Chapter 7
Embedding Methods in Quantum Chemistry

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Abstract An overview over different embedding schemes for electronic-structure calculations is given, with the main focus on methods used for molecular systems. The in-principle exact subsystem DFT formalism is used as a reference point to classify the different approaches according to their components of the exact embedding potential. Special attention is paid to recently proposed ideas from the field of density-based embedding and density matrix reconstruction approaches.

Keywords Embedding methods · Subsystem methods · Fragmentation methods

7.1 Introduction

"Embedding" as a general term encompasses all methods where at some point in a calculation, the effect of an environment on a certain part of the total system is evaluated. The terms "embedding methods" and "fragment-based methods" are therefore closely related, since a division of the total system is unavoidable in order to formulate an embedding theory. A fragment-based method without embedding is theoretically possible, but would be restricted to the treatment of non-interacting fragments (note that we regard many-body expansions as a form of effective embedding in this context). There are two main motivations for embedding methods, which are (i) reduction of the computational cost and (ii) improved interpretability of the total system in terms of fragments and their interactions.

The first motivation can be understood by considering the scaling behavior of typical quantum-chemical methods with the system size. Even Kohn–Sham density functional theory (DFT) methods, which are among the most cost-effective ab initio methods, formally scale at least with $\mathscr{O}(N^3)$. Approaches based on wave function theory (WFT) often lead to scaling of even higher order, such as Hartree–Fock (HF) with $\mathscr{O}(N^4)$, second-order Møller–Plesset perturbation theory (MP2) with $\mathscr{O}(N^5)$,

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or Coupled Cluster with single/double excitations as well as perturbative triple excitations (CCSD(T), often referred to as the “gold standard” of quantum chemistry), which even has a formal scaling behavior of $\mathscr{O}(N^7)$. It is clear that the overall computational cost could be strongly reduced by splitting the total system into small parts to be evaluated sequentially or in parallel.

The second aspect is especially important from a chemist’s perspective. In many cases, individual building blocks of a large system (e.g., functional groups, small molecules, cofactors in a protein) will have similar (though not identical) properties both in a complex and on their own. In fact, this is the way of thinking chemists usually apply to most problems. Quantum-chemical models, however, generally treat the system as a whole without any such classification. It is then much harder or even impossible to define and evaluate interaction terms between different components of the system. Fragment-based methods often have a decisive advantage in this respect. This is also the reason why it can be worthwhile to apply an approach which is *more* expensive than a supermolecular calculation in some cases.

The present chapter attempts to give an overview over the current state of embedding methods in quantum chemistry. However, the sheer number of individual approaches has become so vast that no single article can cover everything. Therefore, this review focuses especially on *actively developed* methods from the field of molecular quantum chemistry, whereas other approaches—though they might be historically significant—are omitted or treated in less detail. For a much broader overview, the reader is referred to a collection of reviews published in the recent Chemical Reviews issue “Calculations on Large Systems” [1], in particular Refs. [2–7], and to further reviews on density-based embedding formalisms [8–11].

This chapter is structured as follows. In Sect. 7.2, some preliminary concepts will be introduced, which are important for several of the methods described later. In addition, our classification of the presented methods will be detailed. In order to be able to relate the wealth of existing approaches, the in-principle exact subsystem DFT formalism will be treated in Sect. 7.3. The embedding potential arising from this theory has many interesting features, which can be used to compare the different approaches with respect to the incorporated interactions. The body of this chapter consists of Sects. 7.4–7.6, where a number of important embedding schemes are reviewed in three different classes. Finally, a short summary is presented in Sect. 7.7.

7.2 General Embedding Strategies

The interest in theoretical fragmentation or embedding methods has increased greatly over the past decades. This results in a situation where not only the number of approaches described in the literature is vast, but even the number of different classification schemes grows continually. A famous early attempt was made by Li et al. [12], who distinguished between density-based and energy-based methods. In the former case, a total density (matrix) of the system is assembled first, from which any supermolecular properties are obtained in a second step. In contrast, energy-based methods directly evaluate the total energy of the system from fragment contributions in a linear fashion. Molecular properties can then be determined by taking derivatives of the energy with respect to appropriate quantities. This classification was generalized by Gordon et al. in the framework of a comprehensive review [13]. Here, the energy-based group is renamed "one-step" group and extends the definition to quantities other than the energy, which can be determined directly from individual fragment contributions. For instance, the extension of the Molecular Fractionation with Conjugate Caps (MFCC) method (see Sect. 7.5.1) to dipole moments and the electrostatic potential [14] now falls into this category, since the total property is constructed in a strictly additive fashion from the fragment contributions. The other class of methods is accordingly termed "two-step" methods and contains all approaches where a supermolecular quantity (usually the density or density matrix) is constructed from fragment contributions and used to nonlinearly determine properties in a second step.

A different approach to classifying fragment-based methods focuses on the geometric nature of the employed fragments. Suárez et al. [15] presented an intuitive distinction between different energy-based methods, depending on whether overlapping or disjoint fragments are constructed. Mayhall and Raghavachari [16] applied the terms "top-down methods" for the former and "bottom-up methods" for the latter. To avoid double counting in top-down methods, derivative subsystems corresponding to the overlapping sections are formed according to the *inclusion–exclusion principle* (IEP) of set theory, which can be symbolically cast as

$$\begin{aligned}|A_1 \cup A_2 \cup \cdots \cup A_{N^\mathrm{F}}| = \sum_{K}^{N^\mathrm{F}} A_K - \sum_{K<L}^{N^\mathrm{F}} |A_K \cap A_L| + \sum_{K<L<M}^{N^\mathrm{F}} |A_K \cap A_L \cap A_M| + \cdots \\ + (-1)^{N^\mathrm{F}-1} |A_K \cap \cdots \cap A_{N^\mathrm{F}}| \quad ,\end{aligned} \tag{7.1}$$

where A_K is one of N^F fragments, $A_K \cup A_L$ represents the union of fragments A_K and A_L, and $A_K \cap A_L$ is their intersection. Thus, overlaps of even order are subtracted, whereas overlaps of odd order enter with a positive sign. Properties of the total system (especially the energy) can be approximated by combining the fragment contributions in the same way.

In contrast, a straightforward *many-body expansion* (MBE) is applied in bottom-up methods, where no overlap exists between the individual fragments. The energy can be determined as

$$E^\mathrm{MBE} = \sum_{K}^{N^\mathrm{F}} E_K + \sum_{K<L}^{N^\mathrm{F}} \mathit{\Delta} E_{KL} + \sum_{K<L<M}^{N^\mathrm{F}} \mathit{\Delta} E_{KLM} + \cdots \tag{7.2}$$

with

$$\mathit{\Delta} E_{KL} = E_{KL} - (E_K + E_L) \tag{7.3}$$

$$\mathit{\Delta} E_{KLM} = E_{KLM} - (\mathit{\Delta} E_{KL} + \mathit{\Delta} E_{KM} + \mathit{\Delta} E_{LM}) - (E_K + E_L + E_M) \quad . \tag{7.4}$$

Here, E_K is the energy of subsystem K, E_{KL} is the energy of a dimer formed from K and L, and so on. While the accuracy of an MBE method is determined primarily by the order to which the expansion is carried out, the most important factor influencing the results of IEP-based approaches is the size and type of the fragments [16].

If fragments are connected by covalent bonds, many approaches apply capping groups to saturate free valences (“dangling bonds”) left over after the original division of the system. It should be noted that the definition of “overlap” between fragments can be ambiguous in this situation. Many authors apply it based only on the original fragmentation; i.e., *before* capping groups are applied. This means that even though the fragments that are subjected to calculations might actually possess some spatial overlap, this is only counted if it consists of atoms originally present in the supermolecule. This is the reason why for instance the MFCC method is regarded as based on overlapping fragments (capping groups consist of the adjacent amino acids, saturated with additional hydrogen atoms), whereas the Kernel Energy Method (KEM, see Sect. 7.5.4) employs disjoint fragments (capped only with hydrogen atoms). The boundary between the two classes is blurred further if intermediate capping groups are applied (such as small amino acid termini in some variants of MFCC). The Fragment Molecular Orbital (FMO) method (see Sect. 7.5.2) is one of the few examples which can be clearly classified as employing disjoint fragments, since no capping atoms are used.

Two further classification schemes were presented by Richard and Herbert [17] and Akimov and Prezhdo [2], who both chose not to establish definitive categories, but rather define a number of attributes to determine for any given method. In this contribution, we thus divide the method space into three empirical categories: (i) QM/MM and related multilevel approaches, (ii) schemes based on an MBE, and (iii) quantum-chemical Divide-and-Conquer (DC) methods. The first class comprises methods where a certain part of the total system is treated with a more approximate description, often based on physical considerations. The second class contains all many-body expansion methods, regardless of the exact description of the interactions (e.g., supplemented by long-range Coulomb interactions or not). Methods of the third class are based on the general DC idea and often can be shown to be in principle exact. As for all classifications, there will be methods that defy categorization under the present scheme. An example is the extension of density-based embedding to the embedding of a WFT description in a DFT environment, which could be attributed to categories (i) or (iii). The fact that we file it into the latter merely reflects the development history. Likewise, Frozen Density Embedding (FDE) itself can be classified either as a QM/QM scheme, where the interaction term is evaluated with orbital-free DFT,[1] or as a DC method where the total orbital space is divided among the subsystems.

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[1] This holds especially if the environmental density is obtained from model considerations instead of separate fragment calculations.

7.3 Exact Embedding Potential

In this section, the in-principle exact subsystem DFT framework [18–20] will be described. The embedding potential that arises from such a treatment has many interesting features that can be used to classify other embedding frameworks. The present approach is somewhat similar to the one taken by Gomes and Jacob in their review on excited-state embedding methods [9].

