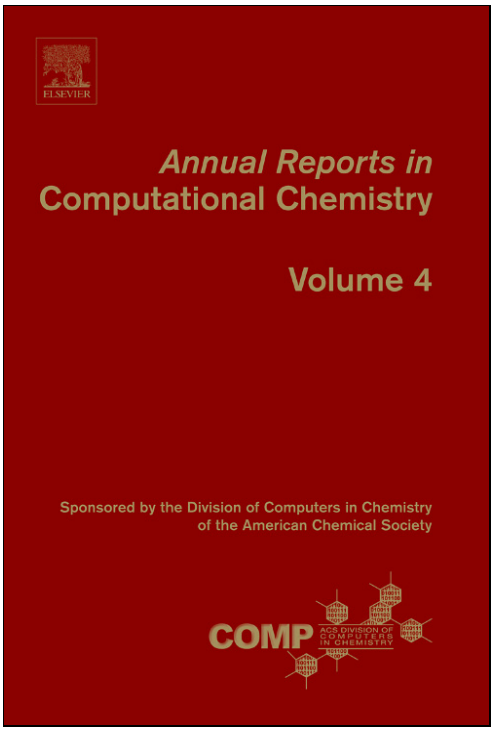

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CHAPTER 7

Implicit Solvent Models in Molecular Dynamics Simulations: A Brief Overview

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Contents

1. INTRODUCTION

The effects of solvent environment must be taken into account for realistic modeling of bio-molecules. Traditionally, this has been accomplished by placing a sufficiently large number of individual water molecules around the solute, and simulating their motion on an equal footing with the molecule of interest. While arguably the most realistic of the current theoretical approaches, this *explicit solvent* methodology suffers from considerable computational costs, which often become prohibitive, especially for large systems or long time-scales, such as those involved in the folding of proteins. Other problems with the approach include the difficulty, and often inability to calculate relative free energies of molecular conformations due to the need to account for very large number of solvent degrees of freedom.

An alternative that is becoming more and more popular—the *implicit solvent model* [1–7]—is based on replacing real water environment consisting of discrete

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molecules by an infinite continuum medium with the dielectric and "hydrophobic" properties of water. Presented below is a very brief overview of the current state of the methodology, with specific focus on the hierarchy of underlying approximations and the use of corresponding computational models in molecular dynamics (MD) simulations. One specific example—the Generalized Born model—is discussed in relatively greater detail, reflecting the author's own experience with the development of this model.

2. IMPLICIT SOLVENT FRAMEWORK

Implicit solvent models have several advantages over explicit water representations, especially in molecular dynamics simulations. These include the following.

Lower computational costs for many molecular systems, and better scaling on parallel machines. The effective cost reduction may be particularly significant if one takes into account the improved sampling: in contrast to explicit solvent models, solvent viscosity that slows down conformational transitions can be turned off completely within implicit representations.

Effective ways to estimate free energies; since solvent degrees of freedom are taken into account implicitly, estimating free energies of solvated structures is much more straightforward than with explicit water models.

Since implicit solvent models correspond to instantaneous dielectric response from solvent, there is no need for the lengthy equilibration of water that is typically necessary in explicit water simulations. This feature of implicit solvent models becomes key when charge state of the system is changed many times during the course of a simulation, as, for example, in constant pH simulations.

Finally, the implicit solvent approach has a clear advantage over explicit solvent in computing and making physical sense of energy landscapes of molecular structures. Here, implicit averaging over solvent degrees of freedom eliminates the "noise"—an astronomical number of local minima arising from small variations in solvent structure.

2.1 The hierarchy of underlying approximations

When contemplating a use of practical techniques based on the implicit solvent framework, one should be keenly aware of the fact that all of the attractive features of the methodology listed above come at a price of making a number of approximations whose effects are often hard, if not impossible, to estimate. Note that the *discrete* → *continuum* step is not the only deviation from reality: as one descends the "tree of approximations" that the methodology is based upon, Figure 7.1, down to models used in practice today, more and more approximations are made. Also note that some familiar descriptors of molecular interaction, such as solute–solvent hydrogen bonds, are no longer explicitly present in the model—instead, they come in implicitly, albeit at a mean-field level, and contribute to the overall solvation energy.

