Mesoscale electrostatics driving particle dynamics in non-homogeneous dielectrics

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Abstract

We introduce a density functional-based formalism to compute the electrostatic energy and forces for a mesoscopic system in the condensed phase, described with molecular resolution. The dielectric permittivity is variable in space, and it is dependent on the density fields of the individual particles present in the system. The electrostatic potential is obtained from standard numerical solutions of the generalized Poisson equation. The presence of a particle-dependent varying dielectrics produces the appearance of mesoscopic polarization forces, which are dependent on the local fluctuations of the permittivity, as well as of the electrostatic field. The proposed implementation is numerically robust, with an error on the Coulomb forces that can be systematically controlled by the mesh of spatial grid used for solving the generalized Poisson equation. We show that the method presented here is able to reproduce the concentration-dependent partitioning of an ideal salt in water/oil mixtures, in particular, reproducing the $\propto 1/\epsilon$ dependency of the partition coefficient for the free ions predicted by Born theory. Moreover, this approach reproduces the correct electrostatic features of both dipolar and charged lipid bilayers, with positive membrane and dipole potentials. The sum of both Coulomb and polarization interactions inside the membrane yields a globally repulsive potential of mean force for the ions, independently on their charge. The computational efficiency of the method makes it particularly suitable for the description of large-scale polyelectrolyte soft-matter systems.
1 Introduction

Polyelectrolytic soft matter systems are associated to a large number of important phenomena in nature, including surfactant action,\(^1\) self-assembly of viral capsids,\(^2\) packing of the genetic code,\(^3\) or membrane electrochemical potentials.\(^4\) Any computational description of polyelectrolytes is complicated by a series of factors, including the \(R^{-1}\) slowly decaying Coulomb potential, the presence of free diffusing ions and a non-homogeneous dielectric environment. These hurdles sum on the general issue that phase-separated systems appear due to selective crowding and self-assembly of the different molecular species composing the systems. This makes any computational model with molecular resolution intrinsically expensive, as the stability of such assemblies require the presence of a non-reducible number of individual components.\(^5\)

Models comprising an all-atom resolution have benefited from years of development of efficient computer algorithms that aim for accurate and efficient computation of electrostatic forces.\(^6,7\) This in turn has led to accurate modelling biological systems, like proteins,\(^8–10\) lipids\(^11,12\) or nucleic acids.\(^13\) Nonetheless, atomistic modelling becomes computationally not feasible when addressing phenomena in the mesoscale (i.e., with size, time characteristic dimensions in the order of at least 100 nm, and milliseconds).\(^14,15\) This is due to both the diverging number of degrees of freedom and inter-molecular interactions that need to be treated, and the relatively short integration timesteps (typically 1 – 2 fs) imposed by the presence of fast vibrational modes.

In coarse-grained models (CG), a low-resolution representation of the molecular structure, is obtained by mapping multiple atoms into single beads.\(^16\) This lower resolution description not only reduces the number degrees of freedom, thereby reducing computation, but also filters out high frequency modes, allowing for longer time steps. Thus, CG models offers a route to study large-scale systems while maintaining the information (albeit, at low-resolution) on the molecular structure.

A variety of approaches to CG modelling,\(^17–22\) allow today to obtain insights on different
dynamic phenomena for soft matter and biological systems, including the complex morphology of lipid membranes, also interacting with membrane proteins the phase behavior of surfactants, as well as the structural fluctuations and folding of proteins, or DNA.

Nonetheless, the reduction of the degrees of freedom used to describe the molecular systems poses direct limitations in the capability of accurately describing all electrostatic features, and in particular the dielectric screening by the environment.

Through the years, several simplified methods aiming for modeling accurately electrostatics while keeping the computational advantage over atomistic approaches have been developed. Existing models can be grouped into three main categories: (i) implicit solvent models, which aim to describe the properties of solutes only, introducing implicitly the presence of the solvent as a background; (ii) explicit non-polarizable solvent models, which treat the solvent as a non-polarizable medium with specific dielectric/electrostatic properties; and (iii) polarizable solvent models, which introduce the dielectric response of the environment via explicit polarization.

In implicit solvent models, such as Generalized Born Implicit Solvent, the screening effect of solvent molecules is modeled by representing the solute within a cavity inside a homogeneous continuum dielectric, representing the solvent. The electrostatic potential inside the cavity is then obtained by solving the generalized linearized Poisson-Boltzmann equation. Such methods can accurately model electrostatic interactions inside the bulk, but are problematic at interfaces or inside membranes. Moreover, they do not account for the entropic effects of solvent molecules.

