

Charge Scaling Manifesto: A Way of Reconciling the Inherently Macroscopic and Microscopic Natures of Molecular Simulations

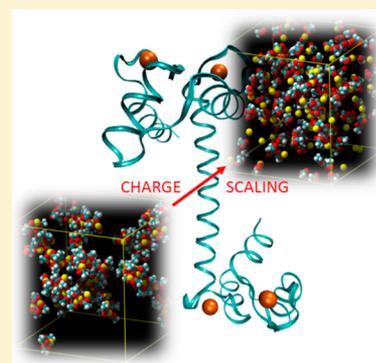
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ABSTRACT: Electronic polarization effects play an important role in the interactions of charged species in biologically relevant aqueous solutions, such as those involving salt ions, proteins, nucleic acids, or phospholipid membranes. Explicit inclusion of electronic polarization in molecular modeling is tedious both from the point of view of force field parametrization and actual performance of the simulations. Therefore, the vast majority of biomolecular simulations is performed using nonpolarizable force fields, which can lead to artifacts such as dramatically overestimated ion pairing, particularly when polyvalent ions are involved. Here, we show that many of these issues can be remedied without extra computational costs by including electronic polarization in a mean field way via charge rescaling. We also lay the solid physical foundations of this approach and reconcile from this perspective the microscopic versus macroscopic natures of nonpolarizable force fields.



Molecular simulations have become invaluable tools for unraveling structural, dynamical, and functional relations of biomolecules.¹ They have evolved from auxiliary techniques that could provide only qualitative results to sophisticated tools that work hand in hand with and quantitatively complement experimental approaches. The usefulness of molecular simulations lies primarily in their unmatched spatial (sub-angstrom) and temporal (subfemtosecond) resolutions, which could hardly be duplicated by experiments. However, the predictions of molecular simulations are only as good as the accuracy of the force field and its consistency with the underlying physics of electrostatic interaction.

Continuum descriptions of electrostatics, predating molecular simulations but widely used until today, inherently use a macroscopic approach. Namely, charges are separated into free and bound ones, with the latter being encompassed by a continuum material property, i.e., the electric permittivity of the material.^{2,3} In contrast, atomistic force field descriptions seek to resolve all charge interactions as best as possible through the use of simplified descriptions of the electrostatics, which typically take the form of integer or partial point charges.⁴

Biological molecules do not perform their function in vacuum, but instead in aqueous electrolyte solutions pertinent to the intra- or extra-cellular environments, as well as in lipids, proteins, and polysaccharides that form biomembrane structures, and the interfaces between them. Viewed through the lens of macroscopic electrostatics, this means that electrostatic interactions driving the biological processes are attenuated by the relative permittivity (dielectric constant),

which can range from ~ 80 in aqueous electrolytes to much smaller values, as low as ~ 2 , in the core of a lipid membrane or a large protein.^{5–7} The dramatic attenuation in aqueous solution is primarily attributable to the ability of water molecules to reorient around charged solutes and thus screen the effect of their charge, whereas in the core of a lipid membrane or a protein the screening occurs dominantly through rearrangement of the electronic cloud surrounding the atomic nuclei. This screening is central to multiple current questions in atomistic simulation of biomolecular interactions.

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Water models used in biomolecular simulations typically assume a rigid intramolecular structure with intermolecular interactions described by a set of fixed partial charges corresponding to the two hydrogen and one oxygen molecule (and/or additional virtual sites) and Lennard-Jones potentials.

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Despite a wide variation in quality, better examples of these rigid nonpolarizable models describe most of bulk thermodynamic properties of water rather well at ambient conditions, with the best models reproducing satisfactorily also the phase space behavior.⁸ However, these water models, developed to manage pure water and aqueous solutions of the most common biologically relevant ions like sodium, potassium, and chloride have often failed badly in the presence of monovalent ions of high charge density and many multivalent ions. Namely, simulations employing nonpolarizable force fields are typically not able to even qualitatively reproduce aqueous solubilities of salts containing high charge density ions like lithium, magnesium, calcium, sulfate, etc., as these artifactually precipitate from the solution already at modest concentrations.^{9,10} Attempts to fix these problems using explicitly polarizable force fields have been of a limited success only because of problems with accurate parametrization and convergence (the so-called polarization catastrophe).^{11,12} Because of these issues, as well as because of significantly increased demands on computer time, explicitly polarizable force fields are only rarely used in biomolecular simulations.^{13–15}

