\vec{E}_{\mu} = \frac{3(\vec{\mu} \cdot \vec{r})\vec{r}}{r^5} - \frac{\vec{\mu}}{r^3}$$

$$T_{pq} = \frac{1}{r_{pq}^3} - \frac{3}{r_{pq}^5} \begin{bmatrix} x^2 & xy & xz \\ yx & y^2 & yz \\ zx & zy & z^2 \end{bmatrix}$$

Polarizabilities

The atomic polarizabilities are determined so to reproduce experimental or calculated molecular polarizabilities.

The additive model

Molecular polarizability reproduced neglecting dipole-dipole interactions. No explicit intramolecular polarization (implicitly included in the parameterization).

The interactive model

Molecular polarizability reproduced considering all dipole-dipole interactions. Explicit intramolecular polarization.

The induced dipoles:
the interactive model

Applequist's model:

standard dipole interaction tensor

This may lead to infinite polarization by the cooperative interaction between two nearby inducible dipoles, resulting in "polarization catastrophe".
The short-range 1-2 and 1-3 interactions are excluded to reduce the potential of "polarization catastrophe".

Thole model:

smeared dipole interaction tensor

This avoids problems due to "polarization catastrophe".

Thole model

Thole proposed distance-dependent screening functions, f_e and f_t

$$\mathrm{T}_{pq} = \frac{f_\mathrm{e}}{r_{pq}^3}\,\mathrm{I} - \frac{3f_\mathrm{t}}{r_{pq}^5}\begin{bmatrix} x^2 & xy & xz \\ yx & y^2 & yz \\ zx & zy & z_2 \end{bmatrix}$$

$$v = r_{pq}/\left[a(\alpha_p\alpha_q)^{1/6}\right]$$

α_p and α_q are the atomic polarizabilities of atoms p and q with distance $r_{pq.}$ *a* (the screening length) is a parameter

In the linear form:

$$\text{if } (v >= 1)\, f_\mathrm{e} = 1.0,\ f_\mathrm{t} = 1.0$$

$$\text{if } (v < 1)\, f_\mathrm{e} = 4v^3 - 3v^4,\ f_\mathrm{t} = v^4$$

In the exponential form

$$f_\mathrm{e} = 1 - \left(\frac{v^2}{2} + v + 1\right)\exp(-v)$$

$$f_\mathrm{t} = 1 - \left(\frac{1}{6}v^3 + \frac{1}{2}v^2 + v + 1\right)\exp(-v)$$

Polarizable QM/classical models

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

an iterative procedure is necessary

It can be solved together with the standard
self-consistent-field problem:

Hartree-Fock or Kohn-Sham (DFT) approach

Self consistent reaction field (SCRF)

Effective Fock or Kohn-Sham operator

$$\hat{F}^{eff} = \hat{F}^{0} + \begin{cases} \hat{X}^{MMpol} \\ \hat{X}^{ASC} \end{cases}$$

new solvent-dependent operators

MMPOL

$$\hat{X}^{MMpol} = \sum_k q_k^{MM} \hat{V}_k - \sum_i \mu_i(\rho) \cdot \hat{E}_i$$

Continuum model (ASC)

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

They change at each SCF iteration

At convergency, solute & solvent are mutually polarized

Alternative polarisable embeddings
(not covered in this lecture)

Drude Model:
It represents the induced dipole at every polarizable atom by two charges of the same magnitude and opposite sign linked by a harmonic spring. The first charge is located at the nucleus of the atom, while the second one is mobile.

Fluctuating Charges:
partial charges are generally assigned on the atomic sites in a molecule, and the charge redistribution in response to the external electric field or conformational change is governed by electronegativity equilibration method (EEM).

Fragment-based methods
(not covered in this lecture)

They can be seen as polarisable embeddings which do not require empirical parameterizations but derive all the terms from QM calculations on fragments.

Effective Fragment Potential (EFP)

Pruitt, S. R.; Bertoni, C.; Brorsen, K. R.; Gordon, M. S.
Efficient and Accurate Fragmentation Methods,
Acc. Chem. Res. 2014, 47, pp 2786–2794.

Explicit Polarization Method (X-Pol)

Xie, W.; Orozco, M.; Truhlar, D. G.; Gao, J.
X-Pol Potential: an Electronic Structure-Based Force Field for Molecular Dynamics Simulation of a Solvated Protein in Water.
J. Chem. Theory Comp. 2009, 5, pp 459–467.