

Modeling environment effects on spectroscopies through QM/classical models

Cite this: *Phys. Chem. Chem. Phys.*, 2013, **15**, 6583

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In this perspective, an overview of the recent progress in the combination of quantum mechanical (QM) simulations of spectroscopies with classical models to include environment effects is presented. Both atomistic and continuum formulations of the classical models are reviewed together with a critical analysis of their respective pros and cons. In particular, the different strategies developed within the two families of methods to include mutual polarization effects between the QM and the classical part or to properly treat the statistical sampling are presented and discussed. Examples of applications to different types of environment are also presented to show how these hybrid approaches can be used to obtain an accurate description of electronic, vibrational and magnetic spectroscopies even when nonequilibrium, heterogeneities, and/or specific and bulk effects are in play.

Received 8th December 2012,
Accepted 8th January 2013

DOI: 10.1039/c3cp44417a

www.rsc.org/pccp

1. Introduction

Historically, spectroscopies have represented one of the most important tools to identify chemical compounds and to study their electronic, vibrational, magnetic or chiral properties. In the last few decades, however, their applications have enormously extended beyond this “analytical” field towards completely new areas. All these new applications of spectroscopic approaches have been made possible by the astonishing improvements achieved in terms of length and time scales. It is now possible to study molecular systems with an atomistic definition as well as to follow time-dependent molecular processes with a femtosecond resolution. However, this new richness of information that we can obtain with spectroscopic measurements has been accompanied by an increased complexity in the interpretation of the data. Now the spectroscopic experiment has become so sensitive and precise not only to detect the response of the molecular system to the applied perturbation but also to “see” how this response is tuned by subtle changes in the “surroundings” even when they happen at a molecular scale and with an ultrafast dynamic. It is therefore extremely useful, if not compulsory, to accompany spectroscopic measurements with theoretical and computational analyses. The latter however will need to accurately account for as many details as possible of the short- and long-range interactions of the molecular probe with its “environment”. Obviously, the two requirements, accuracy and completeness,

cannot be obtained using a homogeneous approach but instead a *multiscale* strategy has to be introduced. In the last few years the multiscale approach, which has shown to possess the most suited characteristics in the fields where a molecular level description is required, is that combining a quantum-mechanical (QM) description of the molecular probe and a classical description of the rest. For such a strategy the term *hybrid QM/classical approach* has been coined even if, under this name, many different formulations exist and many different implementations are available in the most common softwares for molecular modeling.

As a matter of fact the idea of combining a QM description with a classical one is not new but it was proposed many years ago.^{1–9} However, only later the accuracy and the extendibility of these methods have increased so much to make them a real useful computational tool to be applied to spectroscopies.^{10–29} The evolution of QM/classical methods from the realm of very “*ad hoc*” models for specific studies to that of a very general and powerful approach to describe systems of increasing dimension and complexity has been made possible by the efforts of many research groups in the world which have, sometimes independently and other times in collaboration, developed and implemented different versions of the same basic idea (see the review articles^{30–40} for an exhaustive overview). This, in turn, has generated methods that can be applied not only to a solute dissolved in a given solvent but to many kinds of *embedded* systems where the environment can be either a protein matrix, a solid, a liquid–liquid or a liquid–solid interface, a membrane, a composite system containing solid particles of nanoscopic dimensions in solution, and many others.

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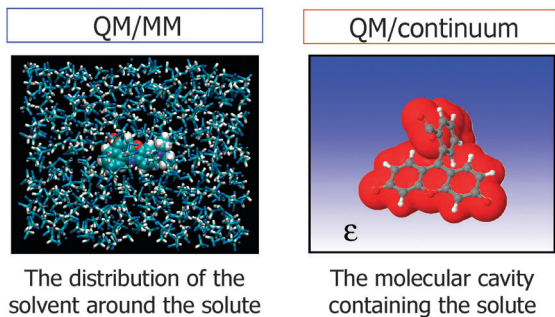


Fig. 1 A graphical comparison between atomistic and continuum formulations of QM/classical approaches.

Due to this large spectrum of formulations and applications, which cannot be properly reviewed in the present perspective, here the attention will be focused only on those versions of QM/classical approaches, which have been proposed to simulate properties and processes connected to spectroscopic analyses. These formulations of QM/classical approaches assume that the QM part can be modified in its electronic and nuclear characteristics by the presence of the classical part: only if this coupling is present, in fact, the simulated spectroscopic property can be tuned by the effects of the environment. Even if limited to these coupled approaches, however, very different formulations can still be found: it is therefore very useful to collect them in two main families, namely those using an atomistic description of the classical part of the system, and those using instead a continuum-like description (see Fig. 1). The methods belonging to the first family are generally indicated as QM/MM methods as they make use of a molecular mechanics (MM) formulation for the classical part, while the members of the other family generally adopt an “apparent surface charge” (ASC) formulation for the response of the environment even if this is not the only possible approach within a continuum description. Examples of non-ASC formulations are well-known within the QM/continuum field, suffice here to cite the Onsager model, and its multipolar extension independently developed by Rivail and collaborators⁴¹ and by Mikkelsen and collaborators,⁴² or the SMx approaches developed by Cramer and Truhlar.⁴³

More in detail, the perspective will be organized into two main parts: a brief presentation of the main theoretical and numerical aspects will be given for each of the selected QM/classical approaches and some exemplificative applications will be reported and discussed.