The central idea of subsystem DFT is to partition the electron density of the total system, ρ^{tot}, into several additive fragment contributions ρ_K,

$$\rho^{\text{tot}}(\vec{r}\,) = \sum_K^{N^{\text{F}}} \rho_K(\vec{r}\,) \ . \tag{7.5}$$

Here, N^{F} is the total number of fragments, and $\vec{r}$ denotes a spatial coordinate. Note that in contrast to the Divide-and-Conquer approach (see Sect. 7.6.1), a fixed number of electrons are contained in each subsystem. All fragment densities can be expressed in terms of the Kohn–Sham (KS) formalism as a sum of subsystem orbital contributions,

$$\rho_K(\vec{r}\,) = \sum_i^{N_K^{\text{orb}}} \left|\psi_{K,i}(\vec{r}\,)\right|^2 \ \ , \tag{7.6}$$

where N_K^{orb} is the number of orbitals $\{\psi_{K,i}\}$ centered on subsystem K. In accordance with the regular KS formalism, the energy of an individual, non-interacting subsystem is simply given by

$$E_K^{\text{iso}}[\rho_K] = T^{\text{s}}[\{\psi_{K,i}\}] + \int v_K^{\text{ext}}(\vec{r}\,)\rho_K(\vec{r}\,)\text{d}\vec{r} + \iint \frac{\rho_K(\vec{r}\,)\rho_K(\vec{r}\,')}{|\vec{r}-\vec{r}\,'|}\text{d}\vec{r}\text{d}\vec{r}\,' + E^{\text{xc}}[\rho_K] \tag{7.7}$$

with T^{s} being the kinetic energy of the electrons in the fictitious reference system and

$$v_K^{\text{ext}}(\vec{r}\,) = -\sum_I^{N_K^{\text{nuc}}} \frac{Z_I}{|\vec{r}-\vec{R}_I|} \tag{7.8}$$

representing the external potential due to the N_K^{nuc} nuclei with charge Z_I and position $\vec{R}_I$ in the current fragment. The second term in Eq. (7.7) thus describes the electrostatic electron–nuclei interaction, while the third and fourth terms contain the Coulomb and exchange–correlation (XC) interactions, respectively, between the electrons within the isolated subsystem. For non-interacting subsystems, the total energy would simply be the sum of all the isolated contributions,

$$E^{\text{tot,non-int}}[\rho^{\text{tot}}] = \sum_{K}^{N^{\text{F}}} E_K^{\text{iso}}[\rho_K] \ , \tag{7.9}$$

but an exact expression for the real (interacting) case can be obtained in the form

$$\begin{aligned} E^{\text{sDFT}}[\rho^{\text{tot}}] = \sum_{K}^{N^{\text{F}}} \Bigg[E_K^{\text{iso}}[\rho_K] + \overbrace{\sum_{L \neq K}^{N^{\text{F}}} \left(\int v_L^{\text{ext}}(\vec{r})\rho_K(\vec{r})\text{d}\vec{r} + \frac{1}{2} \iint \frac{\rho_L(\vec{r})\rho_K(\vec{r}\,')}{|\vec{r}-\vec{r}\,'|}\text{d}\vec{r}\text{d}\vec{r}\,' \right)}^{E_K^{\text{emb,elstat}}} \Bigg] \\ \underbrace{+ E^{\text{xc}}[\rho^{\text{tot}}] - \sum_{K}^{N^{\text{F}}} E^{\text{xc}}[\rho_K] + T^{\text{s}}[\rho^{\text{tot}}] - \sum_{K}^{N^{\text{F}}} T^{\text{s}}[\rho_K]}_{E_K^{\text{emb,nad}}} \ . \end{aligned} \tag{7.10}$$

Although this expression seems complicated, it boils down to a sum of the electrostatic interaction energies between all possible combinations of fragments, $E_K^{\text{emb,elstat}}$, as well as the consideration of kinetic and XC effects through $E_K^{\text{emb,nad}}$. The contributions inherent to each fragment are already contained in E_K^{iso}. The second line of Eq. (7.10) has a more complicated form, since the described effects are of nonadditive nature. Thus, a formally exact nonadditive term is introduced in the form of $E_K^{\text{emb,nad}}$.

While the above expression gives the energy of fixed interacting subsystem densities, the energy (and total density) of the ground state can be determined by minimizing this energy with respect to the KS orbitals of the individual subsystems. This leads to one set of *Kohn–Sham Equations with Constrained Electron Density* (KSCED) [21] per fragment, which can be cast in the form

$$\left[-\frac{\vec{\nabla}^2}{2} + v_K^{\text{eff}}[\rho_K](\vec{r}) + v_K^{\text{emb}}[\rho_K, \rho^{\text{tot}}](\vec{r}) \right] \psi_{K,i}^{\text{KSCED}}(\vec{r}) = \varepsilon_{K,i}\psi_{K,i}^{\text{KSCED}}(\vec{r}) \ , \tag{7.11}$$

yielding optimal fragment KS orbitals $\psi_{K,i}^{\text{KSCED}}$ and orbital energies $\varepsilon_{K,i}$. Here, $\vec{\nabla}$ is the Nabla operator and v_K^{eff} is the effective potential of the isolated fragment, which depends on the fragment density ρ_K and has the same form as in a usual KS-DFT calculation. In addition, however, the *embedding potential* v_K^{emb} is contained in the Hamiltonian and incorporates the effect which the other fragments exert on K. This embedding potential has the form

$$\begin{aligned} v_K^{\text{emb}}[\rho_K, \rho^{\text{tot}}](\vec{r}) = \left(\sum_{L, L \neq K}^{N^{\text{F}}} v_L^{\text{ext}}(\vec{r}) \right) + v^{\text{Coul}}[\rho^{\text{tot}} - \rho_K](\vec{r}) \\ + v^{\text{kin,nad}}[\rho_K, \rho^{\text{tot}}](\vec{r}) + v^{\text{xc,nad}}[\rho_K, \rho^{\text{tot}}](\vec{r}) \ . \end{aligned} \tag{7.12}$$

The embedding potential can be related to certain physical effects by turning to intermolecular perturbation theory (see Ref. [22] for an instructive review). The first term in Eq. (7.12) represents a sum of the individual nuclear potentials of all fragments except K. The second term contains an analogous electronic potential. Physically speaking, these two contributions can be clearly identified with the first-order electrostatic interaction, i.e., the electrostatic potential (ESP) of the environmental subsystems acting on the active fragment. The second line of Eq. (7.12) again contains nonadditive contributions which can be expressed as

$$v^{\text{kin,nad}}[\rho_K, \rho^{\text{tot}}](\vec{r}\,) = \left.\frac{\delta T^{\text{s}}[\rho]}{\delta\rho(\vec{r}\,)}\right|_{\rho=\rho^{\text{tot}}} - \left.\frac{\delta T^{\text{s}}[\rho]}{\delta\rho(\vec{r}\,)}\right|_{\rho=\rho_K} \tag{7.13}$$

and

$$v^{\text{xc,nad}}[\rho_K, \rho^{\text{tot}}](\vec{r}\,) = \left.\frac{\delta E^{\text{xc}}[\rho]}{\delta\rho(\vec{r}\,)}\right|_{\rho=\rho^{\text{tot}}} - \left.\frac{\delta E^{\text{xc}}[\rho]}{\delta\rho(\vec{r}\,)}\right|_{\rho=\rho_K} \quad . \tag{7.14}$$

The nonadditive XC component of the embedding potential is responsible for short-range exchange–correlation effects and can thus be related to higher-order intermolecular interactions such as dispersion. Finally, the nonadditive kinetic potential takes care of non-orthogonality effects between the different fragments and thus incorporates the Pauli repulsion. It should be stressed that the mathematical form of the embedding potential is exact and will lead to the supermolecular KS solution for the limiting case of exact nonadditive functionals. Furthermore, if an exact expression for E^{xc} were known, the physically exact solution would be reached.

The total embedding potential of course depends on the densities of all subsystems. Therefore, the KSCEDs have to be either solved simultaneously or in an iterative fashion [20] (see Sect. 7.6.3) to guarantee that the mutual interactions between all fragments are treated consistently. Physically speaking, this corresponds to an incorporation of inductive effects.

Partition DFT (PDFT) [23, 24] can be considered an alternative formulation to subsystem DFT, which is also in principle exact. The real system of interacting fragments is formally replaced by a system of non-interacting fragments, which are coupled by a common "partition potential" that acts as a constraint to ensure normalization to the total number of electrons in the system. In contrast to subsystem DFT, the number of electrons per subsystem is not fixed, but used as a variational parameter to minimize the total energy. In close relation to PDFT, Huang et al. introduced an embedding theory [25] where active fragment and environment are required to share a common embedding potential, thus avoiding the general non-uniqueness of the density partitioning (see Ref. [10] for details on this problem).

7.4 QM/MM and Related Approaches

In this section, a variety of multilevel approaches will be presented, where a certain part of the total system is described with a more accurate method than its surroundings. In particular, Continuum Solvent Models (CSMs), QM/MM approaches, and methods based on effective potentials will be discussed.

7.4.1 Continuum Solvent Models

One of the oldest strategies to embed a system of interest in an environment is represented by implicit models. The general idea of these approaches is to represent the surroundings (usually a solvent) by a uniform description, often in the form of a featureless continuum. Naturally, any atomistic details about the environment are forfeited in such a representation. Specific interactions such as hydrogen bonds, π-stacking, or salt bridges should therefore be treated by including the participating molecules in the active system.

By far the most common class of implicit solvent models is of the *Apparent Surface Charge* (ASC) type. In this family of methods, a *cavity* is created around the system of interest (solute), which is then discretized and furnished with point charges located on the individual segments. The electrostatic potential due to the solvent continuum is then simply given by

$$\phi^{\mathrm{ASC}}(\vec{r}) = \sum_{\mu} \frac{q_{\mu}}{|\vec{r} - \vec{s}_{\mu}|} \quad , \tag{7.15}$$

where q_{μ} and $\vec{s}_{\mu}$ are the magnitude and position, respectively, of point charge μ. The differences between the various ASC methods lie in the way how these ASC magnitudes are determined (see below).

A crucial feature of all ASC methods is the construction of the cavity. The majority of algorithms is based on either the solvent-accessible surface (SAS) or the solvent-excluded surface (SES), which were pioneered by Connolly [26, 27]. In both cases, a preliminary surface is created by interlocking atom-centered spheres according to the individual van der Waals radii. The actual cavity is then generated by rolling a “solvent ball” of certain radius over this object and tracing either its surface (SES) or its center (SAS).

The ASC approach itself can only represent the electrostatic component of the embedding potential. However, several methods have been combined with empirical treatments to account for dispersion, and a cavitation term is also frequently included to obtain realistic free energies (see, e.g., Ref. [28]).

The polarizable continuum model (PCM) is the oldest ASC method. Its original formulation (nowadays known as D-PCM [29]) has long been superseded by the more recent integral equation formalism (IEF) [30]. In the latter, the electrostatic problem is reformulated in terms of Green's functions, which allows to derive an expression for the ASC without resorting to an evaluation of the normal component of the field on the cavity surface. The solution requires only the knowledge of the molecular ESP, which considerably simplifies the procedure (for details, the reader is referred to the original publication [30]). Besides making the evaluation cheaper, the IEF reformulation contains an inherent correction to the problem of outlying charge, i.e., the fact that part of the solute electron density will always be located outside of the cavity.

An additional variant is the so-called C-PCM method [31], which borrows the assumption of a perfectly conducting dielectric from the COSMO approach (see below). Apart from the choice of the exact screening factor, the two methods can be considered equivalent. It should be noted that the IEF-PCM contains both D-PCM and C-PCM as special cases. A recent review focusing specifically on the PCM family of methods is available [32].

