# The Dielectric Constant: Reconciling Simulation and Experiment

Miguel Jorge[1, a)] and Leo Lue[1]

*Department of Chemical and Process Engineering, University of Strathclyde*

*James Weir Building, 75 Montrose Street, Glasgow G1 1XJ,*

*United Kingdom*

(Dated: 3 February 2019)

In this paper, we present a simple correction scheme to improve predictions of dielectric constants by classical non-polarisable models. This scheme takes into account electronic polarisation effects, through the experimental refractive index of the liquid, and a possible mismatch between the potential energy surface (PES) and the dipole moment surface (DMS). We have described the latter effect by an empirical scaling factor on the point charges, the value of which was determined by fitting the dielectric constant of methanol. Application of the same scaling factor to existing benchmark datasets, comprising four different models and a wide range of compounds, led to remarkable improvements in the quality of the predictions. In particular, the observed systematic underestimation of the dielectric constant was eliminated by accounting for the two missing terms in standard models. We propose that this correction term be included in future development and validation efforts of classical non-polarisable models.

---

a)Electronic mail: miguel.jorge@strath.ac.uk

## I. INTRODUCTION

The static dielectric constant, or relative permittivity, measures the response of a material to an applied electric field and is, therefore, an important property in many electronic applications. It is also a generally good measure of the polarity of a liquid and is, therefore, used to build solvent polarity scales[1]. The ability to predict the dielectric constant of a solvent is thus an essential part of assessing its suitability for particular applications. Conversely, a poor representation of this property in a model may have serious consequences in predictions of solvation and transfer free energies. Despite its importance, the dielectric constant $\varepsilon_r$ is notoriously difficult to predict accurately using classical non-polarizable molecular models[2]. This is mainly for two reasons, one technical and one conceptual. To understand this, let us first introduce the equation that is commonly used to calculate $\varepsilon_r$ from Monte Carlo (MC) or molecular dynamics (MD) simulations:

$$\varepsilon_r = 1 + \frac{\langle \mathbf{M}^2 \rangle - \langle \mathbf{M} \rangle^2}{3\varepsilon_0 k_B T \langle V \rangle} \tag{1}$$

Equation (1) is the so-called dipole fluctuation formula[3], where $\varepsilon_0$ is the vacuum permittivity, $V$ is the volume, $T$ is the temperature, $k_B$ is Boltzmann's constant, and $\mathbf{M}$ is the total dipole moment of the system (in a simulation, this corresponds to the entire simulation box). The angular brackets denote, as usual, an ensemble-averaged property, so in practice, the dielectric constant depends on averaging the fluctuations in the total dipole moment. The technical reason behind the difficulties in predicting $\varepsilon_r$ is that the second term on the right-hand side of equation (1) takes quite a long time to converge, particularly for solvents with a high dielectric constant, and even more so for hydrogen-bonding fluids like water[4]. This means that early attempts to predict $\varepsilon_r$ most likely suffered from insufficient conversion due to computational limitations. Currently, however, improvements in computer hardware and simulation algorithms mean that atomistic simulations of 100 ns or more are relatively easily accessible, and so converged values of $\varepsilon_r$ can be obtained.

Having largely eliminated (or, at least, properly considered) the convergence problem, the simulation community has seen a recent resurgence in attempts to predict the dielectric constant of liquids, with several comprehensive benchmark studies being published in the last few years[5–7]. It is perhaps surprising that predictions of the dielectric constant of common solvents using long simulations with fixed-charge force fields still deviate from experiment by large amounts (sometimes in excess of 100%). More importantly, these deviations seem to be systematic, in that the models generally tend to strongly underpredict $\varepsilon_r$. Following on from this realization, several recent studies have attempted to recalibrate the parameters of fixed-charge force fields by fitting (among other properties) the dielectric constant of the liquid phase. For instance, two new fixed-charge water models have been developed with the specific aim of reproducing its dielectric constant, H2ODC[2] and TIP4P/$\varepsilon$[8]. Moreover, the dielectric constant was included as one of the fitting targets in two other recently developed water

models[9,10]. Fennell et al.[2] also developed new models for chlorinated methane solvents by tuning the parameters so that their dielectric constants were accurately reproduced. Interestingly, in the case of $CCl_4$, this required the introduction of an artificial permanent dipole in the model, which therefore rendered the molecule asymmetric. In a later study, Fennell et al.[5] refitted the parameters of hydroxyl groups in the Generalized Amber Force Field (GAFF)[11] so that the dielectric constant, the density $\rho$, and the enthalpy of vaporization $\Delta H_{\text{vap}}$ of methanol were accurately reproduced. Those parameters were then used to predict $\varepsilon_r$ of 40 other molecules containing hydroxyl groups, showing a significant improvement over predictions of the original GAFF model combined with the standard AM1-BCC[12] charges. It is yet unclear to which extent these parameter recalibrations sacrifice agreement with other liquid properties that were not part of the fitting procedure.

The second reason for the difficulties experienced in predicting $\varepsilon_r$ using classical molecular models is precisely related to the classical approximation itself. This was recently discussed in detail by Vega[13], accompanied by mathematical derivations of the governing equations, and therefore we will focus here on the most important practical consequences of this approximation. The first consequence is that equation (1) has a missing term — a term that depends on the average gradient of the dipole moment with the applied electric field. This term accounts for the change in the polarization of each instantaneous configuration of the system when an external field is applied. In other words, it depends only on fluctuations of the electron cloud of each atom, and not on the positions of the atomic nuclei, leading some authors to identify it with a "purely electronic" component of polarization[14]. When added together with unity, it is denoted by $\varepsilon_\infty$, which is called the high-frequency dielectric constant, leading to a more precise equation for $\varepsilon_r$[15]:

$$\varepsilon_r = \varepsilon_\infty + \frac{\langle \mathbf{M}^2 \rangle - \langle \mathbf{M} \rangle^2}{3\varepsilon_0 k_B T \langle V \rangle} \tag{2}$$

The high-frequency dielectric constant is so called because it corresponds to the value attained by $\varepsilon_r$ when the frequency of an applied electric field is so high that the atomic nuclei have no time to respond — in such a case, the dielectric constant corresponds only to the motion of the electrons in response to the field. A common way to estimate $\varepsilon_\infty$ is to relate it to the refractive index of the medium, measured at the sodium D-line frequency $n_D$, via

$$\varepsilon_\infty = n_D^2, \tag{3}$$

Therefore, the high-frequency dielectric constant is, at least in principle, an experimentally accessible property.

The problem that this poses to calculations of $\varepsilon_r$ from classical non-polarizable models is that in the latter, in contrast with fully quantum mechanical treatments, electrons are not explicitly represented. As such, one cannot hope to be able to describe the electronic contribution to the dielectric

constant under this approximation. With a few exceptions[6,13,14,16], this problem has been largely over-looked in the literature, probably because for even mildly polar fluids the magnitude of the electronic contribution represents only a small fraction of the total dielectric constant. For example, it is less than 1% for water and about 3.5% for ethanol (based on experimental values of the total and the high-frequency dielectric constants of those liquids). These deviations are well within the statistical error of the calculations of $\varepsilon_r$ in molecular simulations, and much smaller than the uncertainty due to the reliability of molecular models employed. However, the dielectric constants of non-polar and weakly polar fluids are much lower, and the impact of $\varepsilon_\infty$ is therefore much larger — for dimethyl ether it is 12%, for chloroform it is 23%, and for cyclohexane it is more than 50%. This leads to the well documented inability of classical non-polarizable force-fields to accurately predict the dielectric constant of alkanes and other non-polar liquids[14,17].

There is another, perhaps less evident, consequence of the classical approximation in the calculation of the dielectric constant of liquids, which was also quite cogently discussed by Vega in his review[13]. It arises from the fact that classical models of liquids make use of parameters that are designed to describe as well as possible the potential energy surface (PES) of the pure fluid. They are normally obtained by fitting against energy profiles obtained from quantum mechanical calculations (e.g., for bonded potential terms) and/or by tuning to match experimental properties that depend directly on the PES (e.g., density and enthalpy of vaporization). The dielectric constant, however, is an exception among physical properties of fluids, in that it depends strongly on the dipole moment surface (DMS) as well as on the PES[13,18], as evidenced in equations (1) and (2). While the PES is obtained by calculating the energy as a function of nuclear configurations, the DMS is obtained by calculating the dipole moment as a function of nuclei positions. Both can be obtained directly from a quantum mechanical treatment of the system[18–20], but at the classical level one requires approximations to compute them — i.e., the functional form and parameters of the force-field. Because "standard" force-field parameters are tuned to reproduce the PES, they may not represent the DMS in the best possible way. This is particularly pertinent for point charges, due to their inherent importance in the calculation of the dipole moment.

