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The QM/MM Method. An Overview

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The QM/MM Method. An Overview[#]

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Abstract

The paper presents an overview of the development of the QM/MM method and its application to the study of enzyme reactivity. Different approaches for the treatment of QM/MM boundary (link–atom, LSCF, pseudoatoms) are review and their strengths and weaknesses are discussed. The QM/MM Hamiltonian is briefly presented, its terms are defined and discussed, and the latest developments of the QM/MM method are presented. Finally, many of the applications of the QM/MM method over the last decade are briefly reviewed and few of the most recent results are discussed (*e.g.* opsin shift in bacteriorhodopsin, tunneling dynamics in liver alcohol dehydrogenase). The QM/MM method proved to be one of the most successful theoretical approach for studying biomolecular systems, and its future development will make it the most sophisticated computational tool for the investigation of enzyme reactivity. In addition, the newly developed linear scaling QM algorithms and the composite Hamiltonian approach are among the latest developments that promise to make the QM/MM method a very efficient and versatile computational tool for biochemistry.

Keywords. QM/MM method; composite Hamiltonian; QM/MM boundary; enzyme reactivitiy.

Abbreviations and notations

QM, quantum mechanical/mechanics	MPn, Möller–Plesset perturbation theory of order n
MM, molecular mechanical/mechanics	CC, coupled–cluster method
QM/MM, quantum mechanical molecular mechanical	MCSCF, multi–configuration self–consistent field
MD, molecular dynamics	DFT, density functional theory
HF, Hartree–Fock theory	LSCF, local self–consistent field
MO, molecular orbital	SLBO, strictly localized bond orbital
SCF, self–consistent field	GHO, generalized hybrid orbital
PES, potential energy surface	QD, quantum dynamics
CI, configuration interaction	$O(N)$, linear scaling method

1 INTRODUCTION

It is well accepted nowadays that the QM method is the ultimate computational tool that can be employed successfully in studying the structural aspects of matter and a variety of its physical and chemical properties [1]. QM calculations are still very demanding in computational resources, but the advent of more powerful computers and the development of efficient algorithms for various QM methodologies (*e.g.* semiempirical, HF, MPn, CC, DFT) over the last two decades led to state of the

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[#] Dedicated on the occasion of the 70th birthday to Professor Alexandru T. Balaban.

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art quantum chemistry software (*e.g*. Gaussian [2], Schrödinger [3], Gamess [4]), which made calculations on small to medium size molecules a routine task [5]. In addition, recently developed algorithms that allow QM methods to scale linearly, *O(N)*, with the system size [6] hint to the fact that many molecular systems of interest in biology or material sciences can be investigated by QM methods in foreseeable future [7].

Presently, the most promising theoretical/computational approach for studying large molecular systems (nano–scale systems, biological systems, supramolecular assembles) is the combined QM/MM approach [8]. The hybrid QM/MM method is becoming increasingly popular for investigating the structure and properties of large systems [9], specially the biological systems [10,11] and the QM/MM Hamiltonian is used in conjunction with MD for studying the dynamical behavior of matter (formation/breaking of chemical bond into a complex intermolecular environment [12]).

This paper presents an overview of the QM/MM approach with emphasis on the application of the QM/MM method to the investigation of enzyme reactivity [10].

2 OVERVIEW OF METHOD DEVELOPMENT

The hybrid QM/MM potential was proposed in 1976 by Warshel and Levitt [13] for the study of the catalytic mechanism of lysozyme. Many of the pertinent ideas were introduced in this seminal paper: *e.g*. the partitioning of the enzyme into QM and MM regions, the construction of the hybrid QM/MM Hamiltonian, the evaluation of the total energy for the mixed system, and the treatment of QM/MM boundary. More than a decade later, Field, Bash and Karplus compared the performance of the QM/MM approach with the full QM and introduced the concept of link atoms for treating the QM/MM boundary [14]. The QM/MM methodology was extensively developed in the last decade [8] and applied to a variety of bio–molecular systems [15].

