Dielectric boundary force and its crucial role in gramicidin

Boaz Nadler,[1,*] Uwe Hollerbach,[2] and R. S. Eisenberg[2]

[1]*Department of Mathematics, Yale University, New Haven, Connecticut 06520, USA*
[2]*Department of Molecular Biophysics and Physiology, Rush Medical Center, 1750 Harrison Street, Chicago, Illinois 60612, USA*

In an electrostatic problem with nonuniform geometry, a charge Q in one region induces surface charges [called dielectric boundary charges (DBC)] at boundaries between different dielectrics. These *induced* surface charges, in return, exert a force [called dielectric boundary force (DBF)] on the charge Q that induced them. The DBF is often overlooked. It is not present in standard continuum theories of (point) ions in or near membranes and proteins, such as Gouy-Chapman, Debye-Huckel, Poisson-Boltzmann or Poisson-Nernst-Planck. The DBF is important when a charge Q is near dielectric interfaces, for example, when ions permeate through protein channels embedded in biological membranes. In this paper, we define the DBF and calculate it explicitly for a planar dielectric wall and for a tunnel geometry resembling the ionic channel gramicidin. In general, we formulate the DBF in a form useful for continuum theories, namely, as a solution of a partial differential equation with boundary conditions. The DBF plays a crucial role in the permeation of ions through the gramicidin channel. A positive ion in the channel produces a DBF of opposite sign to that of the fixed charge force (FCF) produced by the permanent charge of the gramicidin polypeptide, and so the net force on the positive ion is reduced. A negative ion creates a DBF of the same sign as the FCF and so the net (repulsive) force on the negative ion is increased. Thus, a positive ion can permeate the channel, while a negative ion is excluded from it. In gramicidin, it is this balance between the FCF and DBF that allows only singly charged positive ions to move into and through the channel. The DBF is not directly responsible, however, for selectivity between the alkali metal ions (e.g., Li^+, Na^+, K^+): we prove that the DBF on a mobile spherical ion is independent of the ion's radius.

I. INTRODUCTION

Complex systems of atoms are necessarily studied on many length scales. While essential properties often depend on the behavior of the individual atoms at the picosecond/Angstrom time and length scales, the macroscopic function of many systems is usually characterized by the collective behavior at much coarser time and length scales. Studying a system that operates on a micron/microsecond scale, by a detailed molecular simulation of all the motions of all particles, is a daunting process, not always necessary and perhaps even impossible because of the enormous number of numbers needed to describe the wildly fluctuating potentials, forces, concentrations, and fluxes of atoms on the femtosecond and even picosecond time scales. Even if it were possible to calculate so many numbers reliably, it is not clear what one would do with all of them. Clearly, some averaged estimators are needed to characterize atomic motions. Fortunately, atomic fluctuations are usually dramatically smoothed when considered on the micron/microsecond time scale of biological function and can be described in a greatly condensed manner by only a few numbers.

Continuum theories tacitly avoid these fluctuations by using constitutive relations and (macroscopic) conservation laws. In the Gouy-Chapman, Debye-Huckel, Poisson-Boltzmann or Nernst-Planck treatments of ions in solutions, near membranes and proteins [1–4], the concentrations are described by mean values of number density, and the force

acting on the ions is the gradient of a mean-field potential that satisfies a suitable Poisson equation (in self-consistent theories). Continuum theories do not, however, include structure (on the atomic scale) because discrete particles are not found in these theories. Continuum theories usually ignore the finite volume of atoms (and resulting effects of crowding), and so their structure is, in fact, specified (mostly) by the spatial distribution of dielectric coefficient and diffusion coefficient, and a continuum description of fixed charges.

We now see the essence of the problem of computing properties of ions in solutions and proteins. On the one hand, continuum treatments automatically satisfy conservation laws, and are built to describe the constitutive equations that describe the averaged properties of such systems on the micron/microsecond scale, but the roles of atomic structure and forces are unclear. On the other hand, particle treatments have well-defined structures and forces on the atomic scale, but contain huge fluctuations, may be impossible to compute reliably for the required time scales, and may not even satisfy macroscopic conservation laws and constitutive equations.

