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Thirty years of continuum solvation chemistry: a review, and prospects for the near future

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Abstract. With the recent occurrence of the 30th anniversary of the first quantum mechanical continuum solvent code (Rinaldi D, Rivail J-L (1973) Theor Chim Acta 32:57), it seems like an appropriate moment to briefly review the variety of continuum QM models now available. This paper begins with such an overview, before shifting the discussion to a critical examination of some aspects of the basic theory, taking as the definition and evaluation of the solvation energy as an example. Advantages and disadvantages of using continuum-discrete models are examined, with particular attention paid to the evaluation of the solute's response properties. Some guidelines, and an operative definition of specific solute-solvent interactions, are presented.Then the paper moves on to examine problems regarding solutes of very large size, as well as complex systems. An example of the latter is the surface enhancing properties of large metal cluster aggregates with respect to the optical properties of a chromophore in a liquid medium.The paper ends with some extrapolations to the near future, mostly based on the material presented in the preceding sections.

Keywords: Self-consistent reaction field – Polarizable continuum model – Dispersion energy in solution – Response properties in solution – Combined continuum-discrete models

The birth of continuum quantum mechanical descriptions of solvent effects

The title chosen for this contribution to the international conference held in Nancy stresses the desire to commemorate an important anniversary in the evolution of the quantum mechanical description of molecular systems: the birth of the continuum quantum description of solvent effects.

Continuum quantum models represent an extension of the classical and semiclassical models developed in the past (outstanding examples are the models of Born [1], Kirkwood [2], and Onsager [3]) to describe some fundamental properties of solutions. The continuum quantum models, like the classical and semiclassical models, are based on the description of the liquid medium as a dielectric unstructured fluid, but they add to it a detailed quantum mechanical description of the solute.

Nancy is an appropriate place for this commemoration, since it is the place where Jean-Louis Rivail performed the first quantum-mechanical calculations on molecules that included continuum solvent effects [4], proposed the first QM continuum solvation codes [5], and where he consequently developed one of the most important schools of quantum chemistry, at which the study of solvent effects play a very important role. The two papers I have cited represent the cornerstone of the large and systematic work produced over the years by the Nancy school on this subject.

However, the initiative shown by Rivail, with the help of his trusted coworker D. Rinaldi, of addressing solvation problems using quantum mechanical tools, was not entirely from "out of the blue". It was, on the contrary, a personal response to the challenges stimulated by a limited number of scientists from the preceding generation, working in France and in Italy, with strong ties and close contact, in competition and also collaboration with each other, and all having selected the new-born discipline of quantum chemistry as the main subject of their studies. Pullman and Daudel in Paris, Scrocco in Pisa, to mention just the leading lights, shared the same view about the role quantum chemistry should have in the context of chemistry as a whole. Let me stress this point: quantum chemistry addressing real chemical problems. The scientists I have just mentioned

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also shared the positive characteristics of being open to new ideas and of giving a plenty of freedom to younger coworkers to express and to elaborate personal ideas. Their work led to numerous important results in various fields. To quote a few: ab initio codes for polyatomic molecules; semiempirical codes for large molecules; the interpretation and dissection of molecular interactions; the first ab initio descriptions of reaction mechanisms; several methods for exploring solvent interactions.

Consideration of the solvent was of course compulsory during the conception of quantum chemistry, cultivated in our Franco-Italian community. There is no real chemistry without solvent. The choice of continuum models was also almost compulsory because of the limited computer facilities available in our community. Continuum solvation codes were originally developed in Nancy, Paris and Pisa. I have already mentioned Rivail, and to his name I now add others (summarized in Table 1). These codes were originally developed by a few small groups, each comprising three persons or less on average, each of which came up with different solutions to the same problem. The solutions reflect the personal experience of the elder researcher.

In his first papers, Rivail focused on the electric properties of molecules, dipole moments and polarizability, reflecting the interests aroused by his collaboration with Barriol, an eminent spectroscopist, who shared with the other leading lights I mentioned an appreciation of the potential of quantum chemistry, and understood the importance of giving freedom of research to valid young coworkers.

Claverie began with the formal analysis of noncovalent interactions, and he did excellent work in this field, which still constitutes the basis of the theoretical framework for this important part of chemistry. The first solvation topic he considered was related to dispersion interactions [6], an aspect of solvation not fully developed in the models of the first half of the previous century. To do this, at first he paid less attention to the development of combined QM solvation codes in which the electrostatic part, mostly related to the charges and local moments of the solute, plays the main role. Only in later years, after a systematic analysis, did he develop his ideas into a full QM procedure for treating solvent effects, in which continuum and discrete representations of the solvent are combined [7].

Tapia [8] took advantage of the experience gained from working at the laboratory of Professor Daudel, and developed a proposal based on the Onsager model [3]. I remember Orlando Tapia's satisfaction when he announced to me in Paris that he had just obtained good results with a continuum solvation code (he also offered me dinner, a rare event!). The paper was published a short time after, in a very elegant form, from Uppsala where Tapia had moved to. The intervention of Goscinski in this paper indicates the interest of other European groups in continuum solvation models.

Table 1. The first continuum QM solvation codes (from the French-Italian group)

Name	Place, time	Reference
Rivail	Nancy 1973–76	4,5
Claverie	Paris (1972) 1988	6,7
Tapia	Paris–Uppsala 1975	8
Tomasi	Pisa 1981	9

The version developed in Pisa [9] was a product of our studies on non-covalent interactions, performed in a different way to those done by Claverie, and based on the examination of the full QM description of dimers and larger molecular aggregates. This approach was permitted by the availability in Pisa of ab initio codes for molecular calculations, the first in Europe and among the first in the world. These analyses led to a rationale of intermolecular forces based on a Hartree partition of the cluster, followed by a description of the quantum localized molecular subunits interacting according to classical interactions, to which only small quantum corrections were necessary [10]. The prominent role played by the molecular electrostatic potential [11] in such analyses paved the way to the formulation of an ab initio QM continuum solvation code [12].

I have quoted here four different approaches produced within a restricted number of groups with strong ties but able to formulate independent solutions to a common problem, that of introducing quantum chemistry into the realm of solutions. The approaches are different, as I have remarked, and it would be a good idea to characterize them better here. However, before doing so, it is convenient to continue a bit more on the history of continuum solvation methods.

In the following years other methods were created, almost all in Europe, with a notable exception. I have a strong feeling that the interesting (or good) performances given by some of the first generation codes I have mentioned previously spurred on, and gave hints to, other researchers to develop new codes.

I have listed a few examples of the different proposals formulated in the ten years from 1983–1993 in Table 2. These examples are selected for the importance they have had to the evolution of this field, or because they represent other methodological alternatives to the basic problem. I quote only the first paper for each author.

In the following ten years (1993–2003), several other QM methods were published, and at present every computational package of molecular calculations has quantum mechanical continuum solvation codes, more

Table 2. Other continuum solvation codes from the period 1983–1993

Name	Place, time	Reference
Karelson	Estonia (USA) 1986	13
Mikkelsen	Denmark 1987	14
Karlström	Sweden 1988	15
Cramer	USA	16
van Duijnen	Netherlands	17
Klamt	Germany	18

or less complete and more or less flexible, according to the package.

I have not reported continuum solvation methods based on a classical description of the solute in Table 2, although some among them have gained a remarkable popularity, especially in the study of complex biological molecules. These approaches represent an alternative approach to introducing solvation effects into computational chemistry, but they lack the flexibility for treating chemical problems of very different nature, an aspect that constitutes the main subject of the present analysis. There is one good reason, however, to mention them. The most popular codes belonging to this family, often called Poisson-Boltzmann codes, use another approach for describing the electrostatics of solute-solvent interaction effects, of which there are no examples in the two tables I have mentioned. We shall comment later these approaches.

Classifying QM continuum solvation codes

We now have enough examples of continuum solvation methods to attempt a classification according to some key features.

Three of the four initial codes of Table 1 were based on semiempirical descriptions of the solute (the only exception is the code of Pisa); the same remarks hold for the initial versions of most codes of Table 2. This is not a characterizing feature, however. In the 1970s the ab initio codes were extremely expensive and not commonly used; of these, the methods which have evolved further became more sophisticated ab initio descriptions of the molecule, beyond the Hartree-Fock level. Among the first of these are those of Nancy and Pisa, which continue to be the most complete codes at present. Among those reported in Table 2, the codes of Mikkelsen use of a high quality description of the solute and of its property; the codes of van Duijnen, Klamt, and Cramer use use ab initio descriptions of good quality. The other codes have been abandoned or purposely kept at a low level for specific reasons. It must be remarked that the most flexible codes, and we quote again the SCRF code of Nancy and the PCM code of Pisa, to which we shall later restrict our attention, have the ability to treat the solute at almost all of the ab initio levels now available in quantum chemistry, as well as with solutes described with the aid of semiempirical wavefunctions, and with descriptions based on empirical fragment potentials, with or without polarization. The continuum approach is very flexible and does not place limits on the quality of the solute description.

Electrostatic interactions

A characterizing feature of QM continuum models is the way in which the electrostatic interaction term is treated; namely how the solute charge distribution is used to define the molecular potential giving rise to the solvent reaction potential, and how the solvent reaction potential is described. Here we may make reference to the three classical models quoted as references [1, 2, 3].

The first formulation given by Rivail corresponds to the Onsager model [3]: the potential is originated by the molecular dipole, and the reaction potential is described in a corresponding way. The same model has been used by Tapia, by Karelson, and by others.

The second paper of Rivail extends the description. The molecular potential is described in terms of a multipole charge distribution. It may be assimilated to the Kirkwood model [2], which however lacks the essential feature of the back polarization of the solute under the effect of the solvent reaction potential, a feature introduced by Rivail in his method. This feature is rightly emphasized by the acronym assigned to the Nancy model, SCRF, which means self-consistent reaction field. Mikkelsen's model also belongs to the SCRF family. More recent versions of Karelson's model (used mostly in collaboration with M. Zerner) adopt a multipole expansion and are of SCRF nature.