In the QM/MM approach the system is divided into two regions: a small QM region and a significantly larger MM region. The QM part can be described by any level of *ab initio* QM (semiempirical, HF, MPn, CI, CC, MCSCF) or DFT, but a QM/MM potential that uses DFT is the preferred choice because the DFT Hamiltonian can be more efficiently evaluated than any other post Hartree–Fock methods [16,17].

Other developments in the QM/MM method include: *a*) the development of the effective fragment potential method [18]; *b*) the calculation of analytical second derivatives of the total energy [19]; *c*) the calculation of chemical shifts in large systems [20]; *d*) the new QM/QM/MM approach, which employs a composite QM Hamiltonian constructed by mixing together different levels of QM. For example, Morokuma and coworkers developed the IMOMO/ONIOM method [21,22], Gogonea and Merz [23] proposed recently a composite QM Hamiltonian that mixes DFT with the semiempirical QM, and Warshel and coworkers [24] proposed a DFT method in which the electronic density of the environment is either frozen or constrained. The QM/QM/MM approach, together with the newly developed linear scaling algorithms for QM [6], promise to bring increased performance and higher accuracy to the traditional QM/MM approach.

2.1 The QM/MM Boundary

The boundary between the QM and MM regions is of utmost importance and its treatment distinguishes between different QM/MM methodologies. Regardless of the method used to describe the QM/MM boundary, the boundary itself must be chosen far enough from the reaction center such that its influence on the reaction is minimal. This requirement creates a serious challenge for the QM/MM approach in situations where the QM region must spread substantially in order to avoid the computational artifacts introduced by the QM/MM boundary. While there is no general way of deciding on the position of the QM/MM boundary, chemical intuition and careful analysis of the results seem to be the best strategy employed so far. It is not always possible to position the QM/MM boundary between atoms belonging to different molecules and frequently is necessary to 'cut' chemical bonds. The treatment of the bonds that connect atoms positioned on different sides of the QM/MM boundary (*i.e.* in QM and MM regions, respectively) is the most difficult aspect of the QM/MM method. Among different methodologies developed for treating the QM/MM boundary the following can be distinguished: *a*) the link–atom approach [14,15]; *b*) the local self–consistent field approach [26,27]; *c*) the connection atom approach [28]; *d*) the pseudobond approach [29]. These methods will be further reviewed in some detail.

2.1.1 The link–atom approach

Singh and Kollman were the first to suggest the use of hydrogen atoms to 'cap' the dangling bonds resulted from cutting the bonds across the QM/MM boundary [30]. The term *link–atom* was coined by Karplus and coworkers [14]. Link–atoms do not interact with the MM region, but the necessity to take into account this interaction is still debated [31,32]. This method for treating bonds crossing the QM/MM boundary is not theoretically appealing because of the extra hydrogen atoms introduced, but is easy to implement and its results are acceptable if the QM/MM boundary is sufficiently far away from the reaction center. The link–atom approach was used for many applications [33–41].

2.1.2 The local self–consistent field approach

Warshel and Levitt [13] proposed the use of hybrid orbitals to describe the bonds across the QM/MM boundary. Starting from this idea, Rivail and co–workers developed the LSCF method [26,42,43]. In the LSCF approach a frontier bond (*i.e.* one that is crossing the QM/MM boundary) is described by a SLBO. The SLBO's are obtained from model compounds and are assumed to be transferable as long as the QM/MM boundary is far enough from the reaction site. The rest of the MO's, which are orthogonal to the SLBO are obtained by a local self–consistent calculation [42]. LSCF methods based on either *ab initio* or semiempirical Hamiltonians were developed and applied to various organic or biochemical systems [44–47]. Friesner and co–workers [48–50] and Kairys and Jensen [51] developed further the LSCF method.

A method similar with LSCF called GHO was proposed by Gao and coworkers [27,52]. In this approach the frontier orbitals are divided into auxiliary (frozen) and active orbitals. The auxiliary orbitals are used to construct an effective core potential for the QM/MM boundary atoms, while the active orbitals are included in the SCF calculation for determining the MO's. When a semiempirical Hamiltonian is used, the GHO procedure requires new parameters for the boundary atoms.