What is needed is thus a mathematical averaging procedure, to derive exact macroscopic equations from the underlying molecular model. In Ref. [5], we began a systematic general analysis of this problem. Starting from a molecular model of diffusing and interacting particles, a mathematical derivation of continuity equations is presented. As shown in Ref. [5], the averaged single particle density satisfies a Nernst-Planck–(drift-diffusion) type equation, driven by an average force. This force contains three terms. The first is the averaged electrostatic force acting on a point particle, the

*Electronic address: boaz.nadler@yale.edu

second is the average short range force due to particle-particle Lennard-Jones-type interactions, and the third is the dielectric boundary force (DBF). The last two terms, each of considerable importance in the context of molecular biology, are absent from the standard continuum theories.

In this paper, we concentrate on the DBF defined below, show how the DBF can be included in continuum treatments, and estimate its size and importance. In Sec. II, we define precisely the dielectric boundary force, discuss different possible ways to efficiently compute it, and show that for the case of charged spheres, the DBF is independent of the radius of the sphere. It is the same on a point particle and a spherical particle. Mathematically, this result is important because it allows the DBF to be naturally added into the usual continuum treatment of point particles, allowing the considerable investment in such models to remain productive. Biologically, the independence of particle size is also important: the DBF is not directly responsible for the selectivity of protein channels to different (spherical) ions such as the alkali metal ions Li^+, Na^+, K^+. In Sec. III, we calculate the dielectric boundary force for two simple geometries. The first is a point charge near a planar dielectric wall, for which an analytic solution is known. The second is a point charge in a narrow tunnel chosen to resemble the gramicidin channel, widely studied in channology [6]. Our results show that while the DBF is not large even at microscopic distances from a planar dielectric wall, it is certainly large in narrow channels.

In the gramicidin channel, comparing the DBF to the fixed charge force (FCF) gives a striking result, directly related to the function of this macromolecule. In gramicidin, the DBF and FCF nearly *cancel* when the ion in the channel has a single positive charge. It is this almost exact cancellation that allows monovalent positive ions to enter and permeate through gramicidin. When the ion in gramicidin has a negative charge, however, both DBF and FCF forces are repulsive and add up in magnitude. The summation of the two forces keeps negative ions out of gramicidin so that they cannot even begin to permeate through the channel.

The addition of forces for negative ions *does not* depend on a special property of gramicidin. It occurs automatically in any channel with a negatively charged wall: negative ions are excluded from and therefore do not permeate channels with negatively charged walls.

The cancellation of forces for positive ions *does* depend on a special property of gramicidin. The cancellation does not occur automatically for any positive ion in any narrow channel. Cancellation is a consequence of the particular structure of gramicidin, and its spatial distribution of fixed charge. Indeed, our analysis suggests that divalent ions, such as Ca^{++}, do not permeate gramicidin because the DBF and FCF are not in balance for them.

The cancellation of forces is evidently a result of the evolution that optimized the architecture of the gramicidin polypeptide to allow permeation of positive monovalent ions. Properties of the gramicidin polypeptide have been optimized to perform a specific function, e.g., the spatial distributions of fixed charge and dielectric coefficient have been optimized to balance the DBF and FCF and allow the per-

meation of positive ions that make gramicidin a conducting channel. The balance between the DBF and the FCF needs to be investigated further in other proteins and enzymes.

II. THE DIELECTRIC BOUNDARY FORCE

For simplicity, we consider the dielectric boundary force for an electrostatic problem defined in whole space. The modifications needed in a finite computational region with Dirichlet (or other) boundary conditions are straightforward, and do not change the main results of this section.

Consider thus the following setup: The three-dimensional space is composed of an arbitrary number of regions of arbitrary shapes, denoted by Ω_i. Further assume that in each region Ω_i the dielectric coefficient is constant with value ε_i. Now consider a charge distribution located, for example, inside the region Ω_1. A simple example is an ion in an aquatic solution with $\varepsilon_1 = 80$, located near the wall of a biological membrane with $\varepsilon_2 = 2$.

In the presence of a fixed charge, surface charges are induced at all boundaries between regions of different polarizability, and most standard textbooks on electrostatics explicitly write formulas expressing these induced surface charges as gradients of the electrostatic potential [7,8]. However, an important point, which is usually not discussed explicitly, is that these induced surface charges, in turn, exert a force on the charge distribution itself. We denote this force by $\boldsymbol{F}_{ind}$, and refer to it as the *dielectric boundary force*.

The force on a test particle in a homogeneous system can be computed from the gradient of the electrostatic potential due to all *other* charges, evaluated at the particle's location and ignoring the particle itself; this is not the case for an inhomogeneous system. In inhomogeneous systems, an additional component of force—the DBF—is produced by the surface charges induced by the particle in question. Therefore, to compute these induced surface charges, the charge of the test particle (on which we want to compute the force) must be included in the Poisson equation. However, if the test particle is a point charge this introduces a singularity at the location of the particle. In the following section, we explicitly describe the calculation of the DBF for a charge distribution and for a point charge.