In many molecular modeling applications, and especially in molecular dynamics, the key quantity that needs to be computed is the total energy of the

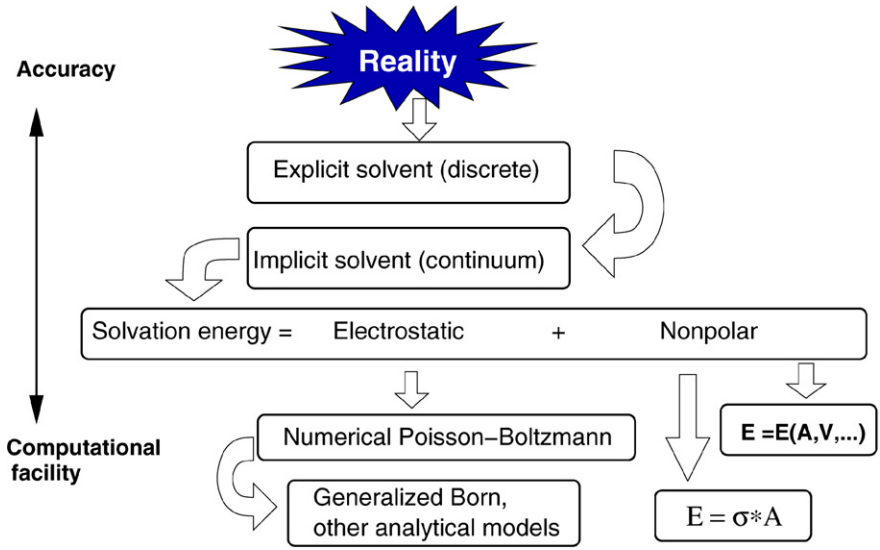

FIGURE 7.1 An "approximations tree" of the implicit solvent framework.

molecule in the presence of solvent. This energy is a function of molecular configuration, its gradients with respect to atomic positions determine the forces on the atoms. The total energy of a solvated molecule can be conveniently written as $E_{\text{tot}} = E_{\text{vac}} + \Delta G_{\text{solv}}$, where E_{vac} represents molecule's potential energy in vacuum (gas-phase), and ΔG_{solv} is defined as the free energy of transferring the molecule from vacuum into solvent, i.e. solvation free energy.[1] In practice, once the choice of the gas-phase potential function, or force-field, E_{vac} is made, its computation is relatively straightforward [8]. The difficulty comes from the need to estimate the effects of solvent, encapsulated by the ΔG_{solv} term in the above equation. At present, the implicit solvent framework makes the following simplifying approximation to estimate ΔG_{solv}:

$$\Delta G_{\text{solv}} = \Delta G_{\text{el}} + \Delta G_{\text{nonpolar}}, \tag{1}$$

where $\Delta G_{\text{nonpolar}}$ is the free energy of solvating a molecule from which all charges have been removed (i.e. partial charges of every atom are set to zero), and ΔG_{el} is the free energy of first removing all charges in the vacuum, and then adding them back in the presence of a continuum solvent environment. To proceed, one needs practical methods of computing both ΔG_{el} and $\Delta G_{\text{nonpolar}}$. The "hydrophobic" part $\Delta G_{\text{nonpolar}}$ represents the combined effect of two types of interaction: the favorable van der Waals attraction between the solute and solvent molecules, and the unfavorable cost of breaking the structure of the solvent (water) around the solute. The common approximation widely in use today [9] assumes both of these contributions to be proportional to the total solvent accessible surface area

[1] Technically, the above decomposition is already an approximation made by most classical (non-polarizable) force-fields, as it assumes this specific separability of the Hamiltonian.

(A) of the molecule, thus taking $\Delta G_{\text{nonpolar}} \approx \sigma \times A$, with the proportionality constant derived from experimental solvation energies of small non-polar molecules. Substantial uncertainty exists in what appropriate value of the surface tension σ should be used in simulations, which perhaps reflects the limitations of this approximation itself. Strong arguments for the use of less drastic approximations for $\Delta G_{\text{nonpolar}}$, e.g. those that treat solute-solvent van der Waals interactions ("volume term") separately from the surface area term, have also been made [10,11]. At the same time, some researchers choose to neglect the surface area term altogether in MD simulations, especially if no large conformational changes are expected, for example in simulations of proteins in their native states. Regardless of the specific form, computing the hydrophobic term has not so far been the computational bottleneck of a typical MD simulation. Currently, the most time-consuming part is the computation of the electrostatic contribution to the total solvation free energy, ΔG_{el}. The underlying long-range interactions are critical to function and stability of many classes of biological and chemical structures, and so it is not surprising that considerable effort was put into making these computations accurate and fast.

