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Improving implicit solvent simulations: a Poisson-centric view

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Recent developments in implicit solvent models may be compared in terms of accuracy and computational efficiency. Based on improvements in the accuracy of generalized Born methods and the speed of Poisson–Boltzmann solvers, it appears that the two techniques are converging to a point at which both will be suitable for simulating certain types of biomolecular systems over sizable time and length scales.

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Introduction

Despite the rapid growth in computing power and the continuing improvements in molecular simulation methods, exhaustive sampling of configuration space is still impractical for most biomolecular systems of interest. The difficulty in simulating these systems lies in their high dimensionality; an average protein from the genomic databases has roughly 350 amino acids or approximately 5500 atoms. Sampling the approximately 30 000 degrees of freedom intrinsic to such an 'average' protein is already very challenging. However, accurate modeling of the system also requires the inclusion of interactions with the aqueous environment, including solvent, co-solutes and mobile ions. A standard explicit solvent approach to simulating the aqueous environment models the water and ions in full molecular detail. For this average 350 amino acid protein surrounded by a standard 10–12 Å of explicit solvent [1•], this can result in the addition of another 20 000–30 000 atoms to the simulation, further exacerbating the sampling problem.

Implicit solvent or 'continuum' methods reduce the degrees of freedom of the system by using an approximate 'pre-averaging' of the interactions of the solvent and mobile ions with the biomolecule [2]. This averaging usually splits solute–solvent interactions into polar and apolar components, which are calculated using a variety of methods (see below and [3••]). The polar component of continuum models typically describes the dielectric response of the solvent to the charge distribution of a solute. Simple dielectric continuum models of ion and protein solvation have been in use for over 80 years [4,5]. These models have since evolved in numerous ways to accurately describe solvation energies and forces for biomolecular systems. Modern dielectric continuum models can be loosely grouped into two basic categories: generalized Born (GB) methods and Poisson or Poisson–Boltzmann (PB) approaches. Implicit solvent models of the apolar component of solvation forces and energies continue to evolve, with several different approaches currently employed in biomolecular simulations.

There have been several reviews of implicit solvent methods over the past few years (see [3••,6–9] and citations therein). Recently, Feig and Brooks [3••] published an article in *Current Opinion in Structural Biology* that provides an excellent review of the GB approach to implicit solvent models. In their article, the authors present an overview of progress in GB methods, various models of apolar solvation and applications of implicit solvent simulations. The goal of this current review is to provide an overview of recent advances in PB methods, compare and contrast GB and PB theory, present some applications of PB solvers to biomolecular systems, discuss some of the limitations of PB theory and speculate on potential future directions for research in implicit solvent methodology.

'It came from the continuum' theory

To complement the introduction to GB approaches by Feig and Brooks [3••], a brief overview of the PB model will be presented here. At the core of PB theory is the approximation of the solvent as a dielectric continuum, that is, the assumption of linear and local polarization of the solvent due to an applied field. Under this approximation, it is possible to derive the Poisson equation from statistical mechanical theories for simple liquids [10]. The Poisson equation assumes a fixed charge distribution (usually solute charges) in a dielectric continuum; the PB equation generalizes this dielectric continuum approximation to include a mobile charge distribution (e.g. counterions and co-ions) that responds to the electrostatic potential. PB theory assumes that the mobile charges follow a Boltzmann distribution in the mean field approximation [11] to give a non-linear partial differential equation for the dimensionless electrostatic potential $\phi(x)$:

$$-\nabla \cdot \varepsilon(x)\nabla\phi(x) - \sum_{i=1}^{m} c_i q_i e^{-q_i\phi(x)-V_i(x)} = \frac{4\pi e_c^2}{kT}\rho(x) \qquad (1)$$

where the coefficients are a function of position x; $\varepsilon(x)$ is the dielectric coefficient describing the variation of the dielectric response between the relatively low polarizability solute and the higher polarizability solvent, c_i is the concentration of mobile ion species i, q_i is the charge of mobile ion species i, $V_i(x)$ describes steric interactions between the solute and ions of species i, e_c is the electron charge, k is the Boltzmann constant, T is the absolute temperature and $\rho(x)$ is the fixed charge distribution of the solvent in units of electrons. This equation is usually solved in conjunction with boundary conditions, which are described by the asymptotic behavior of the solution (e.g. the Debye–Hückel limiting law) [8]. Equation 1 represents the 'full' or non-linear form of the PB equation; this form is often linearized by assuming $q_i\phi(x) << 1$.

