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Polarizable Embedding Based on Multiconfigurational Methods: Current Developments and the Road Ahead

Erik D. Hedegård,* Hans Jørgen Aa. Jensen, and Jacob Kongsted

This perspective gives a brief overview of recent developments within the polarizable embedding (PE) method — a multiscale approach developed over the last years. In particular, we are concerned with a recent coupling of the PE method to a multiconfiguration self-consistent field (MCSCF) code. Current applications and target systems are outlined, and methods to incorporate dynamical correlation are discussed. With respect to dynamical correlation, the focus is on perturbative treatments as well as a range-separated

multiconfigurational hybrid between MCSCF and density functional theory (MC-srDFT). A short discussion of CAS active spaces is also given. A few sample results using a retinal chromophore surrounded by a protein environment illustrate both the importance of the choice of active space and the importance of dynamical correlation. © 2014 Wiley Periodicals, Inc.

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Introduction

This article focuses on the perspectives of recent developments within the polarizable embedding (PE) method,^[1] which is a multiscale approach developed over the last years. Similar methods, such as the effective fragment potential method,^[2] have focused mainly on relative energies and molecular geometries, whereas the PE method has its primary focus on molecular response properties as well as spectroscopic constants. This perspective is in particular concerned with a recent coupling of the PE method with a multiconfiguration self-consistent field (MCSCF) wave function, including linear response properties.^[3] The method is denoted PE-MCSCF and has recently been implemented in a development version of the DALTON program.^[4]

Direct comparison of experimental and theoretical spectroscopic constants may be very important when interpreting ambiguous experimental data. Such a comparison, however, requires highly accurate theoretical methods. In this context, a central development has been the ability to recover dynamical correlation with systematically increasing accuracy, using for instance coupled cluster (CC) methods or the efficient, but less systematic, density functional theory (DFT). Yet, some molecular systems also exhibit large static correlation, and the use of the aforementioned methods can in such cases lead to qualitatively wrong results.^[5–7] Static correlation arises when more than one electronic configuration is of importance and a balanced description requires multireference methods. Typical multireference systems are chemical compounds with energetically close-lying states and/or near-degenerate orbitals, which are often found for chromophores of, for example, photosensitive proteins.^[8] An example is the channel-rhodopsin protein with the retinal chromophore (retinal is a carotenoid derivative, see the right-hand side of Fig. 1). Further examples are enzymes containing transition metals, here illustrated by [NiFe]-hydrogenase with the bimetallic reaction center (see Fig. 1, left-hand side). Quantum chemical investigations of such systems typically treat a specific region of interest (a

chromophore or a reaction center) and neglect the remaining environment. However, the environment can have a significant effect on the spectroscopic constants, but a quantitative, quantum mechanical description of this effect would often require unfeasible calculations with several thousand atoms. This problem has been addressed with multiscale modeling methods. The most renowned of these are probably the combined Quantum Mechanics/Molecular Mechanics (QM/MM) hybrid schemes, which use a quantum mechanical method for the region of interest and an MM description of the environment.^[9,10] Hitherto, the QM method in QM/MM studies has mostly been DFT and especially multiconfigurational treatments are scarce. Further, the interactions between the environment and the QM region are typically described by predefined atomic charges from MM force fields, which are often too inaccurate for calculations of spectroscopic constants. In particular, for electronic excitations this can be a problem, because the electron density of an electronic excited state can differ substantially from that of the ground state, thus inducing polarization effects in the environment that cannot be recovered by predefined charges. Accordingly, the errors for excitation energies can easily exceed 0.2–0.3 eV, which is often more than the inherent difference between DFT and more advanced methods.^[11]

Capitalizing on the ideas of QM/MM methods, the PE scheme^[11,12–14] belongs to a class of next-generation embedding methods which calculate the parameters for the classical region with a quantum-mechanical method, rather than using predefined MM parameters. These methods are more accurate