A corollary of the above realization is that one should not expect a classical model that is optimized to describe thermodynamic properties of a pure fluid to also be able to reproduce its static dielectric constant. Although one cannot rule out the existence of a set of parameters that is able to simultaneously reproduce the PES and the DMS of a particular fluid, one should equally not take this for granted. In fact, the failure of all existing non-polarizable models of water to reproduce the dielectric constant of ice seems to support the idea that no such set of parameters indeed exists[13]. If one abandons the assumption that the PES and the DMS are both accurately described by models fitted to the PES alone (the "dogma", as Vega calls it), this opens the door to further addressing the

shortcomings of classical models.

A relatively simple approach is to adopt a set of scaled charges when dealing with properties that depend on the DMS, while using the standard unscaled charges when calculating properties that depend on the PES alone. This approach has been used successfully in only a few studies so far, focusing on specific molecules[13,14,21–24]. A physical interpretation of the need for applying a scaling factor to the charges was provided by Leontyev and Stuchebrukhov[14] — it represents the screening of the molecular charges (or multipole moments) by the dielectric medium induced by the electron clouds of the liquid. This approach makes it possible to simply correct DMS-dependent properties (such as the dielectric constant or the dipole moment) a posteriori, instead of needing to rerun the simulations. The underlying assumption, of course, is that the configurational space is well sampled by the "standard" model based on the PES, but this is likely to be the case in all but the most complicated systems. Furthermore, this also assumes that the other force-field parameters (most notably the repulsion/dispersion parameters) are equally suitable to describe the PES and the DMS. Again, due to the dominance of electrostatic interactions in calculation of the DMS[18–20], this assumption is likely to be reasonable.

Using this approach, one would run an MD or MC simulation with the standard set of point charges (let's call them $q_{\mathrm{PES}}$), sample configurational space, and then scale the obtained values of the computed DMS-dependent properties. So if the scaling factor operating on the charges is defined as:

$$k = \frac{q_{\mathrm{DMS}}}{q_{\mathrm{PES}}} \tag{4}$$

where $q_{\mathrm{DMS}}$ are the scaled charges that represent the DMS, then the dipole moment is simply:

$$\mathbf{M}_{\mathrm{DMS}} = k\mathbf{M}_{\mathrm{PES}} \tag{5}$$

If the dielectric constant is calculated from a classical simulation, as is usually done using equation (1), while the actual (i.e., quantum) dielectric constant is given by equation (3), then we obtain the following scaling function for $\varepsilon_r$:

$$\varepsilon_{r,\mathrm{DMS}} = \varepsilon_\infty + k^2(\varepsilon_{r,\mathrm{PES}} - 1) \tag{6}$$

This relation was also presented in the review by Vega[13], although the electronic polarization contribution (i.e. the $\varepsilon_\infty$ term) was neglected. Because this term has a nearly negligible effect on the dielectric constant of water, the comparison presented by Vega in his Figure 2 is still valid, however.

Equation (6) provides a simple and straightforward way to correct the dielectric constant obtained from a classical molecular simulation using standard force-fields, to make it closer to a hypothetical quantum-mechanically computed dielectric constant (we recall that accurately computing the dielectric constant directly from quantum mechanical calculations is currently prohibitive due to the need

to sample configurational space during long time scales, as discussed above). It incorporates the purely electronic component of polarization, via $\varepsilon_\infty$, and accounts for the distinct nature of the PES and the DMS, through the application of the scaling factor $k$. But while $\varepsilon_\infty$ can be estimated from experimental data, the question remains of how to determine the value of $k$. Here, several options are possible. An obvious answer is to empirically adjust it so that the best possible agreement is obtained between simulated and experimental dielectric constants. But if one adopts a different scaling factor for each fluid of interest, as is certainly possible, then the predictive nature of the model(s) is lost — any model, even a very poor one, would be able to describe the dielectric constant provided the appropriate value of $k$ was chosen. Ideally, one may wish to estimate $k$ from first principles, making use of experimental information. Unfortunately, this is not as easy as it may sound. Calculating $k$ from equation (4) is not viable because point charges are not experimental (or quantum mechanical) observables, except maybe for ionic fluids. A more reasonable option is perhaps to estimate it from the ratio of the first non-zero multipole moment of the molecule of interest. For a dipolar fluid (like water), this would be expressed by:

$$k = \frac{\mu_{\mathrm{DMS}}}{\mu_{\mathrm{PES}}} \tag{7}$$

where $\mu_{\mathrm{DMS}}$ is the dipole moment of an individual molecule (distinct from $\mathbf{M}$, the total dipole moment of the system) in the actual liquid phase, i.e. the "experimental" molecular dipole moment, and $\varepsilon_{\mathrm{PES}}$ is the dipole moment calculated from the point charges optimized to reproduce the PES of the liquid, i.e. the "model" dipole moment. What remains is to measure the molecular dipole moment experimentally, or to calculate it from a high-level quantum mechanical calculation. Both of these tasks are extremely challenging, although progress has been made over the years for certain specific cases such as liquid water[25–32].

The uncertainty in finding the value of $k$ is best illustrated with a recent example. Vega[13] estimated a scaling factor of $1.15$ for liquid water based on equation (7). He took $\mu_{\mathrm{PES}}$ as the dipole moment of the TIP4P/2005 water model ($2.305\,\mathrm{D}$) and used a value of $2.66\,\mathrm{D}$ for $\mu_{\mathrm{DMS}}$ based on previous estimates for the "real" dipole moment of liquid water[25]. Application of the above scaling led to excellent agreement between corrected and experimental dielectric constants of water over a wide temperature range. On the other hand, Leontyev and Stuchebrukhov[14,22] developed a theoretical framework (called MDEC, standing for Molecular Dynamics with Electrostatic Continuum) to implicitly account for polarization effects in non-polarizable classical models. Under this framework, the scaling factor is assumed, based on an approximate treatment of electrostatic polarization effects, to be equal to:

$$k = \sqrt{\varepsilon_\infty} \tag{8}$$

Substituting in equation (6) leads to a simple multiplicative correction to the static dielectric constant:

$$\varepsilon_{r,\mathrm{DMS}} = \varepsilon_\infty \varepsilon_{r,\mathrm{PES}} \qquad (9)$$

Application of this correction led to good agreement for the dielectric constant of low-polarity fluids[14,22]. Interestingly, they also supported their choice of scaling factor by using equation (7), but now invoking a different set of quantum mechanical studies that estimate $\mu_{\mathrm{DMS}}$ of water as being closer to a value of $3.0\,\mathrm{D}$[27–29].

The main hypothesis of the present paper is that there exists, at best, a universal value of the scaling factor, and, at worst, an optimal scaling factor for each class of liquids (e.g., alcohols, alkanes, ethers, etc.). If the former statement is correct, then an empirical determination of the scaling factor for a set of liquids (or even a single liquid) would enable one to predict the dielectric constant of any other liquid based on classical non-polarizable models that are optimized to reproduce the PES of those liquids. Importantly, this would also enable us to predict the experimental dipole moment of the liquid, through manipulation of equation (7). If, instead, the latter statement is shown to be true, then a separate scaling factor would be required for each class of liquid. Although this would not be an ideal scenario, it would still allow models to be predictive within each type of liquid (e.g., tuning the value of $k$ for, say, ethanol, would allow the dielectric constant of all alcohols to be predicted). In the following, we test the validity of these two related hypotheses by analyzing existing data from a series of recent studies[5–7,17,33–36] that report predictions of the dielectric constant. Those studies were chosen because they address relatively large datasets spanning a range of different fluids and because the simulations were generally long enough to avoid the convergence problem discussed above. Our aim is to compare the direct predictions reported in those works, based on the application of equation (1), with corrected values of $\varepsilon_r$ obtained from equation (6) using several possibilities for the value of the scaling parameter $k$. We show that application of a uniform scaling factor is able to largely eliminate systematic deviations between simulated and experimental dielectric constants for a wide range of compounds and using different molecular models.

## II. METHODOLOGY

Our first step was to gather existing literature data on predictions of the dielectric constant of liquids using classical non-polarizable models. We restricted ourselves to benchmark studies that covered a relatively large set of compounds. Fennell et al.[5] carried out a systematic simulation study of dielectric constants of 41 molecules containing hydroxyl functional groups. They tested the suitability of the Generalized Amber Force Field (GAFF)[11], combined with AM1-BCC point charges[12], to predict the dielectric constant of those liquids. They also tested a re-parameterized version of the

model specifically designed to reproduce the density and dielectric constant of liquid methanol. We will henceforth refer to their predictions using the original GAFF/AM1-BCC model as the "Fennell data set".

The second study we considered was that of Beauchamp et al.[6], who also applied the GAFF model with AM1-BCC charges over 45 different compounds. In contrast with the study of Fennell et al., however, there is a much wider variety of functional groups in the Beauchamp data set. They also took into account dielectric constant data at several different temperatures, whereas all the other data sets focused mostly on ambient temperature. We have considered the raw simulation data from this work, i.e. dielectric constants, calculated directly from MD without including those authors' estimates of the electronic polarization correction[6] (see below). However, we have excluded their simulations of water, as they lead to exaggerated deviations from experimental values — this is due, as discussed by the authors[6], to the fact that the GAFF/AM1-BCC is not an appropriate model for this molecule. This leaves us with a total of 235 data points over 44 different compounds.