2.2 The Poisson–Boltzmann model

If one accepts the continuum, linear response dielectric approximation for the solvent, then the Poisson equation of classical electrostatics provides an exact formalism for computing the electrostatic potential $\phi(\mathbf{r})$ produced by a molecular charge distribution $\rho(\mathbf{r})$. The screening effects of salt can be added at this level via an approximate mean-field treatment, resulting in the so-called *Poisson–Boltzmann* (PB) equation [13]. In general, this is a second order non-linear partial differential equation, but its simpler linearized form is often used in biomolecular applications:

$$\nabla\big[\epsilon(\mathbf{r})\nabla\phi(\mathbf{r})\big] = -4\pi\rho(\mathbf{r}) + \kappa^2\epsilon(\mathbf{r})\phi(\mathbf{r}), \tag{2}$$

where $\epsilon(\mathbf{r})$ is the position-dependent dielectric constant, and the screening effects of salt enter via the Debye–Hückel parameter $\kappa \sim \sqrt{[salt]}$. Once the $\phi(\mathbf{r})$ for a given molecular configuration is obtained via numerical solution of the PB equation, the electrostatic part of the solvation energy, ΔG_{el}, can be computed. Details of numerical procedures for solving the PB equation along with a discussion of some of the related technical issues, can be found in recent literature on the subject, e.g. [12] and references therein. While the numerical PB formalism has been successfully applied to "static" structures for the past 20 years, it was not until quite recently that its use in MD simulations has been reported. In part, this delay was due to the relatively high costs associated with solving the PB equation at every MD step. Technical difficulties associated with computing forces due to dielectric boundary had to be overcome as well. So far, very few, mainly "proof-of-concept" PB-based MD simulations have been reported [7,14–16]. Still, the approach holds tremendous potential for MD simulations [13]. This is because the PB model has

a rigorous physical basis and requires fewer fundamental approximations to physical reality than most other implicit solvent approaches currently in use. The model also serves as a natural reference point on the "approximations tree," Figure 7.1. Comparisons of results from PB-based simulations with those based on the more fundamental explicit solvent model helps reveal basic limitations of the implicit solvent approach itself, while comparisons with even more approximate methods, such as the widely used generalized Born model discussed below, help assess the accuracy of the latter [17].

2.3 The Generalized Born model

The need for computationally facile models for dynamical applications requires further trade-offs between accuracy and speed. Descending from the PB model down the approximations tree, Figure 7.1, one arrives at the generalized Born (GB) model that has been developed as a computationally efficient approximation to numerical solutions of the PB equation. The analytical GB method is an approximate, relative to the PB model, way to calculate the electrostatic part of the solvation free energy, ΔG_{el}, see [18] for a review. The methodology has become particularly popular in MD applications [10,19–23], due to its relative simplicity and computational efficiency, compared to the more standard numerical solution of the Poisson–Boltzmann equation.

2.3.1 The underlying approximations of the GB model

GB models evaluate electrostatic part of solvation free energy as a sum of pairwise interaction terms between atomic charges. For a typical case of aqueous solvation of molecules with interior dielectric of 1, these interactions are approximated by an analytical function introduced by Still et al. [24]:

$$\Delta G_{\mathrm{el}} \approx -\frac{1}{2}\left(1-\frac{1}{\epsilon_w}\right)\sum_{i,j}\frac{q_i q_j}{\sqrt{r_{ij}^2 + R_i R_j \exp(-\frac{r_{ij}^2}{4R_i R_j})}} \tag{3}$$

where r_{ij} is the distance between atoms i and j, q_i and q_j are partial charges and $\epsilon_w \gg 1$ is the dielectric constant of the solvent. Screening effects of monovalent salt can be introduced at the Debye–Hückel level by a simple, computationally inexpensive empirical correction to the above equation [25].

