

## Electronic continuum model for molecular dynamics simulations

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(Received 29 May 2008; accepted 9 December 2008; published online 25 February 2009)

A simple model for accounting for electronic polarization in molecular dynamics (MD) simulations is discussed. In this model, called molecular dynamics electronic continuum (MDEC), the electronic polarization is treated explicitly in terms of the electronic continuum (EC) approximation, while the nuclear dynamics is described with a fixed-charge force field. In such a force-field all atomic charges are scaled to reflect the screening effect by the electronic continuum. The MDEC model is rather similar but not equivalent to the standard nonpolarizable force-fields; the differences are discussed. Of our particular interest is the calculation of the electrostatic part of solvation energy using standard nonpolarizable MD simulations. In a low-dielectric environment, such as protein, the standard MD approach produces qualitatively wrong results. The difficulty is in mistreatment of the electronic polarizability. We show how the results can be much improved using the MDEC approach. We also show how the dielectric constant of the medium obtained in a MD simulation with nonpolarizable force-field is related to the static (total) dielectric constant, which includes both the nuclear and electronic relaxation effects. Using the MDEC model, we discuss recent calculations of dielectric constants of alcohols and alkanes, and show that the MDEC results are comparable with those obtained with the polarizable Drude oscillator model. The applicability of the method to calculations of dielectric properties of proteins is discussed. © 2009 American Institute of Physics. [DOI: 10.1063/1.3060164]

### I. INTRODUCTION

At present, the majority of molecular dynamics simulations are performed by using nonpolarizable force-fields such as AMBER,<sup>1</sup> CHARMM,<sup>2</sup> GROMOS,<sup>3</sup> and OPLS.<sup>4</sup> Presumably, the effects of electronic polarization and screening of electrostatic interactions are incorporated, to some extent, in the effective charges and other empirical parameters of the force-fields. Despite the drastic simplifications, such nonpolarizable models have been remarkably successful in modeling many complex molecular systems.<sup>5</sup> For example, the properties of liquid water are described quite accurately without introducing electronic polarizability explicitly; likewise, the hydration free energies can be computed quite accurately using nonpolarizable simulations.<sup>6,7</sup> However, the simulation of polarization effects in low-polar solvents, e.g., ethers,<sup>8</sup> and especially in nonpolar solvents, e.g., alkanes,<sup>9,10</sup> meet serious problems. The nonpolarizable models can also significantly underestimate the magnitude of the dielectric response in low-dielectric protein environment.<sup>11</sup> For example, the dielectric constant of the inner part of cytochrome *c* was found to be only about 1.5,<sup>12</sup> which is lower than pure electronic dielectric constant  $\epsilon_{el} \cong 2.0$ .<sup>13</sup> Thus, the conventional nonpolarizable molecular dynamics (MD) approaches prove to be unreliable for computation of solvation free energies and  $pK_a$  values in proteins. Many other shortcomings of nonpolarizable MD simulations have been recently discussed in the literature, see Ref. 14 and references therein.

The polarizable models which are currently being developed aim at resolving the problems mentioned above. Most

of such models involve various kinds of coupled polarizable sites<sup>15,16</sup> and the computationally expensive procedure of achieving self-consistency of polarization of such sites at each molecular dynamics time-step. The implementation of such models is yet to be completed; at present, even the simplest classical Drude oscillator model<sup>8,9,15,17</sup> is still not readily available for application to many biological systems.

As fully polarizable force fields are being developed, there is also a growing interest in better understanding the extent to which the empirical nonpolarizable models capture the effects of electronic polarization and screening in the conventional MD simulations. The issue is of particular interest in calculations of absolute values of solvation energies,  $pK_a$  calculations, and computational studies of dielectric properties of proteins.

In this paper we examine a simple model that combines a nonpolarizable (fixed-charge) force-field for MD with a phenomenological electronic continuum (EC) model for electronic polarization.<sup>18</sup> The combined model is referred to as MDEC. In MDEC force-field, the effects of electronic polarization and screening are described by simple scaling of the partial charges. The model is similar but not equivalent to standard nonpolarizable force-fields used in most of MD simulations. Of our particular interest is the calculation of the solvation energy of charging using MD. In the MDEC the electronic polarization part of the solvation energy is calculated explicitly from the electronic continuum model, while the nuclear part is obtained with a fixed-charge MD. The two parts need to be combined to obtain the total solvation energy. We demonstrate that MDEC model and the Drude oscillator model produce comparable results for dielectric con-

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stants of alcohols and alkanes. It is argued that using this model one can rather accurately describe the dielectric properties of nonpolar liquids and proteins. Using similarity of the MDEC approach and standard nonpolarizable MD, we discuss the nature of the underestimated polarization problem encountered in some previous simulations<sup>8,9,12</sup> and show how the results can be much improved by a simple modification of the standard MD approach. The application of the MDEC model to the calculation of charge solvation energies in proteins is discussed.

## II. THE ELECTRONIC AND NUCLEAR POLARIZATIONS

To avoid confusion in the following discussion of electronic and nuclear polarizations, we first introduce terminology that will be used in the paper. In the literature, different fields use different terms which compels us to discuss this issue.

