

Review Article

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Quantum chemistry of molecules in solution. A brief historical perspective

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Abstract: Calculating the wave function and the properties of a molecule in solution is a common procedure today that can be performed with a variety of methods. However, the study of solvated systems did not begin with the establishment of the Schrödinger equation in 1926 and the development of the first methods in computational chemistry. In fact, it took until 1973 to see the first self-consistent field equations that included the electrostatic potential of the solvent. It took another two decades for computational methods and solvent models to become consolidated, with an explosion of applications in the 1990s. This article briefly describes that fascinating story.

Keywords: Ab initio molecular dynamics; history of quantum chemistry; polarizable continuum model; QM/MM; quantum science and technology; solvent models; supermolecule approach.

Introduction

The United Nations has proclaimed 2025 the International Year of Quantum Science and Technology. It celebrates the centenary of the birth of quantum mechanics¹ and the publication of the seminal papers by Werner Heisenberg² in *Zeitschrift für Physik* in 1925, and Erwin Schrödinger^{3,4} in *Annalen der Physik* in the first months of 1926.

In the years that followed, the development of methods for solving Schrödinger's equation for electronic motions in atoms and molecules was incredibly rapid, thanks to the contributions of eminent scientists such as Dirac, Heitler, London, Hund, Slater, Hartree, Fock, Mulliken, Hückel, Pauling, and many others. New methods soon emerged that would establish the physical foundations of modern theoretical chemistry and would have a profound impact on chemical science.

A few years later, in the 1950s and 1960s, the availability of computers led to a revolution in quantum chemistry (as in many other fields of science and technology), opening the way to the field of computational chemistry.⁵ Of course, the limited capacity of computers meant that incipient electronic structure methods could only be applied to systems containing a small number of electrons. As a result, the vast majority of studies initially focused on describing isolated atoms or molecules containing a few atoms. The study of large molecules or complex systems such as liquids or solutions was not contemplated. It was in the 1970s, some 50 years after the advent of quantum mechanics, that theoretical chemists developed the first polarizable continuum solvation models and began to apply them to the study of the electronic structure of molecules in solution. It was not until the 1980s and especially the 1990s that realistic microscopic models and first-principles simulations began to take shape. Figure 1 depicts the main categories of solvation models.

This article describes the main stages of this exciting journey in a fairly compact, formula-free way. It is not an in-depth account of solvation models. There are many exhaustive reviews in the literature, although generally, each review has focused on a particular class of models. For the interested readers, review references will be

Article note: A collection of invited papers to celebrate the UN's proclamation of 2025 as the International Year of Quantum Science and Technology.

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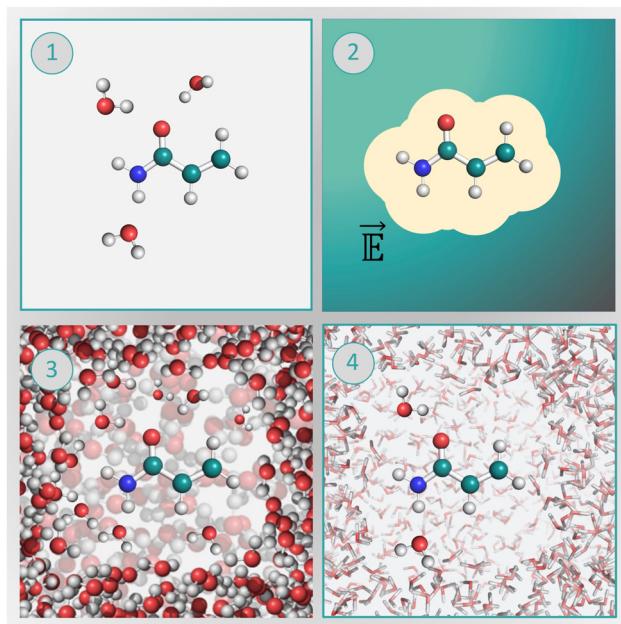


Fig. 1: Scheme presenting the main types of solvation models discussed in the manuscript: supermolecule model (1), continuum model (2), and microscopic models combining quantum chemical methods and statistical mechanics simulations. In this case, the whole solute-solvent system can be described quantum mechanically (3), or using hybrid quantum/classical approaches (4).

provided below. The aim here is to bring together in one place a summary of the main steps that led to the development by theoretical chemists of various models for the study of molecules in solution using quantum chemical methods. Thus, I have taken little, or no account of approaches developed after the late 1990s, giving priority to the birth of methods and the context in which they were developed. Solvation models underwent many interesting developments after 2000, of course, but I regard them as primarily inspired by the models described below. Furthermore, I will not discuss the development of statistical mechanics simulations using Monte Carlo or molecular dynamics techniques, nor that of effective intermolecular interaction potentials. Only statistical simulations incorporating a quantum-mechanical description of the solute, or solute-solvent system will be considered. The available solvent models can be classified according to various criteria, but here I have chosen to present them chronologically, even if in some cases this has obvious limitations, as different models or versions of models were developed in parallel. I have sought to document the facts reported by systematically providing the original bibliographical references, although inevitably parts of the text below are also the reflect of some personal memories.

Simple models: the supermolecule approach

The first attempts to describe the influence of a solvent on the molecular properties of a solute using quantum chemical methods focused on the effect of hydrogen-bonds. This type of intermolecular interaction has received a great deal of attention since the beginning of the twentieth century as a possible cause of certain observed irregularities. A nice example of this was the work by Moore and Winmill⁶ on the dissociation constants of amines, in particular of ammonia and methylamines (I will come back to this issue below). The first detailed description was probably done in 1920 by Latimer and Rodebush,⁷ who were studying the structure and properties of water, and proposed a Lewis-type formalism for the interactions between two water molecules in which a hydrogen nucleus is “held between two octets”. Nevertheless, it was the seminal book by Pauling which popularized the concept and provided the first definition of hydrogen bonds. A brief history of the hydrogen-bond can be found in the paper of Smith,⁸ and also in papers by Bratoz,⁹ Kollman,¹⁰ and Szalewicz,¹¹ for instance.

Theoretical studies of hydrogen bonded systems using electronic theories were carried out by several authors starting in the 1950’s. The works by Pimentel¹² in 1951 and Nukasawa¹³ in 1953 were probably the first attempts done in this direction, and the works by Lennard-Jones,¹⁴ Pople,¹⁵ and Coulson¹⁶ contributed also to

improve the understanding of the hydrogen bond interaction. In the 1960s and early 1970s, a large number of works using SCF theories began to be published. Some reference works of this period are for instance the papers by Clementi (1967),¹⁷ which studied the $\text{NH}_3 + \text{HCl}$ reaction (cited by Kollman¹⁰ as the first ab initio study of an H-bonded system), Morokuma (1968),¹⁸ who studied the H_2O dimer, Del Bene (1972),¹⁹ who described the dimers of H_2O_2 and H_2O , and Alagona et al. (1973),²⁰ devoted to formamide-water complexes. The vast literature covering the mentioned years was compiled in various books and articles, which can be consulted for more details on the progress of hydrogen bonding theory during this period. Let us cite in particular the 1960 book "The Hydrogen Bond" by Pimentel and McClellan,²¹ the 1967 review paper by Bratoz,⁹ and the review by Kollman in 1972.¹⁰