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Hans Jørgen Aagaard Jensen graduated from University of Aarhus in 1980. After a post doc position at Quantum Theory Project, University of Florida (1981-83) he spent the next 8 years at University of Aarhus until he in 1991 obtained a permanent position at University of Southern Denmark. His research has focused on the MCSCF model, relativistic effects, and range-separated hybrids. He has (co-)authored around 130 scientific papers and is one of the founding authors of both the Dalton program system (<http://daltonprogram.org>) and the Dirac program system (<http://diracprogram.org>) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Jacob Kongsted obtained his PhD from the University of Copenhagen in 2005 for a thesis on formulation of a hybrid Coupled Cluster / (polarizable) Molecular Mechanics approach for calculation of general response properties. After two post doc positions (University of Aarhus and Lunds University) he obtained in 2009 a permanent position at the University of Southern Denmark. Kongsted has (co-)authored around 140 scientific papers and received in 2012 a prestigious Sapere Aude award from the Danish Research Councils. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



and seek also to recover the mutual polarization between the environment and the quantum mechanical regions. In case of the PE method, the environment is described through distributed multipole moments and anisotropic polarizabilities derived from QM calculations.

In the following section ("MCSCF and PE") we sketch the main equations of the PE-MCSCF method and also discuss their physical contents. These equations have recently been derived in detail in Refs. [3,15]. Also a few target systems where one would expect that the PE-MCSCF method is to be

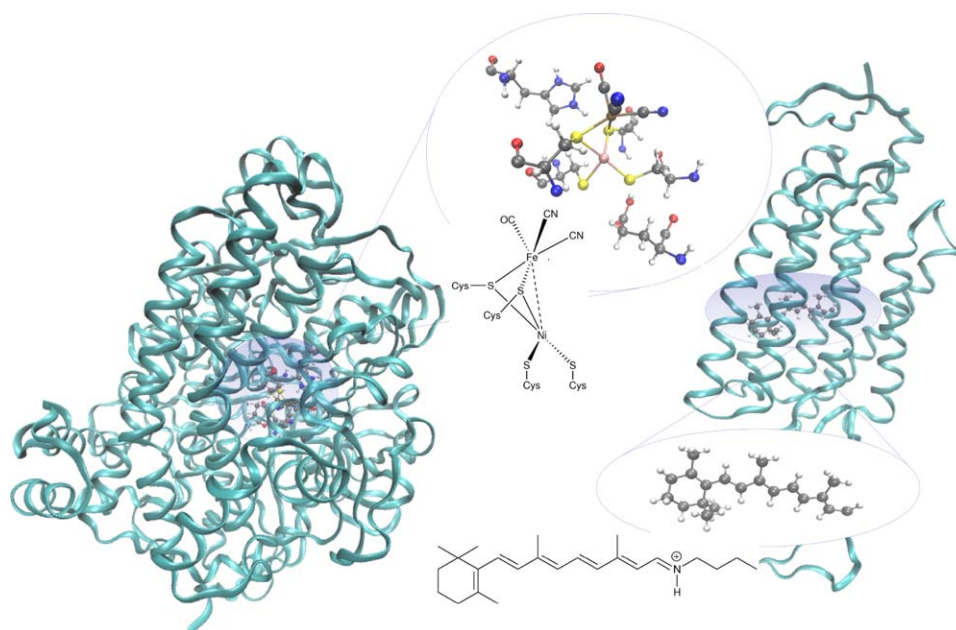


Figure 1. Right-hand side: The channel-rhodopsin protein. Left-hand side: A [NiFe]-hydrogenase enzyme. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

beneficial are discussed. The Section “Choosing an Active Space” discusses active space considerations for such target systems. A few sample calculations on the retinal chromophore will be given to illustrate the concepts. All these calculations include the environment through PE and have not been presented before, but the invoked system was used in recent articles from our group.^[16,17] On the road ahead, an important extension to the current PE-MCSCF scheme is the efficient treatment of dynamical correlation, and a few methods for this task are also discussed here (in Section “Addressing Dynamical Correlation”). Some of these methods are already being used for initial applications in our group, whereas others are still in a development or testing phase.