In the linear response approximation, the electronic polarization, understood as deformation of electronic shells of the medium molecules, is an additive quantity. Therefore, the total electronic polarization of the medium can be partitioned into two parts: one that is due to external field and one due to interaction between the medium molecules themselves, which depends on the nuclear configuration of the system. The electronic subsystem is much faster than the nuclear one; therefore electrons react instantaneously to the new position of the nuclei, when they move, as well as to the external field. Accordingly, in this linear and adiabatic picture, the total polarization  $P$  of the medium can be partitioned into the slow “inertial” polarization  $P_{\text{in}}$ , which depends on the position of solvent nuclei, and fast “inertialess” pure electronic component  $P_{\infty}$ . The inertial polarization includes not only the contribution from the nuclei but also that of the electronic subsystem, which is in equilibrium with the position of the nuclei. The inertial component of the polarization  $P$  is pure electronic; it arises in response to the external field, and is present even when no rearrangement of the medium nuclei occurs, as, e.g., in a fixed protein structure. The notations inertial and inertialess components are borrowed from the nonequilibrium solvation theory,<sup>18–20</sup> (and references therein), although,  $P_{\infty}$  is also called in the literature “dynamic” polarization<sup>21</sup> (and references therein). Hereafter, to simplify notation we will use the terms of pure *electronic* and *nuclear* polarizations for the above inertialess and inertial parts of the total polarization. We will also use terms polarization energy and reaction field energy interchangeably.

In nonpolarizable MD models, the pure electronic component of polarization (e.g., induced by the field of a solute molecule in a solvent, at fixed position of nuclei of the latter) is not present at all, while the remaining electronic part of the inertial polarization is assumed to be included in the effective force-field via properly calibrated atomic partial charges and other nonelectrostatic parameters. The extent to which the nonpolarizable force-fields capture the effects of electronic polarization is difficult to estimate *a priori*; therefore one resorts to a direct comparison of the results of calculations, e.g., of solvation free energy, with experimental

data. In such comparisons, typically high-dielectric or highly polar media, such as water, are considered. In such media, the effect of the missing pure electronic component of polarization can be easily corrected by adjusting solute/solvent Coulomb and van der Waals interactions. The nuclear and electronic parts of polarization energy in this case are about the same, as will be shown later in the paper; the compensation of the missing electronic part (about half of total energy) is typically achieved in nonpolarizable force fields by exaggerating the interaction of the solute molecule with the solvent using unscaled charges, which are roughly a factor of  $\sqrt{2}$  larger than the physical charges which reflect electronic screening of electrostatic interactions.

In the low-polar media, however, such a strategy of force-field tuning<sup>8,10,22</sup> meets serious problems. Thus, van Gunsteren and co-authors<sup>10</sup> were not able to find a universal combination of charges and van der Waals parameters that would reproduce at once the enthalpies of solvation, density, and heat of vaporization of the pure liquid.

Even a more difficult case is presented by nonpolar bulk solvents because in these media the total polarization effect is exclusively due to pure electronic part. For example, dielectric constants of nonpolar alkanes simulated by MacKerell’s group<sup>9</sup> are close to unity; whereas, the experimental values are all about 2.<sup>23</sup> Not surprisingly, therefore, that the standard MD approach results in vanishing ( $\sim k_B T$ ) electrostatic solvation free energies of methyl- and propyl guanidinium cations in cyclohexane,<sup>24</sup> whereas, the modeling by the polarizable Drude oscillator method<sup>24</sup> gives two orders of magnitude larger solvation energies. It is clear that in low-dielectric media the standard nonpolarizable MD approaches do not capture the effects of electronic polarization adequately, rendering MD simulations in this case not very useful.<sup>9,12,17,24,25</sup>

The MDEC model discussed below allows one to drastically improve the results of MD simulations with only a few simple changes of the standard approach.

## III. MDEC MODEL

The MDEC model considers point charges moving in electronic continuum of known dielectric constant  $\epsilon_{\text{el}}$ . In this case all electrostatic interactions are scaled by the factor  $1/\epsilon_{\text{el}}$ , while the electronic polarization energy of the solvated charges is calculated explicitly using the electronic continuum model. Some formal analysis of how the continuum model can be obtained from the polarizable model of point charges is given in the Appendix. Below we discuss the expressions for the solvation free energy and dielectric constant that follow from MDEC model, and propose how the standard MD force fields can be modified to fit into the MDEC formalism.

### A. Solvation energy

In MDEC model, we consider all atoms of the medium and the solute molecule (which would be typically treated quantum mechanically, and therefore will be called the QM system) as point charges immersed in the electronic continuum of known dielectric constant  $\epsilon_{\text{el}}$ , see Fig. 1(a). Ac-

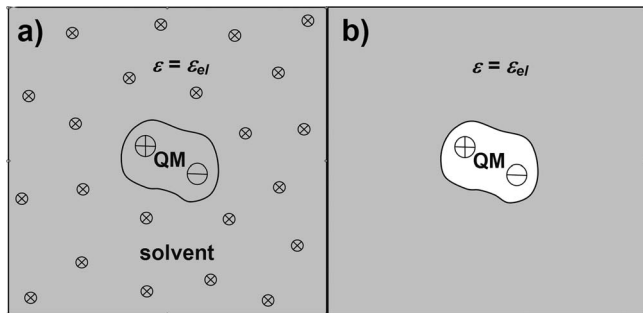


FIG. 1. (a) MDEC model for the electrostatic interactions between solute (large crossed circles) and solvent (small crossed circles) charges in the electronic continuum of dielectric constant  $\epsilon_{el}$ ; the same electronic dielectric constant  $\epsilon_{el}$  is assigned for both the solvent and solute regions; (b) MDEC model for estimation of the pure electronic polarization energy.

cordingly, in MD simulations the effects of electronic dielectric screening can be taken into account implicitly by using scaled partial charges,  $q_i^{eff} = q_i / \sqrt{\epsilon_{el}}$ ; in this case the Coulomb interactions automatically have the correct form  $q_i^{eff} q_j^{eff} / R_{ij} = q_i q_j / \epsilon_{el} R_{ij}$  without explicitly introducing the dielectric constant  $\epsilon_{el}$ . The unscaled original charges are difficult to specify a priori in general (they are not the same as partial atomic charges of a medium molecule in vacuum, see the Appendix), unless one deals with ions or ionized groups in a protein, whose unscaled charges are known.