The apolar components of implicit solvent methods have been reviewed on numerous occasions [2,6], most recently in this journal by Feig and Brooks [3••]. Currently, the apolar solvation term is still the most heuristic component of any implicit solvent model. By far the most popular apolar methods are the 'surface area' (SA) models, which typically represent the apolar terms as linear functions of the molecular SA [12–14], in a manner similar to scaled particle theory [15]. Although these SA implementations have enjoyed some success, they are also subject to several caveats, including widely varying choices of 'surface tension' energetic coefficients [16] and inaccurate description of microscopic energetics [17••,18••]. As shown in recent work by Wagoner and Baker [17••], this inaccurate description of microscopic energetics is also exhibited by the lack of correlation between implicit and explicit apolar forces. Fortunately, several new developments in the treatment of apolar solvation incorporate more of the microscopic details of solvation. In particular, work by Gallichio and Levy [18••], and similar work by Zacharias [19••] have resulted in a new description of apolar hydration energies, which correctly balances the work associated with cavity formation and the non-negligible van der Waals interactions between solute and solvent [20]. Other interesting research in the area of apolar hydration is being carried out by the Dill group; a very simple two-dimensional water model has been developed that captures many of the important physical aspects of water behavior [21••,22]. Although this work is still at the theoretical level, the model offers additional insight into apolar solvation and could eventually lead to alternative continuum solvent methods for describing this phenomenon.

Comparing generalized Born, Poisson–Boltzmann and explicit solvent models

Given the variety of models described above, how can the best method for a particular simulation be chosen? Ideally, all systems would be simulated with highly accurate and transferable explicit water models [23•,24,25]. However, as discussed above, such models add significant complexity to the simulation and therefore can become impractical for very large (or lengthy) molecular simulations. Although implicit solvent methods offer a compromise between detail and computational cost, the would-be simulator is still forced to choose between various approximate implicit solvent methods for the simulation.

PB theory is usually the touchstone of implicit solvent methodology [26]. Most other implicit solvent methods, such as GB, attempt to approximate the solution to the Poisson or PB equation with varying descriptions of dielectric coefficients and ionic accessibilities. In fact, with a few exceptions [18••], GB method accuracy is often assessed by comparison to PB solutions [26,27,28••]. Several studies have shown that, with appropriate parameterization, PB methods can provide polar solvation energies and forces for proteins and small molecules that compare well with results from explicit solvent simulations and experiment ([14,17••,29]; JA McCammon *et al.*, unpublished).

Unfortunately, PB methods are often slow. Although there have been numerous attempts to remedy this problem (see discussion in the next section), the historical problems with PB efficiency have opened the door to GB models and other simpler approximations. Furthermore, there are fundamental limitations to the use of PB theory to describe biomolecular systems, including failures due to the lack of discrete water [17••,27,30•,31•,32,33] and ions in the model [11,34,35•,36,37], limitations of which PB 'consumers' should be aware. However, these limitations are generally not unique to PB and apply to most other implicit solvent models as well.

However, GB methods also have their weaknesses. Recently, Onufriev *et al.* [26] demonstrated that GB methods can, in principle, offer levels of accuracy on a par with PB solvers. However, despite recent advances in GB methods [3••], it is not clear that comparable levels of accuracy are achieved in the routine application of GB models [27,38•,39,40•]. Although several groups have developed methods to address some of these accuracy issues (see Feig and Brooks for a review [3••]), it appears that there is ample room for improvement in GB as well as PB methods. Of course, GB methods are not the only implicit solvent alternatives to PB; Wang and Wade [41•] have presented a new surface-based implicit solvent model, with interesting comparisons to distance-dependent dielectric methods and GB techniques.

