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Biomolecular electrostatics and solvation: a computational perspective

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Abstract. An understanding of molecular interactions is essential for insight into biological systems at the molecular scale. Among the various components of molecular interactions, electrostatics are of special importance because of their long-range nature and their influence on polar or charged molecules, including water, aqueous ions, proteins, nucleic acids, carbohydrates, and membrane lipids. In particular, robust models of electrostatic interactions are essential for understanding the solvation properties of biomolecules and the effects of solvation upon biomolecular folding, binding, enzyme catalysis, and dynamics. Electrostatics, therefore, are of central importance to understanding biomolecular structure and modeling interactions within and among biological molecules. This review discusses the solvation of biomolecules with a computational biophysics view toward describing the phenomenon. While our main focus lies on the computational aspect of the models, we provide an overview of the basic elements of biomolecular solvation (e.g. solvent structure, polarization, ion binding, and non-polar behavior) in order to provide a background to understand the different types of solvation models.

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1. Introduction and overview

An understanding of molecular interactions is essential for insight into biological systems at the molecular scale (Baker, 2004, 2005a, b; Baker *et al.*, 2006; Davis & McCammon, 1990; Dong *et al.*, 2008; Draper *et al.*, 2005; Feig & Brooks, 2004; Feig *et al.*, 2008; Fogolari *et al.* 2002; Gilson & Honig, 1987; Honig & Nicholls, 1995; McLaughlin, 1989; Prabhu & Sharp, 2006; Schutz & Warshel, 2001; Sheinerman *et al.*, 2000; Simonson, 2001, 2003; Warshel & Papazyan, 1998). Molecular interactions determine the structure, dynamics, and binding of biomolecules, and therefore play a central role in how cells develop, operate, communicate, and control their activities. Such interactions include several components (Leach, 2001; Schlick, 2002): contributions from linear, angular, and torsional forces in covalent bonds and non-bonded van der Waals and electrostatic forces (Stone, 1996). Among the various components of molecular interactions, electrostatics are of special importance because of their long-range nature and their influence on polar or charged molecules, including water, aqueous ions, proteins, nucleic acids, carbohydrates, and membrane lipids. In particular, robust models of electrostatic interactions are essential to understand the solvation properties of biomolecules and the effects of solvation upon biomolecular folding, binding, enzyme catalysis, and dynamics. Therefore, electrostatics are of central importance to understanding biomolecular structure and modeling interactions within and among biological molecules.

This paper discusses the solvation of biomolecules, and focuses on electrostatics from a computational perspective. We provide a brief overview of various biomolecular solvation models based on their level of detail. Advantages and caveats of different solvation models are discussed. Non-polar contributions to the solvation are also considered for the models.

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While our main focus lies on the computational aspect of the models, we summarize the basic elements of biomolecular solvation (e.g. solvent structure, polarization, ion binding, and nonpolar behavior) in order to provide a background to understand the solvation models. Examples such as titration state prediction and biomolecular recognition are provided to exhibit the application of solvation models. This review concludes with a short summary, and the directions of future research are stated as concluding remarks.

2. Characteristics of biomolecular solvation by water

Water solvation influences all aspects of biology, ranging from cellular function (Parsegian & Rau, 1984) to biomolecular interactions (Auffinger & Hashem, 2007; Prabhu & Sharp, 2006), to biopolymer stability (Ben-Naim, 1997) and the solvation of simple solutes (Dill *et al.*, 2005). In general, an interaction between solute and solvent is of great importance to understand the solvation. For biomolecular solvation where water is a major solvent, water is not only a passive medium but also actively exhibits unique nature that greatly influences the solvation of biomolecules. To understand this ubiquitous role of water, it is important to appreciate some of its most basic properties.

Solvent and ion interactions influence nearly all aspects of biomolecular structure and function. As a result, it is impossible to provide a comprehensive review of biomolecular solvation. Instead, we focus on those aspects of solvation most amenable to computational treatment. While this discussion includes acid/base chemistry and biomolecular titration state prediction, it exclude several other interesting areas including the role of solvent and ions in catalysis (Bombarda & Ullmann, 2010; Di Cera, 2006; Garcia-Viloca *et al.*, 2004; Martick *et al.*, 2008; Niu *et al.*, 2009; Page *et al.*, 2006; Rhodes *et al.*, 2006; Warshel & Dryga, 2011; Wells & Di Cera, 1992), spectroscopic probes of biomolecular electrostatics (Ensign & Webb, 2011; Hu & Webb, 2000; Stafford *et al.*, 2000; Webb *et al.*, 2011), solvent influences on biomolecular dynamics and flexibility (Bone, 2008; Fenimore *et al.*, 2004; Lubchenko *et al.*, 2005; Lucent *et al.*, 2007), and cosolute influences on biomolecular stability (Drozdov *et al.*, 2004; England *et al.*, 2008; Harries & Rosgen, 2008; Rösgen *et al.*, 2005, 2007; Tran *et al.*, 2008).

2.1 Water structure

Water is a unique, small molecule with all three constituent atoms capable of forming hydrogen bonds. As a result, water molecules can cluster together in various arrangements, driven by their cooperative tendency to maximize the number of hydrogen bonds formed. *Ab initio* calculations suggest that a water hexamer $(H_2O)_6$ has several stable configurations of comparable energies that include cage, cyclic, chair, boat, and prismatic conformations (Moore Plummer & Chen, 1987; Xantheas *et al.*, 2002; Xantheas & Dunning, 1994). Neutron and X-ray scattering have been used to characterize the average structure of bulk water. The radial distribution functions of OO, OH, and HH derived from these measurements provide valuable insight into local water structures (Root *et al.*, 1986; Soper, 2000; Soper & Phillips, 1986; Sorenson *et al.*, 2000). As an illustration, Fig. 1 shows the oxygen radial distribution function (RDF) around K^+, denoting that the first peak of oxygen RDF around K^+ is at an average separation of $\sim$2.8 Å between the closest water pair. The first peak extends to a minimum at $\sim$3.3 Å, indicating approximately 4.5 water molecules in the nearest coordination shell. The local structure of water has been rationalized as a 'dynamic' mixture of two states: one corresponds to a rigid ice-like structure,

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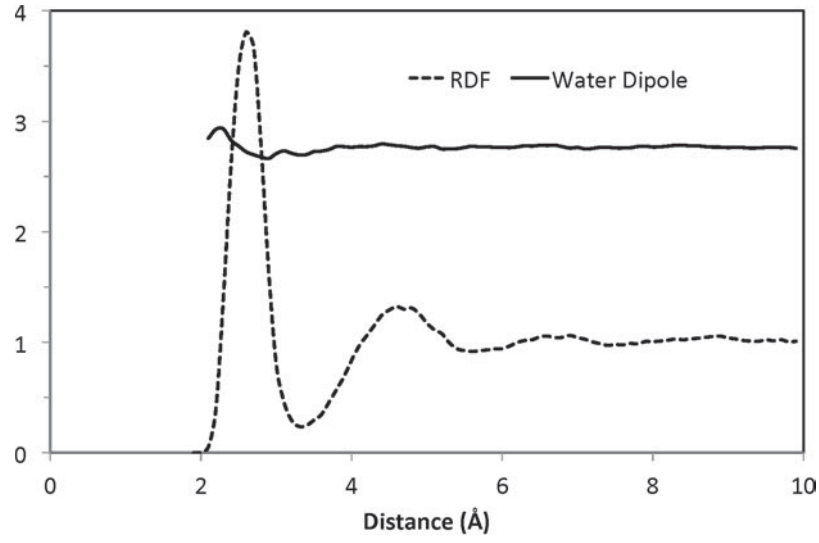


Fig. 1. Water structure and average dipole moment around a K^+ ion. The radial distribution function (RDF) of O … K^+ and water dipole moment were computed from molecular dynamic simulations of K^+ in water using a polarizable potential (Grossfield *et al.*, 2003; Ren & Ponder, 2003). Note that the average dipole moment of the water in the first solvation shell is roughly similar to that of bulk water.

Ice I_h, a hexagonal crystal form of ordinary ice (Fletcher, 1970) with four nearest neighbors at 2.8 Å; another corresponds to a denser ice-like structure, Ice II, a rhombohedral crystalline form with four water molecules at 2.8 Å plus another at 3.3 Å. Data from isochoric temperature differential experiments near the maximum-density-temperature peak, where the same densities can be achieved at two nearby temperatures, support the two-state theory (Bosio *et al.*, 1983; Robinson *et al.*, 1999; Sciortino *et al.*, 1990). Within this framework, properties such as the anomalous temperature dependence of the density can be interpreted as the dynamic competition between the two types of hydrogen-bonding networks in response to changes in temperature (Schmid *et al.*, 2001).

2.2 Bulk water polarization

One of the fundamental properties of water is its role as an excellent solvent for polar molecules. Some aspects of this favorable polar molecular solvation can be understood from the very macroscopic continuum perspective of water bulk polarization. Water molecules have a dipole moment that varies between 1.8 Debye (D) in vacuum (Clough *et al.*, 1973) to estimates of nearly 3 D in bulk water (Ren & Ponder, 2003; Silvestrelli & Parrinello, 1999). In a liquid environment, the molecular dipole moment of water will reorient in response to the application of an external field or the introduction of a solute charge distribution. The resulting reorientation creates a polarization (or dipole) density or so-called 'dielectric response' (Bottcher, 1952; Hansen & McDonald, 2000; Jackson, 1975) (see Figs 1 and 2). From the perspective of continuum electrostatics, this dielectric behavior is modeled as a linear relationship between the local field and electric displacement field because of local polarization—the coefficient of this relationship is the 'dielectric coefficient,' or permittivity. Dielectric coefficients of pure solvent depend on a variety of molecular properties of the solvent, including structure, density, permanent charge distribution, and molecular polarizability. Dielectric coefficients range from values as small

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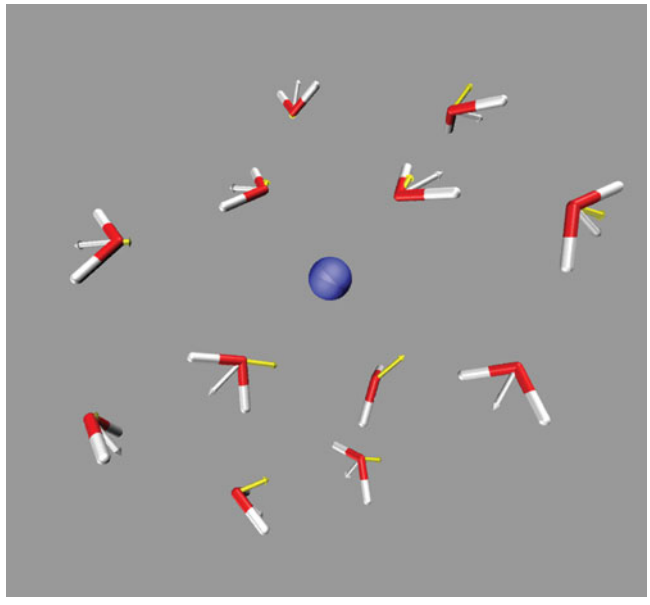


Fig. 2. The reorientation and polarization response of water upon the insertion of a cation (K^+) into the bulk water. The yellow vector on each water molecule represents the net induced dipole moment because of the electric field of the ion and other water molecules. The white vector is the permanent (gas-phase) dipole moments (1.8 Debye) of the water molecule. The average dipole moment of a water molecule in liquid is 2.6–3.0 D according to various theoretical calculations. The snapshot is taken from molecular dynamics simulations of K^+ in water using the AMOEBA potential (Ren & Ponder, 2003).

as 1 for a vacuum, to values of 2–4 for non-polar solvents (alkanes), 10–20 for weakly polar molecules such as ammonia and ethanol, to approximately 80 for water at room temperature, and even larger values for some polar liquids such as formamide (105).

2.3 Electronic and nuclear water polarization

In addition to the bulk polarization of solvent, the charge distributions of solvent and solute molecules interact via mutual polarization, i.e., the reorganization of their electronic charge distributions. The reorganization of electrons is much faster than the overall reorientation and redistribution of solvent molecules (Nicol, 1974). It has been estimated that electronic solvation (as opposed to reorganization solvation) could account for as much as half of the overall electrostatic solvation free energy (Cukier & Zhang, 1997). Processes such as photoexcitation and electron and proton transfers occur on timescales between or close to those of electronic and nuclear responses (Cramer & Truhlar, 2001). Theoretical frameworks have been devised to separate the solvent electronic and nuclear response either adiabatically or non-adiabatically (Marcus & Sutin, 1985; Moser *et al.*, 1992). In theoretical studies, continuum or molecular mechanics (MM) solvent often supplements quantum mechanical treatment of the solutes (reactants).

2.4 Non-polar solvation by water

Another important aspect of solvation involves the mechanism of solvent interactions with uncharged solutes. This type of solvation phenomenon has many names including hydrophobic,

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apolar, and non-polar; we refer to it as non-polar solvation in this review. Non-polar solvation has been extensively studied and modeled, and there are many good references available for interested readers to explore, the following citations are only a few (Ben-Naim, 2006; Hummer *et al.* 1999, 2000; Pratt, 2002; Pratt & Chandler 1977, 1980; Pratt & Pohorille, 2002). This section focuses on the basic properties of non-polar solvation important for the general aspects of biomolecule–solvent interactions.

Water's small size and flexibility in forming infinite hydrogen-bonding networks around solutes contribute to the hydrophobic effect that is widely appreciated in biology. Nuclear magnetic resonance (NMR) (Mizuno *et al.*, 1995), high-performance liquid chromatography (HPLC) (Silveston & Kronberg, 1989), and neutron scattering (Soper, 2000; Soper & Phillips, 1986) experiments suggested that water structure is different around a hydrophobic solute. Atomic and Monte Carlo simulations also support such structural change in water molecules, depending on surrounding environment (Lynden-Bell & Rasaiah, 1997; Madan & Sharp, 1996). Efforts to understand hydration based on water structure and entropy changes date back several decades (Frank & Evans, 1945). Sophisticated theories have been evolved to delineate the entropy and enthalpy contributions to solvation, the influence of dispersion and electrostatics, the effect of solute-length scale, temperatures, and other external factors to understand solvation phenomenon (Chandler, 2005; Garde *et al.*, 1996; Hummer *et al.*, 2000; Schmid *et al.*, 2001). Advancements in molecular simulations have and will continue to help further our understanding of the role of solvation in biomolecular structure and dynamics.

Pioneering work by Pratt and Chandler (Pratt, 2002; Pratt & Chandler, 1977, 1980; Pratt & Pohorille, 1992, 2002) identified some of the fundamental determinants of non-polar solvation. Not surprisingly, a major contribution to the energetics of solvating an uncharged molecule is the energy required to create a cavity in the solvent. This cavity-creation term describes the work involved with accommodating within the solvent: purely strong solute–solvent repulsive interactions. Later work by Hummer *et al.* (Hummer *et al.*, 1996) translated this model in an information theory context by noting that the energetics of cavity creation are intrinsically encoded in the density fluctuations of the solvent. The energetics of cavity creation in water is strongly dependent on both the size and the shape of the non-polar solute with a crossover in energetics and solvent density near the solute interface when the solute size approaches nanometer-length scales (Ashbaugh, 2009; Ashbaugh & Pratt, 2006; Ben-Amotz, 2005; Berne *et al.*, 2009; Choudhury & Pettitt, 2007; Ewell *et al.*, 2008; Hummer & Garde, 1998; Li *et al.*, 2006; Lum *et al.*, 1999; MacCallum *et al.*, 2007; Rajamani *et al.*, 2005). Another important aspect of non-polar solvation is the attractive nature between the solute and the solvent. For non-polar solvation, these attractive interactions are (by definition) not because of the electrostatics of static charge distributions on the solute and solvent, but are generally associated with weak dispersion interactions between solvent and solute originated from the fluctuation of induced dipoles within solvent and solute molecules (Boström & Ninham, 2005; Curutchet *et al.*, 2006; Floris & Tomasi, 1989; Floris *et al.*, 1991; Gallicchio *et al.*, 2000; Levy *et al.*, 2003; Pratt & Chandler, 1980). If sufficiently weak, such attractive non-polar interactions are generally assumed not to affect the density of solvent around the solute, but instead simply change the energetics of solvation for a solvent density distribution determined by repulsive solvent–solute interactions. Note that non-polar solvation cannot be easily decoupled from the polar solvation process: strong attractive solute–solvent interactions can significantly affect local solvent densities and change the non-polar properties of the solvation process (Dzubiella & Hansen, 2004; Dzubiella *et al.*, 2006a, b). Therefore, while the decomposition of solute–solvent interactions into polar and

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non-polar components is a useful conceptual device, the actual solvation process is much more complicated (Cramer & Truhlar, 1999, 2008).

Many biological phenomena are associated with non-polar solvation, ranging from protein folding to protein–protein to the fundamental structure and energetics of lipid bilayers and assemblies (Thirumalai & Hyeon, 2005; Yeagle, 2004; Zhou *et al.*, 2004). A full discussion of the influence of non-polar solvation on the numerous aspects of biomolecular structure, function, and energetics would fill several reviews. Therefore, interested readers are referred to the excellent discussion of the topic provided by Pratt & Pohorille (2002).

2.5 Site-specific binding and recognition

The discussion above has largely focused on the bulk properties of solvent and its non-specific interaction with solutes. However, a solvent such as water can also play a ligand-like role and interact with solutes in a decidedly non-bulk and site-specific manner. Perhaps the most familiar example of such site-bound solvent molecules are the crystallographic waters present at the surface (Kuhn *et al.*, 1992; Merzel & Smith, 2002; Smolin & Winter, 2004) and in cavities (Damjanović *et al.*, 2005a, b 2007; Imai *et al.*, 2005, 2007a) of many higher-resolution X-ray structures. While the physical and functional properties of such waters can be a subject of debate (Nayal & Di Cera, 1996), they are illustrative of the ways in which water can play structural as well as bulk roles in biomolecules. Nucleic acids provide another good illustration of how water can interact with biomolecular surfaces in a non-bulk-like and often sequence-specific manner (Arai *et al.*, 2005; Auffinger & Hashem, 2007; Auffinger & Westhof, 2000a,b; 2001; Bastos *et al.*, 2004; Bonvin *et al.*, 1998; Fuxreiter *et al.*, 2005; Mikulecky & Feig, 2006; Rhodes *et al.*, 2006; Yonetani *et al.*, 2008), such as the zig-zag spine of hydration in the minor grove of B-DNA (Drew *et al.*, 1982). Structurally or specifically bound water can also play an important role in protein structure and function, including allosteric regulation (Bone, 2006; Guinto & Di Cera, 1996; Krem & Di Cera, 1998; Royer *et al.*, 1996) and stability/flexibility (Fischer & Verma, 1999). Finally, water can play a very important role in molecular recognition; ranging from the binding of small molecules and peptides (Barillari *et al.*, 2007; Hamelberg & McCammon, 2004; Kuhn *et al.*, 1992; Petrone & Garcia, 2004; Samsonov *et al.*, 2008; Thilagavathi & Mancera, 2010; van Dijk & Bonvin, 2006; Villacanas *et al.*, 2009), to protein–protein complexes (Ikura *et al.*, 2004), to protein–nucleic acid binding (Billeter, 1996; Fried *et al.*, 2002; LiCata & Allewell, 1997), and water itself in the form of ice-binding and anti-freeze proteins (Doxey *et al.*, 2006; Jorov *et al.*, 2004; Liu *et al.*, 2005; Yang & Sharp, 2004). Such specific characteristics of the solvent obviously need detailed molecular descriptions of the solvent, as described later in this review.

3. Modeling ionic solutions

Ions play an essential role in biomolecular solvation and have a dramatic influence on the stability and function of a wide range of protein (Arakawa & Timasheff, 1984; Baldwin, 1996; Boström *et al.*, 2003a, 2005b, Chen *et al.*, 2007b; Friedman, 2000; Lund *et al.*, 2008a; Ninham & Yaminsky, 1997; Pegram & Record, 2008; Shimizu *et al.*, 2006; Vrbka *et al.*, 2006), membrane (Aroti *et al.*, 2004, 2007; Berkowitz & Vácha, 2012; Boström *et al.*, 2003b; Chen *et al.*, 2007b; Clarke & Lüpfert, 1999; Gurau *et al.*, 2004; Petrache *et al.*, 2006; Sachs & Woolf, 2003), and nucleic acid structures (Anderson & Record, 1990, 1995; Auffinger & Hashem, 2007; Ballin *et al.*, 2004; Chen *et al.*, 2009a, b; Draper, 2008; Draper *et al.*, 2005; García-García & Draper, 2003;

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Gavryushov, 2009; Grilley *et al.*, 2006, 2007; Leipply & Draper, 2000; Misra & Draper, 2000, 2001; Ni *et al.*, 1999; Olmsted *et al.*, 1991; Record *et al.*, 1995, 1978; Tikhomirova & Chalikian, 2004). Several excellent reviews have been written on this subject (Anderson & Record, 1990, 1995; Draper, 2008; Draper *et al.*, 2005; Ni *et al.*, 1999; Record *et al.*, 1978); we provide only a broad overview here.

3.1 Non-specific screening

One of the simplest aspects of ionic behavior is the non-specific 'mean field' screening embodied in Debye–Hückel or Poisson–Boltzmann (PB) treatments of ionic solutions (Baker, 2004; Gilson & Honig, 1988; Grochowski & Trylska, 2008; Lamm, 2003; Lamm & Pack, 2010). Such treatments assume ideal ion behavior where each ion experiences the average influence of its surrounding ionic environment. Therefore, this 'mean field' assumption implies no ion–ion correlations or fluctuations, effects that have been shown to be important in systems with high ion charge density (Angelini *et al.*, 2003, 2006; Ben-Yaakov *et al.*, 2009, 2011; Butler *et al.*, 2003; Holm *et al.*, 2001; Jho *et al.*, 2008; Kanduč *et al.*, 2008; Podgornik & Dobnikar, 2001; Todd *et al.*, 2008; Todd & Rau, 2008), as discussed later in this review. Additionally, these models assume no specific ion–ion, ion–solvent or ion–solute interactions; with a few exceptions (Baer & Mundy, 2011; Boström & Ninham, 2004; Boström *et al.*, 2003a, b; Jancovici, 2006; Parsons *et al.*, 2011), ions are typically treated as inert hard spheres with generic solute interactions based only on charge and steric repulsion. While the assumption of ideality makes such theories very convenient to implement and use, such assumptions are rarely valid in actual biomolecular systems (Anderson & Record, 1995; Collins, 1995; Marcus, 2006; Overman & Lohman, 1994; Record *et al.*, 1978). Nevertheless, these models are very popular and have been successfully used to describe some aspects of ionic effects on biomolecular systems—particularly in highly dilute and low-charge density settings.

3.2 Site-specific binding

Unlike the non-specific aspects of ionic behavior discussed above, many ions interact with protein and nucleic acids in a site-specific manner. About one-third of all proteins contain metal ions as integral components (Chaturvedi & Shrivastava, 2005; Waldron & Robinson, 2009). These metalloproteins—as well as other proteins that transiently bind ions—recognize and associate with only specific types of ions. This specificity allows them to discriminate and bind particular ion species, even in a solution of other ions of similar properties (e.g. charge and size). Specific interactions between ions and biomolecules can be critical for maintaining structure and are often directly involved in function as well. There are several examples where specific ion binding plays a key role in biomolecular structure. These include RNA tertiary structure stability (Adams *et al.*, 2004; Auffinger & Hashem, 2007; Cate *et al.*, 1996; Conn *et al.*, 2002; Draper, 2008; Draper *et al.*, 2005; Grilley *et al.*, 2006, 2007; Leipply & Draper, 2000) as well as several protein assembly and stability examples (Calimet & Simonson, 2006; Ding & Dokholyan, 2008; Li *et al.*, 2008; Wong & Pollack, 2010). Additionally, the functions of many proteins are affected by specific ion binding. For example, thrombin, a key enzyme in blood coagulation, is allosterically activated by Na^+ (Guinto & Di Cera, 1996; Wells & Di Cera, 1992); the NikR DNA-binding protein is activated by Ni^{2+} binding (Benanti & Chivers, 2007; Bradley *et al.*, 2008; Carrington *et al.*, 2003; Chivers & Sauer, 2000); and calmodulin undergoes significant conformational

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transitions in response to calcium binding (Bertini *et al.*, 2004; Evans *et al.*, 2011; Mori *et al.*, 2004). Many other systems are also regulated by ion binding (Benanti & Chivers, 2007; Carrington *et al.* 2003; Chivers & Sauer, 2000; Gohara & Di Cera 2011; Hedstrom *et al.* 1992; Niu *et al.* 2009; Page *et al.* 2006; Reyes-Caballero *et al.* 2011; Shults *et al.* 2003).

The definition of site-specific binding can be broadened somewhat to also include the specific recognition and binding of particular ions to more generic structural features of nucleic acids (Auffinger & Hashem, 2007) and lipid bilayers. For example, different species of ions are known to compete for binding to the DNA minor groove, leading to a preferential accumulation of particular cation species in this region of DNA molecules (Auffinger & Westhof, 2001; Marincola *et al.*, 2004; Savelyev & Papoian, 2006; Tikhomirova & Chalikian, 2004). Such specificity is also observed around other nucleic acid structures, including RNA (Chen & Honig, 1997; Chen *et al.*, 2009a, b; García-García & Draper, 2003; Grilley *et al.*, 2007; Misra & Draper, 1999, 2000, 2001, 2002; Misra *et al.*, 2003; Savelyev & Papoian, 2006; Soto *et al.*, 2007). Ion specificity for particular regions of nucleic acid and protein structure can also manifest itself in effects on protein-DNA recognition (Kozlov & Lohman, 1998; Mauro & Koudelka, 2004; Overman & Lohman, 1994; Record *et al.*, 1978), although such effects can often arise from a wide range of interaction types (Overman & Lohman, 1994; Record *et al.*, 1978, 1995; Zhang *et al.*, 1999). In a similar manner, the differential interface-perturbing behavior of monovalent cations on membrane surface properties and membrane curvature is associated with their different hydration tendencies that will modulate the extent and stability of the hydrogen-bond network along the charged membrane surface (Kraayenhof, 1996).

3.3 Ion–water interactions

Many species-specific ion effects are governed, in part, by ion–water interactions. Studies of such preferential hydration are far too numerous to include in a single review; indeed, many excellent manuscripts and texts have been written on the basic physical chemistry of these interactions (Kielland, 1937; Nightingale, 1959; Robinson & Stokes, 2002) as well as their biophysical implications (Courtenay *et al.*, 2001; Record *et al.*, 1978, 1995; Timasheff, 1998, 2002). Ions are known to significantly perturb the structure of water (Ansell *et al.*, 2006; Hribar *et al.*, 2002; Zangi *et al.*, 2007) and the strength of their interaction with water can significantly influence their affinity for interfaces (Collins, 1995; Pegram & Record, 2006, 2007). One of the most famous observations of this behavior is the Hofmeister effect (Baldwin, 1996; Hofmeister, 1888), which ranks ions based on their ability to precipitate or destabilize protein structures (Baldwin, 1996; Collins, 1995; Timasheff, 1992), or partition to aqueous interfaces (Chen *et al.*, 2007b; Pegram & Record, 2006, 2007, 2008). Hofmeister-like behavior also correlates with specific tendencies to enter the Stern layer and to bind the surface for charge neutralization. Roughly speaking, the Hofmeister effect can be described as a rank of ions (given valence) to adsorb in directly proportional to their unhydrated size. Hofmeister effects are particularly prevalent when local ion concentrations are high and play a role in a wide range of biological processes, including protein folding (Baldwin, 1996; Timasheff, 1992), protein–DNA interactions (Hong *et al.*, 2004; Kozlov & Lohman, 1998; Shimizu, 2004a, b; Shimizu & Smith, 2004; Shimizu *et al.*, 2006; Timasheff, 2002), nucleic acid stability (Pegram *et al.*, 2010; Pincus *et al.*, 2008), and biomembrane behavior (Aroti *et al.*, 2004, 2007; Boström & Ninham, 2005; Boström *et al.*, 2003b; Clarke & Lüpfert, 1999; Fukuma *et al.*, 2007; Leontidis *et al.*, 2007; Sachs & Woolf, 2003; Vácha *et al.*, 2009).

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While there are a number of theories for the detailed physical basis of the Hofmeister effect (Baldwin, 1996; Boström & Ninham, 2004; Boström *et al*., 2003a, b; Parsegian *et al*., 2000; Parsons *et al*., 2010, 2011; Pegram & Record, 2008; Shimizu *et al*., 2006; Tang & Bloomfield, 2002; Zhou, 2005), there is not yet broad consensus on the best way to model this phenomenon in computational treatments of biomolecular electrostatics. Perhaps the most straightforward model currently available uses dispersion effects to reproduce Hofmeister trends in continuum models of ion behavior (Boström & Ninham, 2004; Boström *et al*., 2003a, b, 2005; Parsons *et al*., 2011). While dispersion forces have been implicated in Hofmeister-like behavior (Boström & Ninham, 2004, 2005; Boström *et al*. 2003a, b, 2005a, b; Gurau *et al*., 2004; Ninham & Yaminsky, 1997; Parsons *et al*., 2010, 2011), they are unlikely to be the only contributing interaction (Lund *et al*., 2008a, b; Shimizu *et al*., 2006; Tobias & Hemminger, 2008). Therefore, it is unlikely that any current continuum solvation model completely describes these types of preferential solvation and Hofmeister effects.

4. Modeling biomolecular charge distributions

Generally, we are interested in the behavior of the solute molecules even though there is a clear understanding that the role of solvent is indispensable. Here, we describe the classical models for solutes that have been the dominant approaches in modeling and simulations of macromolecules.

4.1 Electric moments and Coulombic interactions

The importance of Coulombic interactions in molecular energies and forces has been recognized for a long time. Feynman discussed the importance of such interactions in 1939 (Feynman, 1939) while Buckingham (Buckingham, 1967) began his 1967 seminal paper with the statement, 'There is now general agreement that the significant forces between atoms and molecules have an electric origin.' Quantum mechanical forces that act among molecules are electrostatic in nature. For example, repulsion results from electron overlap when atoms approach each other without forming chemical bonds; dispersive attraction can arise from interactions from instantaneous fluctuation of charge distribution inside molecules. In classical mechanics, the non-covalent interatomic interactions are partitioned into electrostatics as described by Coulomb's law, van der Waals exchange-repulsion and dispersion, as well as secondary contributions such as induction and charge transfer (Stone, 1996). Although all major contributions need to be represented effectively in modeling molecular interactions, a consistent and transferable treatment of electrostatic interaction has been particularly challenging. The key issues include representation of charge distribution, efficient and accurate description of long-range interactions, and solvent effects.

The first molecular dynamics simulation of water was reported by Rahman and Stillinger in 1971 (Rahman, 1971). Four artificial point charges (± 0.19e) were placed 1 Å away from the oxygen atom to model the electrostatic interaction between water molecules. The use of effective point charges to represent the charge distribution of atoms and molecules greatly reduces the computational needs to study large molecules and condensed matters in comparison with quantum mechanical methods where electrons are considered in detail. The application of QM-derived point charges to investigate molecular systems dates back at least to the mid-1960s (Bradley *et al*., 1964; Kimel, 1964; Lifson, 1968) with several important later contributions

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(Allinger, 1976). The electrostatic interaction is commonly modeled via partial charges located at atomic centers; for example, in the following force fields: AMBER (assisted model building with energy refinement) (Case *et al.*, 2005; Cornell *et al.*, 1995), MMFF (Merck molecular force field), OPLS (optimized potentials for liquid simulations) (Kaminski *et al.*, 2001), CHARMM (Chemistry at HARvard Macromolecular Mechanics) (MacKerell *et al.*, 1998).

The electrostatic potential (ESP) energy U for a system of point charges follows Coulomb's law:

$$U = \sum_i \sum_{j>i} \frac{q_i q_j}{r_{ij}}, \tag{1}$$

where q denotes the charge value and r is the distance between charge locations. The ESP from atomic partial charges can be systematically improved by using a multipole expansion to describe the charge distribution (Buckingham, 1967). For an arbitrary charge distribution (e.g. an atom or a molecule) described by charges q_i ($i = 1, \ldots, n$), the ESP at a distance R away from the particle is given by the sum:

$$V(R) = \sum_i \frac{q_i}{|\underline{R} - \underline{r}_i|}, \tag{2}$$

where the $|\ \ |$ notation refers to Euclidean distance. For a distance $R > r$, a Cartesian–Taylor expansion of the above equation leads to

$$V(R) = \left\{ \sum_i q_i - \underline{\mu} \cdot \nabla + \frac{1}{2} \underline{\underline{\Theta}} : \nabla^2 - \cdots \right\} \left(\frac{1}{R} \right) \tag{3}$$

a multipole representation where the symbol ∇ denotes the gradient operator. The first term inside the bracket is the sum of charges of the particle or monopole moment. The dipole moment of the charge distribution μ is a vector with three components: $\mu_\alpha = \sum_i q_i r_{i\alpha}$, where $\alpha = x, y, z$. The quadrupole moment tensor ($\underline{\underline{\Theta}}$) has nine components given by $\Theta^{\alpha\beta} = \sum_i q_i r_{i\alpha} r_{i\beta}$. A traceless form of the quadrupole tensor $\Theta^{\alpha\beta} = \sum_i q_i (\frac{3}{2} r_{i\alpha} r_{i\beta} - \frac{1}{2} r_i^2 \delta_{\alpha\beta})$, instead of the traced one, can be used in Equation (3), along with constant 1/2 before $\underline{\underline{\Theta}} : \nabla^2$ replaced by 1/3 (Stone, 1996). A spherical form of multipole expansion can also be obtained by a spherical harmonic expansion (Bottcher, 1952; Hirschfelder *et al.*, 1954; Kirkwood, 1934; Stone, 1996).

Molecular multipole moments can be more efficient than point charges for modeling molecular electrostatic interactions, even though the associated energy and derivatives are more complex. In fact, early simulations of liquid and solid benzene adopted potentials that included a point quadrupole at the center of the benzene molecule (Claessens *et al.*, 1983; Jorgensen & Swenson, 1985; Linse, 1984). It was suggested (Claessens *et al.*, 1983) that the potential with a point multipole was superior to the Lennard–Jones-only potential for crystal structure prediction even though a recent study indicated that electrostatic interactions are not critical in predicting crystal packing of non-polar molecules (Della Valle *et al.*, 2008). Because of the assumption of $R > r$ in the Taylor expansion in Equation (3), however, the molecular multipole expansion is problematic at the short distances that are often relevant in molecular simulation. The multipole expansion may diverge within the sphere R, and lead to an inaccurate ESP. The solution to overcome this issue is to distribute the multipole expansion to a collection of sites within the

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molecule, which effectively reduces the radius of the divergence sphere (Fowler & Buckingham, 1983, 1991; Price, 1985; Stone, 1981).