Rivail's model has further evolved since then. It is available for use with distributed multipole expansions (with multipole expansions centered in different points of the molecule and regarding separate portions of the charge distribution). This extension eliminates a drawback of single-center multipole expansions, which are valid, at the limit of complete expansion, only for points in the space lying outside a sphere containing all of the charge distribution. The distributed expansions extend the use of the method to molecules with an irregular shape, for which part of the solvent lies inside the unique sphere containing all of the charge distribution of the solute.

Claverie explored several versions, but the final version [7] uses multipoles (dipoles and quadrupoles) distributed on atoms and bonds.

The Karlström method [15] has been included in Table 2 because it represents the only ab initio code that makes use of image charges to assess the reaction potential. To this end the molecular distribution is reduced to a set of local multipole distributions (generally interrupted at the dipole level). The image method is amply used in electrostatics, and can also be applied to charge distributions inside a sphere (Friedman [20]). However, in this case it is an approximate method, and for this reason it is not well-suited for refined ab initio calculations.

Cramer's code [16] (actually Cramer and Truhlar; I have used a single name for brevity in the tables) is a generalized version of the Born [1] model (GB), and so the molecular charge distribution is reduced to a set of atomic charges. The generalization of the Born model to polyatomic molecules (there are other more recent versions of the GB model, all sharing this characteristic) requires a modification of the Coulomb interaction operator because the Born atomic spheres are interlocking. The Coulomb operator modified in this way contains some parameters that give a semiempirical flavor to the GB methods.

Van Duijnen's approach to solvation [17] (of which there are different versions) uses continuum descriptions of the solvent as supplementary corrections to an original direct reaction field model based on discrete subunits. The origins of this code date back to models used to describe molecular polarizabilities, with applications to solvation problems using discrete molecules only [21].

Pisa's codes [9], which will be indicated in the following with the acronym PCM (polarizable continuum model) use another version of the classical electrostatic description not considered in the three classical models. This version is based on the definition of an apparent charge distribution (ASC) on the cavity surface. This surface charge is given directly by the normal component of the electric field generated by the molecular charge distribution $\rho(M)$. The molecular wavefunction is therefore used directly, without reduction to atomic charges or to multipole expansions. In a more recent version, called IEF-PCM [22] (IEF stands for integral equation formalism), the molecular electric field on the surface is replaced by the electrostatic potential. This formulation, not present in electrostatic handbooks, is formally completely equivalent to the standard definition of apparent surface charges, but computationally is faster and more stable (for example in the calculation of derivatives).

Klamt's codes [18] also use apparent surface charges, computed with the molecular potential, but using an original trick: performing the calculations for a hypothetical liquid metal and then applying an empirical correction to the results (the alternative formally correct formulation given by IEF was not yet known at that time). This correction works well for liquid with a high dielectric constant and it is not appreciably sensitive to the analytical form one adopts (there are several versions of it, given by other authors).

As remarked above, I have not reported on semiempirical Poisson-Boltzmann codes, of which there are now also QM versions, in Tables 1 and 2. They are to be considered here, however, because they complete the set of methods used to describe electrostatic solvation effects. These P-B methods are also called finite difference or finite elements methods (FDM or FEM, according to the technical details used in solving the integro-differential equation) because they are based on the definition of a 3-D grid covering the whole space filled by the continuum solvent. The mesh of the grid may be refined in terms of the proximity of the solute in order to reach better accuracy, but these methods are in principle more computationally intensive and less accurate that the boundary element methods (BEM or ASC), at least for isotropic solutions. Grid-based methods are also used in other approaches to introduce some discreteness into the description of the solvent, putting, for example, polarizable point dipoles at the grid points.

To conclude this section, we remark that both the methods based on complete distributed multipole descriptions and those based on the apparent surface charge distributions give formally exact descriptions of the electrostatic problem one has to solve in continuum solvation problems. 3-D grid methods also tend to exact calculations. The same cannot be said for the image and the GB methods, which have inherent approximations.

The shape of the cavity

A second feature useful for characterizing methods is the shape adopted for the cavity in the continuum medium in which the molecule is contained. The concept of solute cavity is essential in all continuum methods, and its sharpness represents one of the points often invoked in criticisms of the continuum methods. It should be said that sharpness is not a big problem, as shown in the past on model systems, and quite recently demonstrated by non-sharp ab initio codes (such recent developments will not presented here, however). What is more important is the shape of the cavity. The classical models [1, 2, 3] all used a simple cavity in which the surface is given by a fixed value of one of the coordinates of the reference frame; for example the sphere in polar coordinates. This definition greatly simplifies the mathematical formulation of the electrostatic model when multipolar expansions are used, but the description of the reaction field may turn out to be severely distorted for molecules far from a spherical shape.

The cavity shapes adopted by Claverie in his attempts, and by PCM, were interlocking van der Waals spheres at first, and in later versions were original codes defining both solvent accessible and solvent excluding surfaces (SES and SAS)[23]. The other models of Table 1 adopted spherical cavities.

Rivail quickly extended the SCRF method to cavities with an ellipsoidal shape [24] (the implementation of this code was a big mathematical achievement) and then also provided codes for cavities of irregular shape.

Among the methods listed in Table 2 are codes, like that of Mikkelsen, that have been extensively used in recent years, and that still use a sphere for the cavity, but the general trend is to move to molecularly shaped cavities, This is routinely done, for example, in Cramer's and other GB methods, in Klamt's method (it is not a big problem for ASC methods to adopt whatever cavity one wishes to use, and GB methods are almost compelled to use a set of atomic spheres giving a cavity with a shape similar to that of the molecule).

Before moving on, let me stress again that the shape of the cavity is an important parameter.

Non-electrostatic interactions

It has been well known for a long time that solvation effects are not limited to electrostatic terms. In fact, Claverie started with a description of dispersion terms, and Rivail included dispersion effects, even in his first paper [4], represented on the basis of the dipole approximation elaborated by Linder [25]. The other methods reported in Table 2 were limited to the electrostatic terms. PCM, originally presented as a pure electrostatic method, was given a complete description of the whole machinery of the solvation process, including dispersion,in the same year [26].

An additional term, that is treated separately in continuum methods, takes into account the energy spent forming the cavity (in which the QM solute will be later defined) in the liquid. The calculation of the cavity formation energy is a theme on which there have been proposals since the early 1930s [27]. However, we shall not discuss them here, and we simply state that the best codes have reasonable methods to compute this term too.

Other methods, for example GB, introduce corrections to the electrostatic description in the form of an empirical function, which has the surface of the cavity as an argument, and addresses the descriptions of dispersion, repulsion, cavity formation, and other terms of local origin. The empirical nature of this expression allows us to include energy contributions of disparate physical origin in a simple formula, but also forbids us to make improvements to some of these terms, that may play a very different role in different material systems and in different phenomena.

We shall consider the various contributions to the solute-solvent interaction potential, and to the solvation energy again in the next sections, because they are still open to improvements.

Other features of the continuum methods

There are many other features of the codes that can be used as parameters to characterize methods, and the presence or absence of some features should be the criterion a user adopts when selecting the code most appropriate for the investigation he is planning. The number of these features is currently quite large (solvation codes have progressed tremendously over the last thirty years) and it is not possible to give a comprehensive overview here. Therefore, we briefly quote a few of them, just to give an idea of the potential of several solvation codes: the availability of analytical codes for first and second derivatives with respect to nuclear coordinates; the capability of describing two or more solutes separated by the solvent; the description of non-equilibrium situations; the quality of the descriptions of excited states and of their photophysical evolution; the description of the solute's properties expressed as response functions with respect to external fields of electric and/or magnetic nature; the ability of codes to describe solvation effects for solutes of very large size. Many other questions can be posed by a potential user with a reasonable hope of finding the desired answer, because the most important codes grow rapidly, adding more and more features. Since we cannot give potential users all of information they need to select the most appropriate code here, our advice is to start the analysis from PCM and SCRF, which are the most complete codes, and if the results are not satisfactory, move on to others.

Review of QM continuum solvation methods

As mentioned several times over the preceding pages, there has been a rapid evolution in QM continuum solvation codes in the last thirty years. However, we do not have the space to survey this evolution in any real depth here, even if we limited ourselves to the two main codes I have mentioned, SCRF and PCM. There are two long reviews in Chemical Review that partly document the evolution of continuum solvation methods. In the first, published in 1994 [27], there is a detailed description of the historical evolution until 1993; in the second [28] there is a update of this review to cover 1998–1999, paying particular attention to the large number of ways the various methods have been used, and complementing several reviews written by the same authors in preceding years.

In 1995, Rivail wrote a short review [29] in which some space was dedicated to the important methodological innovations that were being implemented into SCRF at that moment. At the Conference in Nancy, a poster by M. F. Ruiz-Lopez and W. Harb was presented that reviewed the SCRF code, including the most recent additions [30]. I hope that the readers will find an enlarged version of this poster in the Conference papers.

On our part, since 1994 we have written a sizeable number of papers and contributions to handbooks related to various aspects of the QM description of liquid systems. Among them, I have selected three overviews that are rich in detail about PCM [31, 32, 33]. The latter is a short history of the evolution of PCM, that should have been regularly updated on our site but unfortunately has not been for the last two to three years, and is currently without a direct link to citations (an update will be probably be performed in the next future). I am not aware of any more recent detailed reviews. Surely the recent advances merit a new review of what has been done, to give more advice to users and to suggest what could be done in the near future.

Having therefore presented some general features of continuum QM solvation models, we now move on to consider some specific aspects of the models that require more detailed examination. Following this, we will discuss more advanced extensions to these procedures. These extensions form the basis of a possible answer to the question suggested by the title of this review: what are the prospects for the near future?

For brevity's sake, our detailed examination will be limited to a few points (other aspects would require an analogous analysis), and I will base my analysis on PCM, using notations and concepts we have used for PCM. It must be said that a similar analysis could have been formulated using SCRF notations and concepts, but the choice I have made obviously simplifies my task, being more confident with PCM notations, and with the form in which common problems are cast in the PCM codes.