In 1993, Klamt and Schüürmann presented the Conductor-Like Screening Model (COSMO) as an alternative ASC method [33]. The crucial difference between the original PCM and COSMO is the assumption that the solvent can be represented as a perfect conductor (infinite permittivity). This leads to a much simpler boundary condition which requires the total potential to vanish at the cavity surface. The corresponding surface charge distribution can be determined for a given molecular potential (due to the nuclei and electrons inside the cavity) from the equation

$$\mathbf{A}\vec{q} = -(\mathbf{B}\vec{Z} + \vec{C}) \ , \tag{7.16}$$

where

$$A_{\mu\nu} = \begin{cases} |\vec{r}_\mu - \vec{r}_\nu|^{-1} & \text{for } \mu \neq \nu \\ 1.07\sqrt{\frac{4\pi}{F_\mu}} & \text{for } \mu = \nu \end{cases} \tag{7.17}$$

$$B_{A\mu} = |\vec{r}_\mu - \vec{R}_A|^{-1} \tag{7.18}$$

$$C_\mu = \int_V V_\mu(\vec{r})\rho(\vec{r})\mathrm{d}\vec{r} \ . \tag{7.19}$$

Here, $\vec{q}$ is the vector of surface charge magnitudes, while $\vec{Z}$ contains the nuclear charges. The matrices **A** and **B** hold inverse charge–charge and charge–nuclei distances, respectively. For the special case of the diagonal elements of **A**, a "self-interaction" within the surface segment with area F_μ is described, which has been derived in the original article [33]. Finally, the vector $\vec{C}$ represents the interaction between the electron density of the system and each surface charge. Equation (7.16) can be solved directly by matrix inversion, but is more commonly subjected to an iterative procedure. To correct for the assumption of a perfect conductor, the obtained charges are scaled with a permittivity-dependent function which has the form

$$f(\varepsilon) = \frac{\varepsilon - 1}{\varepsilon + g} \ , \tag{7.20}$$

where ε is the (real) permittivity and a value of 0.5 has been suggested for the factor g by the original authors, while others set it to zero in accordance with Gauss' law [34].

The COSMO approach was soon combined with a statistical thermodynamics treatment to yield the Conductor-Like Screening Model for Real Solvents (COSMO-RS) [35], which determines solution properties on a more physical basis by evaluating the chemical potential of each species in terms of interacting surface segments. By first carrying out a regular COSMO calculation for all participating components (solute and solvent alike), a consistent description is achieved. Both COSMO and COSMO-RS are discussed and compared in a recent review [36]. An algorithm similar to COSMO-RS was presented by Lin and Sandler and termed COSMO-SAC [37].

An extension of the COSMO scheme to electronically excited states was presented by Klamt a few years after the original publication of the method [38]. A recent modification of COSMO-RS allows the calculation of response properties also in the framework of this more sophisticated approach [39]. In addition, the problem of missing correlation between different surface segments was first addressed by the COSMO-RS-DARE approach [40], which was specifically intended for dimerization reactions, and later refined to yield the COSMO-RSC method [41]. One notable recent advancement was the development of the domain decomposition COSMO (ddCOSMO) algorithm [42–44], which represents an intrinsically linear-scaling COSMO variant based on a Schwarz decomposition. Significant speedups at almost no loss of accuracy have been reported in combination with different semi-empirical and quantum-chemical methods [45]. In addition, a variant of the COSMO scheme specifically adapted to subsystem electronic-structure approaches has been published under the name "Local COSMO" (LoCOSMO) [46].

The Surface Volume and Polarization for Electrostatics (SVPE) method [47] was specifically designed to remedy the problem of outlying charge. As such, it requires a treatment not only of the cavity surface (surface polarization), but also of the adjacent continuum (volume polarization). In order to avoid the costly integration procedures resulting from this process, the related Surface and Simulation of Volume Polarization for Electrostatics (SS(V)PE) approach [48, 49] was developed. Here, an additional surface charge density distribution is introduced to account for the required boundary conditions. It has later been shown that the SS(V)PE method is equivalent to the isotropic formulation of IEF-PCM [50].

One of the best-known non-ASC continuum models is the SM*x* family of approaches by Cramer and Truhlar [51–53], where x denotes the version (currently 12). These methods are based on a Generalized Born (GB) treatment; i.e., instead of solving a non-homogeneous Poisson equation, the solute is modeled as a collection of monopoles residing on the atomic positions, which are assigned certain radii. The atomic charges are usually obtained from a suitable population analysis scheme, although a density-based scheme called SMD has been introduced recently [54]. The crucial part of setting up a GB model is the determination of suitable Coulomb radii for the individual solute monopoles. Since the original publication [51], a plethora of parameterizations and methodological extensions have been presented, which culminated in the two most recent formulations SM8 [55] and SM12 [53].

7.4.2 QM/MM Approaches

The idea of combining an active region of a system described by quantum-chemical methods with an environmental representation in terms of a force field dates back to the seminal papers by Warshel, Karplus, and Levitt [56, 57] and was eventually awarded the 2013 Nobel Prize in chemistry. Since the original formulation, an overwhelming plethora of different extensions, variants, and improvements have been developed in groups all over the world. A systematic review of the QM/MM method is clearly out of the scope of this work, which is why only the very basics and a small selection of relatively recent developments will be detailed. The reader is referred to several excellent reviews for more details on this topic [7, 58–60].

A central distinction between different QM/MM methods can be made in terms of whether they utilize a subtractive or an additive scheme. For the former, the total energy is expressed as

$$E^{\mathrm{QM/MM}} = E^{\mathrm{QM}}(\mathrm{core}) + E^{\mathrm{MM}}(\mathrm{core} + \mathrm{env}) - E^{\mathrm{MM}}(\mathrm{core}) \ , \qquad (7.21)$$

where “core” and “env” represent the region of interest and the environment, respectively, while E^{QM} and E^{MM} denote the energy obtained with a QM or MM description in the respective region. In order to carry out a subtractive calculation, the energy of the core region thus has to be determined with both methods, in addition to an MM energy evaluation for the whole system. A clear benefit of this approach is the avoidance of a complicated coupling term between QM and MM regions. However, it relies on the assumption that the energy change of the core upon embedding in the environment is transferable between the different descriptions. Furthermore, the subtractive approach requires MM parameters for the core region, which can be problematic if nonstandard moieties are to be modeled. A prime example of this class of methods is the IMOMM scheme [61] and its better known successor, the ONIOM approach [62, 63], which will be discussed below.

In additive QM/MM schemes, the total energy is instead simply expressed as

$$E^{\mathrm{QM/MM}} = E^{\mathrm{QM}}(\mathrm{core}) + E^{\mathrm{MM}}(\mathrm{env}) + E^{\mathrm{QM-MM}} \ , \qquad (7.22)$$

where the energies in the core and environmental regions are evaluated exclusively by either a QM or an MM description, with the additional coupling term $E^{\mathrm{QM-MM}}$ describing the interactions between them. While the bonded terms across the boundary and the non-electrostatic contribution to the non-bonded energy are almost always described by force field terms [58], the electrostatic coupling is usually evaluated following one of three different schemes [64]:

1. Mechanical embedding. In this case, a classical representation of the core charge distribution is created and coupled electrostatically to the environmental force field charges. Only an improved total energy is obtained, while the core density/wave function stays the same.
2. Electrostatic embedding. Here, the environmental charge distribution is incorporated as an embedding potential in the QM Hamiltonian, thus directly altering the core density/wave function.
3. Polarizable embedding. Through the use of a polarizable description of the environment, a mutual polarization between QM and MM regions is modeled. While this approach best represents the underlying physics, the evaluation of environmental polarization can of course make it more costly than the other embedding schemes.

A major hurdle in all additive approaches is the modeling of a smooth boundary between the different regions of the system. This is especially problematic if cuts occur through covalent bonds, as is often the case in biological molecules. Many different solutions have been proposed, a comprehensive review of which can be found in Ref. [58].

The Integrated Molecular Orbital and Molecular Mechanics (IMOMM) method [61] is a prototypical example of a subtractive QM/MM scheme. The total energy is calculated based on Eq. (7.21), such that the energy of the QM core ("model system") has to be determined both with a QM method of choice and with MM. In addition, the total system ("real system") has to be subjected to an MM calculation. The subtraction of the MM energy of the model system eliminates any double counting. However, the latter requires the existence of force field parameters for the compounds in this region. While the bonded parameters play only a minor role (since they are mostly canceled by the subtraction), it is important to employ a good parametrization for long-range interactions [65].

A logical extension was soon presented in the form of the Integrated Molecular Orbital and Molecular Orbital (IMOMO) method [66], where two different QM methods are combined, with the less expensive method taking the role of the MM in IMOMM. Finally, a generalization of both schemes was reported under the name "Our Own *n*-Layered Integrated Molecular Orbital and Molecular Mechanics" (ONIOM) [62, 63]. Here, a general formulation for a system divided into *n* layers was given, each of which are overlapping and described by different theoretical methods. The general notation of all derived methods is ONIOMn(M$_1$:M$_2$:…:M$_n$), where M$_1$…M$_n$ denote the methods used for the different layers. For the most typical case of three layers (i.e., a partitioning of the system into model, *intermediate*, and real system), the energy expression

$$\begin{aligned} E^{\text{ONIOM3}} =& E^{\text{high}}(\text{model}) + E^{\text{medium}}(\text{intermediate}) - E^{\text{medium}}(\text{model}) \\ & + E^{\text{low}}(\text{real}) - E^{\text{low}}(\text{intermediate}) \end{aligned} \tag{7.23}$$

is obtained, such that again no contribution is overcounted.

In the original formulation, the interaction between the two parts of the system was described purely in terms of an MM approach, corresponding to mechanical embedding. The partial charges for the model system have to be either taken from a force field (if available) or computed on the fly from the QM results [67]. By including environmental MM point charges in all calculations for the model system, a situation corresponding to electrostatic embedding can be brought about [65]. Recently, a further extension to ONIOM calculations with polarizable embedding has also been reported [68]. If all layers are described with various QM methods, a total density can be obtained from ONIOM calculations in the same spirit as the total energy [69], although it should be noted that patches of negative density can occur due to the subtraction.

If covalent bonds run through layer boundaries, this can be taken care of by including link atoms, similar to additive QM/MM calculations [69]. Expressions for the ONIOM gradient and other derivatives with and without link atoms have been derived [69]. Furthermore, the ONIOM scheme was combined with the implicit solvent model PCM [70] as well as with an adaptive atomistic description of a solvent shell [71]. In addition, there are ONIOM approaches with other fragmentation schemes applied to parts of the system, leading to methods such as the Multicentered QM:QM approach [72] and Generalized ONIOM [73]. A comprehensive review concerning the history, current developments, and applications of different ONIOM methods can be found in Ref. [5].

The Quantum-regions Interconnected by Local Descriptions (QUILD) method [74] was developed by Swart and Bickelhaupt as a generalized framework for multilevel QM/QM or QM/MM calculations. Although somewhat similar to ONIOM, the different regions can be defined in any desired way, including several overlapping parts. In this way, different interactions can be treated by different methods. For instance, a calculation for a short DNA strand was reported in the original article, where the π-stacking interactions are calculated with a different density functional than the intramolecular interactions and hydrogen bonding effects.