2. Hybrid QM/classical approaches

The QM/classical strategy collects methods in which a target subsystem, from now on defined as the “solute”, is described at the QM level and a secondary subsystem (“the solvent”) is, in contrast, modeled at a classical level using either an MM force field or a continuum medium with suitable macroscopic properties. In both versions of the same strategy, an important common aspect is present; the QM part can be modified in its

electronic and nuclear characteristics by the presence of the classical part. In a QM language this coupling between the two parts is made possible by replacing the Hamiltonian operator representing the solute alone with a new or *effective* one including an additional solute–solvent interacting term, namely:

$$H_{\text{eff}}|\Psi\rangle = (H_0 + H_{\text{env}})|\Psi\rangle = E|\Psi\rangle \quad (1)$$

where H_0 is the Hamiltonian of the isolated solute and H_{env} is the solvent-induced term.

As for isolated molecules, also the effective Schrödinger equation (1) cannot be treated without further approximations. What is important to stress, however, is that the addition of the new operator H_{env} does not change the formal and the numerical strategy to be used. As a result, the most commonly used approximations for isolated systems, are still valid for the “solvated” systems. However, the form of H_{env} , which depends on the specific version of the QM/classical formulation used, introduces some important specificities. Here below the main ones are briefly summarized for each of the two selected families of methods.

2.1. QM/MM

The QM/MM formalism can accommodate almost any combination of QM and MM methods. Traditionally semi-empirical QM methods have been most popular and they are still largely used even if many current QM/MM applications use density-functional theory (DFT) as the QM method owing to its favourable computational-effort/accuracy ratio. In the last few years, however, various highly correlated methods have been coupled with an MM description of the environment.^{44–52}

As far as the choice of the MM method is concerned, all the many force fields available in the literature can, in principle, be coupled with a QM description. Therefore, the effects that the classical part of the system exerts on the QM part are, in general, of electrostatic (Coulomb) and non-bonded van der Waals nature. Here we do not explicitly take into account cases in which the QM part is covalently bound to the classical part: the interested reader can find an exhaustive overview of the methods developed so far to treat the QM/MM boundary in ref. 36 and 37.

The nonelectrostatic terms are of short-range character and in most combined QM/MM methods are described by empirical potentials independent of the QM electronic degrees of freedom, thus not affecting the solute wavefunction. In contrast, the electrostatic contribution will explicitly affect (or polarize) the solute wavefunction. Its effects are introduced into H_{env} in terms of a one-electron operator, which represents the electrostatic energy between a set of point charges generally placed on the atoms of the solvent molecules and a solute charge distribution generating an electrostatic potential at the same points. This formulation of the QM/MM approach is generally indicated as “electrostatic embedding”. Different formulations of partial atomic charges can be used but commonly they are computed by constraining the charges to reproduce calculated physical observables, such as electrostatic potentials.

Conventional electrostatic-potential-fitted charges do not include charge penetration effects while the various procedures which have been proposed to include this effect have shown that the description of the electrostatics for points within or close to the van der Waals surface can greatly improve.^{53,54}

A further improvement can be obtained introducing a mutual polarization contribution. Commonly, this is obtained by including induced dipoles in addition to point charges:^{21,23,29,55,56} each solvent atom (or group of atoms) is described in terms of an atomic charge and an atomic polarizability. As a result, not only the solute will be polarized by the solvent but also the solvent will respond to the solute so as to achieve a mutually polarized system. Within this polarizable QM/MM formulation we get:

$$\hat{H}_{\text{env}} = \hat{H}_{\text{QM/MM}} + \hat{H}_{\text{MM/MM}} \quad (2)$$

$$\hat{H}_{\text{env}} = \hat{H}_{\text{QM/MM}} + \hat{H}_{\text{MM}}$$

$$\begin{aligned} \hat{H}_{\text{QM/MM}} &= \hat{H}_{\text{QM/MM}}^{\text{el}} + \hat{H}_{\text{QM/MM}}^{\text{pol}} \\ &= \sum_m q_m \hat{V}(\mathbf{r}_m) - \frac{1}{2} \sum_a \mu_a^{\text{ind}} \cdot \hat{\mathbf{E}}_a^{\text{solute}}(\mathbf{r}_a) \end{aligned}$$

$$\hat{H}_{\text{MM}} = \hat{H}_{\text{MM}}^{\text{el}} + \hat{H}_{\text{MM}}^{\text{pol}} = \sum_m \sum_{n>m} \frac{q_m q_n}{r_{mn}} - \frac{1}{2} \sum_a \mu_a^{\text{ind}} \cdot \sum_m \frac{q_m (\mathbf{r}_a - \mathbf{r}_m)}{|\mathbf{r}_a - \mathbf{r}_m|^3} \quad (3)$$

where $V(\mathbf{r}_m)$ and $\hat{\mathbf{E}}_a^{\text{solute}}$ represent the electrostatic potential and the electric field operators due to the solute electrons and nuclei calculated at the MM sites. On the other hand, in eqn (3) $\hat{H}_{\text{MM}}^{\text{el}}$ describes the electrostatic self-energy of the MM charges, while $\hat{H}_{\text{MM}}^{\text{pol}}$ represents the polarization interaction between such charges and the induced dipoles. We recall that the former term enters in the effective Hamiltonian only as a constant energetic quantity, while the latter depends on the QM wavefunction through the induced dipoles.