Energy in continuum QM solvation methods

It is convenient to start this analysis from the basic energetic quantity for all solvation codes. The basic energetic quantity in ab initio continuum methods is easy to define. It corresponds to the work spent in assembling the appropriate numbers of electrons and nuclei necessary to build up the molecule of interest into an opportune cavity of the homogeneous liquid. During this process of formation, there is also some work spent to polarize the liquid. This quantity has the status of a free energy, and will be called $G(R)$ here. The symbol R indicates that we are working within the Born-Oppenheimer (BO) approximation and that the molecule (the solute) has a fixed geometry R.

This definition parallels that for the energy of the molecule in vacuo: $E(R)$. In this case too the energy is the work spent in assembling the molecule from non-interacting electrons and nuclei.

However, behind this analogy some important differences are hidden. $E(R)$ is the work spent at 0 K, and at this temperature energy and free energy coincide in the BO approximation. In contrast, $G(R)$ is computed with an effective potential, depending on the response function $Q(r,s)$ of the medium, and this function depends on temperature. In the simplest versions of the continuum model, $Q(r,s)$ is reduced to the electrostatic response, expressed in terms of the dielectric constant of the medium, ϵ, and the dependency on the solvent coordinates s is reduced to a step function, zero inside the cavity, constant at the exterior. Even in this simple case there is a well-defined dependence on the temperature, because the dielectric function ϵ depends on T.

To directly compare E with G – for example to compute the solvation energy – one has to make the two expressions have quantities with the same thermodynamic status. The most reasonable thing to do is to link both expressions to get the full free energy of the two systems at the same given temperature T.

For the system in vacuo, one has to add contributions due to the internal motions of nuclei and due to the rotation of the whole molecule (translations are eliminated by adopting Bein Naim's analysis of the solvation process [34])

$$G^{T}_{\mathrm{vac}}(R) = E^{0}_{\mathrm{vac}}(r) + G^{T,\mathrm{vac}}_{\mathrm{vib,rot}} \tag{1}$$

The same must be done for the system in solution:

$$G^{T}_{\mathrm{sol}}(R) = G_{\mathrm{sol}}(R) + G^{T,\mathrm{sol}}_{\mathrm{vib,rot}} \tag{2}$$

It is not necessary to examine the details of the calculations of these additional entropic calculations here. It is sufficient to remark that for the system in solution we need at least the Hessian matrix elements (in other words a knowledge of the second derivatives of the energy with respect to the nuclear coordinates) to compute vibrational contributions (in the harmonic approximation), and that the rotational term presents some problems, since the continuum model alone is incapable of giving an estimate for this contribution. This is the first open problem we encounter. There are models and approximate formulas to compute this term, but a physically more robust approach is desirable.

The solvation energy is given as the difference in the two quantities reported above. There is however another problem, due to the fact that the equilibrium geometry of the molecule M is, in general, different in the two phases:

$$\Delta G^{T}_{\mathrm{solv}} = G^{T}_{\mathrm{sol}}(R^{\mathrm{sol}}_{\mathrm{eq}}) - G^{T}_{\mathrm{vac}}(R^{\mathrm{vac}}_{\mathrm{eq}}) \tag{3}$$

Both $E^{0}_{\mathrm{vac}}(R)$ and $G_{\mathrm{sol}}(R)$ define a potential energy hypersurface for the motion of nuclei. Doubts about the formal status of the second hypersurface have been raised for several years.

The search for the minimum in vacuo proceeds using the standard methods of quantum mechanics, and the same methods should be applied for the second hypersurface. Note however that in practice this is rarely done. To explain why, and to introduce other aspects of the method that deserve reconsideration, we recall that $G_{\mathrm{sol}}(R)$ is composed of several terms that are never obtained from the same calculation:

$$G_{\mathrm{sol}} = G_{\mathrm{el}} + G_{\mathrm{dis}} + G_{\mathrm{rep}} + G_{\mathrm{cav}} \tag{4}$$

This expression gives the partition in use in PCM, in which all terms have well-defined physical meanings. Other codes, as remarked above, collect the three non-electrostatic terms into a unique term, empirically computed.

Geometry optimizations are often performed using the G_{el} term alone; in other words only the electrostatic part of the continuum model (some codes in circulation only have this component). Should we consider this practice acceptable?

Actually, the three additional terms are far from being negligible. In Tables 3 and 4 we report some data taken from an old paper [35] (with some minor changes) that allows us to get a feel for the relative importance of the various contributions, and how they depend on the chemical nature of the system.

To make this comparison more apparent, the quantities reported in the two tables are actually the components of the free energy of solvation (computed at a fixed geometry of the solute):

$$\begin{aligned} \Delta G^{T}_{\mathrm{solv}} &= G^{T}_{\mathrm{sol}}(R^{\mathrm{sol}}_{\mathrm{eq}}) - G^{T}_{\mathrm{vac}}(R^{\mathrm{vac}}_{\mathrm{eq}}) \\ &= \Delta G_{\mathrm{el}} + G_{\mathrm{dis}} + G_{\mathrm{rep}} + G_{\mathrm{cav}} + \Delta G^{T}_{\mathrm{vib,rot}} \end{aligned} \tag{5}$$

In fact G_{el} is a quite large number when compared to the other components of G_{sol}; this large value is mostly due to the work done in forming the molecular charge distribution inside the liquid, which is not too different from the analogous work spent in vacuo. So the difference between these two values (ΔG_{el}) is more instructive for this comparison. To simplify comparisons we have eliminated the last term of Eq. 5, not directly related to the definition of the free energy hypersurface, from the tables.

Table 3 shows that non-electrostatic terms in water cancel each other out to a large extent. However, the compensation is far from being complete, and in fact an evaluation of the solvation energy solely based on the electrostatic term produces considerable errors, as we can see by comparing the ΔG_{el} and ΔG_{tot} rows. It is true to say, however, that the electrostatic terms dominate the interaction energy. This fact, accompanied by the assumption that the non-electrostatic components are less sensitive than ΔG_{el} to small changes in the geometry, represents the empirical justification for limiting the geometry search to the electrostatic component alone.

This justification is no more valid for non-polar solutes, as Table 4 shows. The dominant term is the dispersion contribution, and so the justification for using the electrostatic component alone is solely based on the assumption of the larger sensitivity of electrostatic terms to changes in the molecular geometry.

We do not present data about this assumption for two reasons. The first is that the numerical data we have available are rather sparse and none too meaningful; the second is that accurate calculations of the dispersion energy contributions are quite rare.

Table 3. Some examples of the relative magnitudes of various components of ΔG_{solv}. Solvent is water. Values in kcal/mol

Solute	ΔG_{el}	G_{rep}	G_{dis}	G_{cav}	ΔG_{tot}	ΔG_{exp}
H_2O	−7.2	+1.7	−4.6	+4.2	−6.0	−6.3
NH_3	−5.3	+2.3	−5.7	+4.6	−4.2	−4.3
H_2O_2	−9.0	+1.9	−6.7	+5.6	−8.3	−8.7
N_2	−0.2	+0.7	−3.9	+5.4	+2.0	+2.3
CH_4	−0.2	+2.0	−6.0	+6.0	+1.8	+2.0
CO	−0.8	+0.7	−4.0	+5.5	+1.4	+2.2
H_2CO	−5.7	+1.6	−4.7	+6.0	−2.8	−2.2
HCN	−5.9	+1.9	−5.6	+6.2	−3.4	−3.2
N_2H_4	−8.6	+2.2	−8.0	+6.5	−8.3	−9.3
CH_3OH	−6.1	+2.2	−7.5	+7.0	−4.4	−5.1
C_2H_2	−3.0	+1.5	−5.1	+6.6	0.0	0.0
C_2H_4	−1.2	+2.8	−7.1	+7.5	+1.9	+1.3
CH_3NH_2	−4.7	+2.2	−8.4	+7.7	−3.2	−4.6
C_2H_6	−0.2	+2.5	−8.8	+8.8	+2.2	+1.8
CH_3CHO	−6.4	+2.0	−8.6	+8.8	−4.2	−3.5
C_2H_5OH	−6.9	+2.6	−10.0	+9.8	−4.5	−5.0
C_3H_8	−0.5	+4.3	−12.9	+11.5	+2.4	+2.0
CH_3COCH_3	−4.8	+3.0	−13.1	+11.6	−3.3	−3.8
C_6H_6	−2.5	+4.7	−15.8	+12.7	−0.9	−0.9
n-C_8H_{18}	−1.3	+8.6	−28.3	+25.0	+3.9	+3.0

The most reliable code for dispersion (and repulsion) contributions we know of is that elaborated by Amovilli and Mennucci [35] and inserted into PCM. In this case, dispersion-repulsion contributions are treated on the same footing as the electrostatic ones, and internal analyses indicate that the level of description of the two contributions is quite comparable. The data reported in Tables 3 and 4 are based on this code.

An annoying aspect is that dispersion contributions computed with this method are quite sensitive to the quality of the basis set. This means that extensive scanning of the $G_{sol}(R)$ to get critical points could require more computational effort than those deemed to be necessary by the user to get the desired geometry. (We recall that one of the strong points of continuum methods is the quite remarkable reduction of computational times with respect to alternative approaches. When developing codes we must attempt to preserve this feature, without causing detriment to the quality of the results.)

There is an alternative way of computing $G_{dis}(R)$ and $G_{rep}(R)$ for geometry search, which is extremely inexpensive. It is based on the use of empirical dispersion and repulsion atom-atom potentials. These interactions, regarding all of the solvent molecules from the solute to infinity (or to the physical limits of the solution in the case of systems with a boundary in the liquid phase), can be recast into a form similar to that used for the electrostatic contribution, namely a finite set of point values, one for each element, or tessera, of the surface [36]. The tesserae in the apparent surface charge (ASC) approach have an area of about 0.4 Å^2 in standard applications, and so the number of local contributions to the dispersion energy is low, less than 60 points per atom. Each contribution requires less than ten floating-point elementary operations, and so the computational time is completely negligible.