As mentioned above, the full mutual polarization between QM and MM regions can be described by using a polarizable force field for the classical part (polarizable embedding, according to Bakowies and Thiel [64]). Interestingly, this approach was already suggested by Warshel and Levitt in one of the first QM/MM articles in the literature [57] and further developed by Luzhkov and Warshel [75, 76]. Thompson and Schenter later presented a more consistent formulation, where the MM region is polarized by the proper QM density instead of derived classical point charges [77, 78]. This framework has since then been referred to as QM/MMpol. The approach was rederived by Curutchet et al. and applied to the description of excitation energy transfer [79]. Furthermore, it was combined with the PCM approach [80], and gradients have been derived for both ground [68, 78] and excited states [81].

7.4.3 *Effective Fragment Potential*

The effective fragment potential (EFP) method [82–84] is an approach where certain molecules (e.g., of a solvent) are represented by embedding potentials which are approximated on the basis of distinct physical effects. Moreover, it is a focused approach in QM/MM style, where a central molecule of interest treated with a quantum-chemical method is embedded in an approximate description of the environment.[2] Since the environmental representation is fully polarizable, EFP is often referred to as a QM-derived polarizable force field.

The original model (nowadays referred to as EFP1) [82, 83] was designed specifically for embedding a system of interest in water. Each solvent molecule ("fragment") is represented by an effective potential, which is derived from ab initio calculations. It is important to note that EFP is a rigid-body method, which means that the fragment potentials for different solvent molecules are usually chosen to be identical (except for their positions in space).

In EFP1, the total energy of the supersystem is obtained in the form

$$E^{\mathrm{EFP1}} = \left\langle \Psi \left| \hat{H}^{\mathrm{QM}} + \hat{V}^{\mathrm{Coul}} + \hat{V}^{\mathrm{ind}} + \hat{V}^{\mathrm{rep}} \right| \Psi \right\rangle + E^{\mathrm{Coul}} + E^{\mathrm{ind}} + E^{\mathrm{rep}} \quad , \tag{7.24}$$

where Ψ is the wave function of the central molecule and $\hat{H}^{\mathrm{QM}}$ represents its unperturbed Hamiltonian, which is modified by three different potentials stemming from the environment. $\hat{V}^{\mathrm{Coul}}$ describes the static Coulomb embedding due to the fragment potentials, whereas $\hat{V}^{\mathrm{ind}}$ and $\hat{V}^{\mathrm{rep}}$ model induction and exchange repulsion effects, respectively. In terms of intermolecular perturbation theory, these are second-order effects. The additional terms E^{Coul}, E^{ind}, and E^{rep} represent the respective interactions among the environmental fragments.

The Coulomb contribution is evaluated by placing multipoles (up to octupoles) on specific points within the solvent molecules. While all multipoles directly affect the molecular wave function (through $\hat{V}^{\mathrm{Coul}}$), the evaluation of E^{Coul} neglects octupole couplings except for monopole–octupole terms (all lower-order terms are coupled to each other). Since the multipole expansion is only valid for large fragment distances [85], damping terms are added to account for short-range charge penetration.

In order to model mutual polarization, the solvent fragments are furnished with anisotropic polarizability tensors at certain locations, which create induced dipoles. These interact with the mentioned (static) multipole moments and with other induced dipoles (E^{ind}), as well as with the quantum region ($\hat{V}^{\mathrm{ind}}$). The polarization contribution is evaluated self-consistently by first iteratively converging the environmental induced dipoles for a frozen density of the QM system, whereafter the wave function or density of the latter is updated and the cycle is repeated until no significant changes occur anymore. The EFP1 exchange repulsion term is described by a highly parametrized form obtained through fitting of several dimer geometries

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[2] It is also possible to describe a system on equal footing by treating all constituents as effective fragment potentials.

for the solvent at hand. By placing Gaussians (for solute–solvent interactions) or single exponentials (for solvent–solvent interactions) on the fragment atoms and centers of mass, a convenient description is obtained, albeit at the price of a rather involved fitting process, which can be considered one of the major drawbacks of the EFP1 method.

In 2001, Gordon and co-workers presented the EFP2 method [84], which addresses several problems of the original formulation. Most importantly, the repulsion term is split into exchange and charge transfer, and a dispersion term is newly introduced. All terms are evaluated on the basis of the actual structure at hand instead of a cumbersome parametrization process. The Coulomb and induction terms are determined similarly to EFP1, although much attention was paid to the construction of improved damping functions [85–87]. The exchange repulsion term is now evaluated on the fly, based on overlap and kinetic energy integrals of Localized Molecular Orbitals (LMOs) centered on the individual fragments (the LMOs and corresponding Fock matrices are determined in a preparation run before the actual calculation). Dispersion is included by modeling the interaction between induced dipoles in a typical R^{-6} form. The dispersion coefficients are also determined on the fly by numerical integration over a certain set of distributed polarizability points [88]. The dispersion term is corrected for charge penetration as well. Finally, charge transfer is treated in a pairwise additive fashion on the basis of interactions between occupied valence orbitals and unoccupied orbitals on different fragments [89, 90], which are also determined before the actual run.

This leads to the favorable situation that no involved parametrization process is required to apply the EFP2 method for a specific solvent. Although several quantities are indeed computed beforehand, this is done solely on the basis of a single isolated molecule of the requested solvent. Furthermore, this process has been automatized in the MAKEFP routine implemented in GAMESS [91, 92]. Analytical gradients for both EFP1 [83, 84] and EFP2 [93, 94] are available, and several studies on EFP MD simulations have been published [95, 96]. EFP1 has been coupled to numerous QM methods (for a summary, see Ref. [13]), whereas a general interface for EFP2 is still under active development [97–99]. An extension to fragments bound covalently to the QM region has been reported [100, 101], and the EFP approach has been coupled to the Fragment Molecular Orbital (FMO) method in the framework of the EFMO [102] and the subsequent FIEFMO scheme [103].

Using a similar approach as in the EFP model, Olsen et al. developed the Polarizable Embedding (PE) method in 2010 [104] (not to be confused with the identically named QM/MM type from Ref. [64]). PE can be regarded as a special QM/MM variant, with the particular aim of obtaining various response properties of the QM system under the self-consistent influence of a structured environment. The energy of the QM core under the influence of the environment is given as

$$E^{\mathrm{PE}} = E^{\mathrm{QM}} + E^{\mathrm{es}} + E^{\mathrm{ind}} + E^{\mathrm{LJ}} \ , \tag{7.25}$$

where E^{QM} is the energy of the isolated QM core, E^{es} and E^{ind} give the electrostatic and induction contributions, respectively, and E^{LJ} covers all other interactions in the form of a classical (density-independent) Lennard-Jones potential. The electrostatic and induction contributions are evaluated as in the EFP method, by placing multipoles (up to octupoles) and anisotropic dipole–dipole polarizability tensors on certain sites of the environment (usually atomic positions and possibly bond midpoints) and self-consistently determining the respective contributions in every SCF step. The multipoles and polarizability tensors are obtained from the LoProp approach [105]. By truncating the multipole expansion at certain orders and applying isotropic or anisotropic polarizabilities, a systematic variety of QM-based embedding potentials for use in the response calculations can be constructed. The salient feature of the PE scheme is the fully self-consistent treatment of many-body environmental response up to arbitrary order (first- and second-order expressions are given in the original article [104], and a third-order form was derived later [106]), allowing for the determination of a wealth of response properties (e.g., vertical excitation energies, static and dynamic (hyper)polarizabilities, and nuclear shielding constants).

The PE formalism was originally derived for HF and DFT, but has since been extended to more sophisticated methods such as Coupled Cluster [107, 108], Multi-Configuration Self-Consistent Field (MCSCF) [109], or Density Matrix Renormalization Group (DMRG) [110] approaches. Gradients have been derived recently [111], and a short review is available [112]. In the framework of the Polarizable Density Embedding (PDE) extension [113], the environment is further partitioned into two regions, with the solvent multipoles replaced by exact densities in the "inner" environment. However, the induction term is still evaluated in the basis of distributed polarizability tensors in both environmental regions. In addition, a short-range non-electrostatic repulsion term is considered in terms of orbital contributions.

7.5 Many-Body and Inclusion–Exclusion-Based Methods

In this section, some approaches based on an MBE will be discussed. A common feature of all these methods is the fact that the interactions between certain fragment combinations are described in a fully quantum-mechanical fashion (by carrying out calculations for fragment oligomers or using overlapping fragments), whereas others are neglected or treated in a more approximate manner (in particular long-range electrostatics).

7.5.1 Molecular Fractionation with Conjugate Caps

The Molecular Fractionation with Conjugate Caps (MFCC) method [114] was one of the earliest subsystem approaches based on overlapping subsystems. In contrast to later, more general schemes, the MFCC method was specifically intended for the description of proteins. In particular, the original scheme only aimed at reproducing protein–ligand interaction energies, but it was soon realized that an application to other quantities, such as dipole moments or electrostatic potentials, is also possible [14].

The general idea of the MFCC algorithm is to split a protein into its constituent amino acid residues (or possibly small combinations thereof) by cutting through peptide bonds. The resulting fragments of course feature dangling bonds, which is why they are patched with certain capping groups. In the original MFCC, these are chosen to be whole residues adjacent to the current fragment. In order to saturate any remaining dangling bonds (to further residues past the ones used for capping), hydrogen atoms are attached. It should be noted that the MFCC approach uses rigid structures for all calculations, such that both cap and non-cap atoms have the same position as in the original structure (except for the additional hydrogens which are not present in the actual protein).

Assuming a protein P with the sequence

$$P = A_1 - A_2 - \cdots - A_{N^{\mathrm{AA}}} \ , \tag{7.26}$$

where A_K are the N^{AA} constituent amino acids, typical capped fragments are formed as $C^{K-1*} - A_K - C^K$, where C^{K*} and C^K represent capping groups on different ends of residue A_K. The total binding energy V^{MFCC} to a ligand L can then be calculated in the MFCC framework by evaluating the expression

$$V^{\mathrm{MFCC}}(P - L) = \sum_{K}^{N^{\mathrm{F}}} V(L - C^{K-1*} - A_K - C^K) - \sum_{M}^{N^{\mathrm{C}}} V(L - C^{M*} - C^M) \ . \tag{7.27}$$

The first sum runs over all combinations of capped protein subsystems with the ligand. Clearly, this includes artificial interactions between the ligand and the attached cap atoms. This is corrected for by the second sum, which contains binding energies of the ligand with pairs of capping groups, called “concaps” by the authors. These are small closed-shell species formed by fusing adjacent capping groups.

