bioexcel
Centre of Excellence for Computational Biomolecular Research

Horizon 2020
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for Research & Innovation

Introduction to QM/MM

Second part

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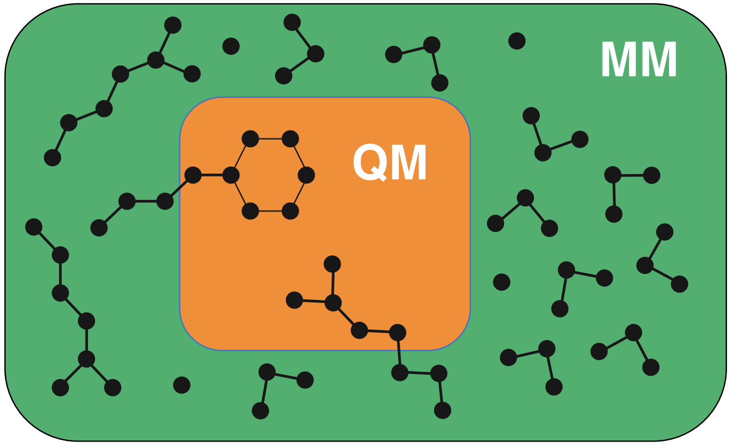
QM/MM Coupling



Hybrid QM/MM scheme:

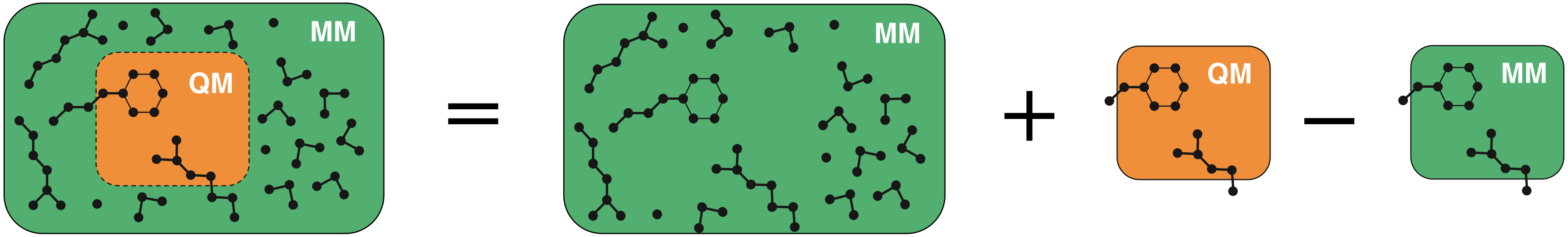
- Small part of the system at quantum (QM) level
- Rest of the system at force field (MM) level

The hybrid QM/MM **potential energy** contains three types of interactions:

- Interactions between particles in the QM region (straightforward description)
- Interactions between atoms in the MM region (straightforward description)
- Interactions between QM and MM particles → Subtractive vs Additive Coupling Schemes

Subtractive Scheme

In the subtractive scheme, the QM/MM potential energy of the system is obtained in three steps:



Pros:

- No communication between the QM and MM routines needed

Straightforward implementation

Cons:

- Force field for QM part required
- Force field has to be "flexible" to describe changes when chemical reactions occur
- Absence of QM polarization due to the MM part

Additive Scheme

In the more advanced additive scheme, the QM/MM potential energy of the whole system is a sum of the MM energy terms, QM energy terms and QM/MM coupling terms:

$$E^{QM/MM} = E^{QM}(\{R_\alpha\}) + E^{MM}(\{R_I\}) + \underbrace{E^{QM-MM}(\{R_\alpha\},\{R_I\})}_{\parallel}$$

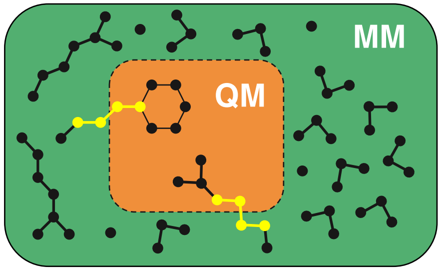
From the DFT Kohn-Sham Hamiltonian $\hat{\mathcal{H}}_e^{KS}$