Given the considerations above, what solvation model should the would-be simulator choose for their system? The glib answer – 'whatever works' – might, in fact, be the most appropriate. The recent literature contains several comparisons of speed and accuracy for GB, PB and explicit solvent models [3••,17••,18••,26,27,28••, 32,40•,42•,43••,44]. GB models, although fast, run the

risk of incorrectly approximating the implicit solvent electrostatics described by solutions to the PB equation. Furthermore, there are situations in which any implicit solvent approach would be expected to fail; for example, when the molecular nature of water [17••,30•,31•,32,33,37] or ions is important [11,34,35•,36,37,45,46•]. The simulator should use caution and determine, perhaps *a priori* or by comparing the results of short model simulations, whether the acceleration offered by GB or PB methods provides the appropriate level of accuracy for the biological system of interest.

Advances in Poisson–Boltzmann methodology

The PB equation has been popular for modeling the electrostatic properties of biomolecular systems since pioneering work by Warwicker and Watson in the early 1980s [47]. Although the PB equation has appeared in numerous biomolecular applications over the past 25 years [8], recent work has focused on the use of PB in molecular dynamics [48••,49••,50,51], free energy calculations [52•,53,54•] and pK_a analysis ([55•,56,57]; see also the review on constant pH simulations by Mongan and Case in this issue). These applications require repeated solution of the PB equation, often millions of times during the course of a simulation. Due to these requirements, current work on PB methodology development has focused on accelerating the solution of the PB equation to make it suitable for such demanding applications.

Several methods have been developed to solve the PB equation in biomolecular contexts. The most common techniques are based on Cartesian mesh discretization of the system; these include the traditional finite difference [58,59] or finite volume/multigrid [60,61] approaches. These methods have evolved from the first sequential solvers, limited to small biomolecules, to large-scale parallel techniques, which allow solution of the PB equation for systems consisting of millions of atoms [61–63]. Several other methods for solving the PB equation have been developed over the past 20 years; these are reviewed in [8,64]. Alternatives to finite difference include new atom-centered methods [46•], as well as continuing work on boundary [65,66] and volume [67–69] finite element discretizations. However, finite difference methods, particularly in conjunction with multigrid solvers, have gained the most widespread use and demonstrate the best speed and efficiency in the applications listed above. The pre-eminence of finite difference methods in applications requiring rapid solution of the PB equation is mainly due to their efficiency; this, however, implies a lack of adaptivity. In fact, these methods can offer a limited 'adaptive' increase in resolution through sequential [70] or parallel [61] focusing methods; however, it is not comparable to the degree of adaptivity provided by finite element approaches. Finite difference techniques use a fixed discretization of the biomolecular system; boundary and volume finite element methods adapt their discretization to specific (and usually dynamic) aspects of the biomolecular structure. This adaptivity can add a significant computational cost to the set-up of the PB equation, and the calculation of observables such as forces and energies. It should be noted that adaptive finite element methods are often the optimal choice for the efficient solution of large non-linear problems with rapid spatial variation (e.g. the non-linear PB equation for very large macromolecules [62]). However, for the applications discussed here, they currently do not provide the level of efficiency necessary for rapid repeated solution of the PB equation in a molecular dynamics setting.

Increasing the speed of PB equation solvers has been of particular interest to the field of molecular simulation, as it offers the possibility that the PB equation could be routinely used to provide solvation forces for molecular dynamics simulations. In 2004, Feig *et al.* [28••] published a performance and accuracy comparison of seven popular PB solvers and also GB methods. As software packages are often optimized for different tasks with widely varying default parameters, simple performance comparisons are not always straightforward to interpret. However, this paper still provides a revealing survey of the 'state of the art' (as of 2004) of readily available PB software packages. The performance comparison covered a wide range of run times, with most PB packages requiring significantly longer than GB methods to evaluate solvation forces. A notable exception to this underperformance was ZAP [71], which combines a Gaussian-based dielectric function with very fast numerical solvers. In the comparison, ZAP obtained solutions to the PB equation at speeds that were comparable to those of GB methods — at the expense of significant deviations in solvation energies from the other PB solvers [28••]. These deviations are most probably due to the unique nature of the dielectric function used in ZAP [71] and can probably be remedied by judicious reparameterization of the force field. This is a common theme of many of the recent faster PB solvers and is discussed in more detail below.