In approaches adopting molecular mechanics-like effective CG potentials, a uniform background dielectric is used to model the screening of electrostatics. This on one hand, greatly decreases computational cost due to the computation of Coulomb interactions of all the solvent molecules present in all atom simulations, but requires the calibration of effective interactions to mimic the presence of higher-order electrostatic forces than charge-charge
ones, appearing especially between charged and polar moieties. Moreover, as in implicit solvent, the use of uniform dielectric is particularly poor near interfaces, making modelling of partitioning phenomena of charged species challenging.\textsuperscript{61}

To obtain higher accuracy, solvent coarse grained models with explicit electrostatic properties have been developed.\textsuperscript{62} The dominant approach has been to map the solvent, and in particular water, into a minimal set of bodies that mimic the existence of and environment prone to polarization by dipole orientation. From the original idea by Warshel of introducing polarizable Langevin dipoles on a grid surrounding the solute,\textsuperscript{63} Borgis\textsuperscript{64} proposed the use of solvating pseudoparticles carrying dipoles which are sensitive to and get polarized by the electric field of the solute. More recent models use a CG mapping either four water molecules into three connected beads with opposite charges,\textsuperscript{65} five water molecules into two charged beads,\textsuperscript{66} or eleven water molecules into four beads in a tetrahedral arrangement, carrying each a partial charge.\textsuperscript{67} The introduction of charges increases accuracy, but at the cost of diminishing computational gain obtained by coarse-graining.

Breaking the bottleneck of simulations toward the mesoscopic scale relies therefore in the definition of efficient potentials that retain the effect of a spatially variable polarizable environment without the introduction of computationally heavy electrostatic features in the solvent model.

The structural and thermodynamic properties of soft condensed systems in the mesoscale are dominated by weak interactions of order $k_b T$.\textsuperscript{68} For this reason, they can be rather accurately described by density functional based potentials in the mean-field limit.\textsuperscript{29,69–77} In this work, we propose a description for electrostatic interactions based on the same logic. In particular, we present a formulation of electrostatics for molecular-resolved models in the condensed phase based on the dielectric screening, the macroscopic effect of molecular polarization, rather than the molecular polarization itself. We do this by introducing a spatially resolved dielectric that depends on the local density field of the different molecular species. Our approach has the advantage of treating all the multipolar interactions that
are higher in order than the direct Coulomb terms via an effective screening controlled by a smooth function, keeping the computational advantages of continuum dielectric models, and avoiding the introduction of additional degrees of freedom into the system, thus offering optimal computational performance.

2 Electrostatics in a dense molecular system

2.1 Electrostatic energy and forces

In a dense system, the total electrostatic interaction energy is expressed by the formula:\textsuperscript{78,79}

\[ W_{\text{elec}}[\{\phi(r)\}] = \frac{1}{2} \int dr \frac{D(r) \cdot D(r)}{\epsilon(r)}, \quad (1) \]

where \( D(r) \), \( \epsilon(r) \) are the electrostatic displacement field and the dielectric function, each dependent on the set of number densities \( \{\phi(r)\} \). The displacement field is particularly useful in the context of non-homogeneous dielectrics because its governing equation, the Maxwell equation for the displacement field, only involves free charges and not polarized charges.

Considering now the case of a molecular system composed by \( M \) species \( \{\phi(r)\} = \{\phi_1, ..., \phi_k, ..., \phi_M\} \) for each \( k \) type. The mean-field potential felt by a particle of type \( k \) at point \( r \), is derived through the saddle point approximation\textsuperscript{80} as the functional derivative

\[ V_{\text{ext},k}(r) = \frac{\delta W_{\text{elec}}}{\delta \phi_k(r)}, \quad (2) \]

which involves two terms, dependent on \( D(r) \) and \( \epsilon(r) \):

\[ V_{\text{ext},k}(r) = \int dr' \left( \frac{\delta W_{\text{elec}}}{\delta D(r')} \frac{\delta D(r')}{\delta \phi_k(r)} + \frac{\delta W_{\text{elec}}}{\delta \epsilon(r')} \frac{\delta \epsilon(r')}{\delta \phi_k(r)} \right). \quad (3) \]