The principal purpose of this Perspective is to show that there is a conceptual disconnect between the vast majority of currently used water models and the language used to describe their putative physical underpinnings. We stress that this issue has been central to propagation of critical errors in recent decades and that proper accounting for what water models actually are trying to do has the potential to improve the quality of biomolecular simulations in aqueous environments. We start from the fact that nonpolarizable water models resolve some of but not all of the polarization associated with water's response to its environment. This is not simply a statement that water models are imperfect; rather, water models without electronic polarization judiciously delineate, on a spatiotemporal time scale, between charge which is to be resolved and that which is to be left unresolved. This delineation is analogous to the classical macroscopic model of electrostatics, and we show below that considerable conceptual simplification is achieved if these water models are treated as macroscopic ones. As shown in detail in the following discussion, this approach naturally leads to the concept of charge scaling as a way to account for electronic polarization effects in a mean-field way within nominally nonpolarizable molecular simulations.^{9,11,16–18}

Although both microscopic and macroscopic approaches to electrostatics are basic and well-known^{2,3} it is worth briefly

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reviewing the associated language. A microscopic model resolves all charges and essentially involves Coulomb's law at an atomistic level. A classical macroscopic model divides the charges into bound and free ones, folding the bound charges into a material property (usually a linear dielectric constant) and resolving the free charge. A linear electrostatic model for

water uses a single material property, i.e., the dielectric constant, to describe the effect of polarization in suppressing electrostatic interactions. The dielectric constant, which appears in the denominator of Coulomb's law, is used to account for all electrostatic interactions as spatially and temporally unresolved (for both nuclear polarization, which occurs on picosecond time scales, and the practically instantaneous electronic polarization).¹⁹

Coulomb's law underpins all of classical electrostatics and is given by $\vec{F} = \frac{q_1 q_2}{4\pi\epsilon_0 r^3} \vec{r}$. This equation describes the force that a test charge q_2 feels in vacuo because of the presence of a source charge q_1 , given a vector distance \vec{r} and length r between the charges. The permittivity of free space ϵ_0 is a fundamental constant. In principle, the classical electrostatic force on any charge can be determined by summing up the forces induced by all other charges. For charges suspended in a dielectric medium, summing up all charges is wildly impractical, and we often find it convenient to separate the charges into free and bound ones, where the free charges are treated as independent charges, which we examine individually, whereas the bound charges are incorporated into a dielectric permittivity. This distinction between free and bound charges is the essence of a macroscopic electrostatic model. Roughly speaking, free charges typically correspond to those that can move at supra-atomic length scales and on laboratory time scales, whereas bound charges move only on (sub)atomic length scales and are assumed to respond very fast. The linear dielectric model for a medium prescribes a permittivity ϵ and a relative permittivity (also called dielectric constant) ϵ_r , where $\epsilon = \epsilon_0 \epsilon_r$; rather than keeping track of the response of each proton and electron in the medium, we in this way incorporate the polarizable charge of the medium in a mean-field approximation. The effect of the medium is thus in replacing the permittivity of free space with that of the medium, and Coulomb's law for the force between two ions becomes $\vec{F} = \frac{q_1 q_2}{4\pi\epsilon r^3} \vec{r}$. This equation and the linear dielectric model describe the behavior of a medium that is instantaneously and linearly polarizable. In other words, the source and test charges, when inserted into a linear dielectric medium, each cause the bound charges around to respond instantaneously, and this response varies linearly with the magnitude of the charges. The net electrostatic effect of this polarization is *opposite* to the electrostatic force of each charge, canceling out a fraction $1 - \frac{1}{\epsilon_r}$ of the electrostatic forces. The final result is that the force is scaled by a factor of $\frac{1}{\epsilon_r}$.

A vector field can be defined, which is a property only of the location, such that the force \vec{F} that a test charge q_2 feels at this location is proportional to both the vector field and q_2 : $\vec{F} \propto q_2 \vec{E}$. Rearranging, this gives $\vec{E} = \frac{k}{q_2} \vec{F}$, where k is an arbitrary constant. Traditionally, this field has been defined with $k = 1$ and called the *electric field* generated by a source charge; this field forms a central underpinning of the microscopic model of electrostatics. In vacuo this field is given by $\vec{E} = \frac{q_1}{4\pi\epsilon_0 r^3} \vec{r}$, whereas in a linear dielectric medium this field is given by $\vec{E} = \frac{q_1}{4\pi\epsilon r^3} \vec{r}$.