A. The dielectric boundary force on a charge distribution

Let $\rho(\boldsymbol{r})$ denote a charge distribution located only inside the region Ω_1 [that is, $\rho(\boldsymbol{r}) = 0$ for $\boldsymbol{r} \notin \Omega_1$]. The electrostatic potential in whole space, $\Phi(\boldsymbol{r})$, satisfies the Poisson equation

$$\boldsymbol{\nabla} \cdot [\varepsilon(\boldsymbol{r}) \boldsymbol{\nabla} \Phi(\boldsymbol{r})] = -\frac{1}{\varepsilon_0} \rho(\boldsymbol{r}), \qquad (1)$$

where $\varepsilon(\boldsymbol{r})$ is the relative dielectric coefficient at $\boldsymbol{r}$. Since $\varepsilon(\boldsymbol{r})$ is discontinuous across the boundaries $\partial\Omega_i$, the potential $\Phi(\boldsymbol{r})$ satisfies the standard jump conditions for the normal component of the field [7]:

$$[\varepsilon(\boldsymbol{r}) \boldsymbol{\nabla} \Phi(\boldsymbol{r}) \cdot \boldsymbol{n}]|_{\partial\Omega_i} = 0, \qquad (2)$$

where $\boldsymbol{n}$ is a unit vector in the outer normal direction to a surface element on $\partial\Omega_i$, and square brackets denote the difference in the variables enclosed within them, between the value outside the region Ω_i and inside it.

In addition, we assume that the electrostatic potential at infinity is zero, so that $\Phi(\boldsymbol{r})$ satisfies the additional condition

$$\Phi(\boldsymbol{r})=0 \quad \text{as} \quad |\boldsymbol{r}|\to\infty.$$

The presence of the charge distribution $\rho(\boldsymbol{r})$ induces surface charges σ_{ind} at the dielectric boundaries $\partial\Omega_i$, given by

$$\sigma_{ind}|_{\partial\Omega_i}=[\boldsymbol{\nabla}\Phi\cdot\boldsymbol{n}]|_{\partial\Omega_i}. \tag{3}$$

These induced surface charges, in return, exert a force on the charge distribution $\rho(\boldsymbol{r})$ that induced them. One way to compute this force is to first calculate these induced surface charges, and then calculate the electric potential $\Phi_{ind}(\boldsymbol{r})$ formed by them. Then, the total force on the charge distribution due to these induced surface charges is given by

$$\boldsymbol{F}_{ind}=-\int \rho(\boldsymbol{r})\boldsymbol{\nabla}\Phi_{ind}(\boldsymbol{r})d\boldsymbol{r}. \tag{4}$$

We now consider the equation that the potential $\Phi_{ind}(\boldsymbol{r})$ satisfies. Since the polarization of the different regions Ω_i has already been taken into account in the computation of the induced surface charges via Eqs. (1)–(3), the potential $\Phi_{ind}(\boldsymbol{r})$ satisfies Laplace's equation with a dielectric coefficient of vacuum, i.e., with a relative dielectric coefficient $\varepsilon(\boldsymbol{r})=1$ throughout the whole space,

$$\Delta\Phi_{ind}(\boldsymbol{r})=0. \tag{5}$$

In addition, as with $\Phi(\boldsymbol{r})$, the potential $\Phi_{ind}(\boldsymbol{r})$ also vanishes as $|\boldsymbol{r}|\to\infty$. The charge distribution $\rho(\boldsymbol{r})$ is not present in Eq. (5), since the potential Φ_{ind} is only due to the surface charges induced at the dielectric interfaces.

While there are no dielectric boundaries for the potential $\Phi_{ind}(\boldsymbol{r})$ [recall that $\varepsilon(\boldsymbol{r})=1$ everywhere], there are surface charges, given by Eq. (3), located at these boundaries. This amounts to the following jump conditions:

$$[\boldsymbol{\nabla}\Phi_{ind}\cdot\boldsymbol{n}]|_{\partial\Omega_i}=\sigma_{ind}|_{\partial\Omega_i}. \tag{6}$$

According to this formulation, in order to compute the dielectric boundary force, one has to compute the solution of two Poisson equations; one for the electrostatic potential $\Phi(\boldsymbol{r})$ throughout space and another for the electrostatic potential created only by the induced surface charges $\Phi_{ind}(\boldsymbol{r})$.