The dipoles induced on each MM polarizable site can be obtained assuming a linear approximation, neglecting any contribution of magnetic character, and using an isotropic polarizability for each selected point in the MM part of the system. The electric field that determines such dipoles contains a sum of contributions from the solute, from the solvent point charges and from the induced dipole moments themselves. This mutual polarization between the dipoles can be solved through a matrix inversion approach, by introducing a matrix equation

$$\mathbf{K}\boldsymbol{\mu}^{\text{ind}} = \mathbf{E} \quad (4)$$

where the matrix \mathbf{K} is of dimension $3N \times 3N$, N being the number of polarizable sites, and the vector \mathbf{E} collects the electric field from the solute and the solvent permanent charge distribution. The form of matrix \mathbf{K} will be determined uniquely by the position of the polarizable sites and the polarizability values.

This formulation is an example of the so-called "polarized embedding" QM/MM approaches but it is not the

only possible choice. There are in fact various alternatives to induced dipoles to simulate the polarizability of MM atoms, such as the fluctuating charges^{57,58} or the classical Drude oscillators.⁵⁹

QM/continuum. The analysis of QM/classical methods is less straightforward if we adopt a continuum description. The basic formulation of continuum models requires in fact the solution for a classical electrostatic problem (the Poisson problem)

$$-\nabla \cdot [\varepsilon(\mathbf{r}) \nabla V(\mathbf{r})] = 4\pi \rho_M(\mathbf{r}) \quad (5)$$

where ρ_M is the solute charge distribution and ε is the general (position-dependent) permittivity. If we assume that ρ_M is contained in a molecular cavity C of proper shape and dimension built within a homogeneous and isotropic solvent, the permittivity is equal to one inside the cavity and equal to the bulk dielectric constant (ε) of the solvent outside.

Within this framework, by introducing the appropriate boundary conditions, the electrostatic problem (5) can be solved in terms of an electrostatic potential V which is the sum of the solute potential plus the contribution due to the reaction of the solvent (e.g. the polarization of the dielectric), namely

$$V(\mathbf{r}) = V_M(\mathbf{r}) + V_\sigma(\mathbf{r}) \quad (6)$$

Under the assumption that the charge distribution is entirely supported inside the cavity C , an integral representation of the reaction potential can be derived which introduces a fictitious (or *apparent*) charge distribution σ on the boundary between the solute and the solvent, i.e. the surface Γ of the cavity C , namely:

$$V_\sigma(\mathbf{r}) = \int_\Gamma \frac{\sigma(\mathbf{s})}{|\mathbf{r} - \mathbf{s}|} d\mathbf{s} \quad (7)$$

The surface charge σ is solution for an integral equation on Γ that is of an equation of the form:

$$(A\sigma)(\mathbf{s}) = \int_\Gamma k_A(\mathbf{s}, \mathbf{s}') \sigma(\mathbf{s}') d\mathbf{s}' = b_{\rho_M}(\mathbf{s}) \quad \forall \mathbf{s} \in \Gamma \quad (8)$$

where k_A is the Green kernel of some integral operator A and b_ρ depends linearly on the charge distribution ρ_M . This formulation has been adopted in different continuum solvation models, the most famous ones being the Polarizable Continuum Model (PCM) (in its different DPCM,⁴ IEFPCM,⁶⁰ CPCM⁶¹ versions), the surface and simulation of volume polarization for electrostatics (SS(V)PE)⁶² and the Conductor-like Screening Model (COSMO).⁶³ Each different version corresponds to different choices for A and b_ρ but in all cases, a specific combination of the following kernels is used for A :

$$k_A(\mathbf{s}, \mathbf{s}') = \begin{cases} \frac{1}{|\mathbf{s} - \mathbf{s}'|} \\ \frac{\partial}{\partial n_s} \frac{1}{|\mathbf{s} - \mathbf{s}'|} \\ \frac{\partial}{\partial n_{s'}} \frac{1}{|\mathbf{s} - \mathbf{s}'|} \end{cases} \quad (9)$$

where \hat{n}_s represents the unit vector normal to the surface at s and pointing toward the dielectric. As regards b_ρ , both electric fields and electrostatic potential operators have been used.

The reduction of the source of the solvent reaction potential to a charge distribution limited to a closed surface greatly simplifies the electrostatic problem with respect to other formulations in which the whole dielectric medium is considered as source of the reaction potential. In spite of this remarkable simplification the integration of eqn (8) over a surface of complex shape is computationally challenging. The solutions are generally based on a discretization of the integral into a finite number of elements. This discretization of Γ automatically leads to a discretization of σ in terms of point-like charges, namely if we assume that on each surface element σ does not significantly change, its effect can be simulated with that of a point charge of value $q(\mathbf{s}_i) = \sigma(\mathbf{s}_i)a_i$ where a_i is the area of the surface element i and \mathbf{s}_i its representative point. The necessary preliminary step in this strategy is the generation of the surface elements (*i.e.* the surface mesh) as, once the mesh has been defined, the apparent charges q are obtained by solving a matrix equation of the type:

$$Tq = -Rf_M \quad (10)$$

where q and f_M are the vectors containing the N charges and the solute electrostatic potential or the normal component of the solute field at the surface points, respectively. T and R are the matrix analogues of the integral operators introduced into eqn (8). We note that more recently the strategy to obtain the apparent charges within the PCM formalism has been largely reformulated by introducing an expansion of the surface charge in terms of Gaussian functions⁶⁴ and by adopting a fully variational approach.⁶⁵

If we now reintroduce a QM description of the charge distribution ρ_M in terms of the wavefunction which is solution for the eqn (1), we can rewrite the solvent induced term as

$$\hat{H}_{\text{env}} = \hat{H}_{\text{QM/cont}} = \sum_m q(\mathbf{s}_i) \hat{V}(\mathbf{s}_i) \quad (11)$$

where q are the solvent apparent charges and \hat{V} is the solute electrostatic potential operator at the positions of the charges.