When the solvation energy of a group is considered, we use a model shown in Fig. 1(b). The solvation energy part related to the medium surrounding the solute molecule (but not the solute molecule itself) consists of the nuclear part evaluated by MD, as described below, and the pure electronic polarization energy part which is evaluated using electronic continuum model with dielectric constant  $\epsilon = 1$  inside the QM region and  $\epsilon = \epsilon_{el}$  outside, as shown in Fig. 1(b). (We emphasize that the solute cavity with  $\epsilon = 1$  arises in the model only when the polarization energy of the electronic continuum by the QM charges is considered. In MD this part of energy should be considered as constant not affecting the forces between atoms.) This part of energy is calculated by solving the Poisson equation, with corresponding boundary conditions and unscaled charges of the QM system.

According to this model, the total solvation energy then is

$$\Delta G = \Delta G_{nuc} + \Delta G_{el}, \quad (1)$$

where the nuclear part  $\Delta G_{nuc}$  is due to the rearrangement of the medium nuclei, whereas  $\Delta G_{el}$  is due to pure electronic polarization response of the medium to charges of the QM system. The nuclear part  $\Delta G_{nuc}$  is modeled using nonpolarizable MD; while the electronic polarization energy  $\Delta G_{el}$  is estimated explicitly as specified above. Such an approach to electrostatic solvation energy calculations was shown to work well both in high- and low-dielectric media<sup>18–20,26</sup> and will be further elaborated in this paper.

When the interaction of the QM system with the solvent molecules surrounding QM is considered in the MD simulation of  $\Delta G_{nuc}$  (but not for electronic solvation energy  $\Delta G_{el}$ ), the charges of the QM system—determined separately in standard quantum mechanical procedure—should be scaled

by  $1/\sqrt{\epsilon_{el}}$ , like all other charges when the forces between atoms are considered. If no scaling of charges of the QM system has been employed, as typically done in standard MD simulations,<sup>6,7,22</sup> the free energies obtained from the MD,  $\Delta G_{MD}$ , should be corrected directly afterward. Since in the linear response approximation the solvation energy is quadratic in charges of the QM system,  $\Delta G_{MD}$ , should be corrected by a factor  $1/\epsilon_{el}$ , giving  $\Delta G_{nuc} = \Delta G_{MD} / \epsilon_{el}$ . The total polarization energy of the medium then can be written as follows:

$$\Delta G = \frac{1}{\epsilon_{el}} \Delta G_{MD} + \Delta G_{el}, \quad (2)$$

where  $\Delta G_{MD}$  is the electrostatic solvation energy obtained in nonpolarizable MD using unscaled QM charges (standard approach), and  $\Delta G_{el}$  is the pure electronic part of the solvation energy evaluated by solving Poisson equations, as described before.

## B. Dielectric constant of the medium

The dielectric constant of the medium is often utilized for the evaluation of the solvation energy in the continuum electrostatic calculations. In microscopic calculations, on the other hand, the solvation energy is obtained directly from MD simulations. The question arises then what is the effective dielectric constant of the medium that corresponds to specific microscopic model of the system. Suppose such correspondence has been established in standard MD simulations, and the corresponding dielectric constant was found to be  $\epsilon_{MD}$ , i.e., the microscopic solvation energy determined with standard MD can be reproduced with a continuum electrostatic model using  $\epsilon_{MD}$  for the medium surrounding the solute molecule. The free energy relationships discussed in the previous section allow one to make a connection between the total (static) dielectric constant  $\epsilon_0$ , which includes both nuclear and electronic polarization effects, and the dielectric constant found in standard MD simulations  $\epsilon_{MD}$ , which does not explicitly treat the pure electronic polarization of the medium.

Suppose we consider the solvation of spherical ions; in this case the solvation energies will be proportional to corresponding Born factors:  $\Delta G \sim (1 - 1/\epsilon_0)$ ,  $\Delta G_{el} \sim (1 - 1/\epsilon_{el})$ , and  $\Delta G_{MD} \sim (1 - 1/\epsilon_{MD})$ .

Using Eq. (2) for the relationship between these energies, we find

$$\epsilon_0 = \epsilon_{MD} \cdot \epsilon_{el}. \quad (3)$$

The above relation can be also derived using the expression<sup>27</sup> for the static dielectric constant,

$$\epsilon_0 = \epsilon_{el} + \frac{4\pi}{3Vk_B T} \langle M^2 \rangle. \quad (4)$$

Here  $\langle M^2 \rangle$  is the mean square fluctuation of the total dipole of the dielectric sample  $V$ , and  $k_B$  and  $T$  are Boltzmann constant and temperature, respectively. According to the MDEC scaling procedure, the actual dipole moment  $\mu$  of particles in the bulk is related to the effective moment  $\mu^{eff}$  of these particles in nonpolarizable model as  $\mu = \sqrt{\epsilon_{el}} \mu^{eff}$ ; therefore,

$\langle M^2 \rangle = \varepsilon_{\text{el}} \langle M_{\text{MD}}^2 \rangle$ , where  $\langle M_{\text{MD}}^2 \rangle$  is the mean square fluctuation of the dipole moment observed in the nonpolarizable MD. Thus, Eq. (3) is obtained from Eq. (4) by noticing that  $\varepsilon_{\text{MD}}$  is defined via fluctuation  $\langle M_{\text{MD}}^2 \rangle$  with  $\varepsilon_{\text{el}}=1$  in Eq. (4). There are still other ways to obtain Eq. (3).