Buckingham and Fowler (Fowler & Buckingham, 1983) were the first to apply distributed multipoles to the study of small molecule complexes. Atomic multipoles can be derived in several ways, including the distributed multipole analysis (DMA) of an *ab initio* wavefunction (Stone, 1981). The combination of a hard sphere potential with atomic multipoles (up to quadrupole) was rather successful in reproducing experimental geometries including hydrogen-bonding distance and angle for several molecular complexes. It has been noted that local atomic charge distributions are usually not spherically symmetrical because of chemical bonding and lone pairs, and thus higher-order electrostatic moments are necessary to describe such features. Systematic study of the accuracy of point multipole models also has been described (Williams, 1988). It was shown that the use of higher-order multipole moments significantly improved the representation of molecular ESP in comparison with *ab initio* reference potential. When only atomic charges were allowed, the relative root-mean-squared error in the ESP around the molecules was of the order of 10%. With the addition of dipole and quadrupole moments, the error was reduced by orders of magnitude to less than 0.1% (Williams, 1988). Considering that higher-order moments decay faster than monopoles, the advantage of a distributed multipole expansion is to improve the short-range description outside the van der Waals surface of a molecule, which is important for interactions such as hydrogen bonding (Dykstra, 1993).

An alternative to multipole expansion is to use a number of charge sites, which should in principle, offer a similar improvement to the accuracy of the molecular ESP. A great advantage of using point charges is the simplicity of the energy and atomic gradient; in contrast, the gradient and torque on point multipoles require significantly more algebra. There have been arguments that a point charge model is more efficient for a given level of accuracy, at least for diatomic molecules such as HF and HCl (Brobjer & Murrell, 1982). There are also models that replace multipole moments by distributed point charges (Sokalski *et al.*, 1993). The extended electron distribution (XED) force field adopts an explicit charge distribution around each atom, which seems to give improvements in interaction energy, conformation, and electrostatic field (Chessari *et al.*, 2002; Vinter, 1996). Some versions of the AMBER force field place charges at important lone-pair sites (Dixon & Kollman, 1997). Another recent example is the TIP5P water model, which employs five charge sites. However, it was shown that the determination of the exact locations of the lone pair charges was not trivial, and involved an extensive fitting procedure to reproduce experimental density-temperature profiles (Mahoney & Jorgensen, 2000; Rick, 2001). Another concern is that charges located away from atomic centers may lead to numerical instability in molecular dynamics or Monte Carlo simulations because of the potential fusion of charge sites.

To evaluate the interaction between multipole moments, Applequist introduced a concise polytensor scheme (Applequist, 1983, 1984, 1985, 1989; Dykstra, 1988). The multipole expansion at site k is written as

$$M_i = \left[q_i,\ \mu_{ix},\ \mu_{ix}\mu_{ix}, \Theta_{ixx}, \Theta_{ixy}, \ldots\right]^t, \tag{4}$$

where the superscript t indicates transpose. The interaction energy between two multipoles at sites i and j is then given by the matrix formula:

$$U_{ij} = M_i^t T_{ij} M_j,$$

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where T is the interaction matrix:

$$\begin{bmatrix} 1 & \frac{\partial}{\partial x_j} & \frac{\partial}{\partial y_j} & \frac{\partial}{\partial z_j} & \cdots \\ \frac{\partial}{\partial x_i} & \frac{\partial^2}{\partial x_i \partial x_j} & \frac{\partial^2}{\partial x_i \partial y_j} & \frac{\partial^2}{\partial x_i \partial z_j} & \cdots \\ \frac{\partial}{\partial y_i} & \frac{\partial^2}{\partial y_i \partial x_j} & \frac{\partial^2}{\partial y_i \partial y_j} & \frac{\partial^2}{\partial y_i \partial z_j} & \cdots \\ \frac{\partial}{\partial z_i} & \frac{\partial^2}{\partial z_i \partial x_j} & \frac{\partial^2}{\partial z_i \partial y_j} & \frac{\partial^2}{\partial z_i \partial z_j} & \cdots \\ \vdots & \vdots & \vdots & \vdots & \ddots \end{bmatrix} \left(\frac{1}{R_{ji}} \right).$$

The multipole moments here are defined in the same global frame. For example, Price reported distributed multipoles for amides and peptides in predefined molecular axes (Faerman & Price, 1990). Alternatively, it is possible to define the multipole moments for each atom type in a local coordinate frame that is constructed with respect to covalently bonded neighboring atoms. Within this scheme, the oxygen atom in the water molecule may use the so-called bisector frame where the z-axis is the bisector of the HOH angle (Kong, 1997; Ren & Ponder, 2003); the x-axis is perpendicular to z and also lies in the HOH plane; and the y-axis is determined via the right-hand rule. For chemical systems without such symmetry, a generic z-then-x local frame can be used, in which one chemical bond to a neighboring atom is selected to define the z-axis.

A rotation matrix converts local multipole moments into the global frame prior to computation of the electrostatic interaction energies. Many algorithms require the evaluation of the analytic electrostatic forces for each molecular configuration. For the atomic charge model, the force is simply the negative derivative of Coulomb energy ($1/r$) with respect to atomic coordinates. For an atomic multipole expansion, forces are derived in a similar fashion by taking the derivative of the interaction matrix T and, using the relationships $T^{(n+1)} = \nabla(T^n)$, and $T^0 = 1/R$. Expressions for the first few derivatives are available (Kong, 1997). A further complication must be considered for dipole and higher-order moments. From a physics point of view, a dipole moment placed in an external field will experience a torque that favors rotation of the site (and its local frame defining neighbors). It is possible to convert each torque into forces at frame-defining sites to permit standard molecular dynamics integration schemes or optimization algorithms (Ren & Ponder, 2003). There is an alternative approach to understand these extra forces mathematically. If the multipole moments defined within their local frames are explicitly included in the energy expression with their rotation matrix, which is a function of atomic coordinates, the product rule leads to these additional forces (Kong, 1997). Besides the Cartesian poly-tensor approach explained above, the spherical tensor formulations of the multipole interaction energy, force, and torque, are available (Price *et al.*, 1984).

Note that even with the better convergence of atomic multipole at short range, there are errors associated with the point approximation of the charge distribution. At a distance where electron density is penetrated, a negative (attractive) penetration effect is missing from the point multipole potential energy (Stone, 1996). It has been suggested that the penetration effect could be absorbed by the repulsive term or possibly by damping the Coulomb energy (Klopper *et al.*, 2000; van Duijnen & Swart, 1998). Wheatley & Mitchell (1994) proposed replacing the point multipole with Gaussian multipoles to correctly model the penetration effect at short range. Piquemal *et al.* (2003) used s-type Gaussian functions distributed at multi-sites to represent the charge density. In the recent development of Quantum Mechanics Polarizable Force Field

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(QMPFF) (Donchev, 2006; Donchev *et al.*, 2005), a model was developed that consists of a nuclear charge and a negative electron cloud of exponential form located off the nuclear center. These more sophisticated treatments are likely to provide greater flexibility and higher accuracy for modeling electrostatics, within the limits of the *ab initio* data to which they are fit, although at higher computational cost.

When formulating an MM potential, conventional wisdom is that intramolecular short-range electrostatic interactions should be masked (scaled), based on the rationale that bond and angle energy terms already include these interactions. However, details of the masking schemes vary among different force fields. For example, charge interactions between the 1–2 (directly bonded) and the 1–3 (separated by two bonds) atoms are almost universally omitted. The 1–4 (atoms separated by three bonds) interaction is scaled down by 5/6 in Amber94, by 1/2 in OPLS-AA, and is not modified in CHARMM. These scaling factors are determined empirically to best reproduce conformational energy profile of flexible molecules.

Parameterization of realistic charge distributions, in the forms of point charges or higher-order moments, is essential to the accuracy of electrostatic energetics. Although atomic charges are not measurable physical quantities (physical observables), it is possible to derive meaningful values from quantum mechanical calculations. A method such as Mulliken population analysis or Bader's Atoms-in-Molecules (AIM) theory partitions electron density into atomic contributions (Bader, 1990). However, different partitioning schemes lead to substantially different atomic charges. Momany first treated atom charges as adjustable parameters and derived values by fitting to *ab initio* Electrostatic potential (ESP) (Momany, 1978). Unlike atomic charges, ESPs are physical observables and are directly associated with intermolecular interactions. Cox & Williams (1981) pointed out that ESPs from Mulliken charges generally had significant errors. Variants of ESP fitting approaches include CHarges from Electrostatic Potentials (CHELP), CHarges from Electrostatic Potentials using a Grid based method (CHELPG) (Breneman & Wiberg, 1990), Merz-Kollman (MK), and Restrained Electrostatic Potential (RESP) (Bayly *et al.*, 1993). These methods differ mostly with respect to the choice of grid points to which the ESP is fit, typically residing in a shell immediately outside the van der Waals surface. Note that at very close distances, the ESP is not as relevant to molecular interactions because the actual wavefunctions of molecules will overlap, leading to penetration and other effects. In RESP, hyperbolic restraints are applied to heavy atoms to avoid artificially large charges obtained for atoms buried inside the molecule during fitting. This type of approach works reasonably well for small molecules, but is inherently limited for larger molecules. In the latter case, such as proteins, model compounds (e.g. dipeptides) are used to derive charges for common molecular fragments.

Various charge parameterization schemes have been compared for their ability to reproduce molecular dipole moments and ESP (Bayly *et al.*, 1993; Martin & Zipse, 2005; Masamura, 2000; Wiberg & Rablen, 1993). Wiberg & Rablen (1993) suggested that atomic charges alone are insufficient to accurately model the anisotropic molecular charge distribution and ESP near the van der Waals surface. They concluded it is necessary to include at least atomic dipoles or even higher-order terms. This is consistent with Williams' conclusion mentioned above (Williams, 1988). Sun (1998) showed that ESP charges were unable to provide quantitatively ion-spherand interaction free energies, unless the region near oxygen was weighted higher than the rest, which is another indication of an over simplification of the spherically symmetric atomic charge approximation. A pitfall of ESP charges is that they may not respond consistently to structural changes such as substituents, which is problematic for developing transferable force field

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parameters. Even determination of charges from quantum mechanics (QM) for water alone can be a difficult task (Martin & Zipse, 2005).

Additional complications arise from the dependency of charge distributions on intramolecular geometry and conformation. This short-range effect is of quantum mechanical origin and is not directly related to through-space induction. Dinur & Hagler (1995) reported empirical formulation that couples geometry to charge distribution. Palmo *et al.* (2006) showed that such a coupling allows a classical water model to capture the expansion of the H-O-H angle moving from gas phase to liquid. In most classical potentials, this conformation dependence is handled by simultaneous fitting to multiple conformations of a flexible molecule (Reynolds *et al.*, 1992a, b; Söderhjelm *et al.*, 2007).

Because of their simplicity and efficiency, partial atomic charge models have been adopted by the majority of common biomolecular force fields including AMBER, CHARMM, GROMOS, and OPLS-AA. Since most of the force fields target the condensed-phase, charges derived from gas-phase, QM calculations are not suitable and further adjustments must be made to account for solvent and other environmental effects. AMBER force fields have traditionally fit charges to ESPs calculated from the HF/6-31G* basis set. It has been argued that because the HF theory overestimates molecular dipole moments, the amplified charges effectively capture the solute polarization response in condense-phase. CHARMM first optimizes the charges to gas-phase molecular interactions and subsequently scales the charges for the neutral polar molecules by 1.16. The OPLS force field adjusts the charges by fitting to neat liquid properties such as density and heat of vaporizations. This process is tedious, but has the advantage of producing reliable condensed-phase properties. We emphasize an important rule, which is not to mix charges from different parameterization strategies (i.e. from different force fields) into a single calculation because each method has its own systematic errors that are more likely to cancel when used consistently. There is also interest in using semi-empirical methods such as AM1 to estimate atomic charges quickly. This can be potentially useful for studying a large number of small molecules. AM1-BCC and CM2 are two examples of such schemes (Jakalian *et al.*, 2000, 2002; Li *et al.*, 1998a, b).

As discussed previously, electrostatic models beyond fixed atomic charges have also been explored in recent years. In addition to the work that incorporates electronic polarization, distributed atomic multipoles have been applied to represent electrostatic interactions within MM force field (Burnham & Xantheas, 2002; Freitag *et al.*, 2000; Grossfield *et al.*, 2003; Holt & Karlström, 2008; Jiao *et al.*, 2006, 2008, 2009; Kong, 1997; Ren & Ponder, 2002, 2003; Xantheas *et al.*, 2002). Similar to point charges, distributed multipole moments can be derived via population analysis or an ESP fit. Although it is known that charges from Mulliken population analysis do not produce an accurate ESP because the method is truncated at monopole order, its extension to DMA as proposed by Stone (Stone, 1981) permits systematic convergence of the ESP. Alternatively, atomic multipoles can be obtained from Bader's AIM theory, which partitions electron density based on zero-flux surfaces (Bader, 1990). Popelier showed that AIM is slow to converge compared to DMA and therefore requires higher-order moments (Popelier *et al.*, 2001). Convergence of AIM multipole expansion can be achieved by adding additional sites at bond midpoints (Joubert & Popelier, 2002). To handle large basis sets in *ab initio* calculations, a recent modification to DMA that uses a grid-based quadrature for partitioning the contributions to the charge density from diffuse basis functions, was introduced (Stone, 2005). Other methods to derive atomic multipoles include natural atomic orbitals (NAO) analysis (Reed *et al.*, 1988) and a recently developed method called LoProp (Gagliardi *et al.*, 2004; Söderhjelm *et al.*, 2007).

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4.2 Polarizability and other many-body effects

The Coulombic energy expression makes use of the assumption that the electrostatic energy is pair-wise additive. In reality, a charge distribution changes under the influence of an electric field produced by the surrounding environment, which can include contributions from solvent, intramolecular sources or externally applied potential differences. For example, the molecular dipole moment of a water molecule increases from 1.8 to 3.0 D when immersed in bath of water (Ren & Ponder, 2003).

Different methods exist to incorporate the polarization effect in molecular mechanic framework, by means of induced dipole, fluctuating charge or Drude oscillator. Stone (Stone, 1981, 2005; Stone & Alderton, 2002) also proposed a more sophisticated treatment. Fluctuating charge and Drude oscillator-based methods are easier to implement within the existing fixed-charge force field framework, while the induced dipole approach is a natural choice for models based on atomic multipoles. Detailed discussion and comparison of the different treatments of polarization can be found in the recent reviews (Cieplak *et al.*, 2009; Halgren, 1992; Lopes *et al.*, 2009; Ponder & Case, 2003; Rick, 2001). Below, we offer a brief account for polarizable force field development and fundamental methodology based on distributed induced dipole model.

In very early studies of enzymatic reactions (Warshel, 1976) and prototype molecular dynamics algorithms (Vesely, 1977), polarization effect was already considered explicitly. In early 1990s, Gresh and co-workers developed THE SIBFA (sum of interactions between fragments *ab initio* computed) potential, which treats the polarization, charge transfer effect, and other second-order electrostatic interactions (Gresh, 1997). Karlström and co-workers have been devoting considerable effect to incorporate induced-dipole based polarization models into classical force fields (Åstrand *et al.*, 1995; Brdarski *et al.*, 2000; Holt & Karlström, 2009). Friesner and co-workers also reported models that use both fluctuating charges and atomic induce dipole to account for polarization (Kaminski *et al.*, 2002; Stern *et al.*, 2001). Patel *et al.* (Bauer & Patel, 2009; Bauer *et al.*, 2011; Patel & Brooks, 2004; Patel *et al.*, 2004, 2009) take a fluctuating charge approach that is based on the charge equilibration scheme (Rappe & Goddard, 1991). MacKerell and Roux base their polarizable potentials on the Drude oscillator approach (Baker *et al.*, 2010; Harder & Roux, 2008; Jiang *et al.*, 2011; Lamoureux & Roux, 2006; Lopes *et al.*, 2007; Roux *et al.*, 2011; Yu *et al.*, 2010). Ren and Ponder have been developing classical force fields that combine the induced dipole with permanent atomic multipoles to represent the electrostatic interactions (Jiao *et al.*, 2008; Kong, 1997; Ren & Ponder, 2002, 2003; Ren *et al.*, 2011). Duan and AMBER community are also continuing with their effort in polarizable force field development (Wang *et al.*, 2011a, 2011b; 2006). Inclusion of polarization allows more rigorous parameterization and validation of the force field against a wide range of molecular systems in different environment, from small molecules to macromolecules, from gas-phase to condensed-phase properties. The advantages of polarizable force fields have been demonstrated for water (Lamoureux *et al.*, 2003; Ren & Ponder, 2003; Stern *et al.*, 2001), amides and other organic molecules (Brdarski *et al.*, 2000; Hagberg *et al.*, 2005; Harder *et al.*, 2008; Lopes *et al.*, 2007; Ren *et al.*, 2011; Wang *et al.*, 2011a, b), ions (Grossfield *et al.*, 2003; Jiao *et al.*, 2008; Patel *et al.*, 2009; Wu *et al.*, 2010; Yu *et al.*, 2010), membranes (Bauer *et al.*, 2011), and ligand–protein complexes (Jiao *et al.*, 2008; Roux *et al.*, 2011). Of equal importance is the development of efficient particle-mesh. Ewald has enabled accurate treatment of long-range electrostatic interactions of partial charges or point multipoles in the simulations of large biomolecules (Darden *et al.*, 1993; Sagui *et al.*, 2004). However, developing

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and parameterizing a consistent force field for biomolecular simulations are still daunting tasks because of the extra complication in a more elaborated physical model. There is no consensus on where the polarization effect would be the most important and what is the best way to treat the polarization effect in classical simulations? As we push for more accurate physical potentials, it is also important to keep in mind the limitation of other contributions in the potential energy function such as partial atomic charge representation, van der Waals interactions, and empirical valence functions.

At the molecular level, an induced dipole moment can be approximated through a linear relation with the total field E:

$$\mu^{\text{ind}} = \alpha E,$$

where α is the molecular polarizability of the molecule, which can be measured by experiment or calculated from *ab initio* theory. Following Buckingham, we define the ground state electron distribution of a molecule as its permanent charge distribution. When several molecules approach each other, each permanent charge distribution will produce an electric field on the others. The induced dipole at each molecule resulting from the total permanent field produces an induced field:

$$\mu_i = \alpha_i \left(\sum_{j \neq i} E^{\text{perm}} + \sum_{k \neq i} T^{11}_{ik} \mu_k \right),$$

where T^{11} is the dipole field operator (e.g. Applequist *et al.*, 1972). Since the induced dipole appears on both sides of the equation, it can be solved self-consistently by iteration or by direct matrix inversion. The energy from the mutual induction is

$$U^{\text{ind}} = \frac{1}{2} \mu^{\text{ind}} E^{\text{perm}}.$$

Although induction always lowers the system energy, the factor $^1/_2$ reflects the positive work required to distort the molecular charge distribution.

While molecular polarization response is a physical observable, measurable from experiment or computed from *ab initio* QM, polarization at the atomic level is modeled empirically by inducing a dipole moment at each atom or charge flow between atoms. To model the molecular dipole polarizability, distributed atomic models – both additive and non-additive (interactive) – have been proposed. In an additive model, the molecular polarizability is the sum of individual bond, atom, or group contributions (Dykstra, 2001). Anisotropic atomic polarizabilities in tensor forms are used to produce anisotropic molecular response (Birge, 1980; Stout & Dykstra, 1995; Stout & Dykstra, 1998). Applequist *et al.* (1972) devised a non-additive model in which atomic response is relayed via neighboring atoms and, as a result, anisotropic molecular response can be captured (Stout & Dykstra, 1995; Stout & Dykstra, 1998). Applequist further incorporated monopole polarizability (atomic charge transfer) into the dipole polarizability model to handle out-of-plane charge flow in the aromatic rings (Applequist, 1993). Thole proposed a damping scheme to handle numerical problems in the interactive model associated with the polarizability catastrophe at the short range (polarization energy approaches negative infinity) (Thole, 1981; van Duijnen & Swart, 1998). Physically, the catastrophe is a consequence of point polarizability approximation and the damping is effectively to replace the point charge with a distribution. Thole's approach has been adopted by several researchers in empirical force fields for classical

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simulations or QM/MM approaches (Åstrand *et al.*, 1995; Bernardo *et al.*, 1994; Brdarski *et al.*, 2000; Burnham & Xantheas, 2002; Engkvist *et al.*, 1996; Grossfield *et al.*, 2003; Holt & Karlström, 2009; Jiao *et al.*, 2006, 2008; Ren & Ponder, 2002, 2003; Van Duijnen & de Vries, 1996; Xantheas *et al.*, 2002). The advantage of additive models is the computational simplicity, whereas the interactive models require the solution of self-consistent mutual induction equations. However, in the interactive polarizability model, the molecular response has explicit dependence of molecular geometry, which is often lacking in the additive models. In addition to the empirical models mentioned above, Stone proposed a more sophisticated distributed polarizability model based on perturbation theory which systematically treats polarization response in monopole to higher-order moments (Stone, 1996).

Different methods exist to incorporate the polarization effect in molecular mechanic framework, by means of induced dipole, fluctuating charge or Drude oscillator. The latter two are easier to implement within the existing fixed-charge force field methodology, while the induced dipole approach makes it a natural choice for models based on atomic multipoles. Detailed discussion and comparison of the different treatments of polarization can be found in the recent reviews (Halgren, 1992; Ponder & Case, 2003; Rick, 2001). Stone (Stone, 1981, 2005; Stone & Alderton, 2002) proposed a more sophisticated treatment.

Efforts to develop classical force fields that explicitly treat the electronic polarization effect are increasing. Ren and Ponder are developing a classical force field that combines the induced dipole with permanent atomic multipoles to represent the electrostatic interactions (Jiao *et al.*, 2008; Kong, 1997; Ren & Ponder, 2002, 2003). Friesner and co-workers also reported models that merge fluctuating charges and atomic induce dipole models together (Kaminski *et al.*, 2002; Stern *et al.*, 2001). Patel *et al.* (Patel & Brooks, 2004; Patel *et al.*, 2004) take a fluctuating charge approach that is based on the charge equilibration scheme (Rappe & Goddard, 1991). MacKerell and Roux base their polarizable potential on the Drude oscillator approach (Lamoureux & Roux, 2006; Lopes *et al.*, 2007). In principle, the inclusion of polarization should provide a more realistic representation of electrostatic interactions and better transferability of force field parameters. Ren and co-workers have shown that electronic polarizability needs to be considered in order to achieve reliable and accurate results in small molecules binding to proteins (Jiao *et al.*, 2008, 2009). Polarization allows more rigorous parameterization and validation of the force field against a wide range of molecular systems in different environment, from small molecules to macromolecules, from gas-phase to condensed-phase properties. Of equal importance is the development of efficient particle-mesh Ewald has enabled accurate treatment of long-range electrostatic interactions of partial charges or point multipoles in the simulations of large biomolecules (Darden *et al.*, 1993; Sagui *et al.*, 2004). However, developing and parameterizing a consistent force field for biomolecular simulations are still daunting tasks because of the extra complication in a more elaborated physical model. It is also important to keep in mind the limitation of other representations in the potential energy function such as van der Waals interactions and short-range valence term.

4.3 Modeling biomolecular titration states

One of the most important aspects of biomolecular charge states is their sensitivity to pH and other environmental influences. The presence of ionizable groups (side chains of acidic and basic amino acids) in a protein affects the protein's electrostatic properties and its solvation in aqueous

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media. The two types of ionizable groups in proteins are titratable and redox groups. Titratable groups participate in acid–base (protonation/de-protonation) reactions to exchange (bind or release) a proton. Redox groups participate in redox reactions to exchange (bind or release) an electron. Therefore, these ionizable groups can acquire charge states that determine the stability, solubility, and enzymatic properties of the proteins important in several biological processes (e.g. enzymatic catalysis, respiration, etc.). In fact, several pH-dependent phenomena associated with proteins have been attributed to the presence of titratable groups. To understand the mechanisms of biological phenomena that depend on the ionization states of proteins, it is important to predict accurately these ionization states and understand the factors that affect the ionization behavior of proteins.

The ionization behavior and the corresponding charge state of an ionizable group can be different when it is part of a protein compared to when it exists independently as part of its model compound (side chain in a blocked peptide) in aqueous solutions. Several factors alter the charge state of ionizable groups in a protein: electrostatic interactions between charges of ionizable groups in the same protein, electrostatic interactions between charges on the ionizable group and the partial charges on non-ionizable groups and backbone atoms, location of the group in the protein, changes in the protein's conformational state, pH of the solution, and polarizability/polarity of the protein's microenvironment.

The ionization behavior of an ionizable group (titratable or redox) can be characterized by the proton/electron binding affinities of the titratable/redox group. The binding affinity of a group can change depending on whether the group is part of a protein or is left free in solution. These affinities can be quantified using ionization equilibrium constants. For instance, Equation (5) is for an acid–base equilibrium (protonation/de-protonation) reaction, where AH denotes the acid, A^- represents the conjugate base and H^+ is the proton:

$$AH \overset{K_a}{\longleftrightarrow} A^- + H^+. \tag{5}$$

K_a is the equilibrium constant, defined as $K_a = [A^-][H^+]/HA$, where the terms in the numerator and denominator are species activities, and K_a determines the strength for the dissociation of the acid into its conjugate base and a proton. Taking negative logarithm on both sides of Equation (5) yields

$$-\log_{10} K_a = -\log_{10}\left(\frac{[A^-]}{[HA]}\right) - \log_{10}[H^+]. \tag{6}$$

The free energy (ΔG) required to de-protonate one mole of an acid is given by the relation

$$\Delta G = -2.303 k_B T \log_{10}\left(\frac{[A^-]}{[HA]}\right), \tag{7}$$

where k_B is the Boltzmann's constant and T is the temperature of the solution. Rearranging these equations gives

$$\Delta G = 2.303 K_B T(-\log_{10} k_a + \log_{10}[H^+]). \tag{8}$$

Substituting $-\log_{10} k_a$ and $-\log_{10}[H^+]$ with pK_a and pH, respectively, we obtain the relation between free energy and pK_a

$$\Delta G = 2.303\ k_B T(pK_a - pH). \tag{9}$$

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The ionization state of a protein is characterized by the pK_a values of all the ionizable groups in the protein. We can write the relation between pK_a (p$K_{a,i}$) of a titratable group (i) in a protein (p) and the change in free energy (ΔG_i^p) required to protonate the titratable group, as shown below:

$$\Delta G_i^p = 2.303\ k_B T(\mathrm{pH} - \mathrm{p}K_{a,i}). \tag{10}$$

Similarly, the pK_a (p$K_{a,mi}$) of the same titratable group (i) in a reference or model state (m) is related to the change in free energy (ΔG_i^m) required to protonate the titratable group, as shown below:

$$\Delta G_i^m = 2.303\ k_B T(\mathrm{pH} - \mathrm{p}K_{a,mi}). \tag{11}$$

Subtracting these two relationships and rearranging gives

$$\mathrm{p}K_{a,i} = \mathrm{p}K_{a,mi} - \frac{\Delta G_i^p - \Delta G_i^m}{2.303\ k_B T}. \tag{12}$$

Equation (12) provides the thermodynamic basis for understanding the differences between the ionization behavior of a titratable group in a protein and that of the same group in its model compound.

A common assumption in pK_a calculations is that the contributions to the free energy of charging a site in the protein or model compound from zero to unit charge (positive or negative) are purely electrostatic in nature (Bashford & Karplus, 1990). These electrostatic contributions include the solvation energy of the charge at the ionizable site (Born), the electrostatic interaction between the charge and the partial charges of backbone atoms and other non-ionizable groups (ic–p interactions), and the electrostatic interaction between the charge and charges on other ionizable groups (ic–jc interactions).

Thus, the pK_a of a titratable state becomes

$$\mathrm{p}K_{a,i} = \mathrm{p}K_{a,mi} - \frac{\Delta G_{i,\,\mathrm{Born}}^p + \Delta G_{i,\,ic-p}^p + \Delta G_{i,\,ic-jc}^p - \Delta G_{i,\,\mathrm{Born}}^m - \Delta G_{i,\,ic-p}^m}{2.303\ k_B T}. \tag{13}$$

To calculate the p$K_{a,i}$ value of the titratable group i, we need to know the values for p$K_{a,mi}$ and for each free energy term in equation above. The p$K_{a,mi}$ value can be obtained experimentally; however, the free energy terms have to be computed using a suitable electrostatic solvation model, as discussed in the subsequent sections. Note that the term $\Delta G_{i.\ ic-jc}^p$ is pH-dependent, which also implies the need to sample against the large space of biomolecular titration states to accurately model the pK_a value (Antosiewicz, 2008).

Significant efforts have been made to accurately measure (Baran *et al.*, 2008; Castañeda *et al.*, 2009; Denisov *et al.*, 2004; Fitzkee & García-Moreno E, 2008; Harms *et al.*, 2008, 2009; Isom *et al.*, 2008, 2010, 2011; Karp *et al.*, 2007, 2010) and predict (Alexov *et al.*, 2011; Antosiewicz *et al.*, 1996a, b, 2008; Bashford & Karplus, 1990; Bryce *et al.*, 1998; Carstensen *et al.*, 2011; Flanagan *et al.*, 1981; Georgescu *et al.*, 2002; Karp *et al.*, 2007; Khandogin & Brooks, 2006; Laurents *et al.*, 2003; Li *et al.*, 2002, 2004, 2005; Mehler & Guarnieri, 1999; Mitra *et al.*, 2011; Nielsen, 2007, 2009, 2011; Nielsen & McCammon, 2003; Nielsen & Vriend, 2001; Shan & Mehler, 2011; Tang *et al.*, 2007; Tynan-Connolly & Nielsen, 2006; Wallace & Shen, 2011; Witham *et al.*, 2011) protein titration states to understand the determinants of pK_a values for the amino acids in the interior and exterior of proteins. A recent special issue of *Proteins* (Alexov *et al.*, 2011) provides an excellent review of the state-of-the-art in the area of biomolecular titration state modeling.

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5. Modeling solvation with high detail: explicit models

5.1 Explicit water models

Water has long been recognized as an important part of biomolecular systems (Kauzmann, 1959). Early theoretical studies of proteins ignored the solvent because of the prohibitive computational cost (McCammon *et al.*, 1977). However, with the advancement of computer technology and quest for realistic simulations, it is now common to represent the solvent explicitly with atomic models.

Numerous water models have been developed over the years beginning with Bernal and Fowler's attempt in 1933 (Bernal, 1933). A detailed review of nearly 50 water models was given by Guillot in 2002 (Guillot, 2002). It would likely require another full-length review to discuss the new models developed since. The water models introduced to date differ from each other in electrostatic representation (number of charge sites, polarizability), internal geometry (angle and flexibility), and the ways by which the parameters were derived.

TIP3P (Jorgensen *et al.*, 1983) and Simple Point Charge (SPC) (Berendsen *et al.*, 1981) are two, three-site, fixed charge models commonly used in biomolecular simulations. The two models have the same equilibrium OH bond lengths and very similar atomic charges but different van der Waals parameters and equilibrium HOH angle values. While the TIP3P adopts a value of 104.52° for the HOH angle, SPC uses 109.47°; the experimentally measured geometry of liquid water at room temperature is 106° (Ichikawa *et al.*, 1991). Both water models were derived originally as rigid water models. A variant of SPC, SPC/E (Berendsen *et al.*, 1987), was developed to take into account the cost of bulk polarization ignored by SPC and other fixed-charge models. Effectively, the correction makes the bulk potential energy of SPC/E model lower than the others. This procedure has not been consistently applied to other liquids or biomolecular systems.

The effort to improve TIP3P has led to four-site (Jorgensen *et al.*, 1983), five-site (Mahoney & Jorgensen, 2000), and even six-site (Nada, 2003) water models, with additional charge sites for better electrostatic descriptions. An extensive reparameterization of TIP4P was made by fitting to properties over a wide range of temperatures and using the Ewald treatment of electrostatics, as opposed to the cut-off scheme used in earlier model development (Horn *et al.*, 2004). TIP5P is one of the best-performing fixed charge water models that reproduce a range of condensed-phase structural, energetic, and dynamic properties including the temperature of maximum density. The use of TIP5P in biomolecular simulations has been limited because of the cost arising from the additional charge sites and concerns about compatible parameterization of amino and nucleic acid residues with this water model.

Recent advancements in water models continue to focus on the electrostatic representation, especially the electronic polarization effect. Water is a high-dielectric solvent and is also very polarizable itself. Examples of water models that explicitly account for polarization include a water model developed by Brodholt, Sampoli and Vallauri (BSV) (Jedlovszky, 2001; Jedlovszky & Vallauri, 1999), Polarizable five-site model, based on triple zeta basis set (POL5/TZ)(QZ) (Stern *et al.*, 2001), Polarizable Point-Charge (PPC) (Svishchev *et al.*, 1996), transferable intermolecular potential, 4-position model/Fluctuation Charge (TIP4P/FQ) (Rick, 2001), POL5 (Stern *et al.*, 2001), Thole-Type Model, version 2 (TTM2) (Burnham & Xantheas, 2002), Atomic Multipole Optimized Energetics for Biomolecular Applications (AMOEBA) (Ren & Ponder, 2003), and SWM4-DP (Lamoureux *et al.*, 2003). Parameterization of these models relies on both quantum mechanical *ab initio* calculations and experimental

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bulk thermodynamic properties, although to different extents. Overall, these studies have demonstrated that a polarizable water model is able to provide a better representation of electrostatic response, and good transferability among different chemical environments.

5.2 Explicit ion models

When explicit water models are used, ions are also typically modeled in atomic detail. Theoretical treatment of specific ion interactions is complicated as the strong electrostatic field around the ions poses challenges to the standard physical water models. Nonetheless, computational studies have offered valuable insights into the atomic details of ion solvation and the interaction of ions with biomolecular solutes.

Specific ion binding to proteins or DNA is a dynamic competition between the biomolecular and aqueous environments. Therefore, it is essential to accurately describe the hydration thermodynamics of single ions. However, this task is not straightforward as only the total solvation free energies of a neutral salt can be measured directly from experiment. As a result, published single ion solvation values differ widely when different parameterizations are employed (Patra & Karttunen, 2004). Furthermore, ion behavior can be very sensitive to the force field, and subtle differences in ion and solvent parameterization may lead to significant ion pairing and clustering problems during simulation (Alejandre & Hansen, 2007; Auffinger *et al.*, 2007; Chen & Pappu, 2007a, b; Joung & Cheatham, 2008).