By comparing eqn (11) with eqn (3), it might seem that there is a perfect equivalence between the nonpolarizable part of the QM/MM Hamiltonian ($H_{\text{QM/MM}}^{\text{el}}$) and the QM/continuum one. As a matter of fact this equivalence is only apparent as the charges entering in eqn (11) are not external parameters as for the MM approach but they are obtained solving a matrix equation which depends on the solute charge distribution. A more similar term in eqn (3) is instead that related to the induced dipoles which in fact depend on the solute charge distribution exactly as the apparent charges. As a result, both the operator $H_{\text{QM/MM}}^{\text{pol}}$ and $H_{\text{QM/cont}}$ introduce nonlinear character in the effective Hamiltonian which can lead to additional difficulties with respect to the same calculation for an isolated system.^{66–70} However, if we remain within the standard Self-Consistent Field (SCF) approach (either in its Hartree–Fock or DFT formulation) no changes are required in the computational

implementation as the common way the SCF equations are solved implies an iterative procedure in which the determination of the MM induced dipoles or the apparent charges is easily nested. The resulting effective SCF scheme is generally known as the Self-Consistent Reaction Field (SCRF), which emphasizes the mutually polarized solute–solvent system obtained at the end of the SCF. Historically, the term SCRF has been coined for the QM/continuum approach but it can be used also for a polarizable QM/MM approach due to the parallelism between the two schemes. It has also to be noted that this nonlinear character becomes of fundamental importance in the simulation of spectroscopic responses as we shall explain later.

The analogies and differences between QM/continuum and QM/MM approaches are not only on the methodological aspects of their formulation and implementation. We cannot in fact forget that the two approaches start from a completely different physical formulation. By definition, continuum models introduce an average (bulk) description of the environment effects. This is necessarily reflected in the results that can be obtained with these methods. While continuum models can be successfully applied in all cases in which the environment acts as a mean-field perturbation, solvent-specific effects such as hydrogen bonding are not well reproduced. By contrast, QM/MM methods have the clear advantage to keep intact all the atomistic features of the environment, however they become more computationally demanding as an explicit sampling of the configurational space of the solute–solvent system is required. To this aim, a preliminary molecular dynamics (MD) or Monte Carlo (MC) simulation is usually performed from which many different solute–solvent configurations are generated and used within the QM/MM scheme to obtain the final averaged picture. In principle, the main advantages of two approaches could be combined in a three-level approach, QM/MM/Cont, in which the atomistic description is limited to the first solvation shells while the rest of the environment is described as a continuum. Various research groups have already proposed this further formulation of QM/classical approaches by combining different versions of the MM and the continuum models.^{23a,29b,58,59,71,72}

3. QM/classical approaches applied to spectroscopies

The presentation of the main theoretical and numerical aspects of the QM/MM and QM/continuum approaches reported in the previous section has already indicated some advantages and disadvantages of the two families of methods. However, here it is important to better clarify their specificities when applied to the simulation of spectroscopies. To have a more complete view, the analysis will be divided according to different types of spectroscopies, in particular we shall focus on the main ones, electronic (such as absorption and emission), vibrational (mainly IR and Raman) and magnetic (mainly NMR) spectroscopies. Moreover, as different theoretical formalisms can be

used to simulate spectroscopies and response properties, here, we shall limit the analysis to the derivative approach in which the selected property is defined as the derivative of the energy of the system with respect to some perturbations, either of geometrical, magnetic or electric nature (or a combination of them). Within this formalism, static properties are most commonly computed with the coupled perturbed Hartree–Fock (CPHF) or Kohn–Sham (CPKS) methods, and frequency dependent properties with a time dependent version of the same coupled perturbed theory (TDHF and TDDFT); however, generalization of the same derivative approach to other QM methods, for example MP2 or CC, are available also for the hybrid QM/classical methods.

3.1. Electronic spectroscopies

When an electronic process has to be simulated for an embedded system, a new aspect of the model has to be properly taken into account. This aspect refers to possible delays in the response of the environment with respect to the ultrafast time scale typical of electronic processes. The delays usually involve the nuclear component of the environment response as the electronic one is generally assumed to be sufficiently fast to immediately follow any change in the solute electronic charge distribution. The delay can therefore be modelled as the nuclear, or inertial, part of the response of the solvent which remains frozen in the initial solvation state: as a result the response of the environment will not be complete and the term *nonequilibrium* solvation is usually introduced. The importance of a correct treatment of the nonequilibrium is larger for polar environments in which the inertial polarization is the dominant one: in all other cases the differences between equilibrium and nonequilibrium descriptions are negligible. Both QM/MM and QM/continuum approaches can properly treat this effect even if with very different computational strategies.

In QM/continuum models using an ASC formulation, the nonequilibrium effects are easily introduced by splitting the solvent charges into a dynamic (or fast) and an inertial (or slow) component: this separation is obtained by extracting the optical component (ϵ_∞) from the static dielectric constant and using it to determine the dynamic charges (see Fig. 2). By using these two

sets of charges we can equally describe situations in which both sets of charges are equilibrated to the actual solute charge distribution or instead just one (the fast one) can immediately rearrange while the slow one remains frozen in the initial state.

In a QM/MM scheme the inclusion of the slow component of the response is automatically taken into account if the spatial distribution of the MM charges does not change, neither their values, during the investigated electronic process. As far as it concerns the fast component, a polarizable description is instead necessary as we have to allow the fast part of the environment response to change: this is automatically obtained, for example, using induced dipoles which do not change their position but instead they change their value.

