QM/QM and QM/MM Hybrid Methods Subsystem and Embedding Methods for Quantum Chemistry

Johannes Neugebauer



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Lecture 1

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- intermolecular interactions

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- mechanical, Hamiltonian, polarizable embedding
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- energy-based partitioning
- density-based partitioning
- density-matrix based partitioning

Introduction

"[A] reliable quantum mechanical description . . . of more than a few atoms was practically impossible for a very long time. . . . The solution to this challenge . . . has emerged from the realization that a description of the properties of complex systems does not require the representation of all parts of the system at the same level of detail."

A. Warshel, Nobel Lecture, December 8, 2013.

Why Care About Environment Effects?



Example: Menshutkin reaction, $NH_3 + CH_3Cl \rightarrow [NH_3CH_3]^+ + Cl^-$

(in kJ/mol)	$\Delta^{\ddagger} G$	$\Delta_R G$
Gas Phase	193.9	2.5
Water (Exp.) ^a	> 101.7	-

Details: M. Bensberg, P.L. Türtscher, J.P. Unsleber, M. Reiher, J. Neugebauer, J. Chem. Theory Comput. 18 (2022), 723.

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Structure of LH2 of Rhodopseudomonas acidophila



• main pigments: Bchl a

G. McDermott et. al, Nature 374 (1995), 517.

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(SAOP/TZP/FDEc; intensities divided by no. of chromophores)

• site energies: 1.59 eV [$\alpha(Q_y)$], 1.57 eV [$\beta(Q_y)$]

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JN, J. Phys. Chem. B, 112 (2008), 2207.

exp. spectrum matches with shifted site energies:
 1.56 eV [α(Q_y)], 1.50 eV [β(Q_y)]

G.D. Scholes, G.R. Fleming, J. Phys. Chem. B 104 (2000), 1854

Why Embedding/Subsystem Approaches?



Some answers:

- standard QC calculations on system+environment may be very costly (or even unfeasible)
- huge amount of CPU time would be spent on a presumably small effect of the environment
- conformational sampling shall be avoided if possible (or made cheaper)
- for analysis, we want to separate solute and solvent properties/effects

Conformational Sampling

Classical Phase-Space Sampling

 if we treat the nuclei classically, we can sample a property A over all points X in phase space

$$\langle A \rangle = \int A(\vec{X}) P(\vec{X}) \mathrm{d}\vec{X}$$

where the probability for finding the system at point \vec{X} is

$$P(\vec{X}) = \frac{e^{-E(\vec{X})/[k_BT]}}{Z}$$

with partition function Z

$$Z = \int e^{-E(\vec{X})/[k_BT]} \mathrm{d}\vec{X}$$

Conformational Sampling

Evaluating the Phase-Space Integral

1) Monte Carlo/Importance Sampling: Numerical integration with points \vec{X}_k generated according to their (Boltzmann) importance

$$\langle A
angle = rac{1}{N_K} \sum_{k=1}^{N_k} A(ec{X}_k)$$

2) use ergodic hypothesis (equivalence of ensemble and time averages) and compute

$$\langle A \rangle = \lim_{t \to \infty} \frac{1}{t} \cdot \int_{t_0}^{t_0 + t} A(\tau) \mathrm{d}\tau.$$

Other common approaches for conformational sampling:

- Boltzmann-average over all relevant local minimum conformations
- weighted random minimum structures (systematic microsolvation)

Subsystem vs. Embedding Approaches



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 embedding ("focussed") approach: high accuracy for active part, lower accuracy for environment and interaction

Subsystem vs. Embedding Approaches



- embedding ("focussed") approach: high accuracy for active part, lower accuracy for environment and interaction
- subsystem (fragmentation) approach: high accuracy within fragments, lower accuracy for fragment interaction

How to approach the problem?



Starting point 1: Isolated subsystems

treat interaction as perturbation

Starting point 2: Total system

• partition quantum mechanical descriptor into subsystem contributions

(e.g., wave function, density, density matrix, Green's function)

derive optimization conditions for subsystems



isolated monomers can be described by individual Hamiltonians:

$$\hat{H}_A \Psi_A = E_A \Psi_A$$

 $\hat{H}_B \Psi_B = E_B \Psi_B$

assuming zero interaction, the total wavefunction can be factorized,

$$(\hat{H}_A + \hat{H}_B)\Psi_A \cdot \Psi_B = (E_A + E_B)\Psi_A \cdot \Psi_B$$

• true dimer Hamiltonian including interaction:

$$\hat{H}_{(A+B)} = \hat{H}_A + \hat{H}_B + \hat{H}_{A\leftrightarrow B}$$



• if interaction is weak: use perturbation theory

$$E^{(1)} = \langle \Psi_A \Psi_B | \hat{H}_{A \leftrightarrow B} | \Psi_A \Psi_B \rangle$$

form of the interaction Hamiltonian:

$$\hat{H}_{A\leftrightarrow B} = -\sum_{l\in A}^{N_A} \sum_{i\in B}^{n_B} \frac{Z_l}{|\mathbf{R}_l - \mathbf{r}_i|} - \sum_{l\in B}^{N_B} \sum_{i\in A}^{n_A} \frac{Z_l}{|\mathbf{R}_l - \mathbf{r}_i|} + \sum_{i\in A}^{n_A} \sum_{j\in B}^{n_B} \frac{1}{|\mathbf{r}_i - \mathbf{r}_j|} + \sum_{l\in A}^{N_A} \sum_{j\in B}^{N_B} \frac{Z_l Z_J}{|\mathbf{R}_l - \mathbf{R}_J|}$$



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conceptual problem: electrons are indistinguishable particles ...