We have also collected the dielectric constant data from Caleman et al.[7], as part of a wider benchmark study of thermodynamic properties of fluids. Their data set covered a total of 124 compounds, most of them at 20 or 25°C, and tested two different models: GAFF combined with RESP charges[37], and OPLS-AA[38]. In total, their GAFF/RESP data set contained 163 data points, while their OPLS-AA set contained 176 data points, and we considered these as separate data sets called "Caleman GAFF" and "Caleman OPLS", respectively. The results of their benchmark calculations are collected and updated in a useful web-based resource (`http://virtualchemistry.org`).

Finally, we have compiled data published in several papers by the group of MacKerell[17,33–36]. The main purpose of these studies was to develop new polarizable models for liquids, but in the process the authors also assessed the performance of the CHARMM non-polarizable force field[39]. Overall, we collected data for 25 different compounds, again mostly at room temperature, and have named this the "MacKerell data set".

Apart from the individual data sets described above, we have also generated an "overall" data set by simply joining all of them together. Using this complete set, we then classified each molecule according to their functionality, in the following groups: (i) hydrocarbons (both aliphatic and aromatic); (ii) halogenated hydrocarbons; (iii) ethers (including heterocycles containing oxygen); (iv) alcohols; (v) ketones and aldehydes; vi) esters, carbonates and carboxylic acids; (vii) alkyl amines; (viii) nitrogen-containing aromatics (including both heterocycles and arylamines); (ix) nitro-containing compounds; (x) nitriles; (xi) amides; (xii) alkanolamines; (xiii) sulfur-containing compounds; and (xiv) phosphates. The aim of this classification is to assess whether the value of the scaling factor should depend on the type of functional group(s) present in the molecule of interest.

We proceeded to apply equation (6) to each of the data sets described above, using different options

for the scaling factor $k$, as discussed in the results section. To estimate the high-frequency dielectric constant, we collected experimental data from the CRC Handbook[40] for the index of refraction of all the compounds considered in the data sets and applied equation (3). This essentially implies assuming that the electronic polarization response is independent of frequency, since we are estimating $\varepsilon_\infty$ at the frequency of the sodium D-line but applying it as an additive polarization correction to the static (i.e. zero frequency) dielectric constant. Another possibility that avoids this particular assumption is to relate $\varepsilon_\infty$ to the molecular dipole polarizability $\alpha$, but this requires assumptions of a different nature. Under the approximation of a point dipolar fluid with uniformly distributed polarizability, this leads to[41]:

$$\varepsilon_\infty = 1 + \frac{\rho\alpha}{\varepsilon_0} \tag{10}$$

where $\rho$ is the number density of the fluid. Alternatively, if we assume a dipole inside a spherical cavity surrounded by a uniform dielectric continuum, the Clausius-Mossotti equation[41] can be rearranged for $\varepsilon_\infty$, as follows:

$$\varepsilon_\infty = 1 + \frac{\rho\alpha}{\varepsilon_0 - \rho\alpha/3}. \tag{11}$$

Equation (10) was applied by Beauchamp et al.[6] and by Horn et al.[16] to estimate the purely electronic contribution to the dielectric constant. In both cases, the experimental liquid number density was used, but Beauchamp et al. applied a simple empirical expression to estimate the molecular polarizability from individual atomic contributions[42], while Horn et al. used the experimental value of $\alpha$ for water. Park et al.[43] recently combined equations (3) and (11) to estimate the index of refraction of several organic compounds. They computed the liquid density from classical molecular dynamics simulations, while the polarizability was computed from quantum density functional theory (DFT). The latter calculations were carried out for isolated molecules in the gas phase, under the assumption that this quantity does not change significantly when the molecule is transferred from a gas to a liquid environment. Despite all the approximations involved, very good agreement was obtained with experimental values of $n_D$. This gives further confidence to our chosen approach of using the experimental refractive index to estimate $\varepsilon_\infty$. It is important to note that any errors arising from the application of equation (3) will be most apparent for low-dielectric fluids (e.g. alkanes), whereas they will be practically negligible for polar fluids like water or alcohols; this is because, as discussed above, the relative electronic contributions to the dielectric constant of these fluids are very low.

To quantify overall deviations between simulation and experiment for each data set and with different choices of scaling parameter, we computed several aggregate metrics. The root-mean-square deviation (RMSD) is generally used as an indicator of the goodness of fit between simulation and

experiment, and was calculated as:

$$\text{RMSD} = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\varepsilon_{\text{SIM}} - \varepsilon_{\text{EXP}})^2}, \tag{12}$$

where $N$ is the total number of points in the analyzed data set. Because it considers the square of the deviation, the RMSD is not particularly suitable to detect systematic deviations between simulation and experiment. For that purpose, we have also computed the mean signed deviation (MSD), as follows:

$$\text{MSD} = \frac{1}{N} \sum_{i=1}^{N} (\varepsilon_{\text{SIM}} - \varepsilon_{\text{EXP}}) \tag{13}$$

Thus defined, a large positive MSD will mean that simulations are systematically overestimating experiment, and vice-versa. Finally, we report also the mean relative deviation (MRD):

$$\text{MRD} = \frac{1}{N} \sum_{i=1}^{N} \frac{|\varepsilon_{\text{SIM}} - \varepsilon_{\text{EXP}}|}{\varepsilon_{\text{EXP}}} \times 100 \tag{14}$$

Compared to the RMSD, the MRD gives more importance to liquids with a lower dielectric constant, so it is useful in assessing the impact of the correction schemes on the lower end of the spectrum. All the data analyzed in the present paper are provided in spreadsheet format as Supporting Information.

## III. RESULTS AND DISCUSSION

We first examine the Fennell data set, which focused only on alcohol-based molecules. In Figure 1a, we compare their results obtained with the original GAFF/AM1-BCC model against experimental data (this is similar to Figure 4a of their paper[5]). It can be readily observed, as discussed by the authors, that the variation is approximately linear, but with a slope significantly below unity. In other words, the model systematically underestimates the dielectric constant of the real liquids. Figure 1b shows the same comparison after applying equation (6) with $k = 1$. This corresponds to including only the effect of the electronic polarization of the liquid phase (i.e., through $\varepsilon_\infty$), but without accounting for the differences between the PES and the DMS (i.e., assuming that the same set of charges applies for both surfaces). As we can see, there is an improvement for molecules with low dielectric constants, namely 2-methylbutan-2-ol, 2,3-dimethylphenol and 3-chlorophenol (the three left-most points in Figures 1a and 1b). However, for liquids with higher dielectric constants, the improvements are marginal. This is because, as discussed above, the importance of the additive high-frequency dielectric term decreases as $\varepsilon_r$ increases. Accounting for the quantum effects of electronic polarization in classical predictions of the dielectric constant is therefore necessary but not sufficient to bring the results into agreement with experiment.
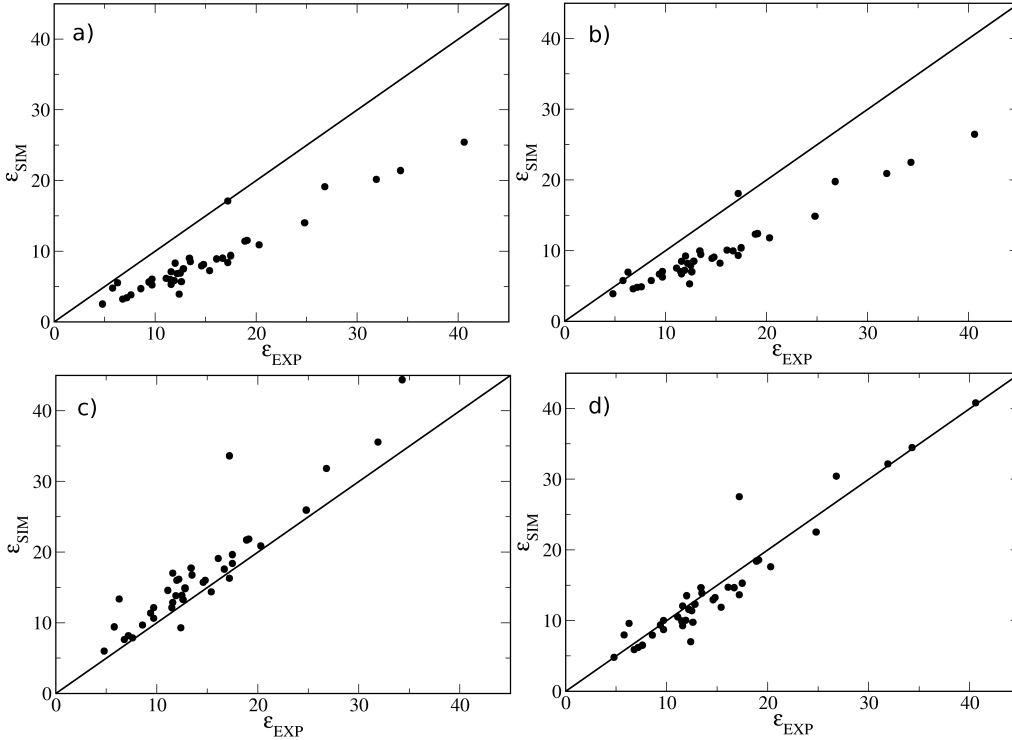
FIG. 1. Comparison between simulated and experimental dielectric constants for the Fennell data set using: (a) the original GAFF/AM1-BCC model[5]; (b) additive correction only (i.e., $k = 1.00$); (c) full correction with $k = \sqrt{\varepsilon_\infty}$; and (d) full correction with $k = 1.26$.