A typical example where nonequilibrium effects are relevant is given by electronic transitions of a molecular system embedded in a very polar environment: an excitation in fact begins from a fully equilibrated solute–environment system but it terminates in a vertical state characterized by a Franck–Condon description both as concerns the solute and the solvent nuclear degrees of freedom. A similar but reverted situation is that of an emission process, in that case in fact the emission starts from an excited solute fully equilibrated with the environment and terminates into a non-equilibrium ground state. We note that this picture is based on the assumption that solvent relaxation times are shorter than the excited state life time: this is usually a reasonable approximation when we study fluorescences in simple solvents while it is surely less valid if, for example, the solvent is extremely viscous.

Another specificity introduced by a polarizable solvent is that already pointed out in the previous section: the nonlinear character of the effective Hamiltonian reflects the fact that the response of the solvent is determined by the charge density of the solute. However in a transition process the involved charge densities are two, that of the initial and of the final state. As a result the change in the solvent polarization should depend on the change in the charge density during the electronic transitions. However, in many QM methods largely adopted to simulate the transition process, such as the linear response (LR) approaches known as CIS, ZINDO, TDDFT, EOCC and others, the charge density of the final state is generally not known as the transition properties, including the transition energies are obtained as response functions of the initial charge density. The coupling of polarizable QM/MM and QM/continuum models with such LR schemes is not univocal neither straightforward.⁷³ As a matter of fact many different formulations have been proposed so far,⁷⁴ but none of them can be considered as exact. The most straightforward of these formulations is the so called LR solvation; namely in this formulation the response of the solvent to the transition process is calculated in terms of charges or dipoles induced by the solute transition density. This formulation is the *default* one in practically all the implementations of polarizable QM/MM schemes^{21,23,29} and in most of the QM/continuum implementations.^{75,76} For QM/continuum models however alternative formulations are available. One of the first proposals⁷⁷ introduces a perturbative correction to the LR transition energy by using dynamic charges calculated with respect to the change in the

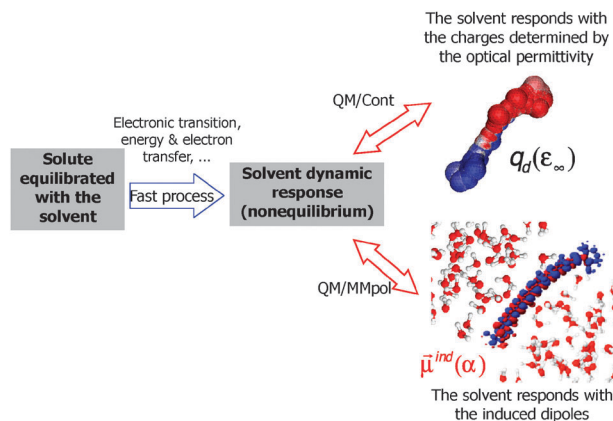


Fig. 2 Graphical representation of the nonequilibrium solvation in polarizable QM/MM and QM/continuum approaches.

solute electronic density (which can be recovered from LR approaches generalizing them to the derivatives): in this approach we still miss the complete coupling between the change the solute-charge density and the parallel change in the solvent response. Another approach, instead, introduces a self-consistent scheme between the density of the final state and the solvent polarization by recalculating the molecular orbitals of the reference state and their response:⁷⁸ in this approach a not completely controllable mixing between what should act as reference for the LR formulation and what should represent the response can appear. More recently, extensions and generalizations of the perturbative approach have been proposed⁷⁹ but still the problem remains open.

If instead a state-specific QM method is used to simulate the electronic transitions, such as using a CASSCF or a standard CI approach, no real difficulties are introduced by the addition of a polarizable solvent, in those cases in fact we can properly define the charge density of each state and consequently we can calculate the correct solvent response. However, a disadvantage of using a polarizable solvent is present also in these apparently simpler formulations: as the effective Hamiltonian becomes state dependent through the solvent term, hence we have to solve separately for each electronic states and the solutions are no more orthogonal.

3.2. Vibrational spectroscopies

Moving from electronic to vibrational spectroscopies the picture apparently simplifies; in fact, nonequilibrium effects are generally negligible and the solvent effects can be introduced using the standard formulations of QM/classical methods. As a matter of fact, nonequilibrium formulations have been proposed also for vibrational properties especially for QM/continuum models.⁸⁰ However, in that case a clear definition of what is fast and what is inertial is less straightforward; in the large part of these applications the fast component is kept equal to that formulated for electronic processes even if now it is not clear why the vibrational components of the solvent response should always be considered slower than the solute vibrations.

By neglecting possible nonequilibrium effects, the application of QM/continuum approaches to vibrational properties and spectroscopies, follows exactly the same path followed for an isolated system: the solute geometry is optimized in the presence of the solvent and the vibrational properties are calculated including the derivatives of the solute-solvent interaction energy. The only specificity is that in the calculation of these derivatives with respect to nuclear displacements the variation of the molecular cavity is to be taken into account as it is generally anchored on the solute atoms. As a result, the simulation of IR spectra is obtained with two calculations, one to obtain the solvated equilibrium structure and one to compute the vibrational frequencies and intensities at the equilibrated geometry as required by the standard harmonic approximation (HA).