However, as shown below, for any arbitrary continuum charge distribution, it is possible to compute this force from just the solution of the first Poisson equation for the electrostatic potential $\Phi(\boldsymbol{r})$. The singular case of a point charge and its connection with the DBF for a charged sphere are postponed to the following section.

We now show the connection between the dielectric boundary force, given by Eq. (4), the induced potential Φ_{ind}, and the electrostatic potential Φ by writing $\Phi_{ind}(\boldsymbol{r})=\Phi(\boldsymbol{r})+W(\boldsymbol{r})$, so that

$$\boldsymbol{F}_{ind}=-\int \rho(\boldsymbol{r})\boldsymbol{\nabla}\Phi(\boldsymbol{r})d\boldsymbol{r}-\int \rho(\boldsymbol{r})\boldsymbol{\nabla}W(\boldsymbol{r})d\boldsymbol{r}. \tag{7}$$

Equations (1) and (5) imply that $W(\boldsymbol{r})$ satisfies the following Poisson equation:

$$\Delta W(\boldsymbol{r})=\frac{\rho(\boldsymbol{r})}{\varepsilon_0\varepsilon_1} \tag{8}$$

as if the whole space was composed of a single dielectric medium of strength ε_1. In addition, because Φ and Φ_{ind} satisfy the same jump conditions at $\partial\Omega_i$, W is continuous,

$$[\nabla W\cdot\boldsymbol{n}]|_{\partial\Omega_i}=0. \tag{9}$$

Therefore, $W(\boldsymbol{r})$ is simply the free space Coulomb potential created by the charge distribution $-\rho(\boldsymbol{r})$,

$$W(\boldsymbol{r})=-\frac{1}{4\pi\varepsilon_1\varepsilon_0}\int\frac{\rho(\boldsymbol{\xi})}{|\boldsymbol{r}-\boldsymbol{\xi}|}d\boldsymbol{\xi}.$$

Thus,

$$\int \rho(\boldsymbol{r})\nabla W(\boldsymbol{r})d\boldsymbol{r}=\frac{1}{4\pi\varepsilon_1\varepsilon_0}\int\int\rho(\boldsymbol{r})\rho(\boldsymbol{\xi})\frac{\boldsymbol{r}-\boldsymbol{\xi}}{|\boldsymbol{r}-\boldsymbol{\xi}|^3}d\boldsymbol{r}d\boldsymbol{\xi}.$$

This integral vanishes, because each pair of points $(\boldsymbol{x},\boldsymbol{y})$ appears twice; once as $\boldsymbol{x}-\boldsymbol{y}$ (when $\boldsymbol{r}=\boldsymbol{x},\boldsymbol{\xi}=\boldsymbol{y}$) and once as $\boldsymbol{y}-\boldsymbol{x}$ (when $\boldsymbol{r}=\boldsymbol{y},\boldsymbol{\xi}=\boldsymbol{x}$). The physical explanation is that this integral is simply the total force that a charge distribution in free space exerts on itself, which is obviously zero according to Newton's third law. Combining this result with Eq. (7) gives

$$\boldsymbol{F}_{ind}=-\int \rho(\boldsymbol{r})\boldsymbol{\nabla}\Phi(\boldsymbol{r})d\boldsymbol{r}. \tag{10}$$

Thus, for the purpose of computing the DBF, there is no need to actually compute the induced potential $\Phi_{ind}(\boldsymbol{r})$.

B. The dielectric boundary force on a point charge and on a sphere

Consider the case where the charge distribution $\rho(\boldsymbol{r})$ is either a point charge or a uniformly charged sphere of radius a, both centered at a point $\boldsymbol{r}_1\in\Omega_1$ and with overall charge q. We denote by $\Phi_0(\boldsymbol{r})$ and $\Phi_a(\boldsymbol{r})$ the corresponding electrostatic potentials throughout space, and by $\boldsymbol{F}_0(\boldsymbol{r}_1)$ and $\boldsymbol{F}_a(\boldsymbol{r}_1)$ the corresponding dielectric boundary forces. In the case of a charged sphere, we assume that its radius a is smaller than the distance from $\boldsymbol{r}_1$ to $\partial\Omega_1$, so that the whole sphere is enclosed inside Ω_1.