We stress that this semiclassical description of the dispersion contribution does not modify the electronic distribution of the solute. This approximation may be considered sufficient for determining the energy, but for applications that address more delicate aspects of the system, like the solute response properties, the fully coupled QM definition must be used.

Table 4. Other examples of the relative magnitudes of the different components of ΔG_{solv}. Solvent is n-hexane. Energy values in kcal/mol

Solute	ΔG_{el}	G_{rep}	G_{dis}	G_{cav}	ΔG_{tot}	ΔG_{exp}
CH_3OH	−2.1	+1.5	−7.3	+6.0	−1.9	−1.4
C_2H_5OH	−2.0	+1.7	−9.8	+7.7	−2.4	−2.0
$C_2H_5NH_2$	−1.4	+1.8	−10.7	+8.0	−2.4	−2.1
CH_3COCH_3	−1.4	+2.0	−12.6	+8.8	−3.2	−2.5
C_6H_6	−0.9	+3.1	−15.4	+9.6	−3.6	−4.0
Aniline	−2.8	+3.6	−17.5	+11.2	−5.5	−5.4
p-Cresol	−2.8	+3.8	−19.3	+12.9	−5.4	−5.9
o-Cresol	−3.5	+3.8	−19.3	+12.7	−6.3	−6.3

As we have just said, the semiclassical description is based on a choice of empirical function. In distributed PCM codes, use is made of the Vigné Mader-Claverie parameters [37]. In the 1980s, we spent some time with Pierre Claverie attempting to validate these parameters for their use in PCM, but is must be said that a complete validation was not performed.

In his first level thesis [38], F. Castelli recently arrived at sizeable reductions in the computational times of the QM calculation of dispersion, and we profited from this reduction in computational times by initiating a systematic scanning of the empirical potentials available in the literature. We present in Tables 5 and 6, for the first time, a limited selection of these comparisons between different sets of empirical potentials compared to QM ab initio calculations.

The comparisons reported in Tables 5 and 6 for n-alkanes and n-primary alcohols, all in water, with the QM calculations performed at the B3LYP/6–32G** level.

A complete systematic scanning of the empirical formulae is a pretty exacting task, since the number of parameters to scan is relatively large, and each has a large range of variation. Parameters that should be taken into account include the chemical nature of the solute, and that of the solvent, as well as the quality of the QM description (other parameters that may be taken into account could be related to excited states and to non-equilibrium solvation). We interrupted this scan after the completion of Castelli's thesis, waiting for the availability of others to continue. The results that are available at present (only a small selection are reported in Tables 5 and 6) indicate that this scan is a worthwhile pursuit, since it should provide users with the means to choose the appropriate formulae for their needs. However, I am also convinced that ab

Table 5. Dispersion energy contribution for a selection of alkanes in water, chloroform, and benzene, as computed using various approaches (energy values in kcal/mol)

Solvent	Molecule	Force field				ab initio	
		Claverie	MM3	Amber	OPLS	HF	B3LYP
Water	CH_4	−6.33	−6.78	−4.40	−4.46	−4.65	−5.47
	CH_3CH_3	−9.01	−9.58	−6.47	−6.46	−7.20	−8.38
	$CH_3CH_2CH_3$	−11.35	−12.56	−8.98	−8.78	−9.27	−10.85
	$CH_3(CH_2)_2CH_3$	−13.61	−15.52	−11.53	−11.12	−11.30	−13.26
	$CH_3(CH_2)_3CH_3$	−15.83	−18.51	−14.17	−13.52	−13.29	−15.62
	$CH_3(CH_2)_4CH_3$	−18.22	−21.03	−16.01	−15.31	−15.26	−17.85
Chloroform	CH_4	−4.55	−5.95	−4.61	-	−5.73	−6.73
	CH_3CH_3	−6.49	−8.38	−6.79	-	−8.88	−10.32
	$CH_3CH_2CH_3$	−8.20	−10.55	−8.70	-	−11.35	−13.27
	$CH_3(CH_2)_2CH_3$	−9.81	−12.59	−10.48	-	−13.78	−16.15
	$CH_3(CH_2)_3CH_3$	−11.43	−14.64	−12.27	-	−16.15	−18.96
	$CH_3(CH_2)_4CH_3$	−13.14	−16.81	−14.16	-	−18.51	−21.62
Benzene	CH_4	−5.99	−7.47	−6.40	−6.57	−5.47	−6.49
	CH_3CH_3	−8.53	−10.53	−9.41	−9.52	−8.46	−9.94
	$CH_3CH_2CH_3$	−10.75	−13.23	−12.00	−12.08	−10.81	−12.77
	$CH_3(CH_2)_2CH_3$	−12.88	−15.82	−14.48	−14.54	−13.11	−15.53
	$CH_3(CH_2)_3CH_3$	−14.98	−18.37	−16.92	−16.95	−15.35	−18.22
	$CH_3(CH_2)_4CH_3$	−17.24	−21.12	−19.55	−19.55	−17.59	−20.76

Table 6. Dispersion energy contribution for a selection of alcohols in water, chloroform, and benzene, as computed using various approaches (energy values in kcal/mol)

Solvent	Molecule	Force field				ab initio	
		Claverie	MM3	Amber	OPLS	HF	B3LYP
Water	CH_3OH	−7.88	−8.25	−5.53	−5.71	−6.62	−7.24
	CH_3CH_2OH	−10.39	−11.47	−8.31	−8.18	−8.92	−10.02
	$CH_3(CH_2)_2OH$	−12.68	−14.13	−14.40	−10.08	−10.09	−12.51
	$CH_3(CH_2)_3OH$	−14.90	−16.37	−11.97	−11.66	−12.91	−14.91
	$CH_3(CH_2)_4OH$	−17.11	−19.42	−14.70	−14.11	−14.89	−17.77
	$CH_3(CH_2)_5OH$	−19.50	−22.44	−17.22	−16.44	−16.84	−19.59
Chloroform	CH_3OH	−5.69	−7.25	−5.81	-	−8.15	−8.91
	CH_3CH_2OH	−7.50	−9.55	−7.87	-	−10.99	−12.34
	$CH_3(CH_2)_2OH$	−9.16	−11.65	−9.72	-	−13.36	−15.31
	$CH_3(CH_2)_3OH$	−10.78	−13.69	−11.49	-	−15.76	−18.19
	$CH_3(CH_2)_4OH$	−12.36	−15.70	−13.25	-	−18.10	−20.97
	$CH_3(CH_2)_5OH$	−14.05	−17.85	−15.12	-	−20.45	−23.77
Benzene	CH_3OH	−7.46	−9.07	−8.01	−8.38	−7.78	−8.55
	CH_3CH_2OH	−9.84	−11.97	−10.86	−11.05	−10.48	−11.85
	$CH_3(CH_2)_2OH$	−12.01	−14.60	−13.39	−13.51	−12.72	−14.71
	$CH_3(CH_2)_3OH$	−14.11	−17.16	−15.82	−15.93	−15.00	−17.47
	$CH_3(CH_2)_4OH$	−16.22	−19.72	−18.28	−18.35	−17.21	−20.13
	$CH_3(CH_2)_4CH_3$	−18.47	−22.45	−20.89	−20.93	−19.44	−22.81

initio QM codes will in standard use in the near future.

There are other aspects of the basic solvation procedure that we have examined that also deserve a critical analysis, such as the cavity formation energy, the repulsion energy, and the terms related to vibration and rotation of the solute, but we prefer to move on now to other aspects of the continuum solvation procedures.

The definition of the solute and the addition of solvent molecules

The part of the system that we focus on – that is treated at the full QM level – does not have to be limited to the nominal solute M. It may be larger or smaller than this: there are various good reasons for enlarging or reducing the size of the area of interest. We shall start by considering an enlargement of the QM subunit of the system first.

About the need to include explicit solvent molecules

An enlargement of the QM part of the system may be done to include some solvent molecules. There are no formal reasons forbidding enlargements of this type, and in fact they are often used by people that consider continuum models to be too crude and lacking in some aspects of discreteness deemed to be necessary to describe specific solute-solvent interactions.

Let me consider this point more in detail. It is clear that an enlargement of the region of interest from M to $M.S_m$, were S indicates a solvent molecule, will lead to an increase in the computational time. There is an enlargement of the QM region, and conventional QM ab initio procedures scale with a relatively large power of the number N of electrons. However, this may be a point of minor importance when the number m of added solvent molecules is small, and calculations are performed at relatively low levels of the QM theory.

More important are the consequences of this enlargement on other aspects of the procedure. As said before, we have to define critical points on the $G(R)$ hypersurface of the quantum system, and then we have to add vibrational and rotational entropic corrections to get the solvation energy. The weak M-S (and S-S) interactions included in the quantum system are in competition with other similar interactions described by the continuum model. The consequence is that geometry optimization is by far more delicate than for the corresponding $M.S_m$ system in vacuo; in other words, we need geometry optimizers of very good quality. The additional degrees of freedom corresponding to intermonomer vibrations are of a floppy nature, not well-described at the harmonic level and giving important contributions to the energy. The standard methods of quantum mechanics used to describe these effects in the supermolecule picture must be applied with care, otherwise we will get a serious error in the value of the solvation free energy, sometimes larger than the confidence bar obtained for continuous procedures using M alone as solute.

There is another problem for the solvation energies computed in such a way. The solvation free energy one wishes to obtain is, in general, that of M alone, and not that of an arbitrarily selected $M.S_m$ cluster. Other assumptions and other calculations are needed to get the desired solvation energy.

The remarks made in the preceding lines do not forbid the use of solvation clusters to get the solvation energy, but are simply a warning against the indiscriminate use of this procedure based only on the consideration that adding something more detailed automatically leads to more accurate results.

There are several claims in the literature that the addition of explicit solvent molecules were found to be necessary to properly describe conformational or tautomeric equilibria. I have the strong suspicion that a considerable number of such claims are due to the use of poor continuum solvation codes or to the imperfect use of good codes. Over the years, we have re-checked about a dozen such claims, always finding that the correct answer was reachable with the appropriate use of continuum solvation based on the bare solute M.