Computing explicitly the two functional derivatives (SI 1 for detailed derivation), we obtain
the mean-field potential experienced by a particle of type \( k \) as:

\[
V_{\text{ext},k}(r) = q_k \psi(r) - \frac{1}{2} \frac{\partial \epsilon(r)}{\partial \phi_k(r)} |E(r)|^2,
\]

(4)

where the first derivation yields the potential energy felt by charged particle \( q_k \) in the electrostatic potential of the system \( \psi(r) \), and the second term defines the potential energy due to the polarization of medium. Here we have introduced the electrostatic field \( E(r) \), which is related to \( D(r) \) and \( \psi(r) \) by the relations:

\[
D(r) = -\epsilon(r) \nabla \psi(r) = \epsilon(r) E(r).
\]

(5)

The corresponding force acting on a particle \( k \) positioned at \( r \) is straightforwardly obtained by the spatial derivative of the potential energy:

\[
F_k(r) = q_k E(r) + \frac{1}{2} \nabla \left( \frac{\partial \epsilon(r)}{\partial \phi_k(r)} |E(r)|^2 \right).
\]

(6)

From the force on the different particles, it is possible to define the force density (force per unit volume) acting on a volume element placed at \( r \). In particular, the force density due to the polarization of the medium is:

\[
f_{\text{pol}}(r) \equiv \frac{1}{2} \sum_k \phi_k(r) \nabla \left( \frac{\partial \epsilon(r)}{\partial \phi_k(r)} |E(r)|^2 \right),
\]

(7)

which is equivalent to the polarization part of the Helmholtz force density defined in a continuous medium\(^{81}\) (see SI 2):

\[
f_{\text{pol}}(r) = \frac{1}{2} \nabla \left( \sum_k \phi_k(r) \frac{\partial \epsilon(r)}{\partial \phi_k(r)} |E(r)|^2 \right) - \frac{1}{2} \nabla \epsilon(r) |E(r)|^2.
\]

(8)

The explicit formulation of the polarization term in equation (4) depends on the modeling of the functional dependence of \( \epsilon(r) \) on the particle densities \( \{ \phi(r) \} \). Here, we model such
relationship by a weighted average of the dielectric value for each \( k \) species present in \( \mathbf{r} \):

\[
\epsilon(\{\varphi(\mathbf{r})\}) = \frac{\sum_{k}^{M} \epsilon_{k} \varphi_{k}(\mathbf{r})}{\varphi_{0}(\mathbf{r})},
\]

(9)

where \( \varphi_{0}(\mathbf{r}) \) is the sum of all particle densities: \( \varphi_{0}(\mathbf{r}) = \sum_{k} \varphi_{k}(\mathbf{r}) \). Assuming equation (9), equation (4) becomes:

\[
V_{\text{ext},k}(\mathbf{r}) = q_{k} \psi(\mathbf{r}) - \frac{1}{2} \frac{\epsilon_{k} - \epsilon(\mathbf{r})}{\varphi_{0}(\mathbf{r})} |\mathbf{E}(\mathbf{r})|^{2},
\]

(10)

and the corresponding force:

\[
F_{k}(\mathbf{r}) = q_{k} \mathbf{E}(\mathbf{r}) + \frac{1}{2} \nabla \left( \frac{\epsilon_{k} - \epsilon(\mathbf{r})}{\varphi_{0}(\mathbf{r})} |\mathbf{E}(\mathbf{r})|^{2} \right).
\]

(11)

The polarization component of the forces is thus formed by two contributions:

\[
F_{k,\text{pol}}(\mathbf{r}) = -\frac{1}{2} \nabla \epsilon(\mathbf{r}) \left( \frac{|\mathbf{E}(\mathbf{r})|^{2}}{\varphi_{0}(\mathbf{r})} \right) + \frac{1}{2} (\epsilon_{k} - \epsilon(\mathbf{r})) \nabla \left( \frac{|\mathbf{E}(\mathbf{r})|^{2}}{\varphi_{0}(\mathbf{r})} \right),
\]

(12)

Assuming homogeneous density \( (\varphi_{0}(\mathbf{r}) = \tilde{\varphi}_{0}) \), the polarization force can be interpreted as follows. The first term corresponds to a force acting on all particles that, in the presence of an external electrostatic field, seeks to homogenize the spatial distribution of the dielectrics. The second term tends to separate the dielectric, attracting the more polar particles (and repelling the less polar ones) towards the regions of the space characterized by a stronger electrostatic field.
2.2 Numerical solution for $\psi(r)$