In a uniform linear dielectric medium, the classical definitions of electric fields and electrical charges can be used, but their use creates an arbitrary difference between “source” and “test” charges, and as such these properties are not mathematical invariants of the system. In fact, in a system with a uniform dielectric constant these quantities can be defined such that the arbitrary distinction between source and test charges disappears. Namely, this is achieved by defining a vector field, which we term the “scaled electric field,” given by $\vec{E}_r = \frac{q_1}{4\pi\epsilon_0\sqrt{\epsilon_r}r^3}\vec{r}$, describing the effect of the charge q_1 by use of the equation $\vec{F} = \frac{q_2}{\sqrt{\epsilon_r}}\vec{E}_r$. The behavior of the charges is thus described by a “scaled electric charge” $q_r = \frac{q}{\sqrt{\epsilon_r}}$.

In a medium with uniform permittivity, two systems with the same q_r are indistinguishable and thus the scaled charge q_r is sufficient to define the system. As an example, divalent cations in a medium with a relative permittivity of 4 behave identically to monovalent cations in vacuo both in terms of their behavior as test charges (feeling a force induced by other charges), as well as source charges (inducing forces in other charges). Note that the same generality cannot be claimed for the charge q or the electric field E as traditionally defined, neither of which is sufficient to define the system. In summary, the “scaled” definitions take into account that the effect of each charge is scaled by the square root of the medium’s permittivity. The resulting “scaled” charge is the key parameter that defines the behavior of charges in a linear dielectric medium. The proper electric field to define is the “scaled” electric field, i.e., the vacuum Coulomb force normalized by the scaled charge, and the proper electrostatic potential to define is the “scaled” potential, i.e., the electrostatic potential energy normalized by the scaled charge.

The definition of permittivity comes from a delineation of which charges need to be resolved in detail and which can be folded into a mean-field approximation. The two (related) criteria that determine this distinction are the spatial range and the characteristic time of charge motion. Consider water as a prominent example. Its electronic polarization occurs at a sub-angstrom length scale and subfemtosecond time scale, whereas its nuclear (orientational) polarization occurs on supra-angstrom length scales and supra-picosecond time scales. Thus, for phenomena at characteristic inverse times smaller than ~ 100 GHz, nuclear and electronic polarizations are effectively instantaneous, and water’s electrical permittivity is approximately 80, whereas at terahertz and higher frequencies the orientational polarization is too slow to be folded into the mean field and, consequently, water’s permittivity drops as low as the high-frequency limit of 1.78 (with the refractive index of water of 1.333 being the square root of this value).²⁰

The dielectric constant is a function of thermodynamic properties (particularly temperature) as well as electric-field frequency. At room temperature and low frequency, water’s dielectric constant is near 80, whereas above 10^{11} Hz water’s dielectric constant quickly drops to approximately 2, as the nuclear polarization happens too slowly to be observed during the period of the electric-field oscillation. In simple terms, nuclear polarization dominates in the low-frequency response, while the high-frequency response is solely due to electronic polarization. The fact that dielectric constant changes with temperature evinces the linear model’s collective nature of the linear macroscopic model, and the fact that the dielectric

constant changes with frequency highlights the limitations of the instantaneous approximation inherent in the model.

Molecular simulations, which treat water molecules as movable “balls” connected with “springs” and carrying partial charges, are good at recovering effects of nuclear polarization in aqueous systems. However, the electronic polarization response is missing in standard (nonpolarizable) force fields with fixed values of partial charges. A straightforward idea to embed the whole system into a dielectric continuum with relative permittivity of 1.78 (corresponding to the electronic part of the polarization response) does not work. The reason is that water force fields are parametrized against experiments; therefore, electronic polarization effects are to some extent, but in a rather uncontrolled way, already implicitly built in. Indeed, for the vast majority of water models the relative permittivity comes up smaller than the experimental value, with the molecular dipole moment being somewhere between the gas phase and aqueous bulk values.⁸

From the above, it is clear that the distinction between atomistic and continuum is different from the distinction between microscopic and macroscopic, in the parlance of electrostatic models. Although nonpolarizable water models are defined on angstrom length scales, the fact that they do not resolve all of the electrostatic interactions means that they still fall to some extent within the category of macroscopic electrostatic models—they resolve some of the electrostatic charges, which we can call free charges, while folding other electrostatic charges, which we can call bound charges, into a catchall material property.