• wave function for N independent subsystems:

 $\Psi^{\text{tot}}(\mathbf{r}_{1_1},\mathbf{r}_{2_1},\ldots,\mathbf{r}_{n_N})=\Psi_1(\mathbf{r}_{1_1}\ldots)\cdot\Psi_2(\mathbf{r}_{1_2}\ldots)\ldots\cdot\Psi_N(\mathbf{r}_{1_N}\ldots\mathbf{r}_{n_N})$

on-interacting subsystems: product ansatz

• wave function for N independent subsystems:

 $\Psi^{\text{tot}}(\mathbf{r}_{1_1},\mathbf{r}_{2_1},\ldots,\mathbf{r}_{n_N}) = \hat{A}\Psi_1(\mathbf{r}_{1_1}\ldots)\cdot\Psi_2(\mathbf{r}_{1_2}\ldots)\ldots\cdot\Psi_N(\mathbf{r}_{1_N}\ldots\mathbf{r}_{n_N})$

- on non-interacting subsystems: product ansatz
- antisymmetrisation necessary (but no effect for non-overlapping wavefunctions)

• wave function for N independent subsystems:

 $\Psi^{\text{tot}}(\mathbf{r}_{1_1},\mathbf{r}_{2_1},\ldots,\mathbf{r}_{n_N})=\sum_{\{K_I\}}c_{\{K_I\}}\hat{A}\Psi_{K_1}(\mathbf{r}_{1_1}\ldots)\cdot\Psi_{K_2}(\mathbf{r}_{1_2}\ldots)\ldots\cdot\Psi_{K_N}(\mathbf{r}_{1_N}\ldots\mathbf{r}_{n_N})$

- on non-interacting subsystems: product ansatz
- antisymmetrisation necessary (but no effect for non-overlapping wavefunctions)
- maybe: configuration interaction

Long-Range Interactions: Results from PT

"Polarization approximation": Antisymmetrization ignored!

first order: electrostatic interaction (unperturbed monomers)

$$\begin{split} E^{(1)} &= E^{(1)}_{\text{elstat}} &= \langle \Psi_{0,A} \Psi_{0,B} | \hat{H}_{A \leftrightarrow B} | \Psi_{0,A} \Psi_{0,B} \rangle \\ &= \int \rho_A(\mathbf{r}) v_{\text{nuc},B}(\mathbf{r}) d\mathbf{r} + \int \rho_B(\mathbf{r}) v_{\text{nuc},A}(\mathbf{r}) d\mathbf{r} \\ &+ \int \frac{\rho_A(\mathbf{r}) \rho_B(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} d\mathbf{r} d\mathbf{r}' + \sum_{I \in A}^{N_A} \sum_{J \in B}^{N_B} \frac{Z_I Z_J}{|\mathbf{R}_I - \mathbf{R}_J|} \end{split}$$

- possible starting point for further approximations:
 - multipole expansion of $\rho_A(\mathbf{r})$ and/or $\rho_B(\mathbf{r})$
 - point-charge representation of total charge density (fitted to ESP) ("distributed monopoles"; higher-order expansion possible)

Long-Range Interactions: Results from PT

• second order:
$$E^{(2)} = E^{(2)}_{ind,A} + E^{(2)}_{ind,B} + E^{(2)}_{disp}$$
,

$$E_{\text{ind},A}^{(2)} = \sum_{K} \frac{\langle \Psi_{0,A}\Psi_{0,B} | \hat{H}_{A\leftrightarrow B} | \Psi_{K,A}\Psi_{0,B} \rangle \langle \Psi_{K,A}\Psi_{0,B} | \hat{H}_{A\leftrightarrow B} | \Psi_{0,A}\Psi_{0,B} \rangle}{E_{A,K} - E_{A,0}}$$

$$E_{\text{ind},B}^{(2)} = \sum_{K} \frac{\langle \Psi_{0,A}\Psi_{0,B} | \hat{H}_{A\leftrightarrow B} | \Psi_{0,A}\Psi_{K,B} \rangle \langle \Psi_{0,A}\Psi_{K,B} | \hat{H}_{A\leftrightarrow B} | \Psi_{0,A}\Psi_{0,B} \rangle}{E_{B,K} - E_{B,0}}$$

$$E_{\text{disp}}^{(2)} = \sum_{KL} \frac{\langle \Psi_{0,A}\Psi_{0,B} | \hat{H}_{A\leftrightarrow B} | \Psi_{K,A}\Psi_{L,B} \rangle \langle \Psi_{K,A}\Psi_{L,B} | \hat{H}_{A\leftrightarrow B} | \Psi_{0,A}\Psi_{0,B} \rangle}{E_{A,K} + E_{B,L} - E_{A,0} - E_{B,0}}$$

Long-Range Interactions: Results from PT

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- induction terms: interaction of transition density (from Ψ^{*}_{0,A}Ψ_{K,A}) with ground-state density (from Ψ^{*}_{0,B}Ψ_{0,B}) distance dependence (lowest order): R⁻⁴ for ion-molecule and R⁻⁶ for dipolar molecule-molecule interactions
- dispersion terms: interaction of two transition densities (from $\Psi_{0,A}^* \Psi_{K,A}$ and $\Psi_{0,B}^* \Psi_{L,B}$)

 \Rightarrow distance dependence (lowest order): R^{-6}

Short-Range Interactions

Phenomenologically:

- exchange-repulsion (exchange + Pauli repulsion), $\propto \exp[-\eta R]$
- "charge-transfer" (sometimes included in induction)
- charge penetration (effect of non-converging multipole expansions)
- additional terms arise if correlation is considered (SAPT)

Short-Range Interactions

Exchange Interaction:

• use antisymmetrized zeroth-order wavefunction:

$$\Psi_{0}^{AB} \approx \hat{A}_{AB} \Psi_{0}^{A} \Psi_{0}^{B} = N_{AB} \sum_{\hat{P}} (-1)^{p} \hat{P} \Psi_{0}^{A} \Psi_{0}^{B}$$

(NAB: normalization factor; sum runs over all permutations \hat{P} of electrons between different monomers with parity p)

first-order energy correction:

$$E^{(1)} = N_{AB}^2 \left\langle \Psi_0^A \Psi_0^B \middle| \hat{H}_{A \leftrightarrow B} \left| N_{AB} \sum_{\hat{P}} (-1)^p \hat{P} \Psi_0^A \Psi_0^B \right\rangle \right\rangle$$

exchange contribution arises from:

$$\left\langle \Psi_0^{\mathrm{A}} \Psi_0^{\mathrm{B}} \left| \hat{H}_{A \leftrightarrow B} \right| N_{\mathrm{AB}} \sum_{\hat{P} \neq \hat{I}} (-1)^p \hat{P} \Psi_0^{\mathrm{A}} \Psi_0^{\mathrm{B}} \right\rangle$$

I. Kaplan, Intermolecular Interactions, John Wiley & Sons, Chichester, 2006.

Exchange–Repulsion

Example: Two hydrogen atoms (A and B), normalized $1s_{\alpha}$ orbitals ψ_a, ψ_b

• for $\langle \psi_A | \psi_B \rangle = S$ with |S| > 0: use antisymmetrized product

$$\begin{split} \tilde{\Psi}(1,2) &= \psi_a(1)\psi_b(2) - \psi_b(1)\psi_a(2) \\ \langle \tilde{\Psi} | \tilde{\Psi} \rangle &= \langle \psi_a(1)\psi_b(2) - \psi_b(1)\psi_a(2) | \psi_a(1)\psi_b(2) - \psi_b(1)\psi_a(2) \rangle \\ \Psi(1,2) &= (2-2S^2)^{-1/2} | \psi_a(1)\psi_b(2) - \psi_b(1)\psi_a(2) \rangle \end{split}$$

Ist order interaction energy:

$$\begin{aligned} \langle \Psi | \hat{H}_{A \leftrightarrow B} | \Psi \rangle &= (1 - S^2)^{-1} \left[\langle \psi_a(1) \psi_b(2) | \hat{H}_{A \leftrightarrow B} | \psi_a(1) \psi_b(2) \rangle \right. \\ &\left. - \langle \psi_a(1) \psi_b(2) | \hat{H}_{A \leftrightarrow B} | \psi_b(1) \psi_a(2) \rangle \right] \end{aligned}$$

result for simple product would be:

$$E_{\text{elstat}}^{(1)} = \langle \psi_a(1)\psi_b(2)|\hat{H}_{A\leftrightarrow B}|\psi_a(1)\psi_b(2)\rangle$$

• difference: exchange-repulsion energy, *E*er

A. Stone, The Theory of Intermolecular Forces, Oxford University Press, 2013, Chapter 6

Exchange–Repulsion

exchange—repulsion energy

$$egin{array}{rcl} E_{
m er} &=& -rac{1}{(1-S^2)} \langle \psi_a(1)\psi_b(2)|\hat{H}_{A\leftrightarrow B}|\psi_b(1)\psi_a(2)
angle \ &+rac{S^2}{(1-S^2)} \langle \psi_a(1)\psi_b(2)|\hat{H}_{A\leftrightarrow B}|\psi_a(1)\psi_b(2)
angle \end{array}$$

- second term: correction to electrostatic energy
- first term: effect of antisymmetrization; with

$$\hat{H}_{A\leftrightarrow B} = \frac{1}{r_{12}} - \frac{1}{R_{B1}} - \frac{1}{R_{A2}} + \frac{1}{R_{AB}}$$

we get for the first term (note that $(1/R_{AB})$ terms cancel out)

$$\begin{aligned} -\left\langle \psi_{a}(1)\psi_{b}(2) \left| \frac{1}{r_{12}} - \frac{1}{R_{B1}} - \frac{1}{R_{A2}} \right| \psi_{b}(1)\psi_{a}(2) \right\rangle \\ &= \left\langle \psi_{a}(1)\psi_{b}(2) \left| \frac{1}{R_{B1}} + \frac{1}{R_{A2}} \right| \psi_{b}(1)\psi_{a}(2) \right\rangle - (\psi_{a}\psi_{b}|\psi_{b}\psi_{a}) \\ &= \left\langle \psi_{b}|\psi_{a} \right\rangle \cdot \left\langle \psi_{a}(1) \left| \frac{1}{R_{B1}} + \frac{1}{R_{A1}} \right| \psi_{b}(1) \right\rangle - (\psi_{a}\psi_{b}|\psi_{b}\psi_{a}) \end{aligned}$$

A. Stone, The Theory of Intermolecular Forces, Oxford University Press, 2013, Chapter 6

Exchange–Repulsion

• from first term (continued):

$$= S \left\langle \psi_a(1) \left| \frac{1}{R_{\text{B1}}} + \frac{1}{R_{\text{A1}}} \right| \psi_b(1) \right\rangle - (\psi_a \psi_b | \psi_b \psi_a)$$

⇒ contains repulsion (due to monomer overlap) and exchange (attractive)

- overall effect of Eer is repulsive (for same spin!)
- distance dependence $\propto \exp[-\eta R]$

see, e.g., H.J. Boehm, R. Ahlrichs, J. Chem. Phys. 77, 2028 (1982).