The computation of forces through equation (11), requires the electrostatic potential $\psi(r)$ and is obtained by solving the generalized Poisson equation (GPE):

$$ \nabla \cdot (\epsilon(r) \nabla \psi(r)) = -\rho(r). $$

(13)

In the context of molecular dynamics, the GPE is a linear equation as $\epsilon(r)$ and $\rho(r)$ are predetermined by particle densities. Numerous methods exist for solving the linear GPE.\textsuperscript{83} We employ a finite difference scheme (which has been used in MD with implicit solvent,\textsuperscript{84} or in the reaction field method\textsuperscript{85}) on regular grid and solve the linear system of equations iteratively using the Successive over relaxation method.\textsuperscript{86} For typical grids ($\sim 0.6-8$ nm) and potential update times ($\delta t \simeq 0.3$ ps) used in hPF calculations, the routine spends only 10% of the total simulation time even using an overly tight convergence criterion for the electrostatic potential (average change per iteration lower than $10^{-6}$ mV). By loosening the criterion of convergence by one order of magnitude ($10^{-5}$ mV), the time spent by the same routine drops to 3% of total time. More details on details on the procedure are provided in SI 3.

2.3 Implementation within the hybrid particle-field molecular dynamics approach

To compute intermolecular interactions, we use the hybrid particle field (hPF) method coupled to molecular dynamics.\textsuperscript{80} In this method, individual molecules are described as non interacting systems coupled via a density-dependent interaction functional:

$$ H = H_0(\{r\}) + W[\{\phi\}], $$

(14)

where $H_0(\{r\})$ is the energy of a single molecule decoupled from the environment and is dependent on the set of particle positions $\{r\}$. $W[\{\phi\}]$ is a density-field functional used for
modeling intermolecular interactions. We split the interaction energy functional into two parts:

\[ W = W_{\text{non-elec}} + W_{\text{elec}}, \]  

(15)

where the electrostatic interaction energy has already been described. The non-electrostatic interaction can be modelled in multiple ways, as in previous publications,\textsuperscript{80} here we use:

\[
W_{\text{non-elec}} \{\phi\} = \frac{1}{\tilde{\phi}_0} \int \text{d}r \left[ \frac{k_b T}{2} \sum_{k,\ell} \chi_{k\ell} \phi_k(r) \phi_\ell(r) + \frac{1}{2\kappa} \left( \sum_k \phi_k(r) - \tilde{\phi}_0 \right)^2 \right],
\]  

(16)

where \( \chi_{k\ell} \) is the mean field coupling term between particles of type \( k \) and \( \ell \), \( \kappa \) is the compressibility constant controlling local fluctuations of densities in the system, and \( \tilde{\phi}_0 \) is the average number density of the whole system. The external field felt by a particle of type \( k \) at position \( r \) is obtained, as in equation (2), by the saddle point approximation:

\[
V_{\text{ext},k}(r) = \frac{1}{\tilde{\phi}_0} \left[ k_b T \sum_\ell \chi_{k\ell} \phi_\ell(r) + \frac{1}{\kappa} \left( \sum_\ell \phi_\ell(r) - \tilde{\phi}_0 \right) \right].
\]  

(17)

The corresponding force is obtained by:

\[
F_{\text{ext},k}(r) = -\frac{1}{\tilde{\phi}_0} \left[ \sum_\ell \left( k_b T \chi_{k\ell} + \frac{1}{\kappa} \right) \frac{\partial \phi_\ell(r)}{\partial r} \right].
\]  

(18)

In practice, these forces are computed by a linear interpolation scheme from local densities and gradients of densities which are computed on a mesh. Details on the procedure can be found in ref.\textsuperscript{80}

The method here introduced was implemented in the OCCAM hybrid particle field molecular dynamics software.\textsuperscript{87} Next, we present three examples to benchmark the performance of the presented scheme for electrostatics coupled to hybrid particle-field molecular dynamics (hPF-MD/e hereafter).
2.4 Benchmarking of the implementation

Figure 1: Benchmark on Coulomb interactions with hPF-MD/e. The main plot (panel a) reports the intensity of the forces acting on two charged particles of opposite signs as a function of the relative distance computed numerically by hPF-MD/e, $F_{\text{hPF-MD/e}}$ for a grid of 0.65 nm compared to the analytic values, $F_{\text{analytic}}$. The inset (panel b) presents the mean relative error in the 1-5 nm range as a function of grid size $b$.