From the chosen classical force field

$$E^{QM-MM} = \boldsymbol{E}_{\boldsymbol{bonded}}^{\boldsymbol{QM-MM}} + E_{non-bonded}^{QM-MM}$$

Bonded interactions

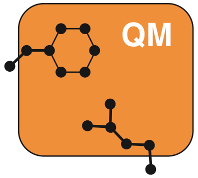
Introduced when covalent bonds connecting the QM and the MM regions are cut:



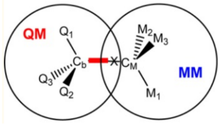
In addition, in this case care has to be taken when evaluating the QM wave function. Some methods to deal with dangling valences:

Available in CP2K

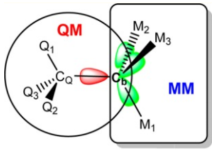
- **Monovalent capping atoms:** usually hydrogen atoms at an appropriate position along the bond vector



- **Link atom pseudopotentials**: linking atom with scaled down pseudopotential and the required valence charge, which requires to constrain the bond distance appropriately.



- **Generalized hybrid orbitals**: hybrid orbitals are placed on the boundary atom and one of them participates in the SCF calculation for the WF of the QM region.



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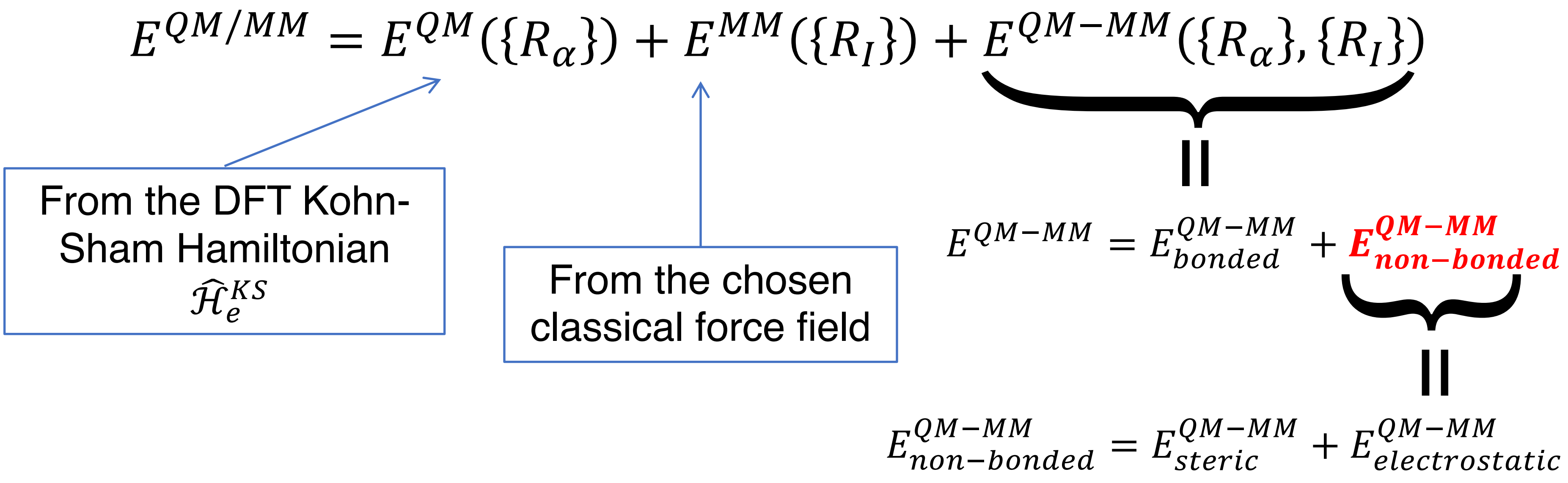

