QM/QM and QM/MM Hybrid Methods

Subsystem and Embedding Methods for Quantum Chemistry

Johannes Neugebauer

ESQC, Sicily, 2026

Lecture 1

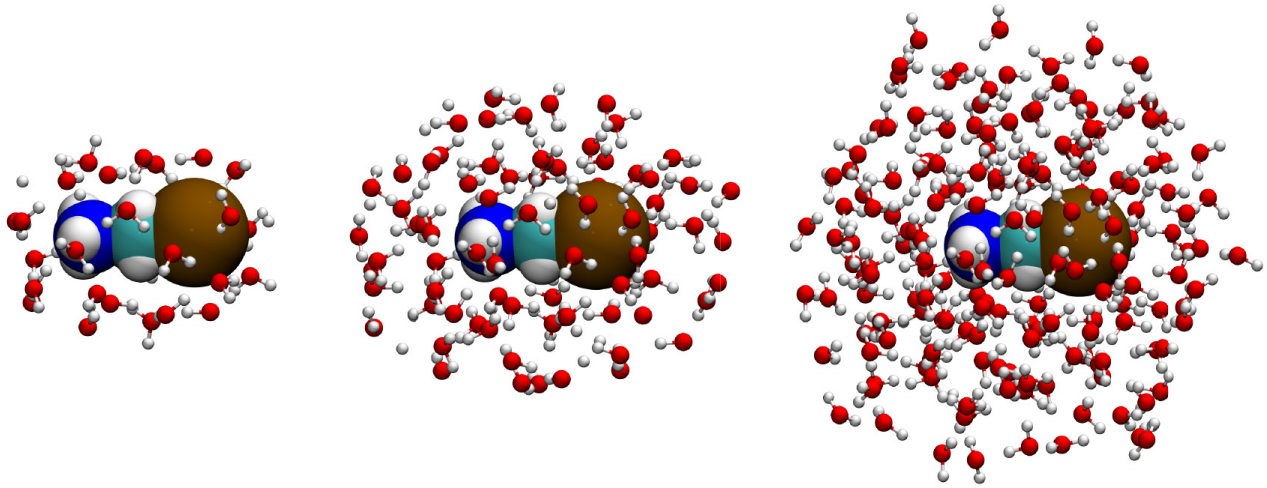
Contents

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	Δ_RG
Gas Phase	193.9	2.5
Water (Exp.)	> 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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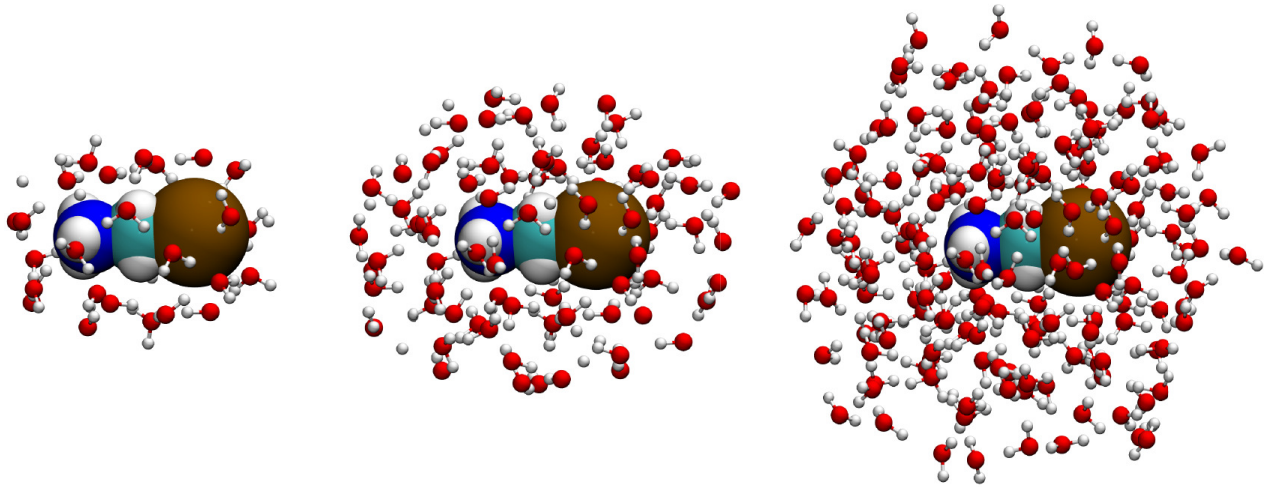

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(in kJ/mol)	$\Delta^{\ddagger}G$	$\Delta_R G$
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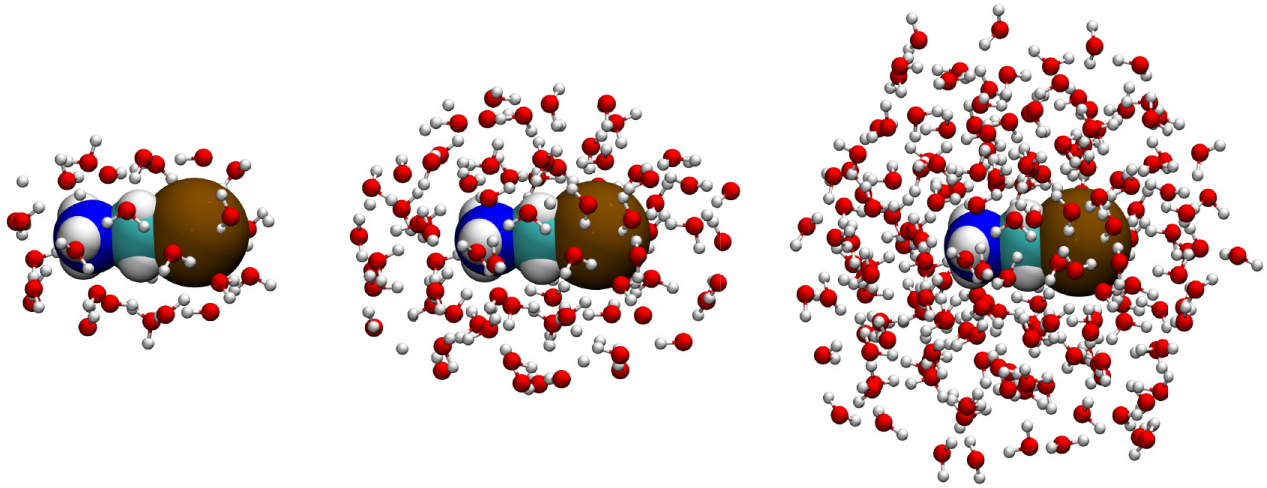

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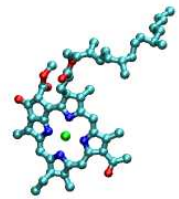
Natural Light-Harvesting Complexes

Structure of LH2 of *Rhodopseudomonas acidophila*



- main pigments: Bchl a

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

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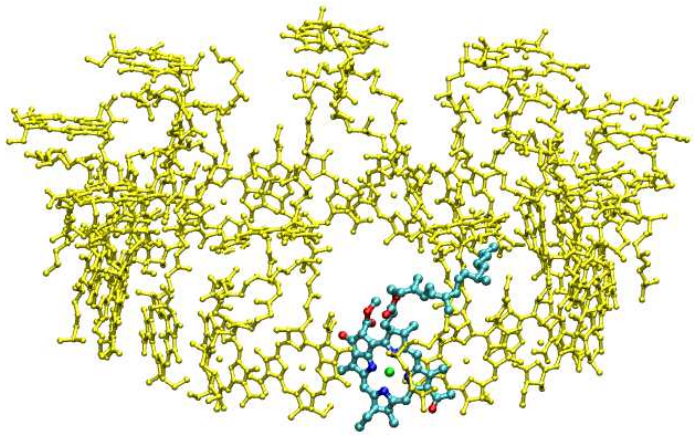

- main pigments: Bchl a
- 9 pairs of $\{\alpha, \beta\}$-Bchl a in B850 unit, 9 Bchl a in B800 unit

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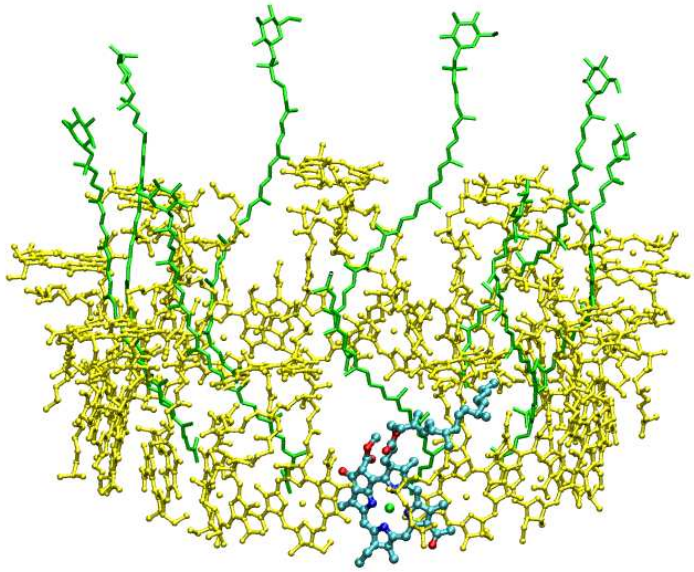

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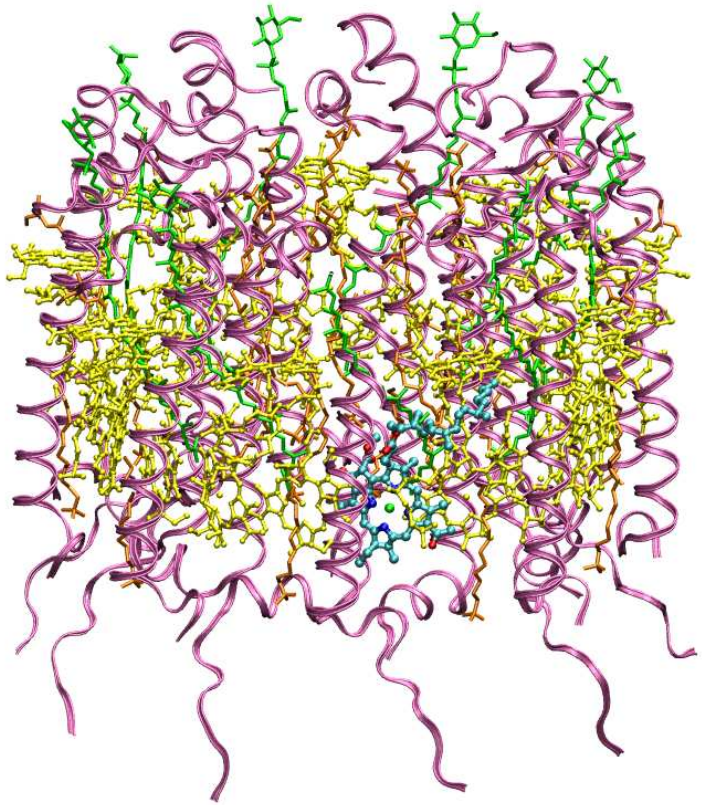

- main pigments: Bchl a
- 9 pairs of $\{\alpha, \beta\}$-Bchl a in B850 unit, 9 Bchl a in B800 unit
- 9 carotenoid pigments (rhodopin glucoside)
- 9 α- and β-apoproteins