When adopting a QM/MM approach the analysis becomes much more delicate.^{11,81–85} For example, in order to apply

the same HA, we have to be in a minimum of the PES but, generally, the solute-solvent configurations used in a QM/MM description do not correspond to optimized structures but instead are obtained from MD or MC simulations. A possible strategy to recover the validity of the HA is to perform a partial optimization of the solute in a frozen distribution of the environment. Unfortunately this optimization has to be repeated for each different solvent configuration: as a result the final computational cost can largely increase.

3.3. Magnetic spectroscopies

With respect to electronic and vibrational spectroscopies, the application of QM/classical methods to magnetic ones is generally easier. For example if we are interested in simulating the NMR nuclear shielding and the classical part is not polarizable, the solvent effects are automatically included in the calculation of the unperturbed system as no explicit solvent-dependent terms appear in the derivative equations which define the specific property as the solute-solvent interaction energy does not explicitly depend on the magnetic applied field and on the nuclear magnetic dipole. In contrast if the classical part is polarizable (such as in QM/continuum and in polarizable QM/MM approaches) a density-dependent response of the solvent is present, and this dependence is also reflected in the coupled perturbed equations which have to be solved to get the derivative of the density matrix with respect to the perturbation(s). Moreover, in most cases the magnetic properties are calculated within the GIAO framework so to properly solve the gauge problem. In such a formalism a dependence of the atomic basis functions on the magnetic field is introduced, and this automatically generates a dependence of the solvent operator on the magnetic field: now an additional explicit solvent term appears in the derivative equations with respect to the magnetic field.^{86,87}

Besides these aspects, the application of QM/classical methods to magnetic spectroscopies presents also other specificities. For example, by definition, the nuclear shielding is a local property which is significantly affected even by small changes in the local chemical environment of the selected nucleus; we therefore have to expect that it is also extremely sensitive to the solvation shells around the selected nucleus. As a matter of fact, not all nuclei are equally sensitive to the effects of the “external” environment. In particular, hydrogen and carbon do not present a large sensitiveness to the solvent while other nuclei, such as N or O, show important solvent-induced effects especially when the selected nucleus is exposed to the solvent and it can strongly and specifically interact with the solvent molecules in the first solvation shells. In all these cases a purely QM/continuum approach is not sufficient and a QM/MM description has to be preferred. Sometimes, even this description is not sufficient as the solute-solvent interactions can include some charge-transfer effects that even if very small can affect the magnetic property. In this case a very effective approach is represented by the so-called *solvated supermolecule*; in this approach we extend the definition of the QM solute to a *cluster* including also some solvent molecules

(exactly those more strongly interacting with the nucleus of interest) and we introduce the longer-range effects either using a continuum or an MM description.^{88–94}

4. Some selected examples

The main specificities of the application of QM/classical methods to spectroscopies described in the previous section are here exemplified in terms of few short summaries of studies we have performed in the last few years using both QM/MM and QM/continuum approaches. We stress that these selected studies are not to be considered as more noteworthy or relevant with respect to others but the reader should use them as a set of notes to start with for a detailed analysis of the literature survey reported in the previous sections.

4.1. Heterogeneity and solvatochromism

Solvatochromism is the change induced by different solvents, in the position (and the shape) of an absorption (or emission) band of a molecular probe. The phenomenon has been often extended to more complex environments than isotropic and homogeneous solvents; for example it has been largely used to establish the polarity of lipid membranes and protein matrices. Historically, solvatochromism was used in combination with empirical polarity scales^{95,96} to relate the solvent-induced shift on the absorption maxima with specific characteristics of the environment. QM/classical approaches now can represent a much more accurate and detailed tool to perform the same type of investigation. Both QM/MM and QM/continuum models have in fact shown to be able to accurately simulate the UV-VIS spectra of very different molecular systems in various solvents. Moreover, they can give additional insight into possible heterogeneities and anisotropies of the environment which can differently tune the shift in dependence of the specific position and orientation of the probe. This second aspect is easier to get when an atomistic version of the QM/classical method is used and in fact the large part of computational studies of solvatochromism in proteins and membranes adopt a QM/MM approach. However, continuum models can be made sensitive to large-scale heterogeneities and anisotropies of the environment, introducing a position dependent permittivity. This extension has been made available within the IEFPCM formulation of QM/continuum models⁹⁷ (see Fig. 3) and recently used to interpret the main features of the fluorescence spectra of two typical fluorescent probes (Prodan and Laurdan) in relation to their position and orientation in a DPPC lipid bilayer.⁹⁸

Calculating the QM/PCM absorption and emission energy profiles of the probes crossing the membrane, we found that the environment polarity alone is not sufficient to explain the large red shifts experimentally observed and that specific effects due to hydrogen bonding must be considered. Finally, by combining the QM/PCM results with a molecular field theory analysis of the positional, orientational and conformational distribution, we also showed that the orientation of the probe is important in determining the accessibility to water of the H-bond-acceptor group.

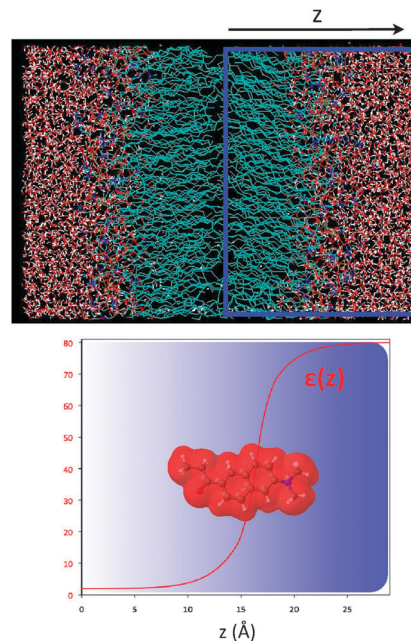


Fig. 3 IEFPCM representation of a molecular probe moving through a lipid bilayer modelled as a dielectric with permittivity changing from 2 (at the center of the apolar region, $z = 0$) to 80 (at the exterior of the bilayer, $z > 25$ Å).