For the case of the charged sphere, we can apply formula (10) to compute $\boldsymbol{F}_a$. However, for the case of a point charge, we cannot use Eq. (10) because $\rho(\boldsymbol{r})$ is a δ function and the potential is singular at the required point. Instead, we have the following relation for this case [5].

Lemma 1. The dielectric boundary force on a point charge of strength q located at $\boldsymbol{r}_1$ can be computed from the total potential throughout space by the following formula:

$$F_0(r_1) = -q \, \nabla_r \left(\Phi_0(r) - \frac{q}{4\pi\varepsilon_0\varepsilon_1 |r-r_1|} \right) \Bigg|_{r=r_1}. \quad (11)$$

In other words, the force acting on the point charge can be computed by subtracting from the total electric potential the singular Coulombic term produced by the point charge, and then computing the gradient of the resulting smooth potential at the charge location.

Proof. Consider as above the decomposition $\Phi_{ind} = \Phi + W$, then $W(r)$ is now given by

$$W(r) = -\frac{1}{4\pi\varepsilon_1\varepsilon_0} \frac{q}{|r-r_1|}.$$

Combining this equation with Eq. (7) proves the lemma. $\square$

Note that the potential $\Phi_0(r)$ is proportional to the charge q at r_1. Thus, according to Eqs. (3) (5), and (6) both the induced surface charges and the potential Φ_{ind} are also proportional to q. This renders the dielectric boundary force, given by Eq. (4), proportional to q^2. Thus, as expected, the dielectric boundary force has the *same* direction and magnitude regardless of the sign of the charge at r_1.

Before showing that the dielectric boundary force is size independent, we prove the following auxiliary lemma.

Lemma 2. A point charge q and a uniformly charged sphere with the same overall charge, both centered at r_1, produce the same induced surface charges at dielectric boundaries [provided the radius of the sphere is less than dist $(r_1, \partial\Omega_1)$].

Proof. We decompose each of the potentials $\Phi_a(r)$ and $\Phi_0(r)$ as the sum of the Coulombic part in a uniform dielectric ε_1 and a correction term due to the different dielectric regions. That is,

$$\Phi_a(r) = W_a(r) + V_a(r), \quad (12)$$

$$\Phi_0(r) = W_0(r) + V_0(r),$$

where

$$W_0(r) = \frac{q}{4\pi\varepsilon_0\varepsilon_1 |r-r_1|}.$$

Here W_a is given by [8]

$$W_a(r) = \begin{cases} \dfrac{3q}{8\pi\varepsilon_0\varepsilon_1 a^3}\left(a^2 - \dfrac{|r-r_1|^2}{3} \right), & |r-r_1| < a \\[2ex] \dfrac{q}{4\pi\varepsilon_0\varepsilon_1} \dfrac{1}{|r-r_1|}, & |r-r_1| > a. \end{cases} \quad (13)$$

The potentials $W_0(r)$ and $W_a(r)$ satisfy Eq. (1) with the corresponding charge distribution, but not the jump conditions at dielectric boundaries $\partial\Omega_i$. Therefore, the potentials $V_0(r)$ and $V_a(r)$ satisfy homogeneous Poisson equations (Laplace equations):

$$\Delta V_0(r) = \Delta V_a(r) = 0, \quad (14)$$

but with nonzero jump conditions at the dielectric boundaries $\partial\Omega_i$,

$$[\varepsilon \nabla V_a \cdot n]|_{\partial\Omega_i} = -[\varepsilon \nabla W_a \cdot n]|_{\partial\Omega_i},$$

$$[\varepsilon \nabla V_0 \cdot n]|_{\partial\Omega_i} = -[\varepsilon \nabla W_0 \cdot n]|_{\partial\Omega_i}. \quad (15)$$

However, according to Eq. (13), $W_a(r) = W_0(r)$ for $|r-r_1| > a$. Therefore, potentials $V_a(r)$ and $V_0(r)$ satisfy the same equation and the same boundary conditions. By the uniqueness of the solution of Poisson's equation, it follows that $V_a(r) = V_0(r)$ for all r. By combining this with Eqs. (13) and (12), we conclude that

$$\Phi_a(r) = \Phi_0(r) \quad \text{for} \quad |r-r_1| > a.$$

Therefore, by Eq. (3), the induced surface charges created by these two charge distributions are the same. $\square$

We can now prove the following theorem concerning the size independence of the DBF.