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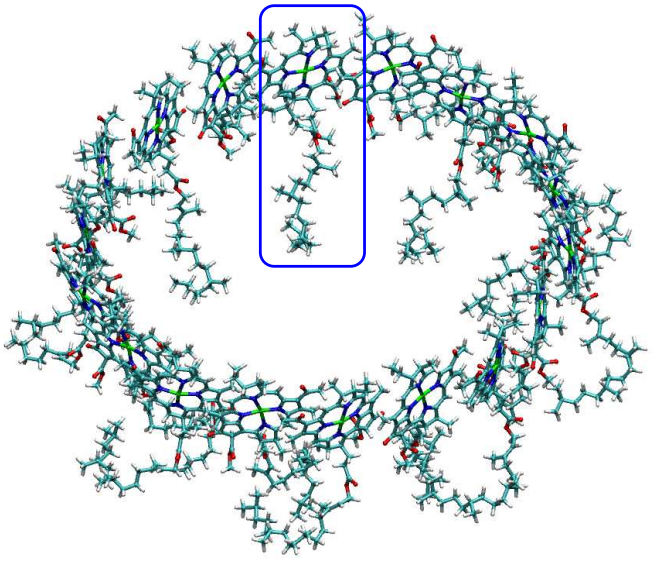
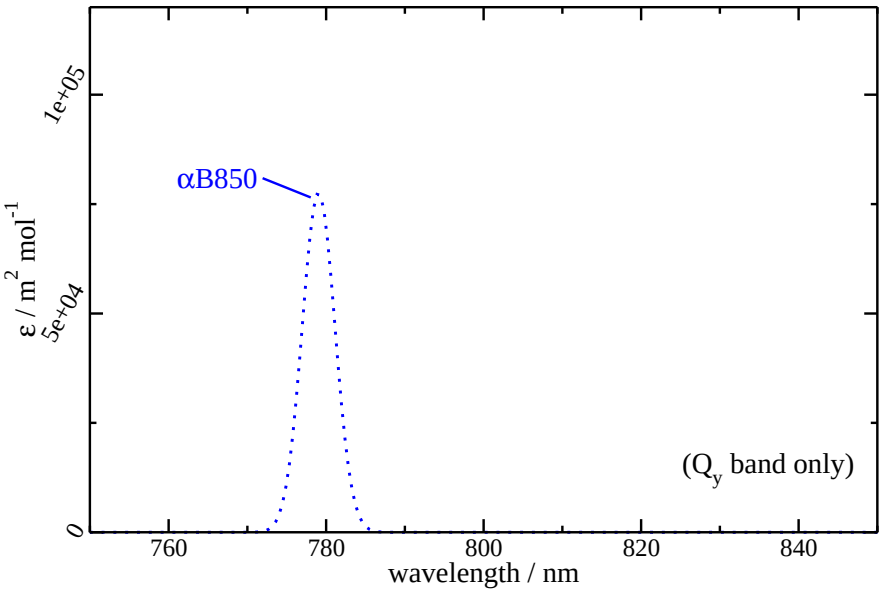
Absorption Spectra of the B850 Unit





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

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

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

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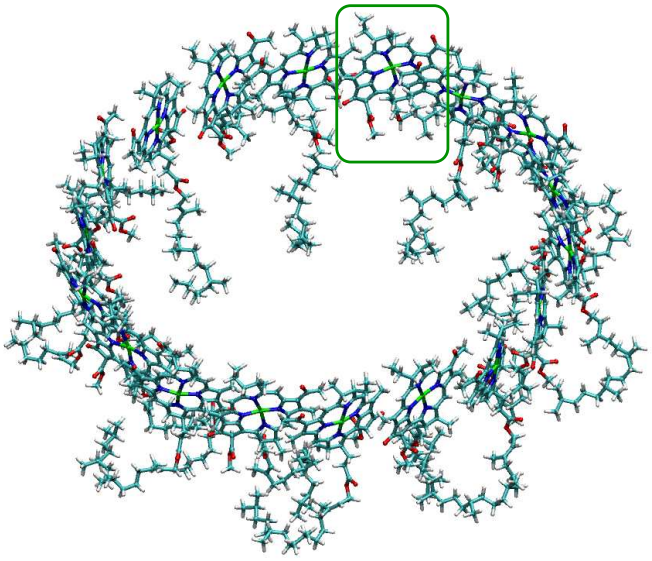

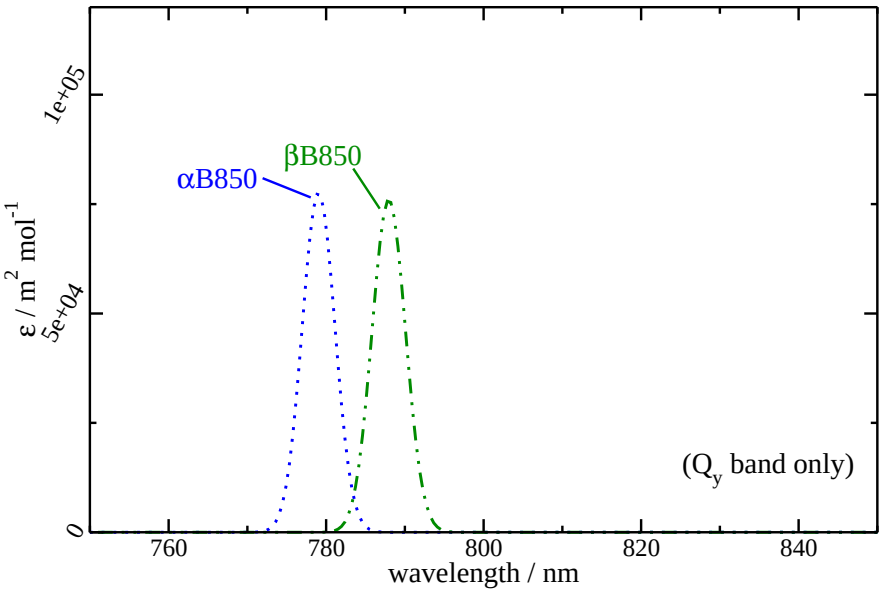

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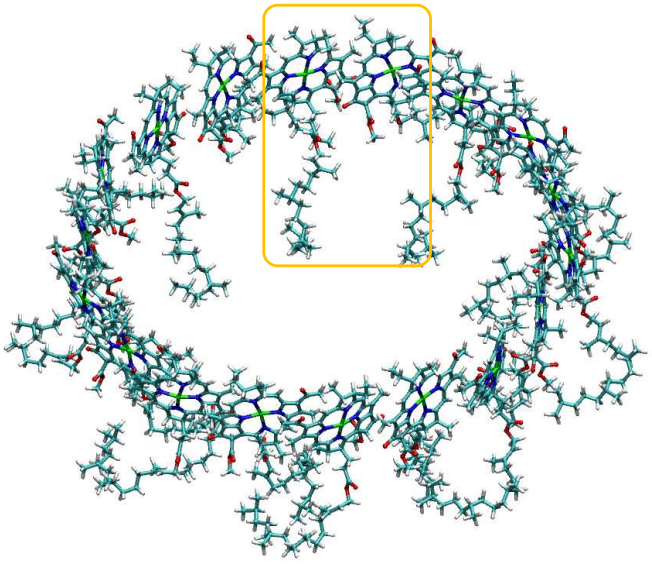

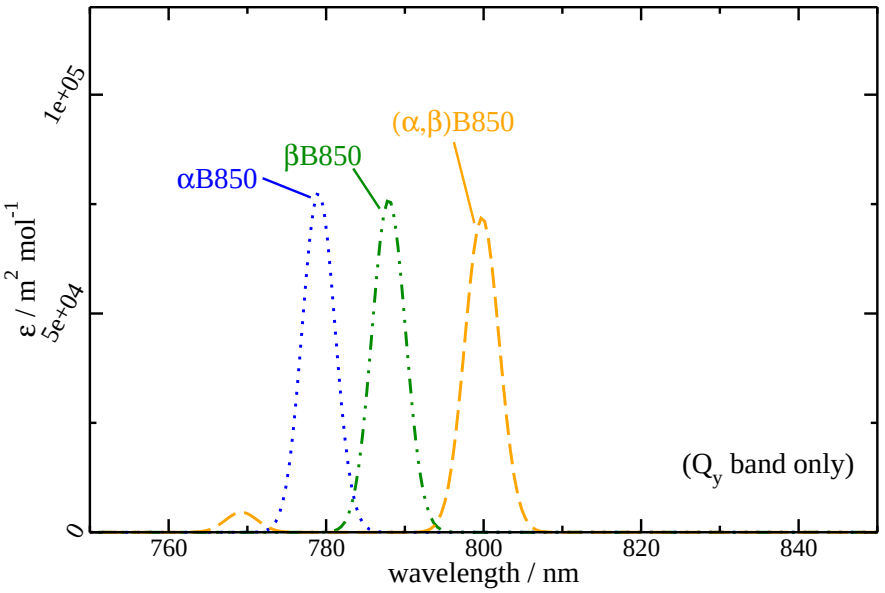

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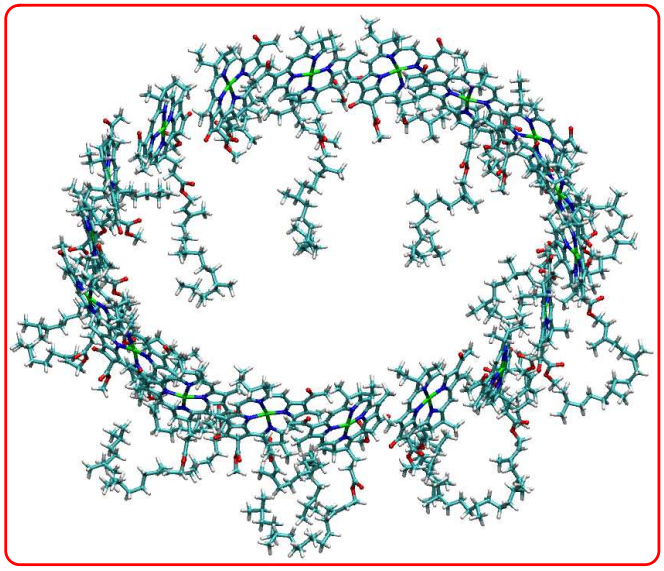

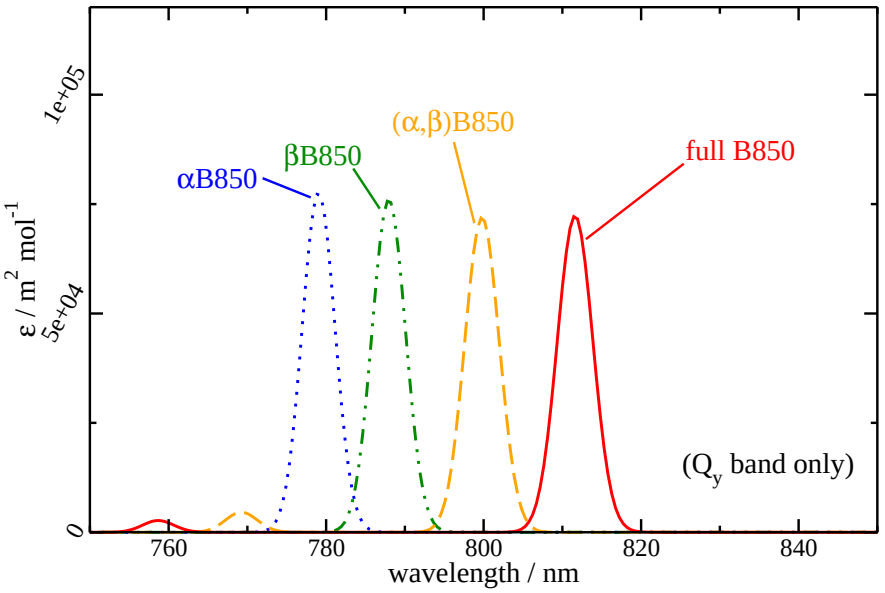

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- site energies: 1.59 eV [$\alpha(Q_y)$], 1.57 eV [$\beta(Q_y)$]

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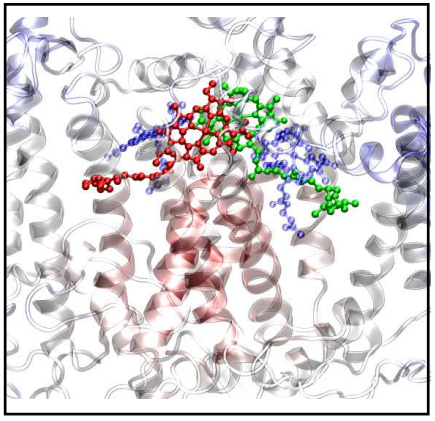
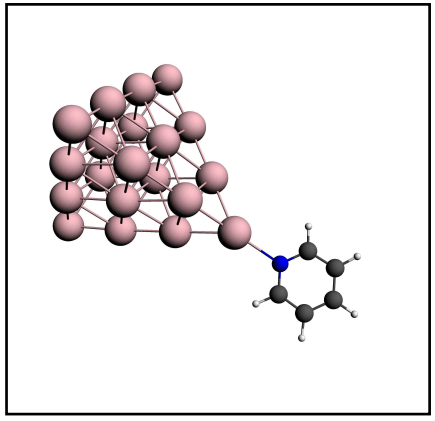
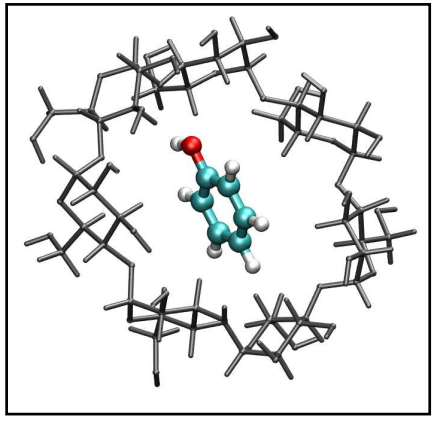
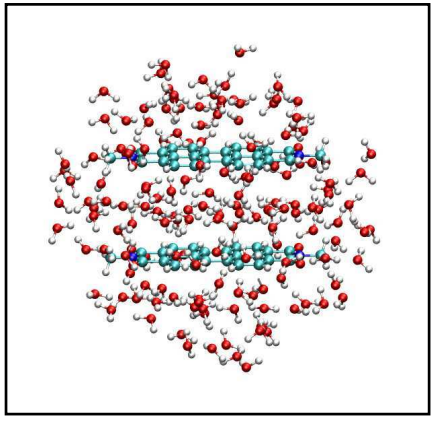
- exp. spectrum matches with shifted site energies: 1.56 eV [$\alpha(Q_y)$], 1.50 eV [$\beta(Q_y)$]