In order to account for the second effect, the discrepancy between the PES and the DMS, one must apply a scaling factor larger than unity. As a first approach, we found the value of $k$ such that the experimental dielectric constant of methanol was perfectly described — i.e., we applied equation (6) in reverse to solve for $k$ by taking $\varepsilon_{r,PES} = 20.13\,D$ and $\varepsilon_{r,DMS} = 31.9\,D$, which led to a value of $k = 1.26$. Figure 1d shows the results of applying this correction to the entire data set. The improvement is remarkable, with the data now lying generally close to the $x = y$ diagonal. The only major outlier is 2-methoxyethanol, which was quite closely described by the original model and whose agreement therefore significantly worsens by applying the correction.

We have also calculated the value of $k$ that leads to the best possible agreement with experiment – i.e., we applied equation (6) to the entire data set with $k$ as a fitting parameter and minimized the RMSD between simulation and experiment. This procedure yielded a value of $k = 1.26$, in exact agreement with the above estimate based on matching methanol alone. Although this precise agreement is likely fortuitous, it does reinforce the consistency of our chosen approach.

Finally, it is also useful to compare the results that would be obtained if one were to apply the MDEC formulation of Leontyev and Stuchebrukhov[14], i.e. assuming that $k$ obeys equation (8). In this case, the scaling factor will be slightly different for each liquid, reflecting the corresponding

11

changes in the high-frequency dielectric constant. The results of such an approach are shown in Figure 1c. Although there is still an improvement over the original model, it is clear that the correction leads to a systematic overestimation of experimental data. In other words, the MDEC correction is overpolarizing the model relative to the real liquid state behavior. In this context, it is worth remarking that Leontyev and Stuchebrukhov themselves recognized that the scaling factor for complex molecular liquids is unlikely to always obey equation (8), since this is based on a simple Born model of a point charge inside a spherical cavity. In fact, in later papers[22,23], they proposed alternative scaling factors for charge-charge, charge-dipole and dipole-dipole interactions. Using our estimate of $\varepsilon_\infty$ for methanol in the different expressions provided by Leontyev and Stuchebrukhov yields scaling factors between $1.14$ and $1.33$. Our optimal value of $k = 1.26$ is close to the middle of this range.

TABLE I. Deviations between simulation and experiment for the Fennell data set[5]. RMSD = root mean squared deviation; MSD = mean signed deviation; MRD = mean relative deviation on a percentage basis.

| Model | RMSD | MSD | MRD (%) |
|---|---|---|---|
| GAFF/AM1-BCC | 6.90 | −6.18 | 42.1 |
| GAFF/AM1-BCC DC | 3.72 | −2.27 | 23.3 |
| GAFF/$k = 1.00$ | 5.99 | −5.09 | 33.5 |
| GAFF/$k = \sqrt{\varepsilon_\infty}$ | 4.37 | 2.74 | 21.7 |
| GAFF/$k = 1.26$ | 2.49 | −0.55 | 13.2 |

Table I collects average statistics for the Fennell data set obtained with each of the approaches described above. This confirms our visual assessment that consideration of the electronic polarization effects alone leads to only a marginal overall improvement (slightly lower RMSD and MSD), but this effect is more significant for lower dielectric liquids (marked drop in the MRD). Table I also confirms that application of equation (8) leads to an overestimation of experimental data (the MSD is now positive). When the optimal value of $k$ is used, all three measures of deviation significantly decrease. Remarkably, the MSD is now quite close to zero, indicating the near lack of systematic deviations in the corrected data.

We also show in Table I the statistical analysis of the improved molecular model for alcohols proposed by Fennell et al.[5]. They adjusted the original GAFF parameters for methanol, so that the model would simultaneously match its experimental dielectric constant, density, and enthalpy of vaporization. This involved changes not only to the Lennard-Jones parameters of the oxygen atom but also, more significantly, to the point charges of the model. The latter were scaled by a factor of $\approx 1.21$ to enhance the polarization relative to the original AM1-BCC charges. The same scaling factor and Lennard-Jones parameters were then applied to the hydroxyl groups of all the other molecules of the

set, with charges on adjacent atoms slightly adjusted to maintain overall charge neutrality. The results obtained with the modified model[5] are plotted in Figure S1, and show a very significant improvement in predicted dielectric constants. However, the enhancement is more significant for high-dielectric fluids, with several less polar fluids still showing a significant underestimation. In quantitative terms, the modified GAFF model yields a significant drop in all measures of deviation relative to the original model (compare the top two rows of Table I), although the improvement obtained by applying equation (6) is greater. In particular, the MSD for the modified GAFF model is still significantly negative, indicating a degree of systematic underestimation of the experimental data. In this context, it is interesting to see that the charge scaling factor applied by Fennell et al. is quite close to, but lower than, our optimal scaling factor of $1.26$.

Another relevant study in this context is that of Gonzalez-Salgado and Vega[24], who recently parameterised a new united atom (UA) model for methanol by fitting to a large set of thermodynamic properties, and compared its performance with several other UA models. As expected, all models significantly underestimated the dielectric constant of methanol. However, quite good agreement with experiment for four of the studied models was obtained by applying equations (6) and (7) to the MD results. Interestingly, the scaling factors obtained from equation (7) for those models, using a recent ab initio estimate for the dipole moment of liquid methanol[44], were between $1.19$ and $1.23$, in reasonable agreement with the value of $1.26$ obtained in the present work.

Figure 1d shows that the scaling factor fitted to match the dielectric constant of methanol is transferable to other molecules containing hydroxyl groups within the same data set. In the following, we consider other data sets that include a much wider variety of molecule types. We begin with the data set of Beauchamp et al.[6], who also applied the GAFF model with AM1-BCC charges. Figure 2a shows once again a significant systematic underestimation of experimental dielectric constants by the original model. Similarly to the Fennell data set, accounting only for the electronic polarization contribution improves predictions at the lower end of the spectrum but retains the strong overall systematic underestimation, while applying the MDEC approach leads to a systematic overestimation (see Figure S2 and Table S1). Application of equation (6) with the value of $k$ determined above for alcohols leads to a remarkable improvement (Figure 2b). Although the spread of values is quite large due to the much greater diversity of molecule types in this data set, the MSD is only $-0.98$, compared to $-7.21$ for the original model (Table S1), which indicates the relative absence of systematic deviations between simulations and experiment when the correction is applied. This can be even further reduced by using $k$ as a fitting parameter — in this case, the MSD goes down to $-0.30$ (Table S1). Notably, the optimal value of the scaling factor is $1.29$, very close to the value of $1.26$ determined above for methanol. This probably reflects the existence of a large number of hydroxyl-containing groups in the Beauchamp data set (red points in Figure 2).
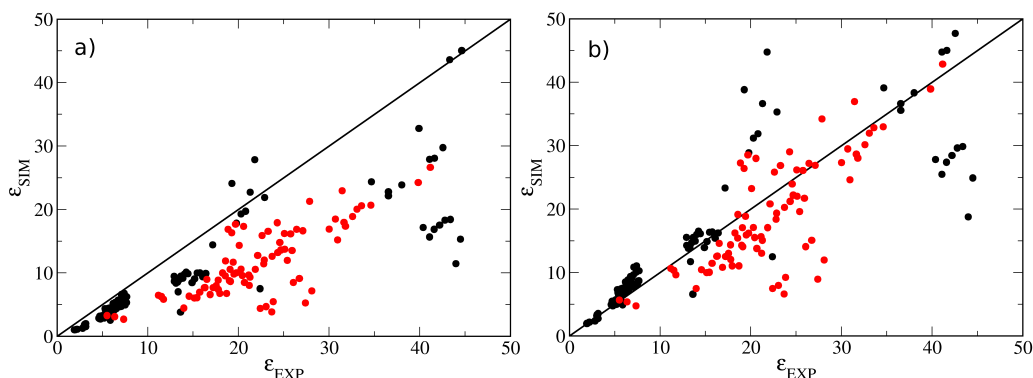
FIG. 2. Comparison between simulated and experimental dielectric constants for the Beauchamp data set using: (a) the original GAFF/AM1-BCC model[6]; and (b) correction with $k = 1.26$. Molecules with hydroxyl functional groups are shown as red points. For clarity, some molecules with very high values of $\varepsilon_r$ were omitted from these plots, but a comparison for the complete data set is shown in Figure S3.