MCSCF and PE

An MCSCF wave function can be defined through orbital-rotation operators, $\hat{\kappa}$, and a configuration interaction (CI) expansion, $|\text{CI}\rangle$, as

$$|\bar{0}\rangle = \exp(\hat{\kappa})|\text{CI}\rangle \quad (1)$$

$$|\text{CI}\rangle = |0\rangle + \sum_i c_i |i\rangle. \quad (2)$$

The wave-function optimization algorithm implemented in DALTON converges the MCSCF state by a second-order method that requires both the electronic gradient, \mathbf{g} , and Hessian, \mathbf{H} (see further Ref. [18] and references therein). The electronic Hessian is calculated by a direct method, meaning that the Hessian is not constructed explicitly. Instead, the linearly transformed Hessian, $\boldsymbol{\sigma} = \mathbf{H}\mathbf{b}$, where \mathbf{b} is a trial vector, is calculated. In a polarizable environment, both \mathbf{g} and $\boldsymbol{\sigma}$ will have additional contributions compared to the vacuum case, and in this section these extensions are briefly sketched. The effect of a polarizable environment on the QM region can be described by introducing the effective one-electron interaction operator

$$\hat{F}^g = \hat{V}^{\text{es}} - \boldsymbol{\mu}^{\text{ind}} \hat{\mathbf{F}}^e, \quad (3)$$

into the Hamiltonian for the isolated (vacuum) system, and the total (effective) Hamiltonian thus becomes $\hat{H} = \hat{H}_{\text{vac}} + \hat{F}^g$. \hat{V}^{es} contains electrostatic interactions between the environment and the QM core. $\boldsymbol{\mu}^{\text{ind}}$ is a super vector that contains all the induced dipoles in the environment. In the PE method, the effects from the environment are modeled as fragments which have a set of associated; localized multipoles (to a given order) and local polarizabilities, all derived from first principle calculations. The term “localized” typically refer to atoms or bond mid-points. $\hat{\mathbf{F}}^e$ is the electronic field operator for the electrons in the QM region; the term $\boldsymbol{\mu}^{\text{ind}} \hat{\mathbf{F}}^e$ accordingly describes the mutual polarization interaction between the environment and the QM region. In the PE scheme, the electronic gradient becomes a sum of a vacuum term and a contribution from the polarizable environment

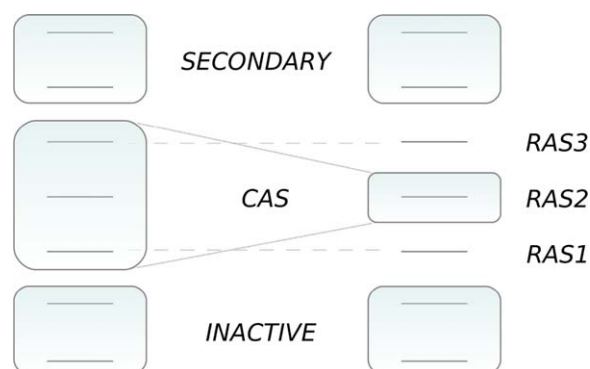


Figure 2. Schematic division of the orbital spaces on CAS and RAS types of wave functions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$$\mathbf{g} = \mathbf{g}_{\text{vac}} + \mathbf{g}_{\text{pe}}, \quad (4)$$

where \mathbf{g}_{pe} is described through the operator in Eq. (3). The linearly transformed Hessian vector is calculated as

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{\text{vac}} + \boldsymbol{\sigma}_{\text{pe}}. \quad (5)$$

The term $\boldsymbol{\sigma}_{\text{pe}}$ involves in addition to the operator in Eq. (3), two other effective operators given by

$$\begin{aligned} \hat{F}^{\text{xc}} &= -\boldsymbol{\mu}_{\text{CI}}^{\text{ind}} \hat{\mathbf{F}}^e \\ \hat{F}^{\text{xo}} &= -\boldsymbol{\mu}_{\text{orb}}^{\text{ind}} \hat{\mathbf{F}}^e, \end{aligned} \quad (6)$$

which describe the polarization interaction from the CI and orbital parts, respectively. The induced dipoles contained in the $\boldsymbol{\mu}^{\text{ind}}$ quantities in Eqs. (3) and (6) depend on the electron density, and are accordingly updated in each iteration.