Thus, gradually, at the end of the 1950s, the idea of performing electronic calculations on molecular edifices comprising a solute molecule interacting with several surrounding molecules through hydrogen bonds emerged as a general approach to considering the effects of the environment on the structure and other properties of molecules in solution. This led to the establishment of the "supermolecule method" which was popularized and strongly developed in the 1960s and 1970s by Alberte and Bernard Pullman. The Pullmans had been working on the applications of quantum theories to biology^{22,23} from the late 1950s and 1960s, and indeed they are recognized as the founders of the field of quantum biochemistry. Since biochemical processes take place mainly in aqueous media, accounting for biomolecule-water interactions is essential to understanding the mechanisms involved, and the main type of interaction to be considered is of course hydrogen bonding. Thus, the supermolecule (or supermolecular) approach was initially implemented by the Pullmans to elucidate the structure of water around the main chemical constituents of living organisms, amino acids, peptides, DNA base pairs, etc., and to clarify how hydration affects their properties.^{24,25} The various features of the supermolecule method, possible calculation strategies and numerous case studies were detailed in a review published by A. Pullman in 1976,²⁶ where she gave the following definition of the method: *"It has become customary in the recent past to call supermolecule or supersystem, an entity made of two (or more) molecules in interaction, when they are treated as a single system by the methods of quantum chemistry, computing the global wave function of the whole set of electrons of the entire system in the field of all the nuclei fixed in the appropriate mutual relative arrangement".*

The model has been widely used until today in many different versions, sometimes being referred as the "discrete" or "explicit" solvation model, in opposition to the so-called "continuum" or "implicit" solvation models described below. Note that the supermolecule technique has been used to study different aspects of intermolecular interactions, not necessarily related to solvation phenomena, though of course this is the focus here. However, in practice, the supermolecule model is useful mainly when there are specific (sufficiently strong) interactions between the solute and the solvent and is not recommended for the study of solutes in "inert" solvents such as hydrocarbons. Another drawback of the model is the small number of solvent molecules that can be handled in practice, as the computational time in quantum chemistry calculations increases very rapidly with the size of the system. In addition, with an increasing number of molecules, a statistical treatment may be mandatory, since many geometrical arrangements with similar energy may occur. Therefore, usually only solvent molecules that interact directly with the solute via hydrogen bonds or other specific interactions are taken into account, thus neglecting the potentially important effect of long-range solute-solvent electrostatic interactions.

Despite the above limitations, the model can be useful to obtain some main trends, for example, on the structure of the first solvation shell or on the solvent effect on the solute properties. The case of the irregular basicity of the ammonia and methylamines molecules in the experiments by Moore and Winmill¹⁶ mentioned above is a simple and nice example illustrating this principle. Thus, by the end of the 1970s, some theoretical studies had already been carried out on the proton affinities of amines in the gas phase,^{27–32} as well as on the solvation energies of ammonium ions (specially by the Pullmans).^{33,34} In this context, using the supermolecule approach and basic semiempirical quantum chemical calculations, we were able to elucidate the origin of the basicity irregularity in aqueous solution experimentally observed,^{35,36} which results of an opposite trend between the gas phase proton affinity and the amine/ammonium solvation energy difference term. The results provided only qualitative trends and pointed out the necessity to perform higher level ab initio calculations that take into account long-range solvation effects to obtain more accurate data.

It was also in the 1970s that the first dielectric continuum models began to emerge. The birthplace of the developments of this method was the University of Nancy, in France, and the context in which they were performed is outlined below.

The birth of dielectric continuum models

The continuum solvation model has completely revolutionized our understanding of the effects of solvation on chemical processes. During the last decades, this model has become a routine technique and is implemented in most of the available quantum chemical programs (Gaussian,³⁷ GAMESS,³⁸ Q-Chem,³⁹ MOLCAS,⁴⁰ etc.). There are probably thousands of publications using it every year. The principles of the model are extremely simple, as is its use, what has certainly contributed to its rapid and broad popularization.

The continuum model is based on the dielectric theory of liquids, which goes back to the works by Mossotti,⁴¹ Clausius,⁴² Debye,⁴³ Born,⁴⁴ Kirkwood,⁴⁵ and Onsager,⁴⁶ among others. The book of Böttcher⁴⁷ “The Theory of Electric Polarization” is a classical reference in the field that offers an excellent treatment of the subject. In the classical electrostatics model, the solvent is represented as a structureless polarizable continuum medium characterized by its macroscopic dielectric properties, and the solute is placed in a cavity created in the dielectric continuum. As a result, there is a mutual polarization: the dielectric is polarized due to the charge distribution (electrons and nuclei) of the solute, and the latter is polarized in turn by the electrostatic potential (the so-called reaction field) created by the polarized dielectric continuum. The book of Böttcher⁴⁷ summarizes the electrostatic equations for a number of simple cases. For instance, the solute can be represented by a non-polarizable or a polarizable point dipole, or by a series of multipole moments, and the cavity shape can be spherical, spheroidal or ellipsoidal.

In Nancy, Jean Barriol, who had held the first chair of Theoretical Chemistry in France since 1948 (for a Barriol's biography, see Ref. 48), was interested on the dielectric behavior and physical properties of liquid mixtures, making key contributions in the field.^{49–51} Although Barriol was a theoretician, he placed primary importance on experimental work, and indeed, students in the laboratory always started their training by doing experiments.⁴⁸ One of his students, Jean-Louis Rivail moved to Coulson's lab in Oxford for a post-doctoral stay in 1967 after completing his doctorate in Nancy. Rivail wanted to complete his training in quantum chemistry and his work in Oxford dealt with computational methods for predicting molecular electrostatic properties and H-bonding in σ -electron systems. Rivail came back to Barriol's lab the same year thanks to a *Maître de Conférence* position and introduced a new line of research based on a theoretical approach to intermolecular interactions involving the use of quantum chemical methods. He supervised the PhD work of Daniel Rinaldi, who had joined the lab from INSA Lyon interested by his reading of Barriol's book on quantum mechanics.

The PhD project of Rinaldi was devoted to the development of the computational code GEOMO^{52,53} for quantum chemical calculations using the most popular semi-empirical methods of the time (CNDO,⁵⁴ INDO,⁵⁵ MINDO⁵⁶), which in addition included, for the first time, an algorithm to optimize molecular geometries.⁵⁷ Obviously, while working in Barriol's laboratory, the idea of including the role of the environment in quantum chemical calculations of molecules in solution, using a dielectric continuum model to represent the solvent effect, came naturally to Rivail and Rinaldi. The aim⁵⁸ was motivated by NMR⁵⁹ and microwave⁶⁰ experiments done in the laboratory showing that simple molecules such as allylamine had a very different structure in solution and in the gas phase, confirming that solvents effects on molecular properties may be very significant.⁶¹ They incorporated the solute-solvent electrostatic interaction into the solute Hamiltonian to obtain the solute wave function in the presence of the solvent. The mutual solute-solvent polarization was accounted for through the self-consistent-field (SCF) equations of the Hartree–Fock method, after adding to the standard equations the interaction of the solute with the solvent reaction field. Nowadays, these equations are usually called the self-consistent reaction-field (SCRF) equations. The reaction field depends on the shape of cavity, the solvent dielectric constant, and the solute charge distribution. There are analytical expressions for the potential when the cavity has regular shapes (e.g. spherical, spheroidal or ellipsoidal), which take the form of a multipolar expansion centered in a given point (or set of points), and logically, the former implementations of the model assumed such

hypothesis. In the very first application of the continuum model published in 1973,⁶² Rivail and Rinaldi studied the properties (geometries, dipole moments, polarizabilities) of the water molecule and of different isomers of the water dimer using a spheroidal cavity, whose ellipticity was defined from the polarizability tensor. The interaction was limited to the first term of the expansion, i.e. the dipole moment, and the calculations were carried out with the CNDO/2 method. It must be emphasized that in the SCF equations of this first paper, electrostatic and dispersion energies were included,⁶² although the influence of the dispersion term was found to play a minor role and will be omitted in future versions of the model.