The key parameters in the GB function are the effective Born radii of the interacting atoms, R_i and R_j, which represent each atom's degree of burial within the solute. More specifically, the effective radius of an atom is defined as the radius of a corresponding spherical ion having the same ΔG_{el} as would the same molecule with partial charges set to zero for all atoms except the atom of interest. Assuming that effective Born radii can be computed efficiently for every atom in the molecule, computational advantages of Eq. (3) relative to numerical PB treatment become apparent: the GB formula is simple, its analytical derivatives with respect to atomic positions immediately provide the forces. In practice, the effective radius for each atom is generally calculated by first approximating the electrostatic energy density due to the atom of interest by some reasonably simple expression and then integrating over the appropriate volume [26–32] or surface [33].

The Coulomb field approximation—CFA—is historically the first approximation of that nature. Although it makes what appears to be a fairly drastic assumption that the electric field generated by the atomic point charge is unaffected by the non-homogeneous dielectric environment created by the solute, practical routines developed on the basis of CFA are still widely used. Fortuitous cancellation of errors [34] and computational efficiency of the approximation have contributed to its success. Empirical corrections to the CFA based on multiple integrals over solute have lead to spectacular improvements in accuracy of the GB model relative to PB treatment [30,31]. Several GB models based on these approximations have been implemented in CHARMM. Recently, it was shown that the same, and possibly even better level of accuracy can be achieved with a single integral [35]. It remains to be seen whether potential advantages of this approximation [36]—termed R6—will translate into practical gains once implemented in MD codes.

Computationally effective integration over physically realistic [37], but geometrically complex molecular volume (or surface) presents a set of its own challenges: routines that match molecular volume closely, such as GBMV models [30,31] in CHARMM, typically come at a price of noticeably higher computational costs [38]. Alternative approaches include the use of physically less justified, but computationally more suitable VDW volume, combined with pairwise descreening approach [27], and empirical corrections that bring in some elements of molecular volume. Such compromise solutions [32,39], e.g. GB-OBC and GBn models in AMBER, are significantly faster, but at a cost of making additional approximations to reality.

Currently, a large variety of flavors of the GB model are available in many molecular simulation packages. The vast majority, if not all, of these models share the same foundation—Eq. (3)—but may differ substantially in the way the effective radii are computed. The algorithmic simplicity and reasonable accuracy of the GB approximation, combined with its availability in popular modeling packages, have made it the current "workhorse" in many practical applications of the implicit solvent methodology.

2.3.2 GB-based MD simulations. Examples

Protein folding. Exploring large conformational transitions is one of several areas where the advantages of implicit solvent framework, and the GB model in particular, become apparent. Several all-atom MD simulations of *ab initio* folding of small proteins have been reported. Examples include 20-residue "trpcage" protein [40], 36-residue villin headpiece [41], and a 46-residue helix bundle [42]. In these simulations the folded state was predicted to within 2 Å from experiment (C_α rmsd), and in some cases [40] within 1 Å. Energy landscapes computed within the implicit solvent framework were used to gain insights into the folding mechanisms [41,43]. Note that experimental folding times for even the fastest folding proteins is of the order of microseconds, whereas in some of the above simulations [40] the native state was reached on 10 ns time-scale. The comparison gives a very rough idea of the magnitude of conformational search speed-ups that one can expect in these types of simulations through the use of the GB approach.

Large-scale motions in proteins. The conformational search speed-up allows one to study large-scale motions in proteins and protein complexes. The use of the methodology to understand large conformational changes of the active site flaps in HIV protease [44] is a representative example: it is unlikely that a comparable explicit solvent study would currently be computationally feasible.

Membrane environment. Membranes are large structures, translocation of molecular structures through membranes may involve significant conformational changes, and so these systems are natural candidates for implicit solvent modeling. One of the challenges here is accurate and computationally facile representation of the complex dielectric environment that, in the case of membranes, includes solvent, solute, and the membrane, all with different dielectric properties. Corrections to the GB model have been introduced [45–47] to account for the effects of variable dielectric environment. Other implicit membrane models, not based on the GB, have also been proposed [48].

The DNA. Compared to proteins, implicit solvent MD simulations of nucleic acids are relatively new, and not as many. A number of methodological issues still await resolution, in particular that of appropriate treatment of multi-valent ions that are often critical for nucleic acid function. So far, the GB methodology has been employed to model free DNA in solution [49,50], binding between proteins and nucleic acids [51–53], as well as for energetic analysis of conformational changes such as the $A \rightarrow B$ transition [21]. The potential of the methodology for modeling large scale dynamics of the DNA has been demonstrated in a recent all-atom study of the nucleosome and its 147-bp DNA free in solution [54].