Theorem. The dielectric boundary force on a uniformly charged sphere of total charge q is independent of the radius of the sphere [provided dist $(r_1, \partial\Omega_1) > a$, where r_1 is the center of the sphere]. Moreover, this force can be computed by the following simplified formula:

$$F_a(r_1) = -q\nabla\Phi_a(r)|_{r=r_1}. \quad (16)$$

Proof. According to Eq. (4), the DBF is given by the following integral:

$$F_a = \int_{|r-r_1|<a} -\frac{q}{\frac{4}{3}\pi a^3} \nabla\Phi_{ind}(r)dr.$$

This integral includes all Coulombic interactions between the induced surface charges and the charged sphere. However, as is well known [7], the force on a charged sphere due to another point (or surface) charge is equal to the force on a point charge located at the center of the sphere. Thus,

$$F_a = -\nabla\Phi_{ind}(r)|_{r=r_1}.$$

As shown in Lemma 2, the induced surface charge is independent of the radius of the sphere. Thus, the DBF is independent of the radius of the sphere. Moreover, using the decomposition $\Phi_{ind}(r) = \Phi_a(r) - W_a(r)$ and noting that by definition (13), $\nabla W_a(r_1) = 0$, we obtain Eq. (16), which finishes the proof of the theorem. $\square$

Corollary. The force on a uniform sphere of charge q, denoted by $F_a(r_1)$, is equal to the force on a point charge of same strength:

$$F_0(r_1) = F_a(r_1). \quad (17)$$

The theorem and its corollary have a simple application for the numerical computation of the dielectric boundary force. For example, for the case of charged ions near a dielectric wall, or inside the pore of a protein channel embedded in a lipid membrane, it is possible to model the ions as

uniformly charged spheres instead of point charges, thus removing the numerical difficulties associated with a singular δ function. Moreover, to compute the dielectric boundary force, it is only necessary to compute with good accuracy the derivative at the center of the sphere and there is no need to perform the volume integral (4). For the case of a Langevin simulation of many charged particles, in which the force on each of the simulated particles is recomputed at every time step of the simulation, our analysis shows that by modeling the mobile particles as charged spheres, one needs to compute only the total electrostatic potential (the solution of Poisson's equation) and then compute the total force on each particle by computing the gradient of the total electrostatic potential at the center of a particle's sphere. Since these forces are independent of the size of the particles, one can solve Poisson's equation with spheres of larger radius than of the physical particles, for better stability and convergence of the numerical scheme.

We note that recently Allen *et al.* have proposed a different approach for the numerical computation of both the induced polarization charges and their effective forces, based on a variational approach [9]. In their method, a numerical computation of the DBC is performed on a two-dimensional grid at different dielectric boundaries, which should be more computationally efficient than solving a three-dimensional Poisson equation.

III. THE DIELECTRIC BOUNDARY FORCE IN TWO SIMPLE GEOMETRIES

We now present explicit computations of the dielectric boundary force for two simple generic geometries. The first is the standard and well-known problem of a charge near an infinite planar dielectric wall, where a closed analytical expression is known, and the other is the dielectric boundary force on the axis of a narrow gramicidin-like channel geometry. In general, closed form analytical solutions are possible only for very few cases, see, e.g., Refs. [7,9–11], so for most practical problems it is necessary to resort to numerical computations.

A. A point charge near a planar dielectric wall

Consider an infinite planar wall located on the (yz) plane, separating two regions with dielectric coefficients ε_1 for $x > 0$ and ε_2 for $x < 0$. Consider a point charge located at a point $(d,0,0)$ $(d > 0)$ in cartesian coordinates. In this case, by the method of images, we can solve explicitly for the electric potential Φ. In Cartesian coordinates, $\boldsymbol{x} = (x,y,z)$, it is given by

$$\Phi(\boldsymbol{x}) = \begin{cases} \dfrac{1}{4\pi\varepsilon_0\varepsilon_1}\left(\dfrac{q}{|\boldsymbol{x}-(d,0,0)|} + \dfrac{q'}{|\boldsymbol{x}-(-d,0,0)|}\right), & x > 0 \\[4mm] \dfrac{1}{4\pi\varepsilon_0\varepsilon_2}\dfrac{q''}{|\boldsymbol{x}-(d,0,0)|}, & x < 0, \end{cases}$$
$$(18)$$