  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 $\vec{X}$ 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

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

with partition function Z

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

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

$$\langle A \rangle \quad = \quad \frac{1}{N_K} \sum_{k=1}^{N_k} A(\vec{X}_k)$$

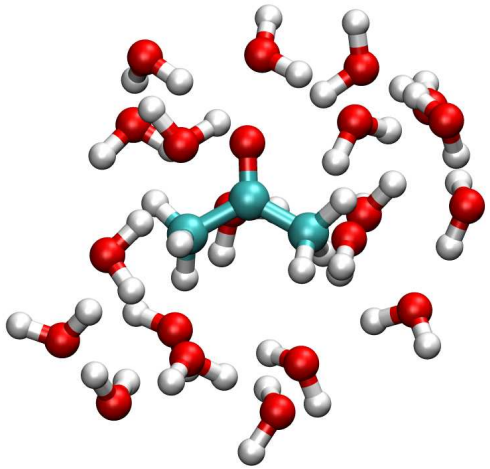
2) use ergodic hypothesis (equivalence of ensemble and time averages) and compute

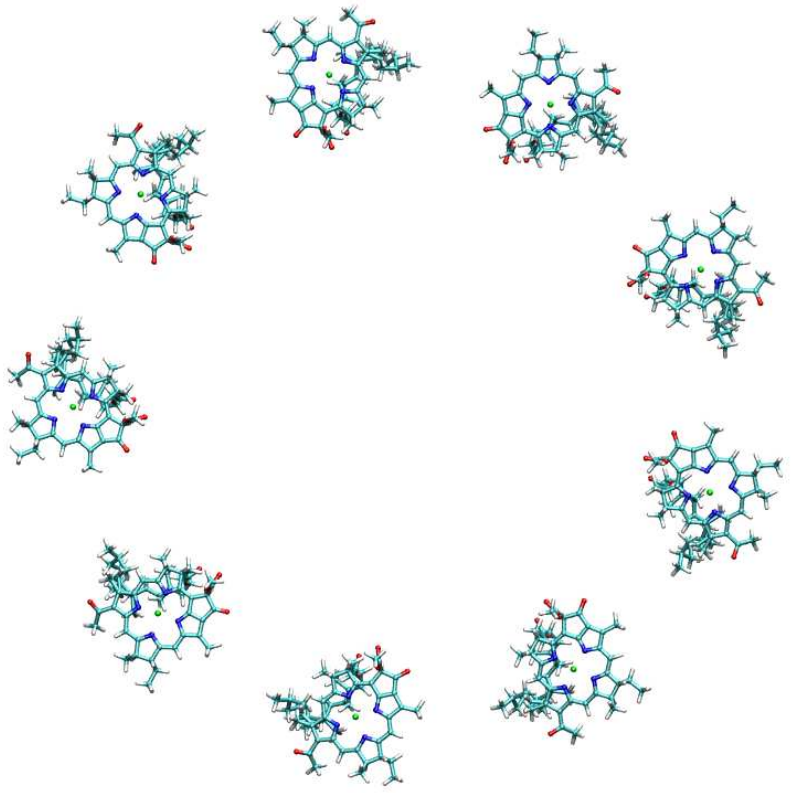
$$\langle A \rangle = \lim_{t \to \infty} \frac{1}{t} \cdot \int_{t_0}^{t_0+t} A(\tau) \mathrm{d}\tau.$$

Other common approaches for conformational sampling:

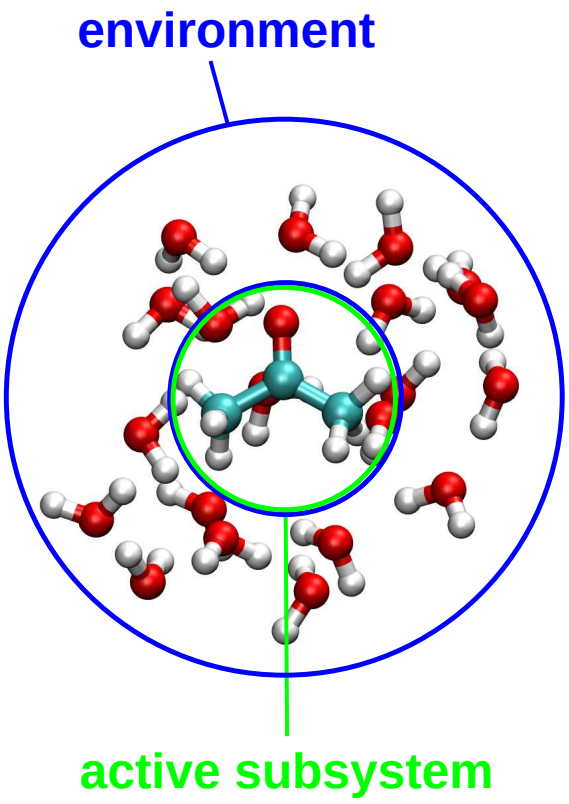
- Boltzmann-average over all relevant local minimum conformations
- weighted random minimum structures (systematic microsolvation)

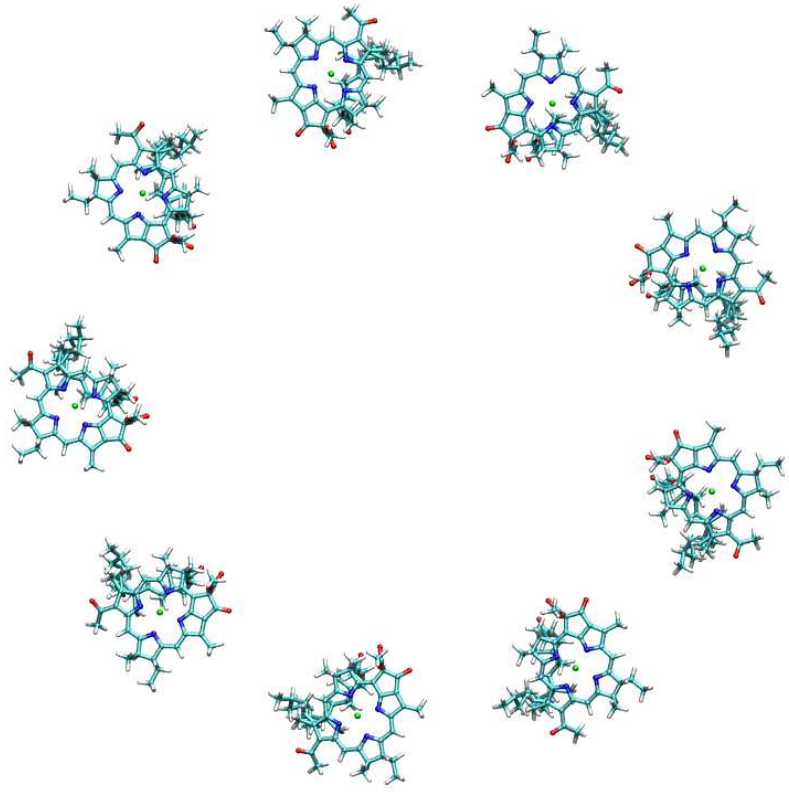
Subsystem vs. Embedding Approaches





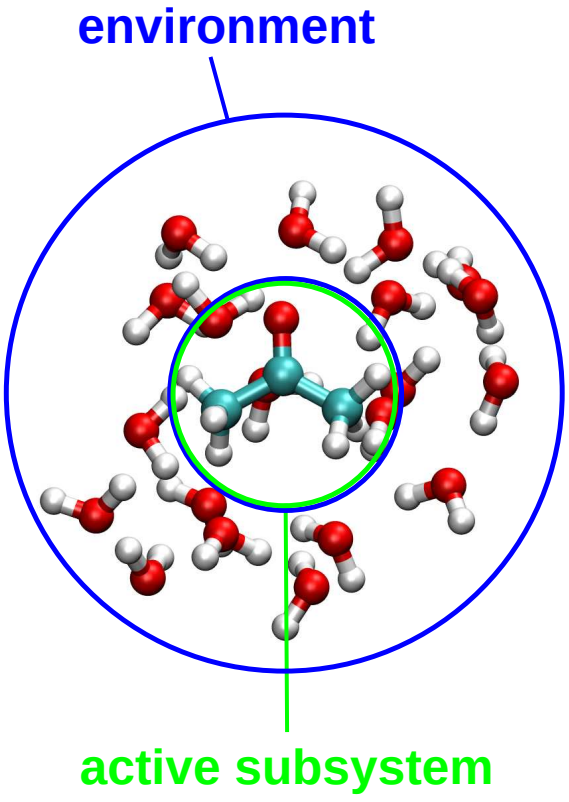
Subsystem vs. Embedding Approaches

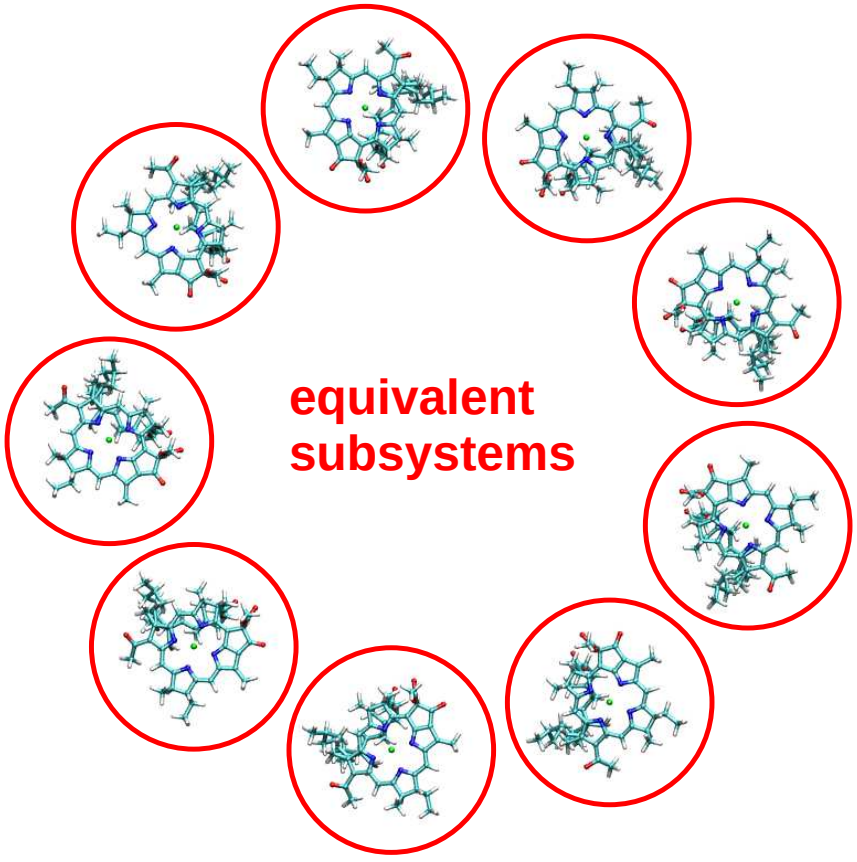




- embedding (“focussed”) approach:
  high accuracy for active part, lower accuracy for environment *and* interaction