- vanishes for S = 0
- ⇒ many exchange-repulsion models are based on overlap

A. Stone, The Theory of Intermolecular Forces, Oxford University Press, 2013, Chapter 6

QM/MM Partitioning
Starting Point for Approximations

• partition Hamiltonian into active system (A) and environment (E)

$$\hat{H}_{A+E} = \hat{H}_A + \hat{H}_E + \hat{H}_{A\leftrightarrow E}$$

- treat A, E, and/or $A \leftrightarrow E$ with different approximations
- maybe several active systems, maybe more layers, ...

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- maybe several active systems, maybe more layers,

But how exactly? At which stage shall we introduce approximations?



• additive QM/MM (more flexibility regarding interaction model):

$$E_{\text{tot}}^{\text{add}} = E_A^{\text{QM}} + E_E^{\text{MM}} + E_{A\leftrightarrow E}^{\text{MM}}$$

• subtractive QM/MM (easier to generalize to QM/QM methods):

$$E_{\text{tot}}^{\text{sub}} = E_{(A+E)}^{\text{MM}} + (E_A^{\text{QM}} - E_A^{\text{MM}})$$

identical if

$$E^{\mathrm{MM}}_{(A+E)} = E^{\mathrm{MM}}_A + E^{\mathrm{MM}}_E + E^{\mathrm{MM}}_{A\leftrightarrow E} \quad \Leftrightarrow \quad E^{\mathrm{MM}}_{A\leftrightarrow E} = E^{\mathrm{MM}}_{(A+E)} - E^{\mathrm{MM}}_A - E^{\mathrm{MM}}_E$$

QM/MM: Partitioning the Energy

Three energy contributions:

(1) active-system energy

$$E_A^{
m QM} = \langle \Psi_A | \hat{H}_A | \Psi_A
angle$$

(note: \hat{H}_A is the isolated-system Hamiltonian for system A)

(2) environment energy

$$E_E^{\text{MM}} = E_{\text{bonded}}(\mathbf{R}_E) + E_{\text{nonbonded}}(\mathbf{R}_E)$$

where typically

$$E_{\text{bonded}}(\mathbf{R}_{E}) = E_{\text{stretch}}(\mathbf{R}_{E}) + E_{\text{bend}}(\mathbf{R}_{E}) + E_{\text{torsion}}(\mathbf{R}_{E})$$
$$E_{\text{nonbonded}}(\mathbf{R}_{E}) = E_{\text{electrostatic}}(\mathbf{R}_{E}) + E_{\text{vdW}}(\mathbf{R}_{E})$$

 $E_{\rm vdW}$ accounts for dispersion and exchange-repulsion

QM/MM: Partitioning the Energy

Prototypical MM energy expressions:

$$E_{\text{stretch}}(\mathbf{R}_{E}) = \sum_{b}^{\text{bonds}} k_{b}(d_{b} - d_{b,0})^{2}$$

$$E_{\text{bend}}(\mathbf{R}_{E}) = \sum_{a}^{\text{angles}} k_{a}(\theta_{a} - \theta_{a,0})^{2}$$

$$E_{\text{torsion}}(\mathbf{R}_{E}) = \sum_{d}^{\text{dihedrals}} k_{d}[1 + \cos(n\phi + \delta)]^{2}$$

$$E_{\text{electrostatic}}(\mathbf{R}_{E}) = \sum_{a < b}^{\text{nb pairs}} \frac{Q_{a}Q_{b}}{R_{ab}}$$

$$E_{\text{vdW}}(\mathbf{R}_{E}) = \sum_{a < b}^{\text{nb pairs}} \epsilon_{ab} \left[\left(\frac{\sigma_{ab}}{r_{ab}} \right)^{12} - \left(\frac{\sigma_{ab}}{r_{ab}} \right)^{6} \right]$$

QM/MM: Partitioning the Energy

Three energy contributions (cont'd):

(3) QM \leftrightarrow MM interaction: Apply MM energy expression

$$E_{A\leftrightarrow E}^{MM} = E_{bonded,A\leftrightarrow E} + E_{vdW,A\leftrightarrow E} + E_{electrostatic,A\leftrightarrow E}$$

Notes:

- availability of suitable FF parameters for QM atoms can be problematic
- bonds across the QM-MM boundary require link-atom formalism



• Mechanical Embedding: Wavefunction of QM part unchanged



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- Hamiltonian/Electronic Embedding: QM part polarized by environment



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Note: This usually only applies to electrostatics, but could be generalized

Mechanical Embedding:

- $E_{\text{electrostatic},A\leftrightarrow E}$ evaluated with MM charges for QM atoms
- \Rightarrow No polarization of QM wavefunction
- ⇒ Only indirect effects (change in equilibrium structure)
- ⇒ Changes in QM charge distribution not reflected in interaction term (e.g., along reaction coordinates)

Hamiltonian Embedding:

• electrostatic interaction Hamiltonian:

$$\hat{H}_{\text{elstat},A\leftrightarrow E} = -\sum_{i}^{\text{el.}} \sum_{a}^{\text{MM atoms}} \frac{q_{a}}{|\mathbf{r}_{i} - \mathbf{R}_{a}|} + \sum_{I}^{\text{nuc.}} \sum_{a}^{\text{MM atoms}} \frac{Z_{I}q_{a}}{|\mathbf{R}_{I} - \mathbf{R}_{a}|}$$
$$= \sum_{i}^{\text{el.}} v_{\text{emb}}^{\text{elstat}}(\mathbf{r}_{i}) + \sum_{I}^{\text{nuc.}} \sum_{a}^{\text{MM atoms}} \frac{Z_{I}q_{a}}{|\mathbf{R}_{I} - \mathbf{R}_{a}|}$$

 \Rightarrow obtain Ψ_A from

$$\hat{H}'_{A}\Psi_{A} = \left(\hat{H}_{A} + \sum_{i}^{\text{el.}} v_{\text{emb}}^{\text{elstat}}(\mathbf{r}_{i})\right)\Psi_{A} = E'_{A}\Psi_{A}$$