2.1.3 The connection–atom approach

In this method developed by Antes and Thiel [28], the MM atoms that bind to QM atoms are assigned an sp^3 orbital which hosts one electron. This procedure introduces a consistent definition for the total energy of the QM/MM system. The connection atoms are parameterized in accordance with the Hamiltonian used (semiempirical, *ab initio* or DFT).

2.1.4 The pseudobond approach

The pseudobond method builds up on the connection–atom idea of Antes and Thiel [28]. Thus, MM atoms connected to QM atoms are replaced with pseudoatoms that have effective core potentials and one free valence electron [29]. The construction of the effective core potential is independent of the MM region and the same potential can be used in both *ab inito* and DFT Hamiltonians. Zhang and Yang used the method to study the catalytic activity of enolase [53].

2.2 The QM/MM Hamiltonian

In the mixed QM/MM system the (normalized) QM wavefunction, Ψ_{QM}, spreads over the QM subsystem (including the link–atoms or localized orbitals/pseudobonds, which are positioned at the QM/MM boundary). The total energy, E, of the mixed QM/MM system is obtained as the expectation value of the QM/MM effective Hamiltonian, $\hat{H}_{QM-MM}$:

$$E = \left\langle \Psi_{QM} \left| \hat{H}_{QM-MM} \right| \Psi_{QM} \right\rangle \tag{1}$$

where the QM/MM effective Hamiltonian is the sum of the QM Hamiltonian, $\hat{H}_{QM}$, the QM/MM interaction potential, $\hat{V}_{QM-MM}$ and the MM energy, E_{MM}:

$$\hat{H}_{QM-MM} = \hat{H}_{QM} + \hat{V}_{QM-MM} + E_{MM} \tag{2}$$

The interaction energy, $E_{QM\text{–}MM}$, is the expectation value of the $\hat{V}_{QM-MM}$ operator, which has the following form:

$$\hat{V}_{QM-MM} = \sum_{i}^{MM}\sum_{\alpha}^{QM}\left(\frac{q_i Z_\alpha}{r_{i\alpha}}\right) - \sum_{i}^{MM}\frac{q_i}{r_i} + \sum_{i}^{MM}\sum_{\alpha}^{QM}\left(\frac{A_{i\alpha}}{r_{i\alpha}^{12}} - \frac{B_{i\alpha}}{r_{i\alpha}^{6}}\right) \tag{3}$$

where the first two terms in equation 3 are operators for the interaction of MM point charges, q_i, with the nuclei, Z_α, and electrons of the QM region, respectively. The third term is the van der Waals interaction between the QM and MM regions The electron–point charge interaction operator leads only to one–electron integrals making the implementation of the QM/MM scheme a relatively straightforward task.

The QM Hamiltonian used in the QM/MM scheme is critical for the quality of the final results. While a high level QM Hamiltonian is desirable, practical considerations limit the sophistication of the QM Hamiltonian used. Semiempirical QM Hamiltonians (AM1, PM3 [54]) are the most efficiently evaluated, but they have deficiencies that are difficult to overcome. For example the AM1 Hamiltonian is deficient in the treatment of H–bond [55,56], while both AM1 and PM3 grossly underestimates the dispersion interaction [57]. In many situations (*e.g.* when transition metals are present in the QM region), an *ab initio* (HF, MPn, MCSCF) or a DFT Hamiltonian is the method of choice [58,59].

3 APPLICATIONS OF THE QM/MM METHOD

The main driving force in the development of the QM/MM method is the need to investigate the reactivity of enzymes. The benefits for understanding the fine details of the mechanism of enzyme reactions fully justifies the considerable amount of work already invested in the development and refinement of the QM/MM method. The large number of papers published in the last decade shows that the QM/MM approach is by now largely accepted as a valuable research tool and the only computational approach, devised so far, which is well suited for studying bio–molecular and nano–scale systems. This fact is emphasized in Field's recent review on the challenges and perspectives of the simulation of enzyme reactions [15].