As mentioned above, quantities other than the binding energy can be obtained in completely analogous fashion [14]. As an important example, the total density of a protein can be expressed simply as

$$\rho^{\mathrm{MFCC}}(P) = \sum_{K}^{N^{\mathrm{F}}} \rho(L - C^{K-1*} - A_K - C^K) - \sum_{M}^{N^{\mathrm{C}}} \rho(L - C^{M*} - C^M) \ , \tag{7.28}$$

which also allows to obtain total energies by numerical integration [115], although it must be mentioned that the total kinetic energy of the electrons is approximated by simply combining the individual fragment contributions in MFCC style. The MFCC approach was put on a more general basis by Chen et al., who reformulated it in terms of density matrices [116]. In the regular MFCC spirit, each element of the total density matrix is constructed as a sum over all corresponding elements obtained for the fragments, with the cap contributions being subtracted. Naturally, many contributions vanish since most atoms are present only in a few fragments. Special care has to be taken with regard to the capping atoms not present in the supermolecule. The respective matrix elements can either be neglected (MFCC-SDM) or accounted for by employing ghost atoms (MFCC-GDM). While the former strategy is cheaper, it does not conserve the total number of electrons.

Even though not explicitly stated by the authors, the MFCC scheme works based on the IEP. From an embedding point of view, the choice of the capping groups as parts of the preceding/succeeding sequence is very important, since it represents the only influence of neighboring fragments onto each other.[3] This is also why we classify MFCC as an IEP-based approach, rather than a DC scheme. However, the fragment overlaps are created solely along the protein sequence. The original scheme thus lacks a number of effects, most importantly the following:

1. Treatment of disulfide bridges
2. Interactions between residues which are spatially close, but far from each other in the sequence
3. Long-range Coulomb interactions between remote parts of the protein
4. Mutual polarization among different fragments

All of these were addressed in different ways over the last decade. First of all, Chen et al. demonstrated that proteins with disulfide bonds can be treated essentially in the same way as regular ones, although different capping groups should be used (usually S-CH_3, yielding dimethyl disulfide as the concap) [119]. Non-bonded interactions between spatially close residues are incorporated in a straightforward MBE spirit in the Energy-Corrected MFCC (EC-MFCC) approach [120]. This is achieved by additionally constructing pairs of such residues (according to a user-specified cut-off radius) and determining a second-order energy correction according to Eq. (7.3). In contrast to bonded pairs, both fragments are only capped with hydrogens instead of the usual larger caps. Since proper quantum-chemical calculations are carried out for the dimers, all types of interaction are included, albeit only at the two-body level. No improved density was computed in this way (although theoretically possible), but EC-MFCC geometry optimizations are still enabled by corresponding energy gradient expressions. In the so-called MFCC-DM-PIC (Pairwise Interaction Correction) scheme [121], however, a similar correction is applied to the MFCC-DM formalism, which allows to obtain an improved density matrix for the total system.

Long-range Coulomb interactions were first treated in the context of the Electrostatic Field-Adapted MFCC (EFA-MFCC) approach by Jiang and co-workers [122]. In this method, the Coulomb interaction with charged groups in the system is included by determining the electronic structure of the individual capped fragments and concaps under the influence of point charges. These are placed on certain charge centers, such as the nitrogen atom of the ammonium group. However, only actually cationic or anionic groups are considered, whereas interactions with polar groups are still treated as in the original MFCC scheme. In the Generalized MFCC (GMFCC) scheme [123], an approach similar to EC-MFCC is pursued. In particular, quantum-chemical interaction energies between pairs of spatially close residues are calculated

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[3] It should be noted that later methods based on the MFCC approach often employ an additional embedding potential, thus allowing for smaller capping groups (see, e.g., Refs. [117, 118]).

and added to the total energy. In addition, however, the interaction between distant pairs is evaluated in MM style by applying Coulomb's law to suitable partial charges as well as a Lennard-Jones potential with corresponding parameters from a force field. Again, only a correction to the total energy is obtained in this way. Some years later, Wang et al. presented the Electrostatically Embedded GMFCC (EE-GMFCC) scheme [124], where a direct Coulomb interaction is now included already on the level of the individual fragment calculations as in the EFA-MFCC scheme, but with atomistic point charges. In this way, the supermolecular density also includes polarization due to the presence of non-neighboring fragments. In addition, both the regular MFCC approach and the EE-GMFCC scheme have been combined with the C-PCM solvent model [125, 126] and the latter has been applied to geometry optimizations and the determination of vibrational frequencies [127] as well as ab initio MD simulations [128].

Finally, it should be noted that even with full electrostatic embedding, the mutual polarization among the fragments is not necessarily taken into account. Ji and co-workers addressed this problem by introducing so-called Polarized Protein-Specific Charges (PPCs) in EE-GMFCC calculations [129], which are determined self-consistently. However, only the Coulomb interaction is recovered in this way, whereas non-classical contributions are missing. An additional problem concerns the subtraction procedure present in all MFCC variants. When a total density is sought for, it is well possible that unphysical areas of negative density occur. Both of these problems are solved in the framework of the 3-FDE approach, which will be discussed in Sect. 7.6.3.

The Generalized Energy-Based Fragmentation (GEBF) formalism was presented by Li et al. in 2007 [12] and is closely related to the MFCC approach. Unlike MFCC, it is not specifically intended for the description of proteins, but of extended systems in general. In the GEBF scheme, the supersystem is partitioned in a general, albeit more complicated way. A detailed description (including an instructive example) can be found in the original article, but the most important points are as follows:

- First, the total structure is split into "fragments," which can be as small as individual functional groups or as large as small molecules (e.g., amino acid residues).
- Subsequently, overlapping "primitive subsystems" are constructed for each fragment by including all nearby fragments which are either covalently bound to the current fragment or have a hydrogen bond to it (alternatively, a distance criterion ζ_1 can be used). Any remaining dangling bonds are capped with hydrogen atoms.
- Primitive subsystems which are identical to or completely contained in any other primitive subsystem are eliminated.
- Possible overcounting of interactions is avoided by using the IEP to construct "derivative subsystems" from all parts which are contained in more than one of the remaining primitive subsystems (i.e., overlap between primitive subsystems). This process is started from the largest possible fragments and repeated for ever smaller fragments until overcounting is eliminated.

The GEBF energy expression has the simple form

$$E = \sum_{K}^{N^{\mathrm{F}}} C_K E_K \ , \tag{7.29}$$

where E_K are the energies of primitive or derivative subsystems and C_K are the corresponding summation coefficients. While primitive subsystems have a positive coefficient (usually +1), derivative subsystems enter with a negative coefficient to cancel the respective overcounting. The magnitude of the negative coefficient depends on the number of times the current interaction would otherwise be overcounted. Note that the GEBF fragmentation would reduce to the MFCC one in case of a linear protein chain, where each primitive subsystem includes a single amino acid capped by its two neighboring residues (and additional hydrogens).

In addition to the general approach outlined above, two-body interactions between residues which are further apart than the primary cutoff radius ζ_1, but less than a larger radius ζ_2 are included in the same manner as in the EC-MFCC approach. Furthermore, a point charge background is used to represent the remainder of the total system already in each subsystem calculation, just like in the later proposed EE-GMFCC approach.

Geometry optimizations and the calculation of vibrational frequencies in the GEBF framework are possible through analytical derivatives [130], and the fragmentation procedure has later been improved and completely automatized by Hua et al. [131, 132]. Use of GEBF as the QM method in a QM/MM scheme has been reported under the name "Fragmentation QM/MM" [133]. Very recently, an extension to periodic boundary conditions was reported [134], and a review on the GEBF method is available [135].

7.5.2 Fragment Molecular Orbital Method

The Fragment Molecular Orbital (FMO) approach was first established by Kitaura et al. in 1999 [136], based on their earlier Pair Interaction Molecular Orbital (PIMO) method [137]. It can be regarded as a truncated MBE, where the electrostatic interactions between different fragments are taken into account self-consistently up to the full *n*th-order expression, while all other interactions are treated on a much lower order (usually two- or three-body expansion).

The FMO approach is based on disjoint fragments, without resorting to the use of capping groups. If covalent bonds have to be split, this is done in a heterolytic fashion, i.e., assigning both electrons of a bond to one of the fragments. The atom which obtains the bonding electrons is referred to as bond-attached atom (BAA), whereas the other binding partner is termed bond-detached atom (BDA). An important point concerns the proper division of basis functions among the fragments. To ensure that the BDA does not generate density contributions in the bonding region, the corresponding hybrid orbital is projected out either by a suitable projection operator [138] or Fock matrix transformation [139]. Conversely, certain orbitals of the BDA are included in the BAA-containing fragment to describe the detached bond.

The choice of fragmentation is in general left to the user, although reasonable defaults have been supplied for standard situations, such as the division of proteins [140, 141]. The workflow of an FMO calculation then proceeds as follows:

1. The electronic structures of all isolated fragments are determined.
2. An ESP contribution due to each of the fragments is extracted from the results.
3. Additional monomer calculations are set up, which include the ESP stemming from all other fragments in their Hamiltonian. Since every such calculation produces a new fragment ESP, the monomers are iterated to self-consistency.
4. Pairs of monomers are combined to dimers, which are subjected to similar calculations. However, the background field is fixed and not updated anymore (single calculation per dimer)
5. If required, higher-order combinations (trimers, tetramers, etc.) can be constructed and treated in the same way as the dimers.

The FMO total energy is then determined based on the calculated energies according to Eqs. 7.3 and 7.4 or corresponding higher-order expansions (currently, expansions up to third [142] and fourth orders [143] have been tested). Since the ESP for the monomer calculations is iterated until convergence, the electrostatic interaction is treated to the full order, while the non-electrostatic contributions are of course only contained up to the chosen order. The physical justification for this approach is the relatively short range of the latter. The incorporation of the Coulomb field into the QM calculations ensures proper coupling of the different kinds of interactions.

There are many different ways to treat the environmental ESP. Originally, the exact ESP was used by evaluating two-electron contributions for the electronic part. Since this was deemed too time-consuming, it was proposed to use either Mulliken populations or derived partial charges to approximate the ESP [144, 145]. In addition, different approximations can be used based on the inter-fragment distance, although this requires a slight reformulation of the energy expression to account for dimers where the constituents are treated on an unequal footing [144, 146]. For far-separated monomers, dimer calculations can even be forfeited and replaced solely by the electrostatic interaction [144]. In principle, an orbital-based exchange term could be included in the embedding potential for the individual fragments. However, this is discouraged on the grounds of imbalancing an otherwise favorable error compensation [147].

In order to obtain a supermolecular density and derived properties, several variants of the FMO method are available. For instance, in the FMO-MO approach [148], a supermolecular density is calculated from an MBE and used to construct a total Fock matrix, from which supermolecular orbitals can be derived. The FMO/F and FMO/FX variants proposed by Fedorov and Kitaura accomplish this without calculating the total density, directly from fragment Fock matrices [147].

Following the initial implementation for HF wave functions, many important classes of QM methods have been interfaced with the FMO scheme, e.g., DFT [149], MP2 [150], Coupled Cluster [151], and MCSCF [152]. Recently, a combination with the semiempirical Density Functional Tight Binding (DFTB) method was also reported [153, 154]. In addition, a multilayer formalism in QM/QM style was presented [140], and based on nearly [155] or fully analytical gradients [156], several applications to geometry optimizations [157] and MD simulations [158, 159] have been reported. Furthermore, a combination with the PCM approach [160], an extension to periodic boundary conditions [161], and several excited-state treatments were published [162, 163]. For more information, the reader is referred to several exhaustive reviews [13, 164, 165] and a book about the method [141].