In addition to the enhancement of the PB solvers tested in the comparison work by Feig *et al.* [28••], there have been several other recent developments. Of particular note is the work by Luo and Gilson assessing various ways in which PB solvers can be accelerated [49••,50]. Luo and co-workers combined a fast solver with increased numerical residuals, decreased update frequency and improved dielectric coefficient definitions; the end result was a fast PB solver that yielded stable simulations for trajectories of up to 4 ns in length. One of the most exciting aspects of this work is that many of the modifications proposed by Luo *et al.* are rather generic and can be applied to other PB solvers as well. Another interesting improvement in PB solution methodology was reported by Rocchia *et al.* [72]. With a few exceptions [73,74], the derivation of solvation

energies and forces from PB electrostatic potentials requires two calculations: the typical calculation with an inhomogeneous dielectric coefficient and a second calculation in a uniform dielectric to remove 'self-energies' implicit in the discrete solution [72,74]. Using concepts from classical continuum electrostatics [75], Rocchia *et al.* demonstrated that solvation energies can be obtained from a single PB calculation by using induced polarization charge rather than electrostatic potential [72]. Although this method is described in terms of discontinuous surface-based dielectric formulations, it appears feasible to extend it to more generic permittivity functions.

It is not surprising that several of the improvements outlined above address the dielectric function describing the protein. This function has evolved significantly over the past 20 years, from a discontinuous molecular surface [76,77] to more smoothly varying functions [49••,71,78]. The latter have the advantage of improved numerical stability in dynamics simulations, simpler construction and evaluation, and arguably a more physically realistic basis. Unfortunately, results obtained with the PB equation are also very sensitive to the choice of dielectric function. Recent work by Dong *et al.* [79•] has demonstrated that electrostatic contributions to protein–protein interaction energies calculated using a discontinuous dielectric function are very sensitive to the surface definition. In retrospect, this result should not have been very surprising; nearly every new dielectric function is accompanied by a new set of PB radius parameters adjusted to give correct solvation energies and forces [17••,29,71]. Although the PARSE parameter set [14] provides excellent results for the older discontinuous dielectric functions, it is not necessarily appropriate for modern dielectric functions. Along the same lines, explicit solvent force field radii should not be expected to give reasonable results when used with implicit methods such as PB or GB [17••]. Instead, each PB method implementing a different dielectric will probably require its own set of radii for accurate results. One can only hope that the resulting dielectric-specific radii will be derived from the existing abundance of explicit solvent force fields in a rational fashion (see, for example, Nina *et al.* [29] or JA McCammon *et al.*, unpublished), rather than further confusing the issue of parameter selection.

Conclusions

Given the rapid rate of improvement in GB and PB methodology, it probably won't be too long before the two methods converge to give similar levels of efficiency and accuracy for polar solvation energies and forces. Furthermore, the advances in apolar models mentioned above and reviewed elsewhere will probably result in improved methods that will eventually permit accurate calculation of apolar energies and forces. The next set of challenges for these methods will probably arise from the assumptions underlying all implicit solvent models. In particular, researchers will undoubtedly want to apply implicit methods to systems in which discrete water and ions play an important role, for example, ion- and ice-binding proteins, nucleic acids, certain ion channels, biomembranes and so on. In such cases, it seems unlikely that current implicit solvent models will offer the necessary accuracy, as they pre-average the very degrees of freedom that are of interest. Therefore, the focus of the simulation methodology in this area is likely to shift from very coarse-grained models of solvation to 'hybrid' models. These models will incorporate details of solvent and ions in the simulation as they are needed, to obtain the desired accuracy for observables such as distribution functions, free energies and so on. Indeed, preliminary work in this area [43••,80–82] demonstrates potential for the application of such multiscale models to the efficient and accurate modeling of biomolecular systems.

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