Although it is outside the scope of this work to perform a detailed analysis of each model, it is worth noting some particular cases in the Beauchamp data set. The largest outliers from the original predictions are the amide molecules. These have very high dielectric constants (above $100$) that are severely underpredicted by the original model (see the rightmost points in Figure S3a). The correction improves the predictions, but it still leads to significantly underestimated values (Figure S3c). The other major outliers are the two sulfur-containing compounds, dimethyl sulfoxide (4 data points) and sulfolane (8 data points), both of which have experimental dielectric constants around $45$. Interestingly, while the former molecule is very seriously overestimated, the latter is significantly underestimated. This hints at a possible major deficiency of the GAFF parameters for sulfur-containing compounds. We will return to this point later in the paper.

Figures 3a and 3c show the original predictions for the simulations of Caleman et al.[7] using the GAFF/RESP and OPLS-AA models, respectively, while Figures 3b and 3d show the respective comparisons after our correction with $k = 1.26$ is applied. The same trends noted above are observed, with both original models leading to a strong systematic underestimation of $\varepsilon_r$, which is virtually eliminated when the correction is applied (see also Tables S2 and S3 for collected statistics). Also, applying only the electronic polarization correction expectedly underestimates results for polar molecules, while applying the MDEC correction leads to a systematic overestimation (see Figures S4 and S6). Finally, it is worth emphasizing the great degree of scatter in the quality of the predictions for these two data sets, even after the correction is applied, which suggests that there is much room for improvement in current non-polarizable molecular models when it comes to predicting the dielectric constant.

If $k$ is used as a fitting parameter over each full data set, values of $1.15$ and $1.17$ for GAFF/RESP
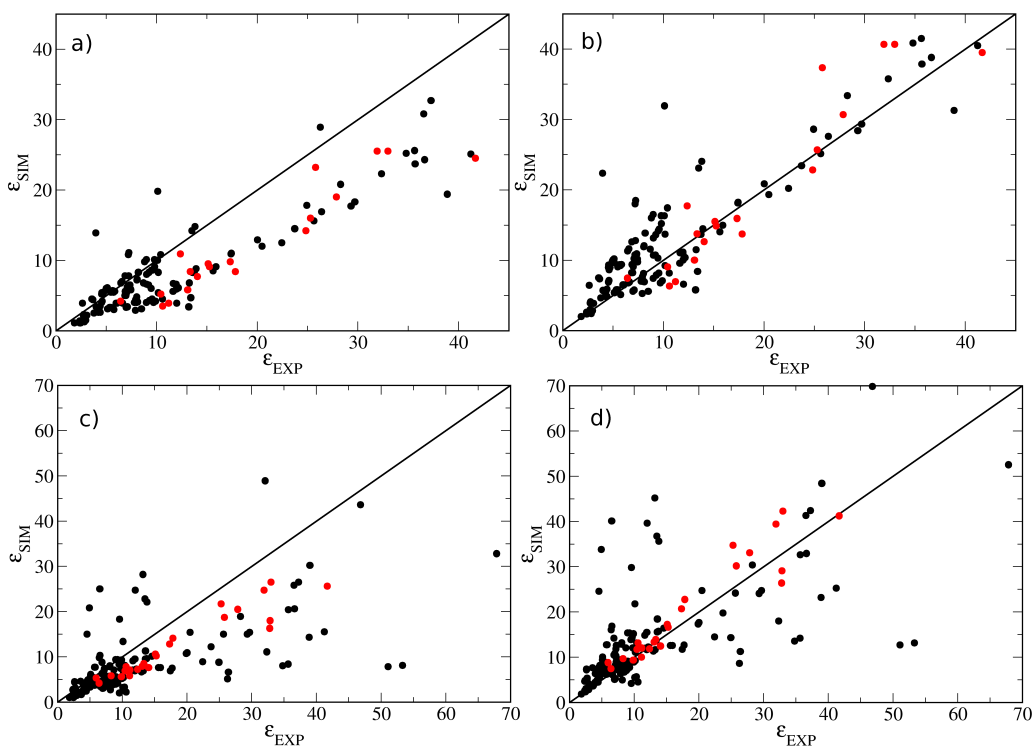
FIG. 3. Comparison between simulated and experimental dielectric constants for the Caleman data sets using: (a) the original GAFF/RESP model[7]; (b) corrected GAFF/RESP with $k = 1.26$; (c) the original OPLS-AA[7]; and (d) corrected OPLS-AA with $k = 1.26$. Molecules with hydroxyl functional groups are shown as red points. For clarity, some molecules with very high values of $\varepsilon_r$ were omitted from the GAFF/RESP plots, but a comparison for the complete data set is shown in Figure S5.

and OPLS-AA, respectively, are obtained. These values are close to, but somewhat lower than the methanol value of 1.26 determined above. This is despite the fact that different values for the point charges are used — the scaling factor was determined from simulations of a model with AM1-BCC charges, while Caleman et al. applied RESP charges or the largely empirical OPLS-AA charges in their simulations. As such, there is no a priori requirement for the scaling factor to be identical for these three different charge sets — the mismatch between the description of the PES and the DMS by each of the different parameterization approaches need not be the same. Nevertheless, it is quite reassuring to see that the hydroxyl-containing molecules in both Caleman data sets are actually quite well reproduced with the scaling factor of 1.26 (red points in Figures 3b and 3d). In fact, the GAFF/RESP data set seems to suggest the existence of two classes of compound — one population that is well described by the original model (see points clustered around the diagonal in Figure 3a) and another population that is well described by the scaling of 1.26 (points along the diagonal in Figure 3b). We will explore this issue later in the paper.

Finally, we present our analysis of the MacKerell data set in Figure 4, where the same trends
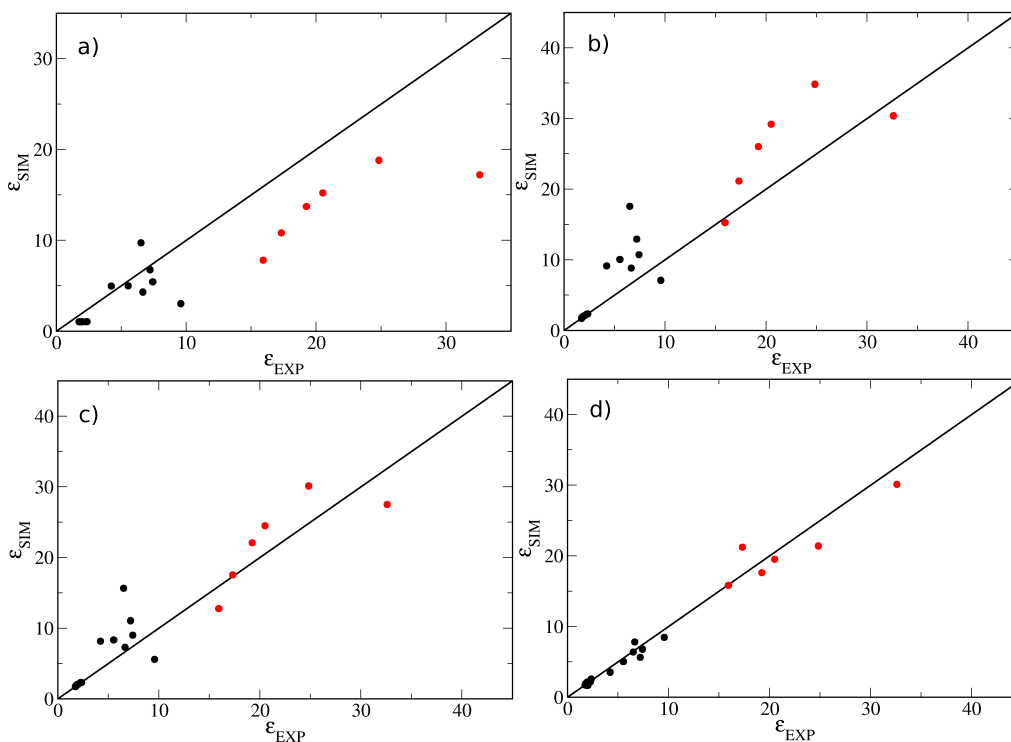
FIG. 4. Comparison between simulated and experimental dielectric constants for the MacKerell data set using: (a) the original CHARMM model[17,33–36]; (b) full correction with $k = \sqrt{\varepsilon_\infty}$; (c) full correction with $k = 1.26$; and (d) the polarizable Drude model[17,33–36]. Molecules with hydroxyl functional groups are shown as red points.

discussed above can be observed. For this particular data set, MacKerell and co-workers[17,33–36] also reported predictions from their polarizable model, shown here in Figure 4d. Improvements over the original CHARMM model are dramatic, with the data lying very close to the diagonal. The polarizable model leads indeed to excellent agreement with experiment (Table S4), although one should notice that the parameters were designed to achieve this. Naturally, such good agreement also comes at the cost of much lower computational efficiency. Although not as accurate, the correction scheme proposed here is able to account for some of the deficiencies of classical non-polarizable models (i.e. absence of electronic polarization and mismatch between the PES and the DMS) at a negligible computational cost. In particular, the alcohol molecules are well described by the correction with $k = 1.26$ (Figure 4c), but generally overestimated by the MDEC approach (Figure 4b). In Table II, we collect results of the statistical analysis over all the simulation data sets considered in this work. The overall improvements over the original predictions are quite significant, particularly if we use the MSD as a measure of deviation (i.e., our approach virtually eliminates systematic deviations). This is all the more remarkable considering that a universal scaling factor was applied across the board, regardless of the nature of the compounds or of the original model employed.