Recent studies using *ab initio* QM/MM models, quasi-chemical theory, and polarizable force fields have demonstrated improved accuracy in explicit ion models. The *ab initio* QM/MM approach has been reviewed extensively (Friesner, 2005; Friesner & Guallar, 2005; Hu & Yang, 2008; Kamerlin *et al.*, 2009; Lin & Truhlar, 2007; Riccardi *et al.*, 2006; Senn & Thiel, 2009). For example, Rode and co-workers have characterized the dynamics and solvation properties of solvated ions by treating the primary region of interest, the first hydration shell of the ions, quantum mechanically and other region using MM (Azam *et al.*, 2009; Rode *et al.*, 2006). Unfortunately, most QM/MM calculations are restricted to small systems or short trajectories since quantum mechanical calculations are extremely expensive.

Aqvist has pioneered the work of applying free energy perturbation (FEP) approaches to derive ion–water potential parameters that can reproduce the experimental solvation free energies of alkali and alkaline earth metal ions in water (Aaqvist, 1990). While there are still efforts to push the limits of the additive non-polarizable force fields for ionic interactions (Joung & Cheatham, 2008), it is generally accepted that polarizability and perhaps even quantum mechanical treatments are essential for accurate descriptions of ion behavior (Halgren & Damm, 2001) in aqueous solutions (Chang & Dang, 2006; Grossfield *et al.*, 2003; Lamoureux & Roux, 2006; Stuart & Berne, 1996) and for more complex environments such as ion–protein interactions (Li *et al.*, 2008) and ion channels (Allen *et al.*, 2000; Bucher *et al.*, 2006; Illingworth & Domene, 2009; Noskov *et al.*, 2004; Roux *et al.*, 2004; Warshel *et al.*, 2007).

Several groups have performed molecular dynamics simulations using polarizable force fields to study ion behavior or to determine ion solvation energies. For example, Dang and co-workers used many-body polarizable potential models in molecular dynamics simulations to study the solvation behavior of Li^+, Na^+, Cl^-, and F^- in water clusters (Dang, 1992; Dang *et al.*, 1991) and the significant role that polarization plays in ion binding to the liquid/vapor interface (Chang & Dang, 2006; Dang & Chang, 2001). A protein Langevin dipole model, developed by Aqvist and Warshel (Aqvist & Warshel, 1989) has been used to calculate the solvation energy of a Na^+ ion

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inside the Gramicidin A channel and in water, and similar methods have been applied to model the polarization effect in the KcsA channel (Burykin *et al.*, 2003; Luzhkov & Åqvist, 2000). Additionally, a polarizable molecular mechanic model based on induced dipole approach was successfully applied to study the absolute solvation free energies for K^+, Na^+, and Cl^- (Grossfield *et al.*, 2003), as well as Mg^{2+} and Ca^{2+} (Jiao *et al.*, 2006). Using a Drude oscillator model for polarizability, Roux and co-workers have developed a polarizable potential function for the hydration of alkali halide salts (Lamoureux & Roux, 2006; Whitfield *et al.*, 2007), which gives results consistent with *ab initio* calculations. In addition, the fluctuating charge method of polarization has been applied to ionic systems (Bryce *et al.*, 1998; Ribeiro, 1999) and has been used to extend classical force fields to include polarization effects (Patel & Brooks, 2004; Patel *et al.*, 2004; Warren & Patel, 2007). Despite all these efforts, modeling explicit ions remains a considerable challenge, owing to the complex, dynamic, and subtle nature of ions, and it is expected that the future direction will be focused on using *ab initio* treatment and polarizable force fields.

6. Modeling solvation with intermediate detail: integral equation and density functional theories

6.1 Solvent distributions from integral equations

As discussed above, modeling explicit solvent effects via computer simulation techniques can be costly since the resulting systems involve a large number of particles with long-range interactions and demand substantial computational resources. An alternative route to solvation is provided by integral equation theories (IETs), which simplify the all-atom description of explicit solvation into a probabilistic treatment of distributions between solute and solvent. As a result of this simplification, these methods generally require less computational expense than explicit solvent methods, but offer more detail than the continuum models discussed below (Attard, 2002; Hansen & McDonald, 2000; Hirata, 2003). Because of this compromise, IETs can be efficient and powerful tools to predict the three-dimensional (3D) spatial organization of the solvent density around large molecular solutes of irregular shape as well as related thermodynamic solvation quantities (Beglov & Roux, 1997; Chandler *et al.*, 1986; Du *et al.*, 2000; Harano *et al.*, 2001; Imai *et al.*, 2001; Kovalenko & Hirata, 1998, 1999, 2000a, b, c). A particularly popular set of integral equations are the interaction site models (Chandler, 1978; Hirata, 2003; Rossky *et al.*, 1983) that specifically model the probability distribution of specific atomic sites on the solvent around atomic sites on the solute. The 1D-RISM (reference interaction site model) theory provides site–site radial distribution functions coming from an angular average over the orientation of both solute and solvent molecules (see Fig. 3). This approach has been successfully applied to small molecules in general (Chuev & Fedorov, 2004; Du *et al.*, 2000, 2008; Freedman & Truong, 2004; Frolov *et al.*, 2000, 2011; Imai *et al.*, 2007a, b; Kiyota *et al.*, 2009, 2011; Kovalenko & Hirata, 1998, 1999, 2000a, b, c; Maruyama *et al.*, 2010; Miyata & Hirata, 2008; Nishiyama *et al.*, 2009; Stumpe *et al.*, 2011; Woelki *et al.*, 2008; Yoshida *et al.*, 2006). Unlike the 1D model, 3D-RISM keeps the orientational dependence of solute molecules, which is necessary to properly describe solvation properties of large molecular solutes. This more accurate 3D integral equation demands a higher computational cost when compared with the 1D theories (Perkyns & Pettitt, 1992). It provides not only an accurate site–site radial pair correlation functions but also the correct dielectric properties of polar liquids, which is a key element to properly describe

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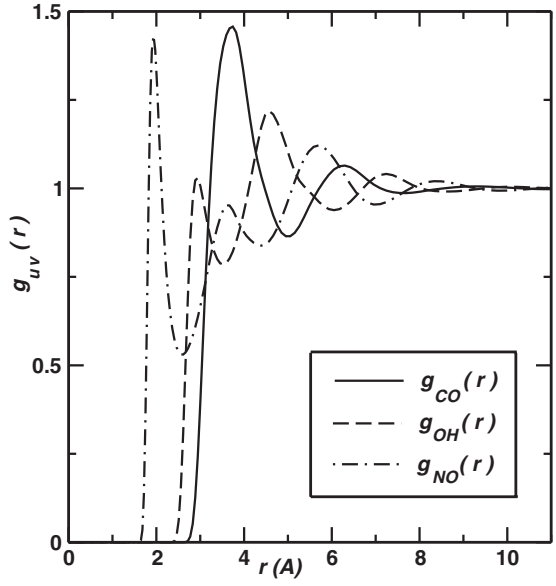


Fig. 3. This figure represents the solute–solvent site–site pair correlation functions $g_{uv}(r)$ as a function of the separation distance r predicted by 1D-RISM for *N*-methyl acetamide immersed in water at infinite dilution. For instance, $g_{NO}(r)$ is the pair correlation function for a nitrogen atom in *N*-methyl acetamide molecule and an oxygen atom in water molecule.

the solvent effects on solutes. Integral equations specify formulae for the total and direct solvent correlation functions. Once solved, these quantities can be used to calculate the solvation chemical potential (Imai *et al.*, 2004; Kovalenko & Hirata, 1999), the potential of mean force for solutes degrees of freedom (Kovalenko & Hirata, 1999, 2000b, c), solvation coordination numbers (Kovalenko & Hirata, 1998) and hydration shells (Imai *et al.*, 2007a), hydrophobic effects (Howard *et al.*, 2008; Kovalenko & Hirata, 2000a), as well as many other quantities.

Despite the successes achieved by IETs in predicting solvation properties, there remain deficiencies that need to be corrected. A serious problem associated with these approaches is that, when they fail to yield physically reasonable predictions, there are no straightforward, systematic methods to improve IET predictive accuracy. A useful avenue to remedy this situation has been to construct thermodynamically consistent integral equation theories for interaction site fluids in which the optimal closure approximation is determined by first principles (Marucho *et al.*, 2008; Marucho & Pettitt, 2007). The re-analysis of the interaction-site formalism has also led to the development of more sophisticated (diagrammatically proper) integral equations eliminating diagrams that are not present in the exact theory (Marucho *et al.*, 2008; Marucho & Pettitt, 2007). Another challenge for IETs lies in the inclusion of solute flexibility; however, some progress has been made in this area. IETs can be properly combined with other methodologies such as Monte Carlo simulations which project solvent degrees of freedom onto the solute at the level of site–site pair correlation functions (Freedman & Truong, 2004; Kinoshita *et al.*, 1999; Kovalenko & Hirata, 2000b, c). Alternatively, dynamical solute processes in solution can be treated by incorporating the IETs into a generalized Langevin equation, which describes the time evolution of solvent densities (Chong & Hirata, 1998).

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6.2 Ion distributions from integral equations and density functional theories

Like solvent, ion distributions can also be modeled by IETs; for example, by the DRISM introduced in section above, which has been shown to account for changes in the water structure caused by the addition of salts near a protein and associated changes in the solvation free energy from the evaluation of site–site total and direct correlation functions (Imai *et al.*, 2000; Perkyns & Pettitt, 1994, 1995, 1996). While more computationally efficient, the 1D RISM theory suffers from its inability to model the solvent inaccessibility of buried solute atoms accurately. There have been several efforts to correct this problem (Imai *et al.*, 2000); however, the 3D RISM theory described above is somewhat more computationally expensive but free from this problem and provides more accurate predictions of ionic behavior (Imai *et al.*, 2004; Yonetani *et al.*, 2008).

Classical density functional theory (DFT) (Chandler *et al.*, 1986) provides another powerful tool for describing ionic behaviors through ion distributions. This approach is based on the simple thermodynamic principle that the system reaches the equilibrium as its grand canonical potential reaches minimum. In particular, for a fluid subject to an arbitrary potential $V_{\text{ext}}(r, \Omega)$, the grand canonical free energy can be written as a functional of the one-particle density. This free energy functional is minimized at the thermodynamic equilibrium density. Thus, its knowledge of this functional and the equilibrium density characterize the fluid completely. However, this functional is not known for most complex systems and, instead, is approximated in various ways. Different approaches and approximations based on DFT have been proposed to evaluate the excess free energy and the density profile depending on the complexity and features of the system. For example, Gao and co-workers (Wang *et al.*, 2004) use the weighted-density approximation to describe the structure and thermodynamics properties of small ions around a polyelectrolyte immersed in a continuum media, observing the charge inversion phenomena of DNA at moderate concentrated solution. Ramirez & Borgis (2005) use the homogeneous reference fluid approximation to develop a general approach that includes the microscopic structure of the solvent, the dipolar saturation effects, and the non-local character of the dielectric constant in the calculation of the average solvent structure solvation properties of molecular solutes of irregular shape. Eisenberg and co-workers (Gillespie *et al.*, 2002) combine a 1D drift–diffusion (Poisson–Nernst–Planck or, PNP) transport system and DFT to model ion transport in biological ion channels. These examples show the theoretical versatility of DFT for describing ionic solvation in complex systems. However, the same energy functional may not be accurate for all applications and systematic improvements of the functional are not generally possible, instead requiring *ad hoc* corrections.

7. Modeling solvation with low detail: continuum approximations

While models of higher resolution can ideally provide better accuracy and quantitative predictions, their computational cost often precludes use in many biomolecular applications. Instead, it is often essential to reduce computational costs by accounting solvent and ion effects in an implicit or continuum manner (Baker, 2004; 2005a, b; Baker *et al.*, 2006; Cramer & Truhlar, 1999; Marenich *et al.*, 2008; Onufriev *et al.*, 2002). Implicit solvent methods have been very successful with a multitude of applications in computational chemistry and biology. However, these models are highly approximate and often empirical; as such, there are several caveats that potential users should keep in mind. First, most implicit solvent models uncouple polar and

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non-polar interactions, even though such a separation can be problematic and unphysical (Cerutti *et al.*, 2007; Chen *et al.*, 2010, 2011a, b; Dzubiella & Hansen, 2004; Dzubiella *et al.*, 2006a, b). Additionally, as discussed in more detail below, implicit models for non-polar and polar solvation are—by their very nature—approximate with several sources of ambiguity in the choice of model parameters and geometries (Swanson *et al.*, 2005, 2007; Teixeira *et al.*, 2005; Tjong & Zhou, 2008). However, despite these caveats, implicit solvent models are very popular and valuable for a variety of biophysical studies.

While continuum models of solvent polarization have had many successes, they provide an incomplete description of water behavior—particularly at small-length scales and in the presence of strong electrostatic fields. In particular, continuum models are limited by their assumption of linear and local solvent polarization in response to electrostatic perturbations (Beglov & Roux, 1996, 1997; Hansen & McDonald, 2000; Roux, 1999). The continuum dielectric assumption of local response implicitly neglects the role of detailed solvent–solvent interactions (e.g. hydrogen bonds, steric clashes, etc.) and solvent molecular shape (Mobley *et al.*, 2008) in dielectric behavior. The continuum assumption of linear response ignores the finite density, dipole moment, and polarizability of solvent by neglecting the non-linear phenomena of electrostriction and dielectric saturation. Finally, the polarization of molecular solvents is also closely linked to variations in local density (Ashbaugh & Truskett, 2001; Beglov & Roux, 1996, 1997; Dzubiella & Hansen, 2004; Dzubiella *et al.*, 2006a, b; Paliwal *et al.*, 2006); e.g. the presence of cavities or other solutes. In particular, the introduction of a cavity or uncharged solute into a polar solvent such as water can create significant interfacial polarization, often resulting in a positive potential inside the cavity (Ashbaugh, 2009; Cerutti *et al.*, 2007; Harder & Roux, 2008; Martin *et al.*, 2011).

7.1 The Poisson equation for polar solvation

The Poisson equation is a fundamental equation of continuum electrostatics (Bottcher, 1952; Jackson, 1975). It is a linear second-order partial differential equation

$$-\nabla \cdot (\varepsilon(\vec{r})\nabla\phi(\vec{r})) = \rho(\vec{r}) \qquad \text{for } \vec{r} \in \Omega,$$

which expresses the ESP ϕ terms of a dielectric coefficient ε and a charge distribution ρ for all points r in some domain Ω. This differential equation must be combined with additional constraints on the potential in order to provide well-posed solutions. These constraints usually take the form of boundary conditions specifying the value of the potential or its derivatives on the boundary $\partial\Omega$ of the domain. The most common boundary conditions for biomolecular electrostatics problems are the simple Dirichlet condition which constrains the potential to an asymptotic approximation on the boundary of the domain.

The biomolecular structure and chemistry are introduced into the Poisson equation through the dielectric and charge coefficients. The charge distribution is often represented by a sum of atomic monopoles or higher-order multipoles as described in the 'Modeling biomolecular charge distributions' section. The dielectric coefficient is generally a sharply varying function that assumes bulk solvent values outside of the biomolecular surface and other values inside the biomolecule. The value of the dielectric coefficient determines the polarization response of the material when subject to an electric field; more easily polarizable materials have higher dielectric values. While the bulk values of the dielectric are straightforward to determine, based on the properties of the homogeneous solvent, the dielectric values inside the biomolecule are much

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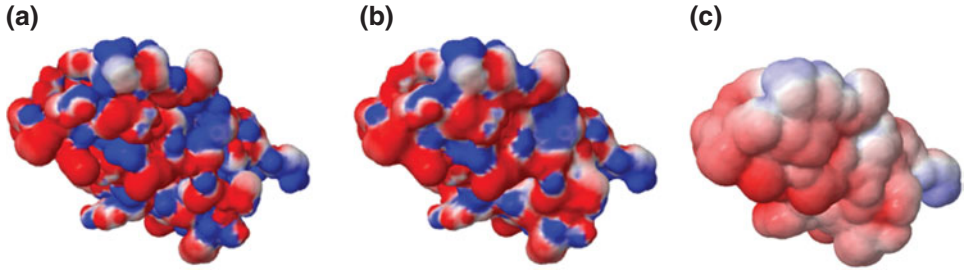


Fig. 4. Images of the varying definitions for the biomolecular surface of fasciculin-2 (PDB ID: 1FAS) with ESP shown ranging from $-5\ kT/e$ (dark red) to $+5\ kT/e$ (dark blue). (A) van der Waals surface. (B) Solvent-excluded, molecular, or Connolly surface. (C) Solvent-accessible surface.

more difficult to interpret and have been subject to much debate and analysis (Roux, 1999; Schutz & Warshel, 2001; Sham *et al.*, 1998; Simonson, 1999, 2001, 2003, 2008; Teixeira *et al.*, 2005; Tjong & Zhou, 2008). In particular, the choice of internal dielectric coefficient values is usually very dependent on the specific application. If the only polarization response of the biomolecular interior results from electronic reorganization, then the most appropriate value of the biomolecular dielectric coefficient should be between 2 and 4 (Landau *et al.*, 1982). Such low dielectric models are appropriate for simulations and calculations such as MM/PBSA (MM/PB surface area) where the molecular flexibility of the molecule is modeled explicitly through conformational sampling. Higher values of the internal biomolecular dielectric are intended to mimic additional relaxation properties, including orientational changes in molecular dipoles, side-chain rearrangement, and even penetration of water into the biomolecular interior. Values from 4 to 20 have been regularly used in a variety of biomolecular applications with lower values generally being successful for protein–ligand interactions (Kollman *et al.*, 2000; Massova & Kollman, 2000), moderate values of 10–12 necessary for protein–protein binding energies (Elcock *et al.*, 2001), and values 20 or higher needed for titration state and pK_a predictions (Chimenti *et al.*, 2011; Schutz & Warshel, 2001).

In addition to the variety of dielectric coefficient values, there are also many choices available for the functional form and shape of the biomolecule-solvent dielectric boundary (see Fig. 4) (Chen *et al.*, 2010, 2011b; Grant & Pickup, 1995; Grant *et al.*, 2001; Im, 1998; Tjong & Zhou, 2008). The results of most biomolecular solvation and electrostatics calculations are very sensitive to the definition of this boundary, so it is not surprising that the optimal choice of biomolecular parameters and dielectric value are dependent on the particular dielectric boundary of choice (Nina *et al.*, 1999; Swanson *et al.*, 2007). As with the dielectric value, the choice of a particular boundary geometry is dependent on many factors, including the specific problem under consideration, the original geometry definitions used to optimize the parameters desired for the given calculation. The most popular biomolecular dielectric interface definition is the molecular surface (Connolly, 1983, 1985) which was used to parameterize the PARSE parameter set for biomolecular solvation calculations (Sitkoff *et al.*, 1994a, b). Zhou and co-workers have suggested the use of van der Waals surface as an alternative to the molecular surface for several different applications (Dong *et al.*, 2003; Tjong & Zhou, 2008). Both the molecular and van der Waals surfaces can introduce significant conformational sensitivity that can be problematic for applications that explicitly sample different conformational states. As a result, a number of smoother surfaces have also been introduced, including Gaussian (Grant *et al.*, 2001;

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Grant & Pickup, 1995) and spline-based representations (Im, 1998; Schnieders *et al.*, 2007). These surfaces require a distinct set of parameters for accurate calculations, as described (Grant *et al.*, 2001, 2007; Grant & Pickup, 1995) for Gaussian interfaces and by others (Nina *et al.*, 1999; Swanson *et al.*, 2007) for spline-based representations. Finally, new generations of molecular surface definitions that are designed to minimize noise from topological artifacts (Bajaj, 2003; Zhang *et al.*, 2006) and to provide a clear physical basis for coupling to non-polar representations (Chen *et al.*, 2010, 2011b; Dzubiella & Hansen, 2004; Dzubiella *et al.*, 2006a, b) are appearing. In particular, new surfaces based on geometric flow (Chen *et al.*, 2001, 2010) provide a self-consistent description of the biomolecular interface that is compatible with the continuum polar and non-polar energy functions. While these new surfaces appear very promising, they will require parameterization before they can be used optimally in biophysical calculations.

The linear and local nature of the dielectric coefficient introduce two major assumptions into the model (Beglov & Roux, 1996, 1997). Linear response implies a proportional increase in system polarization for all strengths of electric field. This approximation clearly breaks down near highly charged interfaces (e.g. nucleic acids or strongly charged proteins) where dielectric saturation and electrostriction processes can become important. Several models have been developed to provide for non-linear response, generally in the form of a Langevin response function (Azuara *et al.*, 2008; Papazyan & Warshel, 1997, 1998). The second major approximation is the local nature of the dielectric constant which implies that local changes in the electric field have only local influences on polarization. However, the molecular nature of water and its associated network of hydrogen bonding and extended structure at interfaces clearly indicate that this approximation is incorrect, particularly at very small (molecular) length scales. Non-local features have also been introduced into the Poisson equation, but incur increased computational expense (Bardhan, 2011; Basilevsky & Parsons, 1998; Rottler & Krayenhoff, 2009).

7.2 The PB equation for polar solvation

The Poisson equation only includes the influence of solvent on the electrostatic properties of a solute. However, as discussed in earlier sections of this review, mobile ions also play a very important role on biomolecular electrostatics and solvation. The PB model was developed to address the need to include simple effects from low valency ions in dilute solutions (Baker, 2004, 2005a, b; Baker *et al.*, 2006; Davis & McCammon, 1990; Dong *et al.*, 2008; Grochowski & Trylska, 2008; Honig & Nicholls, 1995; Honig *et al.*, 1986; Sharp & Honig, 1990a, b). One of the best reviews of the model and its caveats was written by Fixman (Fixman, 1979). The PB model essentially relates the local ESP to the average mobile charge densities. Several important approximations are associated with the PB model (Baker, 2004; Beglov & Roux, 1996, 1997; Fixman, 1979; Holm *et al.*, 2001).

The first approximation, similar to the Poisson equation, is that system solution can be described a continuum, including the dielectric response described above as well as an average density of point-like ions. This density model precludes the treatment of site-specific ion–solute interactions as well as other phenomena that involve details of ionic shape. The PB model cannot explain differences between ion species in solution and thereby prevents effective analysis of specific ion species and the associated phenomena described earlier in this review.

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The second approximation models the distribution of ions in terms of single-species average distribution functions. In other words, ions interact with each other only through their average densities rather than through the steric, Coulombic, and solvent-mediated correlations that occur in real electrolyte systems. As a consequence, the PB model cannot capture a number of phenomena (Chen & Weeks, 2006; Savelyev & Papoian, 2007; Tan & Chen, 2005), including charge inversion (Besteman *et al.*, 2004, 2005; Goel *et al.*, 2008; Kim & Sung, 2005; Luan & Aksimentiev, 2010; Martin-Molina *et al.*, 2009; Nguyen *et al.*, 2000; Qiao & Aluru, 2004; Taheri-Araghi & Ha, 2005; Wen & Tang, 2004) and like-charge attraction (Angelini *et al.*, 2003; Kim *et al.*, 2008; Mukherjee, 2004; Netz & Naji, 2004; Pietronave *et al.*, 2008; Podgornik & Dobnikar, 2001; Qiu *et al.*, 2010; Todd *et al.*, 2008; Zelko *et al.*, 2010) that can be important for highly charged systems. Such systems include solutes such as DNA, charged biomembrane interfaces, and solutions with even moderate concentrations of di- or multi-valent ions. Ionic correlations and fluctuation corrections have been considered in previous studies. Based on the Kirkwood hierarchy (Kirkwood, 1934), a fluctuation potential and an excluded-volume factor have been added to the potential of mean force to represent the effect of ion correlations (Burley *et al.*, 1974; Carnie & Torrie, 2007; Grochowski & Trylska, 2008). The fluctuation potential is associated with the energy for charging ions and implicitly takes into account the inter-ion Coulomb correlations. This modification provides improved predictions for ion distribution and mean ESP profile with multivalent ions, as compared with the conventional PB model (Carnie & Torrie, 2007). However, since the fluctuation potential itself is coupled to the ESP, the 3D numerical solution becomes computationally very expensive and is impractical for applications such as nucleic acid structures (Gavryushov, 2008). Other approaches such as the density functional and integral equation methods were discussed earlier; however, the computational complexity for these approaches is still problematic for many applications.

Another important approximation involves the assumption of infinitesimal ion size which can produce arbitrarily large ion concentrations near highly charged solutes. Borukhov *et al.* (1997) developed a simple analytical approach to include the finite ion size in the original PB model. The modified formula was developed for asymmetric and symmetric electrolytes and matched with the original PB equation when an ionic concentration is low. The size effect was introduced as additional correction terms in the entropic contribution of the total free energy. Such corrections were employed by considering the lattice gas formalism, where each lattice site is occupied at most by one ion; the standard PB model corresponds to one with unlimited number of ions in each lattice site. A similar approach based on the lattice gas formalism was used in other studies (Borukhov *et al.*, 2000; Chaudhry *et al.*, 2011; Coalson *et al.*, 1995; Coalson & Duncan, 1992) to incorporate the finite size effect. This size-modified PB model showed appreciable improvements in predictions for ion-binding properties of monovalent counterions, especially at high-salt concentration, which involves the saturation effect for ion binding. However, the consideration of the finite ion size still cannot capture the binding of the divalent and multivalent ions, which may be because of the absence of ion–ion correlations (Chu *et al.*, 2007).

Despite the caveats and approximations described above, the PB model is simple and captures enough basic solvation behavior to be a popular choice for describing many biomolecular systems. While there are many more interesting ways to drive the PB equation (Holm *et al.*, 2001), the simplest method starts with the Poisson equation, repeated here:

$$-\nabla \cdot (\varepsilon(\vec{r})\nabla\phi(\vec{r})) = \rho(\vec{r}).$$

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In the Poisson discussion above, we considered only a single contribution to the charge density $\rho(\vec{r})$ due to the solute. For the PB equation, the charge distribution is assumed to consist of two separate contributions: the solute charges $\rho_s(\vec{r})$ and the mobile ions in an aqueous medium $\rho_m(\vec{r})$. The charge distribution of the solute was discussed previously; for a simple monopole approximation, the charges Q_i located at each solute atom's position r_i can be modeled via a delta function:

$$\rho_s(\vec{r}) = \sum_i Q_i \delta(\vec{r} - \vec{r}_i).$$

For a mean-field approximation, the charge distribution associated with the mobile ions can be described by a Boltzmann distribution. For m ion species with charges q_j, bulk concentration c_j^b and steric potential $V_j(\vec{r})$ (a potential to describe non-polar interactions with the solute), the charge for the mobile ions is

$$\rho_m(\vec{r}) = \sum_j^m c_j^b q_j \exp\left[\frac{-q_j\phi(\vec{r})}{k_B T} - \frac{V_j(\vec{r})}{k_B T}\right],$$

where k_B is the Boltzmann's constant and T is the system temperature. Substituting the two charge distributions into the Poisson equation, one obtains the full PB equation:

$$-\nabla \cdot (\varepsilon(\vec{r})\nabla\phi(\vec{r})) = \sum_i^N Q_i \delta(\vec{r} - \vec{r}_i) + \sum_j^m c_j^b q_j \exp\left[\frac{-q_j\phi(\vec{r})}{k_B T} - \frac{V_j(\vec{r})}{k_B T}\right].$$

Note that the full PB equation is a non-linear second-order elliptic differential equation, which cannot be solved analytically for most realistic biomolecular geometries.

A simplification to the full PB equation can be made if the exponential term is approximated by the linear term in its Taylor series expansion. This assumption, which is made in addition to those described above, requires $|q_j\phi(\vec{r})/k_B T| \ll 1$. Also assuming identical steric contributions for all ions, the full PB equation becomes the linearized PB equation:

$$-\nabla \cdot (\varepsilon(\vec{r})\nabla\varphi(\vec{r})) + \varepsilon(\vec{r})\kappa^2(\vec{r})\phi(\vec{r}) = \sum_i^N Q_i \delta(\vec{r} - \vec{r}_i),$$

where $\kappa(\vec{r})$ is a modified inverse Debye–Hückel length represented by

$$\kappa(\vec{r}) = \left(\exp\left[-\frac{V(\vec{r})}{k_B T}\right]\frac{2I^2 e_c^2}{k_B T \varepsilon(\vec{r})}\right)^{1/2},$$

where $I = \sqrt{\sum_j c_j^b q_j^2 / 2e_c^2}$ is the ionic strength and e_c is the electron charge. The Debye–Hückel length is considered as a length scale below which mobile ions experience the ESP of the solute and interact with it.

Using the potential obtained by solving the PB equation, the electrostatic free energy can be obtained via a variety of integral formulations (Chen *et al.*, 2010, 2011b; Gilson, 1995; Holm *et al.*, 2001; Micu *et al.*, 1997; Sharp & Honig, 1990a). These free energy expressions arise both from physical considerations as well as from a purely mathematical standpoint. Statistical physics can derive the PB equation and its associated free energy from a saddle-point approximation of a more complicated description of the electrolyte system (Holm *et al.*, 2001). Functional minimization of the resulting free energy gives rise directly to the PB equation. It is also possible

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to differentiate these integral formulations of the electrostatic energy with respect to atomic position in order to obtain the electrostatic (i.e. polar) solvation mean force on each atom (Gilson *et al.*, 1993; Im, 1998; Wagoner & Baker, 2004, 2006).

While the PB equation may be solved analytically for very simple cases (e.g. flat plate with a single symmetrical electrolytes), analytical solutions of the PB equation are not available for biomolecules with realistic shapes and charge distributions. Therefore, a numerical method is a necessary tool for biomolecular electrostatics. After Warwicker and Watson (Warwicker & Watson, 1982) first introduced numerical methods to solve the PB equation at the active site of an enzyme, many different numerical methods have been developed and are being modified. Most numerical methods for the PB equation depend on the discretization of computational domain/space (i.e. a distribution of points and their connections), which is critical to both accuracy and efficiency. These methods include finite differences (Baker *et al.*, 2001b; Davis & McCammon, 1989; Holst & Saied, 1993, 1995; Nicholls & Honig, 1991), finite elements (Baker *et al.*, 2000, 2001a; Cortis & Friesner, 1997a, b; Dyshlovenko, 2002; Holst *et al.*, 2000), and boundary elements (Bajaj *et al.*, 2011; Bordner & Huber, 2003; Boschitsch & Fenley, 2004; Juffer *et al.*, 1991; Zauhar & Morgan, 1988).

Because of their simpler spatial discretization of the computational domain, finite differences have been the most popular numerical methods for the PB equation in bimolecular electrostatics. Finite difference-based PB solvers include APBS (Baker *et al.*, 2001b), matched interface and boundary (MIB) (Chen *et al.*, 2001; Yu & Wei, 2007; Yu *et al.*, 2007a, b; Zhou & Wei, 2006), DelPhi (Klapper *et al.*, 1986; Rocchia *et al.*, 2002), MEAD (Bashford, 1997), UHBD (Madura *et al.*, 1995), ZAP (Grant *et al.*, 2001), the PBEQ (Im, 1998) module in CHARMM (Brooks *et al.*, 2009), and the PB solver in AMBER (Luo *et al.*, 2002). The APBS solver provides scalable electrostatics by uniquely combing standard finite difference focusing techniques (Gilson & Honig, 1987) and the Bank–Holst algorithm (Bank & Holst, 2003) into a parallel focusing method that allows solution of the PB equation for molecules of arbitrary size. A new MIB method (Chen *et al.*, 2001; Geng & Wei, 2001; Xia *et al.*, 2011; Yu *et al.*, 2007a, b ; Zhou & Wei, 2006) implemented the analytical molecular surface in their interface method for solving the PB equation. This method was the first biomolecular PB solver enforcing the continuity conditions of both the ESP and its flux at the molecular surface. Wei *et al.* (Yu & Wei, 2007; Yu *et al.*, 2007a, b) extended their work to further develop MIB-based PB solvers called MIBPB-II and MIBPB-III in order to accommodate geometric and charge singularities, respectively.

Finite-element methods provide more flexibility than finite differences by permitting adaptive mesh refinement in regions of high error. The local nature of this refinement, together with robust multilevel solvers (Holst, 2001), provides unique multiscale capabilities. Significant finite-element work related to the PB equation was performed by Holst and co-workers (Baker *et al.*, 2000, 2001a, b; Holst, 2001; Holst & Saied, 1993, 1995; Holst *et al.*, 2000). More recently, Chen *et al.* (2007a) have provided the first complete convergence result for a numerical discretization technique for the non-linear PB (NLPB) equation with delta distribution sources and introduced the first convergent adaptive method for the PB equation. Finite-element solutions are currently available through the FEtk solver (http://www.fetk.org/) with a biomolecular electrostatics interface provided APBS (http://www.poissonboltzmann.org/).

Boundary element methods (BEM) use Green's theorem to reformulate the linear PB equation as boundary integral equations (Allison, 2001; Altman *et al.*, 2009; Bajaj *et al.*, 2011; Bharadwaj *et al.*, 1995; Boschitsch & Fenley, 2004; Boschitsch *et al.*, 2002; Juffer *et al.*, 1991; Lu *et al.*, 2010; Yoon & Lenhoff, 1990; Zauhar, 1995; Zauhar & Morgan, 1985, 1988; Zhou, 1993).

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Unlike finite differences and finite elements, the unknowns and domain discretization are only on a 2D surface rather than a 3D volume. For the NLPB equation, 3D volume integrals are involved in the integral equations, which reduce the efficiency of the methods, but still require a smaller number of unknowns than finite difference or finite-element methods. BEMs assume a discontinuous dielectric function at the molecular interface with the solvent; as such, they are suitable for a relatively narrow range of dielectric formulations. Advantages of BEM include (i) the reduction of the unknowns, (ii) exact treatment of boundary conditions at infinity, and (iii) explicit treatment of the physical interface conditions (continuity in potential and jump in its normal derivative). However, Green's functions are not available for the NLPB equation and the BEM may not be efficient because of numerous boundary integral operations and singular boundary integrals that can affect the accuracy and/or stability. Recently, a hybrid finite difference BEM approach was introduced to improve computational efficiency (Boschitsch & Fenley, 2004). This approach is based on the separation of ESP into a linear component satisfying the linear PB equation and is solved using a fast BEM and a correction term accounting for non-linear effects and optionally, the presence of an ion-exclusion layer.

A completely different approach to solution of the linearized PB equation has been suggested by Mascagni and co-workers (Mascagni & Simonov, 2004; Simonov *et al.*, 2007). Their technique uses Monte Carlo methods that simulate random walks in the problem domain to solve the linear PB equation. This random walk approach is sufficiently flexible to work with complicated biomolecular geometries and can be used to calculate the molecular electrostatic properties for a series of salt concentration values simultaneously.