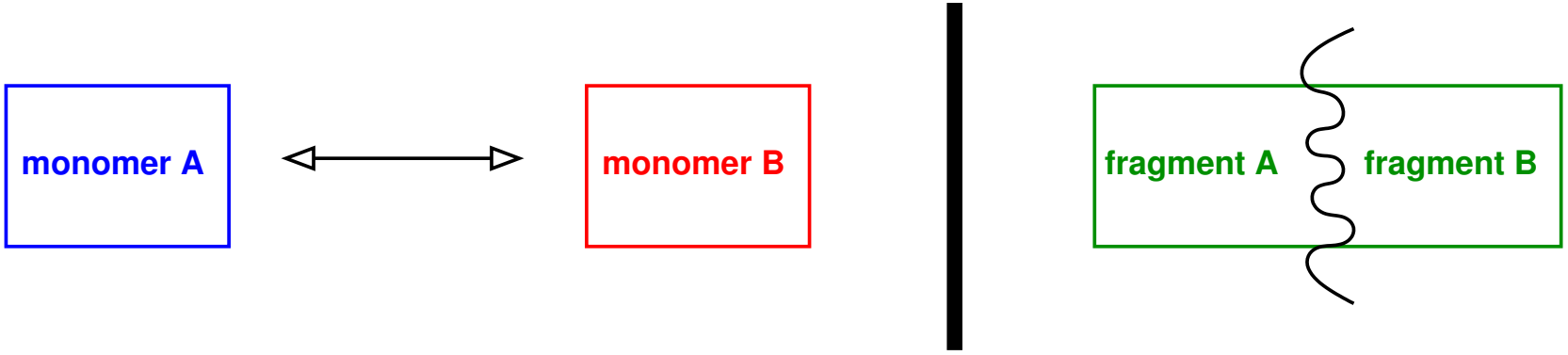
Subsystem vs. Embedding Approaches





- 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

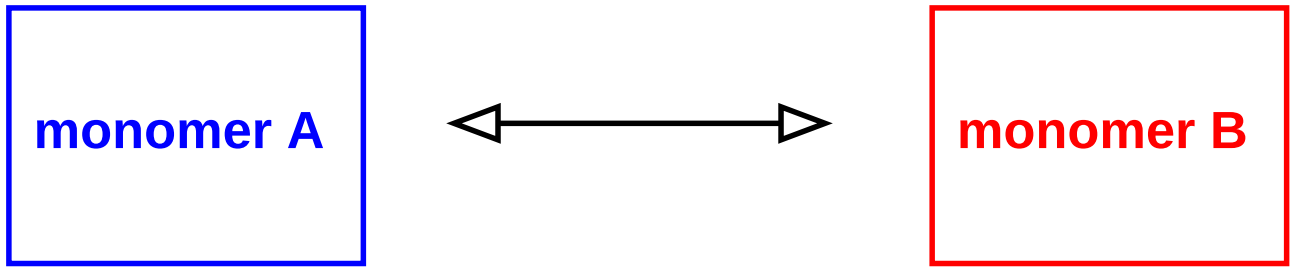
Starting point 2: Total system

- partition quantum mechanical descriptor into subsystem contributions

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

- derive optimization conditions for subsystems

Interacting Subsystems: Some initial thoughts



- isolated monomers can be described by individual Hamiltonians:

$$\begin{aligned} \hat{H}_A \Psi_A &= E_A \Psi_A \\ \hat{H}_B \Psi_B &= E_B \Psi_B \end{aligned}$$

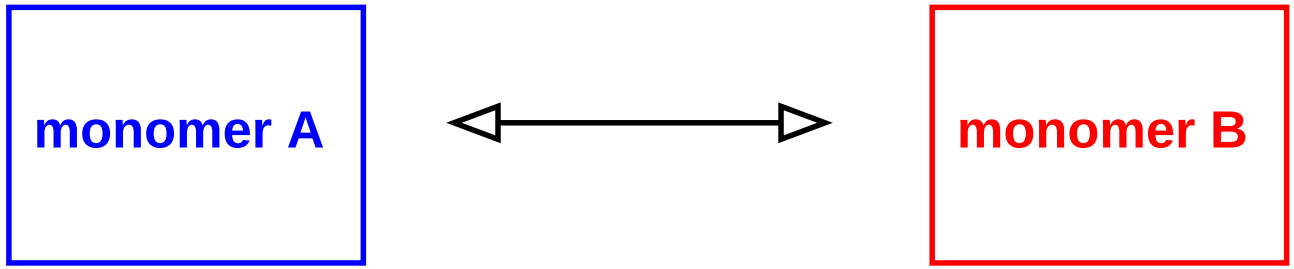
- assuming zero interaction, the total wavefunction can be factorized,

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

- true dimer Hamiltonian including interaction:

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

Interacting Subsystems: Some initial thoughts



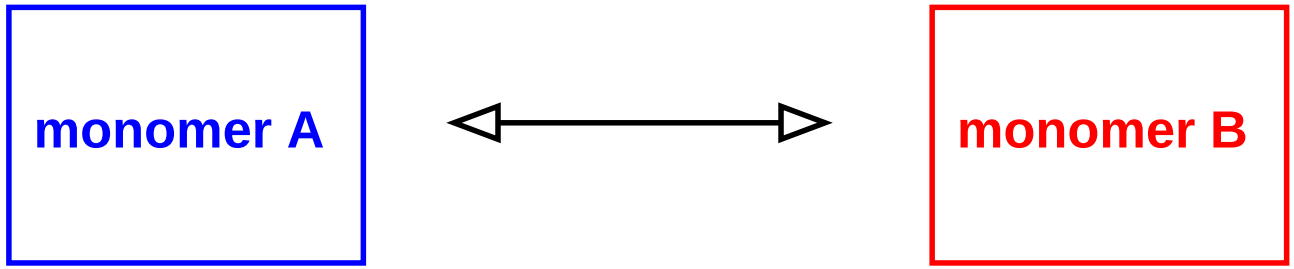
- if interaction is weak: use perturbation theory

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

- form of the interaction Hamiltonian:

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

Interacting Subsystems: Some initial thoughts



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- conceptual problem: electrons are indistinguishable particles . . .

Interacting Subsystems: Some initial thoughts

- wave function for N independent subsystems:

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

- non-interacting subsystems: product ansatz

Interacting Subsystems: Some initial thoughts

- wave function for N independent subsystems:

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

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- antisymmetrisation necessary (but no effect for non-overlapping wavefunctions)

Interacting Subsystems: Some initial thoughts

- wave function for N independent subsystems:

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- 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)

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

- 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: $E^{(2)} = E^{(2)}_{\mathrm{ind,A}} + E^{(2)}_{\mathrm{ind,B}} + E^{(2)}_{\mathrm{disp}}$,

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

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

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

Long-Range Interactions: Results from PT

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

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

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

- **induction terms:**
  interaction of transition density (from $\Psi^*_{0,A}\Psi_{K,A}$) with ground-state density (from $\Psi^*_{0,B}\Psi_{0,B}$)

  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:

$$\Psi_0^{\mathrm{AB}} \approx \hat{A}_{\mathrm{AB}} \Psi_0^{\mathrm{A}} \Psi_0^{\mathrm{B}} = N_{\mathrm{AB}} \sum_{\hat{P}} (-1)^p \hat{P} \Psi_0^{\mathrm{A}} \Psi_0^{\mathrm{B}}$$

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

- first-order energy correction:

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

- exchange contribution arises from:

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

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

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

- 1st order interaction energy:

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

- result for simple product would be:

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

- difference: exchange–repulsion energy, E_{er}

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

Exchange–Repulsion

- exchange–repulsion energy

$$E_{\mathrm{er}} = -\frac{1}{(1-S^2)}\langle\psi_a(1)\psi_b(2)|\hat{H}_{A\leftrightarrow B}|\psi_b(1)\psi_a(2)\rangle + \frac{S^2}{(1-S^2)}\langle\psi_a(1)\psi_b(2)|\hat{H}_{A\leftrightarrow B}|\psi_a(1)\psi_b(2)\rangle$$

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

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

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

$$-\left\langle\psi_a(1)\psi_b(2)\left|\frac{1}{r_{12}} - \frac{1}{R_{\mathrm{B1}}} - \frac{1}{R_{\mathrm{A2}}}\right|\psi_b(1)\psi_a(2)\right\rangle$$

$$= \left\langle\psi_a(1)\psi_b(2)\left|\frac{1}{R_{\mathrm{B1}}} + \frac{1}{R_{\mathrm{A2}}}\right|\psi_b(1)\psi_a(2)\right\rangle - (\psi_a\psi_b|\psi_b\psi_a)$$

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

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

Exchange–Repulsion

- from first term (continued):

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

  $\Rightarrow$ contains repulsion (due to monomer overlap) and exchange (attractive)

- overall effect of E_{er} 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 $S = 0$

$\Rightarrow$ 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, ...

Starting Point for Approximations

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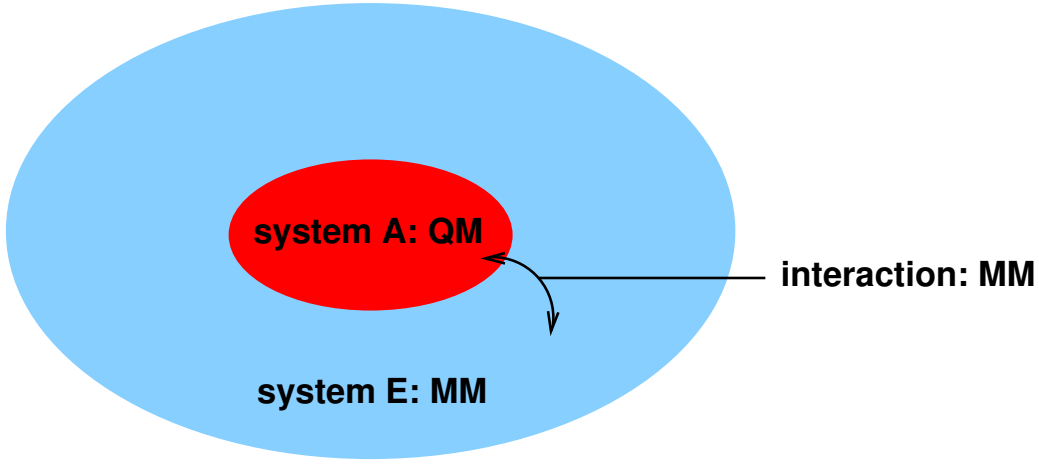
- maybe several active systems, maybe more layers, ...

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

QM/MM Hybrid Methods



- 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

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

QM/MM: Partitioning the Energy

Three energy contributions:

(1) active-system energy

$$E_A^{\mathrm{QM}} = \langle \Psi_A | \hat{H}_A | \Psi_A \rangle$$

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

(2) environment energy

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

where typically

$$\begin{aligned} E_{\mathrm{bonded}}(\mathbf{R}_E) &= E_{\mathrm{stretch}}(\mathbf{R}_E) + E_{\mathrm{bend}}(\mathbf{R}_E) + E_{\mathrm{torsion}}(\mathbf{R}_E) \\ E_{\mathrm{nonbonded}}(\mathbf{R}_E) &= E_{\mathrm{electrostatic}}(\mathbf{R}_E) + E_{\mathrm{vdW}}(\mathbf{R}_E) \end{aligned}$$

E_{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↔MM interaction: Apply MM energy expression

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

Notes:

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

QM/MM: Partitioning the Energy

Three energy contributions (cont'd):

(3) QM↔MM interaction: Apply MM energy expression

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

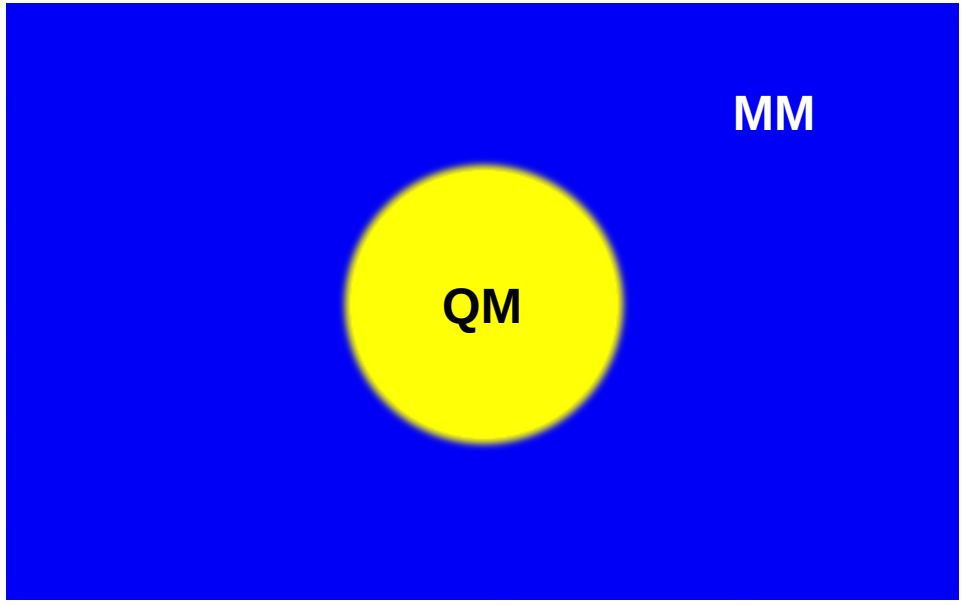
Notes:

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

Automatic parametrization/setup becomes ever more important, e.g.