Soon after this pioneer work, in 1976, the same authors published an extension of the model implementing now the full multipole moment expansion of the solute-solvent interaction, assuming for simplicity a spherical cavity shape.⁶³ The calculations were still done at the CNDO/2 semiempirical level and dealt with the study of different conformational equilibria in solution.

The two papers by Rivail and Rinaldi above marked the birth of continuum models in quantum chemistry, although it is worth mentioning that similar initiatives were undertaken during the same period by Yomosa,⁶⁴ Johnson,⁶⁵ Claverie,^{66,67} Tapia,^{68,69} and others.^{70–72} Coulson himself had been interested in the effect of a dielectric continuum on electronic energy levels as early as 1958,⁷³ but the systems considered were too simple (e.g. the hydrogen atom).^{74,75} Nevertheless, it was the approach developed in Nancy that brought definitive progress in the field and paved the way for the methods we use today. If the 1970s saw the birth of the model, the 1980s saw it grow and develop spectacularly, reaching the somewhat definitive form in various versions and implementations in the 1990s.

Expansion of continuum models

Developments carried out in Nancy

During the 1980s, the development of the continuum model took place essentially in Nancy and Pisa. Let me first to follow up on the developments carried out in Nancy, in which I was strongly involved starting from 1980. I had moved from Madrid to Nancy after defending my Master Thesis at the Autonomous University of Madrid, which was supervised by Juan Bertrán and Antonio Oliva. Bertrán had spent some time in Nancy to explore the capabilities of the continuum model to study solvation phenomena and the result was a fruitful and long-term collaboration⁷⁶ between the two groups. When I joined Rivail's group, one of the most important challenges I faced during my PhD project was to extend the model to ab initio computations. The first version was implemented in the Gaussian 76 program⁷⁷ and incorporated a full multipole moment development of the reaction field using general ellipsoidal molecular cavities. The work was presented at the 4th International Congress of Quantum Chemistry (Uppsala, 1982)⁷⁸ and was published in 1983.⁷⁹ My PhD project⁸⁰ did also focus on applications of the model to the calculation of molecular spectroscopic properties in different domains, IR,⁸⁰ NMR (spin-spin nuclear⁸¹ and nuclear quadrupole⁸² coupling constants), and UV–Vis.^{83,84} In this latter case, a key achievement was the development of a perturbational theory⁸⁴ for the calculation of electronic excited states of solvated molecules in the Random Phase Approximation (RPA) and the implementation of the corresponding code interfacing our SCRF program and the RPA program of Flament.⁸⁵ The role of vibronic coupling on UV–Vis spectra was also considered.⁸⁶

After my PhD, and now as a permanent CNRS researcher in the same laboratory, I turned to the formidable and exciting challenge of studying chemical reactions in solution. The SCRF method had already been applied to study solvent effects on some chemical reactions^{87–89} but only in a qualitative way. To move further, it was compulsory to be able to optimize the geometrical structure of solvated molecules and to compute vibrational frequencies in order to locate transition states and calculate free energies accurately. This became possible in 1991 thanks to the development of highly efficient analytical optimization algorithms by Rinaldi.^{90–92} Indeed, the use of a multipole moment development to represent the reaction-field was a major advantage because it allows to obtain analytical expressions for the energy derivatives. The first application of the model with full geometry optimization was devoted to the structure of the water dimer in liquid water and the analysis of cooperative

effects.⁹³ In 1993–1994, the studies of chemical reactions began to take shape. They focused on isomerization,⁹⁴ Diels-Alder,⁹⁵ and hydrolysis⁹⁶ processes, illustrating the key role solvation may have on their mechanism, chemical selectivity, kinetics and thermodynamics. Two other key extensions of the Nancy continuum model in the 1990s were the implementation into the deMon program,⁹⁷ allowing the use of density functional theory (DFT) methods, which were not yet widely employed by theoretical chemists, and the development of algorithms to deal with general cavity shapes⁹⁸ and distributed multipole moment expansions.⁹⁹

The influence of dispersion forces on the electronic structure of the solute was examined by Costa Cabral after adapting the SCRF equations.^{100,101} The study showed negligible or slight modifications (compared to the electrostatic effect) in the case of polar solutes but non-negligible effects in the case of apolar ones. A parameterized non-electrostatic solvation term including the dispersion energy, as well as cavitation and other contributions, was introduced in the Nancy model a few years later.¹⁰² Costa Cabral also carried out Monte Carlo simulations with a dipolar hard-sphere solvent model and solutes of various types (dipolar, quadrupolar, multipolar) to discuss some of the approximations done (cavity volume/shape) in the continuum model.¹⁰³

I have mentioned that from the beginning we had interfaced our SCRF package with the Gaussian program. In August 1990, I presented the model in an invited talk at a NATO Conference in Vimeiro, Portugal, which several members of the Gaussian development team had attended. The title of my talk was "*The Self-Consistent Reaction Field model for molecular computations in solution*".¹⁰⁴ We had interesting discussions on the model, and the Vimeiro meeting arguably stimulated the development of the SCRF method in the official version of Gaussian 90, with the first publication appearing in 1991¹⁰⁵ (the initial model assumed the simplest Onsager approximation, i. e. a dipole moment in a spherical cavity).

It is interesting to note that in the period considered above, during which only a reduced number of theoretical groups in the world have started to use continuum models and to study solvent effects, the group of Nancy (and to some extent also the group of Pisa, see below) established very fruitful collaborations with several labs in Spanish Universities. I would like to mention a few explicitly because, in my opinion, they had a decisive impact on spreading the popularity of the continuum model at the time. Most of those collaborations involved the study of reaction mechanisms in solution. I have already mentioned the long-term collaboration with Bertrán and Oliva (first in Madrid, then in Barcelona),^{81,87,88,93,102,106,107} but very fruitful collaborations were also carried out with the Universities of Seville (E. Sánchez-Marcos and R. R. Pappalardo; Pappalardo was involved on the program developments during his post-doctoral stay in Nancy),^{89,92,94,106,108,109} and Oviedo (T. Sordo, R. López).^{110–115} The collaboration with the organic chemistry group of the University of Zaragoza (J.A. Mayoral, J.I. García, L. Salvatella) was also key to check the reliability of the model.^{95,116–120}

The development of the continuum model was gradually abandoned in our group for a variety of reasons, the most relevant of which was probably the shift in the 1990s to more elaborate theoretical approaches, as the combined quantum/classical simulations (see below). Nevertheless, the model continued to be used by several groups for some time. Indeed, the use of multipole expansions to represent the reaction field had several advantages with respect to other models being developed in parallel. First, it offered a straightforward physical interpretation of the calculated effects. Second the computations were quite efficient and fast since the SCRF equations involved analytical expressions in terms of spherical harmonics. Of course, when the cavity shape has a non-uniform form, some numerical computations are needed, but they only involve coefficients (the reaction-field factors) that depend on the cavity surface and the solvent dielectric constant (not on the solute electronic density); therefore, they are not recalculated in the SCRF iterations, which saves computing time. Finally, energy derivatives are easily calculated, simplifying geometry optimization and vibrational frequency calculations. In the literature, it has sometimes been said that one of the shortcomings of the model is the poor convergence of the multipole expansion. While this is partly true, in practice, computational issues are generally linked to the amount of electron density external to the cavity. This is a general problem in quantum chemical continuum models¹²¹ and has been treated in different ways by different groups. It can be addressed in the case of the Nancy model too by using corrected multipolar expansions corresponding to a generalized charge distribution inside the cavity that fits the "exact" solute electrostatic potential outside the cavity. A detailed review on the theory and applications of the Nancy continuum model can be found in Ref. 122.