Physically, relation (3) expresses the fact that the static susceptibility  $\chi_0$  of the medium is the sum of the nuclear  $\chi_{\text{nuc}}$  and pure electronic  $\chi_{\text{el}}$  components (as total polarization is the sum of nuclear and pure electronic parts),

$$\chi_0 = \chi_{\text{nuc}} + \chi_{\text{el}}, \quad (5)$$

where  $\chi_0 = (\varepsilon_0 - 1)/4\pi$  and  $\chi_{\text{el}} = (\varepsilon_{\text{el}} - 1)/4\pi$ , while  $\chi_{\text{nuc}}$  is given according to the Eq. (4) as

$$\chi_{\text{nuc}} = \frac{1}{3Vk_B T} \langle M^2 \rangle = \varepsilon_{\text{el}} \left( \frac{1}{3Vk_B T} \langle M_{\text{MD}}^2 \rangle \right) = \varepsilon_{\text{el}} \chi_{\text{MD}}, \quad (6)$$

where  $\chi_{\text{MD}} = (\varepsilon_{\text{MD}} - 1)/4\pi$  is the susceptibility of the model medium represented by the nonpolarizable MD approach. Thus, Eq. (3) is recovered again.

It is worth noticing that with Eq. (3), the nuclear (i.e., inertial) part of the reaction-field energy  $\Delta G_{\text{nuc}} = 1/\varepsilon_{\text{el}} \Delta G_{\text{MD}}$ , automatically takes the correct form proportional to the Pekar factor:  $\Delta G_{\text{nuc}} \sim (1/\varepsilon_{\text{el}} - 1/\varepsilon_0)$  used in electron transfer studies (see, for example Ref. 28). Although the simple relation between dielectric constants Eq. (3) was derived using arguments strictly valid only for spherical ions, and for the bulk solvent modeled with periodic boundary conditions,<sup>27</sup> Eq. (3) provides a good estimate of the static dielectric constant  $\varepsilon_0$  in a wide range of different systems.<sup>11,12,29</sup>

### C. Conventional force fields and MDEC model

The conventional nonpolarizable force-fields of AMBER,<sup>1</sup> CHARMM,<sup>2</sup> GROMOS,<sup>3</sup> or OPLS (Ref. 4) are built on different principles than those discussed in this paper; yet most of the atomic partial charges (which are empirical in their nature, despite the input of *ab initio* calculations in their definitions) can be understood approximately as “scaled MDEC charges,” because these empirical parameters in general reasonably well describe interatomic interactions without explicit introducing the electronic screening. The exception is obviously for ions and ionized groups in proteins, which carry their original charges:  $\pm 1$ , etc: Thus, the interaction between a protonated Lys and deprotonated Asp, for example, is calculated as if there were no electronic screening. In high-dielectric environments such as water or close to a boundary with water, the error made in such cases would not be noticed, because of the strong nuclear screening by itself, which reduces such interactions to become almost insignificant. This is certainly not the case for sites in low-dielectric environment deep inside the protein. Thus the conventional nonpolarizable force fields are not completely consistent with MDEC charge scaling concept. Yet, with additional scaling of charges of ionized groups and treating pure electronic solvation explicitly, the standard nonpolarizable force fields can be utilized for MDEC calculations. This is certainly only an approximation, but as will be shown below a pretty good one; it works both in high- and low-dielectric cases.

It is often tacitly assumed that in order to correctly describe the interaction energy *between* groups in a protein it is sufficient to choose their effective charges in such a way as to reproduce the solvation energy of the individual groups, typically in an aqueous environment.<sup>2</sup> It is important to keep in mind, however, that the correct solvation free energies can be obtained with incorrect charges by adjusting their values so as to compensate for a missing electronic part of the solvation; the correct solvation energies therefore do not guarantee that the groups will have correct interaction energy in the protein environment. Such is clearly the case for charged amino acids and ions.

For noncharged amino acids, we recall for example that in CHARMM (Ref. 2) the calibration of charges is done using TIP3P model of water which itself can be considered to be MDEC model. In this nonpolarizable model, the effective dipole moment of a water molecule is  $\mu^{\text{eff}} = 2.35$  D. The charges of TIP3P model can be understood as scaled effective charges; the actual (unscaled) dipole moment of the TIP3P water molecule should be taken then as  $\mu = \mu^{\text{eff}} \sqrt{\varepsilon_{\text{el}}} = 3.15$ , assuming for optical permeability of water  $\varepsilon_{\text{el}} = 1.8$ . (The value  $\mu = 3.15$  D should not be confused with the vacuum value of water dipole, which is around 1.85 D; the latter value already reflects the effect of electronic polarization “within” the molecule itself.)