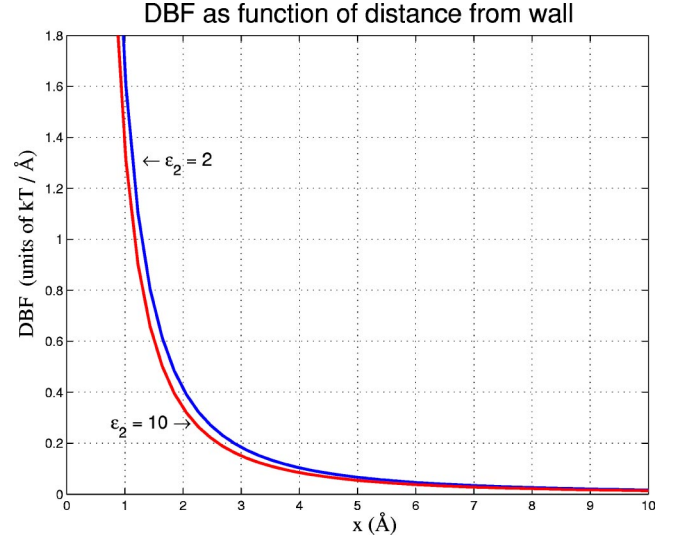where the image charges q' and q'' are given by

FIG. 1. (Color online) The dielectric boundary force on a single point charge of strength e inside an aqueous solution with $\varepsilon_1 = 80$ near a dielectric wall with $\varepsilon_2 = 2$ (upper curve) and with $\varepsilon_2 = 10$ (lower curve).

$$q' = \frac{\varepsilon_1 - \varepsilon_2}{\varepsilon_1 + \varepsilon_2}q, \quad q'' = \frac{2\varepsilon_2}{\varepsilon_1 + \varepsilon_2}q. \qquad (19)$$

Therefore, according to Eq. (11), the force on the charge is only in the x direction and is given by

$$F_{ind,x} = \frac{1}{16\pi\varepsilon_0\varepsilon_1}\frac{\varepsilon_1 - \varepsilon_2}{\varepsilon_1 + \varepsilon_2}\frac{q^2}{d^2}. \qquad (20)$$

The top curve in Fig. 1 shows a plot of this force near a dielectric wall with values $\varepsilon_1 = 80$ and $\varepsilon_2 = 2$. As seen from the figure, the dielectric boundary force is not exceedingly large even at microscopic distances from the wall. It also does not change much as long as $\varepsilon_1 \gg \varepsilon_2$, as can be seen both from the graph and from formula (20).

However, as pointed out in Ref. [12], the fact that a point charge induces surface charges on the wall has additional consequences apart from the DBF on the particle that induced them. For example, in the study of a multiparticle system, the presence of induced surface charges leads to additional interaction forces between any two charged particles near the dielectric wall, other than their standard Coulombic force. For example, consider two equal point charges of strength q located at $\boldsymbol{r}_1 = (d,0,0)$ and at $\boldsymbol{r}_2 = (3d,0,0)$. In this case the force on particle 2 due to particle 1 is only in the x direction and is given by

$$F_{2,1} = \frac{q^2}{4\pi\varepsilon_0\varepsilon_1}\left[-\frac{1}{(2d)^2} + \frac{\varepsilon_1 - \varepsilon_2}{\varepsilon_1 + \varepsilon_2}\frac{1}{(4d)^2}\right].$$

This force should be compared to the standard Coulombic interaction between the two charges. For $\varepsilon_1 \gg \varepsilon_2$, this force is only about 75% of the original Coulombic force between the two particles. Similarly, the force on particle 1 is increased by 25% relative to the free space Coulomb interac-
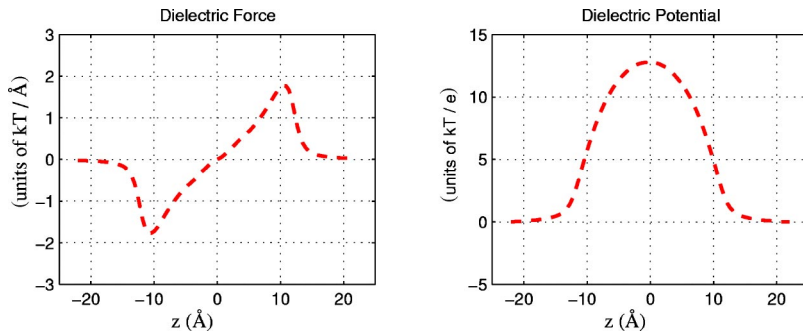
FIG. 2. (Color online) The dielectric boundary force (left) and potential (right) on a point charge of strength e on the channel axis of gramicidin.

tion. The presence of these induced surface charges might thus have a significant effect on the structure of an electrolyte solution near a dielectric wall. This simple example shows that dielectric boundary charges are important in determining the force *between two* (or more) charged particles near a dielectric boundary, as they are important in determining the force on a *single* particle near dielectric boundaries.