 \Rightarrow polarizes Ψ_A , changes all energy terms in $E_A^{
m QM}=\langle\Psi_A|\hat{H}_A|\Psi_A
angle$

Hamiltonian Embedding:

electrostatic interaction energy:

$$E_{\text{elstat},A\leftrightarrow E} = \left\langle \Psi_A \left| \sum_{i}^{\text{el.}} v_{\text{emb}}^{\text{elstat}}(\mathbf{r}_i) \right| \Psi_A \right\rangle + \sum_{I}^{\text{nuc. MM atoms}} \frac{Z_I q_a}{|\mathbf{R}_I - \mathbf{R}_a|}$$

total QM/MM energy:

$$E_{\text{tot}}^{\text{QM/MM}} = E_A^{\text{QM}} + E_E^{\text{MM}} + E_{\text{vdW},A\leftrightarrow E} + \left\langle \Psi_A \left| \sum_{i}^{\text{el.}} v_{\text{emb}}^{\text{elstat}}(\mathbf{r}_i) \right| \Psi_A \right\rangle + \sum_{I}^{\text{nuc. MM atoms}} \sum_{a}^{\text{MM atoms}} \frac{Z_I q_a}{|\mathbf{R}_I - \mathbf{R}_a|} = E_A' + E_E^{\text{MM}} + E_{\text{vdW},A\leftrightarrow E} + \sum_{I}^{\text{nuc. MM atoms}} \sum_{a}^{\text{MM atoms}} \frac{Z_I q_a}{|\mathbf{R}_I - \mathbf{R}_a|}$$

(assuming no bonding interactions across the QM/MM boundary)

Polarizable Embedding: Introduce flexible MM charge model, polarized by QM charge distribution

Induced point dipoles:

- assign polarizabilities to all MM atoms (or general expansion points)
- determine induced dipoles as:

$$\boldsymbol{\mu}_{a}^{\mathrm{ind}} = \boldsymbol{\alpha}_{a} \cdot \vec{F}(\mathbf{R}_{a})$$

 electric field at MM atom *a* originates from MM point charges, other induced dipoles, and QM charge distribution

Alternatives:

- fluctuating charges
- drude oscillators (charge-on-spring models)

An Example: The DRF Model

Discrete Reaction Field Operator

$$\hat{H}_{\text{QM/MM}} = \sum_{i} v^{\text{DRF}}(\mathbf{r}_{i})$$

$$v^{\text{DRF}}(\mathbf{r}) = \sum_{a}^{\text{MM atoms}} \frac{q_{a}}{|\mathbf{r} - \mathbf{R}_{a}|} + \sum_{a}^{\text{MM atoms}} \mu_{a}^{\text{ind}} \cdot \frac{(\mathbf{r} - \mathbf{R}_{a})^{3}}{|\mathbf{r} - \mathbf{R}_{a}|}^{3}$$

induced dipoles are computed self-consistently from

$$\mu_a^{\text{ind}} = \alpha_a \left[\boldsymbol{F}^{\text{QM, nuc}}(\mathbf{R}_a) + \boldsymbol{F}^{\text{QM, el}}(\mathbf{R}_a) + \boldsymbol{F}^{\text{MM charges}}(\mathbf{R}_a) + \boldsymbol{F}^{\text{MM ind. dip}}(\mathbf{R}_a) \right]$$

T.D. Poulsen, P.R. Ogilby, K.V. Mikkelsen, J. Chem. Phys. 2002, 116, 3730;

L. Jensen, P.Th. van Duijnen, J.G. Snijders, J. Chem. Phys. 2003, 118, 514.

Other Polarizable Embedding Schemes

- PE model (Kongsted and co-workers)
- QM/MMpol (Mennucci and co-workers)
- EFP (Gordon, Slipchenko and co-workers)

• . . .

Parameters for charges/polarizabilities

- either calculated for solvent molecules/env. fragments (e.g., CHELPG charges, LOPROP polarizabilities)
- or fitted, e.g., to experimental polarizabilities

Reminder: Interacting Subsystems



• if interaction is weak: use perturbation theory

$$E^{(1)} = \langle \Psi_A \Psi_B | \hat{H}_{A \leftrightarrow B} | \Psi_A \Psi_B \rangle$$

form of the interaction Hamiltonian:

$$\hat{H}_{A\leftrightarrow B} = -\sum_{I\in A}^{N_{A}} \sum_{i\in B}^{n_{B}} \frac{Z_{I}}{|\mathbf{R}_{I} - \mathbf{r}_{i}|} - \sum_{I\in B}^{N_{B}} \sum_{i\in A}^{n_{A}} \frac{Z_{I}}{|\mathbf{R}_{I} - \mathbf{r}_{i}|} + \sum_{i\in A}^{n_{A}} \sum_{j\in B}^{n_{B}} \frac{1}{|\mathbf{r}_{i} - \mathbf{r}_{j}|} + \sum_{I\in A}^{N_{A}} \sum_{j\in B}^{N_{B}} \frac{Z_{I}Z_{J}}{|\mathbf{R}_{I} - \mathbf{R}_{J}|}$$

Reminder: Interacting Subsystems



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$$E^{(1)} = \langle \Psi_A \Psi_B | \hat{H}_{A \leftrightarrow B} | \Psi_A \Psi_B \rangle$$

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• How to get rid of Ψ_B ?

How to get rid of Ψ_B ?