In many microscopic studies the pure electronic contribution to the electrostatic free energy as well as the electronic screening effects are completely ignored, as, e.g., in Refs. 6, 7, and 22, that is, the total solvation energy is simply taken to be  $\Delta G_{\text{MD}}$ . For example, for the Born solvation energy of a charge  $Q$ , say, for  $\text{Na}^{1+}$  ion,  $Q = +1$ , one would have approximately

$$\Delta G = \frac{Q^2}{2R} \left( 1 - \frac{1}{\varepsilon_{\text{MD}}} \right), \quad (7)$$

where  $\varepsilon_{\text{MD}}$  is the dielectric constant of water that corresponds to a specific MD model employed in the calculation. No matter which model is used,  $\varepsilon_{\text{MD}}$  is much larger than unity, hence the overall estimate of the solvation energy is  $Q^2/2R$ , which can match pretty well the experimental value, provided the radius  $R$  is chosen correctly. The interaction between two charges will be taken to be then  $Q^2/R_{ij}$  (see Appendix) with complete disregard to electronic screening of the interaction. The MDEC model suggests instead that the charge  $Q$  should be scaled, and the electronic solvation energy be added explicitly,

$$\Delta G = \frac{(Q/\sqrt{\varepsilon_{\text{el}}})^2}{2R} \left( 1 - \frac{1}{\varepsilon_{\text{MD}}} \right) + \frac{Q^2}{2R} \left( 1 - \frac{1}{\varepsilon_{\text{el}}} \right). \quad (8)$$

Notice that the charge is not scaled when the solvation is calculated in electronic continuum. Since  $\varepsilon_{\text{el}}$  is approximately 2 and  $\varepsilon_{\text{MD}} \gg 1$ , the two expressions [Eqs. (7) and (8)] approximately give the same result. Yet, for the interaction energy of two charges MDEC suggests that the correct expression will be  $Q^2/R_{ij}\varepsilon_{\text{el}}$  instead of  $Q^2/R_{ij}$ . Thus in the standard approach the nuclear part can be understood as overestimated by a factor  $\varepsilon_{\text{el}}$ , while completely neglecting pure electronic part of the solvation energy. For high-

TABLE I. Dielectric constant of bulk alcohols simulated by different MD models at  $T=298.15$  K.

Alcohol	$\epsilon_0$ , Expt. <sup>a</sup>	$\epsilon_{\text{MD}}$ , npol MD <sup>b</sup>	$\epsilon_0$ , pol. MD <sup>c</sup>	$\epsilon_{\text{el}}$ , pol. MD <sup>c</sup>	$\epsilon_0$ , MDEC <sup>d</sup>
MeOH	32.61	17.2	30.1	1.5	25.8
EtOH	24.85	18.8	21.4	1.6	30.08
2-PrOH	19.26	13.7	17.6	1.7	23.29
2-BuOH	15.94	7.8	15.8	1.7	13.26
1-PrOH	20.52	15.2	19.5	1.6	24.32
1-BuOH	17.33	10.8	21.2	1.7	18.36
rmsd of $\theta^e$ , (%)	...	3.7	0.6	...	0.9

<sup>a</sup>Experimental values (Ref. 23).<sup>b</sup>Conventional nonpolarizable MD model (Ref. 17).<sup>c</sup>Polarizable classical Drude oscillator model (Ref. 17).<sup>d</sup>MDEC model [Eq. (3)] where  $\epsilon_{\text{MD}}$  and  $\epsilon_{\text{el}}$  are taken from b and c, respectively.<sup>e</sup>The relative error of the Born factor [Eq. (11)].

dielectric media, and because electronic dielectric constant is about 2, the two expressions give approximately the same solvation free energy. In a low dielectric media, the difference becomes noticeable, however, because now  $\epsilon_{\text{MD}} \approx 1$  in Eq. (8).

One can accurately estimate under what conditions the two approaches produce approximately the same result. As seen from the Eq. (2),  $\Delta G = \Delta G_{\text{MD}}$  when

$$\frac{\Delta G_{\text{el}}}{\Delta G_{\text{MD}}} = \left(1 - \frac{1}{\epsilon_{\text{el}}}\right). \quad (9)$$

For spherical ions, using the proportionality of the free energies to the corresponding Born factors and Eq. (3), we obtain that condition (9) can be approximately satisfied only in high dielectric media,

$$\epsilon_0/\epsilon_{\text{el}} \gg 1. \quad (10)$$

Not surprisingly therefore, the pure nonpolarizable approach works well in aqueous solutions ( $\epsilon_0/\epsilon_{\text{el}} \sim 40$ ), as, e.g., in Refs. 6 and 19; however, the approach fails (i.e., significantly underestimates the polarization effects) in low dielectric media ( $\epsilon_0/\epsilon_{\text{el}} \sim 1$ ) as in Refs. 8, 9, 24, and 25.

#### IV. APPLICATIONS OF MDEC MODEL AND DISCUSSION

To examine the quality of the MDEC model, we consider the dielectric properties of polar (alcohols) and nonpolar (alkanes) solvents published recently.<sup>9,17</sup> The dielectric constants of these solvents were calculated by using both the conventional nonpolarizable model and polarizable classical Drude oscillator model.<sup>15</sup> A significant improvement was obtained when the effects of electronic polarization were included, in particular for nonpolar alkanes. The results of such calculations are reproduced in Tables I and II. The main purpose of the MDEC model is to *avoid* computationally expensive explicit treatment of the electronic polarization, but instead to include these effects in a phenomenological way by using nonpolarizable MD and some effective electronic dielectric constant for electronic continuum.