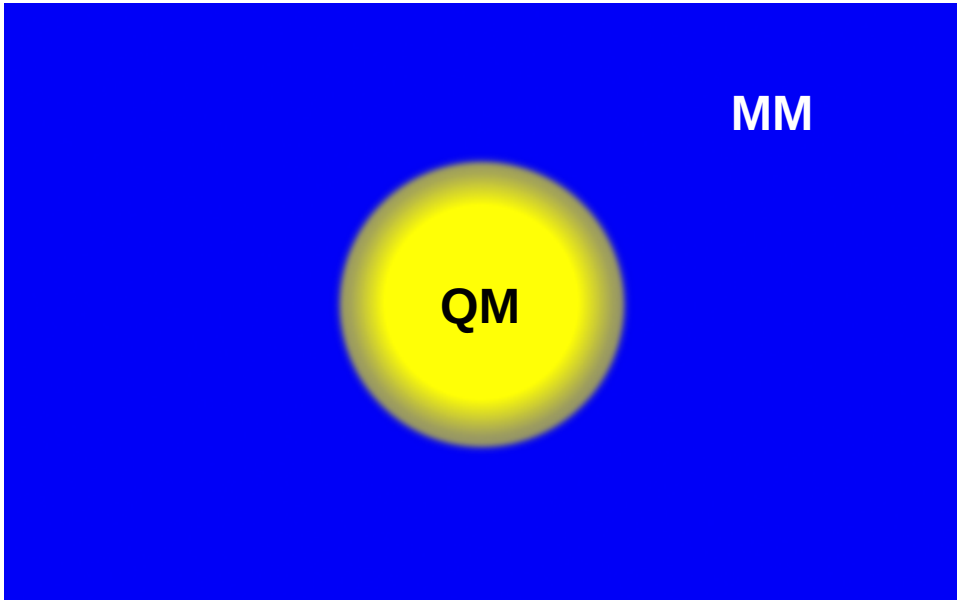
- quantum mechanically derived force field (QMDFF)
  S. Grimme, *J. Chem. Theory Comput.* 2014, **10**, 4497.
- self-parametrizing system-focused atomistic models
  C. Brunken, M. Reiher, *J. Chem. Theory Comput.* 2020, **16**, 1646.
- system-specific parameter optimization incl. polarizable FF
  X. Hu, K.S. Amin, M. Schneider, C. Lim, D. Salahub, C. Baldauf, *J. Chem. Theory Comput.* 2024, **20**, 1448.
- automated FF parameters for metal-containing molecules (easyPARM)
  A. Abdelgawwad, A. Francés–Monerris, *J. Chem. Theory Comput.* 2025, **21**, 1817.

QM/MM Interaction



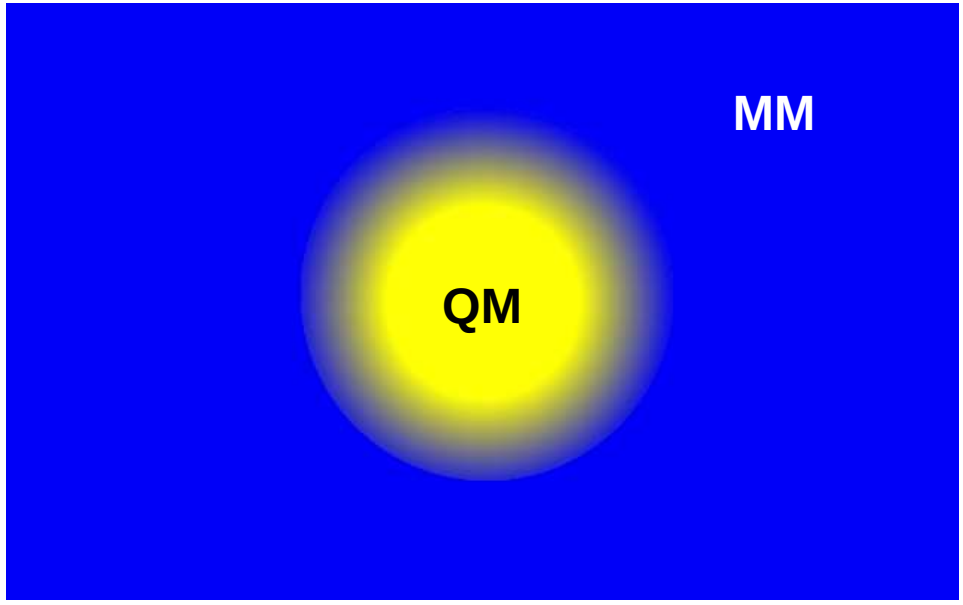
- Mechanical Embedding: Wavefunction of QM part unchanged

QM/MM Interaction



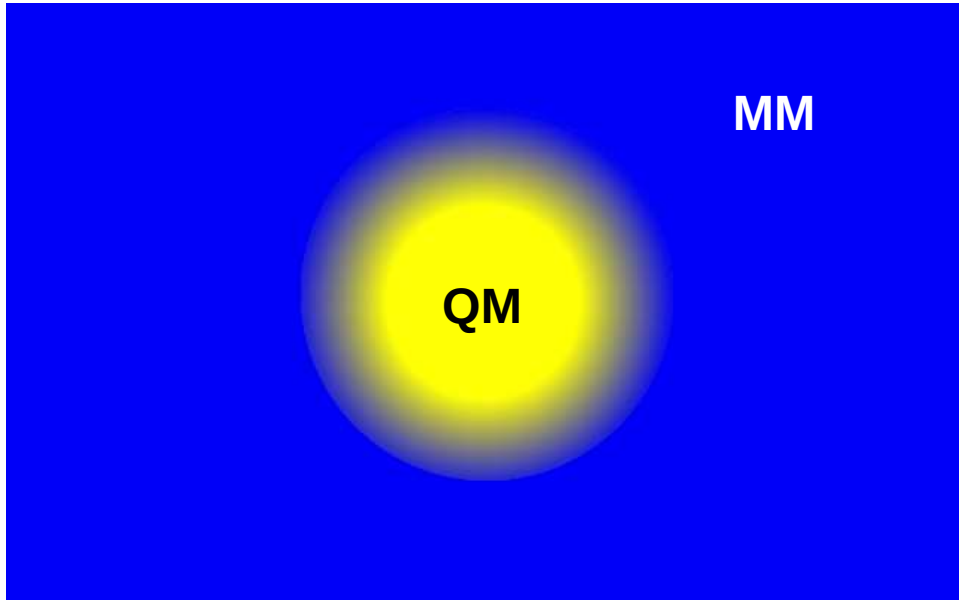
- Mechanical Embedding: Wavefunction of QM part unchanged
- Hamiltonian/Electronic Embedding: QM part polarized by environment

QM/MM Interaction



- Mechanical Embedding: Wavefunction of QM part unchanged
- Hamiltonian/Electronic Embedding: QM part polarized by environment
- Polarizable Embedding: Mutual polarization of QM and MM part

QM/MM Interaction



- Mechanical Embedding: Wavefunction of QM part unchanged
- Hamiltonian/Electronic Embedding: QM part polarized by environment
- Polarizable Embedding: Mutual polarization of QM and MM part

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

QM/MM Interaction

Mechanical Embedding:

- $E_{\text{electrostatic},A\leftrightarrow E}$ evaluated with MM charges for QM atoms

$\Rightarrow$ No polarization of QM wavefunction

$\Rightarrow$ Only indirect effects (change in equilibrium structure)

$\Rightarrow$ Changes in QM charge distribution not reflected in interaction term

(e.g., along reaction coordinates)

QM/MM Interaction

Hamiltonian Embedding:

- electrostatic interaction Hamiltonian:

$$\begin{aligned}\hat{H}_{\text{elstat},A\leftrightarrow E} &= -\sum_{i}^{\text{el.}}\sum_{a}^{\text{MM atoms}}\frac{q_a}{|\mathbf{r}_i-\mathbf{R}_a|}+\sum_{I}^{\text{nuc.}}\sum_{a}^{\text{MM atoms}}\frac{Z_I q_a}{|\mathbf{R}_I-\mathbf{R}_a|}\\ &= \sum_{i}^{\text{el.}} v_{\text{emb}}^{\text{elstat}}(\mathbf{r}_i)+\sum_{I}^{\text{nuc.}}\sum_{a}^{\text{MM atoms}}\frac{Z_I q_a}{|\mathbf{R}_I-\mathbf{R}_a|}\end{aligned}$$

$\Rightarrow$ 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 $E_A^{\text{QM}}=\langle\Psi_A|\hat{H}_A|\Psi_A\rangle$

QM/MM Interaction

Hamiltonian Embedding:

- electrostatic interaction energy:

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

- total QM/MM energy:

$$\begin{aligned} E_{\mathrm{tot}}^{\mathrm{QM/MM}} &= E_A^{\mathrm{QM}} + E_E^{\mathrm{MM}} + E_{\mathrm{vdW},A\leftrightarrow E} \\ &\quad + \left\langle \Psi_A \left| \sum_i^{\text{el.}} v_{\mathrm{emb}}^{\mathrm{elstat}}(\mathbf{r}_i) \right| \Psi_A \right\rangle + \sum_I^{\text{nuc.}} \sum_a^{\text{MM atoms}} \frac{Z_I q_a}{|\mathbf{R}_I - \mathbf{R}_a|} \\ &= E'_A + E_E^{\mathrm{MM}} + E_{\mathrm{vdW},A\leftrightarrow E} + \sum_I^{\text{nuc.}} \sum_a^{\text{MM atoms}} \frac{Z_I q_a}{|\mathbf{R}_I - \mathbf{R}_a|} \end{aligned}$$

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

QM/MM Interaction

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:

$$\boldsymbol{\mu}_a^{\text{ind}} \quad = \quad \boldsymbol{\alpha}_a \cdot \vec{F}(\mathbf{R}_a)$$

- 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

$$\hat{H}_{\mathrm{QM/MM}} = \sum_i v^{\mathrm{DRF}}(\mathbf{r}_i)$$

$$v^{\mathrm{DRF}}(\mathbf{r}) = \sum_a^{\text{MM atoms}} \frac{q_a}{|\mathbf{r}-\mathbf{R}_a|} + \sum_{\mathrm{a}}^{\text{MM atoms}} \boldsymbol{\mu}_a^{\mathrm{ind}} \cdot \frac{(\mathbf{r}-\mathbf{R}_a)}{|\mathbf{r}-\mathbf{R}_a|^3}$$

- induced dipoles are computed self-consistently from

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

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.

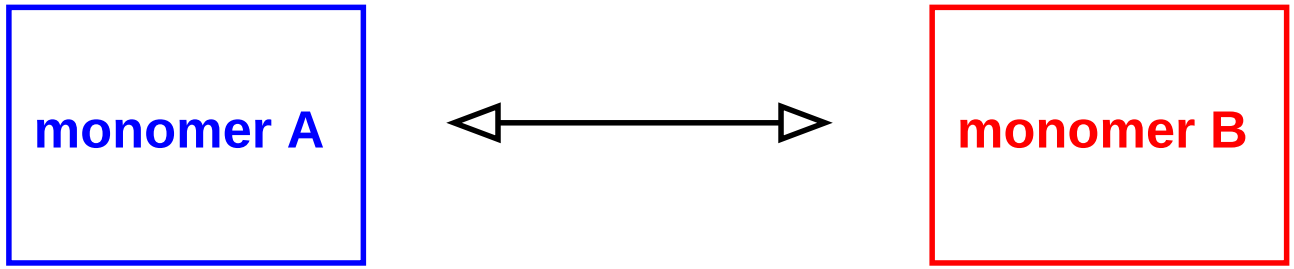
Other Polarizable Embedding Schemes

- 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/environment fragments (e.g., CHELPG charges, LOPROP polarizabilities)
- or fitted, e.g., to experimental polarizabilities

Reminder: Interacting Subsystems



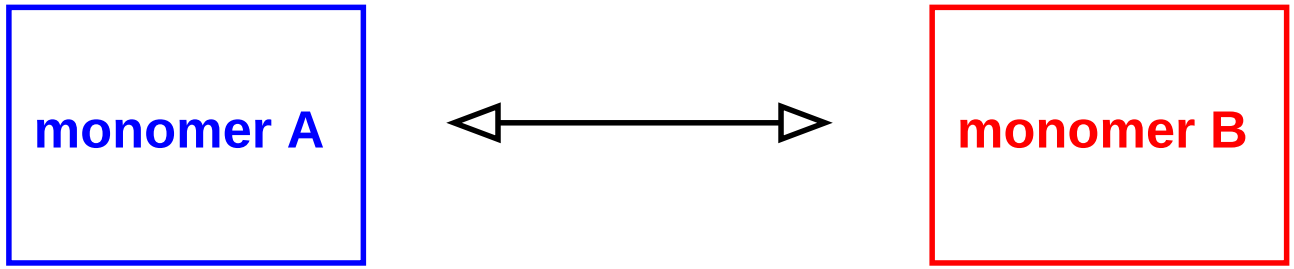
- if interaction is weak: use perturbation theory

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

- 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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- How to get rid of Ψ_B?