• Taylor expansion of $1/(\mathbf{r}_a - \mathbf{r}_b)$ around \mathbf{r}_0

$$\frac{1}{|\mathbf{r}_a - \mathbf{r}_b|} = \sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} \left(\nabla_{\mathbf{r}_a}^k \frac{1}{|\mathbf{r}_a - \mathbf{r}_0|} \right) (\mathbf{r}_b - \mathbf{r}_0)^k$$

with multi-index $k = (k_x, k_y, k_z)$ and interaction tensor

$$T^{(k)}(\mathbf{r}) = \nabla_{\mathbf{r}}^{k} \frac{1}{|\mathbf{r} - \mathbf{r}_{0}|}$$

and

$$\nabla_{\mathbf{r}}^{k} = \left(\frac{\partial}{\partial r_{x}}\right)^{k_{x}} \left(\frac{\partial}{\partial r_{y}}\right)^{k_{y}} \left(\frac{\partial}{\partial r_{z}}\right)^{k_{z}}$$

How to get rid of Ψ_B ? Consider electron–electron interaction:

$$\begin{split} E_{\text{el},\text{el}}^{(1)} &= \sum_{a \in A} \sum_{b \in B}^{n_B} \left\langle \Psi_A \Psi_B \left| \frac{1}{|\mathbf{r}_a - \mathbf{r}_b|} \right| \Psi_A \Psi_B \right\rangle \\ &= \sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} \left\langle \Psi_A \left| \sum_{a \in A}^{n_A} \nabla_{\mathbf{r}_a}^k \frac{1}{|\mathbf{r}_a - \mathbf{r}_0|} \right| \Psi_A \right\rangle \cdot \left\langle \Psi_B \left| \sum_{b \in B}^{n_B} (\mathbf{r}_b - \mathbf{r}_0)^k \right| \Psi_B \right\rangle \\ &= \sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} \left\langle \Psi_A \left| \sum_{a \in A}^{n_A} T^{(k)}(\mathbf{r}_a) \right| \Psi_A \right\rangle Q_{B,\text{el}}^{(k)} \end{split}$$

 $(Q_{B,e}^{(k)})$: electronic part of multipole moment of fragment B)

 \Rightarrow Effective separation of coordinates from fragments A and B

• use such an expansion for every $|\mathbf{r}_a - \mathbf{r}_b|^{-1}$ and $|\mathbf{r}_a - \mathbf{R}_B|^{-1}$,

$$E^{(1)} = \langle \Psi_A \Psi_B | \hat{H}_{A \leftrightarrow B} | \Psi_A \Psi_B \rangle$$

=
$$\sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} (F_{A, \text{nuc}}^{(k)} + \langle \Psi_A | \hat{F}_{A, \text{el}}^{(k)} | \Psi_A \rangle) Q_B^{(k)}$$

with

$$F_{A,\text{nuc}}^{(k)} = \sum_{I \in A}^{N_A} Z_I T^{(k)}(\mathbf{R}_I)$$
$$\hat{F}_{A,\text{el}}^{(k)} = \sum_{i \in A}^{N_A} T^{(k)}(\mathbf{r}_i)$$

and multipole moments of system B,

$$Q_B^{(k)} = \sum_{J \in B}^{N_B} Z_J (\mathbf{R}_J - \mathbf{R}_0)^k - \int \rho_B(\mathbf{r}') (\mathbf{r}' - \mathbf{R}_0)^k d\mathbf{r}'$$

Further aspects of the PE model:

- induction terms can be treated similarly, incl. polarization of the environment
- embedding operator can be derived within DFT by minimizing energy w.r.t. density
- self-consistent solution including induced dipoles in the environment (very similar to DRF model)
- straightforward extension to response theory

Hamiltonian Embedding:

- effects of Pauli repulsion: often not included in Ĥ'_A
- ⇒ MM atoms can act as electron traps (overpolarization, electron spill-out, or electron leaking)
 - one solution strategy: replace Coulombic potential (-1/r) by

$$v_a(r) = -\frac{r_{a,\text{cov}}^n - r^n}{r_{a,\text{cov}}^{n+1} - r^{n+1}}$$

A. Laio, J. VandeVondele, U. Rothlisberger, J. Chem. Phys. 2002, 116, 6941.

but: some models use explicit repulsive contributions

QM-derived Embedding Potentials

The Effective Fragment Potential (EFP) method

- effective-fragment orbitals are obtained from DFT/HF (+ localization)
- interaction Hamiltonian:

$$\hat{H}_{A\leftrightarrow E} = \hat{V}_{elstat} + \hat{V}_{pol} + \hat{V}_{ex-rep}$$

• $\hat{V}_{\text{ex-rep}}$ denotes the exchange-repulsion interaction,

$$\hat{V}_{\text{ex-rep}} = \sum_{i} \sum_{j} \beta_{j} e^{-\alpha_{j}(r_{i}-R_{j})^{2}}$$

(local potential; R_i is coordinate vector of an LMO centroid; α_i and β_i are parameters)

C.I. Viquez Rojas, L.V. Slipchenko, J. Chem. Theory Comput. 2020, 16, 6408.

QM-derived Embedding Potentials

Electrostatic potential in EFP:

- based on a *distributed multipolar analysis* of fragment charge distributions
- expansion points k:
 - each nuclear center
 - each bond midpoint
- multipoles up to octopoles

$$\hat{V}_{k}^{\text{elstat}}(\mathbf{r}) = q_{k}T(\mathbf{r}_{k}) - \sum_{a}^{x,y,z} \mu_{a}^{k}T_{a}(\mathbf{r}_{k}) + \frac{1}{3}\sum_{a,b}^{x,y,z} \Theta_{a,b}^{k}T_{a,b}(\mathbf{r}_{k}) - \frac{1}{15}\sum_{a,b}^{x,y,z} \Omega_{a,b,c}^{k}T_{a,b,c}(\mathbf{r}_{k})$$

• general definition of full interaction tensor: $T^{(k)}(\mathbf{r}_k) = \nabla^k \frac{1}{|\mathbf{r}-\mathbf{r}_k|}$

• here:
$$T(\mathbf{r}_k) = 1/|\mathbf{r} - \mathbf{r}_k|$$
, T_a : element of $T^{(1)}(\mathbf{r}_k) = \nabla \frac{1}{|\mathbf{r} - \mathbf{r}_k|}$ etc.