We notice that the pure electronic dielectric constant  $\epsilon_{\text{el}}$  is a rather well defined quantity for a given type of organic or biological material with typical values in the range of 1.7–2.0; this constant can be determined experimentally, and later used in conjunction with nonpolarizable simulations. Thus, for most of the alcohols the dielectric constant of the electronic continuum can be taken in the range of 1.6–1.7; for alkanes the corresponding value is in the range of 1.8–2.0, see Tables I and II.

TABLE II. Dielectric constant of bulk alkanes simulated by different MD models.

Alkane	$T$ , (K)	$\epsilon_0$ , Expt. <sup>a</sup>	$\epsilon_{\text{MD}}$ , npol MD <sup>b</sup>	$\epsilon_0$ , pol. MD <sup>c</sup>	$\epsilon_{\text{el}}$ , pol. MD <sup>c</sup>	$\epsilon_0$ , MDEC <sup>d</sup>
Ethane	184.55	1.7595	1.014	1.707	1.697	1.721
Propane	231.08	1.7957	1.015	1.798	1.768	1.795
Butane	272.65	1.8098	1.016	1.801	1.774	1.802
Isobutane	261.43	1.8176	1.015	1.905	1.823	1.850
Heptane	298.15	1.9113	1.018	2.021	1.977	2.013
Heptane	312.15	1.8904	1.018	1.976	1.933	1.967
Decane	298.15	1.9846	1.020	2.118	2.066	2.106
Decane	312.15	1.9668	1.019	2.128	2.074	2.113
rmsd of $\theta^e$ , (%)	...	...	96.4	5.1	...	4.3

<sup>a</sup>Experimental values (Ref. 23).<sup>b</sup>Conventional nonpolarizable MD model (Ref. 9).<sup>c</sup>Polarizable classical Drude oscillator model (Ref. 9).<sup>d</sup>MDEC model [Eq. (3)] where  $\epsilon_{\text{MD}}$  and  $\epsilon_{\text{el}}$  are taken from b and c respectively.<sup>e</sup>The relative error of the Born factor [Eq. (11)].

As far as the dielectric constant is concerned, the MDEC model states that the static dielectric constant is simply a product of the value found in nonpolarizable MD simulations and that of the electronic continuum [Eq. (3)]. As nonpolarizable simulations have already been done, we use the published results and check the above relation. The results are shown in Tables I and II for alcohols and alkanes, respectively, where the MDEC model is compared with both polarizable Drude model and with experiment.<sup>23</sup>

To quantify the comparison, we introduce a parameter  $\theta$ , which is a measure of how well a given dielectric constant reproduces the results of charging free energy calculations of spherical ions. Since the free energies are proportional to the corresponding Born factors,  $\Delta G \sim (1 - 1/\epsilon)$ , the parameter  $\theta$  is defined as

$$\theta = \frac{(1 - 1/\epsilon^{\text{sim}}) - (1 - 1/\epsilon^{\text{exp}})}{(1 - 1/\epsilon^{\text{exp}})}. \quad (11)$$

In Tables I and II, parameter  $\theta$  is shown for different types of simulations and for the MDEC model.

As predicted by the criterion in Eq. (10) the conventional nonpolarizable model satisfactorily reproduces the polarization effect in such polar media as alcohols (rmsd of  $\theta < 4\%$ , Table I); although, the polarizable classical Drude oscillator model<sup>17</sup> and the MDEC model demonstrate much better agreement with the experiment (rmsd of  $\theta < 1\%$  for both).

In the case of nonpolar media the conventional MD approach completely fails (rmsd of  $\theta \sim 100\%$ , see Table II); whereas, the polarizable Drude model<sup>9</sup> and the MDEC model satisfactorily describe the polarization of neat alkanes (rmsds of  $\theta$  are 5.1% and 4.3%, respectively). The MDEC approach appears to be even slightly favorable in this case. Thus, in the above examples the MDEC approach performs quite well for both polar and nonpolar media.

We have also examined the comparison of the MDEC model with polarizable calculations of low-polar ethers reported by Vorobyov *et al.*<sup>8</sup> In this case, however, the authors<sup>8</sup> have modified the nonbonded parameters of the nonpolarizable model compared with original CHARMM parametrization.<sup>2</sup> Specifically, to achieve a satisfactory agreement with both pure solvent properties and free energies of aqueous solvation, an “implicit overpolarization” of the charge distribution was introduced.<sup>8</sup> Since in this case the gas-phase dipole moments and the interactions with water were overestimated, the exact comparison with MDEC model was not possible.

We next explored the application of MDEC model to a low-dielectric interior of proteins, which have been studied in the past using nonpolarizable MD simulations.<sup>11</sup> For the dielectric permeability of the most internal region of cytochrome *c*, and several other proteins, Simonson and Brooks<sup>11</sup> and Simonson and Perahia<sup>12</sup> reported a value around 1.5 (and even lower deeper inside). This value is apparently too low to be the actual dielectric constant of the protein; indeed it is lower than the pure electronic permeability  $\epsilon_{\text{el}}=2$  estimated for cytochrome *c* in the polarizable calculation.<sup>13</sup> According to the MDEC model, to obtain the total (static) dielectric constant, the results of nonpolarizable simulations should be modified as given by Eq. (3). Considering the value 1.5 as

corresponding to  $\epsilon_{\text{MD}}$ , and using  $\epsilon_{\text{el}}=2$ , for static dielectric constant we obtain the value  $\epsilon_0=3.0$ , which is in agreement with the value 2.9 estimated by Muegge *et al.*<sup>28</sup>