Given that nonpolarizable water models capture most of the low-frequency dielectric screening, we have been tempted to proceed with such molecular simulations as if they were in fact microscopic electrostatic models, providing a picture of electrolytes and biomolecules with accurate atomistic detail. The truth is that such simulations rest uncomfortably between those where a microscopic approach will be successful and those in which a macroscopic approach will be applicable.

Nonpolarizable water models are best treated as macroscopic models with an associated mean-field high-frequency dielectric constant defined by the component of charge that they do not resolve, i.e., electronic polarization. We note in passing that, on top of electronic polarization, correlated electronic fluctuations give rise to London dispersion forces, which are typically accounted for in a satisfactory way via an empirical Lennard-Jones potential. Given that nonpolarizable water molecules are effectively macroscopic, all Coulomb interactions should be calculated using the high-frequency dielectric constant of the model, i.e., 1.78 for water. However, because existing water models have partial charges defined through calculation and calibration with a microscopic approach using a dielectric constant of 1, implementing the dielectric constant properly would require that the water models themselves change. An alternative but equivalent approach is that all charges associated with both the solvent and solute molecules or ions must be reinterpreted not as electrostatic charges, but instead as scaled charges.^{9,16,17} The scaled charges represent the two-body forces correctly (by renormalizing the charge by the squared root of the models’ dielectric constant) but do not describe the actual charge of the object. In contrast, interactions described in terms of interaction potentials (e.g., the Lennard-Jones potential component of water models) are unaffected by these considerations. Most importantly, the use of an unscaled

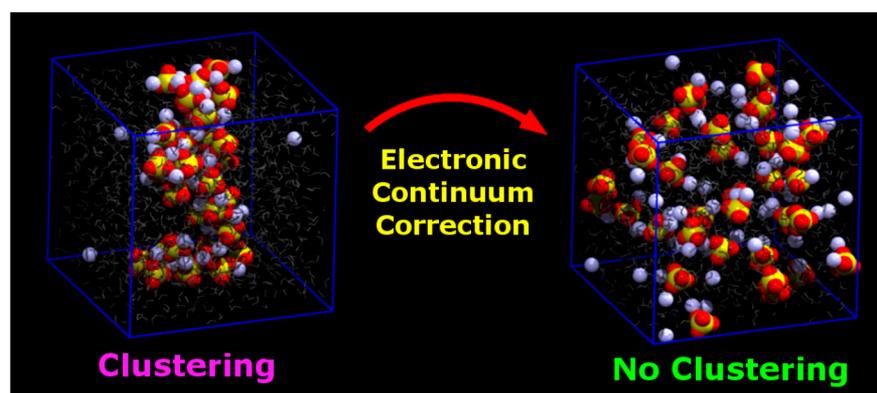


Figure 1. Qualitative effect of the electronic continuum correction on the behavior of aqueous Li_2SO_4 solutions resulting in a dramatic increase of solubility and a molecular structure in quantitative agreement with experiments. Adapted from ref 10. Copyright 2013 American Chemical Society.

integer charge for an ion in solution with a nonpolarizable water model inherently mixes microscopic and macroscopic approaches—it takes partial charges on water which explain only the free component of the charge and, therefore, only makes sense in a macroscopic framework; in addition, it tries to mix them with integral ion charges which could be correct only if the simulation were microscopic and resolved all charge.

Proper handling of Coulomb forces and dissolved ions via charge scaling is straightforward to implement, even if the accounting contradicts the majority of the simulations reported in the literature to date. However, accepting nonpolarizable water models as macroscopic models highlights a key remaining limitation. Inherent in any macroscopic electrostatic model is the accumulation of bound charge at interfaces with dissimilar dielectric constants, or in fact in any domain in which the dielectric constant is nonuniform. Nonpolarizable water models must fail in these conditions proportional to the effect of the omitted bound charge, i.e., the effect of the high-frequency dielectric constant. This is a function first of atomic density and second electron orbital size, which fortunately vary much less for biological molecules in aqueous solutions than properties related to nuclear polarization. Indeed, values of high-frequency dielectric constants of biologically relevant systems and materials are all around 2, while low-frequency values vary dramatically from 80 in water to ~ 2 of the oily interior of a phospholipid membrane. This, however, causes no problem because even nonpolarizable simulations capture the nuclear polarization explicitly and rather accurately.