The implementation described in Ref. [3] gives access to excited states through a state-specific complete active space SCF (CASSCF) or restricted active space SCF (RASSCF) method. As an alternative, excitation energies and oscillator strengths are available through the PE-MCSCF linear response method, which is also described in Ref. [3]. In this context, it should be noted that oscillator strengths are not straightforward to implement in a state-specific method, due to the nonorthogonality between the states. The PE-MCSCF response method has also the additional advantage that it easily can be extended to other spectroscopic constants, for example, nuclear magnetic resonance (NMR) shielding and coupling constants. It is formally built from the time-dependent Hamiltonian

$$\hat{H}(t) = \hat{H} + \hat{V}(t) = \hat{H}_{\text{vac}} + \hat{F}^g + \hat{V}(t), \quad (7)$$

where $\hat{V}(t)$ is a perturbing, time-dependent field. In a polarizable environment, the operator \hat{F}^g (see Eq. (3)) thus enters in the response equations where it describes the interaction between the environment and the reference state (either the ground state or an excited state). The perturbed state is also modified through its interaction with the environment, which is described using operators similar to the \hat{F}^{xc} and \hat{F}^{xo}

Table 1. NO occupation numbers for the retinal chromophore (see Fig. 1 in the introduction).

Method	NO (1)	NO (2)	NO (3)	NO (4)	NO (5)	NO (6)	NO (7)
MP2	1.949	1.948	1.944	1.939	1.930	1.920	1.906
CAS(6,6)	2	2	2	2	1.926	1.921	1.906
CAS(10,10)	2	2	1.943	1.935	1.919	1.890	1.835
	NO (8)	NO (9)	NO (10)	NO (11)	NO (12)	NO (13)	NO (14)
MP2	0.086	0.069	0.056	0.046	0.038	0.033	0.030
CAS(6,6)	0.098	0.080	0.069	0	0	0	0
CAS(10,10)	0.179	0.112	0.078	0.059	0.051	0	0
The basis set used was 6-31G*.							

operators^[3,15] in Eq. (6). These operators thus handle the dynamical polarization effect from the environment.

Initial applications of this code have focused on solutes in simple solvents.^[3] However, more challenging systems can be addressed: our ongoing studies are now focusing on photo-sensitive proteins such as the retinal chromophore (see next subsection), but also transition metals such as [NiFe]-hydrogenase is currently being investigated. The choice of active space for such systems will be discussed in the following section.

Choosing an Active Space

Practical calculations with the PE-MCSCF method have so far used a CASSCF type of wave function and accordingly they rely on a good choice of the active space. Recognizing that the number of configurations grows factorial with the size of active space, the limit in most CASSCF implementations is around a CAS(18,18) space. To avoid this limit, the more general RAS type of wave functions has been defined and the PE-MCSCF scheme has also been extended to RAS type of wave functions. A RAS wave function has a RAS2 space which is defined as in a regular CAS (see Fig. 2) while only certain configurations up to a given excitation order are considered in RAS1 and RAS3. The choice of active space has by many been considered the Achilles heel of CASSCF (and RASSCF). Importantly, the active space is molecule dependent and a poor choice will of course affect the final results. The challenge is to define a minimal active space without compromising accuracy. This section discusses a few rules of thumb, exemplified with compounds of our current interest, namely, d-block metal complexes and unsaturated organic chromophores. For the choice of active spaces, we will here advocate to use both

chemical indicators and physical indicators as described below, using the retinal chromophore as an example. For chemical indicators, comprehensive rules can in addition be found elsewhere.^[19,20]