We verified the accuracy on the calculation of the forces for a simple model system composed of two oppositely unit charged particles placed in a large box ($20 \times 20 \times 20 \text{ nm}^3$) separated by a distance $d$ under uniform dielectric $\epsilon_r = 1$. Figure 1 reports benchmarking of the accuracy (Top and middle panels). The force between two charges shows an excellent agreement with theoretical Coulomb force. For inter-particle distance approaching the grid size, the force goes towards zero. This is due to having distributed charges and not point particles. The primary determining factor of accuracy is the grid size $b$ used for solving the GPE. The inset panel shows how the relative error of the computed force depends on the grid resolution $b$. The electrostatic forces can be systematically improved by increasing the grid mesh to the required precision (Figure 1). Already, using a grid size between 0.6 and 0.7 nm, good accuracy is obtained. It is worth noting that, a similar grid size has been prescribed to correctly describe several non charged systems by using a density field description for non-charged matter systems by hPF-MD.\textsuperscript{24,88}
3 Results and discussion

3.1 Partitioning of ions in a bi-phase system

As a first test, we investigated the ability of our model to reproduce the behavior of an ideal monovalent binary salt \( A^+B^- \) dissolved in a bi-phase solution composed by water, characterized by a dielectric \( \epsilon_w = 80 \), and an oil of dielectric \( \epsilon_o \leq \epsilon_w \). The salt species are expected to distribute between the two solvents according the chemical equilibria shown in Figure 2, which include the thermodynamic dissociation constants \( K_w \) and \( K_o \) in the water and the oil phases, and the partition coefficients \( P^{p_{ip}}_{o/w} \) and \( P^{\pm}_{o/w} \) for the ion couples and for the free ions, respectively. Here we assume that, for ideal ions, the partition coefficients of the positive and negative free ions are identical. The distribution coefficient, which is the most easily attainable quantity in experiments,\(^{80}\) measures the total partitioning of the salt, irrespective of its protolytic state, and it is given by:

\[
D_{o/w} = \frac{c_o}{c_w},
\]  

(19)

where \( c_o \) and \( c_w \) are the total concentrations of salt \( ([AB] + [A^+]) \) in oil and water, respectively. Contrary to the individual equilibrium constants \( (K_w, K_o, P^{p_{ip}}_{o/w}, P^{\pm}_{o/w}) \), \( D_{o/w} \) is
dependent on the nominal salt concentration in the whole system $c$ by the relationship:\cite{89}

\[
D_{o/w} = \frac{P_{o/w}^{ip} + \alpha(P_{o/w}^{\pm} - P_{o/w}^{ip})}{1 + \alpha(P_{o/w}^{ip} - P_{o/w}^{\pm})},
\]  

(20)

where

\[
\alpha = \frac{-A + \sqrt{A^2 + 4A(1 + P_{o/w}^{ip})c}}{2(1 + P_{o/w}^{ip})(1 + P_{o/w}^{\pm})c},
\]  

(21)

and

\[
A = K_w(1 + P_{o/w}^{\pm})^2.
\]  

(22)

Figure 3: Partition coefficient and dissociation constants for an ideal salt in an oil/water mixture from hPF-MD/e. (Top) Distribution coefficient $D_{o/w}$ as function of the total salt concentration at different values of the dielectric constant for the oil $\epsilon_o$. (Bottom) Partition coefficients of unpaired ions and paired ions, obtained by fitting equation (20) on the data in the top graph. The black line is obtained by fitting $\gamma$ in equation (23) from data points of $P_{o/w}^{\pm}$. (Bottom inset) Dissociation constants of the ion pair in water and oil. The continuous black line is the prediction obtained from equation (24), using $\gamma$ obtained from fitting (23) and assuming $P_{o/w}^{ip} = 1$. 