The FMO scheme has been combined with the EFP approach in two ways. Nagata et al. employed FMO as the QM method in an EFP1 calculation and gave a detailed description of the interactions between the two regions [166]. Steinmann et al. presented the Effective Fragment Molecular Orbital (EFMO) method [102], where the self-consistency cycle for the molecular ESP is avoided by applying the EFP polarizability model, and long-range electrostatics are described by a multipole expansion, just like in the EFP scheme. In its successor, the Fully Integrated EFMO (FIEFMO) method [103], exchange repulsion, dispersion, and charge transfer are also included in EFP style instead of merely through low-order many-body terms.

There are several methods which are related to the FMO approach. The Fast Electron Correlation (FEC) method by Hirata et al. employs the same functional principle, but approximates the electrostatic interaction solely by dipole–dipole terms [167] or even by atom-centered point charges [168]. The Electrostatically Embedded Many-Body (EE-MB) scheme [169] is also very similar to FMO, but uses a constant charge background (thus avoiding iterative optimization). In the Hybrid Many-Body Interaction (HMBI) scheme [170], higher-order terms are approximated by a polarizable force field with a special focus on applications for periodic systems. In particular, a non-periodic method for short-range interactions (e.g., within a unit cell) can be combined with a periodic treatment of all long-range interactions.

7.5.3 Molecular Tailoring Approach

After the initial proposal of the Molecular Tailoring Approach (MTA) in 1994 [171], development lay silent for almost a decade until a much improved version and an automatic fragmentation scheme were presented by Babu et al. [172]. Similar to DC schemes (see Sect. 7.6.1), the total density matrix of the system is constructed ("tailored") from fragment contributions in the original approach. For each element of the total density matrix, one of many overlapping fragments is identified where the two corresponding atoms (or single atom in case of intraatomic elements) are embedded in the best representation of their molecular environment (as defined in the following). In the original implementation [172], this is evaluated by counting the minimum number of bonds to be traced until the fragment edge is encountered. A refined version was reported under the name Cardinality-Guided MTA (CG-MTA) in 2006 [173]. The sophisticated automatic fragmentation algorithm will be detailed in the following. The central quantity is the "R-goodness" parameter R_g, which is used on several levels. The atomic R-goodness $R_g^K(A)$ of atom A in a certain fragment K is defined as the maximum radius of a sphere centered on that atom, such that the sphere only includes other atoms belonging to K. In this way, $R_g^K(A)$ describes "how embedded" an atom is in a given fragment. Each atom will be represented by the fragment in which it has the largest R-goodness. The general R-goodness of atom A, $R_g(A)$, is then simply determined as the maximum of all obtained values for that atom, i.e., the value obtained for the representing fragment. Finally, the total R-goodness of a given fragmentation scheme, R_g, is defined as the minimum of all atomic values, giving the minimum radius of the embedding molecular environment around each atom.

The fragmentation algorithm requires two parameters, a minimum R-goodness $R_g^{\min}$ and a maximum fragment size in terms of atoms per fragment. First, certain moieties which should not be fragmented, such as aromatic rings, are identified. A large set of overlapping fragments is then created by centering a sphere of radius $R_g^{\min}$ on each heavy atom in the system. This ensures that every such atom will have at least an R-goodness of $R_g^{\min}$ in its parent fragment. A complicated set of rules is used to merge adjacent fragments, depending on their overlap. The given maximum fragment size determines the end of the merging process. Any dangling bonds are then capped with hydrogen atoms. The electronic structure now has to be determined for the resulting subsystems as well as for additional fragments created from the overlap between the basic subsystems. Instead of constructing the total density matrix as in the original approach, the energy of the system can be evaluated directly, based on the IEP (see Eq. (7.1)). Here, all overlaps of even order (e.g., between two or four fragments) are subtracted, whereas all odd-order terms (e.g., ternary intersections) are subtracted. One of the major benefits of the refined version is its treatment of bonded and non-bonded effects on the same footing, since the atom-centered spheres are bond-independent. The set-theoretical evaluation can be extended to other properties [174]. It should be noted that without any additional embedding components, the total interaction is only described through the molecular overlap between the fragments.

Gradients and other derivatives have been derived for the CG-MTA [173], and the method has been combined with several quantum-chemical methods [175, 176]. In addition, it was noticed that the MTA error in the correlation energy (as opposed to the HF energy) is approximately independent of the basis set. Thus, a "grafting correction" was introduced, where this error is determined with a smaller basis set and used to correct the MTA correlation energy in a calculation with a large basis set [177]. This concept was soon extended to the estimation of the total error at the level of the small basis set [178], and a variant which utilizes different fragment sizes to completely avoid supermolecular calculations was also reported [179]. Recently, CCSD(T) was employed in the context of grafting corrections [180].

In regular (CG-)MTA, each fragment is only embedded within directly overlapping fragments. Although the embedding potential has the correct quantum-chemical form, it usually does not represent the full environment, but merely a comparatively small region, which can lead to problems for charged or very polar systems. Ganesh et al. already suggested to create additional fragments by combining charged moieties and include them in the MTA expansion [173]. In order to account for all long-range Coulomb effects, the Electrostatically Embedded MTA (EE-MTA) approach [181] was conceived by the Truhlar group. Here, all quantum-chemical calculations are performed in an electrostatic field created by point charges representing the rest of the system (as in FMO or EE-GMFCC), which was found to clearly improve the description of polar and charged systems. The overcounting of Coulomb interactions is taken care of by a suitable energy expression. Furthermore, the use of a tuned fluorine atom was put forward in this work as an alternative to regular hydrogen caps. Many details about the MTA, especially concerning the current implementation, can be found in a recent book chapter [182], and a review is available as well [174].

7.5.4 Kernel Energy Method

The Kernel Energy Method (KEM) was first reported by Huang, Massa, and Karle in 2005 [183] and specifically aims at the description of biological entities. The total system is decomposed into fragments ("kernels"), which are capped with hydrogen atoms and subjected to isolated calculations. Subsequently, pairs of these kernels are formed and additional calculations are performed. The total energy is simply obtained as

$$E^{\mathrm{KEM}} = \sum_{K}^{N^{\mathrm{F}}-1} \left(\sum_{K=1}^{N^{\mathrm{F}}-m} \sum_{L=K+m}^{N^{\mathrm{F}}-m} E_{KL} \right) - (N^{\mathrm{F}} - 2) \sum_{K=1}^{N^{\mathrm{F}}} E_K \ , \tag{7.30}$$

which has been shown to be equivalent to the regular two-body expansion in Eq. (7.3) [15]. The effect of the cap atoms is expected to cancel due to inclusion in both single and double kernels. In principle, all double kernels can be included in the calculation, although this might be very expensive for large systems. In the original publication, the double kernels were therefore restricted to bonded pairs. In applications to DNA, the important hydrogen bonds between base pairs were added by including the corresponding double kernels [184]. Straightforward extension to higher orders is possible, and tests including up to fourth-order terms have been reported [185]. In 2010, a generalized scheme based on earlier work by Deev and Collins [186, 187] was introduced, where only those combinations of kernels are taken into account which are connected in the molecular graph [188].

From an embedding point of view, the interaction between different kernels is taken into account only at the N-body level (where N is the order of the expansion), and no additional terms are added. The KEM can thus be likened to the FMO approach without inclusion of the environmental ESP in the quantum-chemical calculations. To our knowledge, no particular automatic fragmentation algorithm has been reported for the KEM. However, for the treatment of graphene flakes, a “fissioning” process was proposed in order to cut through aromatic bonds [189]. In this approach, an aromatic bond is cut along the bond instead of across it, yielding two single bonds which are capped with hydrogen atoms.

The original tests were based on HF/STO-3G results, but the method was soon shown to be applicable in combination with a variety of methods and basis sets [190]. Gradients have not yet been derived, although a derivation according to the MBE should be straightforward. Recently, the KEM was used to determine Atoms-in-Molecules (AIM) charges for a collection of large molecules [191].

7.5.4.1 Other Methods

Independent of each other, the Generalized Many-Body Expansion (GMBE) by Richard and Herbert [17] and the Many-Overlapping-Body Expansion (MOBE) by Mayhall and Raghavachari [16] were put forward in 2012. Both approaches attempt to unify methods based on the IEP (overlapping fragments) with those based on an MBE (non-overlapping fragments) in a common framework. The resulting energy expressions are very similar, although not quite identical. Furthermore, a somewhat different fragmentation scheme is used, although this is not an essential ingredient of either method [3]. A detailed comparison of the two schemes was carried out later by Richard and Herbert [192], who confirmed that the two schemes are not exactly equivalent, although very similar numerical results are obtained for many cases.

The Systematic Molecular Fragmentation (SMF) algorithm by Deev and Collins [186] is very similar to the original MFCC approach, where whole neighboring residues were used as caps. The SMF scheme is also based on creating overlapping fragments and combining their individual energies or properties according to the IEP. However, it is formulated in a more general way and employs functional groups as the smallest non-breakable units (as opposed to amino acid residues). A hierarchy of fragmentation schemes can be generated by specifying a desired “fragmentation level,” which corresponds to the number of overlapping groups between adjacent fragments (and thus to the fragment size). By increasing the fragmentation level, the supermolecular result is systematically approached. Non-bonded interactions are treated by including additional two- or three-body correction terms. To avoid excessive calculations for far-separated fragments, long-range electrostatic interactions have also been modeled by a multipole expansion [187] or effective fragment potentials [193]. The fragmentation scheme has been refined in the Systematic Molecular Fragmentation by Annihilation (SMFA) approach [194], among other new features allowing for automatic ring fragmentation. The SMF and SMFA methods have been reviewed and compared to the Combined Fragmentation Method [195] in a recent article [196].

After reviewing and comparing several existing fragmentation methods, Suárez et al. presented the Fragment Energy Method (FEM) in Ref. [15], which can be regarded as a generalization of the MFCC scheme and a special case of the SMF approach. The Multilevel Fragment-Based Approach (MFBA) [197] works in a similar way, but different theoretical methods are used to determine fragment interactions based on a distance criterion. Gradients have been derived, and the method has been deemed especially suitable for fragment-based geometry optimizations. The same strategy was pursued by Mayhall and Raghavachari with their very general Molecules-in-Molecules (MIM) scheme [198]. The original formulation combines a GEBF-like fragmentation scheme with the multilevel treatment of ONIOM approaches. However, instead of treating a central fragment of interest with a more sophisticated model than its surroundings, one or more cutoff criteria are introduced to determine interaction terms in different ways. While many existing ideas were incorporated in the MIM approach, these have been combined to a conglomerate of remarkable generality, which can treat a variety of different situations (e.g., overlapping/non-overlapping fragments, different fragmentation schemes, one or several different theoretical treatments) within a common framework. Gradients for the MIM approach are available [199], and it has recently been applied to the calculation of vibrational, circular dichroism and Raman spectra [200–202].