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$$E^{QM-MM} = E^{QM-MM}_{bonded} + \underbrace{\boldsymbol{E^{QM-MM}_{non-bonded}}}_{\parallel}$$

$$E^{QM-MM}_{non-bonded} = E^{QM-MM}_{steric} + E^{QM-MM}_{electrostatic}$$

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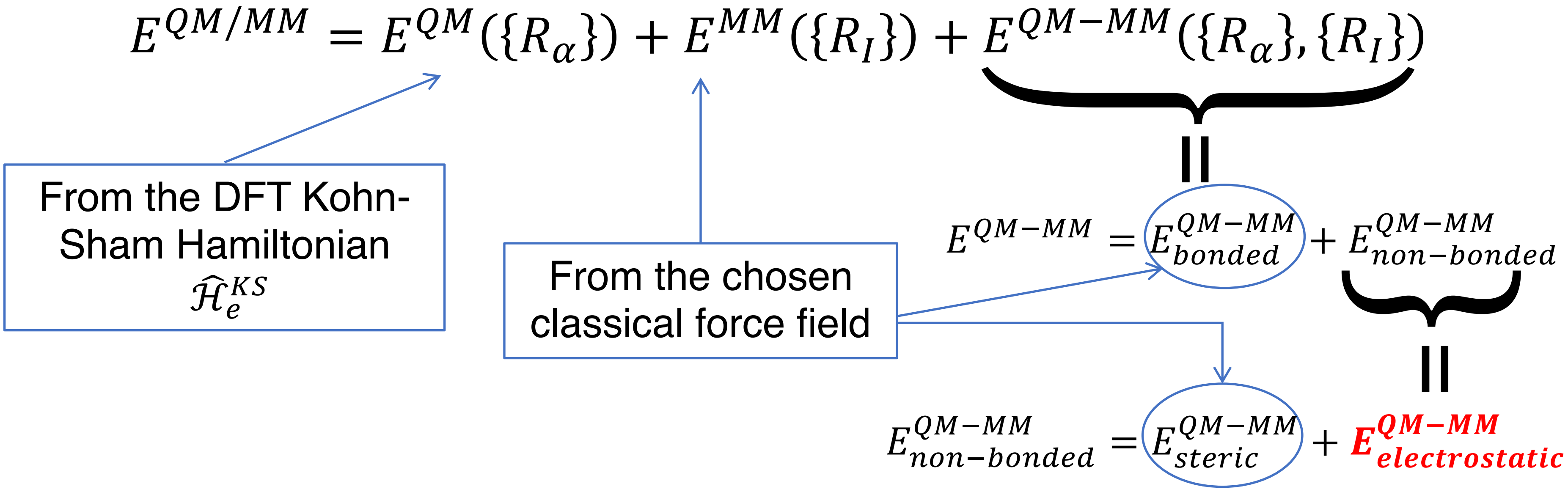

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$$E^{QM-MM}_{non-bonded} = E^{QM-MM}_{steric} + \boldsymbol{E^{QM-MM}_{electrostatic}}$$

$E^{QM-MM}_{electrostatic}$ = Electrostatic interaction between MM charges and QM charge density

Electrostatic Coupling Approaches

- **Mechanical embedding**: **no influence of MM charges on the QM part**, i.e QM calculation is gas-phase-like without additional potential due to the MM atoms.

$E^{QM-MM}_{electrostatic}$

  - Neglected
  - Established by assigning a fixed set of effective charges to the QM region (for example, those given by the force field)
  - QM partial charges re-computed at every integration step of the simulation (least-squares fitting procedure)

- **Electrostatic embedding**: **QM polarization due to the MM part included**.

$E^{QM-MM}_{electrostatic}$

Estimated through an additional term to the QM Hamiltonian, where it is taken into account in terms of an external charge distribution.

- **Polarized embedding**: **MM polarization due to the QM part included as well** (non-self consistently or fully self-consistently).

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Electrostatic Embedding

- Electrostatic interactions between QM and MM subsystems are handled during the computation of the electronic wave function

- The charged MM atoms enter the QM Hamiltonian as one-electron operators:

$$E^{QM-MM}_{electrostatic} = -\sum_{i\in QM}\sum_{I\in MM}\frac{q_I e}{|\mathbf{r}_i - \mathbf{R}_I|} \longrightarrow \sum_{I\in MM} q_I \int \frac{\rho(\mathbf{r})}{|\mathbf{r}_i - \mathbf{R}_I|}\, d\mathbf{r}$$

- Two problems arise due to the peculiar short-range and long-range behavior of this term:

SHORT-RANGE

↓

Electron spill-out problem at the bondaries

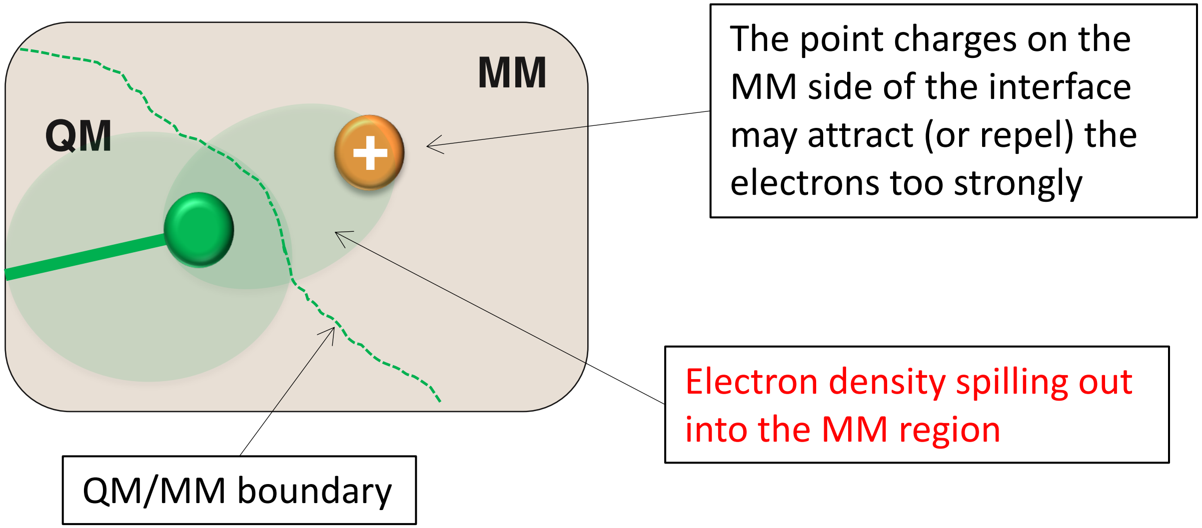
LONG-RANGE

↓

Huge computational cost to evaluate the integral

Electron Spill-out

A problem that may arise when using standard MM atomic charges to describe the charge distribution in the MM system, is the risk of **over-polarization** near the boundary:



The point charges on the MM side of the interface may attract (or repel) the electrons too strongly

Electron density spilling out into the MM region

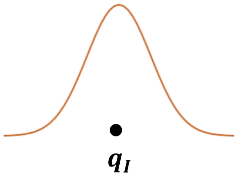
QM/MM boundary

Such artifacts can become serious if large flexible basis set (e.g., with polarization and diffuse functions), or as in our case **plane waves** are used in the QM calculations

Electron Spill-out

The electron spill-out can be avoided by using smeared-out charges instead of the traditional point charges:

$$E_{electrostatic}^{QM-MM} = \sum_{I \in MM} q_I \int \frac{\rho(\mathbf{r})\, v_I^{smear}(|\mathbf{r}_i - \mathbf{R}_I|)}{|\mathbf{r}_i - \mathbf{R}_I|} d\mathbf{r}$$



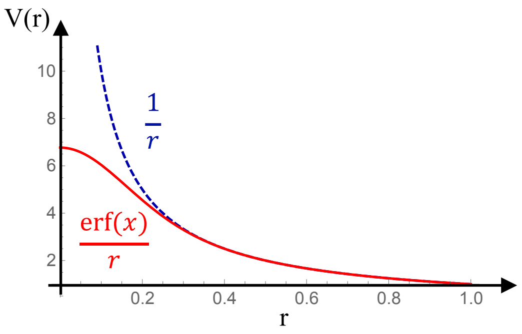
where the smearing function can be a Gaussian distribution or another suitable function centered at the MM atom.

$$v_I^{smear}(r) = \frac{\mathrm{Erf}\left(\frac{r}{r_{c,I}}\right)}{r}$$

$r_{c,I}$ = covalent radius of the atom *I*

Smearing function implemented in CP2K

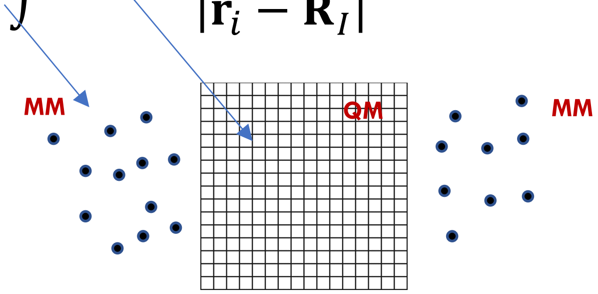
In contrast to the point charge model, the Coulomb interaction between the QM electrons and the smeared charge distributions does not diverge if the electrons approach the MM atoms.