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The concentration-independent constants can be extrapolated by fitting equation (20) against \( c \). Figure 3 reports \( D_{o/w} \) obtained from hPF-MD/e simulations for different concentrations \( c \) and values of \( \epsilon_o \) (simulation details in SI 4.1). In agreement with equation (20), by increasing the total salt concentration we observe a decrease in the partitioning between the two phases. Figure 3 also reports the corresponding equilibrium constants for a range of dielectric values obtained by our fitting. In particular, the dependence of the partitioning coefficient \( P_{o/w}^\pm \) on \( \epsilon_o \) found in our simulations respects the Born theory of ions,\(^90\) predicting that:

\[
\log P_{o/w}^\pm = \gamma \left( \frac{1}{\epsilon_w} - \frac{1}{\epsilon_o} \right),
\]

(23)

where \( \gamma \) is a constant dependent on the ion.

\( P_{o/w}^{ip} \), the partition coefficient for the ion pairs, takes values near 1, and varies little with \( \epsilon_o \). This is due to the fact that the ion pairs, having a zero net charge, are not affected as much as the free ions by the difference in the dielectric between the two media. The ion dissociation \( K_o \) is determined by the thermodynamic cycle in Figure 2:\(^91\)

\[
\log K_o = \log K_w - \log P_{o/w}^{ip} + 2\gamma \left( \frac{1}{\epsilon_w} - \frac{1}{\epsilon_o} \right),
\]

(24)

which is also in good agreement with the data from the hPF/e simulations.

### 3.2 Ion permeation in charged and polar membranes

After having verified the correct behavior of the bulk charge distribution in two liquids, we now consider the simulation of a concentration of 100 mM of ideal salt in the presence of model membranes. Specifically we take into consideration the two cases of (i) a dipolar lipid bilayer of palmitoyloleoyl phosphatidylcholine (POPC), and (ii) a negatively-charged membrane consisting of palmitoyloleoyl phosphatidyglycerol (POPG). The lipid molecules are represented using a coarse-grained mapping analogous to that of the Martini CG force-field,\(^23\) as presented in previous works,\(^92\) restraining the lipids to an ideal packing structure.
Figure 4: Scheme of the structure of the constituted lipid bilayers. The indigo region is occupied by the hydrophobic lipid tails, the gray spheres represent the polar or charged lipid heads. Ions distribute in the surrounding water. Water is not shown for clarity. The red plot reports the average dielectric value along normal axis of the lipid bilayer, as obtained from equation (9).

This is done to provide optimal comparison for the different systems, as differences in the observed results are necessarily due to the different electrostatic treatment only. Details on the system setup are provided in SI 4.2.

In a first set of simulations, a uniform dielectric value was assigned to all beads. In particular, we tested both a uniform value of $\epsilon_{80} \equiv 80$, corresponding to the relative dielectric constant of water, as well as $\epsilon_{15} \equiv 15$ which is a commonly used value in the literature in CG studies on constituted lipid bilayers.\(^{23}\) In a second set of simulations, water and ions were assigned a dielectric $\epsilon_r = 80$, while a low dielectric value ($\epsilon_r = 1$) was used for the lipids ($\epsilon_{1,80}$).

As depicted in Figure 5, the electrostatic potentials obtained for both the uniform and varying dielectric conditions contain the expected key features of charged and zwitterionic membranes. In particular, the potentials always feature a global minimum at the quota of the negatively charged phosphorous, the dipole potential (the electrostatic potential at the midpoint of the membrane) features a local maximum, and the surface potential (the potential difference between the bulk and the membrane) is positive. The intensity of the
Figure 5: Average electrostatic potential $\psi$ along the normal axis to the membrane $z$ from its midpoint. The graph reports values of $\psi$ obtained for the charged (panel a) and polar membranes (panel b), using varying ($\epsilon_{1,80}$) or constant values ($\epsilon_{15}, \epsilon_{80}$) of the dielectric.

The surface potential obtained for charged membranes is consistent with past Poisson-Boltzmann calculations (in the order of 100-200 mV). We observe that for both systems, the use of a varying dielectric produces systematically higher values for both the dipole and the surface potentials. In particular, in Zwitterionic membranes the dipole potential raises up to $\sim$300 mV, falling within the experimentally observed range of 200 – 1000 mV.