Constant pH simulations. The charge states of all ionizable groups remain fixed throughout the course of a typical MD simulation, regardless of the conformational changes that the structure may undergo. In reality, changes in protonation state and conformational changes are strongly coupled; this coupling may lead to non-trivial effects. To model these effects, several models have been developed. One of them employs a continuous protonation state model [55], in which equations of motion are used to time-evolve the protonation coordinate; convergence to physical protonation state of 1 or 0 is enforced by an adjustable potential barrier. An alternative approach [56] operates directly in the physical protonation space: protonation states are accepted or rejected on the fly, according to a Metropolis criterion, during the course of the MD simulation. It is the instantaneous dielectric response of the implicit solvent model that makes these on-the-fly estimates of relative energies possible.

2.3.3 Limitations of the GB model

The generalized Born model is separated from reality by several layers of approximations, Figure 7.1, each of them adding its own limitations to the method. The fundamental "discrete → continuum" approximation obviously eliminates a number of solvent effects that depend on the finite size of water molecule, such as de-wetting. Likewise, the implicit solvent model cannot describe effects of tightly bound water molecules, which may be a serious limitation when those are important for function or stability of the structure of interest. One also wonders how well the approximation works inside deep binding pockets, where solvent

can hardly be considered as having properties of the bulk. Also, the additivity of ΔG_{el} and $\Delta G_{\mathrm{nonpolar}}$ in the decomposition of total solvation free energy holds only approximately: if it were exact, absolute values of solvation energies of ions of the same size and opposite charge (and the same magnitude) would be identical, which is not the case in reality [57]. The Poisson–Boltzmann approximation inherits generic limitations of mean-field theories and linear response approximations. In particular, the neglect of correlation between counterions, especially multi-valent ones such as Mg^{2+}, may be a serious problem in the modeling of nucleic acids.

While all of these limitations are well known, their combined effect is hard, if not impossible to quantify in realistic biomolecular simulations. Understanding the effects of a single approximation, such as the $PB \rightarrow GB$ step, may be somewhat easier. Note that the GB and PB models share the same physical basis, and so one can, in principle, "derive" the GB from the PB. For example, it was recently shown that, without the heuristic exponential term, the key formula of the GB model, Eq. (3), is the limiting case ($\epsilon_w \rightarrow \infty$) of the exact solution of the Poisson equation for an arbitrary charge distribution inside an ideal sphere [36,58]. It is also possible to differentiate the effects of the $PB \rightarrow GB$ approximation from the more fundamental limitations of the PB model itself. For example, it was shown [59] that the folding landscape of β-hairpin derived from GB-based simulations is substantially different from that predicted by an explicit solvent model, which is generally more consistent with experiment. A subsequent study [60] revealed that a significant part of this discrepancy was already present at the PB level. Direct comparisons of ΔG_{el} between GB, PB, and explicit solvent are especially valuable in the context of understanding the separate effects of the approximations made. For example, it was found that even the use of "perfect" [34] effective radii in the GB Eq. (3) did not match the accuracy of the PB in predicting relative energies of poly-alanine conformational states [61]. The error of the PB itself, relative to explicit solvent treatment, was found to be smaller, but not negligible. Overall, ensembles of poly-alanine conformations generated in this study with the GB-based MD showed an overabundance of α-helical secondary structure relative to the explicit solvent results.

Raw computational speed has been considered one of the key advantages of the GB model. However, note that the cost of a calculation based directly on Eq. (3) is generally $O(N^2)$ for a system of N atoms, while the scaling is more favorable, $N \log(N)$, for Ewald-based methods used in explicit solvent simulations. For large systems, e.g. the nucleosome (25,000 atoms), the number of nanoseconds of MD per CPU hour may actually be less in a GB-based simulation (without additional approximations such as cut-offs) than in a comparable explicit solvent run [54], although the conformational search is still much faster in the implicit solvent.

2.4 Other models based on implicit solvation

While at present the GB models are arguably the most often used practical approaches in MD simulations based on implicit solvation, they are by no means the only ones. Some representative alternatives to the GB (and the PB) are listed below, in an order that roughly corresponds to their place on the "approximations

tree" of Figure 7.1. In an ideal world, models that employ fewer approximations to reality may be expected to be more accurate, but this expectation may not apply to practical implementations of the methods.