The polarizable continuum model developed in Pisa

As mentioned above, the other cornerstone of the continuum model in the early years was the Pisa group. The version of the model developed by Jacopo Tomasi and collaborators in Pisa¹²³ has its origins on the work done in the group on molecular aggregates in the early seventies at the ab initio level.¹²⁴ Though the Pisa and Nancy continuum models share the same physical foundations, they differ by the mathematical approach used to obtain the reaction field, i. e. the electrostatic potential interacting with the solute. While in the Nancy model, expressions based on multipolar expansions were used to develop the potential of the polarized dielectric medium in a point or a set of points, in the Pisa model, the potential was obtained from a discrete set of virtual charges on the cavity surface, whose values are derived by numerically solving the Poisson-Laplace equations with the appropriate boundary conditions. The two approaches are equivalent in the classical electrostatics model, as described in the book by Böttcher,⁴⁷ but present different features in their implementation for quantum chemistry calculations.

The Polarizable Continuum model (PCM) first developed at Pisa is certainly the most broadly used continuum solvation model nowadays and it has been the subject of many methodological improvements along the years. Some of the most important milestones achieved on PCM until about the year 2000 are the following. Dispersion and repulsion contributions to the free energy were introduced at the end of the 1980s.^{125,126} Adaptation to the study of non-equilibrium phenomena began in 1992.^{127,128} In 1996 the model was implemented in the Gaussian 94 program,¹²⁹ which marked the beginning of the collaboration of the Pisa group with Gaussian Inc, and at the same time the start of the methodological work on PCM carried out by the Naples group.¹³⁰ In 1997, problems related to the effect of the solute charge lying out of the cavity were addressed using a classical electrostatics approach.¹³¹ In 1997–1998, two new formalisms of the PCM model were proposed. The integral equation formalism (IEF)^{132–134} appeared to be computationally faster and more stable than the standard one and could be used with anisotropic dielectrics. This formalism was shown, in addition, to provide an accurate treatment of the issues related to the solute electronic charge outside the cavity.¹²¹ The conductor-like PCM model (CPCM)¹³⁵ was developed by the Barone group at Naples, and was based on the continuum metallic model of Klamt.¹³⁶ Finally, in 1998–1999, the development of analytical first¹³⁷ and second¹³⁸ derivatives of the energy with respect to nuclear coordinates opened new perspectives for applications in chemical reactivity and spectroscopy.

As mentioned above for Nancy, in the early years of the continuum model, several collaborations with Spanish groups contributed to its quick development. In the case of PCM, one can stress the collaborations with the University of Badajoz (F. Olivares del Valle, M. Aguilar) on molecular spectroscopy¹³⁹ and non-equilibrium phenomena,^{140,141} the University of Valencia (E. Silla, J.L. Pascual-Ahuir) on the development of the GEPOL algorithm to deal with molecular surfaces,^{142–145} and the University of Barcelona (J. Luque, M. Orozco), who developed a home version of PCM (known as MST) with several methodological innovations.^{146–150}

For further details on the PCM approach, the reader may consult the many reviews published in the past by the authors, in particular those of Tomasi in 2011¹⁵¹ and Mennucci in 2012.¹⁵² Another very detailed historical perspective of the model has been written by Tomasi and is available at the webpage of the *Dipartimento di Chimica e Chimica Industriale* of the University of Pisa.¹⁵³ Other general reviews on PCM and continuum models will be listed below, at the end of Section “Expansion of Continuum Models”.

Other continuum models

Some other approaches using continuum models were proposed in the 1980s and 1990s, such as those reported by Karelson et al.,¹⁵⁴ Mikkelsen et al.,¹⁵⁵ Karlström et al.,¹⁵⁶ van Duijnen et al.,¹⁵⁷ or Chipman.¹⁵⁸ But those developed by Cramer and Truhlar¹⁵⁹ and by Klamt¹³⁶ have occupied a special place in subsequent literature, and deserves special mention here.

The COSMO (conductor-like screening model) model of Klamt,¹³⁶ like PCM, uses apparent surface charges to calculate the reaction-field, though it uses a different technique to solve the electrostatic problem. The method first treats the solvent as it was a hypothetical conductor medium. In practice, this means that the dielectric

constant of the solvent is changed to infinity, which simplifies the electrostatic equations. Afterwards, an empirical correction is applied to the results to recover the dielectric behavior of the solvent under consideration. The recent extension of the model to COSMO-RS (COSMO for realistic solvation)^{160,161} relays on a statistical thermodynamics approach. It can be used to predict various thermodynamic properties of solvents and solvent mixtures at different temperatures and has become a widely used method within the chemical engineering community.

The philosophy of the solvation models proposed by Cramer and Truhlar in Minnesota differed significantly from the previous ones. In the different versions of the SMx approach (Solvation Model),^{159,162} the solvation free energies are obtained using a generalized Born (GB) approximation. In the GB approximation, the solute charge distribution is reduced to a series of partial atomic charges, and the interaction with the continuum takes the form of a generalized Born expression in which some parameters are introduced. The way of obtaining the atomic charges and the parameters depend on SMx version (see the original references). More recently,¹⁶³ the authors have developed a different implementation of the method called SMD, where the electrostatic contribution is computed in terms of the integral equation formalism. The D in the SMD acronym stands for density and stresses the fact that the full solute electron density is used, and not just partial atomic charges as in SMx models.

Continuum model final remarks

The simple continuum model is still widely used in the literature because it allows fast calculations of solvated species that are not much more expensive than the equivalent calculations for isolated systems. Over the past decades, different versions of the continuum model have provided invaluable insights into the effects of solute-solvent interactions on spectroscopy, chemical reactivity, and molecular properties in general. Each model has its advantages and drawbacks, and the choice is often a question of taste. Indeed, the electrostatic components of the solvation energy calculated through the self-consistent reaction field equations are similar when the different methods are used in a consistent way. This was shown for instance in Ref. 164 for the Nancy and PCM models, and in Ref. 165 for the Nancy, PCM (MST) and SM5 models. All models contemplate a way to obtain the non-electrostatic component, which includes the cavitation energy (the energy required to create an empty volume in the continuum), the solute-solvent dispersion-repulsion energy, and possibly other contributions not included in the preceding ones. Though there are differences between models, the non-electrostatic component is generally assigned a certain proportionality with surface area and parameterized to reproduce some reference data. The definition of the cavities (shape and volume) has also been a central question in this field, with assumptions going from regular surfaces to cavity surfaces based on the superposition of nuclear-centered spheres, solvent excluding or solvent accessible surfaces, isodensity or isopotential surfaces, etc. For the volume, early works^{80,166} used the proportionality existing between liquid densities and the van der Waals molecular volume (i.e. the volume enclosed by atomic spheres with Bondi radii), in consistency with Onsager's recipe. Later, optimized atomic radii were derived allowing to improve the agreement between experimental and theoretical solvation energies (see for instance^{167–169} and references cited therein).