The polarization forces acting on the individual particles are about two orders of magnitude weaker than the Coulomb ones (for the charged lipid bilayer $\langle |\mathbf{F}_{\text{pol}}| \rangle = 0.07 \text{ kJ mol}^{-1}\text{ nm}^{-1}$ and $\langle |\mathbf{F}_{\text{Coul}}| \rangle = 6.92 \text{ kJ mol}^{-1}\text{ nm}^{-1}$). Nonetheless, as they act on the totality of the particles present in the system, they contribute to the $\sigma_{zz}$ component of the stress tensor with a comparable magnitude to the one of the Coulomb term (Figure 6). As also previously reported, the contribution to the stress profile due to the electrostatic forces in the presence of a constant dielectric is reduced to a peak at the quota of the polar/charged heads. On the contrary, in the presence of variable dielectric, the Coulomb and polarization forces contribute differently to the stress, also depending on the electrostatic nature of the lipid head yielding an inner value different from the one at the solvent quota.
Figure 6: Contributions to the stress tensor $\sigma_{zz}$ along the normal axis $z$ using a uniform and nonuniform dielectric ($\epsilon_{15}$ and $\epsilon_{1,80}$) for a charged (panel a) and a polar membrane (panel b). The origin of the $z$ axis is set at the midpoint of the membrane.

Figure 7: (Panels a, b) Concentrations $c$ and (Panels c, d) corresponding potentials of mean force $w$ for both the positive and negative ions $A^+$, $B^-$ as a function of the normal axis $z$ from the membrane midpoint. The graphics report values for both the charged and polar membranes, using different modelling of the dielectric.
Figure 7 reports the statistical distribution of the positive and negative ions as a function of $z$, which results from the combined effect of both the Coulomb and polarization force contributions. In the presence of a zwitterionic dipolar head, the use of a constant dielectric systematically produces a rather flat potential of mean force (PMF) for the positive ions, which can almost freely diffuse through the membrane. On the contrary, the permeation in a varying dielectric environment is hindered, with a concentration of positive charges inside the membrane two orders of magnitude lower than in the bulk solvent. The permeation of the negative ions is strongly influenced by the surface potential, which for all dielectric values, is high enough to keep negatively charged ions away from the membrane and out in the bulk. The distribution of the ions in the system depends on the combined action of both the electrostatic and the polarization forces. Remarkably, only the use of a varying dielectric produces a significant increase of the potential of mean force $w$ for both the positive and negative ions inside the membranes, which is consistent with an expected low ion permeation through the bilayer. On the contrary, the use of a constant dielectric is less capable of producing a partitioning between the aqueous and lipid phases, regardless of the dielectric value. In particular, we observe a systematic underestimation of $w$ for the positive ions, and a consequent excessive diffusion of the same ions into the lipid bilayer.

4 Conclusion

The development of a density field-mediated particle potential for electrostatics allows a computationally inexpensive treatment of electrostatic interactions which is able to take into account the spatial distribution of individual particles producing a non-homogeneous dielectric screening. In particular, the present model describes the effect of polarization into the motion of the individual particles composing the system without the need of treating this term via additional degrees of freedom like charge-resolved solvent models, Drude-polarization charges or induced dipoles. Our tests show how this model describes well the mesoscopic
behaviour of ideal ions in the presence of phase-separated solvents, or at water/lipid interfaces. In the latter case, the model is able to predict the appearance of membrane potentials that prevent both positive and negative ions from diffusing through it. This is a result that is not easily attainable in the absence of a spatially-varying dielectric, in which case reproducing the correct ion permeation requires the introduction of additional non-electrostatic effective potentials acting between the ions and the membrane or the solvent. The combined effect of the Coulomb and polarization forces produce a more complex stress profile along the normal axis of a lipid bilayer, which is absent when using a constant effective dielectric background. The appearance of such features in the stress profile implies the presence of additional physical features into the systems, which can be exploited in future calibrations of lipids and surfactants with improved structural properties like the average area-per-head or the lateral diffusion in self-assembled structures such as micelles or vesicles.

In this work, we restricted our analysis to systems containing ideal ions. This choice was done to determine with clarity what features are directly captured by the proposed electrostatic model. In fact, the description of the chemical variability of different species can be straightforwardly included by other non-electrostatic terms of the potential, for example by the standard hPF functionals described so far in the literature.\textsuperscript{80,96–98}

In this perspective, the proposed model provides an excellent route toward an improved description of very large and complex polyelectrolytic multi-phase systems like those found in biological environments, consistently with the definition of hPF-consistent CG models for bio-polymers where the electrostatic features are explicitly taken into account.\textsuperscript{51}

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Supporting Information Available

Full derivation of the polarization forces, documentatition on numerical solver for the GPE, and system setup for ion partitioning and ion/membrane simulations.

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∇(\epsilon(r)\nabla\psi(r)) = -\rho(r)