7.3 Simpler models for polar solvation

In addition to the PB model, simpler models have also been developed based on continuum electrostatics principles. These simple models include distance-dependent dielectric functions, analytic continuum methods (Schaefer & Karplus, 1996), the so-called Effective Energy Function (EEF) approach (Lazaridis & Karplus, 1999) and the improved ABSINTH model (Vitalis & Pappu, 2009) and generalized Born (GB) models. The GB model is one of the most popular models and was developed by Still *et al.* in 1990 (Still *et al.*, 1990) and subsequently revised by several others (Anandakrishnan *et al.*, 2011; Bashford & Case, 2000; Brown & Case, 2006; Chen, 2010; Chen *et al.*, 2006; Clark *et al.*, 2009; Dominy & Brooks, 1999; Feig & Brooks, 2004; Feig *et al.*, 2004, 2008; Gallicchio *et al.*, 2002, 2009; Grant *et al.*, 2007; Grycuk, 2003; Im *et al.*, 2003b; Jorgensen *et al.*, 2004; Labute, 2008; Lee *et al.*, 2002; Onufriev *et al.*, 2000, 2002; Osapay *et al.*, 1996; Tjong & Zhou, 2007b; Tsui & Case, 2000; Xu *et al.*, 2011; Zhu *et al.*, 2005). The GB model describes the solvent as a continuum medium, similar to the PB model, but provides a faster calculation of solvation energies and forces. The model is an approximation to the Poisson equation energy; it models a solute particle as a sphere whose internal dielectric permittivity coefficient is different from that of the external solvent. Specifically, it uses the analytical solvation energy resulting from the solution of the Poisson equation for a simple sphere (Born, 1920).

Analytical solutions to electrostatic problems associated with various simple dielectric boundary conditions are discussed in many textbooks (Bottcher, 1952; Jackson, 1975). A simple electrostatic model of a biomolecule in solution is a cavity with a charge distribution embedded in a high-dielectric continuum medium. The problem can be further simplified by considering a spherical cavity within which electrostatic interactions are calculated explicitly. By Gauss' Law,

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the ESP outside the sphere is given by the usual Coulomb formula. However, since electric charges within the cavity polarize the high-dielectric medium, the total electric potential inside the cavity includes this effect as well as the direct Coulomb interactions between charges within the cavity. The electric potential associated with the polarization is called the 'reaction field (RF)' potential and can be represented by a summation of Legendre polynomials (Kirkwood, 1934) or by the Coulomb potential associated with image charges outside the cavity.

The image charge approach is usually formulated when the dielectric constant of medium is much larger than that of the cavity, the RF potential inside the cavity is approximately (Deng & Cai, 2007; Friedman, 1975)

$$\Phi_{\mathrm{RF}}(r) = \sum_{i=1}^{N} \frac{q_i'}{\varepsilon_{in}|\underline{r} - \underline{r}_i'|},$$

$$q_i' = \frac{\varepsilon_{in} - \varepsilon_o}{\varepsilon_{in} + \varepsilon_o} \frac{R}{r_i} q_i,$$

$$\underline{r}_i' = (R/r_i)^2 \underline{r}_i,$$

where q' is the image charge that will interact with the solute and r' is the location of the image charge outside the cavity. The total energy of the system, including both the gas-phase interaction energy of source charges and the RF energy, becomes (Wang & Hermans, 1995):

$$U = \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{q_i q_j}{\varepsilon_{in}|\underline{r}_i - \underline{r}_j|} + \frac{1}{2} \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{q_i q_j'}{\varepsilon_{in}|\underline{r}_i - \underline{r}_j'|},$$

where the sums implicitly exclude self-interactions for $i=j$. The first term of this energy expression indicates the direct electrostatic interactions between source charges in the cavity, whereas the second term includes the RF effect through the interactions between the source charges and image charges. Note that the second term includes not only the interaction between each source charge with the image charges of other source charges but also that between each source charge with its own image charge. By placing solute molecules in a spherical water droplet, Wang & Hermans (1995) adapted the Friedman's image charge method in molecular dynamic simulations to account for the dielectric effect outside the simulated sphere. Deng & Cai (2007) showed that Friedman's formula is the zeroth-order term in the Kirkwood series expansion with respect to $\varepsilon_{in}/\varepsilon_o$. It is also noted that Friedman's approximation is inconsistent with Born formula when all the charges are located at the center of the spherical cavity. Based on the work by Neumann (Neumann, 1883), a multiple image of charge method was proposed whereby the single image charge is replaced by a charge distribution extending from the image charge position to infinity in the radial direction (Lindell, 1992; Norris, 1995). An efficient fast multipole algorithm was developed to take advantage of the accuracy of the multiple image method while making it computational tractable for simulation purposes (Cai *et al.*, 2007; Deng & Cai, 2007).

The Legendre polynomial solution of the spherical system was given by Kirkwood in 1934 (Kirkwood, 1934). For a system with a set of point charges q_k in a spherical cavity of radius a, the RF potential at r inside the sphere is given by

$$V(r) = \frac{1}{\varepsilon_{in}} \sum_{l=0}^{\infty} \frac{(l+1)(\varepsilon_{in} - \varepsilon_o)}{(n+1)\varepsilon_o + n\varepsilon_{in}} \frac{r^l}{a^{2l+1}} \sum_{k=1}^{N} q_k r_k^l P_l(\cos\theta).$$

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In the equation above, the dielectric constants inside the spherical cavity is ε_{in}. The terms $q_k r_k^l$ ($l=0, 1, 2, \ldots$) are the multipole moments of the charge distribution inside the sphere. The expansion reduces to the Born (Born, 1920) or Onsager (Onsager, 1936) approximation in the special case of a single ion or dipole buried at the center of the spherical cavity.

With growing interests in sophisticated electrostatic models involving point multipoles and electronic polarization, the Kirkwood's RF theory has been extended beyond partial charges. Orttung generalized the Kirkwood–Westheimer model (Kirkwood, 1938) for different shapes, charges, and polarizabilities (Orttung, 1978). Warshel developed a multiscale model to describe the interactions among explicit solute (point charge), immediate solvation shell (point dipole) and the surrounding continuum (RF) (Warshel, 1979). Felder and Applequist introduced inducible dipoles to represent the solute electrostatics and derived the corresponding RF expressions for spherical and ellipsoidal cavities (Felder & Applequist, 1981). Kong and Ponder obtained the RF energy and force for arbitrary point multipole distributions located off the center of the spherical cavity (Kong, 1997). Nymand and Linse developed a RF model for solutes of point charges, dipoles and polarizabilities (Nymand & Linse, 2000). Recently, Schnieders and Ponder introduced generalized Kirkwood (GK) model to eliminate the partial charge restriction inherent to GB analytic continuum electrostatics (Schnieders & Ponder, 2007). GK defines a self-consistent RF for solutes modeled by polarizable atomic multipoles, which are not only more accurate and transferable than partial charges but also more expensive. Davis developed an inducible multipole solvation model that exhibits an exact series representation of the external electrostatic field for a collection of dielectric cavities with centrosymetric internal charge distributions and arbitrary external charge distributions (Davis, 1994). Fenley *et al.* (2008) derived a closed-form analytical approximation to the Poisson equation for an arbitrary distribution of point charges and a spherical dielectric boundary. Their simple, parameter-free formula was obtained from the Kirkwood solution by an approximate summation method and presents continuous ESP everywhere in space.

The GB model can be thought of as a good analytical approximation to the analytical models described above. In particular, it uses the analytical solvation energy resulting from the solution of the Poisson equation for a simple sphere and needs a much lower computational cost, compared to solving the PB equation. Using the GB model, the electrostatic solvation-free energy can be approximated by a modified form of the analytical solvation energy for a sphere (Still *et al.*, 1990):

$$G_{el} \cong -\frac{1}{2}\left(1-\frac{1}{\varepsilon_{\text{sol}}}\right)\sum_{i,j}\frac{Q_i Q_j}{f_{ij}^{\text{GB}}},$$

where f_{ij}^{GB} denotes the effective Born radii (when $i=j$) and the effective interaction distance (when $i\neq j$), respectively. The most common form given by Still *et al.* (1990) is

$$f_{ij}^{\text{GB}} = \left[r_{ij}^2 + R_i R_j \exp\left(-\frac{r_{ij}^2}{4R_i R_j}\right)\right]^{1/2},$$

where R_i are the effective radii of the atoms and r_{ij} are the distance between atoms i and j. It is essential to calculate the effective radii of the atoms efficiently and accurately. A previous study (Onufriev *et al.*, 2002) demonstrated that the GB model can provide comparable results to the Poisson equation when one uses perfect GB radii that reproduce the atoms' self-energies as obtained from the Poisson equation. This observation implies that an accurate estimation of the

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radii is critical for reliability of the GB model. Many studies have been performed to improve the GB model not only with general corrections (Mongan *et al.*, 2007) but also with revised formulations aiming at biomacromolecules such as proteins and nucleic acids (Dominy & Brooks, 1999; Onufriev *et al.*, 2000; Sigalov *et al.*, 2006) and biological membranes (Im *et al.*, 2003a; Tanizaki & Feig, 2005). The GB model has also been extended to provide approximations to the full NLPB equation because of its computational benefit (Tjong & Zhou, 2007a, 2007b).

7.4 Continuum models for non-polar solvation

The low-detail continuum polar solvation models above are generally decoupled from the non-polar energetics of the system. Therefore, non-polar contributions must be added into the system to complement the polar energetics. The importance of non-polar solvation is well known, but has often been treated with a very simple approximation that assumes non-polar energy is proportional to solvent-accessible area (Chothia, 1974; Massova & Kollman, 2000; Sharp *et al.*, 1991a, b; Wesson & Eisenberg, 1992)

$$G_{\text{non-polar}}(\vec{x}) \cong \gamma A(\vec{x}).$$

This approximation is motivated by the solvation area of linear alkanes in water. Here γ is a microscopic solvent surface tension parameter (not a macroscopic surface tension of solvent) which can be chosen to reproduce the solvation free energy of non-polar molecules (Sharp *et al.*, 1991a, 1991b; Simonson & Brunger, 1994; Sitkoff *et al.*, 1994b), including model side chain analogs (Wesson & Eisenberg, 1992; Wimley *et al.*, 1996). The surface tension parameter can be modeled as a single universal value used for all atoms or different values may be assigned for each atom type. While the simplest description has been successful, it has several caveats, including the difficulty of rationalizing surface tension parameter values (Chothia, 1974; Eisenberg & McLachlan, 1986; Sharp *et al.*, 1991a, 1991b; Sitkoff *et al.*, 1994b) as well as inaccurate descriptions of detailed aspects of non-polar solvation energies (Gallicchio & Levy, 2004), peptide conformations (Su & Gallicchio, 2004), and non-polar solvation forces (Wagoner & Baker, 2006).

Recent work (Gallicchio *et al.*, 2000; Gallicchio & Levy, 2004; Levy *et al.*, 2003; Wagoner & Baker, 2006) has built upon a significant amount of existing research into non-polar effects (Ashbaugh, 2009; Ashbaugh & Pratt, 2006; Ben-Naim, 2006; Chandler, 2005; Gu *et al.*, 2004; Huang & Chandler, 2002; Huang *et al.*, 2001; Hummer, 1999; Hummer & Garde, 1998; Hummer *et al.*, 1996, 2000; Pitera & van Gunsteren, 2001; Pratt, 2002; Pratt & Chandler, 1977; Pratt & Pohorille, 1992, 2002; Rajamani *et al.*, 2005; Tan *et al.*, 2007) to develop computationally efficient, but more energetically complete, models for non-polar solvation energy that include important attractive van der Waals interactions between solvent and solute (Gallicchio & Levy, 2004; Gallicchio *et al.*, 2000, 2002; Wagoner & Baker, 2006) and repulsive solvent-accessible volume terms (Wagoner & Baker, 2006). For example, Wagoner and Baker proposed a non-polar solvation model based on the free energy functional (Wagoner & Baker, 2006):

$$G_{\text{non-polar}}(\vec{x}) \cong \gamma A(\vec{x}) + pV(\vec{x}) + \bar{\rho} \sum_{i=1}^{N} \int_{\Omega} u_i^{\text{att}}(\vec{x}_i, \vec{y}) \theta(\vec{x}, \vec{y}) \, \mathrm{d}\vec{y},$$

where p is a solvent hydrodynamic pressure parameter, V is a solvent accessible volume, and $\bar{\rho}$ is the bulk solvent density. Here Ω denotes the solvent accessible region outside the solute,

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$u_i^{\text{att}}(\vec{x}_i, \vec{y})$ is the attractive component of the non-polar interaction potential (for atom i) between a solute in conformation $\vec{x}$ and solvent at position $\vec{y}$, and $\theta(\vec{x}, \vec{y})$ is a characteristic function defined as a product of per-atom characteristic functions θ_i. This model showed very good agreement with explicit solvent results, which suggests that the addition of appropriate dispersion and volume terms is essential to describe atomic scale non-polar forces.

Recent studies on the solvation of atomistic and nanoscale solutes reveal that a coupling exists between the hydrophobic, dispersion, and electrostatic contributions to the solvation-free energy. The fact that the effective location of the solvent–solute interface can rely on the local electrostatic and dispersive (Huang & Chandler, 2002) potentials suggests that such polar and non-polar components should be coupled in implicit solvent models. For example, Ashbaugh & Paulaitis (1998) pointed out that a correct balance between non-polar and polar (or electrostatic) contributions is critical in their study of amphiphiles. To take into account polar–non-polar coupling, Dzubiella *et al.* (2006a, b) proposed a theoretical formalism based on the minimization of the Gibbs-free energy of the solvent with respect to a solvent volume exclusion function. Unlike existing implicit solvent approaches, the solvent–solute interface is an output of the model. Therefore, the coupling is indeed implemented by the geometrical description of capillary interfaces. The formalism captures the sensitivity of hydration to the particular form of the solute–solvent interactions in agreement with recent computer simulations. More recently, as discussed above, Wei, Baker, and Chen have combined the non-polar free energy functional introduced above with the PB polar solvation free energy functional for a self-consistent description of solvation and biomolecular surfaces (Chen *et al.*, 2010, 2011b).

8. Hybrid models: the best of both worlds?

In a hybrid approach, physical models of different resolutions are used to treat different regions of the molecular system. The region of interest is often modeled with a high level of detail, using techniques such as QM or explicit solvent, while the remainder of the system is treated at lower levels of resolution. Such models are intrinsically multiresolution and therefore include a wide range of multiscale simulation methodologies that have been recently developed. This section will focus on a few key hybrid methodologies that are either commonly used or particularly interesting as a complete review of this broad field of multiscale modeling is infeasible.

8.1 Quasi-chemical theory

Many solute–solvent interactions, typically short-ranged and structurally specific, can be characterized as chemical associations. Therefore, it is feasible to identify an inner shell around the solute that will accommodate strongly associating solvent molecules, and an outer shell that corresponds to the rest of the system, so that these regions can be treated with high-detail and low-detail models, respectively (Pratt & Laviolette, 1998; Pratt *et al.*, 2001). Quasi-chemical theory provides a framework for such decomposition. The solvation free energy of Li^+, Na^+, K^+, Zn^{2+}, and other alkaline divalent metal cations in water have been successfully predicted on the basis of quasi-chemical theory and *ab initio* molecular dynamics and provided good agreement with experiment (Asthagiri *et al.*, 2004; Rempe *et al.*, 2004). The quasi-chemical method can provide a level of accuracy comparable to that reported in QM, but it is far less expensive than the standard QM/MM method. However, this method still has several limitations, including difficulty treating strongly disordered solvation shells and heterogeneous environments.

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8.2 Implicit–explicit solvation models

Over the years, a number of generalized RF methods have been implemented in molecular simulations based on the continuum Kirkwood expansion (Tironi *et al.*, 1995) with a variety of applications in explicit solvent molecular simulation methodology (Alper & Levy, 1993; Baker *et al.*, 1999; Beglov & Roux, 1994; Brooks, 1985, 1987; Hünenberger & Gunsteren, 1998; Lau *et al.*, 1994; Schreiber & Steinhauser, 1992a, b; Steinbach & Brooks, 1994; Tironi *et al.*, 1995). However, such RF methods also have a natural application to hybrid models. One such example is the general solvent boundary potential (GSBP), where a sphere contains an explicit solvent region while reaction influence of the surrounding environment is represented by a continuum model (Im *et al.*, 2001). The generalized solvent boundary model has been applied to the calculation of protein–ligand binding free energy (Banavali *et al.*, 2002; Deng & Roux, 2008) and recently extended to QM/MM settings (Schaefer *et al.*, 2005).

Lee *et al.* (2004) developed a hybrid solvation scheme to incorporate a continuum RF via GB theory and use a generalized sum-over-spheres boundary, where water molecules are constrained with respect to their closet solute atom location. The hybrid method was first tested on single ion and protein L simulations; and the results achieved similar equilibrium and dynamical observables as the conventional explicit solvent simulations except for some deviations near the boundaries. The hybrid solvent model combined with replica exchange molecular dynamics has been used to study the free energy of formation of ion pairs using model peptides. This work suggested that the structure of salt bridge in explicit solvent can be reproduced by the hybrid solvent approach, but not by GB alone (Okur *et al.*, 2006, 2008).

An important long-standing difficulty of mixed resolution solvent models is structural artifacts near the explicit–implicit solvent boundary. A promising approach to solve this challenging problem is the smoothly decoupled particle interface (SDPI) described recently by Wagoner and Pande (Wagoner & Pande, 2011), which introduces a third, buffering shell between an inner region of explicit solvent and an outer continuum solvent. The function of the buffering shell is to transition smoothly the explicit particle density between that of the innermost region to zero at the interface with the outer continuum.

8.3 Particle-based continuum models

An interesting particle-based macroscopic solvent model, which represents electronic and oriental polarization of water molecules by an ensemble of polarizable pseudo-particles (PPP) (Basdevant *et al.*, 2004, 2006) in a framework that bears some similarity to the polarizable Langevin dipoles of Warshel (Papazyan & Warshel, 1997, 1998) has recently been proposed. In this approach, the solute electric field induces dipoles at the centers of the solvent PPPs which, in turn, interact with the solute charge distribution. However, the solvent PPPs only interact with each other through the van der Waals interactions. The theoretical foundation is built upon on Marcus' functional for solvation free energy (Marcus, 1956). The functional is minimized to the equilibrium condition following the Coulomb field approximation and a localized, off-lattice Langevin dipole approach (Florián & Warshel, 1997) in which the solvent–solvent polarization is ignored (HaDuong *et al.*, 2002). This novel approach has the potential to bridge the gap between implicit and explicit solvent-based solvent methods. The PPP is computationally more efficient than explicit solvent methods as it produces the macroscopic dielectric response instantaneously. However, unlike implicit solvent methods, it aims to directly capture non-polar influences via solvent–solute van der Waals interactions without resorting to additional approximations.

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While this method shows lower computational cost than explicit models and can be extended to coarse-grained solutes (Basdevant *et al.*, 2007; Ha-Duong *et al.*, 2009), the parameterization of the model is complicated, involving empirically scaling the van der Waals radius based on the Born energy of ions and charges of solute atoms to match Kirkwood solvation energy of a spherical cavity.

9. Outlook and future directions

Despite the underlying assumptions and inconsistencies, researchers are dedicated to develop and refine implicit models to be more accurate. Therefore, further research efforts based on implicit solvent models should continue to focus on modifications to overcome such limitations without significantly reducing the computational efficiencies of these models.

Additionally, there is increasing effort to incorporate explicit polarization into the general classical mechanics in different forms such as point dipole induction and Drude oscillators to improve the electrostatic representation of biomolecules. Adoption of such polarizable potentials in routine studies remains limited, mostly because of concerns about the computational expense. Advances in computing power and efficient simulation algorithms; however, will continue to reveal shortcomings of oversimplified fixed-charge potentials and remind us of the missing physics. Additionally, development of advanced classical electrostatic model beyond simple polarization is ongoing. In addition to polarization effect, the local charge-transfer (CT) and penetration effects are demonstrated to play important role for short-range molecular interactions in water (Kumar *et al.*, 2010), aromatics (Tafipolsky & Engels, 2011), and high-valence ions (Cisneros *et al.*, 2008; Wu *et al.*, 2010). Incorporation of such effects significantly improves the accuracy in modeling the structural and energetic details of these molecular clusters. Empirical, additive terms for CT (Hagberg *et al.*, 2005; Kumar *et al.*, 2010) and penetration effects (Cisneros *et al.*, 2008; Tafipolsky & Engels, 2011) have been shown to be rather effective. Because of their short-range nature, these interactions can be treated with local cut-offs and incur negligible additional computational cost relative to polarizable electrostatics treated with particle-mesh Ewald summation.

Advancements in the electrostatic representation of biomolecules and their solvent environment have led to successful applications including small molecule solvation, pK_as and protein–ligand-binding affinity prediction (Jiao *et al.*, 2006, 2008, 2009; Ren *et al.*, 2011; Shi *et al.*, 2011; Yang *et al.*, 2011). Computational sampling can, however, be the next bottleneck in achieving more accurate thermodynamic quantities in complex molecular systems. Advancements in statistical mechanics theories are as important. Although approaches such as FEP (Grossfield *et al.*, 2003; Jorgensen, 1985; Postma *et al.*, 1982; Torrie & Valleau, 1974) and application of Bennett's acceptance ratio (BAR) (Charles H, 1976; Jiao *et al.*, 2008) may require little additional work beyond what is required for molecular dynamics, methods such as thermodynamic integration, lambda dynamics (Kong & Brooks Iii, 1996), meta-dynamics (Barducci *et al.*, 2011; Laio & Parrinello, 2002), and the orthogonal space random walk (OSRW) strategy are more time consuming to implement for polarizable atomic multipole descriptions of electrostatics (Zheng *et al.*, 2008, 2009). Tenable, but non-trivial, complications arise with the latter methods because of their dependency on the derivative of the potential energy with respect to the state variable λ. For example, to the best of our knowledge, a soft-core method to smoothly decouple atomic multipolar interactions with respect to λ has yet to be described. Given the power of metadynamics-based methods to enhance molecular dynamics sampling and reconstruct the free energy surface

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along a few collective variables (Barducci *et al.*, 2011), there is great motivation for force field experts to work closely with developers of the leading statistical mechanics algorithms in the future.

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11. References

Aaqvist, J. (1990). Ion–water interaction potentials derived from free energy perturbation simulations. *Journal of Physical Chemistry* **94**, 8021–8024.

Adams, P. L., Stahley, M. R., Kosek, A. B., Wang, J. M. & Strobel, S. A. (2004). Crystal structure of a self-splicing group I intron with both exons. *Nature* **430**, 45–50.

Alejandre, J. & Hansen, J. (2007). Ions in water: from ion clustering to crystal nucleation. *Physical Review E* **76**, 061505.

Alexov, E., Mehler, E. L., Baker, N. M., Baptista, A., Huang, Y., Milletti, F., Erik Nielsen J., Farrell, D., Carstensen, T., Olsson, M. H. M., Shen, J. K., Warwicker, J., Williams, S. & Word, J. M. (2011). Progress in the prediction of pK_a values in proteins. *Proteins: Structure, Function, and Bioinformatics* **79**, 3260–3275.

Allen, T. W., Kuyucak, S. & Chung, S.-H. (2000). Molecular dynamics estimates of ion diffusion in model hydrophobic and KcsA potassium channels. *Biophysical Chemistry* **86**, 1–14.

Allinger, N. L. (1976). Calculation of molecular structure and energy by force-field methods. In *Advances in Physical Organic Chemistry*, vol. 13 (eds. V. Gold & D. Bethell), pp. 1–82. Academic Press, San Diego, CA.

Allison, S. (2001). Boundary element modeling of biomolecular transport. *Biophysical Chemistry* **93**, 197–213.

Alper, H. & Levy, R. M. (1993). Dielectric and thermodynamic response of a generalized reaction field model for liquid state simulations. *Journal of Chemical Physics* **99**, 9847–9852.

Altman, M. D., Bardhan, J. P., White, J. K. & Tidor, B. (2009). Accurate solution of multi-region continuum biomolecule electrostatic problems using the linearized Poisson–Boltzmann equation with curved boundary elements. *Journal of Computational Chemistry* **30**, 132–153.

Anandakrishnan, R., Daga, M. & Onufriev, A. (2011). An *n* log *n* generalized Born approximation. *Journal of Chemical Theory and Computation* **7**, 544–559.

Anderson, C. F. & Record, M. T. (1990). Ion distributions around DNA and other cylindrical polyions: theoretical descriptions and physical implications. *Annual Review of Biophysics and Biophysical Chemistry* **19**, 423–463.

Anderson, C. F. & Record, M. T. (1995). Salt-nucleic acid interactions. *Annual Review of Physical Chemistry* **46**, 657–700.

Angelini, T., Golestanian, R., Coridan, R., Butler, J., Beraud, A., Krisch, M., Sinn, H., Schweizer, K. & Wong, G. (2006). Counterions between charged polymers exhibit liquid-like organization and dynamics. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 7962–7967.

Angelini, T., Liang, H., Wriggers, W. & Wong, G. (2003). Like-charge attraction between polyelectrolytes induced by counterion charge density waves. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 8634–8637.

Ansell, S., Barnes, A. C., Mason, P. E., Neilson, G. W. & Ramos, S. (2006). X-ray and neutron scattering studies of the hydration structure of alkali ions in concentrated aqueous solutions. *Biophysical Chemistry* **124**, 171–179.

Antosiewicz, J. (2008). Protonation free energy levels in complex molecular systems. *Biopolymers* **89**, 262–269.

Antosiewicz, J., Briggs, J., Elcock, A., Gilson, M. & Mccammon, A. (1996a). Computing ionization states of proteins with a detailed charge model. *Journal of Computational Chemistry* **17**, 1633–1644.

Antosiewicz, J., Mccammon, J. A. & Gilson, M. K. (1996b). The determinants of pK_as in proteins. *Biochemistry* **35**, 7819–7833.

Applequist, J. (1983). Cartesian polytensors. *Journal of Mathematical Physics* **24**, 736–741.

Applequist, J. (1984). Fundamental relationships in the theory of electric multipole moments and multipole polarizabilities in static fields. *Chemical Physics* **85**, 279–290.

Applequist, J. (1985). A multipole interaction theory of electric polarization of atomic and molecular assemblies. *Journal of Chemical Physics* **83**, 809–826.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Applequist, J. (1989). Traceless Cartesian tensor forms for spherical harmonic-functions – new theorems and applications to electrostatics of dielectric media. *Journal of Physics A* (*Mathematical and General*) **22**, 4303–4330.

Applequist, J. (1993). Atom charge transfer in molecular polarizabilities: application of the Olson–Sundberg model to aliphatic and aromatic hydrocarbons. *Journal of Physical Chemistry* **97**, 6016–6023.

Applequist, J., Carl, J. R. & Fung, K.-K. (1972). An atom dipole interaction model for molecular polarizability. Application to polyatomic molecules and determination of atom polarizabilities. *Journal of the American Chemical Society* **94**, 2952–2960.

Aqvist, J. & Warshel, A. (1989). Energetics of ion permeation through membrane channels. Solvation of Na+ by gramicidin A. *Biophysical Journal* **56**, 171–182.

Arai, S., Chatake, T., Ohhara, T., Kurihara, K., Tanaka, I., Suzuki, N., Fujimoto, Z., Mizuno, H. & Niimura, N. (2005). Complicated water orientations in the minor groove of the B-DNA decamer d(CCATTAATGG)2 observed by neutron diffraction measurements. *Nucleic Acids Research* **33**, 3017–3024.

Arakawa, T. & Timasheff, S. (1984). Mechanism of protein salting in and salting out by divalent cation salts: balance between hydration and salt binding. *Biochemistry* **23**, 5912–5923.

Aroti, A., Leontidis, E., Dubois, M. & Zemb, T. (2007). Effects of monovalent anions of the Hofmeister series on DPPC lipid bilayers part I: swelling and in-plane equations of state. *Biophysical Journal* **93**, 1580–1590.

Aroti, A., Leontidis, E., Maltseva, E. & Brezesinski, G. (2004). Effects of Hofmeister anions on DPPC Langmuir monolayers at the air-water interface. *Journal of Physical Chemistry B* **108**, 15238–15245.

Ashbaugh, H. (2009). Entropy crossover from molecular to macroscopic cavity hydration. *Chemical Physics Letters* **477**, 109–111.

Ashbaugh, H. & Paulaitis, M. (1998). A molecular/continuum thermodynamic model of hydration. *Journal of Physical Chemistry B* **102**, 5029–5032.

Ashbaugh, H. & Pratt, L. (2006). Colloquium: scaled particle theory and the length scales of hydrophobicity. *Reviews of Modern Physics* **78**, 159–178.

Ashbaugh, H. & Truskett, T. (2011). Putting the squeeze on cavities in liquids: quantifying pressure effects on solvation using simulations and scaled-particle theory. *Journal of Chemical Physics* **134**, 014507.

Asthagiri, D., Pratt, L., Paulaitis, M. & Rempe, S. (2004). Hydration structure and free energy of biomolecularly specific aqueous dications, including Zn^{2+} and first transition row metals. *Journal of the American Chemical Society* **126**, 1285–1289.

Åstrand, P. O., Linse, P. & Karlström, G. (1995). Molecular dynamics study of water adopting a potential function with explicit atomic dipole moments and anisotropic polarizabilities. *Chemical Physics* **191**, 195–202.

Attard, P. (2002). *Thermodynamics and Statistical Mechanics: Equilibrium by Entropy Maximisation*. San Diego, CA: Academic Press.

Auffinger, P., Cheatham, T. & Vaiana, A. (2007). Spontaneous formation of KCl aggregates in biomolecular simulations: a force field issue? *Journal of Chemical Theory and Computation* **3**, 1851–1859.

Auffinger, P. & Hashem, Y. (2007). Nucleic acid solvation: from outside to insight. *Current Opinion in Structural Biology* **17**, 325–333.

Auffinger, P. & Westhof, E. (2000a). RNA solvation: a molecular dynamics simulation perspective. *Biopolymers* **56**, 266–274.

Auffinger, P. & Westhof, E. (2000b). Water and ion binding around RNA and DNA (C,G) oligomers1. *Journal of Molecular Biology* **300**, 1113–1131.

Auffinger, P. & Westhof, E. (2001). Water and ion binding around r(UpA)12 and d(TpA)12 oligomers – comparison with RNA and DNA (CpG)12 duplexes1. *Journal of Molecular Biology* **305**, 1057–1072.

Azam, S. S., Hofer, T. S., Randolf, B. R. & Rode, B. M. (2009). Hydration of sodium(I) and potassium(I) revisited: a comparative QM/MM and QMCF MD simulation study of weakly hydrated ions. *Journal of Physical Chemistry A* **113**, 1827–1834.

Azuara, C., Orland, H., Bon, M., Koehl, P. & Delarue, M. (2008). Incorporating dipolar solvents with variable density in Poisson–Boltzmann electrostatics. *Biophysics Journal* **95**, 5587–5605.

Bader, R. F. W. (1990). *Atoms in Molecules – A Quantum Theory*. Oxford: Oxford University Press.

Baer, M. & Mundy, C. (2011). Toward an understanding of the specific ion effect using density functional theory. *Journal of Physical Chemistry Letters* **2**, 1088–1093.

Bajaj, C. (2003). Dynamic maintenance and visualization of molecular surfaces. *Discrete Applied Mathematics* **127**, 23–51.

Bajaj, C., Chen, S.-C. & Rand, A. (2011). An efficient higher-order fast multipole boundary element solution for Poisson–Boltzmann-based molecular electrostatics. *SIAM Journal on Scientific Computing* **33**, 826.

Baker, C. M., Lopes, P. E., Zhu, X., Roux, B. & Mackerell, A. D., Jr. (2010). Accurate calculation of hydration free energies using pair-specific Lennard–Jones parameters in the CHARMM drude polarizable force field. *Journal of Chemical Theory and Computation* **6**, 1181–1198.

Baker, N. (2005a). Biomolecular applications of Poisson–Boltzmann methods. *Reviews in Computational Chemistry* **21**, 349–379.

Baker, N. (2005b). Improving implicit solvent simulations: a Poisson-centric view. *Current Opinion in Structural Biology* **15**, 137–143.

Baker, N., Bashford, D. & Case, D. (2006). Implicit solvent electrostatics in biomolecular simulation. In *New Algorithms for Macromolecular Simulation*, vol. 49

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

(eds. T. Barth, M. Griebel, D. Keyes, R. Nieminen, D. Roose, T. Schlick, B. Leimkuhler, C. Chipot, R. Elber, A. Laaksonen, A. Mark, C. Schütte & R. Skeel), pp. 263–295. Berlin, Heidelberg: Springer.

Baker, N., Holst, M. & Wang, F. (2000). Adaptive multilevel finite element solution of the Poisson–Boltzmann equation II. Refinement at solvent-accessible surfaces in biomolecular systems. *Journal of Computational Chemistry* **21**, 1343–1352.

Baker, N., Hünenberger, P. & Mccammon, A. (1999). Polarization around an ion in a dielectric continuum with truncated electrostatic interactions. *Journal of Chemical Physics* **110**, 10679–10692.

Baker, N. A. (2004). *Poisson–Boltzmann Methods for Biomolecular Electrostatics*, vol. 383, pp. 94–118. Amsterdam: Elsevier.

Baker, N. A., Sept, D., Holst, M. J. & Mccammon, J. A. (2001a). The adaptive multilevel finite element solution of the Poisson–Boltzmann equation on massively parallel computers. *IBM Journal of Research and Development* **45**, 427–438.

Baker, N. A., Sept, D., Joseph, S., Holst, M. J. & Mccammon, J. A. (2001b). Electrostatics of nanosystems: application to microtubules and the ribosome. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 10037–10041.

Baldwin, R. L. (1996). How Hofmeister ion interactions affect protein stability. *Biophysical Journal* **71**, 2056–2063.

Ballin, J., Shkel, I. & Record, T. (2004). Interactions of the KWK6 cationic peptide with short nucleic acid oligomers: demonstration of large Coulombic end effects on binding at 0.1–0.2 M salt. *Nucleic Acids Research* **32**, 3271–3281.

Banavali, N., Im, W. & Roux, B. (2002). Electrostatic free energy calculations using the generalized solvent boundary potential method. *Journal of Chemical Physics* **117**, 7381–7388.

Bank, R. & Holst, M. (2003). A new paradigm for parallel adaptive meshing algorithms. *SIAM Review* **45**, 291–323.

Baran, K., Chimenti, M., Schlessman, J., Fitch, C., Herbst, K. & Garcia-Moreno, B. (2008). Electrostatic effects in a network of polar and ionizable groups in staphylococcal nuclease. *Journal of Molecular Biology* **379**, 1045–1062.

Bardhan, J. (2011). Nonlocal continuum electrostatic theory predicts surprisingly small energetic penalties for charge burial in proteins. *Journal of Chemical Physics* **135**, 104113.