Historically, MD simulations often relied on the so-called distance-dependent dielectric model [62] to account for solvation effects. In this approach, electrostatic effects are modeled by Coulomb's law with the dielectric being some fixed function of the charge–charge distance, e.g. $\epsilon(r) = r$ in the most basic form of the model. Even though the model is generally expected to be less accurate than the GB [17], its utmost simplicity and computational efficiency keep it in active use today [63,64].

Several methods for computing ΔG_{el} can be placed at roughly the same level of approximation as the GB. Examples include the generalized reaction field method [65] and the ALPB [66] model. The latter has a simple functional form similar to the GB, but contains an extra physical parameter (effective electrostatic size of the solute) and a more realistic dependence on dielectric constants. Another example of models in this group are approaches for estimation of ΔG_{el} based on image-charge solutions [67,68]. Yet another approach, AGBNP [10], combines the basic GB framework with a model for $\Delta G_{\mathrm{nonpolar}}$ that goes beyond the surface area approximation.

At the "PB level," a model based on a very different paradigm has recently been tested in a "proof-of-concept" simulation: Maxwell's equations for the electric and magnetic field, coupled with the usual Newton's equations of motion for the charges were used to determine time-evolution of the system [69].

Going beyond the mean-field level, several "hybrid" approaches are now being explored in MD simulations. Examples include a recent model [70] in which the immediate hydration of the solute is modeled explicitly by a layer of water molecules, and the GB model is used to treat the bulk continuum solvent outside the explicit simulation volume. A similar idea was recently found very effective in the context of replica-exchange simulations [71]. An explicit ion/implicit water (PB) solvation model for molecular dynamics of nucleic acids has recently been tested [72].

Some approaches approximate the total solvation energy ΔG_{solv} without explicitly assuming additivity of the ΔG_{el} and $\Delta G_{\mathrm{nonpolar}}$ components. One example is a Gaussian solvent-exclusion model [73] based on an empirical decomposition of ΔG_{solv} into contributions from different chemical groups. Models based on "first-principles" free energy functionals have also been proposed [74].

3. CONCLUSIONS AND OUTLOOK

An accurate description of the solvent environment is essential for realistic biomolecular modeling, but often becomes prohibitively expensive computationally if water is treated explicitly. Implicit solvent framework is an attractive alternative that offers several significant advantages over the explicit water representation, including lower computational costs, faster conformational search, and very effective ways to estimate relative free energies of conformational ensembles. However, these advantages come at a price of making several fundamental,

hierarchical approximations to reality. Additional accuracy/speed trade-offs are often made in the development of computationally facile models for practical MD simulations.

Prominent among these models is the generalized Born (GB) model: although separated from reality by several layers of approximation, it apparently captures enough of the key physics of aqueous solvation to be practically useful. Compared to other models based on implicit solvation, this algorithmically simple model is arguably the one that is currently used most often in MD simulations. Many successful applications of the model to challenging problems, such as the protein folding, or the exploration of large-scale motions in proteins or DNA, have been reported. For some types of simulations, e.g. constant pH molecular dynamics, models based on implicit solvation such as the GB appear to be the only ones currently available in practice.

At the same time, examples where the GB model breaks down are also well known. Part of the overall error in these cases is attributable to the $PB \rightarrow GB$ approximation, while the remainder comes from the more fundamental limitations of the general implicit solvent framework itself. These examples are extremely important for defining the current boundaries of applicability of the GB model; they also suggest directions for future improvements.

A number of alternatives to the GB, both below and above it on the "approximations tree" have been tested in molecular dynamics simulations. Approaches that make fewer fundamental approximations to reality, such as those based directly on the Poisson–Boltzmann treatment of solvation or ones that even go beyond the mean-field level, are particularly attractive from the accuracy point of view. More testing is needed to better characterize the overall performance of these models in practical MD simulations.

In summary, the use of implicit solvation models in molecular simulations offers considerable rewards, both at conceptual and practical levels. However, compared to the more established explicit solvent approach, less is known about the domain of applicability of these models, and so extra care must be taken when using them in practice. Drawing on the analogy with the development of the empirical explicit solvent force-fields over the past 30 years, it is likely that improvements in the implicit solvent framework accompanied by accumulation of practical experience will eventually make the framework a standard approach within its reasonably well-defined domain.

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