Among the many applications of the QM/MM method are studies on the reactions catalyzed by acetyl cholinesterase [60], thermolysin [47], aldose reductase [61], carbonic anhydrase [62–64], catechole *O*–methyltransferase [65–67], chorismate mutase [68,69], citrate synthase [70–72], dihydroxyfolate reductase [73–75], enolase [76], formate dehydrogenase [77], glycoxalase I [78,79], haloalkane dehydrogenase [80], HhaI methyltransferase [81], orotidine 5'–monophosphate decarboxylase [82,83], phenol hydroxylase [84], protein tyrosine phosphatase [85,86], the GTPase reaction of p21 RAS [87], ribonuclease A [88], and trypsin [41,89].

Many of the enzymes are metalloproteins. If the involvement of the metal ion in the reaction is only by its electrostatic field, then its effect can be modeled using the MM force field or the semiempirical QM potential. This approach was employed in the study of acetohydroxy–

isomeroreductase [90], D–xylose isomerase [91], carbonic anhydrase [63] and metallothionein [92]. When the metal ion assists in bond formation/breaking, then DFT or an *ab inito* method is necessary for a satisfactory treatment of the electronic structure of the atom groups directly involved in the reaction. The DFT method is most often employed for the QM part. DFT studies that neglect the protein environment include the investigation of soluble methane monooxygenase [93], cytochrome *c* oxidase and the water–oxidizing complex in photosystem II [58,59]. Using a DFT or *ab initio* Hamiltonian to describe the QM region is still expensive in terms of computational resources, thus up to date there are only a few DFT/MM studies of metalloenzymes. Among these are the investigations of nickel–iron hydrogenase [94], galactose oxidase [95], copper proteins [96], and bacteriorhodopsin [97,98].

Many of the references to work published before 1999 can be found in the review of Amara and Field [10]. Some of the most recently published work will be overviewed in the last part of this section.

Influence of the heme pocket conformation on the structure and vibrations of the Fe–CO bond in myoglobin. Rovira *et al*. [99] used QM/MM (DFT) calculations to study the influence of the conformation of the distal pocket of myoglobin (MbCO) on the vibrations of the heme–CO bond. They showed that the heme–CO structure (described by QM) is quite rigid and is not influenced by the conformation of distal pocket (described by MM). They concluded that a relation between Fe–CO distortions and the different CO infrared absorptions is less likely to exist. On the other hand, the CO stretch frequency and the strength of the CO...His64 interaction depends strongly on the orientation and tautomerization state of His64.

Substrate autocatalysis in uracil–DNA glycosylase (UDG). Karplus and co–workers [100] used a hybrid QM/MM to determine the mechanism of catalysis by UDG and showed that the reaction proceeds in a stepwise dissociative manner contrary to earlier suggestions (concerted mechanism). In their reaction mechanism, the glycosylic bond cleavage yields an intermediate (comprising an oxocarbenium cation and an uracilate anion), which reacts with a water molecule and the products are obtained following the transfer of a proton to D145. The authors also found that a substantial contribution to lowering the activation energy is due to the substrate, rather than due to enzyme. They concluded that the observed autocatalysis is due to the burial and positioning of four phosphate groups that stabilize the rate–determining transition state, and that the residual activity observed for mutants that lack key residues confirms the important role of the phosphates.

Surface crossing process in bacteriorhodopsin. Warshel and Chu [97] have investigated the QD of the photoisomerization process in bacteriorhodopsin (bR). They evaluated the surface crossing probability using a hybrid QM/MM Hamiltonian of the chromophore–protein–solvent system. The QM/MM Hamiltonian was adjusted to reproduce relevant *ab initio* results for the chromophore. The authors found that the change in the absorption spectrum of the chromophore is due to the effect of protein permanent dipoles, ionized residues, water molecules (in and around the protein), and the induced dipoles of the protein plus water system. They also demonstrated that the motion along the excited state surface begins with bond vibrations and continues with torsional motion, some trajectories passing through strict conical intersections whereas others cross through regions with nonzero energy gap and a large nonadiabatic coupling, a feature that ensures the stability of the photo–biological process with respect to mutations. The average surface crossing probability provides an approximation for the calculated quantum yield, which the authors found to be in good agreement with the experimental value.