Barducci, A., Bonomi, M. & Parrinello, M. (2011). Metadynamics. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **1**, 826–843.

Barillari, C., Taylor, J., Viner, R. & Essex, J. W. (2007). Classification of water molecules in protein binding sites. *Journal of the American Chemical Society* **129**, 2577–2587.

Basdevant, N., Borgis, D. & Ha-Duong, T. (2004). A semi-implicit solvent model for the simulation of peptides and proteins. *Journal of Computational Chemistry* **25**, 1015–1029.

Basdevant, N., Borgis, D. & Ha-Duong, T. (2007). A coarse-grained protein–protein potential derived from an all-atom force field. *The Journal of Physical Chemistry B* **111**, 9390–9399.

Basdevant, N., Ha-Duong, T. & Borgis, D. (2006). Particle-based implicit solvent model for biosimulations: application to proteins and nucleic acids hydration. *Journal of Chemical Theory and Computation* **2**, 1646–1656.

Bashford, D. (1997). *An Object-Oriented Programming Suite for Electrostatic Effects in Biological Molecules an Experience Report on the MEAD Project Scientific Computing in Object-Oriented Parallel Environments*, vol. 1343 (eds. Y. Ishikawa, R. Oldehoeft, J. Reynders & M. Tholburn), pp. 233–240. Berlin/Heidelberg: Springer.

Bashford, D. & Case, D. A. (2000). Generalized born models of macromolecular solvation effects. *Annual Review of Physical Chemistry* **51**, 129–152.

Bashford, D. & Karplus, M. (1990). pK_a's of ionizable groups in proteins: atomic detail from a continuum electrostatic model. *Biochemistry* **29**, 10219–10225.

Basilevsky, M. & Parsons, D. (1998). Nonlocal continuum solvation model with exponential susceptibility kernels. *Journal of Chemical Physics* **108**, 9107–9113.

Bastos, M., Castro, V., Mrevlishvili, G. & Teixeira, J. (2004). Hydration of ds-DNA and ss-DNA by neutron quasielastic scattering. *Biophysical Journal* **86**, 3822–3827.

Bauer, B. A., Lucas, T. R., Meninger, D. J. & Patel, S. (2011). Water permeation through DMPC lipid bilayers using polarizable charge equilibration force fields. *Chemical Physics Letters* **508**, 289–294.

Bauer, B. A. & Patel, S. (2009). Properties of water along the liquid–vapor coexistence curve via molecular dynamics simulations using the polarizable TIP4P-QDP-LJ water model. *The Journal of Chemical Physics* **131**, 084709.

Bayly, C., Cieplak, P., Cornell, W. & Kollman, P. (1993). A well-behaved electrostatic potential based method using charge restraints for deriving atomic charges: the RESP model. *The Journal of Physical Chemistry* **97**, 10269–10280.

Beglov, D. & Roux, B. (1994). Finite representation of an infinite bulk system: solvent boundary potential for computer simulations. *Journal of Chemical Physics* **100**, 9050–9063.

Beglov, D. & Roux, B. (1996). Solvation of complex molecules in a polar liquid: an integral equation theory. *Journal of Chemical Physics* **104**, 8678–8689.

Beglov, D. & Roux, B. (1997). An integral equation to describe the solvation of polar molecules in liquid water. *Journal of Physical Chemistry B* **101**, 7821–7826.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Ben-Amotz, D. (2005). Global thermodynamics of hydrophobic cavitation, dewetting, and hydration. *Journal of Chemical Physics* **123**, 184504.

Ben-Naim, A. (1997). Solvation and solubility of globular proteins. *Pure and Applied Chemistry* **69**, 2239–2244.

Ben-Naim, A. (2006). *Molecular Theory of Solutions*. Oxford: Oxford University Press.

Ben-Yaakov, D., Andelman, D., Harries, D. & Podgornik, R. (2009). Beyond standard Poisson–Boltzmann theory: ion-specific interactions in aqueous solutions. *Journal of Physics: Condensed Matter* **21**, 424106.

Ben-Yaakov, D., Andelman, D., Podgornik, R. & Harries, D. (2011). Ion-specific hydration effects: extending the Poisson–Boltzmann theory. *Current Opinion in Colloid and Interface Science* **16**, 542–550.

Benanti, E. L. & Chivers, P. T. (2007). The N-terminal arm of the *Helicobacter pylori* Ni^{2+}-dependent transcription factor NikR is required for specific DNA binding. *Journal of Biological chemistry* **282**, 20365–20375.

Berendsen, H. J. C., Grigera, J. R. & Straatsma, T. P. (1987). The missing term in effective pair potentials. *Journal of Physical Chemistry* **91**, 6269–6271.

Berendsen, H. J. C., Postma, J. P. M., Van Gunsteren, W. F. & Hermans, J. (1981). Interaction models for water in relation to protein hydration. In *Intermolecular Forces* (ed. B. Pullmann), pp. 331–342. Dordrecht: D. Reidel Publishing Company.

Berkowitz, M. & Vácha, R. (2012). Aqueous solutions at the interface with phospholipid bilayers. *Accounts of Chemical Research* **45**, 74–82.

Bernal, J. (1933). A theory of water and ionic solution, with particular reference to hydrogen and hydroxyl ions. *Journal of Chemical Physics* **1**, 515.

Bernardo, D. N., Ding, Y., Krogh-Jespersen, K. & Levy, R. M. (1994). An anisotropic polarizable water model: incorporation of all-atom polarizabilities into molecular mechanics force fields. *Journal of Physical Chemistry* **98**, 4180–4187.

Berne, B., Weeks, J. & Zhou, R. (2009). Dewetting and hydrophobic interaction in physical and biological systems. *Annual Review of Physical Chemistry* **60**, 85–103.

Bertini, I., Del Bianco, C., Gelis, I., Katsaros, N., Luchinat, C., Parigi, G., Peana, M., Provenzani, A. & Zoroddu, M. A. (2004). Experimentally exploring the conformational space sampled by domain reorientation in calmodulin. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 6841–6846.

Besteman, K., Zevenbergen, M. A. G., Heering, H. A. & Lemay, S. G. (2004). Direct observation of charge inversion by multivalent ions as a universal electrostatic phenomenon. *Physical Review Letters* **93**, 170802.

Besteman, K., Zevenbergen, M. A. G. & Lemay, S. G. (2005). Charge inversion by multivalent ions: dependence on dielectric constant and surface-charge density. *Physical Review E* **72**, 061501.

Bharadwaj, R., Windemuth, A., Sridharan, S., Honig, B. & Nicholls, A. (1995). The fast multipole boundary element method for molecular electrostatics: an optimal approach for large systems. *Journal of Computational Chemistry* **16**, 898–913.

Billeter, M. (1996). Hydration and DNA recognition by homeodomains. *Cell* **85**, 1057–1065.

Birge, R. R. (1980). Calculation of molecular polarizabilities using an anisotropic atom point dipole interaction model which includes the effect of electron repulsion. *Journal of Chemical Physics* **72**, 5312–5319.

Bombarda, E. & Ullmann, M. M. (2010). pH-dependent pK_a values in proteins – A theoretical analysis of protonation energies with practical consequences for enzymatic reactions. *Journal of Physical Chemistry B* **114**, 1994–2003.

Bone, S. (2006). Dielectric studies of water clusters in cyclodextrins: relevance to the transition between slow and fast forms of thrombin. *Journal of Physical Chemistry B* **110**, 20609–20614.

Bone, S. (2008). Structural flexibility in hydrated proteins. *Journal of Physical Chemistry B* **112**, 10071–10075.

Bonvin, A., Sunnerhagen, M., Otting, G. & Van Gunsteren, W. (1998). Water molecules in DNA recognition II: a molecular dynamics view of the structure and hydration of the trp operator1. *Journal of Molecular Biology* **282**, 859–873.

Bordner, A. J. & Huber, G. A. (2003). Boundary element solution of the linear Poisson–Boltzmann equation and a multipole method for the rapid calculation of forces on macromolecules in solution. *Journal of Computational Chemistry*. **24**, 353–367.

Born, M. (1920). Volume and heat of hydration of ions. *Zeitschrift fur Physik* **1**, 45–48.

Borukhov, I., Andelman, D. & Orland, H. (1997). Steric effects in electrolytes: a modified Poisson–Boltzmann equation. *Physical Review Letters* **79**, 435–438.

Borukhov, I., Andelman, D. & Orland, H. (2000). Adsorption of large ions from an electrolyte solution: a modified Poisson–Boltzmann equation. *Electrochimica Acta* **46**, 221–229.

Boschitsch, A. & Fenley, M. (2004). Hybrid boundary element and finite difference method for solving the nonlinear Poisson–Boltzmann equation. *Journal of Computational Chemistry* **25**, 935–955.

Boschitsch, A., Fenley, M. & Zhou, H.-X. (2002). Fast boundary element method for the linear Poisson–Boltzmann equation. *Journal of Physical Chemistry B* **106**, 2741–2754.

Bosio, L., Chen, S. H. & Teixeira, J. (1983). Isochoric temperature differential of the X-ray structure factor and structural rearrangements in low-temperature heavy water. *Physical Review A* **27**, 1468.

Boström, M., Kunz, W. & Ninham, B. W. (2005a). Hofmeister effects in surface tension of aqueous

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

electrolyte solution. *Langmuir: the ACS Journal of Surfaces and Colloids* **21**, 2619–2623.

Boström, M. & Ninham, B. W. (2004). Contributions from dispersion and born self-free energies to the solvation energies of salt solutions. *Journal of Physical Chemistry B* **108**, 12593–12595.

Boström, M. & Ninham, B. W. (2005). Energy of an ion crossing a low dielectric membrane: the role of dispersion self-free energy. *Biophysical Chemistry* **114**, 95–101.

Boström, M., Tavares, F. W., Bratko, D. & Ninham, B. W. (2005b). Specific ion effects in solutions of globular proteins: comparison between analytical models and simulation. *Journal of Physical Chemistry B* **109**, 24489–24494.

Boström, M., Williams, D. R. M. & Ninham, B. W. (2003a). Specific ion effects: why the properties of lysozyme in salt solutions follow a hofmeister series. *Biophysics Journal* **85**, 686–694.

Boström, M., Williams, D. R. M., Stewart, P. R. & Ninham, B. W. (2003b). Hofmeister effects in membrane biology: the role of ionic dispersion potentials. *Physical Review E* **68**, 041902.

Bottcher, C. J. F. (1952). *Theory of Electrostatic Polarisation*. Amsterdam: Elsevier.

Bradley, D. F., Lifson, S. & Honig, B. (1964). Theory of optical and other properties of biopolymers: applicability and elimination of the first-neighbor and dipole-dipole approximations. In *Electronic Aspects of Biochemistry*. New York: Academic Press.

Bradley, M., Chivers, P. & Baker, N. (2008). Molecular dynamics simulation of the *Escherichia coli* NikR protein: equilibrium conformational fluctuations reveal interdomain allosteric communication pathways. *Journal of Molecular Biology* **378**, 1155–1173.

Brdarski, S., Astrand, P.-O. & Karlstrom, G. (2000). The inclusion of electron correlation in intermolecular potentials: applications to the formamide dimer and liquid formamide. *Theoretical Chemistry Accounts* **105**, 7–14.

Breneman, C. & Wiberg, K. (1990). Determining atom-centered monopoles from molecular electrostatic potentials. The need for high sampling density in formamide conformational analysis. *Journal of Computational Chemistry* **11**, 361–373.

Brobjer, J. T. & Murrell, J. N. (1982). A method for calculating the electrostatic energy between small polar molecules. The multipole-fitted point-charge method. *Journal of the Chemical Society, Faraday Transactions 2: Molecular and Chemical Physics* **78**, 1853–1870.

Brooks, B. R., Brooks, C. L., Mackerell, A. D., Nilsson, L., Petrella, R. J., Roux, B., Won, Y., Archontis, G., Bartels, C., Boresch, S., Caflisch, A., Caves, L., Cui, Q., Dinner, A. R., Feig, M., Fischer, S., Gao, J., Hodoscek, M., Im, W., Kuczera, K., Lazaridis, T., Ma, J., Ovchinnikov, V., Paci, E., Pastor, R. W., Post, C. B., Pu, J. Z., Schaefer, M., Tidor, B., Venable, R. M., Woodcock, H. L., Wu, X., Yang, W., York, D. M. & Karplus, M. (2009). CHARMM: the biomolecular simulation program. *Journal of Computational Chemistry* **30**, 1545–1614.

Brooks, C. (1985). Structural and energetic effects of truncating long ranged interactions in ionic and polar fluids. *Journal of Chemical Physics* **83**, 5897.

Brooks, C. L. (1987). The influence of long-range force truncation on the thermodynamics of aqueous ionic solutions. *Journal of Chemical Physics* **86**, 5156–5162.

Brown, R. & Case, D. (2006). Second derivatives in generalized Born theory. *Journal of Computational Chemistry* **27**, 1662–1675.

Bryce, R. A., Vincent, M. A., Malcolm, N. O. J., Hillier, I. H. & Burton, N. A. (1998). Cooperative effects in the structuring of fluoride water clusters: *ab initio* hybrid quantum mechanical/molecular mechanical model incorporating polarizable fluctuating charge solvent. *Journal of Chemical Physics* **109**, 3077–3085.

Bucher, D., Raugei, S., Guidoni, L., Dal Peraro, M., Rothlisberger, U., Carloni, P. & Klein, M. L. (2006). Polarization effects and charge transfer in the KcsA potassium channel. *Biophysical Chemistry* **124**, 292–301.

Buckingham, A. D. (1967). Permanent and induced molecular moments and long-range intermolecular forces. *Advances in Chemical Physics* **12**, 107–142.

Burley, D. M., Hutson, V. C. L. & Outhwaite, C. W. (1974). A treatment of the volume and fluctuation term in Poisson's equation in the Debye–Huckel theory of strong electrolyte solutions. *Molecular Physics* **27**, 225–236.

Burnham, C. J. & Xantheas, S. S. (2002). Development of Transferable interaction models for water. I. prominent features of the water dimer potential energy surface. *Journal of Chemical Physics* **116**, 1479–1492.

Burykin, A., Kato, M. & Warshel, A. (2003). Exploring the origin of the ion selectivity of the KcsA potassium channel. *Proteins: Structure, Function, and Bioinformatics* **52**, 412–426.

Butler, J., Angelini, T., Tang, J. & Wong, G. (2003). Ion multivalence and like-charge polyelectrolyte attraction. *Physical Review Letters* **91**, 028301.

Cai, W., Deng, S. & Jacobs, D. (2007). Extending the fast multipole method to charges inside or outside a dielectric sphere. *Journal of Computational Physics* **223**, 846–864.

Calimet, N. & Simonson, T. (2006). Cys(x)His(y)–Zn^{2+} interactions: possibilities and limitations of a simple pairwise force field. *Journal of Molecular Graphics and Modelling* **24**, 404–411.

Carnie, S. L. & Torrie, G. M. (2007). The statistical mechanics of the electrical double layer. In *Advances in Chemical Physics*, pp. 141–253. Hoboken, NJ: John Wiley and Sons Inc.

Carrington, P., Chivers, P., Al-Mjeni, F., Sauer, R. & Maroney, M. (2003). Nickel coordination is regulated by the DNA-bound state of NikR. *Nature Structural Biology* **10**(2), 126–130.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Carstensen, T., Farrell, D., Huang, Y., Baker, N. A. & Nielsen, J. E. (2011). On the development of protein pK(a) calculation algorithms. *Proteins-Structure Function and Bioinformatics* **79**, 3287–3298.

Case, D. A., Cheatham, T. E., Darden, T., Gohlke, H., Luo, R., Merz, K. M., Onufriev, A., Simmerling, C., Wang, B. & Woods, R. J. (2005). The Amber biomolecular simulation programs. *Journal of Computational Chemistry* **26**, 1668–1688.

Castañeda, C., Fitch, C., Majumdar, A., Khangulov, V., Schlessman, J. & García-Moreno, B. (2009). Molecular determinants of the pK_a values of Asp and Glu residues in staphylococcal nuclease. *Proteins* **77**, 570–588.

Cate, J. H., Gooding, A. R., Podell, E., Zhou, K., Golden, B. L., Kundrot, C. E., Cech, T. R. & Doudna, J. A. (1996). Crystal structure of a group I ribozyme domain: principles of RNA packing. *Science* **273**, 1678–1685.

Cerutti, D., Baker, N. & Mccammon, A. (2007). Solvent reaction field potential inside an uncharged globular protein: a bridge between implicit and explicit solvent models? *Journal of Chemical Physics* **127**, 15510.

Chandler, D. (1978). Structures of molecular liquids. *Annual Review of Physical Chemistry* **29**, 441–471.

Chandler, D. (2005). Interfaces and the driving force of hydrophobic assembly. *Nature* **437**, 640–647.

Chandler, D., Mccoy, J. D. & Singer, S. J. (1986). Density functional theory of nonuniform polyatomic systems. I. General formulation. *Journal of Chemical Physics* **85**, 5971–5976.

Chang, T.-M. & Dang, L. (2006). Recent advances in molecular simulations of ion solvation at liquid interfaces. *Chemical Reviews* **106**, 1305–1322.

Charles H. B. (1976). Efficient estimation of free energy differences from Monte Carlo data. *Journal of Computational Physics* **22**, 245–268.

Chaturvedi, U. C. & Shrivastava, R. (2005). Interaction of viral proteins with metal ions: role in maintaining the structure and functions of viruses. *FEMS Immunology and Medical Microbiology* **43**, 105–114.

Chaudhry, J., Bond, S. & Olson, L. (2011). Finite element approximation to a finite-size modified Poisson–Boltzmann equation. *Journal of Scientific Computing* **47**, 347–364.

Chen, A., Draper, D. & Pappu, R. (2009a). Molecular simulation studies of monovalent counterion-mediated interactions in a model RNA kissing loop. *Journal of Molecular Biology* **390**, 805–819.

Chen, A., Marucho, M., Baker, N. & Pappu, R. (2009b). *Simulations of RNA Interactions with Monovalent Ions*, vol. 469, pp. 411–432. Amsterdam: Elsevier.

Chen, A. & Pappu, R. (2007a). Parameters of monovalent ions in the AMBER-99 forcefield: assessment of inaccuracies and proposed improvements. *Journal of Physical Chemistry B* **111**, 11884–11887.

Chen, A. & Pappu, R. (2007b). Quantitative characterization of ion pairing and cluster formation in strong 1:1 electrolytes. *Journal of Physical Chemistry B* **111**, 6469–6478.

Chen, D., Chen, Z., Chen, C., Geng, W. & Wei, G.-W. (2011a). MIBPB: a software package for electrostatic analysis. *Journal of Computational Chemistry* **32**, 756–770.

Chen, J. (2010). Effective approximation of molecular volume using atom-centered dielectric functions in generalized born models. *Journal of Chemical Theory and Computation* **6**, 2790–2803.

Chen, J., Im, W. & Brooks, C. (2006). Balancing solvation and intramolecular interactions: toward a consistent generalized Born force field. *Journal of the American Chemical Society* **128**, 3728–3736.

Chen, L., Holst, M. & Xu, J. (2007a). The finite element approximation of the nonlinear Poisson–Boltzmann equation. *SIAM Journal on Numerical Analysis* **45**, 2298.

Chen, S.-W. & Honig, B. (1997). Monovalent and divalent salt effects on electrostatic free energies defined by the nonlinear Poisson–Boltzmann equation: application to DNA binding reactions. *Journal of Physical Chemistry B* **101**, 9113–9118.

Chen, X., Yang, T., Kataoka, S. & Cremer, P. (2007b). Specific ion effects on interfacial water structure near macromolecules. *Journal of the American Chemical Society* **129**, 12272–12279.

Chen, Y.-G. & Weeks, J. (2006). Local molecular field theory for effective attractions between like charged objects in systems with strong Coulomb interactions. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 7560–7565.

Chen, Z., Baker, N. & Wei, G. (2011b). Differential geometry based solvation model II: lagrangian formulation. *Journal of Mathematical Biology* **63**, 1139–1200.

Chen, Z., Baker, N. & Wei, G. W. (2010). Differential geometry based solvation model I: Eulerian formulation. *Journal of Computational Physics* **229**, 8231–8258.

Chessari, G., Hunter, C. A., Low, C. M. R., Packer, M. J., Vinter, J. G. & Zonta, C. (2002). An evaluation of force-field treatments of aromatic interactions. *Chemistry – A European Journal* **8**, 2860–2867.

Chimenti, M. S., Castañeda, C. A., Majumdar, A. & García-Moreno E. B. (2011). Structural origins of high apparent dielectric constants experienced by ionizable groups in the hydrophobic core of a protein. *Journal of Molecular Biology* **405**, 361–377.

Chivers, P. T. & Sauer, R. T. (2000). Regulation of high affinity nickel uptake in bacteria. Ni^{2+}-dependent interaction of NIKR with wild-type and mutant operator sites. *Journal of Biological Chemistry* **275**, 19735–19741.

Chong, S.-H. & Hirata, F. (1998). Interaction-site-model description of collective excitations in classical molecular fluids. *Physical Review E* **57**, 1691–1701.

Chothia, C. (1974). Hydrophobic bonding and accessible surface area in proteins. *Nature* **248**, 338–339.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Choudhury, N. & Pettitt, B. M. (2007). The dewetting transition and the hydrophobic effect. *Journal of the American Chemical Society* **129**, 4847–4852.

Chu, V., Bai, Y., Lipfert, J., Herschlag, D. & Doniach, S. (2007). Evaluation of ion binding to DNA duplexes using a size-modified Poisson–Boltzmann theory. *Biophysical Journal* **93**, 3202–3209.

Chuev, G. & Fedorov, M. (2004). Wavelet algorithm for solving integral equations of molecular liquids. A test for the reference interaction site model. *Journal of Computational Chemistry* **25**, 1369–1377.

Cieplak, P., Dupradeau, F. Y., Duan, Y. & Wang, J. M. (2009). Polarization effects in molecular mechanical force fields. *Journal of Physics-Condensed Matter* **21**, 333101–333121.

Cisneros, G. A., Tholander, S. N. I., Parisel, O., Darden, T. A., Elking, D., Perera, L. & Piquemal, J. P. (2008). Simple formulas for improved point-charge electrostatics in classical force fields and hybrid quantum mechanical/molecular mechanical embedding. *International Journal of Quantum Chemistry* **108**, 1905–1912.

Claessens, M., Ferrario, M. & Ryckaert, J. P. (1983). The structure of liquid benzene. *Molecular Physics* **50**, 217–227.

Clark, M., Meshkat, S. & Wiseman, J. (2009). Grand canonical free-energy calculations of protein-ligand binding. *Journal of Chemical Information and Modeling* **49**, 934–943.

Clarke, R. & Lüpfert, C. (1999). Influence of anions and cations on the dipole potential of phosphatidylcholine vesicles: a basis for the hofmeister effect. *Biophysics Journal* **76**, 2614–2624.

Clough, S., Beers, Y., Klein, G. & Rothman, L. (1973). Dipole moment of water from Stark measurements of H_2O, HDO, and D_2O. *Journal of Chemical Physics* **59**, 2254.

Coalson, R., Walsh, A., Duncan, A. & Tal, N. (1995). Statistical mechanics of a Coulomb gas with finite size particles: a lattice field theory approach. *Journal of Chemical Physics* **102**, 4584–4594.

Coalson, R. D. & Duncan, A. (1992). Systematic ionic screening theory of macroions. *Journal of Chemical Physics* **97**, 5653–5653.

Collins, K. D. (1995). Sticky ions in biological systems. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 5553–5557.

Conn, G. L., Gittis, A. G., Lattman, E. E., Misra, V. K. & Draper, D. E. (2002). A compact RNA tertiary structure contains a buried backbone–K+ complex. *Journal of Molecular Biology* **318**, 963–973.

Connolly, M. L. (1983). Solvent-accessible surfaces of proteins and nucleic acids. *Science* **221**, 709–713.

Connolly, M. L. (1985). Computation of molecular volume. *Journal of the American Chemical Society* **107**, 1118–1124.

Cornell, W. D., Cieplak, P., Bayly, C. I., Gould, I. R., Merz, K. M., Ferguson, D. M., Spellmeyer, D. C., Fox, T., Caldwell, J. W. & Kollman, P. A. (1995). A second generation force field for the simulation of proteins, nucleic acids, and organic molecules (Vol. 117, Pg 5179, 1995). *Journal of the American Chemical Society* **118**, 2309–2309.

Cortis, C. & Friesner, R. (1997a). An automatic three-dimensional finite element mesh generation system for the Poisson–Boltzmann equation. *Journal of Computational Chemistry* **18**, 1570–1590.

Cortis, C. & Friesner, R. (1997b). Numerical solution of the Poisson–Boltzmann equation using tetrahedral finite-element meshes. *Journal of Computational Chemistry* **18**, 1591–1608.

Courtenay, E. S., Capp, M. W. & Record, M. T. (2001). Thermodynamics of interactions of urea and guanidinium salts with protein surface: relationship between solute effects on protein processes and changes in water-accessible surface area. *Protein Science* **10**, 2485–2497.

Cox, S. R. & Williams, D. E. (1981). Representation of the molecular electrostatic potential by a net atomic charge model. *Journal of Computational Chemistry* **2**, 304–323.

Cramer, C. & Truhlar, D. (2008). A universal approach to solvation modeling. *Accounts of Chemical Research* **41**, 760–768.

Cramer, C. J. & Truhlar, D. G. (1999). Implicit solvation models: equilibria, structure, spectra, and dynamics. *Chemical Reviews* **99**, 2161–2200.

Cramer, C. J. & Truhlar, D. G. (2001). Solvation thermodynamics and the treatment of equilibrium and nonequilibrium solvation effects by models based on collective solvent coordinates. *In Free Energy Calculations in Rational Drug Design* (eds. M. Rami Reddy & M. D. Erion). New York: Kluwer.

Cukier, R. I. & Zhang, J. J. (1997). Simulation of proton transfer reaction rates: the role of solvent electronic polarization. *Journal of Physical Chemistry B* **101**, 7180–7190.

Curutchet, C., Orozco, M., Luque, F. J., Mennucci, B. & Tomasi, J. (2006). Dispersion and repulsion contributions to the solvation free energy: comparison of quantum mechanical and classical approaches in the polarizable continuum model. *Journal of Computational Chemistry* **27**, 1769–1780.

Damjanović, A., García-Moreno, B., Lattman, E. & García, A. (2005a). Molecular dynamics study of water penetration in staphylococcal nuclease. *Proteins* **60**, 433–449.

Damjanovic, A., Garciamorenoe, B., Lattman, E. & Garcia, A. (2005b). Molecular dynamics study of hydration of the protein interior. *Computer Physics Communications* **169**, 126–129.

Damjanović, A., Schlessman, J., Fitch, C., García, A. & García-Moreno E. B. (2007). Role of flexibility and

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

polarity as determinants of the hydration of internal cavities and pockets in proteins. *Biophysical Journal* **93**, 2791–2804.

Dang, L. X. (1992). Development of nonadditive intermolecular potentials using molecular dynamics: Solvation of Li+ and F? ions in polarizable water. *Journal of Chemical Physics* **96**, 6970–6977.

Dang, L. X. & Chang, T.-M. (2001). Molecular mechanism of ion binding to the liquid/vapor interface of water. *The Journal of Physical Chemistry B* **106**, 235–238.

Dang, L. X., Rice, J. E., Caldwell, J. & Kollman, P. A. (1991). Ion solvation in polarizable water: molecular dynamics simulations. *Journal of the American Chemical Society* **113**, 2481–2486.

Darden, T., York, D. & Pedersen, L. (1993). Particle mesh Ewald: an *N* [center-dot] log(*N*) method for Ewald sums in large systems. *Journal of Chemical Physics* **98**, 10089–10092.

Davis, M. & Mccammon, A. (1990). Electrostatics in biomolecular structure and dynamics. *Chemical Reviews* **90**, 509–521.

Davis, M. E. (1994). The inducible multipole solvation model: a new model for solvation effects on solute electrostatics. *Journal of Chemical Physics* **100**, 5149–5159.

Davis, M. E. & Mccammon, J. A. (1989). Solving the finite difference linearized Poisson–Boltzmann equation: a comparison of relaxation and conjugate gradient methods. *Journal of Computational Chemistry* **10**, 386–391.

Della Valle, R. G., Venuti, E., Brillante, A. & Girlando, A. (2008). Do computed crystal structures of nonpolar molecules depend on the electrostatic interactions? The case of tetracene. *Journal of Physical Chemistry A* **112**, 1085–1089.

Deng, S. & Cai, W. (2007). Extending the fast multipole method for charges inside a dielectric sphere in an ionic solvent: high-order image approximations for reaction fields. *Journal of Computational Physics* **227**, 1246–1266.

Deng, Y. & Roux, B. (2008). Computation of binding free energy with molecular dynamics and grand canonical Monte Carlo simulations. *Journal of Chemical Physics* **128**, 115103–115103.

Denisov, V., Schlessman, J., García-Moreno E. B. & Halle, B. (2004). Stabilization of internal charges in a protein: water penetration or conformational change? *Biophysical Journal* **87**, 3982–3994.

Di Cera, E. (2006). A structural perspective on enzymes activated by monovalent cations. *Journal of Biological Chemistry* **281**, 1305–1308.

Dill, K., Truskett, T., Vlachy, V. & Hribar-Lee, B. (2005). Modeling water, the hydrophobic effect, and ion solvation. *Annual Review of Biophysics and Biomolecular Structure* **34**, 173–199.

Ding, F. & Dokholyan, N. (2008). Dynamical roles of metal ions and the disulfide bond in Cu, Zn superoxide dismutase folding and aggregation. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 19696–19701.

Dinur, U. & Hagler, A. T. (1995). Geometry-dependent atomic charges: methodology and application to alkanes, aldehydes, ketones, and amides. *Journal of Computational Chemistry* **16**, 154–170.

Dixon, R. W. & Kollman, P. A. (1997). Advancing beyond the atom-centered model in additive and nonadditive molecular mechanics. *Journal of Computational Chemistry* **18**, 1632–1646.

Dominy, B. & Brooks, C. (1999). Development of a generalized Born model parametrization for proteins and nucleic acids. *Journal of Physical Chemistry B* **103**, 3765–3773.

Donchev, A. G. (2006). *Ab initio* quantum force field for simulations of nanostructures. *Physical Review B* **74**, 235401.

Donchev, A. G., Ozrin, V. D., Subbotin, M. V., Tarasov, O. V. & Tarasov, V. I. (2005). A quantum mechanical polarizable force field for biomolecular interactions. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 7829–7834.

Dong, F., Olsen, B. & Baker, N. (2008). *Computational Methods for Biomolecular Electrostatics*, vol. 84, pp. 843–870. Amsterdam: Elsevier.

Dong, F., Vijayakumar, M. & Zhou, H.-X. (2003). Comparison of calculation and experiment implicates significant electrostatic contributions to the binding stability of Barnase and Barstar. *Biophysical Journal* **85**, 49–60.

Doxey, A. C., Yaish, M. W., Griffith, M. & Mcconkey, B. J. (2006). Ordered surface carbons distinguish antifreeze proteins and their ice-binding regions. *Nature Biotechnology* **24**, 852–855.

Draper, D. (2008). RNA folding: thermodynamic and molecular descriptions of the roles of ions☆. *Biophysical Journal* **95**, 5489–5495.

Draper, D. E., Grilley, D. & Soto, A. M. (2005). Ions and RNA folding. *Annual Review of Biophysics and Biomolecular Structure* **34**, 221–243.

Drew, H. R., Samson, S. & Dickerson, R. E. (1982). Structure of a B-DNA dodecamer at 16 K. *Proceedings of the National Academy of Sciences of the United States of America* **79**, 4040–4044.

Drozdov, A., Grossfield, A. & Pappu, R. (2004). Role of solvent in determining conformational preferences of alanine dipeptide in water. *Journal of the American Chemical Society* **126**, 2574–2581.

Du, Q.-S., Liu, P.-J. & Huang, R.-B. (2008). Localization and visualization of excess chemical potential in statistical mechanical integral equation theory 3D-HNC-RISM. *Journal of Molecular Graphics and Modelling* **26**, 1014–1019.

Du, Q., Beglov, D. & Roux, B. (2000). Solvation free energy of polar and nonpolar molecules in water: an extended interaction site integral equation theory in

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

three dimensions. *Journal of Physical Chemistry B* **104**, 796–805.

Dykstra, C. E. (1988). Intermolecular electrical interaction: a key ingredient in hydrogen bonding. *Accounts of Chemical Research* **21**, 355–361.

Dykstra, C. E. (1993). Electrostatic interaction potentials in molecular force fields. *Chemical Reviews* **93**, 2339–2353.

Dykstra, C. E. (2001). Intermolecular electrical response. *Journal of Molecular Structure: THEOCHEM* **573**, 63–71.

Dyshlovenko, P. E. (2002). Adaptive numerical method for Poisson–Boltzmann equation and its application. *Computer Physics Communications* **147**, 335–338.

Dzubiella, J. & Hansen, J. P. (2004). Competition of hydrophobic and Coulombic interactions between nanosized solutes. *Journal of Chemical Physics* **121**, 5514–5530.

Dzubiella, J., Swanson, J. M. J. & Mccammon, J. A. (2006a). Coupling hydrophobicity, dispersion, and electrostatics in continuum solvent models. *Physical Review Letters* **96**, 087802.

Dzubiella, J., Swanson, J. M. J. & Mccammon, J. A. (2006b). Coupling nonpolar and polar solvation free energies in implicit solvent models. *Journal of Chemical Physics* **124**, 084905.

Eisenberg, D. & Mclachlan, A. D. (1986). Solvation energy in protein folding and binding. *Nature* **319**, 199–203.

Elcock, A., Sept, D. & Mccammon, A. (2001). Computer simulation of protein–protein interactions. *Journal of Physical Chemistry B* **105**, 1504–1518.

Engkvist, O., Åstrand, P.-O. & Karlström, G. (1996). Intermolecular potential for the 1,2-dimethoxyethane—water complex. *Journal of Physical Chemistry* **100**, 6950–6957.

England, J. L., Pande, V. S. & Haran, G. (2008). Chemical denaturants inhibit the onset of dewetting. *Journal of the American Chemical Society* **130**, 11854–11855.

Ensign, D. & Webb, L. (2011). Factors determining electrostatic fields in molecular dynamics simulations of the ras/effector interface. *Proteins-Structure Function and Bioinformatics* **79**, 3511–3524.

Evans, T. I. A., Hell, J. W. & Shea, M. A. (2011). Thermodynamic linkage between calmodulin domains binding calcium and contiguous sites in the C-terminal tail of CaV1.2. *Biophysical Chemistry* **159**, 172–187.