QM/MM Partitioning

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

$$\nabla_{\mathbf{r}}^k = \left(\frac{\partial}{\partial r_x} \right)^{k_x} \left(\frac{\partial}{\partial r_y} \right)^{k_y} \left(\frac{\partial}{\partial r_z} \right)^{k_z}$$

J.M.H. Olsen, J. Kongsted, Adv. Quantum Chem. **61**, 107 (2011).

QM/MM Partitioning

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

$$
\begin{aligned}
E^{(1)}_{\mathrm{el,el}} &= \sum_{a\in A}^{n_A}\sum_{b\in B}^{n_B} \left\langle \Psi_A\Psi_B \left| \frac{1}{|\mathbf{r}_a - \mathbf{r}_b|} \right| \Psi_A\Psi_B \right\rangle \\
&= \sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} \left\langle \Psi_A \left| \sum_{a\in A}^{n_A} \nabla^k_{\mathbf{r}_a} \frac{1}{|\mathbf{r}_a - \mathbf{r}_0|} \right| \Psi_A \right\rangle \cdot \left\langle \Psi_B \left| \sum_{b\in B}^{n_B} (\mathbf{r}_b - \mathbf{r}_0)^k \right| \Psi_B \right\rangle \\
&= \sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} \left\langle \Psi_A \left| \sum_{a\in A}^{n_A} T^{(k)}(\mathbf{r}_a) \right| \Psi_A \right\rangle Q^{(k)}_{B,\mathrm{el}}
\end{aligned}
$$

($Q^{(k)}_{B,\mathrm{el}}$: electronic part of multipole moment of fragment B)

$\Rightarrow$ Effective separation of coordinates from fragments A and B

J.M.H. Olsen, J. Kongsted, Adv. Quantum Chem. **61**, 107 (2011).

QM/MM Partitioning

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

$$\begin{aligned} E^{(1)} &= \langle \Psi_A \Psi_B | \hat{H}_{A \leftrightarrow B} | \Psi_A \Psi_B \rangle \\ &= \sum_{|k|}^{\infty} \frac{(-1)^{|k|}}{k!} (F^{(k)}_{A,\mathrm{nuc}} + \langle \Psi_A | \hat{F}^{(k)}_{A,\mathrm{el}} | \Psi_A \rangle) Q^{(k)}_B \end{aligned}$$

with

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

and multipole moments of system B,

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

J.M.H. Olsen, J. Kongsted, Adv. Quantum Chem. **61**, 107 (2011).

QM/MM Partitioning

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

J.M.H. Olsen, J. Kongsted, Adv. Quantum Chem. **61**, 107 (2011).

QM/MM Interaction

Hamiltonian Embedding:

- effects of Pauli repulsion: often not included in $\hat{H}'_A$

$\Rightarrow$ MM atoms can act as electron traps (*overpolarization*, *electron spill-out*, or *electron leaking*)

- one solution strategy: replace Coulombic potential $(-1/r)$ by

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

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:

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

- $\hat{V}_{\text{ex-rep}}$ 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_j is coordinate vector of an LMO centroid; α_j and β_j are parameters)

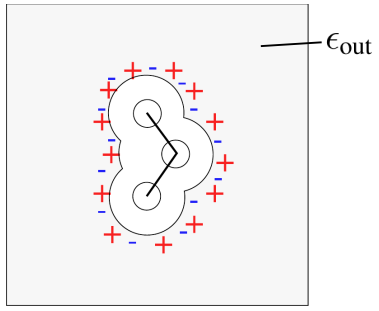
M. Gordon *et al.*, J. Phys. Chem. A 2001, **105**, 293.

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

Continuum Solvation Models

Continuum Solvation Models

Idea: Place molecule in a dielectric continuum with relative permittivity ϵ_{out}



- charge density of the molecule polarizes the continuum

$\Rightarrow$ gives rise to electrostatic interaction

Continuum Solvation Models

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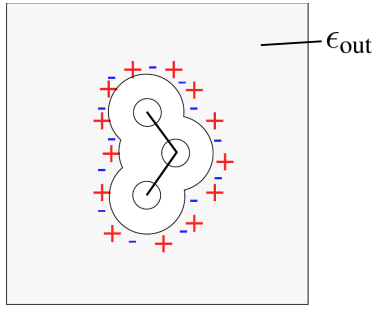


- charge density of the molecule polarizes the continuum

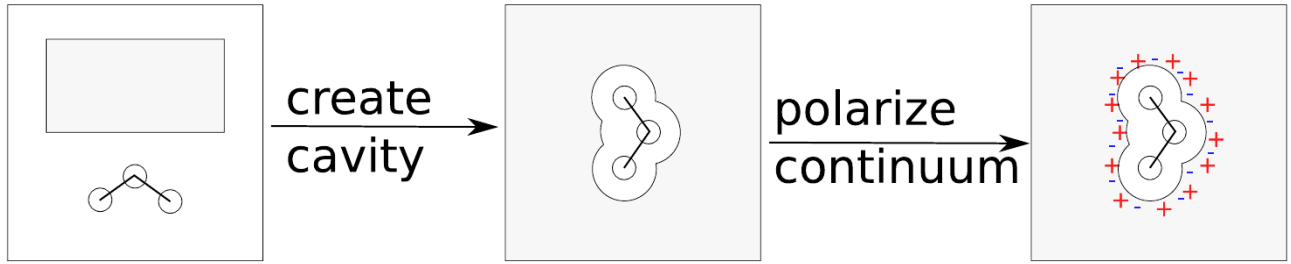
$\Rightarrow$ gives rise to electrostatic interaction

If molecule is described by QM method:

- molecule polarizes the environment
- environment polarizes the molecule

$\Rightarrow$ *self-consistent reaction field* (SCRF) problem

Continuum Solvation Models



Common Goal: Computation of Solvation Free Energies

- usually, electrostatics alone is not accurate enough
- write free-energy change as

$$\Delta G_{\text{solv}} = \Delta G_{\text{elstat}} + \Delta G_{\text{nonelstat}}$$

Phenomenologically, $\Delta G_{\text{nonelstat}}$ may carry contributions from

- cavity formation
- dispersion interaction
- Pauli repulsion
- hydrogen bonding etc.

Not entirely independent! Other terms may be included; see: J.M. Herbert, *WIREs Comput. Mol. Sci.* 2021, **11**, e1519.

Continuum Solvation Models

Common parametrization of non-electrostatic terms:

$$\begin{aligned} \Delta G_{\text{nonelstat}} &= \Delta G_{\text{cavity}} + \Delta G_{\text{Dispersion}} \\ &= \beta V_{\text{cavity}} + \gamma A_{\text{SASA}} \qquad \text{with} \quad A_{\text{SASA}} = \sum_{K}^{\text{atoms}} A_K^{\text{exposed}} \end{aligned}$$

(A_{SASA}: solvent-accessible surface area)

or, alternatively,

$$\Delta G_{\text{nonelstat}} = \sum_{K}^{\text{atoms}} \gamma_K A_K^{\text{exposed}}$$

(β, γ, γ_K: empirical parameters; V_{cavity}: cavity volume; A_K^{exposed} solvent-exposed surface area of atom K)

$\Rightarrow$ Non-electrostatic terms: often assumed proportional to “solute surface”

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.

Continuum Solvation Models

Computation of the electrostatic interaction:

- solvent: homogeneous medium with dielectric constant ϵ_{out}
- electrostatic potential $\varphi(\mathbf{r})$: from Poissson's equation,

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

- note: $\epsilon(\mathbf{r}) = \epsilon_{\text{in}} = 1$ within QM region, ϵ_{out} outside
- potential can be separated into two parts:

$$\varphi(\mathbf{r}) = \varphi_{\text{mol}}(\mathbf{r}) + \varphi_{\text{reac}}(\mathbf{r})$$

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.

Continuum Solvation Models

- reaction potential: $\varphi_{\mathrm{reac}}(\mathbf{r}) = \varphi(\mathbf{r}) - \varphi_{\mathrm{mol}}(\mathbf{r})$, with

$$\varphi_{\mathrm{mol}}(\mathbf{r}) = \int \frac{\rho_{\mathrm{mol}}(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \mathrm{d}\mathbf{r}'$$

  (electrostatic potential generated by molecular charge density)

- electrostatic solvation energy:

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

- 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

$$\varphi_{\text{reac}}(\mathbf{r}) = \int_{\text{surface}} \frac{\sigma(\mathbf{s})}{|\mathbf{r}-\mathbf{s}|} \mathrm{d}\mathbf{s}$$

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

$$\epsilon_{\text{out}}(\vec{n}_s \cdot \vec{\nabla})\varphi(\mathbf{s})|_{\text{out}} \quad = \quad \epsilon_{\text{in}}(\vec{n}_s \cdot \vec{\nabla})\varphi(\mathbf{s})|_{\text{in}}$$

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

- in practice: surface charge is discretized (tesserae),

$$\varphi_{\text{reac}}(\mathbf{r}) \approx \sum_k \frac{\sigma(\mathbf{s}_k)A_k}{|\mathbf{r}-\mathbf{s}_k|} = \sum_k \frac{q_k}{|\mathbf{r}-\mathbf{s}_k|}$$

(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:

$$\varphi(\mathbf{r}) \quad = \quad \varphi_{\text{reac}}(\mathbf{r}) + \varphi_{\text{mol}}(\mathbf{r}) = 0$$

  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

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

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

A. Klamt, G. Schüürmann, *J. Chem. Soc. Perkin Trans.* **2** (1993), 799;
J.M. Herbert, *WIREs Comput. Mol. Sci.* 2021, **11**, e1519.

Conductor-Like Screening Model (COSMO)

- electrostatic part of solvation energy in COSMO

$$G_{\text{elstat}}^{\text{COSMO}} = \frac{1}{2}\sum_{\mu}\sum_{\nu} q_\mu A_{\mu\nu} q_\nu + \sum_{A}\sum_{\mu} q_\mu B_{A\mu} Z_A + \sum_{\mu} q_\mu C_\mu$$

$q_\mu =$ apparent surface charges (ASCs), from minimization of $G_{\text{elstat}}^{\text{COSMO}}$,

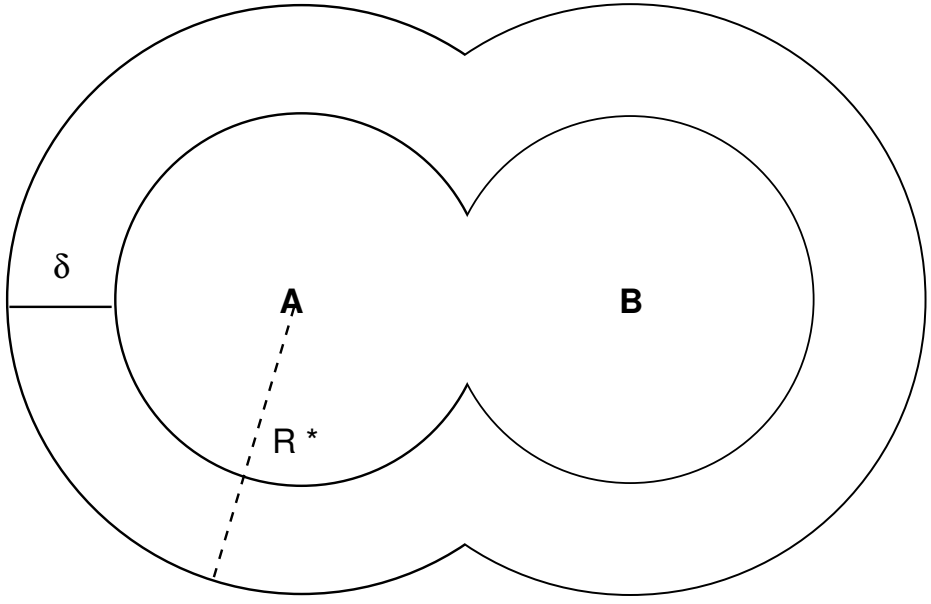
$$\mathbf{A}\vec{q} = -(\mathbf{B}\vec{Z} + \vec{C})$$

with

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

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



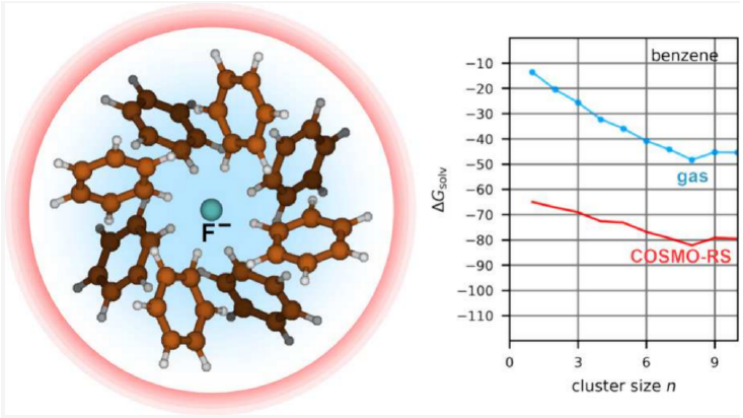
$$(R^* = R_A + R_{\mathrm{vdW}}^{\mathrm{solv}})$$

Further important aspects:

- shape of molecular cavity
- outlying charge corrections
- physically motivated extensions for dispersion, exchange–repulsion, etc.