What are the reasons for such (apparent) failures of continuum methods? Some have been already expressed in the preceding pages and there is no reason to repeat them here. Others are related to the choice of the cavity and to definition of the solute electrostatic potential (or field). The cavity must be accurately modeled on the shape of the molecule, and in doing so attention must also be paid to the main features of the solute charge distribution. There are many papers that address the problem of refining the cavity radii for the various solvents, taking into account the local characteristics of the molecular charge distribution; I quote just one of them [39] as testimony to the patient and very useful work performed over the last ten years by the Luque-Orozco group in comparing different solvation procedures and improving PCM.

A typical example of false conclusions reached by the hurried use of continuum models is that of the equilibrium between the neutral and zwitterionic forms of amino acids, almost completely shifted in favor of the zwitterionic form in aqueous solution. There are a dozen, or more, papers that say that continuum solvation methods favor the neutral form in water, unless some explicit water molecules are added to the QM subsystem. All of the calculations that use a spherical cavity need additional water molecules to give a hint of the greater stability for the zwitterion, while accurate cavity models do not need this addition to get a quite reasonable approximation of the relative free energies of the two forms, at least for glycine and alanine that are the only two aminoacids we have examined.

Other examples could be mentioned here, but we do not need to labor the point. However, there is another issue we should address: how are hydrogen bonds described by continuum models?

Solute-solvent hydrogen bonds

In Pisa we were motivated to create continuum solvation codes by empirical numerical evidence, backed by accurate analyses, that indicated that hydrogen bonds can be described in terms of electrostatic interactions supplemented by a repulsion potential. This was the basis of several papers we published on hydrogen bond analysis for dimers and large clusters, and it represented an important point in our development of a semiclassical model for chemical interactions (called semiclassical because it is based on a classical description of the interactions between constituents which are accurately described at the quantum level). The solvation code was, at first, a way to test this model. Many checks, repeated over the years, confirmed the basic validity of the model. Among such tests, I quote the comparison of the solvation energy of $M.S_m$ clusters with that of corresponding $M.S_{m-1}$ clusters plus the solvation of S (a molecule of water, in our tests). Such tests were also used to calibrate better PCM, and the results were always satisfactory; the deviations between the two calculations are quite small and essentially due to BSSE errors which can be corrected by CP procedures. (CP corrections also work with continuum models [40].) In performing such tests, we systematically paid attention to eliminating S molecules both connected and unconnected to M via a hydrogen bond, and we have found no appreciable changes in the results. It must be added, as a cautionary remark, that such checks have been performed with a simplified version of the model (no separate optimization for the $M.S_{m-1}$ cluster, no dispersion contributions) and that only a limited number of tests have been performed on the competition between internal hydrogen bonds within M with solute-solvent H-bonds. In spite of these limitations, these tests are sufficient for me to consider with some diffidence claims about the necessity of introducing explicit water molecules to describe hydrogen bond effects.

These remarks only regard the energy of the system and no other properties. There is no guarantee, on our part, that this semiclassical picture is sufficient to describe other properties.

My last remark opens the way to another problem: how can we describe solvation effects on other properties of the solute? There are a large variety of molecular properties sensitive to solvent effects, and there is substantial empirical evidence that solvent effects on properties cannot be reduced to a unique cause (dielectric effects or others), for all properties and all combinations of solute and solvent. The most complex empirical solvation indexes [41] try to combining effects of different types, with more or less success according to the case, but without giving clear-cut indications about the physical origin of such effects. Reference is often made to vague local specific solvent effects, the nature of which surely changes for different classes of compounds.

There is a clear need to study such effects more in detail, using QM procedures.

About the use of explicit solvent molecules for the description of molecular response properties

We are now entering into a field that is quite complex, but of remarkable importance. The study of solvent effects cannot be limited to the solvation energy only, or to properties related to energy differences, in spite of their importance in chemistry (we quote as examples the properties related to equilibriums of various types: among different conformations or different tautomers; between reactants and products in a reaction; of distributions of the solute between two immiscible liquid phases, and so on).

The calculation of solute properties that are indirectly related to the energy represents the main path to reaching a better understanding of the complex network of molecular interactions on which chemistry is based. Molecular response properties cover an extremely large variety of phenomena related to very different physical interactions, and accurate studies of the influence the medium has on these properties provide the theoretician with the means to illuminate fine details of the interactions among molecules. For these reasons it is important to examine the options available for these studies in a systematic way.

A possible solution is to resort to $M.S_m$ clusters with m sufficiently large to saturate all local interactions that have an effect on the property. It is well known that $m = 50$ is not sufficient to completely describe solvation effects for a small solute, and so even with a large cluster there is the need to use a continuum model for most of the solution, or other procedures like classical Monte Carlo or Molecular Dynamics simulations. Distant interactions are to a good extent ruled by electrostatic interactions, and so classical or semiclassical descriptions like those given by classical simulations or by continuum models should be acceptable, even for sensitive properties.

The problem is therefore shifted to describing large $M.S_m$ clusters. The supermolecule approach we considered in the preceding section is out of the question. Geometry optimization of such clusters is a very hard task, and the optimal geometry, even in the case it is reached, should be followed by appropriate averages to reach the thermally equilibrated description of the region of solvent corresponding to the S_m molecules. This is a computational task even harder than the geometry optimization

To alleviate the computational effort of this approach, different options are possible. One consists of in reducing the quality of the QM description of the *m* solvent molecules using a layered (or hierarchical) description of the QM cluster. We shall consider this option in a following section, but it is clear that when *m* is large (say 50 molecules) the reduction in computational times is still not sufficient to make the layered QM description accessible to currently available computers.

More appealing are the options based on computer simulations. There is a wide choice of methods here.

First of all we should consider simulations at the quantum mechanical level, of which the leading example is the Car-Parrinello method [42]. With this approach, it is currently possible to treat $M.S_m$ clusters with $m = 50$ or even larger, with all the molecules of the clusters treated in a consistent way at the QM level and with the appropriate average. The problem of molecular properties is then shifted to the quality of the QM calculation. Several response properties are strongly sensitive to the quality of the QM calculation (level of the theory, size and quality of the basis set). A complete QM simulation fully performed a the level necessary for some properties still represents a very intensive computational task, and the best way to proceed, while waiting for further progress in computing power, consists of moving to other methods that give a description of the target solute M with a high level method but that still preserve the nice features given by the Car-Parrinello method (namely a quantum mechanical description of the surrounding solvent, with the appropriate averages). There are several possible strategies to reach this goal, and some will be commented on here.

An option to consider is given by the use of QM/MM simulation methods. QM/MM methods represent a very important improvement in standard classical simulations for a key problem of chemistry, that of chemical reactions that describe bond forming and bond breaking processes. The potential of this approach was evident from the first formulations of the method [43, 44] and was well-documented in the first comprehensive review, written by J. Gao (who has since continued to provide important developments and applications of the method) about nine years ago [45]. QM/MM procedures have greatly improved over the last few years, and calculations may now be performed with descriptions of the QM part at a relatively good level, for example by using DFT [46] or MCSCF procedures [47]; a level sufficient to also describe the response properties we are considering here (or at least a good number of them). The limitations of QM/MM methods lie in the MM part. In fact, classical descriptions of the nearby solvent molecules cannot be used to investigate the specific effects of the solvent on the property. The whole equilibrated description of the solvent given by these simulations is similar, in this aspect, to the continuum description.

However, simulations can be used in a different way. From the sequence of Monte Carlo moves or from Molecular Dynamics steps, some configurations can be extracted, and their geometries used to define QM clusters. The desired property is computed on each cluster defined in this way (without geometry optimization, of course), and as final step of the calculation an average of these values is then obtained.

This strategy must to be better defined, on the basis of the many options thus for explored. We report here on some points that characterize the procedure.

The clusters to be selected obviously cannot cover the whole simulation box: generally a strategy based on a physical distance criterion is adopted, often with some constraint on the number *m* of solvent molecules to be included in the cluster.

The selected clusters must be representative of the averaged distribution actually felt by the solute M during the evaluation of the property. To this end, use is often made of parameters drawn from the simulation, in some way measuring the "distance" between clusters in the simulation. The final average of the property is often a simple arithmetic mean, but procedures using a sort of Boltzmann weight have been also adopted.

The number of clusters used in the average is another parameter of the strategy. In principle this number is unconstrained, but there is a tendency to increase it. There are now calculations on 500 clusters or more. Such an increase in the number of clusters is probably due to a lack of confidence in the reliability of the final average, which is actually performed on a limited number of randomly chosen specimens.

Procedures of this type have gained a remarkable popularity in the last few years. They are related in some senses to ideas expressed by Warshel in various forms in several papers [48], upgraded for solute properties by Hush and Reimers [49, 50], and used consistently by Canuto and Coutinho in recent years [51, 52, 53]. Canuto has suggested the acronym SMC/QM for the procedure he uses: Sequential Monte Carlo followed by Quantum Mechanics calculations. The adjective "sequential" is a good suggestion, and it should be used more extensively, even if other procedures sharing the same philosophy are not well-described by a linear sequence of steps. I cite here some recent examples of such procedures [54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64] without adding comments, for brevity's sake.

The present discussion should be sufficient to show that this field is methodologically quite active: there are many problems to solve to get efficient and reliable computational codes, but the outlook is bright, not only for solvation effects on thermally equilibrated systems, but also for the dynamical evolution of such systems (this last topic is quite broad, and of great methodological interest, but it is one that unfortunately I do not have the space to discuss here).

We might therefore conclude by saying that there are methods that are able to compute specific solvent effects on molecular properties, but we in Pisa are not fully satisfied with this conclusion.

The reasons for this partial dissatisfaction can be found by reconsidering the goals that prompted us (and all the other people reported in Table 1) to create solvation models thirty years ago.

The idea that ruled our work in those years, and also in more recent times, was that the real goal of theoretical investigations into molecular systems is not to compute a specific property, but to give an interpretation of the phenomenon. A good number of calculations done for molecular systems (including almost all of those I am discussing in this paper) aim to reproduce some experimental datum. Such calculations are necessary to validate and to calibrate computational methods, but cannot constitute the final goal of theoreticians.