Ewell, J., Gibb, B. C. & Rick, S. W. (2008). Water inside a hydrophobic cavitand molecule. *Journal of Physical Chemistry B* **112**, 10272–10279.

Faerman, C. H. & Price, S. L. (1990). A transferable distributed multipole model for the electrostatic interactions of peptides and amides. *Journal of the American Chemical Society* **112**, 4915–4926.

Feig, M. & Brooks, C. (2004). Recent advances in the development and application of implicit solvent models in biomolecule simulations. *Current Opinion in Structural Biology* **14**, 217–224.

Feig, M., Onufriev, A., Lee, M., Im, W., Case, D. & Brooks, C. (2004). Performance comparison of generalized Born and Poisson methods in the calculation of electrostatic solvation energies for protein structures. *Journal of Computational Chemistry* **25**, 265–284.

Feig, M., Tanizaki, S. & Sayadi, M. (2008). Chapter 6 implicit solvent simulations of biomolecules in cellular environments. *Annual Reports in Computational Chemistry* **4**, 107–121.

Felder, C. E. & Applequist, J. (1981). Energies of solute molecules from an atom charge-dipole interaction model with a surrounding dielectric: application to Gibbs energies of proton transfer between carboxylic acids in water. *Journal of Chemical Physics* **75**, 2390–2398.

Fenimore, P. W., Frauenfelder, H., Mcmahon, B. H. & Young, R. D. (2004). Bulk-solvent and hydration-shell fluctuations, similar to alpha- and beta-fluctuations in glasses, control protein motions and functions. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 14408–14413.

Fenley, A. T., Gordon, J. C. & Onufriev, A. (2008). An analytical approach to computing biomolecular electrostatic potential. I. Derivation and analysis. *Journal of Chemical Physics* **129**, 075102.

Feynman, R. P. (1939). Forces in molecules. *Physical Review* **56**, 340–343.

Fischer, S. & Verma, C. (1999). Binding of buried structural water increases the flexibility of proteins. *Proceedings of the National Academy of Sciences of the United States of America* **96**, 9613–9615.

Fitzkee, N. & García-Moreno E. B. (2008). Electrostatic effects in unfolded staphylococcal nuclease. *Protein Science* **17**, 216–227.

Fixman, M. (1979). The Poisson–Boltzmann equation and its application to polyelectrolytes. *Journal of Chemical Physics* **70**, 4995–4146.

Flanagan, M., Ackers, G., Matthew, J., Hanania, G. & Gurd, F. (1981). Electrostatic contributions to the energetics of dimer–tetramer assembly in human hemoglobin: pH dependence and effect of specifically bound chloride ions. *Biochemistry* **20**, 7439–7449.

Fletcher, N. H. (1970). *The Chemical Physics of Ice*. New York: Cambridge University Press.

Florián, J. & Warshel, A. (1997). Langevin dipoles model for *ab initio* calculations of chemical processes in solution: parametrization and application to hydration free energies of neutral and ionic solutes and conformational analysis in aqueous solution. *Journal of Physical Chemistry B* **101**, 5583–5595.

Floris, F. & Tomasi, J. (1989). Evaluation of the dispersion contribution to the solvation energy a simple computational model in the continuum approximation. *Journal of Computational Chemistry* **10**, 616–627.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Floris, F. M., Tomasi, J. & Ahuir, P. (1991). Dispersion and repulsion contributions to the solvation energy: refinements to a simple computational model in the continuum approximation. *Journal of Computational Chemistry* **12**, 784–791.

Fogolari, F., Brigo, A. & Molinari, H. (2002). The Poisson–Boltzmann equation for biomolecular electrostatics: a tool for structural biology. *Journal of Molecular Recognition : JMR* **15**, 377–392.

Fowler, P. W. & Buckingham, A. D. (1983). The long range model of intermolecular forces. *Molecular Physics* **50**, 1349–1361.

Fowler, P. W. & Buckingham, A. D. (1991). Central or distributed multipole moments? Electrostatic models of aromatic dimers. *Chemical Physics Letters* **176**, 11–18.

Frank, H. S. & Evans, M. W. (1945). Free volume and entropy in condensed systems III. Entropy in binary liquid mixtures; partial molal entropy in dilute solutions; structure and thermodynamics in aqueous electrolytes. *Journal of Chemical Physics* **13**, 507.

Freedman, H. & Truong, T. N. (2004). Coupled reference interaction site model/simulation approach for thermochemistry of solvation: theory and prospects. *Journal of Chemical Physics* **121**, 2187–2198.

Freitag, M. A., Gordon, M. S., Jensen, J. H. & Stevens, W. J. (2000). Evaluation of charge penetration between distributed multipolar expansions. *Journal of Chemical Physics* **112**, 7300–7306.

Fried, M. G., Stickle, D. F., Smirnakis, K. V., Adams, C., Macdonald, D. & Lu, P. (2002). Role of hydration in the binding of lac repressor to DNA. *Journal of Biological Chemistry* **277**, 50676–50682.

Friedman, H. L. (1975). Image approximation to the reaction field. *Molecular Physics* **29**, 1533–1543.

Friedman, R. (2000). Ions and the protein surface revisited: extensive molecular dynamics simulations and analysis of protein structures in alkali-chloride solutions. *Journal of Physical Chemistry B* **28**, 234–242.

Friesner, R. A. (2005). *Ab initio* quantum chemistry: methodology and applications. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 6648–6653.

Friesner, R. A. & Guallar, V. (2005). *Ab initio* quantum chemical and mixed quantum mechanics/molecular mechanics (QM/MM) methods for studying enzymatic catalysis. *Annual Review of Physical Chemistry* **56**, 389–427.

Frolov, A., Ratkova, E., Palmer, D. & Fedorov, M. (2011). Hydration thermodynamics using the reference interaction site model: speed or accuracy? *Journal of Physical Chemistry B* **115**, 6011–6022.

Fukuma, T., Higgins, M. & Jarvis, S. (2007). Direct imaging of individual intrinsic hydration layers on lipid bilayers at Angstrom resolution. *Biophysical Journal* **92**, 3603–3609.

Fuxreiter, M., Mezei, M., Simon, I. & Osman, R. (2005). Interfacial water as a 'hydration fingerprint' in the noncognate complex of BamHI. *Biophysical Journal* **89**, 903–911.

Gagliardi, L., Lindh, R. & Karlström, G. (2004). Local properties of quantum chemical systems: The LoProp approach. *Journal of Chemical Physics* **121**, 4494–4500.

Gallicchio, E., Kubo, M. M. & Levy, R. M. (2000). Enthalpy-entropy and cavity decomposition of alkane hydration free energies: numerical results and implications for theories of hydrophobic solvation. *Journal of Physical Chemistry B* **104**, 6271–6285.

Gallicchio, E. & Levy, R. (2004). AGBNP: an analytic implicit solvent model suitable for molecular dynamics simulations and high-resolution modeling. *Journal of Computational Chemistry* **25**, 479–499.

Gallicchio, E., Paris, K. & Levy, R. (2009). The AGBNP2 implicit solvation model. *Journal of Chemical Theory and Computation* **5**, 2544–2564.

Gallicchio, E., Zhang, L. Y. & Levy, R. (2002). The SGB/NP hydration free energy model based on the surface generalized born solvent reaction field and novel nonpolar hydration free energy estimators. *Journal of Computational Chemistry* **23**, 517–529.

García-García, C. & Draper, D. (2003). Electrostatic interactions in a peptide–RNA complex. *Journal of Molecular Biology* **331**, 75–88.

Garcia-Viloca, M., Gao, J., Karplus, M. & Truhlar, D. G. (2004). How enzymes work: analysis by modern rate theory and computer simulations. *Science* **303**, 186–195.

Garde, S., Hummer, G., García, A. E., Paulaitis, M. E. & Pratt, L. R. (1996). Origin of entropy convergence in hydrophobic hydration and protein folding. *Physical Review Letters* **77**, 4966.

Gavryushov, S. (2008). Electrostatics of B-DNA in NaCl and $CaCl_2$ solutions: ion size, interionic correlation, and solvent dielectric saturation effects. *The Journal of Physical Chemistry B* **112**, 8955–8965.

Gavryushov, S. (2009). Mediating role of multivalent cations in DNA electrostatics: an epsilon-modified Poisson–Boltzmann study of B-DNA–B-DNA interactions in mixture of NaCl and $MgCl_2$ solutions. *Journal of Physical Chemistry B* **113**, 2160–2169.

Geng, W. & Wei, G. W. (2011). Multiscale molecular dynamics using the matched interface and boundary method. *Journal of Computational Physics* **230**, 435–457.

Georgescu, R., Alexov, E. & Gunner, M. (2002). Combining conformational flexibility and continuum electrostatics for calculating pK_as in proteins. *Biophysical Journal* **83**, 1731–1748.

Gillespie, D., Nonner, W. & Eisenberg, R. (2002). Coupling Poisson–Nernst–Planck and density functional theory to calculate ion flux. *Journal of Physics: Condensed Matter* **14**, 12129–12145.

Gilson, M., Davis, M., Luty, B. & Mccammon, A. (1993). Computation of electrostatic forces on solvated

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

molecules using the Poisson–Boltzmann equation. *Journal of Physical Chemistry* **97**, 3591–3600.

Gilson, M. K. (1995). Theory of electrostatic interactions in macromolecules. *Current Opinion in Structural Biology* **5**, 216–223.

Gilson, M. K. & Honig, B. (1988). Calculation of the total electrostatic energy of a macromolecular system: solvation energies, binding energies, and conformational analysis. *Proteins* **4**, 7–18.

Gilson, M. K. & Honig, B. H. (1987). Calculation of electrostatic potentials in an enzyme active site. *Nature* **330**, 84–86.

Goel, T., Patra, C., Ghosh, S. & Mukherjee, T. (2008). Molecular solvent model of cylindrical electric double layers: a systematic study by Monte Carlo simulations and density functional theory. *Journal of Chemical Physics* **129**, 154707.

Gohara, D. & Di Cera, E. (2011). Allostery in trypsin-like proteases suggests new therapeutic strategies. *Trends in Biotechnology* **29**, 577–585.

Grant, A., Pickup, B. & Nicholls, A. (2001). A smooth permittivity function for Poisson–Boltzmann solvation methods. *Journal of Computational Chemistry* **22**, 608–640.

Grant, J. A. & Pickup, B. T. (1995). A Gaussian description of molecular shape. *Journal of Physical Chemistry* **99**, 3503–3510.

Grant, J. A., Pickup, B. T., Sykes, M. J., Kitchen, C. A. & Nicholls, A. (2007). The Gaussian generalized Born model: application to small molecules. *Physical Chemistry Chemical Physics* **9**, 4913–4922.

Gresh, N. (1997). Inter- and intramolecular interactions. Inception and refinements of the SIBFA, molecular mechanics (SMM) procedure, a separable, polarizable methodology grounded on *ab initio* SCF/MP2 computations. Examples of applications to molecular recognition problems. *Journal De Chimie Physique et de Physico-Chimie Biologique* **94**, 1365–1416.

Grilley, D., Misra, V., Caliskan, G. & Draper, D. (2007). Importance of partially unfolded conformations for Mg(2+)-induced folding of RNA tertiary structure: structural models and free energies of Mg^{2+} interactions. *Biochemistry* **46**, 10266–10278.

Grilley, D., Soto, A. M. & Draper, D. (2006). Mg^{2+}–RNA interaction free energies and their relationship to the folding of RNA tertiary structures. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 14003–14008.

Grochowski, P. & Trylska, J. (2008). Continuum molecular electrostatics, salt effects, and counterion binding–a review of the Poisson–Boltzmann theory and its modifications. *Biopolymers* **89**, 93–113.

Grossfield, A., Ren, P. & Ponder, J. (2003). Ion solvation thermodynamics from simulation with a polarizable force field. *Journal of the American Chemical Society* **125**, 15671–15682.

Grycuk, T. (2003). Deficiency of the Coulomb-field approximation in the generalized Born model: an improved formula for Born radii evaluation. *Journal of Chemical Physics* **119**, 4817–4826.

Gu, W., Rahi, S. & Helms, V. (2004). Solvation free energies and transfer free energies for amino acids from hydrophobic solution to water solution from a very simple residue model. *Journal of Physical Chemistry B* **108**, 5806–5814.

Guillot, B. (2002). A reappraisal of what we have learnt during three decades of computer simulations on water. *Journal of Molecular Liquids* **101**, 219–260.

Guinto, E. R. & Di Cera, E. (1996). Large heat capacity change in a protein-monovalent cation interaction. *Biochemistry* **35**, 8800–8804.

Gurau, M., Lim, S.-M., Castellana, E., Albertorio, F., Kataoka, S. & Cremer, P. (2004). On the mechanism of the Hofmeister effect. *Journal of the American Chemical Society* **126**, 10522–10523.

Ha-Duong, T., Basdevant, N. & Borgis, D. (2009). A polarizable coarse-grained water model for coarse-grained proteins simulations. *Chemical Physics Letters* **468**, 79–82.

Haduong, T., Phan, S., Marchi, M. & Borgis, D. (2002). Electrostatics on particles: phenomenological and orientational density functional theory approach. *Journal of Chemical Physics* **117**, 541–556.

Hagberg, D., Karlstrom, G., Roos, B. O. & Gagliardi, L. (2005). The coordination of uranyl in water: a combined quantum chemical and molecular simulation study. *Journal of the American Chemical Society* **127**, 14250–14256.

Halgren, T. A. (1992). The representation of van der Waals (vdW) interactions in molecular mechanics force fields: potential form, combination rules, and vdW parameters. *Journal of the American Chemical Society* **114**, 7827–7843.

Halgren, T. A. & Damm, W. (2001). Polarizable force fields. *Current Opinion in Structural Biology* **11**, 236–242.

Hamelberg, D. & Mccammon, J. A. (2004). Standard free energy of releasing a localized water molecule from the binding pockets of proteins: double-decoupling method. *Journal of the American Chemical Society* **126**, 7683–7689.

Hansen, J. P. & Mcdonald, I. R. (2000). *Theory of Simple Liquids*. New York, NY: Academic Press.

Harano, Y., Imai, T., Kovalenko, A., Kinoshita, M. & Hirata, F. (2001). Theoretical study for partial molar volume of amino acids and polypeptides by the three-dimensional reference interaction site model. *Journal of Chemical Physics* **114**, 9506–9511.

Harder, E., Anisimov, V. M., Whitfield, T., Mackerell, A. D., Jr. & Roux, B. (2008). Understanding the dielectric properties of liquid amides from a polarizable force field. *Journal of Physical Chemistry B* **112**, 3509–3521.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Harder, E. & Roux, B. (2008). On the origin of the electrostatic potential difference at a liquid–vacuum interface. *Journal of Chemical Physics* **129**, 234706–234706.

Harms, M. J., Castañeda, C. A., Schlessman, J. L., Sue, G. R., Isom, D. G., Cannon, B. R. & García-Moreno E. B. (2009). The pKa values of acidic and basic residues buried at the same internal location in a protein are governed by different factors. *Journal of Molecular Biology* **389**, 34–47.

Harms, M. J., Schlessman, J. L., Chimenti, M. S., Sue, G. R., Damjanović, A. & García-Moreno, B. (2008). A buried lysine that titrates with a normal pK_a: role of conformational flexibility at the protein–water interface as a determinant of pK_a values. *Protein Science* **17**, 833–845.

Harries, D. & Rosgen, J. (2008). A practical guide on how osmolytes modulate macromolecular properties. *Methods in Cell Biology* **84**, 679–735.

Hedstrom, L., Szilagyi, L. & Rutter, W. J. (1992). Converting trypsin to chymotrypsin: the role of surface loops. *Science* **255**, 1249–1253.

Hirata, F. (2003). *Molecular Theory of Solvation*. Boston, MA: Kluwer Academic Publishers.

Hirschfelder, J. O., Curtiss, C. F. & Bird, R. B. (1954). *Molecular Theory of Gases and Liquids*. New York: Wiley.

Hofmeister, F. (1888). Zur Lehre von der Wirkung der Salze. II. *Archives of Experimental Pathology and Pharmakology* **24**, 247–260.

Holm, C., Kekicheff, P. & Podgornik, R. (2001). *Electrostatic Effects in Soft Matter and Biophysics; NATO Science Series*. Dordrecht, Netherlands: Kluwer Academic Publishers.

Holst, M. (2001). Adaptive numerical treatment of elliptic systems on manifolds. *Advances in Computational Mathematics* **15**, 139–191.

Holst, M., Baker, N. & Wang, F. (2000). Adaptive multilevel finite element solution of the Poisson–Boltzmann equation I. Algorithms and examples. *Journal of Computational Chemistry* **21**, 1319–1342.

Holst, M. & Saied, F. (1993). Multigrid solution of the Poisson–Boltzmann equation. *Journal of Computational Chemistry* **14**, 105–113.

Holst, M. J. & Saied, F. (1995). Numerical solution of the nonlinear Poisson–Boltzmann equation: developing more robust and efficient methods. *Journal of Computational Chemistry* **16**, 337–364.

Holt, A. & Karlström, G. (2008). An intramolecular induction correction model of the molecular dipole moment. *Journal of Computational Chemistry* **29**, 1084–1091.

Holt, A. & Karlström, G. (2009). Improvement of the NEMO potential by inclusion of intramolecular polarization. *International Journal of Quantum Chemistry* **109**, 1255–1266.

Hong, J., Capp, M. W., Anderson, C. F., Saecker, R. M., Felitsky, D. J., Anderson, M. W. & Record, M. T. Jr. (2004). Preferential interactions of glycine betaine and of urea with DNA: implications for DNA hydration and for effects of these solutes on DNA stability. *Biochemistry* **43**, 14744–14758.

Honig, B. & Nicholls, A. (1995). Classical electrostatics in biology and chemistry. *Science* **268**, 1144–1149.

Honig, B. H., Hubbell, W. L. & Flewelling, R. F. (1986). Electrostatic interactions in membranes and proteins. *Annual Review of Biophysics and Biophysical Chemistry* **15**, 163–193.

Horn, H. W., Swope, W. C., Pitera, J. W., Madura, J. D., Dick, T. J., Hura, G. L. & Head-Gordon, T. (2004). Development of an improved four-site water model for biomolecular simulations: TIP4P-Ew. *Journal of Chemical Physics* **120**, 9665–9678.

Howard, J. J., Perkyns, J. S., Choudhury, N. & Pettitt, B. M. (2008). An integral equation study of the hydrophobic interaction between graphene plates. *Journal of Chemical Theory and Computation* **4**, 1928–1939.

Hribar, B., Southall, N. T., Vlachy, V. & Dill, K. A. (2002). How ions affect the structure of water. *Journal of the American Chemical Society* **124,**12302–12311.

Hu, H. & Yang, W. (2008). Free energies of chemical reactions in solution and in enzymes with *ab initio* quantum mechanics/molecular mechanics methods. *Annual Review of Physical Chemistry* **59**, 573–601.

Hu, W. & Webb, L. (2000). Direct measurement of the membrane dipole field in bicelles using vibrational stark effect spectroscopy. *Journal of Physical Chemistry Letters* **2**, 1925–1930.

Huang, D., Geissler, P. & Chandler, D. (2001). Scaling of hydrophobic solvation free energies†. *Journal of Physical Chemistry B* **105**, 6704–6709.

Huang, D. M. & Chandler, D. (2002). The hydrophobic effect and the influence of solute-solvent attractions. *Journal of Physical Chemistry B* **106**, 2047–2053.

Hummer, G. (1999). Hydrophobic force field as a molecular alternative to surface-area models. *Journal of the American Chemical Society* **121**, 6299–6305.

Hummer, G. & Garde, S. (1998). Cavity expulsion and weak dewetting of hydrophobic solutes in water. *Physical Review Letters* **80**(19), 4193–4196.

Hummer, G., Garde, S., García, A. E., Pohorille, A. & Pratt, L. R. (1996). An information theory model of hydrophobic interactions. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 8951–8955.

Hummer, G., Garde, S., Garcia, A. E. & Pratt, L. R. (2000). New perspectives on hydrophobic effects. *Chemical Physics* **258**, 349–370.

Hünenberger, P. H. & Gunsteren, W. F. V. (1998). Alternative schemes for the inclusion of a reaction-field correction into molecular dynamics simulations: Influence on the simulated energetic, structural, and dielectric properties of liquid water. *Journal of Chemical Physics* **108**, 6117–6134.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Ichikawa, K., Kameda, Y., Yamaguchi, T., Wakita, H. & Misawa, M. (1991). Neutron-diffraction investigation of the intramolecular structure of a water molecule in the liquid phase at high temperatures. *Molecular Physics* **73**, 79–86.

Ikura, T., Urakubo, Y. & Ito, N. (2004). Water-mediated interaction at a protein-protein interface. *Chemical Physics* **307**, 111–119.

Illingworth, C. J. & Domene, C. (2009). Many-body effects and simulations of potassium channels. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Science* **465**, 1701–1716.

Im, W. (1998). Continuum solvation model: computation of electrostatic forces from numerical solutions to the Poisson–Boltzmann equation. *Computer Physics Communications* **111**, 59–75.

Im, W., Berneche, S. & Roux, B. (2001). Generalized solvent boundary potential for computer simulations. *Journal of Chemical Physics* **114**, 2924–2937.

Im, W., Feig, M. & Brooks, C. L. III (2003a). An implicit membrane generalized born theory for the study of structure, stability, and interactions of membrane proteins. *Biophysical Journal* **85**, 2900–2918.

Im, W., Lee, M. S. & Brooks, C. L. III, (2003b). Generalized born model with a simple smoothing function. *Journal of Computational Chemistry* **24**, 1691–1702.

Imai, T., Harano, Y., Kovalenko, A. & Hirata, F. (2001). Theoretical study for volume changes associated with the helix–coil transition of peptides. *Biopolymers* **59**, 512–519.

Imai, T., Hiraoka, R., Kovalenko, A. & Hirata, F. (2005). Water molecules in a protein cavity detected by a statistical–mechanical theory. *Journal of the American Chemical Society* **127**, 15334–15335.

Imai, T., Hiraoka, R., Kovalenko, A. & Hirata, F. (2007a). Locating missing water molecules in protein cavities by the three-dimensional reference interaction site model theory of molecular solvation. *Proteins* **66**, 804–813.

Imai, T., Hiraoka, R., Seto, T., Kovalenko, A. & Hirata, F. (2007b). Three-dimensional distribution function theory for the prediction of protein-ligand binding sites and affinities: application to the binding of noble gases to hen egg-white lysozyme in aqueous solution. *Journal of Physical Chemistry B* **111**, 11585–11591.

Imai, T., Kovalenko, A. & Hirata, F. (2004). Solvation thermodynamics of protein studied by the 3D-RISM theory. *Chemical Physics Letters* **395**, 1–6.

Imai, T., Miyashita, N., Sugita, Y., Kovalenko, A., Hirata, F. & Kidera, A. (2000). Functionality mapping on internal surfaces of multidrug transporter AcrB based on molecular theory of solvation: implications for drug efflux pathway. *Journal of Physical Chemistry B* **134**, 16417.

Isom, D. G., Cannon, B. R., Castañeda, C. A., Robinson, A. & García-Moreno E. B. (2008). High tolerance for ionizable residues in the hydrophobic interior of proteins. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 17784–17788.

Isom, D. G., Castañeda, C. A., Cannon, B. R. & García-Moreno E. B. (2011). Large shifts in pK_a values of lysine residues buried inside a protein. *Proceedings of the National Academy of Sciences of the United States of America* **108**, 5260–5265.

Isom, D. G., Castañeda, C. A., Cannon, B. R., Velu, P. D., García-Moreno E. B. & García, M. (2010). Charges in the hydrophobic interior of proteins. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 16096–16100.

Jackson, J. D. (1975). *Classical Electrodynamics*. New York: John Wiley and Sons.

Jakalian, A., Bush, B. L., Jack, D. B. & Bayly, C. I. (2000). Fast, efficient generation of high-quality atomic charges. AM1-BCC model: I. Method. *Journal of Computational Chemistry* **21**, 132–146.

Jakalian, A., Jack, D. B. & Bayly, C. I. (2002). Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. *Journal of Computational Chemistry* **23**, 1623–1641.

Jancovici, B. (2006). A van der Waals free energy in electrolytes revisited. *European Physical Journal E: Soft Matter* **19**, 1–4.

Jedlovszky, P. (2001). Thermodynamic and structural properties of liquid water around the temperature of maximum density in a wide range of pressures: a computer simulation study with a polarizable potential model. *Journal of Chemical Physics* **115**, 3750.

Jedlovszky, P. & Vallauri, R. (1999). Temperature dependence of thermodynamic properties of a polarizable potential model of water. *Molecular Physics* **97**, 1157–1163.

Jho, Y., Kanduč, M., Naji, A., Podgornik, R., Kim, M. & Pincus, P. (2008). Strong-coupling electrostatics in the presence of dielectric inhomogeneities. *Physical Review Letters* **101**, 188101.

Jiang, W., Hardy, D. J., Phillips, J. C., Mackerell, A. D., Jr., Schulten, K. & Roux, B. (2011). High-performance scalable molecular dynamics simulations of a polarizable force field based on classical Drude oscillators in NAMD. *Journal of Physical Chemistry Letters* **2**, 87–92.

Jiao, D., Golubkov, P. A., Darden, T. A. & Ren, P. (2008). Calculation of protein-ligand binding free energy by using a polarizable potential. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 6290–6295.

Jiao, D., King, C., Grossfield, A., Darden, T. A. & Ren, P. (2006). Simulation of Ca^{2+} and Mg^{2+} solvation using polarizable atomic multipole potential. *Journal of Physical Chemistry B* **110**, 18553–18559.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Jiao, D., Zhang, J., Duke, R. E., Li, G., Schnieders, M. J. & Ren, P. (2009). Trypsin-ligand binding free energies from explicit and implicit solvent simulations with polarizable potential. *Journal of Computational Chemistry* **30**, 1701–1711.

Jorgensen, W. (1985). Monte Carlo simulation of differences in free energies of hydration. *The Journal of Chemical Physics* **83**, 3050.

Jorgensen, W. L., Chandrasekhar, J., Madura, J. D., Impey, R. W. & Klein, M. L. (1983). Comparison of simple potential functions for simulating liquid water. *Journal of Chemical Physics* **79**, 926.

Jorgensen, W. L. & Swenson, C. J. (1985). Optimized intermolecular potential functions for amides and peptides. Structure and properties of liquid amides. *Journal of the American Chemical Society* **107**, 569–578.

Jorgensen, W. L., Ulmschneider, J. P. & Rives, J. T. (2004). Free energies of hydration from a generalized Born model and an all-atom force field. *Journal of Physical Chemistry B* **108**, 16264–16270.

Jorov, A., Zhorov, B. S. & Yang, D. S. C. (2004). Theoretical study of interaction of winter flounder antifreeze protein with ice. *Protein Science* **13**, 1524–1537.

Joubert, L. & Popelier, P. L. A. (2002). Improved convergence of the 'atoms in molecules' multipole expansion of electrostatic interaction. *Molecular Physics* **100**, 3357–3365.

Joung, I. S. & Cheatham, T. E. (2008). Determination of alkali and halide monovalent ion parameters for use in explicitly solvated biomolecular simulations. *Journal of Physical Chemistry B* **112**, 9020–9041.

Juffer, A., Botta, E., Vankeulen, B., Vanderploeg, A. & Berendsen, H. (1991). The electric potential of a macromolecule in a solvent: a fundamental approach. *Journal of Computational Physics* **97**, 144–171.

Kamerlin, S. C. L., Haranczyk, M. & Warshel, A. (2009) Progress in *ab Initio* QM/MM free-energy simulations of electrostatic energies in proteins: accelerated QM/MM studies of pK_a, redox reactions and solvation free energies. *Journal of Physical Chemistry B* **113**, 1253–1272.

Kaminski, G., Friesner, R. A., Rives, J. T. & Jorgensen, W. L. (2001). Evaluation and reparameterization of the OPLS-AA force field for proteins via comparison with accurate quantum chemical calculations on peptides. *Journal of Physical Chemistry B* **105**, 6474–6487.

Kaminski, G. A., Stern, H. A., Berne, B. J., Friesner, R. A., Cao, Y. X., Murphy, R. B., Zhou, R. & Halgren, T. A. (2002). Development of a polarizable force field for proteins via *ab initio* quantum chemistry: First generation model and gas phase tests. *Journal of Computational Chemistry* **23**, 1515–1531.

Kanduč, M., Trulsson, M., Naji, A., Burak, Y., Forsman, J. & Podgornik, R. (2008). Weak- and strong-coupling electrostatic interactions between asymmetrically charged planar surfaces. *Physical Review E* **78**, 2270–2270.

Karp, D. A., Gittis, A. G., Stahley, M. R., Fitch, C. A., Stites, W. E. & Garcia-Moreno E. B. (2007). High apparent dielectric constant Inside a protein reflects structural reorganization coupled to the ionization of an internal Asp. *Biophysical Journal* **92**, 2041–2053.

Karp, D. A., Stahley, M. R. & García-Moreno, B. (2010). Conformational consequences of ionization of Lys, Asp, and Glu buried at position 66 in staphylococcal nuclease. *Biochemistry* **49**, 4138–4146.

Kauzmann, W. (1959). Some factors in the interpretation of protein denaturation. *Advances in Protein Chemistry* **14**, 1–63.

Khandogin, J. & Brooks, C. L. (2006). Toward the accurate first-principles prediction of ionization equilibria in proteins. *Biochemistry* **45**, 9363–9373.

Kielland, J. (1937). Individual activity coefficients of ions in aqueous solutions. *Journal of the American Chemical Society* **59**, 1675–1678.

Kim, Y. W. & Sung, W. (2005). Charge inversion on membranes induced by multivalent-counterion fluctuations. *Journal of Physics: Condensed Matter* **17**, S2943–S2949.

Kim, Y. W., Yi, J. & Pincus, P. A. (2008). Attractions between like-charged surfaces with dumbbell-shaped counterions. *Physical Review Letters* **101**, 208305.

Kimel, S. (1964). Intermolecular potential in solid methane. I. Cohesive energy and crystal structure. *Journal of Chemical Physics* **40**, 3351.

Kinoshita, M., Okamoto, Y. & Hirata, F. (1999). Analysis on conformational stability of C-peptide of ribonuclease A in water using the reference interaction site model theory and Monte Carlo simulated annealing. *Journal of Chemical Physics* **110**, 4090–4100.

Kirkwood, J. (1934). Theory of solutions of molecules containing widely separated charges with special application to zwitterions. *Journal of Chemical Physics* **2**, 351–361.

Kirkwood, J. (1938). The electrostatic influence of substituents on the dissociation constants of organic acids. I. *Journal of Chemical Physics* **6**, 506.

Kiyota, Y., Hiraoka, R., Yoshida, N., Maruyama, Y., Imai, T. & Hirata, F. (2009). Theoretical study of CO escaping pathway in myoglobin with the 3D-RISM theory. *Journal of the American Chemical Society* **131**, 3852–3853.

Kiyota, Y., Yoshida, N. & Hirata, F. (2011). A new approach for investigating the molecular recognition of protein: toward structure-based drug design based on the 3D-RISM theory. *Journal of Chemical Theory and Computation* **7**, 3803–3815.

Klapper, I., Hagstrom, R., Fine, R., Sharp, K. & Honig, B. (1986). Focusing of electric fields in the active site of Cu-Zn superoxide dismutase: effects of ionic strength and amino-acid modification. *Proteins* **1**, 47–59.

Klopper, W., Van Duijneveldt-Van De Rijdt, J. G. C. M. & Van Duijneveldt, F. B. (2000).

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Computational determination of equilibrium geometry and dissociation energy of the water dimer. *Physical Chemistry Chemical Physics* **2**, 2227–2234.

Kollman, P., Massova, I., Reyes, C., Kuhn, B., Huo, S., Chong, L., Lee, M., Lee, T., Duan, Y., Wang, W., Donini, O., Cieplak, P., Srinivasan, J., Case, D. & Cheatham, T. (2000). Calculating structures and free energies of complex molecules: combining molecular mechanics and continuum models. *Accounts of Chemical Research* **33**, 889–897.

Kong, X. & Brooks, C. L. III (1996). Lambda-dynamics: a new approach to free energy calculations. *Journal of Chemical Physics* **105**, 2414–2423.

Kong, Y. (1997). Calculation of the reaction field due to off-center point multipoles. *Journal of Chemical Physics* **107**, 481.

Kovalenko, A. & Hirata, F. (1998). Three-dimensional density profiles of water in contact with a solute of arbitrary shape: a RISM approach. *Chemical Physics Letters* **290**, 237–244.

Kovalenko, A. & Hirata, F. (1999). Potential of mean force between two molecular ions in a polar molecular solvent: a study by the three-dimensional reference interaction site model. *Journal of Physical Chemistry B* **103**, 7942–7957.

Kovalenko, A. & Hirata, F. (2000a). Hydration free energy of hydrophobic solutes studied by a reference interaction site model with a repulsive bridge correction and a thermodynamic perturbation method. *Journal of Chemical Physics* **113**, 2793–2793.

Kovalenko, A. & Hirata, F. (2000b). Potentials of mean force of simple ions in ambient aqueous solution. I. Three-dimensional reference interaction site model approach. *Journal of Chemical Physics* **112**, 10391–10391.

Kovalenko, A. & Hirata, F. (2000c). Potentials of mean force of simple ions in ambient aqueous solution. II. Solvation structure from the three-dimensional reference interaction site model approach, and comparison with simulations. *Journal of Chemical Physics* **112**, 10403–10403.

Kozlov, A. G. & Lohman, T. M. (1998). Calorimetric studies of *E. coli* SSB protein-single-stranded DNA interactions. Effects of monovalent salts on binding enthalpy. *Journal of Molecular Biology* **278**, 999–1014.

Kraayenhof, R. (1996). Monovalent cations differentially affect membrane surface properties and membrane curvature, as revealed by fluorescent probes and dynamic light scattering. *Biochimica et Biophysica Acta–Biomembranes* **1282**, 293–302.

Krem, M. & Di Cera, E. (1998). Conserved water molecules in the specificity pocket of serine proteases and the molecular mechanism of Na+ binding. *Proteins: Structure, Function, and Genetics* **30**, 34–42.

Kuhn, L. A., Siani, M. A., Pique, M. E., Fisher, C. L., Getzoff, E. D. & Tainer, J. A. (1992). The interdependence of protein surface topography and bound water molecules revealed by surface accessibility and fractal density measures. *Journal of Molecular Biology* **228**, 13–22.

Kumar, R., Wang, F. F., Jenness, G. R. & Jordan, K. D. (2010). A second generation distributed point polarizable water model. *Journal of Chemical Physics* **132**, 014309.