The continuum model for describing solvated molecules with quantum chemical methods continue to be developed after half a century of history. Together with J.-L.Rivail,⁵⁸ I recently published a short article to celebrate its 50th anniversary. Years before, Tomasi had written a remarkable historical perspective¹⁷⁰ on the occasion of the 30th anniversary of the model⁶² and the congress I organized in Nancy for the official retirement of J.-L. Rivail (a satellite meeting of the 11th International Congress of Quantum Chemistry). To finish this section, let me cite some reviews which can be consulted by readers wishing to get further details on the mathematical formulation of the model and on its applications in different domains:

- Tomasi et al. (1994),¹⁷¹ (2005),¹⁶⁹ (2007),¹⁷² and (2011).¹⁵¹
- Cramer & Truhlar (1995),¹⁷³ (1999),¹⁷⁴ (2002)¹⁷⁵ and (2008).¹⁶²
- Mennucci (2010),¹⁷⁶ (2012).¹⁵²
- Ruiz-López (2008).¹²²

Beyond the continuum: moving towards microscopic models

The approximations inherent to continuum models are clearly too crude and, in many cases, a realistic modeling of the system is not possible without considering the microscopic structure of the solvent. Naturally, handling systems containing a very large number of molecules requires recourse to statistical mechanics. The combination of quantum chemistry methods with statistical mechanics simulations was an ambition that had long been in the air to study solvation phenomena, but it was not until the 1980s, with the increase of computer performances, that it became a reality in various forms. Rivail¹⁷⁷ used the expression “real molecules in model liquids” to refer to the quantum chemical continuum model, by contrast with classical models using statistical simulations with effective interaction potentials, referred to as “real liquids of model molecules”. Following the same terminology, models using statistical simulations coupled with a quantum chemical description of the full solute-solvent system could be described as “real molecules in real liquids”. These types of approaches will be presented in the next section, but the road to them will be paved by the development of several methods coined in parallel to the continuum model, which are outlined now.

The limitations of the supermolecule and the continuum were partially solved through the combination of the two approaches, that is by carrying out quantum chemical calculations for a solute-solvent cluster embedded in a dielectric continuum. The cluster contains the solute plus one or more solvation shells, and hence the possible role of specific solute-solvent interactions is explicitly treated. The continuum, on the other hand, allows taking into account the long-ranged electrostatic contribution from solvent effects beyond the explicit solvent shell(s), which is often a fundamental term. This intuitive scheme is known as the discrete-continuum model. It was used from the very beginning of the continuum model. Indeed, in the first paper by Rinaldi and Rivail in 1973,⁶² they already studied a supermolecular system, the water dimer. However, the first study using the discrete-continuum model in the form given by the definition above was reported by Claverie et al. in 1978.³⁴ The authors made a detailed comparison of the calculated solvated energies using the supermolecule (or discrete), the continuum, and the combined discrete-continuum solvation models for methanol and ammonium ions. A few years later, a similar model was used in Nancy to revisit the above mentioned problem, the irregular order of the basicity of amines.¹⁰⁸ The discrete-continuum model in the Nancy version was also used by Sánchez-Marcos et al.¹⁷⁸ to study the coordination of water around metallic cations in aqueous solutions.¹⁷⁸ The work was to anticipate a very fruitful avenue of research in Seville on the development of intermolecular potentials for statistical simulations of metal ions using the “hydrated ion” concept.¹⁷⁹ Among the large number of works using similar discrete-continuum combined models, let us mention a few pioneers. Aleman et al.¹⁸⁰ used the model of Pisa to study the solvent effect in aqueous solution on the activation barrier of the S_N2 reaction. Pappalardo and Sánchez-Marcos used the model of Nancy to analyze the influence of solvation on the isomeric equilibria of nitroenamines. The same model was used by Tuñón et al. to study the hydration of the proton¹⁸¹ and the hydroxide ion¹⁸² in aqueous solution. Similar approaches focused on diverse hydrated cations.^{183–185} The work by Pliego¹⁸⁵ established the basis for the calculation of thermodynamic properties with this model, which opened the door to the calculation of acid dissociation constants.^{186,187} Another important achievement was the work by Antonczak et al. in 1994⁹⁶ devoted to the mechanism of the formamide hydrolysis reaction, which to our knowledge was the first study of water-assisted reactions using a discrete-continuum approach. Many other key studies using the discrete-continuum model could be cited. But, despite its attractiveness, the model also showed important limitations concerning, in particular, the small number of explicit solvent molecules that can be efficiently handled in a single calculation.

At this point, we must return to the 1970s. A fundamental contribution in this decade came from Martin Karplus, Michael Levitt and Arieh Warshel, the 2013 Nobel Laureates in Chemistry. In 1972,¹⁸⁸ as part of the postdoctoral project of Arieh Warshel with Martin Karplus at Harvard, they published a method to calculate potential energy surfaces of large conjugated systems. The π electronic system was described by a semiempirical quantum chemical method while a σ bonding orbital representing the connection to the rest of the system was described through an empirical potential. The idea of combining Quantum Mechanics (QM) and Molecular Mechanics (MM) approaches was incipient in this work! It will be further explored and extended by Warshel with the

aim of studying enzymatic reactions. Thus, in 1976, now in collaboration with Levitt (sharing their time between the Weizmann Institute, Rehovot, Israel, and the Laboratory of Molecular Biology, Cambridge, England) they proposed a hybrid classical/quantum mechanical approach in which the atoms of the substrate involved in the reaction are described quantum mechanically, while the rest of the enzyme and the surrounding water solvent are treated classically.¹⁸⁹ The polarization (dielectric behavior) of the surroundings was accounted for by calculating the electrostatic field stemming from induced dipoles on the protein atoms and water molecules, the latter being represented by a grid of polarizable Langevin type dipoles. The model of course needed to be calibrated, using for instance some reference solvation free energies. The two articles mentioned in this paragraph are considered to be the foundational works of the hybrid QM/MM methodology which will be described in the next section.

In the following years, Warshel will report several improvements of the approach aimed at obtaining accurate solvation free energies for the study of chemical reactions in solution. Thus, the surface constrained soft sphere dipoles (SCSSD) model will be published in 1979,¹⁹⁰ and the more elaborated surface constraint all atom solvent (SCAAS) model¹⁹¹ a few years later, in 1985. The methods were broadly applied in connection with Warshel's Empirical Valence Bond (EVB) approach,^{192,193} in which a reacting system is described by a calibrated Hamiltonian in terms of diabatic states corresponding to classical valence bond structures (typically ionic and covalent resonance states). The strengths of this approach were demonstrated in numerous applications, as for instance in the study of S_N2 reactions in aqueous solution,¹⁹⁴ in which the importance of solvent fluctuations in driving the system toward the transition state was revealed. Later, the EVB approach will also be used in QM/MM simulations, as presented below. Additional material on the applications of the above mentioned methods and on other contributions of Warshel to solvation modeling can be found in Ref. 195, in his Nobel lecture,¹⁹⁶ and in the references cited therein.

Another innovative approach to calculate the free energy profile of chemical reactions in solution was the one developed by William Jorgensen and his group,^{197,198} which basically has three steps. First, the minimum energy reaction path for the process of interest in the gas phase is calculated using any quantum chemical method chosen. Then, for the series of structures along the reaction coordinate calculated in the previous step, suitable solute-solvent interaction potentials are defined in order to carry out statistical simulations. In principle, this can be done by fitting the potential to ab initio calculations on complexes containing the reactant system and solvent molecules in different configurations. However, in many cases, the problem is reduced to calculating the net charges on the atoms of the reactant system along the reaction path, taking other necessary parameters from a universal force field such as OPLS^{199–202} (solvent parameters and Lennard-Jones parameters for the reactant system). Finally, statistical simulations (usually Monte Carlo) are carried out to calculate the potential of mean force in solution. The use of techniques such as perturbation theory allows this objective to be achieved by obtaining solvation free energy differences between nearby structures. The method was used to study the S_N2 reaction,²⁰³ which was a process extensively investigated by theoreticians due to the remarkable solvation effect observed in experiments and the possibility of defining simple model systems (its variant, the Menshutkin reaction displays even more spectacular effects and became also popular thanks in particular to works by Bertrán and coworkers²⁰⁴). The approach of Jorgensen aimed at study general organic reactions and was applied to many different processes, such as the Diels-Alder²⁰⁵ and Claisen rearrangement²⁰⁶ reactions. The methodology revealed to be very useful to calculate free energy profiles in solution provided the reaction path in the gas phase does not differ much from the reaction path in solution, and the challenge was to know when this is really the case. Calculations with the continuum model, which were shown to produce solvation free energies similar to simulations using the free energy perturbation method,¹⁴⁶ offered the possibility to optimize transition structures and reaction pathways in solution, and thus to check the greater or lesser degree of variation with respect to gas-phase reaction pathways (see, e.g., Refs. 94, 117).