M. Gordon et al., J. Phys. Chem. A 2001, 105, 293.

C.I. Viquez Rojas, L.V. Slipchenko, J. Chem. Theory Comput. 2020, 16, 6408.

QM-derived Embedding Potentials

Polarization in EFP:

- based on distributed polarizabilities on LMO centroids
- ⇒ localized "orbital" polarizabilities from finite field calculations

M. Gordon et al., J. Phys. Chem. A 2001, 105, 293.

C.I. Viquez Rojas, L.V. Slipchenko, J. Chem. Theory Comput. 2020, 16, 6408.



Overall Goal: Solvation Free Energies

$$\Delta G_{\text{solv}} = \Delta G_{\text{cavity}} + \Delta G_{\text{Dispersion/vdW}} + \Delta G_{\text{elstat}}$$

Consider two-step process:

- (1) cavity formation
- (2) interaction ("polarization") between molecule and solvent

Overall Goal: Solvation Free Energies

 $\Delta G_{\text{solv}} = \Delta G_{\text{cavity}} + \Delta G_{\text{Dispersion/vdW}} + \Delta G_{\text{elstat}}$

- cavity formation and dispersion terms: often assumed proportional to "solute surface"
- only electrostatic term enters the QM Hamiltonian
- solvent: homogeneous medium with dielectric constant ϵ_{out}
- electrostatic potential $\varphi(\mathbf{r})$: from Poissson's equation,

$$\boldsymbol{\nabla} \cdot [\boldsymbol{\epsilon}(\mathbf{r})\boldsymbol{\nabla}\varphi(\mathbf{r})] = -4\pi\rho(\mathbf{r})$$

• note: $\epsilon(\mathbf{r}) = \epsilon_{in} = 1$ within QM region, ϵ_{out} outside

J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 2005, 105, 2999; J.M. Herbert, WIREs Comput. Mol. Sci. 2021, 11, e1519; F. Jensen, Introduction to Compututational Chemistry, 2nd ed., Wiley, 2007, Section 14.7.

• reaction potential: $\varphi_{\rm reac}({\bf r}) = \varphi({\bf r}) - \varphi_{\rm mol}({\bf r})$, with

$$arphi_{\mathrm{mol}}(\mathbf{r}) = \int rac{
ho_{\mathrm{mol}}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \mathrm{d}\mathbf{r}'$$

(electrostatic potential generated by molecular charge density)

electrostatic solvation energy:

$$\Delta G_{\text{elstat}} = \frac{1}{2} \int \varphi_{\text{reac}}(\mathbf{r}) \rho_{\text{mol}}(\mathbf{r}) d\mathbf{r}$$

analytic solutions available for

- charge monopole in a spherical cavity (Born model)
- point dipole in a spherical cavity (Onsager model)
- general multipoles in a spherical cavity (Kirkwood model)
- ... and in ellipsoidal cavities (Kirkwood–Westheimer model)

Polarizable Continuum Models

- 3D polarization problem is turned into a surface charge problem
- reaction potential can be expressed exactly as

$$arphi_{
m reac}({f r}) = \int_{
m surface} rac{\sigma({f s})}{|{f r}-{f s}|} {
m d}{f s}$$

• surface charge $\sigma(s)$: defined through *jump* condition for E-field,

$$\epsilon_{
m out}(ec{n}_s\cdotec{
abla})arphi_{
m out} = \epsilon_{
m in}(ec{n}_s\cdotec{
abla})arphi_{
m in}$$

 $(\vec{n}_s:$ outward-pointing unit vector normal to cavity surface at s)

in practice: surface charge is discretized (tesserae),

$$arphi_{ ext{reac}}(\mathbf{r}) pprox \sum_k rac{\sigma(\mathbf{s}_k)A_k}{|\mathbf{r}-\mathbf{s}_k|} = \sum_k rac{q_k}{|\mathbf{r}-\mathbf{s}_k|}$$

(A_k : tesserae area; $q_k = \sigma(\mathbf{s}_k)A_k$: apparent surface charge)

Conductor-Like Screening Model (COSMO)

- dielectric constant is set to $\epsilon = \infty$
- most important consequence:

$$arphi(\mathbf{r}) ~=~ arphi_{
m reac}(\mathbf{r}) + arphi_{
m mol}(\mathbf{r}) = 0$$

at boundary between molecule and dielectric environment

- this condition fixes the values of the surface charges
- the same condition is obtained by minimizing the electrostatic energy of the molecule–surface charge system w.r.t. the surface charges
- ideal, unscreened charges are finally scaled by

$$f(\epsilon) = \frac{\epsilon - 1}{\epsilon + k}$$

(k = 0.5 in original work by Klamt, later versions often use k = 0)