Labute, P. (2008). The generalized Born/volume integral implicit solvent model: estimation of the free energy of hydration using London dispersion instead of atomic surface area. *Journal of Computational Chemistry* **94**, 3137–3149.

Laio, A. & Parrinello, M. (2002). Escaping free-energy minima. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 12562–12566.

Lamm, G. (2003). *Reviews in Computational Chemistry; The Poisson–Boltzmann Equation*, pp. 147–366. New York, NY: John Wiley and Sons Inc.

Lamm, G. & Pack, G. (2010). Counterion condensation and shape within Poisson–Boltzmann theory. *Biopolymers* **93**, 619–639.

Lamoureux, G., Mackerell, A. D. & Roux, B. (2003). A simple polarizable model of water based on classical Drude oscillators. *Journal of Chemical Physics* **119**, 5185–5197.

Lamoureux, G. & Roux, B. (2006). Absolute hydration free energy scale for alkali and halide ions established from simulations with a polarizable force field. *Journal of Physical Chemistry B* **110**, 3308–3322.

Landau, L. D., Lifshitz, E. M. & Pitaevskii, L. P. (1982). *Electrodynamics of Continous Media; Landau and Lifshitz Course of Theoretical Physics*. Oxford: Butterworth-Heinenann.

Lau, K. F., Alper, H. E., Thacher, T. S. & Stouch, T. R. (1994). Effects of switching functions on the behavior of liquid water in molecular dynamics simulations. *Journal of Physical Chemistry* **98**, 8785–8792.

Laurents, D., Huyghues-Despointes, B., Bruix, M., Thurlkill, R., Schell, D., Newsom, S., Grimsley, G., Shaw, K., Treviño, S., Rico, M., Briggs, J., Antosiewicz, J., Scholtz, M. & Pace, N. (2003). Charge-charge interactions are key determinants of the pK values of ionizable groups in ribonuclease Sa (pI = 3.5) and a basic variant (pI = 10.2). *Journal of Molecular Biology* **325**, 1077–1092.

Lazaridis, T. & Karplus, M. (1999). Effective energy function for proteins in solution. *Proteins: Structure, Function, and Bioinformatics* **35**, 133–152.

Leach, A. R. (2001). *Molecular Modelling: Principles and Applications*. Harlow, England; New York: Prentice Hall.

Lee, M. S., Salsbury, F. R. Jr. & Brooks, C. L. III (2002). Novel generalized Born methods. *Journal of Chemical Physics* **116**, 10606–10614.

Lee, M. S., Salsbury, F. R. & Olson, M. A. (2004). An efficient hybrid explicit/implicit solvent method for

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

biomolecular simulations. *Journal of Computational Chemistry* **25**, 1967–1978.

Leipply, D. & Draper, D. (2000). Effects of Mg^{2+} on the free energy landscape for folding a purine Riboswitch RNA. *Biochemistry* **50**, 2790–2799.

Leontidis, E., Aroti, A., Belloni, L., Dubois, M. & Zemb, T. (2007). Effects of monovalent anions of the Hofmeister series on DPPC lipid bilayers Part II: modeling the perpendicular and lateral equation-of-state. *Biophysical Journal* **93**, 1591–1607.

Levy, R. M., Zhang, L. Y., Gallicchio, E. & Felts, A. K. (2003). On the nonpolar hydration free energy of proteins: surface area and continuum solvent models for the solute–solvent interaction energy. *Journal of the American Chemical Society* **125**, 9523–9530.

Li, H., Hains, A. W., Everts, J. E., Robertson, A. D. & Jensen, J. H. (2002). The prediction of protein pKa's using QM/MM: the pK_a of lysine 55 in turkey ovomucoid third domain. *Journal of Physical Chemistry B* **106**, 3486–3494.

Li, H., Robertson, A. D. & Jensen, J. H. (2004). The determinants of carboxyl pK_a values in turkey ovomucoid third domain. *Proteins* **55**, 689–704.

Li, H., Robertson, A. D. & Jensen, J. H. (2005). Very fast empirical prediction and rationalization of protein pK_a values. *Proteins* **61**, 704–721.

Li, J., Hawkins, G. D., Cramer, C. J. & Truhlar, D. G. (1998a). Universal reaction field model based on *ab initio* Hartree–Fock theory. *Chemical Physics Letters* **288**, 293–298.

Li, J., Zhu, T., Cramer, C. J. & Truhlar, D. G. (1998b). New class IV charge model for extracting accurate partial charges from wave functions. *Journal of Physical Chemistry A* **102**, 1820–1831.

Li, W., Zhang, J., Wang, J. & Wang, W. (2008). Metal-coupled folding of Cys2His2 zinc-finger. *Journal of the American Chemical Society* **130**, 892–900.

Li, X., Li, J., Eleftheriou, M. & Zhou, R. (2006). Hydration and dewetting near fluorinated superhydrophobic plates. *Journal of the American Chemical Society* **128**, 12439–12447.

Licata, V. J. & Allewell, N. M. (1997). Functionally linked hydration changes in *Escherichia coli* aspartate transcarbamylase and its catalytic subunit. *Biochemistry* **36**, 10161–10167.

Lifson, S. (1968). Consistent force field for calculations of conformations, vibrational spectra, and enthalpies of cycloalkane and n-Alkane molecules. *Journal of Chemical Physics* **49**, 5116.

Lin, H. & Truhlar, D. (2007). QM/MM: what have we learned, where are we, and where do we go from here? *Theoretical Chemistry Accounts: Theory, Computation, and Modeling* (*Theoretica Chimica Acta*) **117**, 185–199.

Lindell, I. V. (1992). Electrostatic image theory for the dielectric sphere. *Radio Science* **27**, 1–8.

Linse, P. (1984). Thermodynamic and structural aspects of liquid and solid benzene. Monte Carlo study. *Journal of the American Chemical Society* **106**, 5425–5430.

Liu, K., Jia, Z., Chen, G., Tung, C. & Liu, R. (2005). Systematic size study of an insect antifreeze protein and its interaction with ice. *Biophysical Journal* **88**, 953–958.

Lopes, P. E. M., Lamoureux, G., Roux, B. & Mackerell, A. D. (2007). Polarizable empirical force field for aromatic compounds based on the classical drude oscillator. *Journal of Physical Chemistry B* **111**, 2873–2885.

Lopes, P. E. M., Roux, B. & Mackerell, A. D. (2009). Molecular modeling and dynamics studies with explicit inclusion of electronic polarizability: theory and applications. *Theoretical Chemistry Accounts* **124**, 11–28.

Lu, B., Cheng, X., Huang, J. & Mccammon, A. (2010). AFMPB: an adaptive fast multipole Poisson–Boltzmann solver for calculating electrostatics in biomolecular systems. *Computer Physics Communications* **181**, 1150–1160.

Luan, B. & Aksimentiev, A. (2010). Electric and electrophoretic inversion of the DNA charge in multivalent electrolytes. *Soft Matter* **6**, 243–246.

Lubchenko, V., Wolynes, P. G. & Frauenfelder, H. (2005). Mosaic energy landscapes of liquids and the control of protein conformational dynamics by glass-forming solvents. *Journal of Physical Chemistry B* **109**, 7488–7499.

Lucent, D., Vishal, V. & Pande, V. S. (2007). Protein folding under confinement: a role for solvent. *Proceedings of the National Academy of Sciences of the United States of America* **104**, 10430–10434.

Lum, K., Chandler, D. & Weeks, J. D. (1999). Hydrophobicity at small and large length scales. *Journal of Physical Chemistry B* **103**, 4570–4577.

Lund, M., Jungwirth, P. & Woodward, C. E. (2008a). Ion specific protein assembly and hydrophobic surface forces. *Physical Review Letters* **100**, 258105–258109.

Lund, M., Vacha, R. & Jungwirth, P. (2008b). Specific ion binding to macromolecules: effects of hydrophobicity and ion pairing. *Langmuir* **27**, 3387–3391.

Luo, R., David, L. & Gilson, M. (2002). Accelerated Poisson–Boltzmann calculations for static and dynamic systems. *Journal of Computational Chemistry* **23**, 1244–1253.

Luzhkov, V. B. & Åqvist, J. (2000). A computational study of ion binding and protonation states in the KcsA potassium channel. *Biochimica et Biophysica Acta* (*BBA*) – *Protein Structure and Molecular Enzymology* **1481**, 360–370.

Lynden-Bell, R. & Rasaiah, J. C. (1997). From hydrophobic to hydrophilic behaviour: a simulation study of solvation entropy and free energy of simple solutes. *Journal of Chemical Physics* **107**, 1981.

Maccallum, J. L., Moghaddam, M. S., Chan, H. S. & Tieleman, D. P. (2007). Hydrophobic association of alpha-helices, steric dewetting, and enthalpic barriers to

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

protein folding. *Proceedings of the National Academy of Sciences of the United States of America* **104**, 6206–6210.

Mackerell, A. D., Bashford, D., Dunbrack, R. L., Evanseck, J. D., Field, M. J., Fischer, S., Gao, J., Guo, H., Ha, S., Joseph-Mccarthy, D., Kuchnir, L., Kuczera, K., Lau, F. T. K., Mattos, C., Michnick, S., Ngo, T., Nguyen, D. T., Prodhom, B., Reiher, W. E., Roux, B., Schlenkrich, M., Smith, J. C., Stote, R., Straub, J., Watanabe, M., Wiórkiewicz-Kuczera, J., Yin, D. & Karplus, M. (1998). All-atom empirical potential for molecular modeling and dynamics studies of proteins†. *Journal of Physical Chemistry B* **102**, 3586–3616.

Madan, B. & Sharp, K. (2001). Heat capacity changes accompanying hydrophobic and ionic solvation: a Monte-Carlo and random network model study. Bhupinder Madan and Kim Sharp: 1996, volume 100. *Journal of Physical Chemistry B*, **105**, 2256.

Madura, J. D., Briggs, J. M., Wade, R. C., Davis, M. E., Luty, B. A., Ilin, A., Antosiewicz, J., Gilson, M. K., Bagheri, B., Scott, L. R. & Mccammon, J. A. (1995). Electrostatics and diffusion of molecules in solution – simulations with the University of Houston Brownian Dynamics program. *Computer Physics Communications* **91**, 57–95.

Mahoney, M. W. & Jorgensen, W. L. (2000). A five-site model for liquid water and the reproduction of the density anomaly by rigid, nonpolarizable potential functions. *Journal of Chemical Physics* **112**, 8910–8910.

Marcus, R. A. (1956). Electrostatic Free Energy and Other Properties of States Having Nonequilibrium Polarization. *Journal of Chemical Physics* **24**, 979–989.

Marcus, R. A. & Sutin, N. (1985). Electron transfers in chemistry and biology. *Biochimica et Biophysica Acta* **811**, 265–322.

Marcus, Y. (2006). Ionic volumes in solution. *Biophysical Chemistry* **124**, 200–207.

Marenich, A. V., Cramer, C. J. & Truhlar, D. G. (2008). Perspective on foundations of solvation modeling: the electrostatic contribution to the free energy of solvation. *Journal of Chemical Theory and Computation* **4**, 877–887.

Marincola, F. C., Denisov, V. P. & Halle, B. (2004). Competitive Na+ and Rb+ binding in the minor groove of DNA. *Journal of the American Chemical Society* **126**, 6739–6750.

Martick, M., Lee, T.-S., York, D. M. & Scott, W. G. (2008). Solvent structure and hammerhead ribozyme catalysis. *Chemistry and Biology* **15**, 332–342.

Martin-Molina, A., Calero, C., Faraudo, J., Quesada-Perez, M., Travesset, A. & Hidalgo-Alvarez, R. (2009). The hydrophobic effect as a driving force for charge inversion in colloids. *Soft Matter*.

Martin, D., Friesen, A. & Matyushov, D. (2011). Electric field inside a "Rossky cavity" in uniformly polarized water. *Journal of Chemical Physics* **135**, 084514.

Martin, F. & Zipse, H. (2005). Charge distribution in the water molecule: a comparison of methods. *Journal of Computational Chemistry* **26**, 97–105.

Marucho, M., Kelley, C. T. & Pettitt, B. M. (2008). Solutions of the optimized closure integral equation theory: heteronuclear polyatomic fluids. *Journal of Chemical Theory and Computation* **4**, 385–396.

Marucho, M. & Pettitt, B. M. (2007). Optimized theory for simple and molecular fluids. *Journal of Chemical Physics* **126**, 124107.

Maruyama, Y., Yoshida, N. & Hirata, F. (2010). Revisiting the salt-induced conformational change of DNA with 3D-RISM theory. *Journal of Physical Chemistry B* **114**, 6464–6471.

Masamura, M. (2000). Error of atomic charges derived from electrostatic potential. *Structural Chemistry* **11**, 41–45.

Mascagni, M. & Simonov, N. (2004). Monte Carlo methods for calculating some physical properties of large molecules. *SIAM Journal on Scientific Computing* **26**, 339.

Massova, I. & Kollman, P. A. (2000). Combined molecular mechanical and continuum solvent approach (MM-PBSA/GBSA) to predict ligand binding. *Perspectives in Drug Discovery and Design* **18**, 113–135.

Mauro, S. A. & Koudelka, G. B. (2004). Monovalent cations regulate DNA sequence recognition by 434 repressor. *Journal of Molecular Biology* **340**, 445–457.

Mccammon, J. A., Gelin, B. R. & Karplus, M. (1977). Dynamics of folded proteins. *Nature* **267**, 585–590.

Mclaughlin, S. (1989). The electrostatic properties of membranes. *Annual Review of Biophysics and Biophysical Chemistry* **18**, 113–136.

Mehler, E. & Guarnieri, F. (1999). A self-consistent, microenvironment modulated screened Coulomb potential approximation to calculate pH-dependent electrostatic effects in proteins. *Biophysical Journal* **77**, 3–22.

Merzel, F. & Smith, J. C. (2002). Is the first hydration shell of lysozyme of higher density than bulk water? *Proceedings of the National Academy of Sciences of the United States of America* **99**, 5378–5383.

Micu, A. M., Bagheri, B., Ilin, A. V., Scott, L. R. & Pettitt, B. M. (1997). Numerical considerations in the computation of the electrostatic free energy of interaction within the Poisson–Boltzmann theory. *Journal of Computational Physics* **136**, 263–271.

Mikulecky, P. J. & Feig, A. L. (2006). Heat capacity changes associated with nucleic acid folding. *Biopolymers* **82**, 38–58.

Misra, V. K. & Draper, D. E. (1999). The interpretation of Mg(2+) binding isotherms for nucleic acids using Poisson–Boltzmann theory. *Journal of Molecular Biology* **294**, 1135–1147.

Misra, V. K. & Draper, D. E. (2000). Mg(2+) binding to tRNA revisited: the nonlinear Poisson–Boltzmann model. *Journal of Molecular Biology* **299**, 813–825.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Misra, V. K. & Draper, D. E. (2001). A thermodynamic framework for Mg^{2+} binding to RNA. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 12456–12461.

Misra, V. K. & Draper, D. E. (2002). The linkage between magnesium binding and RNA folding. *Journal of Molecular Biology* **317**, 507–521.

Misra, V. K., Shiman, R. & Draper, D. E. (2003). A thermodynamic framework for the magnesium-dependent folding of RNA. *Biopolymers* **69**, 118–136.

Mitra, R., Zhang, Z. & Alexov, E. (2011). In silico modeling of pH-optimum of protein-protein binding. *Proteins* **79**, 925–936.

Miyata, T. & Hirata, F. (2008). Combination of molecular dynamics method and 3D-RISM theory for conformational sampling of large flexible molecules in solution. *Journal of Computational Chemistry* **29**, 871–882.

Mizuno, K., Oda, K., Maeda, S., Shindo, Y. & Okumura, A. (1995). 1H-NMR study on water structure in halogenoalcohol–water mixtures. *Journal of Physical Chemistry* **99**, 3056–3059.

Mobley, D. L., Barber, A. E., Fennell, C. J. & Dill, K. A. (2008). Charge asymmetries in hydration of polar solutes. *Journal of Physical Chemistry B* **112**, 2405–2414.

Momany, F. A. (1978). Determination of partial atomic charges from *ab initio* molecular electrostatic potentials – application to formamide, methanol, and formic acid. *Journal of Physical Chemistry* **82**, 592–601.

Mongan, J., Simmerling, C., Mccammon, A., Case, D. & Onufriev, A. (2007). Generalized Born model with a simple, robust molecular volume correction. *Journal of Chemical Theory and Computation* **3**, 156–169.

Moore Plummer, P. & Chen, T. S. (1987). Investigation of structure and stability of small clusters: molecular dynamics studies of water pentamers. *Journal of Chemical Physics* **86**, 7149.

Mori, M., Erickson, M. & Yue, D. (2004). Functional stoichiometry and local enrichment of calmodulin interacting with Ca^{2+} channels. *Science* **304**, 432–435.

Moser, C. C., Keske, J. M., Warncke, K., Farid, R. S. & Dutton, P. S. (1992). Nature of biological electron-transfer. *Nature* **355**, 796–802.

Mukherjee, A. K. (2004). The attraction between like-charged macroions—the crucial roles of macroion geometry and charge distribution. *Journal of Physics: Condensed Matter* **16**, 2907–2930.

Nada, H. (2003). An intermolecular potential model for the simulation of ice and water near the melting point: a six-site model of H_2O. *Journal of Chemical Physics* **118**, 7401.

Nayal, M. & Di Cera, E. (1996). Valence screening of water in protein crystals reveals potential Na + binding sites. *Journal of Molecular Biology* **256**, 228–234.

Netz, R. R. & Naji, A. (2004). Attraction of like-charged macroions in the strong-coupling limit. *European Physical Journal E: Soft Matter and Biological Physics* **13**, 43–59.

Neumann, C. (1883). *Hydrodynamische Untersuchungen: Nebst Einem Anhange über die Probleme der Elektrostatik und der Magnetischen Induction*. Leipzig: B. G. Teubner.

Nguyen, T. T., Grosberg, A. Y. & Shlovskii, B. I. (2000). Screening of a charged particle by multivalent counterions in salty water: strong charge inversion. *Journal of Chemical Physics* **113**, 1110–1125.

Ni, H., Anderson, C. F. & Record, M. T. (1999). Quantifying the thermodynamic consequences of cation (M^{2+}, M+) accumulation and Anion (X−) Exclusion in mixed salt solutions of polyanionic DNA using Monte Carlo and Poisson–Boltzmann calculations of Ion-polyion preferential interaction coefficients. *Journal of Physical Chemistry B* **103**, 3489–3504.

Nicholls, A. & Honig, B. (1991). A rapid finite difference algorithm, utilizing successive over-relaxation to solve the Poisson–Boltzmann equation. *Journal of Computational Chemistry* **12**, 435–445.

Nicol, M. F. (1974). Solvent effects on electronic spectra. *Applied Spectroscopy Reviews* **8**, 183–227.

Nielsen, J., Gunner, M. R. & Bertrand García-Moreno, E. (2011). The pK_a cooperative: a collaborative effort to advance structure-based calculations of pKa values and electrostatic effects in proteins. *Proteins-Structure Function and Bioinformatics* **79**, 3249–3259.

Nielsen, J. E. (2009). Analysing enzymatic pH activity profiles and protein titration curves using structure-based pKa calculations and titration curve fitting. In *Methods in Enzymology*, vol. **454** (eds. L. J. Michael & B. Ludwig), pp. 233–258. Academic Press, New York.

Nielsen, J. E. (2009). Chapter 9. Analyzing enzymatic ph activity profiles and protein titration curves using structure-based pK_a calculations and titration curve fitting, vol. 454, pp. 233–258.

Nielsen, J. E. & Mccammon, J. A. (2003). On the evaluation and optimization of protein X-ray structures for pKa calculations. *Protein Science* **12**, 313–326.

Nielsen, J. E. & Vriend, G. (2001). Optimizing the hydrogen-bond network in Poisson–Boltzmann equation-based pK(a) calculations. *Proteins – Structure Function and Genetics* **43**, 403–412.

Nightingale, E. R. (1959). Phenomenological theory of ion solvation. effective radii of hydrated ions. *Journal of Physical Chemistry* **63**, 1381–1387.

Nina, M., Im, W. & Roux, B. (1999). Optimized atomic radii for protein continuum electrostatics solvation forces. *Biophysical Chemistry* **78**, 89–96.

Ninham, B. W. & Yaminsky, V. (1997). Ion binding and ion specificity: the Hofmeister effect and Onsager and Lifshitz theories. *Langmuir* **13**, 2097–2108.

Nishiyama, K., Yamaguchi, T. & Hirata, F. (2009). Solvation dynamics in polar solvents studied by means of RISM/mode-coupling theory. *Journal of Physical Chemistry B* **113**, 2800–2804.

Niu, W., Chen, Z., Bush-Pelc, L. A., Bah, A., Gandhi, P. S. & Di Cera, E. (2009). Mutant N143P reveals how

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Na+ activates thrombin. *Journal of Biological Chemistry* **284**, 36175–36185.

Norris, W. T. (1995). Charge images in a dielectric sphere. *IEE Proceedings–Science, Measurement and Technology* **142**, 142–150.

Noskov, S. Y., Im, W. & Roux, B. (2004). Ion permeation through the alpha-hemolysin channel: theoretical studies based on Brownian dynamics and Poisson–Nernst–Plank electrodiffusion theory. *Biophysical Journal* **87**, 2299–2309.

Nymand, T. M. & Linse, P. (2000). Ewald summation and reaction field methods for potentials with atomic charges, dipoles, and polarizabilities. *Journal of Chemical Physics* **112**, 6152–6160.

Okur, A., Wickstrom, L., Layten, M., Geney, R., Song, K., Hornak, V. & Simmerling, C. (2006). Improved efficiency of replica exchange simulations through use of a hybrid explicit/implicit solvation model. *Journal of Chemical Theory and Computation* **2**, 420–433.

Okur, A., Wickstrom, L. & Simmerling, C. (2008). Evaluation of salt bridge structure and energetics in peptides using explicit, implicit, and hybrid solvation models. *Journal of Chemical Theory and Computation* **4**, 488–498.

Olmsted, M. C., Anderson, C. F. & Record, M. T. (1991). Importance of oligoelectrolyte end effects for the thermodynamics of conformational transitions of nucleic acid oligomers: a grand canonical Monte Carlo analysis. *Biopolymers* **31**, 1593–1604.

Onsager, L. (1936). Electric moments of molecules in liquids. *Journal of the American Chemical Society* **58**, 1486–1493.

Onufriev, A., Bashford, D. & Case, D. (2000). Modification of the generalized Born model suitable for macromolecules. *The Journal of Physical Chemistry B* **104**, 3712–3720.

Onufriev, A., Case, D. A. & Bashford, D. (2002). Effective Born radii in the generalized Born approximation: the importance of being perfect. *Journal of Computational Chemistry* **23**, 1297–1304.

Orttung, W. H. (1978). Extension of the Kirkwood-Westheimer model of substituent effects to general shapes, charges, and polarizabilities. Application to the substituted bicyclo[2.2.2]octanes. *Journal of the American Chemical Society* **100**, 4369–4375.

Osapay, K., Young, W. S., Bashford, D., Brooks, C. L. III & Case, D. A. (1996). Dielectric continuum models for hydration effects on peptide conformational transitions. *Journal of Physical Chemistry* **100**, 2698–2705.

Overman, L. B. & Lohman, T. M. (1994). Linkage of pH, anion and cation effects in protein-nucleic acid equilibria. *Journal of Molecular Biology* **236**, 165–178.

Page, M. J., Bleackley, M. R., Wong, S., Macgillivray, R. T. A. & Di Cera, E. (2006). Conversion of trypsin into a Na(+)-activated enzyme. *Biochemistry* **45**, 2987–2993.

Paliwal, A., Asthagiri, D., Pratt, L. R., Ashbaugh, H. S. & Paulaitis, M. E. (2006). An analysis of molecular packing and chemical association in liquid water using quasichemical theory. *Journal of Chemical Physics* **124**, 224502.

Palmo, K., Mannfors, B., Mirkin, N. G. & Krimm, S. (2006). Inclusion of charge and polarizability fluxes provides needed physical accuracy in molecular mechanics force fields. *Chemical Physics Letters* **429**, 628–632.

Papazyan, A. & Warshel, A. (1997). Continuum and dipole-lattice models of solvation. *Journal of Physical Chemistry B* **101**, 11254–11264.

Papazyan, A. & Warshel, A. (1998). Effect of solvent discreteness on solvation. *Journal of Physical Chemistry B* **102**, 5348–5357.

Parsegian, V. A., Rand, R. P. & Rau, D. C. (2000). Osmotic stress, crowding, preferential hydration, and binding: a comparison of perspectives. *Proceedings of the National Academy of Sciences of the United States of America* **97**, 3987–3992.

Parsegian, V. A. & Rau, D. C. (1984). Water near intracellular surfaces. *Journal of Cell Biology* **99**, 196–200.

Parsons, D., Boström, M., Nostro, P. & Ninham, B. (2011). Hofmeister effects: interplay of hydration, nonelectrostatic potentials, and ion size. *Physical Chemistry and Chemical Physics* **13**, 12352–12367.

Parsons, D. F., Boström, M., Maceina, T. J., Salis, A. & Ninham, B. W. (2010). Why direct or reversed Hofmeister series? Interplay of hydration, non-electrostatic potentials, and ion size. *Langmuir: the ACS Journal of Surfaces and Colloids* **26**, 3323–3328.

Patel, S. & Brooks, C. L. (2004). CHARMM fluctuating charge force field for proteins: I parameterization and application to bulk organic liquid simulations. *Journal of Computational Chemistry* **25**, 1–16.

Patel, S., Davis, J. E. & Bauer, B. A. (2009). Exploring ion permeation energetics in gramicidin A using polarizable charge equilibration force fields. *Journal of the American Chemical Society* **131**, 13890–13891.

Patel, S., Mackerell, A. D. & Brooks, C. L. (2004). CHARMM fluctuating charge force field for proteins: II Protein/solvent properties from molecular dynamics simulations using a nonadditive electrostatic model. *Journal of Computational Chemistry* **25**, 1504–1514.

Patra, M. & Karttunen, M. (2004). Systematic comparison of force fields for microscopic simulations of NaCl in aqueous solutions: Diffusion, free energy of hydration, and structural properties. *Journal of Computational Chemistry* **25**, 678–689.

Pegram, L. M. & Record, M. T. (2006). Partitioning of atmospherically relevant ions between bulk water and the water/vapor interface. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 14278–14281.

Pegram, L. M. & Record, M. T. (2007). Hofmeister salt effects on surface tension arise from partitioning of

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

anions and cations between bulk water and the air—water interface. *The Journal of Physical Chemistry B* **111**, 5411–5417.

Pegram, L. M. & Record, M. T. (2008). Thermodynamic origin of Hofmeister ion effects. *Journal of Physical Chemistry B* **112**, 9428–9436.

Pegram, L. M., Wendorff, T., Erdmann, R., Shkel, I., Bellissimo, D., Felitsky, D. J. & Record, M. T. (2010). Why Hofmeister effects of many salts favor protein folding but not DNA helix formation. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 7716–7721.

Perkyns, J. & Pettitt, B. M. (1994). Integral equation approaches to structure and thermodynamics of aqueous salt solutions. *Biophysical Chemistry* **51**, 129–146.

Perkyns, J. & Pettitt, B. M. (1992). A site–site theory for finite concentration saline solutions. *Journal of Chemical Physics* **97**, 7656–7656.

Perkyns, J. & Pettitt, B. M. (1996). Dependence of hydration free energy on solute size. *Journal of Physical Chemistry* **100**, 1323–1329.

Perkyns, J. S. & Pettitt, B. M. (1995). Peptide conformations are restricted by solution stability. *Journal of Physical Chemistry* **99**, 1–2.

Petrache, H. I., Zemb, T., Belloni, L. & Parsegian, V. A. (2006). Salt screening and specific ion adsorption determine neutral-lipid membrane interactions. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 7982–7987.

Petrone, P. M. & Garcia, A. E. (2004). MHC-peptide binding is assisted by bound water molecules. *Journal of Molecular Biology* **338**, 419–435.

Pietronave, S., Arcesi, L., D'Arrigo, C. & Perico, A. (2008). Attraction between like-charged polyelectrolytes in the extended condensation theory†. *Journal of Physical Chemistry B* **112**, 15991–15998.

Pincus, D. L., Hyeon, C. & Thirumalai, D. (2008). Effects of trimethylamine N-Oxide (TMAO) and crowding agents on the stability of RNA hairpins. *Journal of the American Chemical Society* **130**, 7364–7372.

Piquemal, J.-P., Williams-Hubbard, B., Fey, N., Deeth, R. J., Gresh, N. & Giessner-Prettre, C. (2003). Inclusion of the ligand field contribution in a polarizable molecular mechanics: SIBFA-LF. *Journal of Computational Chemistry* **24**, 1963–1970.

Pitera, J. W. & Van Gunsteren, W. F. (2001). The importance of solute-solvent van der Waals interactions with interior atoms of biopolymers. *Journal of the American Chemical Society* **123**, 3163–3164.

Podgornik, R. & Dobnikar, J. (2001). Casimir and pseudo-Casimir interactions in confined polyelectrolytes. *Journal of Chemical Physics* **115**, 1951–1959.

Ponder, J. W. & Case, D. A. (2003). Force fields for protein simulations. *Advances in Protein Chemistry* **66**, 27–85.

Popelier, P. L. A., Joubert, L. & Kosov, D. S. (2001). Convergence of the electrostatic interaction based on topological atoms. *Journal of Physical Chemistry A* **105**, 8254–8261.

Postma, J. P. M., Berendsen, H. J. C. & Haak, J. R. (1982). Thermodynamics of cavity formation in water. A molecular dynamics study. *Faraday Symposia of the Chemical Society* **17**, 55–67.

Prabhu, N. & Sharp, K. (2006). Protein-solvent interactions. *Chemical Reviews* **106**, 1616–1623.

Pratt, L. R. (2002). Molecular theory of hydrophobic effects: 'She is too mean to have her name repeated.'. *Annual Review of Physical Chemistry* **53**, 409–436.

Pratt, L. R. & Chandler, D. (1977). Theory of the hydrophobic effect. *Journal of Chemical Physics* **67**, 3683–3683.

Pratt, L. R. & Chandler, D. (1980). Effects of solute–-solvent attractive forces on hydrophobic correlations. *The Journal of Chemical Physics* **73**, 3430.

Pratt, L. R. & Laviolette, R. A. (1998). Quasi-chemical theories of associated liquids. *Molecular Physics* **94**, 909–915.

Pratt, L. R., Laviolette, R. A., Gomez, M. A. & Gentile, M. E. (2001). Quasi-chemical theory for the statistical thermodynamics of the hard-sphere fluid†. *Journal of Physical Chemistry B* **105**, 11662–11668.

Pratt, L. R. & Pohorille, A. (1992). Theory of hydrophobicity: transient cavities in molecular liquid. *Proceedings of the National Academy of Sciences of the United States of America* **89**, 2995–2999.

Pratt, L. R. & Pohorille, A. U. (2002). Hydrophobic effects and modeling of biophysical aqueous solution interfaces. *Chemical Reviews* **102**, 2671–2691.

Price, S. L. (1985). A distributed multipole analysis of the charge densities of some aromatic hydrocarbons. *Chemical Physics Letters* **114**, 359–364.

Price, S. L., Stone, A. J. & Alderton, M. (1984). Explicit formulae for the electrostatic energy, forces and torques between a pair of molecules of arbitrary symmetry. *Molecular Physics* **52**, 987–1001.

Qiao, R. & Aluru, N. R. (2004). Charge inversion and flow reversal in a nanochannel electro-osmotic flow. *Physical Review Letters* **92**.

Qiu, X., Parsegian, A. & Rau, D. (2010). Divalent counterion-induced condensation of triple-strand DNA. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 21482–21486.

Rahman, A. (1971). Molecular dynamics study of liquid water. *Journal of Chemical Physics* **55**, 3336.

Rajamani, S., Truskett, T. M. & Garde, S. (2005). Hydrophobic hydration from small to large lengthscales: understanding and manipulating the crossover. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 9475–9480.

Ramirez, R. & Borgis, D. (2005). Density functional theory of solvation and its relation to implicit solvent models. *Journal of Physical Chemistry B* **109**, 6754–6763.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Rappe, A. K. & Goddard, W. A. (1991). Charge equilibration for molecular dynamics simulations. *Journal of Physical Chemistry* **95**, 3358–3363.

Record, M. T., Anderson, C. F. & Lohman, T. M. (1978). Thermodynamic analysis of ion effects on the binding and conformational equilibria of proteins and nucleic acids: the roles of ion association or release, screening, and ion effects on water activity. *Quarterly Reviews of Biophysics* **11**, 103–178.

Record, M. T., Olmsted, M. C., Bond, J. P., Anderson, C. F. & Record, M. T. Jr. (1995). Grand canonical Monte Carlo molecular and thermodynamic predictions of ion effects on binding of an oligocation (L8+) to the center of DNA oligomers. *Biophysical Journal* **68**, 634–647.

Reed, A. E., Curtiss, L. A. & Weinhold, F. (1988). Intermolecular interactions from a natural bond orbital, donor–acceptor viewpoint. *Chemical Reviews* **88**, 899–926.

Rempe, S. B., Asthagiri, D. & Pratt, L. R. (2004). Inner shell definition and absolute hydration free energy of K+(aq) on the basis of quasi-chemical theory and *ab initio* molecular dynamics. *Physical Chemistry Chemical Physics* **6**, 1966–1969.

Ren, P. & Ponder, J. W. (2002). Consistent treatment of inter- and intramolecular polarization in molecular mechanics calculations. *Journal of Computational Chemistry* **23**, 1497–1506.

Ren, P. & Ponder, J. W. (2003). Polarizable atomic multipole water model for molecular mechanics simulation. *Journal of Physical Chemistry B* **107**, 5933–5947.

Ren, P., Wu, C. & Ponder, J. W. (2011). Polarizable atomic multipole-based molecular mechanics for organic molecules. *Journal of Chemical Theory and Computation* **7**, 3143–3161.

Reyes-Caballero, H., Campanello, G. & Giedroc, D. (2011). Metalloregulatory proteins: metal selectivity and allosteric switching. *Biophysical Chemistry*.

Reynolds, C. A., Essex, J. W. & Graham Richards, W. (1992a). Errors in free-energy perturbation calculations due to neglecting the conformational variation of atomic charges. *Chemical Physics Letters* **199**, 257–260.

Reynolds, C. A., Essex, J. W. & Richards, W. G. (1992b). Atomic charges for variable molecular conformations. *Journal of the American Chemical Society* **114**, 9075–9079.

Rhodes, M. M., Réblová, K., Sponer, J. & Walter, N. G. (2006). Trapped water molecules are essential to structural dynamics and function of a ribozyme. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 13380–13385.