Unfortunately, when the heterogeneity of the environment acts at a smaller scale, such as in a protein matrix where each position/orientation of the probe feels a different local environment due to the different residues in contact with it, continuum models necessarily fail. In all these cases the QM/MM formulation has to be preferred but with careful attention to the conformational disorder which can generate fluctuations of the transition energies of the same order of that characterizing the solvatochromic shift. To show such an effect, Fig. 4 reports the excitation energies calculated by a polarizable QM/MM approach for the eight bilin chromophores contained in the phycoerythrin PE545 antenna protein.⁹⁹ The two sets of data have been obtained using (i) the crystal structure of the protein and (ii) an average on the MD trajectory of the solvated protein.

As it can be seen from the graph, the eight bilin chromophores, characterized by a linear tetrapyrrole structure covalently linked to the protein scaffold, present a significantly different energetic ordering in the two descriptions. In particular, the crystal structure leads to unphysical differences in the energies of the pseudosymmetric pairs (namely $\text{PEB}_{5061\text{C}}-\text{PEB}_{5061\text{D}}$ and $\text{PEB}_{82\text{C}}-\text{PEB}_{82\text{D}}$) which are instead largely smoothed by the averaged description in which both the intramolecular and the intermolecular fluctuations have been taken into account.

4.2. Specific vs. bulk effects on spectroscopies

As already discussed, most of the spectroscopic signals of molecular systems are sensitive to both specific and bulk effects due to the environment; however, the sensitivity is not the same for all spectroscopies. Absorption and emission energies, for example, are not largely affected by solute–solvent specific interactions and generally they do not require an

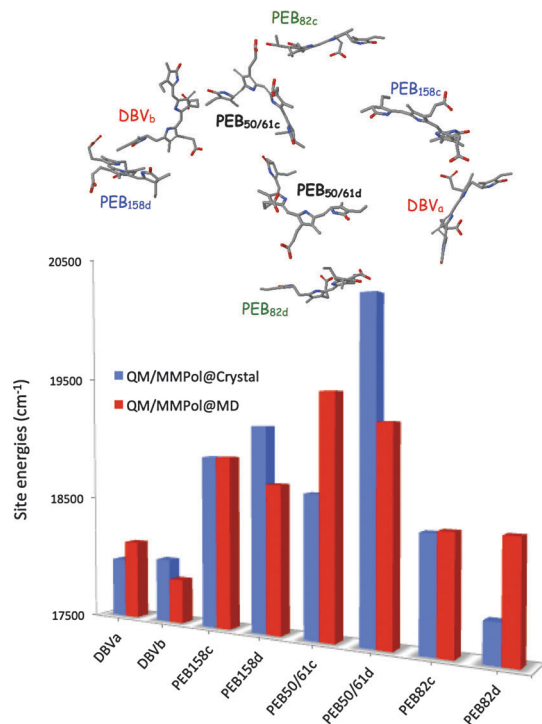


Fig. 4 Comparison of the QM/MMPol site energies obtained for the 8 bilins of the LH complex in PE545 either using the crystal structure (blue histograms) or averaging on many MD configurations (red histograms).⁹⁹

atomistic description of the first solvation shells, with some important exceptions. The exceptions are represented by excitations mainly localized on molecular groups with can interact through hydrogen-bonding with the solvent molecules: typical examples are the anomalous shifts in the $n\pi^*$ excitations in carbonyl-containing molecules when solvated by protic solvents.

In the case of magnetic and vibrational properties instead, the role of the solvent molecules locally surrounding the investigated molecule, is usually important. For magnetic properties the main reasons have been already explained in the previous section but here we further analyse them using a simple example extracted from a study of solvent effects on various spectroscopic properties of *N*-methyl acetamide (NMA):⁹¹ namely the nuclear magnetic shielding for nitrogen and oxygen nuclei of NMA in water and in acetone. In Fig. 5 the errors with respect to experiments obtained using three different solvation models are reported. The three solvation methods correspond to a simple QM/PCM approach, and two alternative QM/QM/PCM approaches. The first one uses QM optimized supermolecules formed by (i) NMA and three H-bonded water molecules in the case of aqueous solution, and (ii) NMA with two solvent molecules in acetone. The second approach uses instead averages on QM clusters obtained from MD simulations in the two solvents.

As expected the QM/PCM approach largely underestimates the ^{17}O signal in water as the oxygen atom is involved in strong H-bonding interactions with the solvent. By explicitly introducing these effects in terms of QM water molecules, the error is