In the last few years, the progress in computational chemistry has led to a greater confidence in the reliability of molecular calculations, and it is now a reasonable goal to use calculations to get chemical information on systems and processes in parallel to, or instead of, laboratory experiments. The "sequential' methods we have outlined have, at present or prospectively, the right qualities to reach this goal. The outputs of these methods are however too complex for the interpretative analysis we are envisaging. We have therefore moved in another direction, with an elaboration of the methodological strategy which is still in progress, and this will be outlined in the following section.

Towards a theoretical analysis of solvation phenomena

The main criterion for this analysis we have adopted consists of starting from simple descriptions of the phenomenon, and when necessary, move on to more refined models. To do it we have to base our descriptions on phenomena for which there are reliable experimental data; the era of predictions for unmeasured phenomena will follow, when the models have been sufficiently tested.

It must be said that in our still limited experience, we have found that a surprisingly large number of experimental data are not precise or reliable enough, for a variety of reasons, which includes the use of old and very crude models to obtain the raw experimental data. This fact has been documented in some of our papers from the last few years, and it has compelled us to enter into direct contact with good experimental laboratories willing to perform more accurate measurements. The results have been quite satisfactory in several cases, but on the whole the moderate reliability of experimental data represents an obstacle to our research. This said, I now move on to describe the steps in our strategy.

A sketch of the strategy

A "simple" starting description is given by the use of the continuum model with the QM part limited to the target molecule M. In many cases, for a large variety of systems and properties, this model works satisfactorily. In other cases, for other systems and/or for other properties, there are sizeable deviations from experiment.

For cases exhibiting deviations, we use the continuum model again, but with the QM part described by a small $M.S_m$ cluster, starting with $m=1$ and progressively adding more solvent molecules step by step. At each m an assessment is made on the value of the property. For small values of m (1–3), geometry optimized clusters are compared with others selected on the basis of some hypotheses for the interaction (such hypotheses depend on the chemical nature of the two components of the solution). For larger clusters, a variant of the technique of the sequential methods is adopted, and simulations are often performed in parallel using rigid or non-rigid MM potentials.

This stage of the study is terminated when a sufficient agreement with the experimental value of the property is reached.

It is possible to summarize the studies performed so far at this stage of our research program. The studied properties are those more commonly used in the characterization of chemical substances, namely NMR shielding, molecular vibrations, and molecular excitation energies, and are accompanied by other more complex properties, such as IR and Raman intensities, vibrational circular dichroism, optical rotation, linear and nonlinear optical properties, and so on. The solutes are in general small organic molecules, while the solvents range from water to cyclohexane, covering the whole range of solvent polarity.

The first conclusion we have obtained from these studies is that for most property/system combinations additional solvent molecules are not required in the QM subsystem to describe the property. In a sizeable number of cases, there is the need to add one or two solvent molecules to reach a good description of the property, and in a quite limited number of cases there is the need to add a larger number of solvent molecules (typically 4–6, and in the worst cases about 10).

As expected, some properties are more sensitive than others, in agreement with experimental evidence; for example, generally in protic solvents the X–H stretches require one explicit solvent molecule, and the carbonyl stretches two molecules, while the other vibrations do not require explicit solvent at all.

In Table 7 we report some examples of this search of specific interactions, for nitrogen shielding. Oxygen and nitrogen shielding are among the properties more sensitive to specific solvent interactions. The examples reported in the table give a representative view of the variety of results given by this analysis. The addition of a second explicit water molecule to (1,2) diazines modifies the solvent shift by about 0.1 ppm, and for this reason it has not been reported in the table. Of particular interest is the comparison of the effect of two solvents, water and chloroform, on the solvent shift in pyridine and in acetonitrile. Pyridine behaves like the other N-heterocycles: the water molecule is connected to the nitrogen of the ring by a hydrogen bond. The behavior of CH_3CN is typical of nitriles, and this behavior is also found for other solvents such as acetone and DMSO: there are no hydrogen bonds here and the specific interaction is of another kind.

Table 7. The solvent shift for the14N NMR shielding (ppm)

Solute	Solvent	n of added molecules	Computed	Experimental value	Continuum contribution
(1,2)Diazine	Water	1	41.92	41.55	12.4
(1.3)Diazine	Water	2	15.93	16.84	3.2
(1,4)Diazine	Water	2	16.27	16.85	2.7
(1,2)Diazine	DMSO	0	11.26	9.46	11.26
(1.3)Diazine	DMSO	0	2.61	3.60	2.61
(1,4)Diazine	DMSO	0	2.26	3.17	2.26
(1,2)Diazine	Acetone	0	12.29	14.38	12.29
(1.3)Diazine	Acetone	0	2.26	3.11	2.26
(1,4)Diazine	Acetone	0	1.94	2.71	1.94
Pyridine	Water	1	−30.0	−29.70	10.0
Pyridine	CH_3Cl	0	−13.97	−14.01	13.97
CH3CN	Water	0	−16.79	−17.2	−16.79
CH3CN	CH_3Cl	6	−6.32	−6.2	+0.2

We have not reported the analysis performed in parallel on the (n–π^*) electronic excitations of these systems in the table. The trend is similar in many cases. These are aspects to examine in successive stages of the procedure.

The next step consists of the analysis of the electronic structures of the QM systems to get a better description of the property, using the abundant variety of analytical tools created for the study of molecular interactions in vacuo.

I am not going to enter into much more detail about the results from these analyses (the results are provisional and restricted to a limited number of cases); suffice to say that a factor that plays an important role in these corrections given by explicit solvent molecules is the electronic charge transfer.

This point leads to an interesting methodological problem. In the cases in which charge transfer plays an important role, it is more difficult to assign the value of a property that belongs to an particular M molecule. Our naive picture of solutions as being composed of individual molecules maintaining their identity shows its limits here. The charge transfer component of the interaction energy is not described by continuum solvation methods. All of the continuum methods are implicitly based on a Hartree partition of the wavefunction of the whole liquid system (and the same happens for the perturbation theory descriptions of molecular interactions, to which all of our descriptions of liquid systems owe a great deal). The development of a continuum model that includes this effect would be of remarkable interest, but little has been done so far on this subject which represents one important issue for the future development of our theories on solutions.

The analysis based on the dissection and analysis of the charge distribution can be accompanied by the analysis of the performance of the various empirical solvent scales. They are of great use in practical chemistry, and a better appraisal of their justifications and their performances could be quite useful, for instance in reducing the possibility of erroneous interpretations of the correlations found by using such functions. Little has been done toward this end so far, and even less has been published [56, 65], but the limited numerical evidence available so far indicates that this approach should be rewarding.

So far I have expressed opinions based on limited numerical evidence, and they have to be considered more as guesses than firmly determined facts. In this vein of expressing opinions and guesses, I close this section by discussing a provisional classification of solute-solvent interactions.

Classifying solute-solvent interactions

By tradition, solvent effects are divided into *generic* (or general) and *specific* components. Many theories of current use in practical chemistry are based upon this division. However, we prefer to start from other considerations. In disordered and mobile media, as liquids are, each molecular component feels the effects of interactions with other partners. Some of these interactions are *local*, others can be called *non-local*.

The non-local interactions are, to a good extent, described by the continuum model, which is an integral model. I shall not consider these interactions any more here. More detailed models for these non-local interactions are necessary for studies of systems that have a large amount of matter in discrete form.

Local interactions can also be split down, into *labile* and *persistent* interactions. This distinction, which has a dynamical connotation, is apparently based on the strength of the interaction, but other more subtle factors play an important role:

- Labile interactions must be averaged, and continuum models automatically do this.
- Persistent interactions can be described by explicitly including both partners in the solute model, but here a further distinction can be made. The effective Hamiltonian used in good continuum models actually describes all of the interactions between partners, certainly not at the same level as a well performed and complete quantum mechanical description, but at a level that often turns out to be sufficient. Therefore, we have to introduce a division among the persistent interactions, into *specific* and *non-specific* persistent interactions.

The solvent molecules added to the solute should address the description of specific-persistent interactions. The key point is that the definition of such interactions strongly depends on the property and it is therefore not strictly related to the strength of the interaction or to the dynamical *permanence* of the interaction, which is another concept. But what operative method can we use to introduce this distinction to actual cases?

We have shown a way to proceed in the preceding pages. The basic criterion is the following: a solvent molecule causing interactions that are not specific-persistent can be eliminated from the model without detriment to the computational result, or conversely, when added to a simpler model it does not improve the result. We prefer to use the second approach: from simpler to more complex models.

Simplifying the QM region

As remarked at the beginning of the section before last, continuum models permit both the enlargement and the reduction of the region described at the highest QM level. We have so far considered enlargements, and will now move on to look at reductions.

The more direct motivation for exploring reductions is related to the size of the solute M. When the size is too large, a full QM description of the solute becomes impossible, and alternative descriptions must be developed. However, later in this section we will encounter other motivations for controlled reductions in the QM part of the model.

Linear scaling of the solvation procedure

When the size of the solute is large, there are problems; both with the description of M and in its solvation. The problems related to the description of a large isolated molecule are well-known in quantum chemistry, and there is no reason to delve any further into this point. Let me comment, in contrast, on some technical points of the solvation procedure.

I will consider PCM codes in the following (as I did in the preceding sections), but I should remark here that the SCRF codes of Nancy face similar problems, even if expressed in a different way.

In standard PCM, to solve the nonlinear problem of the definition of the solute-solvent interaction potential we use a formula based on the solution of a set of linear equations, each containing T elements, where T is the number of apparent surface point charges (or tesserae) employed to describe the apparent surface charge distribution. The number T of point charges is roughly proportional to the molecular surface S (in standard calculations $T = 2.55\ S$, with S measured in Å^2) and has a more complex relationship with the number of electrons N of the molecule: T is proportional to N^{β}, where β ranges from 1–2/3. To solve the linear equations we use an inversion of the matrix of the coefficients, which has dimensions $T \times T$. The procedure therefore scales as T^3, and we may conservatively say as N^3 too. This matrix inversion is performed just once in the whole calculation, and for small molecules the cubic dependence on N does not represent a computational problem. On the other hand, when moving to large molecules it does constitute a serious bottleneck. Over the years we have developed several alternatives to this standard procedure that have not been inserted in distributed codes for various different reasons, but we state here that we do have efficient, tested linear and parallelized codes which are based on semi-iterative procedures performed with the aid of a generalized discrete interpolative scheme (GDIIS) [66], which are very effective in reducing computational times [67, 68].