Meanwhile, classical Monte Carlo and Molecular Dynamics simulations were being widely used to calculate equilibrium and non-equilibrium properties in the liquid phase. The understanding of reaction dynamics received a great deal of attention in the 1970s and 1980s, and the availability of computer simulations was particularly attractive for testing new theories and analytical models. The work by James T. Hynes and coworkers on the theory of chemical reaction dynamics in solution²⁰⁷ occupies a prominent place in this context. The theory

of activated reactions known as Grote-Hynes theory (GHT) was published in two papers^{208,209} and the predictions of the theory were confirmed via molecular dynamics simulations for the S_N1 and S_N2 reactions,^{210–212} and others. An important finding in the simulations was that the transmission coefficients are typically not very far from 1, as assumed in Transition State Theory (TST), with values in the range 0.5–0.8 being usual in GHT. A note by Hynes in a recent personal perspective on the subject offers a reading of those findings: “*my interpretation was, and is, that these results show that TST is in fact an excellent rate constant theory for reactions with notable barriers and that GHT shows why this is so*”.²¹³ In addition to the S_N1 and S_N2 reactions, pioneer studies on reaction dynamics using simulations by Hynes and other authors were devoted to the study of fundamental processes such as ion pair association, electron and proton transfer, etc. (see for instance Refs. 210, 212, 214–223) and have strongly contributed to the understanding of chemical reaction dynamics in solution. The simulation techniques and applications up to 1993 were reviewed in the excellent book chapter written by Whitnell and Wilson.²²⁴

By the mid-1980s, much experience had been accumulated using continuum models, classical simulations and mixed quantum/classical partitions. Things were mature enough to take a step forward.

The success of models combining quantum chemical methods and statistical mechanics simulations

Ab initio molecular dynamics and related methods

In 1985, Roberto Car and Michele Parrinello working at SISSA (Trieste, Italy) reported an innovating method that will mark a milestone in the field of the theoretical study of complex systems.²²⁵ The Car-Parrinello (CP) method offered the possibility of combining a classical molecular dynamics of the nuclear motions with a full quantum chemical description of the electronic structure of the system using density functional theory. The method was applied to the study of crystalline silicon. In CP molecular dynamics simulations, the interactions in the system (forces on atoms) are computed on the fly from first principles using the Kohn–Sham formulation of DFT. The electronic orbitals are expanded in a plane-wave basis set and in contrast to standard DFT calculations, in the CP method, they are not obtained from a minimization procedure via a self-consistent field calculation. Instead, the electronic degrees of freedom are treated as fictitious classical variables, having a fictitious time-dependence and a parametric fictitious mass. The whole dynamics of the system (nuclei, electronic orbitals) is described by an extended Lagrangian operator. The orbitals are propagated from an initially fully minimized set. They are maintained at a fictitious temperature which is well below the real nuclear temperature but allows the orbitals to relax rapidly under the effect of nuclear movements. The CP approach bears similarities with the principles of the simulated annealing minimization technique published a couple of years before,²²⁶ as is clearly depicted in the review by Dominik Marx.²²⁷ Since the CP method accounts for the electronic structure of the whole system, global polarization effects are explicitly included, and of course, the method can describe chemical events such as the formation and breaking of chemical bonds. Computational resources required to carry out simulations of this type are, however, considerably large, and the simulations were initially limited to small systems (tens of atoms) and short times (a few ps). Although the CP method was developed assuming classical dynamics for the nuclei, and is generally used that way, it was extended to incorporate nuclear quantum effects via the Feynman path integral approach.^{228–230}

Early applications of the CP method were devoted to amorphous and liquid carbon and silicon, liquid metals, and semiconductors.²³¹ But the CP method will soon be applied by Parrinello and coworkers to the study of the structure and properties of liquid water and of water autoionization,^{232–238} in some cases including quantum effects.^{239–241} The study of liquid water with the CP method was an important breakthrough in the field of solvation and initiated new avenues in simulations of liquids and solutions (see the review by Sprik²⁴²), chemical reactions (see for instance Refs. 243–248), surfaces,^{249–253} systems of biochemical interest,^{254,255} etc. The study of reactions having a significant activation barrier (typically much greater than kT) by molecular dynamics simulations is confronted to the low probability of sampling the transitions state region within the time scale

explored in usual calculations. The CP method did not escape of course to this issue and *ad hoc* solutions based on biased simulations were proposed.^{256–258}

The development of the Car-Parrinello method incited the development of many other related approaches that include electronic structure calculations in molecular dynamics simulations. In the Born-Oppenheimer molecular dynamics approach, the DFT energy is fully minimized at each time step. In other words, the electronic structure is fully converged by solving the Kohn-Sham equations for each nuclear configuration along the simulation. The electronic structure still depends on time but its time-dependence is linked to the movements of the nuclei and is not intrinsic, as in the CP method. A method combining the advantages of the Car-Parrinello and Born-Oppenheimer molecular dynamics was proposed by Parrinello and coworkers aiming at accelerating the simulations.²⁵⁹ The choice of the basis set type has also generated considerable discussion. The use of plane waves in the original CP method had various advantages (orthogonality, independence of nuclei positions) and appeared as a natural choice for treating periodic systems. However, properties of chemical systems are usually local, and this prompted out different groups to explore simulations using other basis sets with localized functions, Gaussians^{260,261} and discrete variable representations^{262,263} were proposed, each choice presenting its own advantages and drawbacks.

Born-Oppenheimer and extended Lagrangian molecular dynamics methods are now grouped under the general name of *ab initio* molecular dynamics (AIMD). Furthermore, the basic principles of AIMD simulations are not limited to the use of DFT-based electronic structure methods and similar simulations can be done using other QM theories. References to numerous works using AIMD simulations at the density functional, Hartree-Fock, generalized valence bond, complete active space SCF (CASSCF), full configuration interaction, semiempirical, and other approximate QM levels until 2006 were collected in Ref. 227. More recently, simulations using the self-consistent charge density functional tight-binding method have attracted interest too.^{264–266} The term “direct molecular dynamics” (DMD) is increasingly being used to refer to all those simulations²⁶⁷ in which the time-independent Schrödinger equation is solved at each time step to calculate the forces on the nuclei. It is worth mentioning that the first DMD simulations at the semiempirical²⁶⁸ or *ab initio*²⁶⁹ levels of simple systems were carried more than 50 years ago.

For more details on the formalisms used and examples of the application of CP, AIMD and related methods, the reader is invited to consult the many general reviews available in the literature.^{231,242,262,270–277}

The rise of AIMD simulations and the growing interest in complex systems led to the appearance of several techniques for performing full QM calculations of systems of hundreds or thousands of atoms at an affordable computational cost. The combination of such techniques with statistical mechanics to perform DMD simulations has had a variable degree of success but for completeness, I will briefly mention some of them in this subsection.