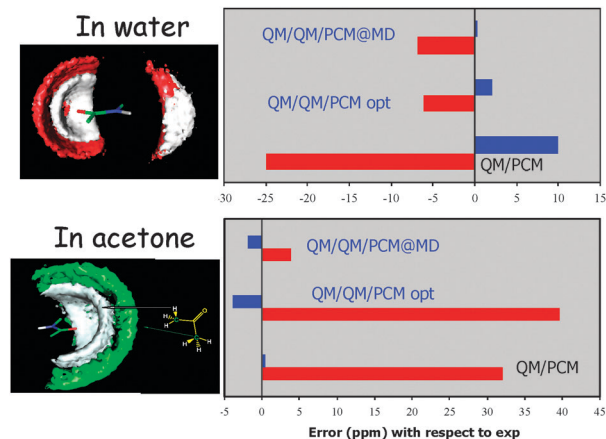


Fig. 5 Errors with respect to experiments (ppm) for the ^{17}O (red bars) and ^{15}N (blue bars) nuclear magnetic shieldings of NMA in water (upper graph) and in acetone (lower graph). On the left the MD-derived spatial distribution functions are also reported for both solvents: white points indicate hydrogen, red oxygen, and green carbon distributions, respectively. For all the details of the calculations we refer the reader to the reference paper.⁹¹

immediately reduced within the accuracy of the method. It has also to be noted that the static picture in terms of a single QM optimized supermolecule and the dynamic one using an average on QM clusters from MD trajectories give very similar results. This similarity indicates that the NMA-water H-bonds are so strong that they can properly be described without taking into account fluctuations in the number, relative position and orientation of the H-bonded molecules. When moving to acetone, the picture becomes much more complex. In this solvent in fact, the QM/PCM approach largely overestimates the effect of the solvent on the oxygen. The reason for that can be explained comparing the results obtained with the two alternative QM/QM/PCM approaches. The one using a single optimized supermolecule still maintains the overestimation found with PCM alone while the average on MD clusters correctly reproduces the experiments. In acetone, the structuring of the solvent molecules around the NMA carbonyl group is the result of the combination of weak H-bonds with the methyl hydrogens and dipole–dipole interactions (see the SDF reported in Fig. 5). In this case, a proper consideration of fluctuations in the solvent shells becomes compulsory to obtain the correct effect.

For vibrational properties, the dependence on the local environment can be explained observing that now the solute–solvent short-range interactions not only can induce an additional shift in the frequency as in the NMR property but they can also modify the normal mode. This effect can accurately be described only by including some specific solvent molecules within the QM portion of the system, therefore neither QM/continuum nor QM/MM approaches can be used in their standard formulations but they have to be reformulated within the *supermolecular* framework. This approach clearly introduces some further difficulties such as the number of solvent molecules to be included in the QM part but also some artificial effects, as we have split the solvent into two parts, one acting

through classical effects and the other entering as a QM component. The same artificial effects can become of paramount importance when we are simulating chiral spectroscopies both of electronic or vibrational nature. In that cases in fact, the use of solute–solvent QM clusters to account for short-range effects introduces an additional chirality, which depends on the dimension of the cluster and the configuration of the solvent molecules.

As it comes out from this brief resume, the correct treatment of short-range effects due to the environment is a delicate problem, especially when applied to spectroscopies. Unfortunately, it is not possible to define a unique strategy but each case has to be analysed independently; however, some general rules can be defined. The use of QM/MM approaches is generally sufficient but only if accompanied by a correct sampling of the solvent distribution and a proper inclusion of longer-range effects. While the latter aspect can be easily solved by using an external continuum, the sampling issue introduces an additional difficulty. In most cases in fact, the sampling is obtained by using classical MD or MC configurations but it is not always the case that classical force fields can properly describe the correct positional and orientational distributions of the solvent molecules more strongly interacting with the solute. An ideal strategy would be that of using *ab initio* MD simulations^{100,101} but the applicability of these techniques is still limited both in the simulation times and in dimension of the systems. However, in the next future, studies of this type will become feasible for systems of real chemical interest, and they will represent a fundamental benchmark for a better understanding of the role of the first solvation shells.

5. Conclusions

In this perspective I have reviewed some of the most common QM/classical approaches used to include environment effects into the simulation of spectroscopic properties of molecular probes. From this excursus, it should come out clearly that it is not possible to identify the optimal protocol but that different formulations have to be selected for different processes and phenomena and, in some cases, only a combination of these approaches can lead to the correct picture. Moreover, the same methods are not yet definitive in their theoretical and numerical formulation but they continuously improve. Therefore, due to this still “fluid” situation, in the future we can expect important developments. For sure, one of the possible developments will involve the application of QM/classical approaches in dynamic simulations. Some formulations have been already presented^{102–116} even if they are not competitive with the decoupled strategies using classical MD followed by QM/classical calculations of the property or process of interest. However, QM/classical MD simulations surely present the required characteristics to become the optimal computational approach to study fast phenomena in which the main role is played by the coupling of electronic and vibrational motions such as in charge and energy transfer processes. For this kind of applications, the atomistic formulation of QM/classical

methods appears the best suited, however QM/continuum models can represent a very interesting alternative strategy due to some of their specificities, especially their easiness to include nonequilibrium and memory effects.^{117,118} Another possible direction of progress is represented by extensions of these methods to a “nonelectrostatic embedding”. Until now in fact QM/MM approaches have almost exclusively been limited to electrostatic (and polarized) embeddings while van der Waals effects are introduced at the purely classical level. Only recently, QM/MM approaches adopting a fragmentation framework,¹¹⁹ have been extended to include these effects into the effective Hamiltonian. Within QM/continuum methods such an extension has a longer tradition,¹²⁰ but the formulation is still open to improvements.¹²¹ Finally, QM/classical methods are still mostly limited to describe traditional environments (namely homogeneous solvents for QM/continuum and protein matrices for QM/MM formulations) while their potentials are much more general. In the last few years, applications of QM/classical methods to less standard environments have started to appear^{122–126} but still many important areas (such as those of the material and biomedical sciences) are still too poorly covered. It is exactly in these fields that we have to expect the major breakthroughs of the hybrid methods in the next future.

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