I report here on some examples of computational times. Table 8 compares the computational times for the solvation of a set of BCN nanotubes with stoichiometry $B_{12k}C_{24k}N_{12k}H_{12}$ (N in the table is the number of atoms) performed (Case A) with the DIIS linear scaling, and (Case B) with the standard inversion matrix technique. T is the number of point apparent charges; times are given in seconds and refer to the calculation of the solvation energy (electrostatic term alone) performed with a PC (Pentium II 400 MHz). The data are drawn from [68].

It is clear from looking at the table why we have not performed the inversion matrix calculations for larger values of k.

The scaling of times are given by fits with the following equations:

Case A: $t = a + bT$, with $a = 36.50$; $b = 0.0269$; $r = 0.9992$

Case B: $t = a + bT^3$, with $a = 2.04$; $b = 0.90 \times 10^{-7}$; $r = 0.9987$

Similar scalings have been found with other large molecular systems.

The most recent implementations have further improved performances. For the calculation of pK_a of residues in the protease inhibitor turkey ovomucin third domain (a 56 residues protein), described with a hybrid QM/MM model imbedded into a PCM surface, the code elaborated by Pomelli reduces the time for the electrostatic part to about 22 s and the whole computational time to about 150 min (on a parallel four CPU RS/

Table 8. Comparison of computational times for the calculation of solvation energy for a set of BCN nanotubes

k	N	T	Time for Case A (s)	Time for Case B (s)
1	60	2099	22	891
2	108	3472	54	3672
3	156	4841	95	10208
10	492	14501	352	n.a
20	972	28301	3008	n.a

600 44P 70 machine) [69]. We may therefore conclude that the bottleneck problems with the calculation of the solute-solvent interaction potential for large solutes have been greatly reduced.

The computational details we have reported constitute a preliminary step in the development of models for large solutes. Of course, full QM calculations on a large solute are far more computationally demanding than the calculation of the interaction potential.

For some problems of chemical interest, like the study of conformations of proteins, the use of MM descriptions for the whole solute could be employed. Practically all of the PCM versions developed in the past few years have also been tested with MM calculations, with fairly good results, and the same happened, I assume, with the tests done with other continuum codes. What PCM lacks in the present version is an efficient code to describe polarization effects in large MM systems (but we are working on it!).

Full MM descriptions are however limited to a small part of the solvent effects of interest. MM models in which one part of the system is treated at a given (and relatively good) QM level, while the other parts are treated at lower levels are more flexible. Years ago we suggested [70] introducing a distinction between two types of models of this kind. We suggested that those in which the partition between high and low level parts requires the breaking of a covalent bond should be called *hybrid* models, and those in which the partition is made at the level of non-covalent interactions should be known as *combined* models. Combined models are often used in the study of liquids. The QM/MM simulations are based on combined models in which the solute M is treated at the QM level, while the solvent molecules are described with classical MM potentials. The clusters MS_m introduced in the section before last can be treated in a similar way. The *m* solvent molecules, or a portion of them, can be described at a lower level. It is clear that with this remark we are introducing more complex formulations of this strategy, because the clusters we considered in that section are immersed within a continuum and a complete reduction of the *m* solvent molecules of the cluster has no effect on the search for specific-persistent interactions. An example of hybrid QM/MM with the inclusion of continuum solvent effects was given above, in [56].

However, to progress with this discussion it is better to speak of *layered* or *hierarchical* models, in which is possible to introduce a variety of partitions of both combined and hybrid type, to be selected and defined in the appropriate way according to the scope of the study.

The ONIOM-PCM layered model

Layered models offer remarkable flexibility and can be used for a wide variety of scopes in addition to the description of large solutes. Although we will now report on some examples based on Morokuma's ONIOM hybrid method [71], other layering methods could of course be used instead; the excellent performances of the methods developed by the Nancy school are well-known [72].

In principle, ONIOM's structure allows us to use an indefinite number *N* of layers, that may be denoted by separating the acronyms indicating the level of each layer with a slash. For example, $QM_1/QM_2/MM$ is a three-layer model in which the whole molecular system is first described at the lower level (in this case MM), and then refined by adding elements described at the preceding higher level (and by subtracting the same elements described at the lowest level), in a sequence of processes ending with the highest level. A model with *N* layers needs $2N-1$ subcalculations. The procedure is simple, but the description will be clearer with an example.

Let me use Morokuma's terminology applied to a two-level ONIOM. The whole *real* system is described at a relatively low level (there is complete freedom in selecting this lower level), and the molecule corresponding to the fragment of the system under scrutiny is described both at the same low level, and at the higher level at the desired accuracy. This fictitious molecule is called the *model*. All of the desired properties are computed using the same scheme, namely as the combination of three terms: the first regarding the whole real system at the low level, subtracting the model at the low level, and adding the model at the high level. The energy, for example, can be written in the following form:

$$E^{\mathrm{ONIOM}} = E^{\mathrm{real,\ low}} - E^{\mathrm{model,\ low}} + E^{\mathrm{model,\ high}}$$

and a property *P* in the following form:

$$P^{\mathrm{ONIOM}} = P^{\mathrm{real,\ low}} - P^{\mathrm{model,\ low}} + P^{\mathrm{model,\ high}}$$

The low level description of the real system represents a kind of background, modified by a kind of replacement of the low level description of the region of interest with a higher level description. We are skipping over the description of other details here, such as how gradients are defined.

We have implemented ONIOM-PCM solvation codes [73] that offer four different schemes for the definition of the solute-solvent interaction potential in the distributed version of the program [74]. Each scheme has different advantages and shortcomings, related in part to computational considerations. I have to remark, in fact, that ONIOM-PCM codes are provided with an analytical energy derivative with respect to the nuclear coordinates, and this added feature often influences the decision one has to make about the optimal computational strategy to adopt.

We have used ONIOM/PCM so far to explore the performance of the method and to test its usefulness for the interpretation of properties. In fact, ONIOM offers as yet unexplored possibilities for exploring intramolecular effects as well as intermolecular effects (in particular solvent effects), because it offers the possibility of highlighting one or more groups within the molecule (or the cluster) with respect to the others.

The first results have been very positive. ONIOM-PCM has been applied to the MS_m clusters we have already discussed. The analyses considered in the previous section, regarding the search for specific-persistent interactions, have been repeated using QM_1/QM_2/Cont descriptions, with the high level regarding M only, with very good results. The values reported in Table 7, to give a numerical example, have been reproduced with deviations not larger than 0.1–0.2 ppm in the computed solvent shifts of the nuclear shielding. This means that the quantum effects found with this analysis are robust enough to be well-described at a lower QM level. In addition, this finding can be exploited to reduce computational costs in further studies.

ONIOM and ONIOM-PCM have been shown to be good at describing intramolecular effects, and the influence the solvent has on these effects. In the paper that presented the method [73], we considered a merocyanine molecule, $H_2N(CH_2)_3CHO$, both in gas phase and in aqueous solution. Merocyanines present a feature of great importance for the non-linear optical properties exhibited by this class of molecules. The $-(CH_2)_n-$ bridge between acceptor and donor groups, which is formally described as a sequence of alternate single and double bonds, actually assumes an intermediate structure among the two extremes, in which there is a partial delocalization of the π electron system. The degree of this delocalization can be measured by a numerical parameter, the bond length alternation (BLA), which depends on the nature of the acceptor and donor groups for molecules in the gas phase, and on the length of the carbon chain. It is a property clearly dependent on intermolecular interactions involving the whole molecule. BLA is also highly sensitive to the nature of the solvent: the time dependent hyperpolarizabilities (and so the related nonlinear optical properties) are strongly connected to the BLA value and are so strongly dependent on the solvent.

We performed a sequence of ONIOM and ONIOM-PCM calculations using increasing portions of the molecule, starting from H_2NH and moving on to $H_2N(CH_2)_2H$, $H_2N(CH_2)H$, and so on, as the high-level model. Correct BLA values are recovered in parallel both for the gas phase and the solution, indicating the collective nature of solvent effects on this property. Additional calculations have been performed on the ^{15}N nuclear shielding which also show the collective influence of other groups and of the solvent on this property.

More complex studies using ONIOM and ONIOM-PCM in parallel have been initiated in recent times, mostly by B. Mennucci and C. O. da Silva. I cannot give details of as yet unfinished investigations, but I can confirm my initial opinion that ONIOM hybrid models in solution are very promising analytical tools.

Metal surface enhanced properties and layering of other systems

The concept of layering descriptions of the whole macroscopic system into portions treated at different levels can be applied in a very large variety of ways, and for a very large variety of phenomena.

I will not express my personal views on general strategies for the use of layered models in “complex systems” here (it would take too long). I move immediately on to an example, from which we have obtained very good results in the last few years, and one that can be used to better appreciate the potential of continuum methods beyond the realm of isotropic solutions.

It is experimentally well-known that metal specimens can strongly modify the intrinsic characteristics of an adjacent molecule when the composite system is subjected to an appropriate external electromagnetic field. Since 1979 these properties have been known as *surface enhanced*. The most famous property is of this type is surface enhanced Raman scattering (SERS), but many others have been experimentally studied and theoretically analyzed.

In Table 9, I report a list of properties of this type, both those on which we have sizable results and those on which studies are under completion or simply planned.

The number of properties is too large to give a more detailed description of the different phenomena here, to describe the experimental conditions in which these effects can be observed, and to explain the importance they play in a better understanding of the behavior of condensed media and technological applications.