In a related work, we have used the MDEC model for the analysis of dielectric properties of the interior of redox protein cytochrome *c* oxidase.<sup>29</sup> We have studied the charge insertion process that models deprotonation of His291 residue of  $\text{Cu}_B$  catalytic center in (dehydrated) CcO. The pure MD reaction-field energy (nonpolarizable force field was used, and no pure electronic polarization included explicitly) was found to correspond to an unphysically low protein dielectric constant of 1.3. However, when the pure electronic ( $\epsilon_{\text{el}}=2.0$ ) polarization energy was added explicitly, using Eq. (2), the microscopic reaction-field energy could be reproduced with a more realistic value of dry protein dielectric (i.e., no internal water is included) of 2.6. The estimated magnitude of the dry CcO dielectric constant in the region of the active site is consistent with earlier results for cytochrome *c* which are 2.9 (Ref. 28) or 3.0 [the value<sup>12</sup> corrected by Eq. (3)].

## V. CONCLUSIONS

- (1) In the MDEC model, the pure electronic polarization is explicitly described by the electronic continuum with phenomenological parameter  $\epsilon_{\text{el}}$ , while the nuclear dynamics is modeled in terms of a nonpolarizable force-field. The MDEC force-field deals with effective atomic charges, which are understood as “actual” charges scaled by factor  $1/\sqrt{\epsilon_{\text{el}}}$ . Thus the effective charges of ionized protein groups are not  $\pm 1$ , but instead  $\pm 1/\sqrt{\epsilon_{\text{el}}}$ .
- (2) To obtain the total solvation energy, the electronic solvation energy part is calculated explicitly using the Poisson equation, and added to the part found in MD simulations, as given by Eq. (2).
- (3) The dielectric constant of the medium obtained with standard MD is related to the static dielectric constant  $\epsilon_0$  by Eq. (3).
- (4) The conventional nonpolarizable force-fields are based on different principles, but can be modified by scaling charges of ionized groups to fit approximately the MDEC format.
- (5) To prove the concept, we demonstrated that dielectric constant estimations for polar alcohols<sup>17</sup> and nonpolar alkanes<sup>9</sup> as well as for the low-dielectric interior of proteins cytochrome *c* (Refs. 11 and 12) and cytochrome *c* oxidase<sup>29</sup> can be significantly improved once the data of conventional nonpolarizable MD simulations are considered according to the MDEC model. The MDEC model produces comparable results with the polarizable MD technique in many physically important cases;<sup>9,17</sup> whereas, a computational cost of the MDEC approach is no more than that of the conventional nonpolarizable MD.

Given the above examples and earlier reports,<sup>18–20,26,29</sup> we conclude that MDEC model is expected to work rather

well both in high- and low-dielectric media and can be considered as a low-cost alternative to fully polarizable MD algorithms.<sup>8,9,15-17</sup>

## ACKNOWLEDGMENTS

This work has been supported in part by the NSF Grant No. PHY 0646273. We would like to thank Dr. Igor Vorobyov for valuable discussion of his simulations using the polarizable Drude oscillator model.

## APPENDIX: FROM POLARIZABLE FORCE-FIELD TO ELECTRONIC CONTINUUM

The MDEC model considers point charges moving in homogeneous electronic continuum of known dielectric constant  $\epsilon_{\text{el}}$ . The interactions between charges in such a system are scaled by the factor  $1/\epsilon_{\text{el}}$ . It is instructive to see how this model appears from a microscopic polarizable model, such as the Drude model, as an approximation. Typically, a polarizable model deals with a system of polarizable point charges. The real system of course is neither a homogeneous electronic continuum nor the point polarizable dipoles; in fact, the polarizable point dipoles and the continuum model are two limiting approximations of the real system.

Consider a system of polarizable point charges. The energy of such a system is written as follows:

$$W(R_1, \dots, R_N) = \frac{1}{2} \sum_{i \neq j}^N \frac{q_i q_j}{R_{ij}} + \frac{1}{2} \sum_{i,j=1}^N d_i K(i,j) d_j - \sum_{i=1}^N E'(R_i) d_i + \sum_{i=1}^N W_{i0}, \quad (\text{A1})$$

where  $q$ 's are partial atomic charges, and  $d$ 's are the point dipoles located at the positions of the corresponding charges. The dipoles are induced by the electric field from other charges and other dipoles. The dipole-dipole interaction is quadratic and is described by the matrix  $\mathbf{K}$ ; the diagonal elements of this matrix are inverse polarizabilities  $1/\alpha$ , which are assumed to be the same for all charges. In addition to the dipole-dipole interactions, the dipoles also interact with the electric field of other point charges  $E'(R_i)$ . The field is taken at the position of the point dipole (and corresponding charge)  $R_i$ , and the prime indicates that the electric field does not include the field of the point charge itself. The last term, a constant, is not essential for dynamics of the coordinates  $R_i$ , yet a specific value can be assigned when the free energy of solvation is considered, as will be clear below. Here we write this constant as sum of "self-energies" of charges  $W_{i0} = q_i^2 / 2R_{ii}$ , where  $R_{ii}$  are the radii of the charges.

The polarizable dipoles represent the electronic polarizability of the atoms, and therefore respond to an external field "instantaneously." The external field here is the field of point atomic charges, which is changing together with the position of the nuclei on a much slower time-scale than the electronic response. Thus the polarization dipoles are always in equilibrium, and the dynamics of the nuclei coordinates  $R$  can be described with a Born–Oppenheimer type of effective

potential energy  $W(R_1, \dots, R_N)$ ; the dynamic coordinates of the dipoles are not present explicitly in this picture.