TABLE II. Deviations between simulation and experiment for all the data sets considered in this work. For each entry, we report the RMSD and, in parenthesis, the MSD.

| Data set | Uncorrected | Corrected ($k = 1.26$) |
|---|---|---|
| Fennell GAFF/AM1-BCC | 6.90 ($-6.18$) | 2.49 ($-0.55$) |
| Beauchamp GAFF/AM1-BCC | 14.08 ($-7.21$) | 10.20 ($-0.98$) |
| Caleman GAFF/RESP | 15.75 ($-4.79$) | 15.29 (1.20) |
| Caleman OPLS-AA | 15.89 ($-5.23$) | 15.23 (0.48) |
| MacKerell CHARMM | 4.55 ($-2.66$) | 3.01 (0.87) |

We suggested earlier that the scaling factor may be different for different types of compounds. To further explore this issue, we have regrouped our data according to the type of functional groups present in each molecule, as described in section II, and analyzed each set separately by compound type. More specifically, we compared the quality of the predictions obtained using $k = 1.00$ (i.e. accounting only for electronic polarization effects, but not for the PES/DMS mismatch) and $k = 1.26$ (i.e., accounting for both effects using the scaling factor optimized for methanol). We also optimized $k$ to minimize the MSD between simulation and experiment for each data set. In this analysis, we have removed a total of 15 points that showed unrealistic deviations from experimental data, as described in Table S5, so as to avoid biasing the analysis; this was particularly important considering that some of the "compound type" data sets contained a relatively small number of points. The results of the statistical analysis by compound type are collected in Table III.

Our analysis revealed that most of the compound types, namely alcohols, esters, ketones/aldehydes, nitro-containing molecules, nitriles, and nitrogen-containing aromatics, are indeed much better described by accounting for both polarization effects using $k = 1.26$. For these data sets, all measures of deviation between simulation and experiment are significantly lower for $k = 1.26$, compared to $k = 1.00$ (see first block of data in Table III). Figure 5 shows an example of this comparison for the alcohols data set, with similar plots shown in the SI for the other data sets of this block (Figures S8–S12). Visual observation confirms that application of the scaling factor yields much better agreement between simulation and experiment. Furthermore, when $k$ is used as a fitting parameter for each of these individual sets, values relatively close to 1.26 are obtained in all cases (Table III). Looking more closely at these optimal scaling factors, however, suggests that esters, ketones and nitro-containing compounds may require somewhat lower scaling factors than alcohols, while nitrogen-containing aromatics may require a larger scaling. However, the uncertainty in our estimate of $k$ is too large to allow us to reach more definitive conclusions at this stage.

Interestingly, some of the compound types, namely hydrocarbons, halogenated hydrocarbons,

TABLE III. Statistical analysis of deviations between simulation and experiment by compound type (see text). The total number of points in each set, the measures of deviation for two choices of scaling parameter, and the optimal scaling parameter for each set are reported. The first block of compounds benefit from applying a scaling factor, the second block do not benefit from scaling, whereas the last block show too much scatter for a reliable statistical analysis.

| Block | Data set | Nr. points | $k = 1.00$ | | $k = 1.26$ | | Optimal $k$ |
|---|---|---|---|---|---|---|---|
| | | | RMSD | MSD | RMSD | MSD | |
| 1 | Alcohols | 153 | 8.15 | −7.09 | 4.30 | −1.25 | 1.26 |
| 1 | Esters | 101 | 3.01 | −1.71 | 2.13 | 0.83 | 1.18 |
| 1 | Ketones | 40 | 4.73 | −4.11 | 3.99 | 0.86 | 1.22 |
| 1 | Nitro | 12 | 8.39 | −8.14 | 6.78 | 4.18 | 1.18 |
| 1 | Nitrile | 14 | 10.86 | −10.48 | 2.99 | −0.71 | 1.28 |
| 1 | Aromatic_N | 34 | 3.93 | −3.69 | 2.01 | −1.28 | 1.38 |
| 2 | Hydrocarbons | 41 | 0.07 | 0.01 | 0.13 | 0.05 | 0.94 |
| 2 | Halogenated | 62 | 2.05 | −0.49 | 3.99 | 2.54 | 1.05 |
| 2 | Ethers | 49 | 1.36 | −0.02 | 2.87 | 1.74 | 1.00 |
| 2 | Alkylamines | 31 | 1.32 | 0.86 | 3.83 | 3.07 | 0.88 |
| 3 | Alkanolamines | 29 | 9.95 | −5.24 | 13.65 | 3.58 | 1.16 |
| 3 | Sulfur | 44 | 12.12 | −3.75 | 15.70 | 4.30 | 1.13 |
| 3 | Amides | 13 | 84.92 | −62.36 | 72.32 | −44.76 | 1.76 |
| 3 | Phosphates | 4 | 11.94 | 3.42 | 21.60 | 11.68 | 0.87 |

ethers and alkylamines, are actually better described with a scaling factor of $k = 1.00$. For these classes, the measures of deviation are lower for $k = 1.00$ than for $k = 1.26$, while optimization of $k$ leads to values quite close to $1.00$ (see second block in Table III). An example of this comparison, for the halogenated hydrocarbons data set, is shown in Figure 6 (see also Figures S13–15 for the other data sets in this block), from which it is clear that the unscaled points agree better with experiment. This suggests that for these compounds, the current models are probably able to accurately approximate both the PES and the DMS. It is perhaps no coincidence that for all of these data sets, the experimental values of the dielectric constant are almost always lower than 11.

Finally, the last block in Table III contains four data sets for which we were not able to draw statistically meaningful conclusions regarding the benefit of applying a scaling factor. For all these sets, the scatter in the data is very large (see the example for alkanolamines in Figure 7, and also
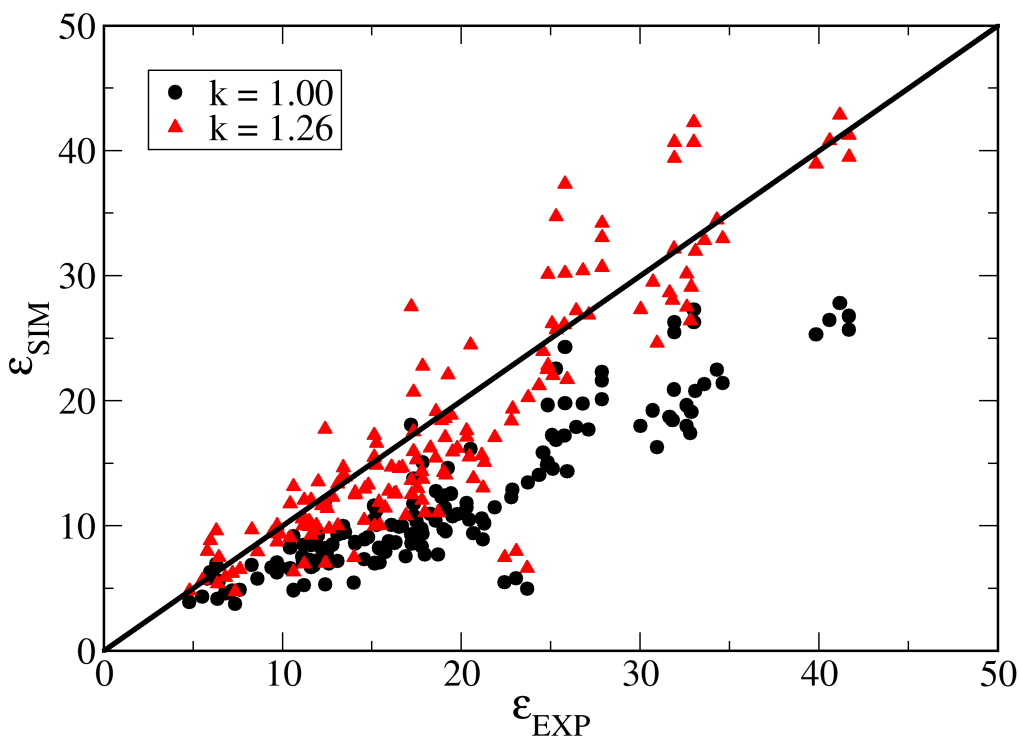
FIG. 5. Comparison between experimental and simulated dielectric constants for the alcohols data set using scaling factors of $k = 1.00$ (black circles) and $k = 1.26$ (red triangles).