Evaluating the integral

Due to the Coulomb long-range behaviour, the computational cost of the $E^{QM-MM}_{electrostatic}$ integral is extremely large:

$$E^{QM-MM}_{electrostatic} = \sum_{I \in MM} q_I \int \frac{\rho(\mathbf{r})\, v_I^{smear}(|\mathbf{r}_i - \mathbf{R}_I|)}{|\mathbf{r}_i - \mathbf{R}_I|}\, d\mathbf{r}$$



Direct evaluation

$$\#\,\text{op} \sim N_{MM} * N_{grid} \gtrsim 10^{10}$$

GEEP: Gaussian Expansion of the Electrostatic Potential

$$q_I v_I^{smear}(|\mathbf{r}_i - \mathbf{R}_I|) = q_I \frac{\mathrm{Erf}\left(|\mathbf{r}_i - \mathbf{R}_I|/r_{c,I}\right)}{|\mathbf{r}_i - \mathbf{R}_I|} = \sum_{N_g} A_g e^{-\left(|\mathbf{r}_i - \mathbf{R}_I|/G_g\right)^2} + R_{low}(|\mathbf{r}_i - \mathbf{R}_I|)$$

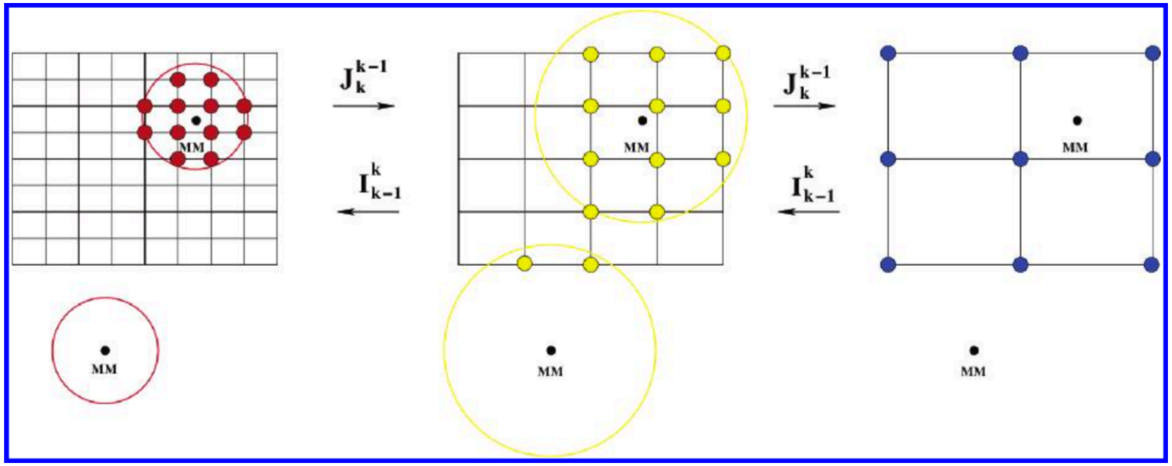
+

Real space multigrid approach

Real space multi-grid approach

GEEP

$$q_I v_I^{smear}(|\mathbf{r}_i - \mathbf{R}_I|) = q_I \frac{\mathrm{Erf}\left(|\mathbf{r}_i - \mathbf{R}_I|/r_{c,I}\right)}{|\mathbf{r}_i - \mathbf{R}_I|} = \sum_{N_g} A_g e^{-\left(|\mathbf{r}_i - \mathbf{R}_I|/G_g\right)^2} + R_{low}(|\mathbf{r}_i - \mathbf{R}_I|)$$



Algorithm

1. **Collocation**
   - Gaussian (G) distribution of each MM atom
   - GEEP expansion
   - Mapping on the grids
   - Make G domain compact
2. **Interpolation**
   - The multi-grid expansion sequantially interpolated from the coarsest grid level up to the finest

T. Laino *et al.*, J. Chem Theory Comp. 1, 1176 (2005)