The equilibrium values of the dipoles can be found by minimizing the energy with respect to the dipole values. Each of the dipoles will have the following equilibrium value:

$$\bar{d}_i = \alpha \left( E'(R_i) - \sum_{j \neq i}^N K(i,j) \bar{d}_j \right), \quad (\text{A2})$$

where the first term in parenthesis is the electric field of the charges other than  $q_i$ , and the second is the electric field of other dipoles  $d_j$  at the position of the dipole  $d_i$ . All equilibrium values of the dipoles depend self-consistently on each other, and on the position of the nuclei, which determine the "external" field to which the dipoles are subjected to. The substitution of the above equilibrium values for dipoles into energy expression gives

$$W(R_1, \dots, R_N) = \frac{1}{2} \sum_{i \neq j}^N \frac{q_i q_j}{R_{ij}} - \frac{1}{2} \sum_{i=1}^N E'(R_i) \bar{d}_i + \sum_{i=1}^N W_{i0}. \quad (\text{A3})$$

The middle part of the above equation is the energy of the dipoles, which is the same as electronic polarization energy. The point dipole polarization is now written in terms of the polarized continuum as follows:

$$\bar{d}_i = \int_{V_{ai}} P'(r) dr, \quad (\text{A4})$$

where  $P(r)$  is the polarization density, and the integration is over the volume of the  $i$ th atom,  $V_{ai}$ . Since the boundaries between atoms are not well defined, here already the approximate character of the treatment becomes evident. The prime of the polarization density indicates that, in fact, this is only part of total polarization at point  $r$  caused by the electric field other than the field of the atom itself. (The rest of polarization, which is additive, is caused by the charge of the atom itself.) This polarization is proportional to the local external field, as in the usual macroscopic continuum electrostatics (here the electric displacement  $D$  is the same as  $E'$ ),

$$P'(r) = \frac{1}{4\pi} \frac{\epsilon_{\text{el}} - 1}{\epsilon_{\text{el}}} E'(r). \quad (\text{A5})$$

Assuming now that the external electric field  $E'(r)$  does not change significantly within the atomic dimensions (this is the second major approximation), the polarization energy can be written as follows:

$$W_{\text{el}} = - \frac{1}{2} \sum_{i=1}^N E'(R_i) \bar{d}_i = - \left( \frac{1 - \epsilon}{\epsilon} \right) \sum_{i=1}^N \int_{V_{ai}} \frac{E'^2(r)}{8\pi} dr, \quad (\text{A6})$$

which after some additional transformations becomes

$$W_{\text{el}} = - \left( \frac{1 - \epsilon}{\epsilon} \right) \left( \frac{1}{2} \sum_{i \neq j}^N \frac{q_i q_j}{R_{ij}} + \sum_{i=1}^N W_{i0} \right). \quad (\text{A7})$$

The substitution of the above relations into Eq. (3) gives for the total energy the following:

$$W(R_1, \dots, R_N) = \frac{1}{\epsilon_{\text{el}}} \left( \frac{1}{2} \sum_{i \neq j}^N \frac{q_i q_j}{R_{ij}} + \sum_{i=1}^N W_{i0} \right). \quad (\text{A8})$$

As expected, all interaction energies are scaled by the factor  $1/\epsilon_{\text{el}}$ , including self-energies  $W_{i0}/\epsilon_{\text{el}} = q_i^2/2\epsilon_{\text{el}}R_{ii}$ ; the energy of the polarization due to charges' own field is  $(1-1/\epsilon_{\text{el}})W_{i0}$ .

The above expression could have been written from the start for a system of charges in electronic continuum. The above derivation shows how the system of polarizable dipoles can be approximated by the continuum model. It follows from the above derivation that the dielectric constant  $\epsilon_{\text{el}}$  of the electronic continuum is related to polarizability of the dipoles  $\alpha$  and density of the system  $\rho$  in the usual way,

$$\epsilon_{\text{el}} - 1 = \frac{4\pi\alpha\rho}{1 - (4\pi/3)\alpha\rho}. \quad (\text{A9})$$

Thus, the energy of a system of point polarizable dipoles can be approximated by that of an equivalent continuum model; the numerical quality of the approximation is difficult to evaluate *a priori*, however, despite the known steps of the derivation that involve approximations. We check the quality of this approximation by comparing directly the results of calculations using the Drude model and an equivalent continuum model in Sec. IV of the paper.

From the above treatment it follows that the system of polarizable point charges can be substituted by a system of nonpolarizable point charges of scaled values  $q^{\text{eff}} = q/\sqrt{\epsilon_{\text{el}}}$ , so that the interaction between the scaled charges correctly reproduces the actual energy  $q_i^{\text{eff}} q_j^{\text{eff}}/R_{ij} = q_i q_j/\epsilon_{\text{el}} R_{ij}$  as if they were in vacuum. If one deals with groups of charges, which represent molecules, e.g., water, instead of individual point charges, the results are formally the same as above; in this case, however, there is no simple relation between partial charges of molecules in vacuum and effective charges in the condensed phase, because the vacuum charges already represent a polarized state of the molecule. In this case one can only say that there are effective charges that represent the scaled original point charges out of which the molecule is constructed. A good example of such a situation is the water molecule discussed in the text.

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