On the basis of the above analysis, we conclude that current nonpolarizable water models are macroscopic and are thus incomplete without an attendant high-frequency dielectric constant designed to be used with them. We further expect that the most expedient results will be achieved by implementing this dielectric constant by treating all charges in these models, both partial charges in the water molecule and charges of any other species, e.g., ions in solution, as scaled charges, and thus ions in solutions should have charges scaled by $\frac{1}{\sqrt{1.78}} = 0.75$ as originally suggested by Leontyev and Stuchebrukhov.^{16,17,21} By comparison to neutron scattering data, we have shown that this simple accounting for the macroscopic nature of the water models leads to significant improvements in description of the structure of aqueous salt solutions.^{9,22–24} This is because the inherent imbalance between ion–ion and ion–water interactions, which stems from the microscopic–macroscopic inconsistency, is elimi-

nated when charges are scaled. In particular, for ions with high charge density which strongly electronically polarize the neighboring water molecules the improvement is dramatic (Figure 1).^{9,17,22,23,25,26} From most recent studies, we see these considerations to be very important when molecular simulations used to describe the effects of series of ions on

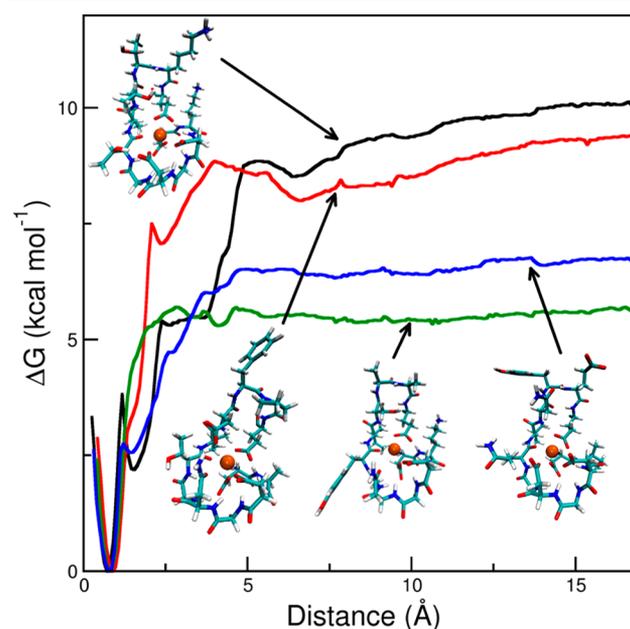


Figure 2. Binding free energy curves of Ca_2^+ at the four EF-hand pockets of the calcium binding protein calmodulin, the values of which were significantly improved with respect to experiment by introduction of charge scaling. Adapted from ref 31. Copyright 2014 American Chemical Society.

solvation and function of biomolecules (Figure 2),^{27–31} as well as interactions with charged solid surfaces.^{32,33}

Despite all the recent progress in methodology and force field development, multiple open questions remain. First, can nonpolarizable water models be used to handle interfaces between materials with different high-frequency dielectric constants, such as the air/water interface,³⁴ if these models do not take any account of the bound charge at the interface? And how can one account for bound charge separately? Second, how shall one properly scale partial charges of charged

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or polar groups of biomolecular solutes, such as peptides or proteins, nucleic acids, or membrane phospholipids?^{16,28,29} Force fields for these molecules have been to varying degrees parametrized against experimental data. Therefore, depending on how exactly these force fields were generated, the degree to which the partial charges of these models already account for the macroscopic nature of the electrostatic model needs to be considered in order not to “overscale” the charges.

In conclusion, nonpolarizable water models are atomistic but macroscopic, have a dielectric constant associated with them, are naturally implemented with scaled charges, and thus cannot be expected to properly handle gradients or discontinuities of high-frequency permittivity. Luckily, for biological simulations of proteins, lipids, nucleic acids, or polysaccharides, high-frequency permittivities of biomolecules are not much different from that of water; therefore, implementation of water models viewed through the lens of macroscopic electrostatics is justified and has led to a number of recent successes. Nevertheless, implementation of scaled charges based on existing interaction potentials for these biomolecules must be done with extreme caution to avoid introducing contradictions between microscopic and macroscopic modeling.

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