J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* 2005, **105**, 2999;
J.M. Herbert, *WIREs Comput. Mol. Sci.* 2021, **11**, e1519;
L. Wittmann, A. Pausch, ChemRxiv preprint, DOI: 10.26434/chemrxiv.15003893/v2.

QM/MM vs. Continuum Approaches



M. Lehmann, F. Jameel, M. Kaupp, *J. Phys. Chem. A* 2026, **130**, 3736, DOI: 10.1021/acs.jpca.6c00886;

QM/MM:

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

Continuum Models:

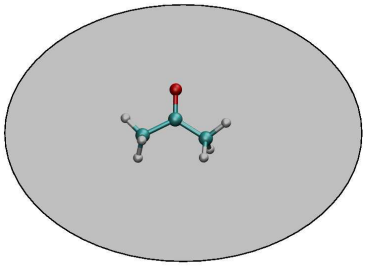
- implicitly include conformational sampling $\Rightarrow$ much cheaper
- mimic the polarizable part of QM/MM models
- no specific interactions

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

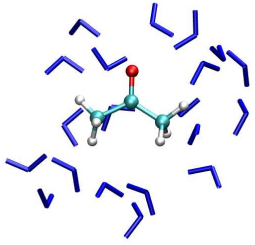
J.R. Pliego Jr., J.M. Riveros, WIREs Comput. Mol. Sci. **10** e1440 (2020).

QM/QM Hybrid Methods: An Introduction

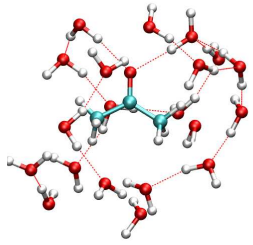
Methods for Environmental Effects



continuum models



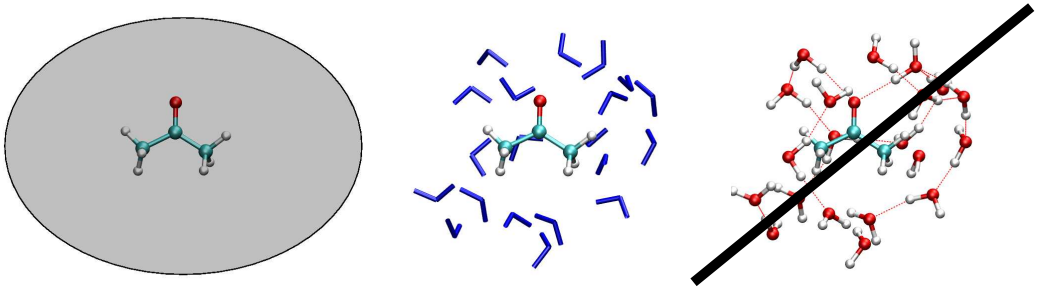
QM/MM methods



pure QM methods

Wish list for an “ideal” environmental model:

Methods for Environmental Effects

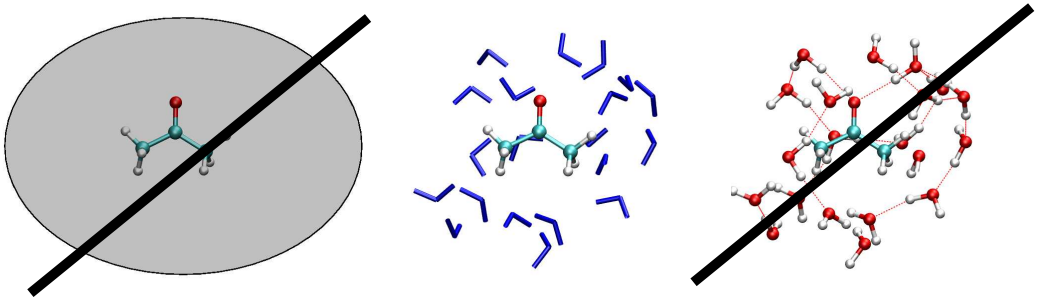


continuum models QM/MM methods pure QM methods

Wish list for an “ideal” environmental model:

- should be efficient (comparable to isolated molecule)

Methods for Environmental Effects



continuum models QM/MM methods pure QM methods

Wish list for an “ideal” environmental model:

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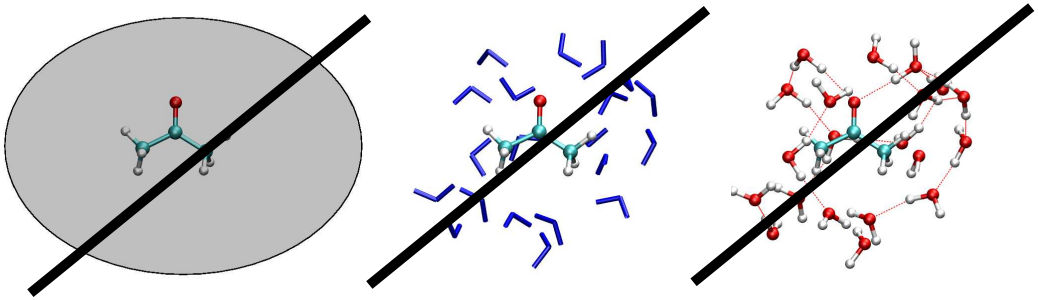

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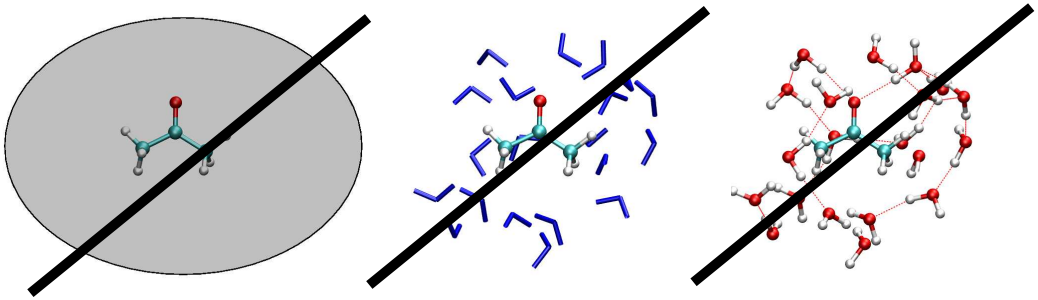
(But what about QM-derived MM models?)

Methods for Environmental Effects



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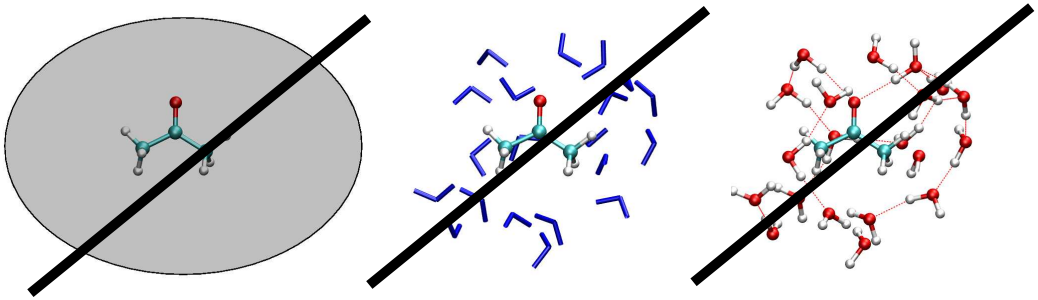

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  (But what about QM-derived MM models?)

- should focus on the embedded system

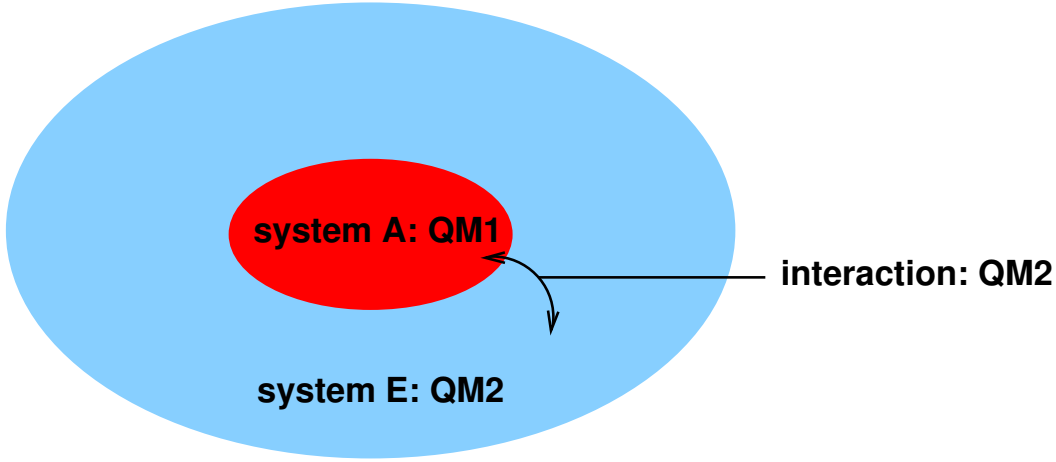
$\Rightarrow$ QM/QM embedding methods

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

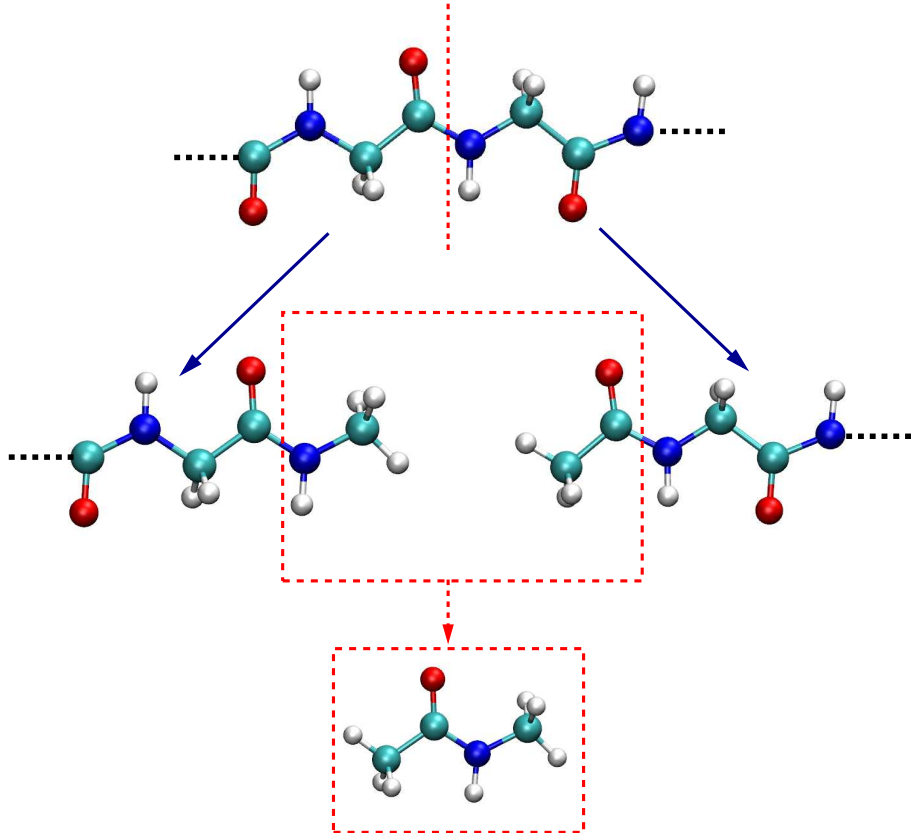
$$E_{\text{tot}}^{\text{QM/QM}} = E_{(A+E)}^{\text{QM2}} + (E_A^{\text{QM1}} - E_A^{\text{QM2}})$$