Figures S16–17). Clearly, significant improvement is required in current molecular models before they are able to accurately describe the dielectric constant for these classes of compound.

At this stage, it is worth turning our attention to the most important compound that is missing in our analysis — water. None of the data sets considered here included simulations of water using a realistic model (as explained above, the predictions of Beauchamp et al.[6] using GAFF were inadequate). However, a recent paper by Farahvash et al.[15] shed some new light on this issue by comparing the performance of several popular non-polarizable water models. They observed that application of the MDEC approach (i.e. equation (9)) led to significant overestimations of the dielectric constant by all the models. However, if we apply equations (6) and (7) to their data, using a recent ab initio estimate of 2.86 D for the dipole moment of liquid water[45], reasonable agreement is obtained for the TIP4P[46] model — 86.7 compared to the experimental value of 78.4. Although this agreement is not perfect, it does suggest that our approach may be applicable also to water. Interestingly, we have recently found that "first-generation" water models like TIP4P are better than more recent models at predicting the enthalpy of vaporization and the hydration free energy when appropriate polarization corrections are applied[47]. We strongly recommend that development and validation of non-polarizable water models be revisited in light of these new findings.

Another issue that warrants further exploration is the effect of scaling on the dynamic dielectric
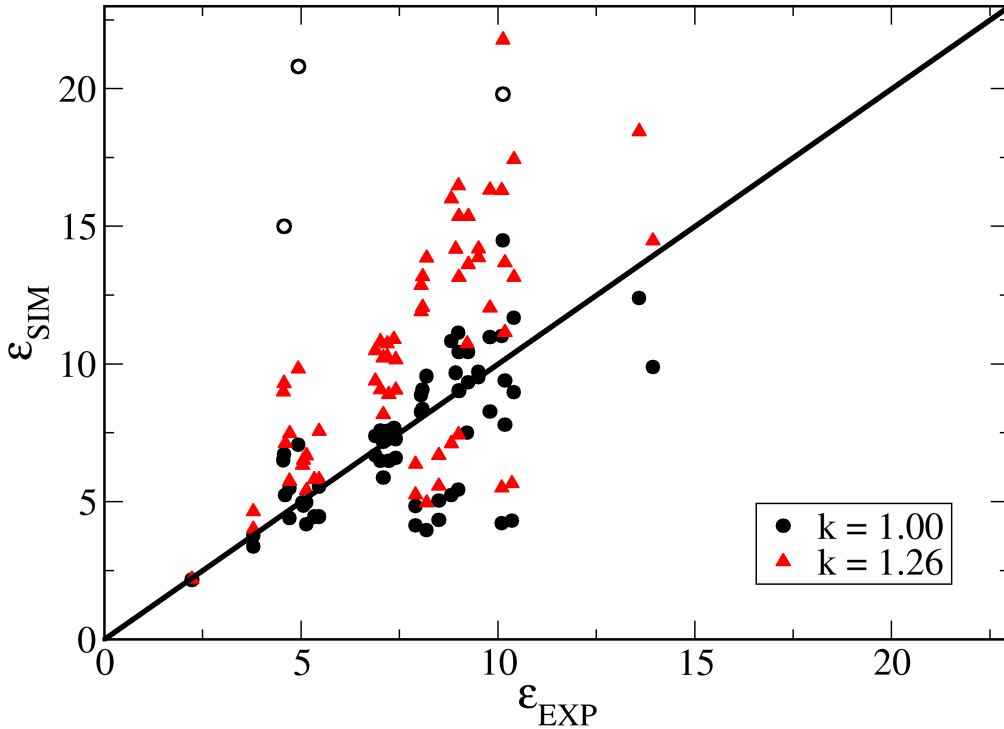
19

FIG. 6. Comparison between experimental and simulated dielectric constants for the halogenated hydrocarbons data set using scaling factors of $k = 1.00$ (black circles) and $k = 1.26$ (red triangles). Open circles represent outliers that were removed from the analysis.

response of fluids[15,48]. Indeed, it has been recently shown that, at least for some fluids, classical non-polarizable models are able to describe the dynamic response over a wide range of frequencies, provided the simulation results are scaled to match the corresponding experimental static dielectric constant[48]. Application of our scaling approach to those systems would make for interesting future research.

## IV. CONCLUSIONS

In this paper, we have shown that applying a simple correction to the values of dielectric constants calculated from classical non-polarizable models is able to bring these predictions into much better agreement with experimental values. The correction accounts for two particular shortcomings of classical models: (i) the lack of consideration of electronic polarization (a purely quantum effect), solved by applying an additive correction to the dielectric constant based on the experimental refractive index of the liquid; and (ii) the mismatch between the classical description of the potential energy surface, commonly used to parameterize the models, and the dipole moment surface, which dominates the calculation of $\varepsilon_r$. The latter was taken into account by applying a constant scaling factor ($k = 1.26$ in equation (6)), determined so that the simulated dielectric constant of a single compound — methanol
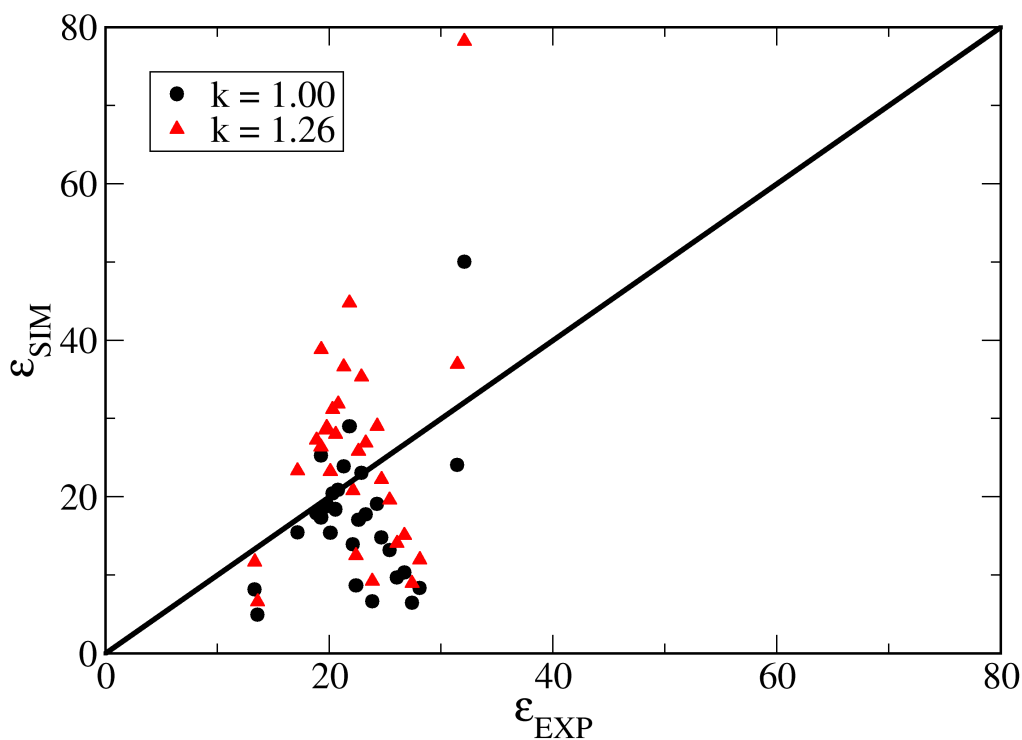
FIG. 7. Comparison between experimental and simulated dielectric constants for the alcohol data set using scaling factors of $k = 1.00$ (black circles) and $k = 1.26$ (red triangles).

— matched the experimental value.

The predictive ability of this approach was tested on several literature data sets that span a wide range of compounds and four different molecular models. Our results show that the same value of the scaling factor can be applied with confidence to predict the dielectric constant of other molecules containing hydroxyl groups, at least for the four models considered here. When applied to molecules with other functional groups, the correction scheme also led to significant general improvement in predictions of the dielectric constant. However, the wide scatter observed in the larger data sets suggests that different types of compound may benefit from different scaling factors. Indeed, our analysis in terms of compound types shows that molecules with hydroxyl, ester, carbonyl, nitro, nitrile and aromatic amine functional groups are well described using scaling factors close to the methanol value of 1.26. Conversely, hydrocarbons, halogenated hydrocarbons, ethers and alkylamines require only the consideration of electronic polarisation and no DMS/PES scaling. In general, the former tend to be much more polar than the latter, and this may explain our observations. Finally, for amides, alkanolamines, phosphates and sulfur-containing compounds, predictions of standard non-polarisable models are so scattered that they cannot be systematically improved by our correction scheme. This suggests the existence of major shortcomings in the description of these classes of molecule, and we suggest that they should be the target of specific parameterization efforts.