A. Klamt, G. Schüürmann, J. Chem. Soc. Perkin Trans. 2 (1993), 799;

Conductor-Like Screening Model (COSMO)

electrostatic part of solvation energy in COSMO

$$E_{\rm el,COSMO} = \frac{1}{2} \sum_{\mu} \sum_{\nu} q_{\mu} A_{\mu\nu} q_{\nu} + \sum_{A} \sum_{\mu} q_{\mu} B_{A\mu} Z_{A} + \sum_{\mu} q_{\mu} C_{\mu}$$

 q_{μ} = apparent surface charges (ASCs), from minimization of $E_{el,COSMO}$,

$$\mathbf{A}\vec{q} = -(\mathbf{B}\vec{Z} + \vec{C})$$

with

$$A_{\mu\nu} = \begin{cases} |\vec{r}_{\mu} - \vec{r}_{\nu}|^{-1} & \text{for } \mu \neq \nu \\ 1.07\sqrt{\frac{4\pi}{S_{\mu}}} & \text{for } \mu = \nu \end{cases}$$
$$B_{A\mu} = |\vec{r}_{\mu} - \vec{r}_{A}|^{-1}$$
$$C_{\mu} = \nu_{\text{Coul}}[\rho](\vec{r}_{\mu})$$

A. Klamt, G. Schüürmann, J. Chem. Soc. Perkin Trans. 2 (1993), 799;
 C.C. Pye, T. Ziegler, Theor. Chem. Acc. 101 (1999), 396

Polarizable Continuum Models



 $(R^* = R_A + R_{\rm vdW}^{\rm solv})$

Further important aspects:

- shape of molecular cavity
- outlying charge corrections
- extensions for dispersion, exchange-repulsion

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J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 2005, 105, 2999; J.M. Herbert, WIREs Comput. Mol. Sci. 2021, 11, e1519.
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QM/MM vs. Continuum Approaches: Conclusions

QM/MM:

- can model specific interactions
- electrostatics can be systematically improved
- self-consistent polarization possible with polarizable force fields
- repulsive short-range correction needed to avoid overpolarization

Continuum Models:

- $\bullet\,$ implicitly include conformational sampling \Rightarrow much cheaper
- are comparable to the polarizable part of QM/MM models
- no specific interactions

Best-of-both-worlds? Cluster-Continuum hybrid models

J.R. Pliego Jr., J.M. Riveros, WIREs Comput. Mol. Sci. 10 e1440 (2020).

QM/QM Hybrid Methods: An Introduction


continuum models

QM/MM methods

pure QM methods

Wish list for an "ideal" environmental model:



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should be efficient (comparable to isolated molecule)



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- should be efficient (comparable to isolated molecule)
- should be able to model specific effects (atomistic structure)



Wish list for an "ideal" environmental model:

- should be efficient (comparable to isolated molecule)
- should be able to model specific effects (atomistic structure)
- should be transferable (parameter-free)

(But what about QM-derived MM models?)



Wish list for an "ideal" environmental model:

- should be efficient (comparable to isolated molecule)
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(But what about QM-derived MM models?)

should focus on the embedded system



Wish list for an "ideal" environmental model:

- should be efficient (comparable to isolated molecule)
- should be able to model specific effects (atomistic structure)
- should be transferable (parameter-free)

(But what about QM-derived MM models?)

- should focus on the embedded system
- ⇒ QM/QM embedding methods

QM/QM Hybrid Methods

Partitioning is possible at different levels:

- energy partitioning
- wavefunction partitioning
- density-matrix partitioning
- Green's function partitioning
- density partitioning

Simple QM/QM Hybrid Methods



• ONIOM: a generalization of subtractive QM/MM

$$E_{\rm tot}^{\rm QM/QM} = E_{(A+E)}^{\rm QM2} + (E_A^{\rm QM1} - E_A^{\rm QM2})$$

interaction defined as

$$E_{A\leftrightarrow E}^{\text{QM2}} = E_{(A+E)}^{\text{QM2}} - E_A^{\text{QM2}} - E_E^{\text{QM2}}$$

- generalizations for many layers (QM1/QM2/MM/continuum) and electrostatic embedding
- properties require corresponding definitions

Fragmentation Methods

Molecular Fractionation with Conjugated Caps (MFCC)

- developed for proteins; partition into oligopeptides
- use model for neighboring fragments as caps
- sum up results for all capped fragments, subtract concaps
- no electrostatic embedding; better with larger caps

D.W. Zhang, J.Z.H. Zhang, J. Chem. Phys. 119 (2003), 3599.

Increment Methods

General idea:

- largest part of *E*_{tot} is due to energies of (isolated) subsystems
- interaction energy: mainly due to pair interactions
- general energy expression:

$$E_{\text{tot}} = \sum_{I} E_{I} + \sum_{I < J} E_{I \leftrightarrow J} + \sum_{I < J < K} E_{I \leftrightarrow J \leftrightarrow K} + \dots$$
$$E_{I \leftrightarrow J} = E_{IJ} - E_{I} - E_{J}$$
$$E_{I \leftrightarrow J \leftrightarrow K} = E_{IJK} - E_{I} - E_{J} - E_{K}$$
$$-(E_{IJ} - E_{I} - E_{J}) - (E_{IK} - E_{I} - E_{K}) - (E_{JK} - E_{J} - E_{K})$$

nth-order increment method: exact for n subsystems

Increment Methods



Increment Methods



Fragment Molecular Orbital Method (1)



FMO-1

- fragmentation without separation of bond electron pairs
- fragment calculations under full electrostatic embedding
- no capping applied

K. Kitaura et al., Chem. Phys. Lett. 313 (1999), 701.

Fragment Molecular Orbital Method (1)



generate localized MOs for capped fragment



use these LMOs as basis for "true" fragments

FMO-1

- fragment orbitals are expressed through localized orbitals obtained from reference compound (capped fragment)
- minimal basis is applied ⇒ bond electron pairs have no freedom to change compared to reference compound

Fragment Molecular Orbital Method (2)



FMO-2

- 2nd order increment method
- monomers and dimers are obtained with full electrostatic embedding potential, based on localized orbitals
- \Rightarrow FMO-2 implicitly contains higher-order terms

More about QM/QM tomorrow ...