Wesolowski and Warshel developed a frozen density functional approach^{278,279} for solute-solvent systems in which solvent molecules are represented by the nuclei and a frozen electron density. The eigenvalue problem is solved for the solute interacting with the frozen charge distribution of the solvent molecules. The interaction energy of the system is calculated in the DFT framework using the sum of the densities of the fragments, which in addition to the exchange-correlation functional, requires the use of a kinetic energy functional. Wesolowski, Weber and Chermette^{280–282} made a comparative study using several kinetic energy functionals. Besides, important efforts were made by different groups to develop linear-scaling algorithms, i. e. approximate quantum-mechanical techniques where the computational cost scales linearly with the increasing size of the system (instead of $\sim N^3$ scaling in DFT or semiempirical QM computations and even much higher in correlated *ab initio* computations). In the Divide and Conquer (D&C) method first developed by Yang,^{283–286} the molecular system is partitioned into subsystems for which the electronic problem is solved, and the electron density or density matrix of the whole system is then assembled appropriately. Merz and coworkers^{287,288} made important developments of the model, specially at the semiempirical level. They also developed a composite Hamiltonian where part of the system is described at the DFT level while the rest of the system is described at a lower level.²⁸⁹ Our study of liquid water is an example of application of the D&C approach in the field of solvation by Born-Oppenheimer semiempirical molecular dynamics.²⁹⁰

A similar philosophy to D&C was adopted by Gadre and coworkers^{291,292} in the Molecular Tailoring Approach (MTA), where the large system is divided also into small overlapping fragments and the *ab initio* energy of the

whole system is obtained from the energies of the fragments using the so-called inclusion-exclusion principle. The Fragment Molecular Orbital (FMO) approach of Kitaura, Komeiji and coworkers^{293–295} exploits the theory of molecular interactions and defines the total energy of the system as a sum of the fragment energies and intermolecular interaction energies. Finally, some methods make use of the transferability principle, such as the Lego method developed by Mezey,^{296,297} which uses a library of fragment density matrices, or the ELMO method of Genoni and coworkers^{298,299} which uses tail-free strictly localized molecular orbitals on small molecular subunits.

Combined QM/MM methods

Slightly after the emergence of the Car-Parrinello method, another cutting-edge approach for simulations of large systems based on hybrid quantum/classical potentials was going to emerge. The idea of coupling quantum mechanics and molecular mechanics (QM/MM) went back to the works of Levitt, Warshel and Karplus in the 1970s but papers by Singh and Kollman in 1986,³⁰⁰ and by Bash, Field and Karplus in 1987³⁰¹ made key steps forward. In another paper published in 1990 by Field, Bash and Karplus,³⁰² the use of such a hybrid potential in molecular dynamics simulations was extensively discussed and the approach now known as QM/MM was definitively established.

In the QM/MM approach, a large system is divided into two subsystems or regions: the chemically interesting subsystem is described quantum mechanically (QM), while its environment is described by a classical molecular mechanics (MM) force-field. In the case of a solution, which is our focus here, the solute will be typically chosen as the QM subsystem and the solvent as the MM subsystem. The two subsystems are allowed to interact through electrostatic and non-electrostatic terms. The non-electrostatic QM/MM term is calculated using a Lennard-Jones potential (or equivalent expression), as in classical simulations. The electrostatic QM/MM term takes into account the interaction of the classical charges in the MM subsystem with the nuclei and electrons in the QM subsystem. In the original papers of Karplus and coworkers, the authors used a semi-empirical approach. Since in these methods there is no precise definition of the electrostatic potential, QM/MM electrostatic interactions are not simply expressed by Coulombic formulae but require a special treatment. Several possibilities were explored, although the question raised a lot of discussion during several years (see for instance Refs. 303–306 and references therein). Whatever the approximation used, the part of the QM/MM interaction involving electronic coordinates is introduced into the Hamiltonian of the QM subsystem in the SCF procedure.

The QM/MM approach knew an immediate success. Tapia et al.³⁰⁷ developed a generalized reaction-field theory where the fluctuations of the solvent response were accounted for through QM/MM calculations, though they used solute-solvent configurations from classical simulations. The first QM/MM simulations were carried out at the semiempirical level, as in the original papers by Karplus and coworkers. In the early 1990s, Jiali Gao made fundamental contributions in this field using Monte Carlo simulations, in particular assessing the role of polarization effects^{308,309} and developing methods to calculate solvation free energies³¹⁰ and free energy surfaces of chemical reactions.³¹¹ Some other QM/MM semiempirical studies in the 1990s were reported by Vasilyev et al.,³¹² Bash et al.,³¹³ Bakowies and Thiel,^{305,314} Thompson,³¹⁵ Field,³¹⁶ Cummins and Gready,³¹⁷ and Li et al.³¹⁸ Simulations using the EVB methodology were also performed by Warshel and coworkers.^{195,319} The first DFT/MM simulations were carried out by Kenny Merz^{320–322} and by us^{323–327} and were quickly followed by studies of Freindorf and Gao,³²⁸ Lyne et al.,³²⁹ Amara et al.,³³⁰ among others. Wei and Salahub³³¹ proposed a kind of sequential scheme in which DFT/MM calculations were done on snapshots obtained in a classical simulation. Part of our DFT/MM molecular dynamics simulations were devoted to exploring reaction dynamics in solution. Simulating reactive trajectories at the DFT theoretical level was a major challenge being undertaken for the first time, and its realization required an enormous computational effort. Two different kinds of processes were studied. The first one was a proton transfer in a strongly hydrogen-bonded system in aqueous solution presenting a low activation barrier, so that reactive trajectories were spontaneously obtained during the simulations.³²⁶ The second one was the charge separation process in water occurring in the second step of ethylene bromination, a process displaying a significant activation barrier.³²⁷ Since in this case the process cannot be observed spontaneously at the time

scale of the simulations (tens of ps), we applied a “rare event” sampling technique.³³² It allowed us to obtain a set of reactive and non-reactive trajectories from which barrier recrossings and non-equilibrium solvent effects could be quantified, leading finally to the calculation of the overall transmission coefficient of the process.

There are some technical issues in QM/MM simulations (semi-empirical or ab initio) that have generated considerable debate in the literature. We will briefly comment on some of them. One concerns the non-electrostatic QM/MM interaction energy. Typically, a Lennard-Jones potential or similar is used to calculate its contribution, but the parameters for QM atoms are not defined *a priori* and, in principle, should be optimized for each application and QM level in use.³²⁸ In addition, the optimum parameters for QM atoms could change during the course of a chemical reaction and there is no reason to keep them constant throughout the process. A systematic technique to optimize Lennard-Jones parameters for QM/MM simulations was reported in Ref. 333. It should be noted that, in some cases, the use of parametric expressions for non-electrostatic QM/MM energy can also be seen as an advantage of the method over full ab initio MD simulations, where solute-solvent and solvent-solvent dispersion energy terms are very approximate at commonly used QM levels. Another issue is related to electronic polarization effects. It was noted³³⁴ that the interaction of point charges with a QM molecule can lead to non-physical distortions of the electronic cloud, and that this distortion tends to be worse as the basis set increases. At short distances, this can create artifacts in QM/MM simulations. A possible solution was proposed³³⁵ consisting of replacing the short-range repulsion term in the Lennard-Jones potential (or its equivalent) by pseudopotentials that include an explicit dependence on electronic coordinates. Another point of intense discussion was the treatment of the QM/MM frontier when the QM and MM subsystems are linked by a covalent bond. This is a key question for the study of enzymatic reactions, or the study of large molecules in general. Different solutions were proposed to deal with a QM/MM boundary. The simplest one was the use of a “link-atom” (typically a monovalent atom, H or halogen, a pseudoatom, etc.) to saturate the valency of the QM system.^{300,302} In the local-SCF (LSCF) method of Rivail and coworkers^{336,337} the frontier bond is a strictly localized bond obtained in a reference calculation, a concept extended by Gao, Field and coworkers^{338,339} through the generalized hybrid orbital (GHO) approach, in which the frontier orbital is a hybrid orbital calculated on the fly during simulations. Finally, though former QM/MM works did not include explicit polarization effects on the classical solvent partition, it is possible to do so by using either self-consistent of matrix inversion methods.^{315,340} The method known as Direct Reaction Field (DRF) developed by van Duijnen and co-workers^{341–343} is an elegant and general approach to deal with solvent polarization. Depending on how QM/MM methods take electrostatic interactions into account (or not), Bakowies and Thiel³¹⁴ made a classification into methods involving mechanical embedding, electrostatic embedding and polarized embedding, a definition that is still used today. It is not possible to provide here an exhaustive list of papers devoted to these and related issues, so the reader is referred to the various reviews on QM/MM methods presented below.