  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/Many-Body Expansions

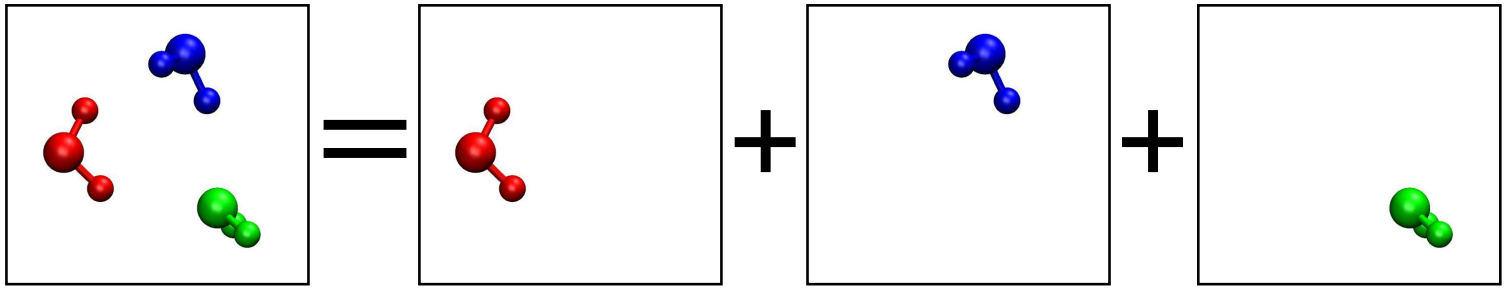
General idea:

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

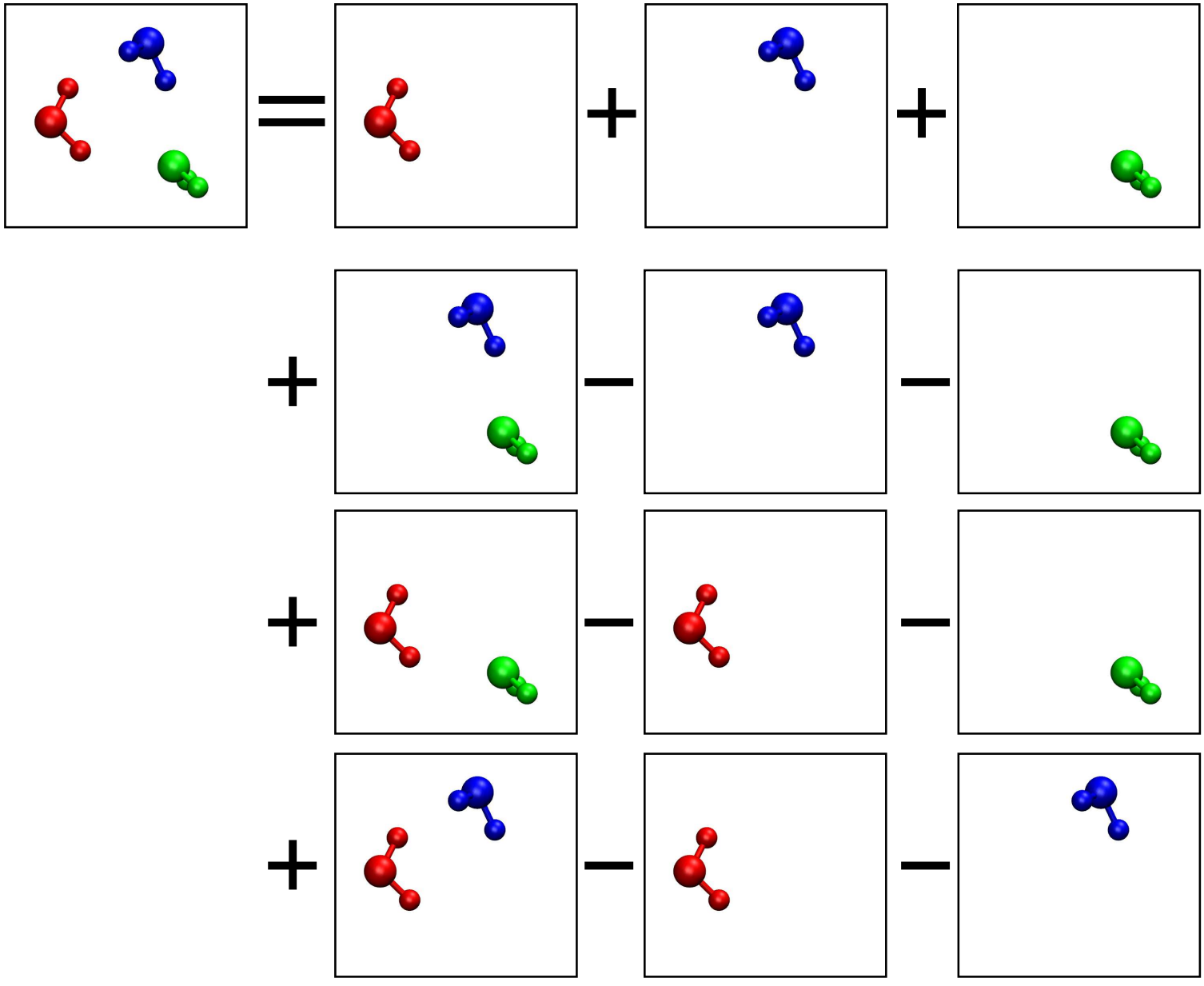
$$
\begin{aligned}
E_{\text{tot}} &= \sum_{I} E_I + \sum_{I<J} E_{I\leftrightarrow J} + \sum_{I<J<K} E_{I\leftrightarrow J\leftrightarrow K} + \ldots \\
E_{I\leftrightarrow J} &= E_{IJ} - E_I - E_J \\
E_{I\leftrightarrow J\leftrightarrow K} &= E_{IJK} - E_I - E_J - E_K \\
&\quad -(E_{IJ} - E_I - E_J) - (E_{IK} - E_I - E_K) - (E_{JK} - E_J - E_K)
\end{aligned}
$$

- nth-order increment method (MBEn): exact for n subsystems

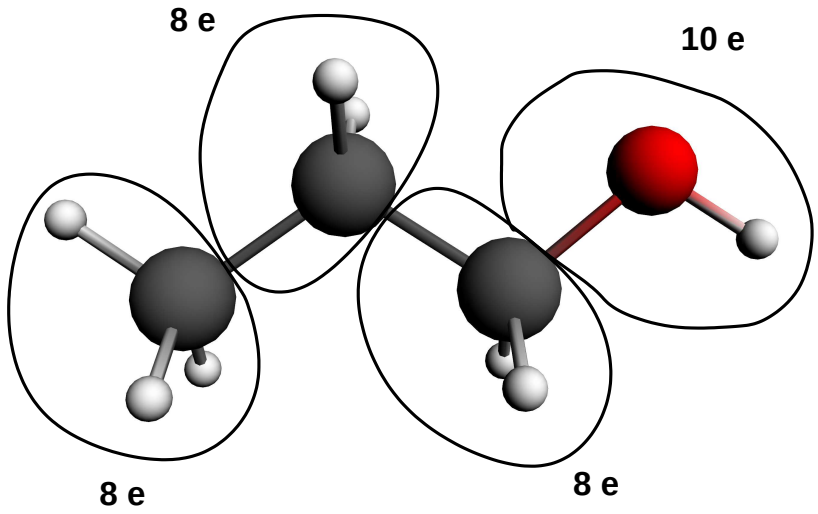
Increment Methods/Many-Body Expansions



Increment Methods/Many-Body Expansions



Fragment Molecular Orbital Method (1)

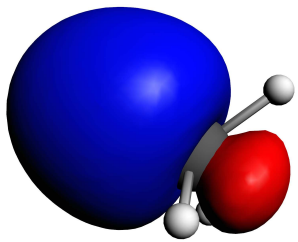


FMO-1

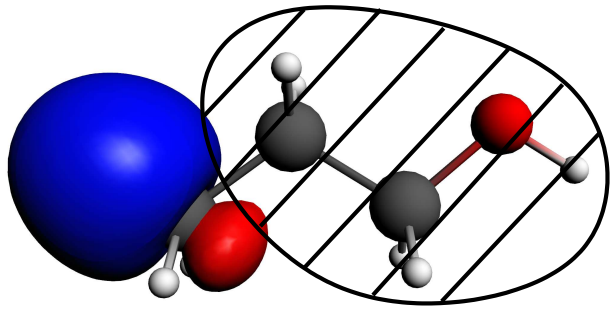
- fragmentation without separation of bond electron pairs
- fragment calculations under full electrostatic embedding
- no capping applied

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

Fragment Molecular Orbital Method (1)



generate localized MOs for capped fragment

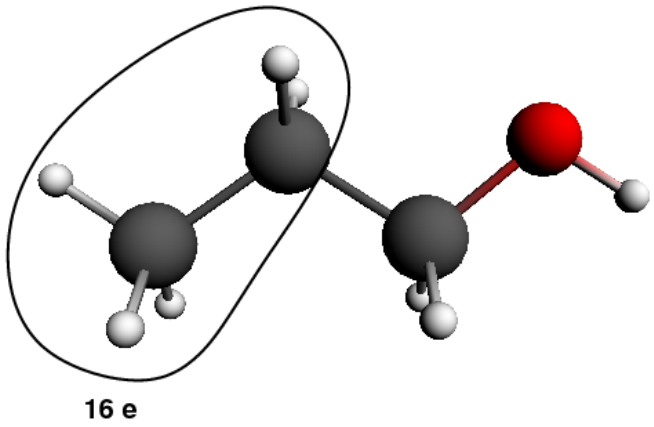


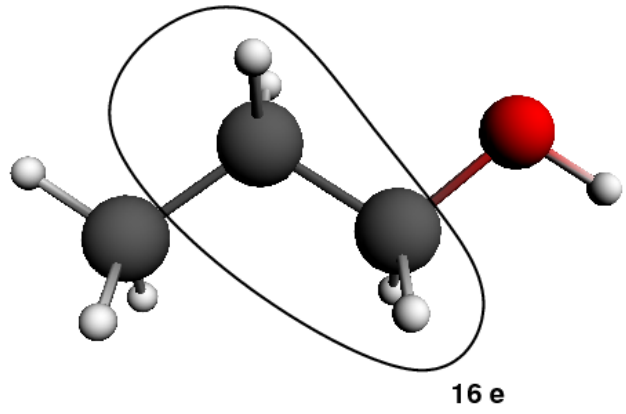
use these LMOs as basis for "true" fragments

FMO-1

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

Fragment Molecular Orbital Method (2)





etc.

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

A Density-Based Many-Body Expansion

- in a DFT context, use MBE for the electron density,

$$
\begin{aligned}
\rho_{\mathrm{tot}}(\mathbf{r}) &= \rho^{(1)}_{\mathrm{tot}}(\mathbf{r}) + \rho^{(2)}_{\mathrm{tot}}(\mathbf{r}) + \rho^{(3)}_{\mathrm{tot}}(\mathbf{r}) + \dots \\
&= \sum_I \rho^{(1)}_I(\mathbf{r}) + \sum_{I<J} \rho^{(2)}_{I\leftrightarrow J}(\mathbf{r}) + \sum_{I<J<K} \rho^{(3)}_{I\leftrightarrow J\leftrightarrow K}(\mathbf{r}) + \dots \\
\rho^{(2)}_{I\leftrightarrow J}(\mathbf{r}) &= \rho_{IJ}(\mathbf{r}) - \rho^{(1)}_I(\mathbf{r}) - \rho^{(1)}_J(\mathbf{r}) \\
\rho^{(3)}_{I\leftrightarrow J\leftrightarrow K} &= \rho_{IJK}(\mathbf{r}) - \rho^{(1)}_I - \rho^{(1)}_J - \rho^{(1)}_K - [\rho_{IJ}(\mathbf{r}) - \rho^{(1)}_I(\mathbf{r}) - \rho^{(1)}_J(\mathbf{r})] \\
&\quad -[\rho_{IK}(\mathbf{r}) - \rho^{(1)}_I(\mathbf{r}) - \rho^{(1)}_K(\mathbf{r})] - [\rho_{JK}(\mathbf{r}) - \rho^{(1)}_J(\mathbf{r}) - \rho^{(1)}_K(\mathbf{r})]
\end{aligned}
$$

  and approximate

$$
E_{\mathrm{tot}}[\rho] \approx E^{(n)}_{\mathrm{db-MBE}} = E_{\mathrm{tot}}[\rho^{(n)}_{\mathrm{tot}}]
$$

- converges faster than energy-based MBE
- think about this one:
  in n-th order db-MBE, we only have access to n-body orbitals

D. Schmitt-Monreal, C.R. Jacob, *J. Chem. Theory Comput.* **17** (2021), 4144.

More about QM/QM tomorrow . . .