Chemical indicators

For compounds with π bonds, usually the bonding and anti-bonding π orbitals are included in the active space. In case of conjugated systems, all π bonds within the conjugated system should be included, but for large systems, it can become necessary to use only the conjugated π orbitals of highest energy. For transition metal compounds, all valence d-orbitals will generally have to be included. An extra shell of d-orbitals is sometimes required for compounds containing metals between Chromium and Copper in the 3d row. Metals in high oxidation states typically require additional ligand orbitals due to the high covalency in the metal-ligand bonds for such compounds. This is a most peculiar problem and results in that a simple compound such as the permanganate ion (MnO_4^-) requires a CAS(24,17) space^[20] which is beyond reach for most MCSCF codes. In the particular case of MnO_4^- , using only the valence d-orbitals as active space leads to nonphysical solutions, which display symmetry breaking.^[21] Examples of a large conjugated system have already been given in the introduction, where the photo-sensitive channel-rhodopsin protein was shown in Figure 1. The active retinal chromophore contains 11 π -bonds, but as will be shown below, it is not necessary to include all π orbitals.

Physical indicators

As a complement to using chemical intuition, physical indicators also provide valuable information for choosing an appropriate active space. It has been customary to use orbital energies, but that can be a bad choice, in particular when the basis set used includes diffuse functions. We have instead used natural orbital (NO) occupation numbers, obtained from the MP2 method. The active space will then often be defined by groups of orbitals which have similar NOs. A conservative choice is to include all orbitals with NO occupation numbers within 0.02–1.98.^[20] Less strictly, one can also apply the range 0.05–1.95 or even 0.10–1.90. That multireference character is reflected in the NO occupation numbers was used already in the late 1970s MCSCF schemes for the dissociation of

Table 2. Excitation energies of the $\pi \rightarrow \pi^*$ excitation in the retinal chromophore.

Method	CAS(6,6)	CAS(10,10)	CAS(6,6)-srPBE	Exp. ^[17]
Excitation energy (eV)	4.08	4.70	3.15	≈ 2.70
The protein environment is treated through PE and the QM part is treated using the 6-31G* basis set. The potential in the CAS-srPBE calculations do not include polarizabilities.				

ethylene.^[22] Here, the σ and π bonds involved in the double bond all decrease from around 2.00 toward 1.00 as the $\text{H}_2\text{C}=\text{CH}_2$ is split to two methylenes. Similarly, the corresponding σ^* and π^* occupation numbers increase from around 0.01 to 1.00. Thus, occupation numbers between 1.90 and 0.10 are found for the stretched ethylene bond, and can be considered an indication of considerable multireference character.^[19] In Table 1, the MP2 occupation numbers of the frontier orbitals in the retinal chromophore are shown. Here, occupation numbers that deviate significantly from 2 to 0 are already apparent in the ground state structure. The smallest choice of a CAS space is a CAS(6,6) because the MP2 occupation numbers here are well separated. This space will unfortunately not contain all π orbitals. Enlarging to CAS(8,8) or CAS(10,10) would also be a possibility. As NO(1) and NO(2) have occupation numbers that are very close these should be grouped together, thus leading to an active space of CAS(14,14). This would still be within the limits (and contain all π -orbitals), but is rather large. Here, CAS(6,6) and CAS(10,10) are investigated: the obtained occupation numbers from calculations with these two active spaces are also shown in Table 1. Notably, the CAS(6,6) and MP2 occupation numbers are rather similar, while increasing the expansion to CAS(10,10) has a large effect on especially NOs (6)–(9) in Table 1. This suggests that important static correlation is left out in the CAS(6,6) calculation, and a good choice is thus a CAS(10,10) active space. However, even the CAS(10,10) will miss a major part of the dynamical correlation. Examples of the effect on the $\pi \rightarrow \pi^*$ transition from choosing different active spaces are shown in Table 2, and the lack of dynamical correlation is manifested in significantly overestimated excitation energies. Methods to recover this correlation are treated in the following section.