Despite the QM/MM partition represented a tremendous advancement for the theoretical study of chemical properties in solution, simulations remained quite expensive and different groups worked on algorithms to reduce the computational cost. Enhanced sampling techniques and free energy perturbation theory, for instance, appeared promising.^{344,345} From a different perspective, some authors developed QM/MM methods within the mean field approximation, also assumed in continuum models, which resulted in a drastic reduction of the number of quantum chemical calculations. In the mean field approximation, an average solvent potential is used to calculate the solute wavefunction, instead of calculating this potential and the wavefunction at each time step along the simulation, then making appropriate averages. In the RISM-SCF model (RISM³⁴⁶ stands for reference interaction site method) developed by Hirata, Kato, and coworkers^{347–350} the average solvent structure was obtained by using an integral equation method for atomic charges of the solute coming from quantum chemical calculations with a modified Hamiltonian. Instead, in the average solvent electrostatic potential (ASEP) approach developed by Aguilar, Olivares del Valle and coworkers,^{351–353} the average solvent potential acting on the solute is obtained from classical molecular dynamics simulations. The ASEP method is iterative. In the simulations, the solute is represented by a set of atomic charges obtained in the QM calculation of the previous iteration (plus a suitable set of Lennard-Jones parameters). From the simulation, the average solvent electrostatic potential acting on the solute is calculated and introduced into the solute QM Hamiltonian to calculate a new wavefunction and a new set of charges. The ASEP can also be replaced by an average solvent electrostatic configuration (ASEC), and

this possibility has successfully been explored by the group of Canuto and Coutinho.^{354,355} Both ASEP and ASEC can efficiently be used to study reaction mechanisms and spectroscopic properties in solution^{356,357} in connection with the free energy gradient (FEG) theory developed by Nagaoka and coworkers,^{358–360} which allows to calculate first and second derivatives of the free energy of a solvated system within a QM/MM scheme. By means of free energy perturbation theory, in addition, the calculation of such derivatives can be done at very high ab initio levels.^{361,362}

Of course, the QM/MM approach has also been used in combination with other solvation models. A multilayer QM/MM/continuum approach was explored using either multipole expansions³⁶³ or apparent surface charge³⁶⁴ alternatives for describing the reaction field. The idea is similar to that developed in the discrete-continuum model presented at the beginning of this section, but in this case solvent molecules are described with a classical force-field.

A combination of QM/MM and CP methods was first proposed by Ziegler and coworkers to study transition metal catalysis with isolated systems³⁶⁵ but also model solvated systems,³⁶⁶ and by Eichinger et al.³⁶⁷ The approach has extensively been developed and used by Ursula Rothlisberger and coworkers to study a variety of chemical and biochemical problems.^{368–374}

Before closing this section, it is worth mentioning the innovative family of methods developed by Keiji Morokuma and coworkers^{375–381} which eventually led to an approach known presently as the ONIOM method (for our own *n*-layered integrated molecular orbital and molecular mechanics).^{378,382} In ONIOM, the molecular system is divided into two or three layers which are described using theoretical levels of different complexity, by either quantum mechanics or molecular mechanics. The energy of the system is obtained by the combination of calculations with the different methods and layers, and may include or not electrostatic embedding. Though in principle it can be used to simulate systems in solution,^{383–387} the method is principally oriented towards the treatment of very large molecular systems in organic chemistry or biochemistry.

For additional details on the QM/MM approach, many reviews^{340,388–393} are available and can be consulted by the reader.

Concluding remarks and perspectives

During the past 50 years, the development of various quantum chemical models has allowed to do an immense progress on the understanding of solvation phenomena. The wide variety of solvation models that are routinely used today to study the spectroscopy of molecules and the dynamics of reactions in solution have different levels of elaboration, so they can be chosen according to the degree of accuracy required and the computational resources available. For the sake of conciseness, this brief historical perspective has focused on the main steps that led to the models most commonly used today, although, of course, there have been many other interesting contributions that could be mentioned. For example, the development of reactive force-fields is a very useful tool for the simulation of chemical reactions in solution.^{394–396}

However, despite enormous theoretical advances in the field of solvation phenomena, there are important challenges ahead. On one hand, the study of some complex processes requires a change of scale, from the typical molecular scale (nm, ns) of present models, to the mesoscale (μm, ms), or even the macroscale. Examples of such complex processes are the reactions occurring at surfaces or interfaces, as in heterogeneous catalysis³⁹⁷ or water microdroplets,³⁹⁸ where various difficult reactions have been shown to proceed spontaneously.^{399,400} On the other hand, the need of the chemical industry to move to greener synthetic reactions by reducing the use of organic solvents is promoting the development of non-conventional solvents such as ionic liquids, deep eutectic solvents, or supercritical fluids.^{401,402} Solvation and chemical reactivity in these media are still poorly understood and much progress need to be done. Some examples are discussed in Refs. 403–409.

Like many other fields of science and technology, computer simulation of chemical processes in solution has recently benefited from the rapid expansion of artificial intelligence. Machine learning techniques, and deep learning based on neural networks, in particular, have been used to improve the efficiency (computing time, accuracy, functionality) of ab initio molecular dynamics, QM/MM methods, reactive force-fields, etc. The reader can already consult several reviews on this subject.^{410–416} Likewise, the emerging field of quantum computing

offers very interesting perspectives for the future of quantum chemistry in general,^{417–419} and some preliminary studies using the variational quantum eigensolver algorithm⁴²⁰ have been done for solvated molecules using the PCM model,⁴²¹ and for very simple systems using ab initio molecular dynamics simulations.⁴²²

We are undoubtedly on the threshold of a new era of computational chemistry, and it is likely that the advancement of techniques and computers in the next 10–20 years will mark a qualitative leap in the way of thinking and working in molecular modeling. This formidable evolution should help theoretical chemists solve complex problems that cannot be addressed today and contribute to tackling the major challenges that chemistry will be facing in the transition to a post-fossil fuel world. The history of the quantum chemistry of molecules in solution is certainly not over yet.

Dedication

This perspective article is dedicated to Professors Juan Bertrán, Antonio Oliva and Jean-Louis Rivail, as well as to the memory of Dr. Daniel Rinaldi, who were pioneers in the field of solvation and who taught me the essentials. It is also dedicated to the long list of doctoral students and postdoctoral researchers with whom I have had the privilege of working on the subject throughout my career.

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