Tunneling dynamics in liver alcohol dehydrogenase. Alhambra *et al.* [101] proposed a theoretical formalism which combines variational optimization with QM tunneling dynamics, for the calculation of rate constants for enzyme reactions. The dynamics is calculated by canonical variational theory with optimized multidimensional tunneling contributions, allowing for Boltzmann averaging over an ensemble of reactant and activated complex conformations. The authors applied the method to the calculation of the reaction rate constant for oxidation of benzyl alcoholate to benzaldehyde by horse liver alcohol dehydrogenase and the PES for this reaction was determined by using a QM/MM (GHO) semiempirical valence bond method. The authors found that the variation of the protein mean field as a function of reaction coordinate is significant and affects qualitatively the reaction.

Studies of the active site of the blue copper proteins amicyanin and rusticyanin. Comba *et al.* [96] studied the structures of the oxidized form of the two blue copper proteins amicyanin and rusticyanin. The QM region was described with a DFT Hamiltonian, and it was found that the optimized structures are similar to the X–ray crystal structures.

The opsin shift in bacteriorhodopsin. Rajamani and Gao [98] performed molecular dynamics simulations of bacteriorhodopsin (bR) in membrane matrix. They found that polar solvents (methanol, acetonitrile, water) and protein interaction significantly shift the absorption maximum of the retinal protonated Schiff base. In bR, retinal changes conformation from 6–s–*cis* (solution) to 6–s–*trans* (in bR). The extension of the π–conjugated system and the change in dispersion interactions further increase the red–shift. The QM/MM calculations gave a theoretical opsin shift of 5200 cm^{-1} in bR, in good agreement with the experimental value of 5100 cm^{-1}.

4 CONCLUSIONS

The increasing number of publications that present the application of the QM/MM method to a variety of biochemical reactions is clear evidence of the importance of the QM/MM approach as a theoretical tool for our understanding of the fine details of the structure and function of enzymes. There is no question that at present the QM/MM method together with the computer simulation methods are the most sophisticated theoretical tools that can be used for determining the reaction mechanism of enzyme catalysis, or in calculating other quantities like *e.g.* binding constants, and pK_a values. The QM/MM model for describing biomolecules, while successful, still requires further development, which will lead to a better integration of the QM and MM formalisms by solving the problem of the QM/MM boundary in a general way. In this sense, the latest developments based on the LSCF methods seem to be a step in the right direction. Another aspect of the QM/MM approach is the quality of the QM Hamiltonian used. Because many of the enzymatic reactions involve transition metals, the QM Hamiltonian must include the electron correlation. The post HF methods are computationally still very expensive, hence the implementation of linear scaling QM methods will have a great impact on the efficiency of the QM/MM method. They will further extend the use of the QM/MM method to even larger enzymes and will extend the use of the QM/MM method for enzymatic reactions where excited states are involved (photo–chemical processes). The treatment of electronic excited states are even more challenging due to the complexity of the electronic structure, which usually requires a high level *ab inito* Hamiltonians (CI, CCSDT, MCSCF). Finally, the development of composite Hamiltonians, which will mix consistently different levels of QM, will greatly assist in obtaining the best ratio of computational resources to the accuracy of calculation. This composite QM/QM/MM description of a biomolecule, which combines different levels of QM with MM will probably be one of the most efficient computational tool for investigating the electronic structure and the properties deriving from it for biomolecules. Thus, it is expected that both the development and the application of QM/MM method will continue to expand strongly in the current decade and that the information obtained from QM/MM calculations will be essential for a deep understanding of biochemical processes.

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