7.6 Quantum-Chemical Divide-and-Conquer Methods

In this section, several methods originating from a mathematical decomposition of the supermolecular solution are presented. All approaches are at least related to the DC scheme, although the nature of the embedding can be very different. A major distinction from the methods presented so far is the fact that hardly any embedding components are included based on empirical considerations (except for those arising naturally, such as the Coulomb contribution of the subsystem DFT embedding potential).

7.6.1 Divide and Conquer

The Divide-and-Conquer (DC) method was originally formulated by Yang in terms of DFT [203]. Very similar to subsystem DFT (see Sect. 7.3), the additivity of the electron density is exploited to partition the total density into fragment contributions. To this end, a positive partition function $p^K(\vec{r}\,)$ for each subsystem is introduced under the requirement that

$$\sum_{K}^{N^{\mathrm{F}}} p^K(\vec{r}\,) = 1 \;\forall\, \vec{r} \;, \tag{7.31}$$

i.e., the values of the individual subsystem partition functions must add up to unity at each particular point in space. A subsystem density $\rho^K(\vec{r}\,)$ can then be expressed in terms of the total density $\rho(\vec{r}\,)$ as

$$\rho^K(\vec{r}\,) = p^K(\vec{r}\,)\rho(\vec{r}\,) \tag{7.32}$$

and it thus follows that

$$\rho(\vec{r}\,) = \sum_{K}^{N^{\mathrm{F}}} \rho^K(\vec{r}\,) \ . \tag{7.33}$$

Clearly, the value of the partition functions will be large within and close to their corresponding subsystem, while it will be small far away from it. An example for a smooth partition function was given in the original article in terms of spherical atomic densities [203]. The crucial point of the DC formalism is to express the individual subsystem densities through localized subsystem orbitals instead of supersystem functions. This is accomplished by rewriting these densities as

$$\rho^K(\vec{r}\,) = 2p^K(\vec{r}\,) \sum_{m}^{N^{\mathrm{orb}}} f_\beta \left(\varepsilon_{\mathrm{F}} - \varepsilon_m^K\right) \left|\psi_m^K(\vec{r}\,)\right|^2 \ , \tag{7.34}$$

where $f_\beta(x) = [1 + \exp(-\beta x)]^{-1}$ is a smooth distribution function of width β, ε_{F} is the Fermi energy, and ψ_m^K are *local* eigenfunctions of a subsystem Hamiltonian obtained through projection of the total KS Hamiltonian on a basis set unique to subsystem K (thus, ψ_m^K are localized on the latter). The Fermi energy can be obtained from the normalization condition to the total number of electrons N^{el},

$$N^{\mathrm{el}} = 2 \sum_{K} \sum_{m} f_\beta \left(\varepsilon_{\mathrm{F}} - \varepsilon_m^K\right) \left\langle \psi_m^K \middle| p^K(\vec{r}\,) \middle| \psi_m^K \right\rangle \ . \tag{7.35}$$

It should be noted that only the total number of electrons is fixed, but not the subsystem values. The density-based DC strategy can be summarized as follows: First, a local basis set has to be chosen for each subsystem. For instance, a straightforward choice would be the basis functions centered on a certain subset of nuclei. Furthermore, a form for the partition functions must be selected. Subsequently, the total Hamiltonian has to be projected on the local basis sets, generating a set of subsystem eigenfunctions (orbitals) and eigenvalues (orbital energies). The Fermi energy can then be determined from Eq. (7.35), which allows to determine subsystem densities from Eq. (7.34) and thus a total density. This process must be iterated to self-consistency (until identical Fermi energies for the individual subsystems are obtained), since the total Hamiltonian depends on all fragment densities and thus couples them. For a more detailed derivation, the reader is referred to the original article [203] as well as an excellent review [2].

In order to avoid the evaluation of three-dimensional integrals over the partition functions and to generalize the DC approach to wave function methods, Yang and Lee soon introduced a reformulation where the total density matrix is partitioned instead of the spatial electron density distribution [204]. The density matrix **D** is defined as (for simplicity, we consider a single-determinant closed-shell case here)

$$D_{ij} = 2 \sum_{m}^{N^{\mathrm{orb}}} C_{im} C_{jm} \ , \tag{7.36}$$

where C_{im} and C_{jm} are the coefficients for atomic orbitals i and j in the LCAO expansion for occupied molecular orbital m. The spatial partition functions of the original scheme are replaced by corresponding partition matrices $\mathbf{P}^K$ with the requirement that

$$\sum_K P_{ij}^K = 1 \ , \tag{7.37}$$

such that the subsystem contributions for each matrix element of $\mathbf{P}$ add up to 1. The original proposal for the form of the partition matrix was simply

$$P_{ij}^K = \begin{cases} 1 & \text{if } \ i \in K \text{ and } \ j \in K \\ 0.5 & \text{if } \ i \in K \text{ and } \ j \notin K \\ 0 & \text{if } \ i \notin K \text{ and } \ j \notin K \end{cases} \ , \tag{7.38}$$

which guarantees the above normalization condition. All further expressions correspond directly to the density-based formulation. In particular, the subsystem density matrix contribution is given as

$$D_{ij}^K = 2P_{ij}^K \sum_m f_\beta \left(\varepsilon_{\mathrm{F}} - \varepsilon_m^K\right) C_{im}^K C_{jm}^K \tag{7.39}$$

and the total density matrix can be obtained by simply summing over all subsystem contributions.

As mentioned above, a simple and chemically intuitive choice for the local basis sets would consist of the functions centered on a certain subset of nuclei. In order to improve the description, basis functions of adjacent nuclei can be included in the subsystem description, leading to the concept of “buffer regions” [205]. In its simplest form, all basis functions located within a certain cutoff distance of the current fragment are added to the subsystem basis. Buffer regions are central to the embedding aspect of DC techniques, since it is through this overlap in terms of basis functions that the individual subsystem Hamiltonians are coupled. The subsystems are usually defined by “core regions,” which are mutually exclusive, and buffer regions, which are allowed to overlap with the core and/or buffer regions of adjacent fragments. In particular, the core of one fragment could play the role of buffer region for another fragment [2]. Several advanced partition matrix prescriptions utilizing multiple buffer regions have been put forward by Dixon and Merz [206, 207], where the density matrix elements corresponding to combinations of buffer functions are set to zero. This allows to improve the SCF results for a fragment, while ensuring that its density matrix contributions exclusively stem from the primary functions of that fragment. Lee et al. demonstrated that upon growing the total system but maintaining the size of the subsystems and their buffer regions, linear scaling can be achieved [208].

Some related methods, which can be regarded as non-self-consistent DC variants, were proposed by the Mezey group. In the Molecular Electron Density Lego Approach (MEDLA) [209], total densities are obtained by simply combining densities from a fragment library in an additive fashion. The fragment densities are obtained by carrying out calculations for small analogous molecules (e.g., CH_4 for an sp^3 carbon) and extracting a partial density by considering only certain density matrix contributions according to Eq. (7.38). The Adjustable Local Density Assembler Method (ALDA) [210, 211] used the same strategy, but instead of fragment densities on a grid, only the fragment density matrices are stored and evaluated on the fly, which also allows for small geometric modifications. Finally, the Adjustable Density Matrix Assembler (ADMA) approach [210, 211] is used to directly construct a supermolecular density matrix from subsystem matrices, as in other DC schemes. This approach has also been combined with a classical treatment of long-range electrostatics [212].

As mentioned above, the density matrix formalism allows to apply the DC strategy to a variety of electronic-structure methods. For instance, a combination with semiempirical methods was explored [206, 207] and Li et al. carried out first tests for correlated methods [213]. Subsequently, interfaces to HF/hybrid DFT [214], MP2 [215, 216], and Coupled Cluster [217, 218] approaches have been reported. Kobayashi et al. exploited the multilevel nature of the buffer region concept by using differently sized buffer regions (and thus basis functions) for the HF and correlation part of post-HF calculations [217, 219]. Song and co-workers separately optimized the exchange contributions for different fragments based on CCSD(T) calculations in a DC framework [220]. Guidon et al. introduced the idea of evaluating HF exchange in a smaller basis through introduction of an auxiliary density matrix, which is then corrected by a suitable density functional [221]. Recent progress on the DC family of methods includes the extension to time-dependent calculations [222, 223], a GPU implementation [224], and several developments with respect to AIMD simulations [225, 226]. Furthermore, Fornace and co-workers presented the Embedded Mean-Field Theory (EMFT) approach [227], which is also based on a division of the total density matrix into blocks, facilitating the representation of different parts of the system using different theoretical approaches. Unfortunately, no comprehensive review on DC methods seems to be available, but many useful details can be found in two perspectives [228, 229] and in Ref. [2].

7.6.2 Density Matrix Embedding Theory

Density Matrix Embedding Theory (DMET) is a very recent approach proposed by Knizia and Chan [230, 231] to treat strong embedding effects, such as between two fragments linked by a covalent bond. It is related to the earlier Dynamical Mean-Field Theory (DMFT), which employs the many-body Green's function as the central object (reviews on DMFT can be found, e.g., in Refs. [11, 232, 233]). One notable recent advancement in the context of Green's function embedding was the

Self-Energy Embedding Theory (SEET) presented by the Zgid group [234–236]. In contrast to both of these methods, DMET employs the density matrix as the partitioned object.

The central idea of DMET is to represent the total wave function of a system by a Schmidt decomposition into a linear combination of states of an embedded open quantum system (fragment) F and states of the environment (bath) B, i.e.,

$$|\Psi\rangle = \sum_{i}^{N^{\mathrm{fs}}} \lambda_i |F_i\rangle |B_i\rangle \ , \tag{7.40}$$

where λ_i is a coefficient, $|\Psi\rangle$ is the total wave function, and $|F_i\rangle$ and $|B_i\rangle$ are states local to fragment or environment, respectively. It can be shown [230, 231] that the number of effective bath states N^{bs} required to recover the exact solution as described above is at most the same as the number of fragment states N^{fs}.

This approach yields the exact wave function, but already requires it for the determination of effective bath states. In practice, solutions for individual fragments are therefore determined with a sophisticated correlation method, while the bath states are approximated by a cheap supermolecular solution (e.g., a single Slater determinant). An “embedding basis” of effective bath states that interact with the fragment and its embedding Hamiltonian is determined by several projection procedures onto the fragment states. This yields N^{fs} interacting (“entangled”) bath states and a number of non-interacting (“pure”) bath states. Only the former need to be taken into account to express the effect of the bath on the active fragment, while the latter merely form a multiplicative “core determinant.”