Ribeiro, M. (1999). Fluctuating charge model for polyatomic ionic systems: a test case with diatomic anions. *Journal of Chemical Physics* **110**, 11445.

Riccardi, D., Schaefer, P., Yang Yu, H., Ghosh, N., Prat-Resina, X., König, P., Li, G., Xu, D., Guo, H., Elstner, M. & Cui, Q. (2006). Development of effective quantum mechanical/molecular mechanical (QM/MM) methods for complex biological processes. *Journal of Physical Chemistry B* **110**, 6458–6469.

Rick, S. W. (2001). Simulations of ice and liquid water over a range of temperatures using the fluctuating charge model. *Journal of Chemical Physics* **114**, 2276–2283.

Robinson, G., Cho, C. H. & Urquidi, J. (1999). Isosbestic points in liquid water: further strong evidence for the two-state mixture model. *Journal of Chemical Physics* **111**, 698.

Robinson, R. A. & Stokes, R. H. (2002). *Electrolyte Solutions: Second Revised Edition*. Mineola, NY: Dover.

Rocchia, W., Sridharan, S., Nicholls, A., Alexov, E., Chiabrera, A. & Honig, B. (2002). Rapid grid-based construction of the molecular surface and the use of induced surface charge to calculate reaction field energies: applications to the molecular systems and geometric objects. *Journal of Computational Chemistry* **23**, 128–137.

Rode, B., Hofer, T., Randolf, B., Schwenk, C., Xenides, D. & Vchirawongkwin, V. (2006). *Ab initio* quantum mechanical charge field (QMCF) molecular dynamics: a QM/MM – MD procedure for accurate simulations of ions and complexes. *Theoretical Chemistry Accounts: Theory, Computation, and Modeling* (*Theoretica Chimica Acta*) **115**, 77–85.

Root, J. H., Egelstaff, P. A. & Hime, A. (1986). Quantum effects in the structure of water measured by gamma ray diffraction. *Chemical Physics* **109**, 437–453.

Rösgen, J., Pettitt, B. M. & Bolen, D. W. (2005). Protein folding, stability, and solvation structure in osmolyte solutions. *Biophysical Journal* **89**, 2988–2997.

Rösgen, J., Pettitt, B. M. & Bolen, D. W. (2007). An analysis of the molecular origin of osmolyte-dependent protein stability. *Protein Science* **16**, 733–743.

Rossky, P. J., Pettitt, B. M. & Stell, G. (1983). The coupling of long and short range correlations in ISM liquids. *Molecular Physics* **50**, 1263–1271.

Rottler, J. & Krayenhoff, B. (2009). Numerical studies of nonlocal electrostatic effects on the sub-nanoscale. *Journal of Physics: Condensed Matter* **21**, 255901.

Roux, B. (1999). Implicit solvent models. *Biophysical Chemistry* **78**, 1–20.

Roux, B., Allen, T., Bernèche, S. & Im, W. (2004). Theoretical and computational models of biological ion channels. *Quarterly Reviews of Biophysics* **37**, 15–103.

Roux, C., Bhatt, F., Foret, J., De Courcy, B., Gresh, N., Piquemal, J. P., Jeffery, C. J. & Salmon, L. (2011). The reaction mechanism of type I phosphomannose isomerases: new information from inhibition and polarizable molecular mechanics studies. *Proteins* **79**, 203–220.

Royer, W. E., Pardanani, A., Gibson, Q. H., Peterson, E. S. & Friedman, J. M. (1996). Ordered water molecules as key allosteric mediators in a cooperative dimeric hemoglobin. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 14526–14531.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Sachs, J. N. & Woolf, T. B. (2003). Understanding the Hofmeister effect in interactions between chaotropic anions and lipid bilayers: molecular dynamics simulations. *Journal of the American Chemical Society* **125**, 8742–8743.

Sagui, C., Pedersen, L. G. & Darden, T. A. (2004). Towards an accurate representation of electrostatics in classical force fields: efficient implementation of multipolar interactions in biomolecular simulations. *Journal of Chemical Physics* **120**, 73–87.

Samsonov, S., Teyra, J. & Pisabarro, M. T. (2008). A molecular dynamics approach to study the importance of solvent in protein interactions. *Proteins: Structure, Function, and Bioinformatics* **73**, 515–525.

Savelyev, A. & Papoian, G. (2007). Inter-DNA electrostatics from explicit solvent molecular dynamics simulations. *Journal of the American Chemical Society* **129**, 6060–6061.

Savelyev, A. & Papoian, G. A. (2006). Electrostatic, steric, and hydration interactions favor Na+ condensation around DNA compared with K+. *Journal of the American Chemical Society* **128**, 14506–14518.

Schaefer, M. & Karplus, M. (1996). A comprehensive analytical treatment of continuum electrostatics. *Journal of Physical Chemistry* **100**, 1578–1599.

Schaefer, P., Riccardi, D. & Cui, Q. (2005). Reliable treatment of electrostatics in combined QM/MM simulation of macromolecules. *Journal of Chemical Physics* **123**.

Schlick, T. (2002). *Molecular Modeling and Simulation: An Interdisciplinary Guide*. New York, NY: Springer-Verlag.

Schmid, B., Michalsky, J. J., Slater, D. W., Barnard, J. C., Halthore, R. N., Liljegren, J. C., Holben, B. N., Eck, T. F., Livingston, J. M., Russell, P. B., Ingold, T. & Slutsker, I. (2001). Comparison of columnar water–vapor measurements from solar transmittance methods. *Applied Optics* **40**, 1886–1896.

Schnieders, M., Baker, N., Ren, P. & Ponder, J. (2007). Polarizable atomic multipole solutes in a Poisson–Boltzmann continuum. *Journal of Chemical Physics* **126**, 124114.

Schnieders, M. J. & Ponder, J. W. (2007). Polarizable atomic multipole solutes in a generalized Kirkwood continuum. *Journal of Chemical Theory and Computation* **3**, 2083–2097.

Schreiber, H. & Steinhauser, O. (1992a). Molecular dynamics studies of solvated polypeptides: why the cut-off scheme does not work. *Chemical Physics* **168**, 75–89.

Schreiber, H. & Steinhauser, O. (1992b). Taming cut-off induced artifacts in molecular dynamics studies of solvated polypeptides: the reaction field method. *Journal of Molecular Biology* **228**, 909–923.

Schutz, C. N. & Warshel, A. (2001). What are the dielectric 'constants' of proteins and how to validate electrostatic models? *Proteins* **44**, 400–417.

Sciortino, F., Geiger, A. & Stanley, H. E. (1990). Isochoric differential scattering functions in liquid water: the fifth neighbor as a network defect. *Physical Review Letters* **65**, 3452.

Senn, H. M. & Thiel, W. (2009). QM/MM methods for biomolecular systems. *Angewandte Chemie International Edition* **48**, 1198–1229.

Sham, Y. Y., Muegge, I. & Warshel, A. (1998). The effect of protein relaxation on charge-charge interactions and dielectric constants of proteins. *Biophysical Journal* **74**, 1744–1753.

Shan, J. & Mehler, E. L. (2011). Calculation of pK_a in proteins with the microenvironment modulated-screened Coulomb potential (MM-SCP). *Proteins-Structure Function and Bioinformatics* **79**, 3346–3355.

Sharp, K. A. & Honig, B. (1990a). Calculating total electrostatic energies with the nonlinear Poisson–Boltzmann equation. *Journal of Physical Chemistry* **94**, 7684–7692.

Sharp, K. A. & Honig, B. (1990b). Electrostatic interactions in macromolecules – theory and applications. *Annual Review of Biophysics and Biophysical Chemistry* **19**, 301–332.

Sharp, K. A., Nicholls, A., Fine, R. F. & Honig, B. (1991a). Reconciling the magnitude of the microscopic and macroscopic hydrophobic effects. *Science* **252**, 106–109.

Sharp, K. A., Nicholls, A., Friedman, R. & Honig, B. (1991b). Extracting hydrophobic free energies from experimental data: relationship to protein folding and theoretical models. *Biochemistry* **30**, 9686–9697.

Sheinerman, F. B., Norel, R. & Honig, B. (2000). Electrostatic aspects of protein-protein interactions. *Current Opinion in Structural Biology* **10**, 153–159.

Shi, Y., Wu, C. J., Ponder, J. W. & Ren, P. Y. (2011). Multipole electrostatics in hydration free energy calculations. *Journal of Computational Chemistry* **32**, 967–977.

Shimizu, S. (2004a). Estimating hydration changes upon biomolecular reactions from osmotic stress, high pressure, and preferential hydration experiments. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 1195–1199.

Shimizu, S. (2004b). Estimation of excess solvation numbers of water and cosolvents from preferential interaction and volumetric experiments. *Journal of Chemical Physics* **120**, 4989–4990.

Shimizu, S., Mclaren, W. M. & Matubayasi, N. (2006). The Hofmeister series and protein-salt interactions. *Journal of Chemical Physics* **124**, 234905.

Shimizu, S. & Smith, D. J. (2004). Preferential hydration and the exclusion of cosolvents from protein surfaces. *Journal of Chemical Physics* **121**, 1148–1154.

Shults, M., Pearce, D. & Imperiali, B. (2003). Modular and tunable chemosensor scaffold for divalent zinc. *Journal of the American Chemical Society* **125**, 10591–10597.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Sigalov, G., Fenley, A. & Onufriev, A. (2006). Analytical electrostatics for biomolecules: beyond the generalized Born approximation. *Journal of Chemical Physics* **124**, 124902.

Silveston, R. & Kronberg, B. (1989). Water structuring around nonpolar molecules as determined by HPLC. *Journal of Physical Chemistry* **93**, 6241–6246.

Silvestrelli, P. L. & Parrinello, M. (1999). Water molecule dipole in the gas and in the liquid phase. *Physical Review Letters* **82**, 3308.

Simonov, N., Mascagni, M. & Fenley, M. (2007). Monte Carlo-based linear Poisson–Boltzmann approach makes accurate salt-dependent solvation free energy predictions possible. *Journal of Chemical Physics* **127**, 185105.

Simonson, T. (1999). Dielectric relaxation in proteins: microscopic and macroscopic models. *International Journal of Quantum Chemistry* **73**, 45–57.

Simonson, T. (2001). Macromolecular electrostatics: continuum models and their growing pains. *Current Opinion in Structural Biology* **11**, 243–252.

Simonson, T. (2003). Electrostatics and dynamics of proteins. *Reports on Progress in Physics* **66**, 737–787.

Simonson, T. (2008). Dielectric relaxation in proteins: the computational perspective. *Photosynthesis Research* **97**, 21–32.

Simonson, T. & Brunger, A. T. (1994). Solvation free energies estimated from macroscopic continuum theory: an accuracy assessment. *Journal of Physical Chemistry* **98**, 4683–4694.

Sitkoff, D., Sharp, K. & Honig, B. (1994a). Accurate calculation of hydration free energies using macroscopic solvent models. *Journal of Physical Chemistry* **98**, 1978–1988.

Sitkoff, D., Sharp, K. A. & Honig, B. (1994b). Correlating solvation free energies and surface tensions of hydrocarbon solutes. *Biophysical Chemistry* **51**, 397–409.

Smolin, N. & Winter, R. (2004). Molecular dynamics simulations of staphylococcal nuclease: properties of water at the protein surface. *Journal of Physical Chemistry B* **108**, 15928–15937.

Söderhjelm, P., Krogh, J. W., Karlström, G., Ryde, U. & Lindh, R. (2007). Accuracy of distributed multipoles and polarizabilities: comparison between the LoProp and MpProp models. *Journal of Computational Chemistry* **28**, 1083–1090.

Sokalski, W. A., Keller, D. A., Ornstein, R. L. & Rein, R. (1993). Multipole correction of atomic monopole models of molecular charge distribution. I. Peptides. *Journal of Computational Chemistry* **14**, 970–976.

Soper, A. (2000). The radial distribution functions of water and ice from 220 to 673 K and at pressures up to 400 MPa. *Chemical Physics* **258**, 121–137.

Soper, A. K. & Phillips, M. G. (1986). A new determination of the structure of water at 25 °C. *Chemical Physics* **107**, 47–60.

Sorenson, J. M., Hura, G., Glaeser, R. M. & Gordon, T. H. (2000). What can X-ray scattering tell us about the radial distribution functions of water? *Journal of Chemical Physics* **113**, 9149–9161.

Soto, A. M., Misra, V. & Draper, D. E. (2007). Tertiary structure of an RNA pseudoknot is stabilized by 'diffuse' Mg^{2+} ions. *Biochemistry* **46**, 2973–2983.

Stafford, A., Ensign, D. & Webb, L. (2000). Vibrational stark effect spectroscopy at the interface of Ras and Rap1A bound to the Ras binding domain of RalGDS reveals an electrostatic mechanism for protein-protein interaction. *Journal of Physical Chemistry B* **114**, 15331–15344.

Steinbach, P. J. & Brooks, B. R. (1994). New spherical-cutoff methods for long-range forces in macromolecular simulation. *Journal of Computational Chemistry* **15**, 667–683.

Stern, H. A., Rittner, F., Berne, B. J. & Friesner, R. A. (2001). Combined fluctuating charge and polarizable dipole models: application to a five-site water potential function. *Journal of Chemical Physics* **115**, 2237–2251.

Still, C., Tempczyk, A., Hawley, R. & Hendrickson, T. (1990). Semianalytical treatment of solvation for molecular mechanics and dynamics. *Journal of the American Chemical Society* **112**, 6127–6129.

Stone, A. J. (1981). Distributed multipole analysis, or how to describe a molecular charge distribution. *Chemical Physics Letters* **83**, 233–239.

Stone, A. J. (1996). *The Theory of Intermolecular Forces*. Oxford: Oxford University Press.

Stone, A. J. (2005). Distributed multipole analysis: stability for large basis sets. *Journal of Chemical Theory and Computation* **1**, 1128–1132.

Stone, A. J. & Alderton, M. (2002). Distributed multipole analysis methods and applications. *Molecular Physics* **100**, 221–233.

Stout, J. M. & Dykstra, C. E. (1995). Static dipole polarizabilities of organic molecules. *Ab initio* calculations and a predictive model. *Journal of the American Chemical Society* **117**, 5127–5132.

Stout, J. M. & Dykstra, C. E. (1998). A distributed model of the electrical response of organic molecules. *Journal of Physical Chemistry A* **102**, 1576–1582.

Stuart, S. J. & Berne, B. J. (1996). Effects of polarizability on the hydration of the chloride ion. *Journal of Physical Chemistry* **100**, 11934–11943.

Stumpe, M., Blinov, N., Wishart, D., Kovalenko, A. & Pande, V. (2011). Calculation of local water densities in biological systems: a comparison of molecular dynamics simulations and the 3D-RISM-KH molecular theory of solvation. *Journal of Physical Chemistry B* **115**, 319–328.

Su, Y. & Gallicchio, E. (2004). The non-polar solvent potential of mean force for the dimerization of alanine dipeptide: the role of solute-solvent van der Waals interactions. *Biophysical Chemistry* **109**, 251–260.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Sun, H. (1998). COMPASS: an *ab initio* force-field optimized for condensed-phase applications overview with details on alkane and benzene compounds. *Journal of Physical Chemistry B* **102**, 7338–7364.

Svishchev, I. M., Kusalik, P. G., Wang, J. & Boyd, R. J. (1996). Polarizable point-charge model for water: results under normal and extreme conditions. *Journal of Chemical Physics* **105**, 4742–4750.

Swanson, J. M. J., Mongan, J. & Mccammon, J. A. (2005). Limitations of atom-centered dielectric functions in implicit solvent models. *Journal of Physical Chemistry B* **109**, 14769–14772.

Swanson, J. M. J., Wagoner, J. A., Baker, N. A. & Mccammon, J. A. (2007). Optimizing the Poisson dielectric boundary with explicit solvent forces and energies: lessons learned with atom-centered dielectric functions. *Journal of Chemical Theory and Computation* **3**, 170–183.

Tafipolsky, M. & Engels, B. (2011). Accurate intermolecular potentials with physically grounded electrostatics. *Journal of Chemical Theory and Computation* **7**, 1791–1803.

Taheri-Araghi, S. & Ha, B.-Y. (2005). Charge renormalization and inversion of a highly charged lipid bilayer: effects of dielectric discontinuities and charge correlations. *Physical Review E* **72**, 021508.

Tan, C., Tan, Y. H. & Luo, R. (2007). Implicit nonpolar solvent models. *Journal of Physical Chemistry B* **111**, 12263–12274.

Tan, Z.-J. & Chen, S.-J. (2005). Electrostatic correlations and fluctuations for ion binding to a finite length polyelectrolyte. *Journal of Chemical Physics* **122**, 44903–44903.

Tang, C. L., Alexov, E., Pyle, A. M. & Honig, B. (2007). Calculation of pKas in RNA: on the structural origins and functional roles of protonated nucleotides. *Journal of Molecular Biology* **366**, 1475–1496.

Tang, K. E. S. & Bloomfield, V. A. (2002). Assessing accumulated solvent near a macromolecular solute by preferential interaction coefficients. *Biophysical Journal* **82**, 2876–2891.

Tanizaki, S. & Feig, M. (2005). A generalized Born formalism for heterogeneous dielectric environments: application to the implicit modeling of biological membranes. *Journal of Chemical Physics* **122**, 124706.

Teixeira, V. H., Cunha, C. A., Machuqueiro, M., Oliveira, A. S. F., Victor, B. L., Soares, C. M. & Baptista, A. M. (2005). On the use of different dielectric constants for computing individual and pairwise terms in Poisson–Boltzmann studies of protein ionization equilibrium. *Journal of Physical Chemistry B* **109**, 14691–14706.

Thilagavathi, R. & Mancera, R. L. (2010). Ligand-protein cross-docking with water molecules. *Journal of Chemical Information and Modeling* **50**, 415–421.

Thirumalai, D. & Hyeon, C. (2005). RNA and protein folding: common themes and variations. *Biochemistry* **44**, 4957–4970.

Thole, B. T. (1981). Molecular polarizabilities calculated with a modified dipole interaction. *Chemical Physics* **59**, 341–350.

Tikhomirova, A. & Chalikian, T. V. (2004). Probing hydration of monovalent cations condensed around polymeric nucleic acids. *Journal of Molecular Biology* **341**, 551–563.

Timasheff, S. N. (1992). Water as ligand: preferential binding and exclusion of denaturants in protein unfolding. *Biochemistry* **31**, 9857–9864.

Timasheff, S. N. (1998). In disperse solution, 'osmotic stress' is a restricted case of preferential interactions. *Proceedings of the National Academy of Sciences of the United States of America* **95**, 7363–7367.

Timasheff, S. N. (2002). Protein-solvent preferential interactions, protein hydration, and the modulation of biochemical reactions by solvent components. *Proceedings of the National Academy of Sciences of the United States of America* **99**, 9721–9726.

Tironi, I. G., Sperb, R., Smith, P. E. & Gunsteren, W. F. V. (1995). A generalized reaction field method for molecular dynamics simulations. *Journal of Chemical Physics* **102**, 5451–5459.

Tjong, H. & Zhou, H. X. (2007a). GBr6: a parameterization-free, accurate, analytical generalized born method. *Journal of Physical Chemistry B* **111**, 3055–3061.

Tjong, H. & Zhou, H. X. (2007b). GBr6NL: a generalized Born method for accurately reproducing solvation energy of the nonlinear Poisson–Boltzmann equation. *Journal of Chemical Physics*, **126**.

Tjong, H. & Zhou, H. X. (2008). On the dielectric boundary in Poisson–Boltzmann calculations. *Journal of Chemical Theory and Computation* **4**, 507–514.

Tobias, D. J. & Hemminger, J. C. (2008). Chemistry: getting specific about specific ion effects. *Science* **319**, 1197–1198.

Todd, B. A., Parsegian, V. A., Shirahata, A., Thomas, T. J. & Rau, D. C. (2008). Attractive forces between cation condensed DNA double helices. *Biophysical Journal* **94**, 4775–4782.

Todd, B. A. & Rau, D. C. (2008). Interplay of ion binding and attraction in DNA condensed by multivalent cations. *Nucleic Acids Research* **36**, 501–510.

Torrie, G. M. & Valleau, J. P. (1974). Monte Carlo free energy estimates using non-Boltzmann sampling: application to the sub-critical Lennard-Jones fluid. *Chemical Physics Letters* **28**, 578–581.

Tran, H. T., Pappu, R. V. & Mao, A. (2008). Role of backbone-solvent interactions in determining conformational equilibria of intrinsically disordered proteins. *Journal of the American Chemical Society* **130**, 7380–7392.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Tsui, V. & Case, D. (2000). Theory and applications of the generalized born solvation model in macromolecular simulations. *Biopolymers* **56**, 275–291.

Tynan-Connolly, B. M. & Nielsen, J. E. (2006). pKD: re-designing protein pK_a values. *Nucleic Acids Research* **34** (Web Server issue), W48–W51.

Vácha, R., Siu, S. W., Petrov, M., Böckmann, R. A., Barucha-Kraszewska, J., Jurkiewicz, P., Hof, M., Berkowitz, M. L. & Jungwirth, P. (2009). Effects of alkali cations and halide anions on the DOPC lipid membrane. *Journal of Physical Chemistry A* **113**, 7235–7243.

Van Dijk, A. D. J. & Bonvin, A. M. J. J. (2006). Solvated docking: introducing water into the modelling of biomolecular complexes. *Bioinformatics* **22**, 2340–2347.

Van Duijnen, P. T. & De Vries, A. H. (1996). Direct reaction field force field: a consistent way to connect and combine quantum-chemical and classical descriptions of molecules. *International Journal of Quantum Chemistry* **60**, 1111–1132.

Van Duijnen, P. T. & Swart, M. (1998). Molecular and atomic polarizabilities: Thole's model revisited. *The Journal of Physical Chemistry A* **102**, 2399–2407.

Vesely, F. J. (1977). N-particle dynamics of polarizable stockmayer-type molecules. *Journal of Computational Physics* **24**, 361–371.

Villacanas, O., Madurga, S., Giralt, E. & Belda, I. (2009). Explicit treatment of water molecules in protein-ligand docking. *Current Computer-Aided Drug Design* **5**, 145–154.

Vinter, J. G. (1996). Extended electron distributions applied to the molecular mechanics of some intermolecular interactions. II. Organic complexes. *Journal of Computer-Aided Molecular Design* **10**, 417–426.

Vitalis, A. & Pappu, R. (2009). ABSINTH: a new continuum solvation model for simulations of polypeptides in aqueous solutions. *Journal of Computational Chemistry* **30**, 673–699.

Vrbka, L., Jungwirth, P., Bauduin, P., Touraud, D. & Kunz, W. (2006). Specific ion effects at protein surfaces: a molecular dynamics study of bovine pancreatic trypsin inhibitor and horseradish peroxidase in selected salt solutions. *Journal of Physical Chemistry B* **110**, 7036–7043.

Wagoner, J. & Baker, N. (2004). Solvation forces on biomolecular structures: a comparison of explicit solvent and Poisson–Boltzmann models. *Journal of Computational Chemistry* **25**, 1623–1629.

Wagoner, J. & Baker, N. (2006). Assessing implicit models for nonpolar mean solvation forces: the importance of dispersion and volume terms. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 8331–8336.

Wagoner, J. A. & Pande, V. S. (2011). A smoothly decoupled particle interface: new methods for coupling explicit and implicit solvent. *Journal of Chemical Physics* **134**, 214103.

Waldron, K. J. & Robinson, N. J. (2009). How do bacterial cells ensure that metalloproteins get the correct metal? *Nature Reviews Microbiology* **7**, 25–35.

Wallace, J. & Shen, J. (2011). Continuous constant pH molecular dynamics in explicit solvent with pH-based replica exchange. *Journal of Chemical Theory and Computation* **7**, 2617–2629.

Wang, J., Cieplak, P., Li, J., Cai, Q., Hsieh, M., Lei, H., Luo, R. & Duan, Y. (2011a). Development of polarizable models for molecular mechanical calculations II: induced dipole models significantly improve accuracy of intermolecular interaction energies. *Journal of Physical Chemistry B* **115**, 3100–3111.

Wang, J., Cieplak, P., Li, J., Hou, T., Luo, R. & Duan, Y. (2011b). Development of polarizable models for molecular mechanical calculations I: parameterization of atomic polarizability. *Journal of Physical Chemistry B* **115**, 3091–3099.

Wang, K., Yu, Y.-X. & Gao, G.-H. (2004). Density functional study on the structures and thermodynamic properties of small ions around polyanionic DNA. *Physical Review E* **70**, 011912.

Wang, L. & Hermans, J. (1995). Reaction field molecular dynamics simulation with Friedman's image charge method. *Journal of Physical Chemistry* **99**, 12001–12007.

Wang, Z. X., Zhang, W., Wu, C., Lei, H., Cieplak, P. & Duan, Y. (2006). Strike a balance: optimization of backbone torsion parameters of AMBER polarizable force field for simulations of proteins and peptides. *Journal of Computational Chemistry* **27**, 781–790.

Warren, G. L. & Patel, S. (2007). Hydration free energies of monovalent ions in transferable intermolecular potential four point fluctuating charge water: An assessment of simulation methodology and force field performance and transferability. *Journal of Chemical Physics* **127**, 064509.

Warshel, A. (1976). Bicycle-pedal model for the first step in the vision process. *Nature* **260**, 679–683.

Warshel, A. (1979). Calculations of chemical processes in solutions. *Journal of Physical Chemistry* **83**, 1640–1652.

Warshel, A. & Dryga, A. (2011). Simulating electrostatic energies in proteins: perspectives and some recent studies of pKas, redox, and other crucial functional properties. *Proteins-Structure Function and Bioinformatics* **79**, 3469–3484.

Warshel, A., Kato, M. & Pisliakov, A. V. (2007). Polarizable force fields: history, test cases, and prospects. *Journal of Chemical Theory and Computation* **3**, 2034–2045.

Warshel, A. & Papazyan, A. (1998). Electrostatic effects in macromolecules: fundamental concepts and practical modeling. *Current Opinion in Structural Biology* **8**, 211–217.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Warwicker, J. & Watson, H. C. (1982). Calculation of the electric potential in the active site cleft due to alpha-helix dipoles. *Journal of Molecular Biology* **157**, 671–679.

Webb, H., Tynan-Connolly, B., Lee, G., Farrell, D., O'Meara, F., Søndergaard, C., Teilum, K., Hewage, C., Mcintosh, L. & Nielsen, J. (2011). Remeasuring HEWL pK_a values by NMR spectroscopy: methods, analysis, accuracy, and implications for theoretical pK_a calculations. *Proteins* **79**, 685–702.

Wells, C. M. & Di Cera, E. (1992). Thrombin is a Na(+)-activated enzyme. *Biochemistry* **31**, 11721–11730.

Wen, Q. & Tang, J. X. (2004). Absence of charge inversion on rodlike polyelectrolytes with excess divalent counterions. *Journal of Chemical Physics* **121**, 12666–12670.

Wesson, L. & Eisenberg, D. (1992). Atomic solvation parameters applied to molecular dynamics of proteins in solution. *Protein Science* **1**, 227–235.

Wheatley, R. J. & Mitchell, J. B. O. (1994). Gaussian multipoles in practice: electrostatic energies for intermolecular potentials. *Journal of Computational Chemistry* **15**, 1187–1198.

Whitfield, T. W., Varma, S., Harder, E., Lamoureux, G., Rempe, S. B. & Roux, B. (2007). Theoretical study of aqueous solvation of K+ comparing *ab initio*, polarizable, and fixed-charge models. *Journal of Chemical Theory and Computation* **3**, 2068–2082.

Wiberg, K. B. & Rablen, P. R. (1993). Comparison of atomic charges derived via different procedures. *Journal of Computational Chemistry* **14**, 1504–1518.

Williams, D. E. (1988). Representation of the molecular electrostatic potential by atomic multipole and bond dipole models. *Journal of Computational Chemistry* **9**, 745–763.

Wimley, W. C., Creamer, T. P. & White, S. H. (1996). Solvation energies of amino acid side chains and backbone in a family of host–guest pentapeptides. *Biochemistry* **35**, 5109–5124.

Witham, S., Talley, K., Wang, L., Zhang, Z., Sarkar, S., Gao, D., Yang, W. & Alexov, E. (2011). Developing hybrid approaches to predict pK_a values of ionizable groups. *Proteins-Structure Function and Bioinformatics* **79**, 3389–3399.

Woelki, S., Kohler, H. H., Krienke, H. & Schmeer, G. (2008). Improvements of DRISM calculations: symmetry reduction and hybrid algorithms. *Physical Chemistry and Chemical Physics* **10**, 896–910.

Wong, G. C. L. & Pollack, L. (2010). Electrostatics of strongly charged biological polymers: ion-mediated interactions and self-organization in nucleic acids and proteins. *Annual Review of Physical Chemistry* **61**, 171–189.

Wu, J. C., Piquemal, J. P., Chaudret, R., Reinhardt, P. & Ren, P. Y. (2010). Polarizable molecular dynamics simulation of Zn(II) in water using the AMOEBA force field. *Journal of Chemical Theory and Computation* **6**, 2059–2070.

Xantheas, S., Burnham, C. J. & Harrison, R. J. (2002). Development of transferable interaction models for water. II. Accurate energetics of the first few water clusters from first principles. *Journal of Chemical Physics* **116**, 1493.

Xantheas, S. S. & Dunning, T. H. (1994). Structures and energetics of F-$(H_2O)_n$, n = 1–3 clusters from *ab Initio* calculations. *Journal of Physical Chemistry* **98**, 13489–13497.

Xia, K., Zhan, M. & Wei, G.-W. (2011). MIB method for elliptic equations with multi-material interfaces. *Journal of Computational Physics* **230**, 4588–4615.

Xu, Z., Cheng, X. & Yang, H. (2011). Treecode-based generalized Born method. *Journal of Chemical Physics* **134**, 064107.

Yang, C. & Sharp, K. (2004). The mechanism of the type III antifreeze protein action: a computational study. *Biophysical Chemistry* **109**, 137–148.

Yang, T., Wu, J. C., Yan, C., Wang, Y., Luo, R., Gonzales, M. B., Dalby, K. N. & Ren, P. (2011). Virtual screening using molecular simulations. *Proteins: Structure Function and Genetics* **79**, 1940–1951.

Yeagle, P. L. (2004). *The Structure of Biological Membranes*. Boca Raton, FL: CRC Press.

Yonetani, Y., Maruyama, Y., Hirata, F. & Kono, H. (2008). Comparison of DNA hydration patterns obtained using two distinct computational methods, molecular dynamics simulation and three-dimensional reference interaction site model theory. *Journal of Chemical Physics* **128**, 185102–185102.

Yoon, B. & Lenhoff, A. M. (1990). A boundary element method for molecular electrostatics with electrolyte effects. *Journal of Computational Chemistry* **11**, 1080–1086.

Yoshida, N., Phongphanphanee, S., Maruyama, Y., Imai, T. & Hirata, F. (2006). Selective ion-binding by protein probed with the 3D-RISM theory. *Journal of the American Chemical Society* **128**, 12042–12043.

Yu, H., Whitfield, T. W., Harder, E., Lamoureux, G., Vorobyov, I., Anisimov, V. M., Mackerell, A. D., Jr. & Roux, B. (2010). Simulating monovalent and divalent ions in aqueous solution using a drude polarizable force field. *Journal of Chemical Theory and Computation* **6**, 774–786.

Yu, S., Geng, W. & Wei, G. W. (2007a). Treatment of geometric singularities in implicit solvent models. *The Journal of Chemical Physics* **126**, 944–954.

Yu, S. & Wei, G. (2007). Three-dimensional matched interface and boundary (MIB) method for treating geometric singularities. *Journal of Computational Physics* **227**, 602–632.

Yu, S., Zhou, Y. & Wei, G. (2007b). Matched interface and boundary (MIB) method for elliptic problems with sharp-edged interfaces. *Journal of Computational Physics* **224**, 729–756.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press

Zangi, R., Hagen, M. & Berne, B. J. (2007). Effect of ions on the hydrophobic interaction between two plates. *Journal of the American Chemical Society* **129**, 4678–4686.

Zauhar, R. J. (1995). SMART: a solvent-accessible triangulated surface generator for molecular graphics and boundary element applications. *Journal of Computer-Aided Molecular Design* **9**, 149–159.

Zauhar, R. J. & Morgan, R. S. (1985). A new method for computing the macromolecular electric potential. *Journal of Molecular Biology* **186**, 815–820.

Zauhar, R. J. & Morgan, R. S. (1988). The rigorous computation of the molecular electric potential. *Journal of Computational Chemistry* **9**, 171–187.

Zelko, J., Iglič, A., Iglič, V. & Kumar, S. (2010). Effects of counterion size on the attraction between similarly charged surfaces. *Journal of Chemical Physics* **133**, 204901.

Zhang, W., Ni, H., Capp, M. W., Anderson, C. F., Lohman, T. M. & Record, M. T. (1999). The importance of coulombic end effects: experimental characterization of the effects of oligonucleotide flanking charges on the strength and salt dependence of oligocation (L8+) binding to single-stranded DNA oligomers. *Biophysical Journal* **76**, 1008–1017.

Zhang, Y., Xu, G. & Bajaj, C. (2006). Quality meshing of implicit solvation models of biomolecular structures. *Computer-Aided Geometric Design* **23**, 510–530.

Zheng, L., Chen, M. & Yang, W. (2008). Random walk in orthogonal space to achieve efficient free-energy simulation of complex systems. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 20227–20232.

Zheng, L., Chen, M. & Yang, W. (2009). Simultaneous escaping of explicit and hidden free energy barriers: application of the orthogonal space random walk strategy in generalized ensemble based conformational sampling. *Journal of Chemical Physics* **130**, 234105.

Zhou, H. X. (1993). Boundary element solution of macromolecular electrostatics: interaction energy between two proteins. *Biophysical Journal* **65**, 955–963.

Zhou, H. X. (2005). Interactions of macromolecules with salt ions: an electrostatic theory for the Hofmeister effect. *Proteins* **61**, 69–78.

Zhou, R., Huang, X., Margulis, C. J. & Berne, B. J. (2004). Hydrophobic collapse in multidomain protein folding. *Science* **305**, 1605–1609.

Zhou, Y. & Wei, G. (2006). On the fictitious-domain and interpolation formulations of the matched interface and boundary (MIB) method. *Journal of Computational Physics* **219**, 228–246.

Zhu, J., Alexov, E. & Honig, B. (2005). Comparative study of generalized Born models: born radii and peptide folding. *Journal of Physical Chemistry B* **109**, 3008–3022.

https://doi.org/10.1017/S003358351200011X Published online by Cambridge University Press