In terms of force field development, we recommend that the correction term proposed here be applied when comparing predictions from classical non-polarizable models with experimental dielectric constants. If the dielectric constant is included as a fitting target in the parameterization, ignoring the correction, particularly the linear scaling term, means that one is trying to find the best set of parameters that simultaneously reproduce the potential energy surface (PES) and the dipole moment surface (DMS). As also discussed by Vega[13], this is likely to hinder a more accurate description of the PES, on which the vast majority of thermodynamic and dynamic properties is based. Applying the correction enables one to concentrate on finding the optimal parameters for describing the PES, while still obtaining good predictions of properties that depend on the DMS. Moreover, it is likely to reduce or even eliminate inconsistencies in force field parameterization between homologous series of molecules. For example, as discussed by Beauchamp et al.[6], the standard approach generates inherent inconsistencies when moving from symmetric molecules like $CCl_4$ or benzene to closely related asymmetric molecules like $CHCl_3$ and toluene — in the former case, fixed-charge models are simply unable to describe the experimental dipole moment and dielectric constant, while they can be tuned to do so for the asymmetric counterparts. Our simple correction solves this issue by decoupling the PES from the DMS and explicitly accounting for electronic polarization effects.

Naturally, during a given simulation, the (uncorrected) liquid will still be underpolarized with respect to the real (experimental) liquid — the correction is only applied as a post-processing step. This means that other properties that depend on the dielectric behavior of the liquid will themselves need to be corrected. Important examples are solvation or transfer free energies. Although there have been efforts to implicitly include polarization effects in calculations of solvation free energies, a universally accepted approach has not yet been reached[47]. We expect this to be an area of significant attention in the near future, and we believe our paper makes an important contribution in this direction.

**SUPPLEMENTARY MATERIAL**

Spreadsheets containing the raw data and analysis of the dielectric constant, organized by model and by compound type, as well as additional figures and tables, are included.

## REFERENCES

[1] T. R. Griffiths and D. C. Pugh, Coord. Chem. Rev. **29**, 129 (1979).

[2] C. J. Fennell, L. Li, and K. A. Dill, J. Phys. Chem. B **116**, 6936 (2012).

[3] M. Neumann, Mol. Phys. **50**, 841 (1983).

[4] T. W. Whitfield, G. J. Martyna, S. Allison, S. P. Bates, H. Vass, and J. Crain, J. Phys. Chem. B **110**, 3624 (2006).

[5] C. J. Fennell, K. L. Wymer, and D. L. Mobley, J. Phys. Chem. B **118**, 6438 (2014).

[6] K. A. Beauchamp, J. M. Behr, A. S. Rustenburg, C. I. Bayly, K. Kroenlein, and J. D. Chodera, J. Phys. Chem. B **119**, 12912 (2015).

[7] C. Caleman, P. J. van Maaren, M. Hong, J. S. Hub, L. T. Costa, and D. van der Spoel, J. Chem. Theory Comput. **8**, 61 (2011).

[8] R. Fuentes-Azcatl and J. Alejandre, J. Phys. Chem. B **118**, 1263 (2014).

[9] S. Izadi, R. Anandakrishnan, and A. V. Onufriev, J. Phys. Chem. Lett. **5**, 3863 (2014).

[10] L.-P. Wang, T. J. Martinez, and V. S. Pande, J. Phys. Chem. Lett. **5**, 1885 (2014).

[11] J. Wang, R. M. Wolf, J. W. Caldwell, P. A. Kollman, and D. A. Case, J. Comput. Chem. **25**, 1157 (2004).

[12] A. Jakalian, D. B. Jack, and C. I. Bayly, J. Comput. Chem. **23**, 1623 (2002).

[13] C. Vega, Mol. Phys. **113**, 1145 (2015).

[14] I. V. Leontyev and A. A. Stuchebrukhov, J. Chem. Phys. **130**, 085102 (2009).

[15] A. Farahvash, I. Leontyev, and A. Stuchebrukhov, J. Phys. Chem. A **122**, 9243 (2018).

[16] H. W. Horn, W. C. Swope, J. W. Pitera, J. D. Madura, T. J. Dick, G. L. Hura, and T. Head-Gordon, J. Chem. Phys. **120**, 9665 (2004).

[17] I. V. Vorobyov, V. M. Anisimov, and A. D. MacKerell, J. Phys. Chem. B **109**, 18988 (2005).

[18] H. Liu, Y. Wang, and J. M. Bowman, J. Phys. Chem. B **120**, 1735 (2015).

[19] Y. Wang, X. Huang, B. C. Shepler, B. J. Braams, and J. M. Bowman, J. Chem. Phys. **134**, 094509 (2011).

[20] G. R. Medders and F. Paesani, J. Chem. Phys. **142**, 212411 (2015).

[21] J. L. Aragones, L. G. MacDowell, and C. Vega, J. Phys. Chem. A **115**, 5745 (2011).

[22] I. Leontyev and A. Stuchebrukhov, Phys. Chem. Chem. Phys. **13**, 2613 (2011).

[23] I. V. Leontyev and A. A. Stuchebrukhov, J. Chem. Phys. **141**, 014103 (2014).

[24] D. Gonzalez-Salgado and C. Vega, J. Chem. Phys. **145**, 034508 (2016).

[25] J. K. Gregory, D. C. Clary, K. Liu, G. Brown, and R. J. Saykally, Science **275**, 814 (1997).

[26] Y. S. Badyal, M.-L. Saboungi, D. L. Price, S. D. Shastri, D. R. Haeffner, and A. K. Soper, J. Chem. Phys. **112**, 9206 (2000).

[27]P. L. Silvestrelli and M. Parrinello, Phys. Rev. Lett. **82**, 3308 (1999).

[28]P. L. Silvestrelli and M. Parrinello, J. Chem. Phys. **111**, 3572 (1999).

[29]M. Sharma, R. Resta, and R. Car, Phys. Rev. Lett. **98**, 247401 (2007).

[30]C. Zhang, J. Wu, G. Galli, and F. Gygi, J. Chem. Theory Comput. **7**, 3054 (2011).

[31]A. Bankura, A. Karmakar, V. Carnevale, A. Chandra, and M. L. Klein, J. Phys. Chem. C **118**, 29401 (2014).

[32]P. Schienbein and D. Marx, J. Phys. Chem. B **122**, 3318 (2017).

[33]V. M. Anisimov, I. V. Vorobyov, B. Roux, and A. D. MacKerell, J. Chem. Theory Comput. **3**, 1927 (2007).

[34]I. Vorobyov, V. M. Anisimov, S. Greene, R. M. Venable, A. Moser, R. W. Pastor, and A. D. MacKerell, J. Chem. Theory Comput. **3**, 1120 (2007).

[35]P. E. M. Lopes, G. Lamoureux, B. Roux, and A. D. MacKerell, J. Phys. Chem. B **111**, 2873 (2007).

[36]X. Zhu and A. D. Mackerell, J. Comput. Chem. , 2330 (2010).

[37]C. I. Bayly, P. Cieplak, W. Cornell, and P. A. Kollman, J. Phys. Chem. **97**, 10269 (1993).

[38]W. L. Jorgensen, D. S. Maxwell, and J. Tirado-Rives, J. Am. Chem. Soc. **118**, 11225 (1996).

[39]A. D. MacKerell, D. Bashford, M. Bellott, R. L. Dunbrack, J. D. Evanseck, M. J. Field, S. Fischer, J. Gao, H. Guo, S. Ha, and et al., J. Phys. Chem. B **102**, 3586 (1998).

[40]D. R. Linde, ed., *CRC Handbook of Chemistry and Physics*, 70th ed. (CRC Press, Boca Raton, FL, USA, 1981).

[41]M. Neumann and O. Steinhauser, Chem. Phys. Lett. **106**, 563 (1984).

[42]R. Bosque and J. Sales, J. Chem. Inf. Comput. Sci. **42**, 1154 (2002).

[43]S. S. Park, S. Lee, J. Y. Bae, and F. Hagelberg, Chem. Phys. Lett. **511**, 466 (2011).

[44]M. Pagliai, G. Cardini, R. Righini, and V. Schettino, J. Chem. Phys. **119**, 6655 (2003).

[45]P. Schienbein and D. Marx, J. Phys. Chem. B **122**, 3318 (2017).

[46]W. L. Jorgensen, J. Chandrasekhar, J. D. Madura, R. W. Impey, and M. L. Klein, J. Chem. Phys. **79**, 926 (1983).

[47]A. W. Milne and M. Jorge, J. Chem. Theory Comput. (2018), 10.1021/acs.jctc.8b01115.

[48]J. Cardona, R. Fartaria, M. B. Sweatman, and L. Lue, Mol. Simul. **42**, 370 (2016).