In order to ensure consistency between the different electronic-structure methods, the density matrix difference between the (correlated) fragment solutions and the (mean-field) supersystem solution should be minimal. This is achieved by introducing additional embedding operators u_K for all fragments, which are added to the fragment Hamiltonians as well as to the supersystem Hamiltonian. As summarized in Ref. [231], the whole DMET self-consistency procedure thus takes the following form:

1. Determine the (mean-field) supersystem solution.
2. Construct an embedding basis and a fragment Hamiltonian for each fragment by projection and solve its electronic structure with a correlated method.
3. Construct embedding operators for each fragment to minimize the difference between the low- and high-level density matrices.
4. Repeat above steps with the embedding operators added to each Hamiltonian (except the fragment’s own) until self-consistent operators are obtained.

DMET has been applied to physical model systems such as a 2D Hubbard model [230, 237] as well as to first chemical problems like molecular chains and rings [231, 238], solids [239], and even a chemical reaction [238]. A short review including a comparison between density-based embedding, DMFT, and DMET is available [11].

An interesting variant was recently published under the name “Bootstrap Embedding” [240]. The motivation was to improve the slow convergence of the DMET solution with respect to the fragment size, which was shown to depend on the volume-to-surface ratio. In contrast to regular DMET, the system is partitioned in multiple ways, such that each atom is close to the fragment boundary in some partitionings and buried deeper within the fragment in others. Instead of trying to match the environment density matrix of the mean-field description to the one obtained from a correlated description of the fragment (which is bound to fail due to the restriction to a single Slater determinant), the “edge” region of one fragment is matched to the “core” region of a corresponding fragment from a different partitioning scheme. In this way, the total density matrix is improved systematically. Since wave functions of the same type (e.g., Full Configuration Interaction (FCI) in the original article) are matched to each other, the condition can be fulfilled exactly, which decreases the influence of the nature of the bath. In addition, the choice of partitioning scheme clearly becomes less important, since multiple different types are constructed and made consistent with each other. Bootstrap Embedding has only been applied to lattice models so far, but could theoretically be extended to molecular systems, even though a division in terms of atomic orbitals might not be straightforward [240].

7.6.3 *Frozen Density Embedding*

Frozen Density Embedding (FDE) [21] is one particularly interesting variant of subsystem DFT, which has been introduced in Sect. 7.3. FDE can be regarded as the special case of solving the KSCEDs for a single (“active”) subsystem while keeping all environmental densities frozen. The active density is thus relaxed in the embedding potential generated by the frozen density. On the one hand, FDE could thus be used as a focused approach, with the environmental density obtained from a different method or from model considerations (see, e.g., Ref. [241]). On the other hand, the subsystem DFT solution can be recovered by successively interchanging the roles of active and frozen density (or densities) and running additional calculations. When this process is carried out until self-consistency is reached, an iterative (but equivalent) solution to the subsystem DFT problem is obtained. In the literature, these relaxation cycles are often referred to as “Freeze-and-Thaw” (FT) cycles [20]. Physically speaking, the FT cycles introduce the inductive component of the intermolecular interaction between the subsystems (see Ref. [22]), although this interpretation formally has to be taken with a grain of salt (see the discussions in, e.g., Refs. [242, 243]).

Certain approximations are usually made in practical FDE calculations. The first is to introduce approximate forms for the XC potential (fragment contributions as well as nonadditive correction) and the nonadditive kinetic energy. This approach is necessitated by the fact that exact expressions are not known. Since the total density is available in each step of an FDE calculation, all common density-dependent forms can be used to evaluate the XC contributions (e.g., the Local Density Approximation (LDA) or functionals derived from the Generalized Gradient Approximation (GGA)). Hybrid functionals, however, cannot be used directly, since the evaluation of their orbital-dependent contribution would require orbitals for the supersystem [244–246]. Optimized Effective Potential (OEP) methods [247] could offer a solution here.

For the same reason, it is difficult to obtain a suitable form for the nonadditive kinetic energy. Purely density-dependent forms can be employed for this contribution as well, but this is a much more severe approximation, as it is known that density functionals for the kinetic energy, such as the Thomas–Fermi functional [248, 249], only work for limiting cases. However, since in practice the nonadditive kinetic term is often relatively small, they can still be viable in many situations. In particular, for weakly bound complexes, good results have been obtained [20, 250, 251] with the PW91k functional [252], whereas the interactions between covalently connected subsystems are described qualitatively wrong [253, 254]. In these cases, a better description could be obtained by potential reconstruction approaches [253, 255, 256], although these require a preliminary supermolecular calculation. A comprehensive discussion of different approaches for constructing nonadditive kinetic potentials can be found in Refs. [6, 10].

It has been shown that the kinetic energy contribution vanishes if the subsystems' orbitals are orthogonal to each other [257, 258], although this is not a strict requirement to recover the exact KS solution [259]. If such an orthogonalization is desired, it can be carried out by employing the projection technique introduced by Manby et al. [260]. In this approach, localized orbitals are determined for different fragments, which allows to use a simple projection operator to orthogonalize environmental fragment orbitals, eliminating the nonadditive kinetic energy. Since a full calculation of the supersystem is required to obtain localized orbitals, the approach is mainly suitable for WFT-in-DFT embedding (see below). An alternative is the use of additional Lagrangian multipliers to enforce intersubsystem orbital orthogonality [257].

A further simplification is to employ different subsystem basis sets for the individual fragment calculations. Clearly, this reduces the computational effort tremendously, since most matrix operations during the solution of the SCF problem scale with the number of basis functions. However, one important consequence is that charge transfer between fragments becomes impossible by construction (which might be desired in some situations [261]). It should be noted that the approximation of a subsystem basis set is by no means a requirement for FDE calculations, but merely facilitates calculations for large molecules.

Early applications of the FDE method were especially concerned with the description of hydrogen-bonded and van der Waals complexes, as summarized in Ref. [262]. Soon, attention turned to molecular properties and spectra. An extension to time-dependent DFT (TDDFT) was published by Casida and Wesołowski in 2003 [263], and several studies concerning solvent/environment-induced shifts were reported [264, 265]. An extension to NMR shifts was presented by Jacob and Visscher [266]. In 2007, Neugebauer rederived the FDE-TDDFT approach and extended it to coupled excitations, delocalized over different subsystems [267]. Such a scheme is particularly suitable for the treatment of coupled chromophores, e.g., in photosynthetic light-harvesting complexes, where the subsystem picture enables a natural approach to the investigation of excitonic interactions. Several subsequent studies applied this approach for the determination of spectral properties of natural light-harvesting proteins (see Refs. [268, 269] for reviews of earlier work, Refs. [270–274] for methodological extensions and Refs. [275, 276] for more recent applications). Much effort has also been dedicated to the application of FDE for the investigation of spin densities and charge transfer processes [261, 277–279].

Already in 1998, the purely density-based FDE formalism was extended to the embedding of WFT methods in a DFT environment [280, 281]. In such a formalism, the same working equations as outlined in Sect. 7.3 can be used by determining the density of an embedded system with a WFT method and letting it enter the energy expression. In addition, the embedding potential is added to the Hamiltonian for the embedded system. The WFT-in-DFT formalism was later refined to produce self-consistent densities for all subsystems [282] and has been extended to excited states [283, 284]. Recently, thorough rederivations of the excited-state formalism for state-specific approaches [285] and response theory treatments [286] have been presented, and a corresponding implementation for coupled excitations was reported [287]. In WFT-in-DFT embedding, the bottleneck is often the high-level calculation of the embedded cluster. Thus, more sophisticated methods for estimating the nonadditive kinetic energy can be used, which require a calculation of the full system on the basis of DFT. This was first exploited by Roncero et al. [255] and later used by the Miller group to construct an accurate WFT-in-DFT embedding scheme [288].

Proteins can be considered a unique challenge for FDE, since they comprise extremely large, covalently connected units (necessitating cuts through covalent bonds), while routinely being too large even for a cheap DFT calculation (preventing the use of exact embedding schemes). An interesting variant of FDE specifically adapted for the treatment of proteins was therefore devised by Jacob and Visscher [117], based on earlier work by Casida and Wesołowski [263]. In the so-called Three-Partition FDE (3-FDE) method, the fragmentation scheme of the MFCC method (see Sect. 7.5.1) is combined with the embedding potential of FDE. Fragments are thus constructed by cutting certain peptide bonds and applying small capping groups to saturate remaining free valences. Since the fully quantum-chemical embedding potential is applied to represent the environment of each fragment, the caps can be chosen much smaller than originally intended by the MFCC developers and usually consist of neutral or methylated amino acid termini [117, 289]. An important feature of the 3-FDE method is the application of an additional cap potential, which forces the density in the region of the cap atoms to be identical to the one obtained for the concaps. This guarantees that upon subtraction of the latter, no negative density patches are obtained. The 3-FDE method has been tested on some small example systems [117, 289] and was used to obtain a fully quantum-chemical density of the Fenna–Matthews–Olson complex of green sulfur bacteria, which consists of more than 6,500 atoms [276]. Subsequently, a robust protocol to construct fully converged 3-FDE protein densities was presented [290], and a comprehensive benchmark was published [291].

Analytical gradients for regular FDE were first implemented by Wesołowski [292] and have been used for geometry optimizations [293] as well as MD simulations [294, 295]. Recently, a detailed derivation and new implementation in the Amsterdam Density Functional (ADF) program were reported [296]. In addition, approximate analytical gradients for WFT-in-DFT embedding are available [297].

Recent developments include a variant of the COSMO scheme especially suited to subsystem calculations [46], the embedding of DMRG [298] and ADC(2) [299] wave functions in a DFT environment, and the derivation of excited-state gradients [300]. Many more details about the different flavors of FDE can be found in several extensive reviews [6, 9, 10, 268, 269].

7.7 Summary and Conclusions

In the present chapter, we have attempted to give an overview over different classes of embedding methods, focusing especially on actively developed approaches, many of which have been put forward only recently. Three major classes of methods have been identified, which are (i) QM/MM and related approaches (Sect. 7.4), which in general require the identification of a chemically interesting part of the total system, (ii) methods based on an MBE or the IEP (Sect. 7.5), where a truncated expansion is usually supplemented by physically motivated embedding components, and (iii) DC-like approaches (Sect. 7.6), most of which are potentially able to recover the exact solution from fragment calculations. Clearly, this division is somewhat arbitrary, as the boundaries between different classes have been blurred over the last decades through the adaptation and combination of different ideas.

Especially, the approaches from the first two categories have been compared to an exact embedding potential, which emerges from the subsystem DFT approach (see Sect. 7.3). In many cases, distinct physical effects can be identified as particular terms of the interaction expressions, whereas this is more difficult for the approaches presented in Sect. 7.6. Therefore, the benefits of the first two classes of methods lie in their practical and often computationally cheap form, whereas the DC-like approaches are much more deeply rooted in formally exact theories.

Contributions from all these classes of methods will most certainly continue to be highly relevant in the field of large-scale calculations, where many systems only become accessible through fragment-based approaches, as well as with respect to the investigation of molecular interactions, where embedding facilitates interpretation and leads to chemical insight. The many recent developments presented in this chapter bear testimony to the continued interest in such approaches and their importance in both chemistry and physics.

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