It is sufficient to say that electromagnetic theory [75] gives a unifying view of these phenomena. The properties can be grouped into three classes, depending on the presence of: (a) radiation entering the system (SEEA, SEIRA, and SEPTA); (b) radiation coming out of the system (SEET, via luminescence), or; (c) both (SERS, SEHRS SEHG, and SESFG).

The electromagnetic theory I have quoted explains the phenomena in terms of collective resonances of the electron gas of the metal (surface plasmons) which for opportune morphologies of the metal specimen can create an evanescent electromagnetic field localized in the proximity of the metal surface. A molecule close to the surface of such a portion of the metal specimen feels

Table 9. Acronyms of the most important surface enhanced phenomena

Acronym	Full name
SEEA	Surface enhanced electronic absorption
SERS	Surface enhanced Raman scattering
SEIRA	Surface enhanced infrared absorption
SEHRS	Surface enhanced hyper Raman scattering
SEEET	Surface enhanced electronic energy transfer
SESHG	Surface enhanced second harmonic generation
SESFG	Surface enhanced sum frequency generation
SETPA	Surface enhanced two-photon absorption

a local field more intense than the incident one, so its effective response will be greatly amplified. Many other details should be added to give a reasonable account of this complex theoretical description of the essential aspects of these phenomena, but the interested reader will find them in the cited review.

What prompted me to remark upon this is that this theory neglects several aspects of the phenomena, grouped under the title of "chemical mechanisms", which are not analyzed. Actually many aspects are hidden under this collective title, and all of them are of interest to chemists. Why are some responses of the chromophore enhanced and others not? What combination of solvent, dye and metal must be chosen to have a strong enhancement at a given frequency? What must the local and the global morphology of the metal specimen be to give a strong effect? And so on. Clearly there is the need for more detailed modeling, performed from a "chemical" viewpoint.

To this end the layered models may be of considerable help. We cannot delve deeper into our models here due to lack of space, so we shall move on to briefly summarize one such model that has reproduced the most intense SERS signals detected over the past few years quite well [76].

The material part of the model system is composed of a cluster of metal particles within a liquid, to which a molecular chromophore is added. The metal cluster is composed of a variable number of spherical particles, all with the same diameter. To be in agreement with experiments, the number of spheres has been set in the range 5–1000, and the sphere radii in the range $r=$ 5–20 nm. The metal clusters are statistical aggregates, in a mono-dispersed distribution. Each cluster has its own geometry, but all clusters in a given experiment have the same fractal dimension (the fractal dimension is dictated by the fabrication technique of the cluster). The liquid is modeled by a continuum dielectric characterized by a dielectric constant $\epsilon(0)$ and by a dielectric function $\epsilon(\omega)$ (we need to use a non-equilibrium description of solvent effects to take into account the frequency dependence of the chromophore response under the combined action of the external electromagnetic field and of the radiation coming from the chromophore). The molecular chromophore is described at the B3LYP level by a basis set of reasonable quality (found to be sufficient to describe Raman intensities in isotropic liquids [77, 78]).

The strategy for the investigation may be decomposed into several steps:

a. To submit the metal cluster to an electromagnetic field of a given frequency, and to compute the evanescent field on the various regions of the cluster.
b. To identify the surface regions in which the evanescent field, (and then the local field) has higher values. These portions of the surface are called "hot spots", and are the regions in which the enhancement is present. The number of hot spots, classified according to their intensity and their local morphology (shape and size), are collected for further analyses.
c. To insert the chromophore into the material model, placing it at appropriate positions (near the hot spots, but for control also in other places), and to compute vibrational frequencies and Raman intensities for each case.
d. To analyse.

For step (a), a low level description of the cluster system may be sufficient: we have used a dielectric description of the metal, with polarization expressed in terms of local Langevin dipoles centered on each metal sphere. Also, here the description of the liquid can be kept at a level lower than in the other PCM calculations considered in this paper, but the number, strength, and location of hot spots are sensitive to the solvent dielectric properties.

When the chromophore is placed at a hot spot (or at other regions of the metal surface) the description of the local region of the metal must be refined. A local spot is composed of a limited number of spheres (typically 3–4 spheres), in a linear arrangement parallel to the direction of the incident polarization. The solvent-exposed surface of these spheres is tessellated with the recipes used by PCM for the study of molecular solvation effects, and the same is done for the liquid encircling the chromophore.

The results have been quite satisfactory. Experimental data for Ag and Au clusters in methanol-water mixtures [79] have been satisfactorily reproduced. The dissection of the huge enhancement factors permitted by these detailed calculations has given a rationale of the effects, expressed as the combination of three terms having a different physical origin.

There is no need to give more detailed information about either the results or the numerous parameters we investigated in the analyses. To give an idea of the complexity of the scanning of the chemical variables, it is sufficient to say that we have examined clusters of seven metals and two semiconductors, that we have systematically varied the size and number of the spheres that define clusters, and that statistical averages of the performances of clusters have been performed for material systems composed of a fixed number of spheres (2000, say, which may consist of two clusters composed of 1000 spheres or 100 clusters composed of 20 spheres for instance). Readers wishing to find more information on this are referred to an overview of molecular properties in solution [80], to the original paper [76], and for more details still to Stefano Corni's doctoral thesis [81].

I hope that I have demonstrated, with this relatively long (albeit incomplete) summary of a single research project, that the layered formulations of the model can be exploited, and that continuum methods can be extended considerably beyond the realm of isotropic dilute solutions, to treat problems of chemical interest even for domains unfamiliar to standard chemistry.

Future prospects for continuum methods

In the preceding pages I considered some aspects of the continuum solvation theory that impact on research fields in which continuum models will presumably play a more important role in the near future than at present.

The field of molecular properties, and of related physico-chemical experiments (especially of the spectroscopic type) is enormous, and it is only very recently that researchers investigating molecular QM have obtained computational tools that are efficient and reliable enough to give accurate descriptions, interpretations and predictions for the more complex phenomena of this type. In the notes for a course I give at the University of Pisa, I present more than 100 properties that can be examined with the available theoretical QM tools, and the number is increasing every month.

In the last part of the preceding section, I gave an example of the application of continuum methods to "complex systems", centered on their application to a specific type of property. Complex systems can be defined as composite systems in which the overall behavior is very different from that of the isolated components that comprise the system. Let me stress that the variety of complex systems is quite large, and this variety represents a challenge to the development of procedures that are able to describe properties of different types, modified in different ways in the various complex systems. As an example, included among these complex systems are apparatuses created to get more detailed experimental information on the properties of material systems subjected to external excitations; in fact we are seeking in a sizeable, and increasing, number of cases the responses of apparatuses defined at the atomic level. We may unify material systems and experimental tools into a unique subject of research performed using quantum mechanical approaches. It is an interesting perspective.

I have here put (what I believe to be) due emphasis on response properties, but this field is just one of the areas in which continuum models can be profitably used.

Research in chemistry, physics, and molecular biology is being directed more and more toward the study of complex systems in which the properties of molecular components are heavily modified by the system, from heterogeneous catalysis to biological light harvesting (to give two examples for which model studies are currently feasible). This is another enormous field open to theoreticians that could exploit the positive features of continuum models.

I have only touched on another field, that of the study of large molecular systems, limiting myself to some comments on a technical aspect of the problem. One of the main advantages of continuum methods is the strong reduction in the number of degrees of freedom of the system they permit. This reduction can be controlled, modified or tempered with ease, and this is an important factor that suggests that continuum methods should have a brilliant future in this field.

A topic of central interest in chemistry is that of reaction mechanisms. So far I have not considered this very important area in which positive results have been reached using continuum models: an example is given by the results of the Nancy school. There is now the tendency to use discrete molecular simulations for the study of mechanistic processes. In some cases, this means, in my opinion, spending more computer time than is strictly necessary, but this is not the point I want to consider here. In the study of chemical reactions in solution, is easy to use the interpretative models created for molecular mechanisms in the gas phase. In particular, the definition of the transition state geometry (and of the aspects of the reaction deriving from this basic concept) is often quite arbitrary, because the molecular hypersurface in full discrete models presents a large number of almost equivalent points eligible for an approximate description of the transition state. In some cases this blurring of the definition can be accepted, in other cases it cannot. It would be better to adopt a scheme of controlled reduction in the degrees of freedom, similar to that I described in the section before last for the observables. In this specific context continuum models play an essential role.

Most chemical reaction studies are performed using models that are intrinsically limited to small systems; other studies are performed with brute force methods by examining the evolution of the system as described by molecular dynamics simulations. Both approaches are unsatisfactory, for different reasons.

What we need for the dynamics of the reactions, as well as for the dynamics of other molecular processes, is the availability of computational methods accurate enough to reach a precision sufficient to preserve the essential features of phenomena of real chemical interest, but simple enough to permit analyses and interpretations. Here again a controlled reduction in the number of the degrees of freedom given by continuum models may play an important role.

In this paper I have not mentioned several aspects of the continuum methods that have already been developed and amply used, and which will play an important role in the development of continuum or semi-continuum methods, such as the use of nonequilibrium solvation to name an example independently elaborated by the Pisa and Nancy groups. Many other proposals have been made in the last few years by others, such as Basilevsky 82, 83], Borgis [84, 85, 86], and Frediani [87], to name but a few, who are modifying some basic aspects of the continuum models.

In one section of this paper I underlined the need for a continuous critical examination of the existing implementation, with examples drawn from the basic model, but it should be clear that this need is even more urgent for the far more complex formulations that people working on the continuum theory are now working on.

To conclude, allow me to reiterate the salient points of this review. Theoretical and computational chemistry must pursue two goals: to give a description and interpretation of phenomena of chemical interest, and to provide representations of phenomena not yet studied, or that are impossible to study with experimental laboratory tools. The two goals must not be confused, but to some extent they may be pursued in parallel. Continuum approaches that are not limited to the liquid phase but can be extended to other types of condensed matter have some characteristics that are useful for both theoretical analysis and chemical computation. Such characteristics are related to the controlled reduction in the number of degrees of freedom of the system one has to monitor during the study. I feel confident that the advantages of exploiting these characteristics will attract many young people into this area of scientific research, bringing with them enthusiasm and innovative ideas.

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