Addressing Dynamical Correlation

A well-known deficiency of an MCSCF method is that it neglects large parts of the local dynamical correlation, which has to be recovered in a subsequent step. This problem is obviously carried over to the PE-MCSCF method and is one of the main challenges to address in the future. Popular approaches to recover dynamical correlation have traditionally been based on multireference perturbation theory.^[23] More accurate methods are multireference CI (MRCI) or CC (MRCC) schemes, but these schemes also exhibit steep exponential scaling with respect to system size. DFT is, conversely, very efficient in obtaining the local dynamical correlation. An appealing alternative consists in coupling wave function theory with DFT.^[24,25]

Perturbation theory

Two popular approaches based on perturbation theory are second-order complete active space perturbation theory (CASPT2)^[23,26] and second-order N-electron valence state perturbation theory (NEVPT2).^[27] In the PE-MCSCF code, it is possible to use the NEVPT2 method and include the environment through CASSCF. It should be emphasized that in the current

implementation, the additional perturbative terms have not been corrected for the presence of the environment. It is expected that these terms will be of importance when charge-reorganization due to the presence of the environment is large for the low lying excited states of a given molecular system.^[28] To quantify this, future studies should be devoted to testing of how well the method of only including the effect of the environment through the CASSCF performs in practice. An alternative route to dynamical correlation is described below.

Range-separated MC-srDFT

The dynamical correlation method, we have mainly focused on so far, is the MC-srDFT approach.^[29] A recent preliminary test for excitation energies of (mainly) organic molecules showed promising results,^[16] especially for cases which are multiconfigurational or for excitations with a large degree of double excitation character. Notably, such excitations cannot be treated within regular DFT. These results prompted us to extend the method to include a polarizable environment and the resulting method is denoted PE-MC-srDFT. The extension uses the same routines as the PE-MCSCF^[3] and PE-DFT^[12] codes.

As initial applications of the PE-MCSCF and PE-MC-srDFT methods, a series of calculations on excitation energies for solvated systems has been conducted. Accurate solvent shifts compared to both experiment and other theoretical methods can in fact be obtained from both methods (as shown in Ref. [3] for PE-MCSCF), but only the MC-srDFT method also gives accurate absolute excitation energies, as the accurate solvent shift for PE-MCSCF relies on large error cancellations. We are currently investigating the solvent shift of the permanganate ion, which is a known problematic case. The MC-srDFT method seems suitable for such systems, as the simultaneous treatment of dynamical and static correlation typically leads to that much smaller active spaces can be used. Thus, symmetry breaking in MnO_4^- might be avoided with affordable active spaces. A first indication of this has already been shown for retinal (Fig. 1) in vacuum calculations, where a CAS(6,6) space was sufficient to give results comparable to CASPT2(12,12)^[16] for excitation energies. We are currently investigating the effect of a polarizable (protein) environment for the retinal chromophore using the PE-MC-srDFT method. A preliminary result (in Table 2) shows that inclusion of dynamical correlation remedies the overestimation from regular CAS to a large extent. Note that the CAS(6,6)-srPBE result in Table 2 includes static multipoles up to second-order (quadrupoles), but polarizabilities are not included in these preliminary results. Polarization effects are in the order of 0.2 eV^[17] and are expected to shift the result further toward the experiment.

Conclusions and Outlook

The first steps into the multireference regime for the PE method have been taken with the recent derivation and implementation of the working equations for the PE MCSCF (PE-MCSCF) scheme and its linear response equations. Current

studies are addressing photosensitive proteins and transition metal complexes. Inclusion of dynamical correlation through a new MC-srDFT (response) method has opened the possibility for large scale multiference calculations with efficient inclusion of both dynamical correlation and the surrounding environment. In terms of including dynamical correlation, the developed code offers several alternative possibilities to the MC-srDFT model, which has not yet been explored in detail. For instance, moving to larger active spaces using a RAS formulation or perturbative approaches are obvious to investigate. As a final note, a very interesting alternative to CASSCF is the density matrix renormalization group^[30] method which could also be combined with PE. Thereby much larger active spaces could be accessed, but these developments are still somewhat into the future.

A next important code-development is to include also quadratic response functions as well as triplet perturbations which give access to better description of effects from an environment for NMR J-couplings and phosphorescence, both important for spectroscopy in molecular life sciences.

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Keywords: polarizable embedding • multiconfiguration self-consistent field • MC-srDFT • retinal • [NiFe]-hydrogenase

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