In standard continuum theories, discrete charges are replaced by continuum averaged densities that obviously leave out the DBF. The above analysis shows that interactions between discrete pairs of particles are also incorrectly described in such analysis. All in all, the correct treatment of polarization effects of discrete particles in continuum Poisson-Boltzmann-type theories requires further investigation.

B. Dielectric boundary force in gramicidin

We now consider the dielectric boundary force inside a gramicidin-type channel geometry embedded in a membrane. Gramicidin is a small polypeptide (nearly a protein), widely used as a model of more complex natural channels [6]. A dielectric boundary force in such a narrow channel was present in the three-dimensional treatment of electrostatics of Barcilon *et al.* [13,14], but the leading (one-dimensional) term of their perturbation expansion provided only a poor approximation to the DBF acting on ions in narrow channels. Dieckmann *et al.* [15] were amongst the first to realize the importance of the correct calculation and inclusion of the DBF into Nernst-Planck-type equations for ionic permeation through narrow channels. Contemporaneously, Corry *et al.* [16,17] as well as Graf *et al.* [18] also realized the importance of this term in the context of Brownian dynamics and Monte Carlo simulations, respectively. The need for the inclusion of this force in a continuum description, derived from an underlying molecular model has been shown in a

mathematically rigorous manner by Schuss *et al.* [5]. Recently, both Corry *et al.* [19], and Mamonov *et al.* [20] have studied the effects of the inclusion of this force term in modified Poisson-Boltzmann and Poisson-Nernst-Planck equations applied to gramicidin-like and other channel-like geometries. Both groups report that explicit inclusion of the dielectric boundary force in a continuum formulation yields better results than the standard theories that omit this force term.

For the sake of our analysis, we assume that gramicidin is embedded in a lipid membrane with a uniform low dielectric constant of value $\varepsilon = 2$, while the pore of the channel and the surrounding aquatic baths have dielectric constant $\varepsilon = 80$. Since gramicidin is a long and narrow channel, the movement of mobile ions inside it is almost one dimensional along the channel axis. Thus, we consider only the dielectric boundary force along its axis, denoted the z axis. All numerical computations presented in this section were performed with the "gramicidin" model described by Elber *et al.* [21], with ions represented as Gaussian spheres with effective radii of 0.8 Å. As predicted by the analysis of Sec. II, and verified numerically, changing this value (while keeping the whole ion inside the channel pore) does not change the computed values for the dielectric boundary force.

(A forthcoming paper of Allen *et al.*, [22] proposes and analyzes a significantly different structure for gramicidin. The proposed structure will modify estimates of energetics, however they are made.)

In the left part of Fig. 2, the dielectric boundary force is plotted as a function of position along the channel axis, while in the right part the corresponding potential is plotted. As seen from the figure, the dielectric boundary force creates a high potential barrier of more than $12kT$. Therefore, a simple hole with the same geometry as the gramicidin channel, i.e., length of about 25 Å and diameter of about 4 Å, but
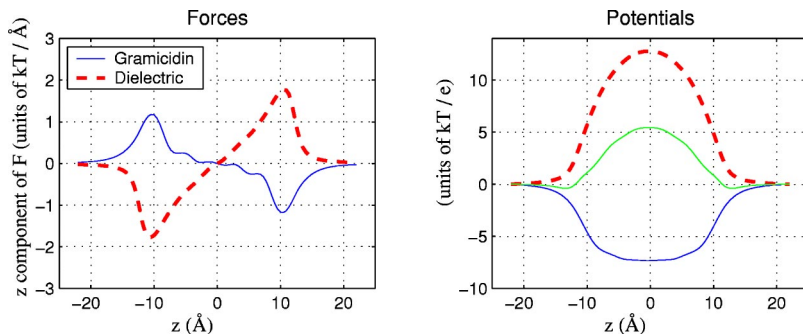

FIG. 3. (Color online) The DBF and corresponding potential on a point charge of strength $+e$ on the channel axis of gramicidin (dashed red line), compared to the corresponding force and potential due to the gramicidin fixed charges (solid blue). The thin green line is the sum of the two potentials and represents the net potential.
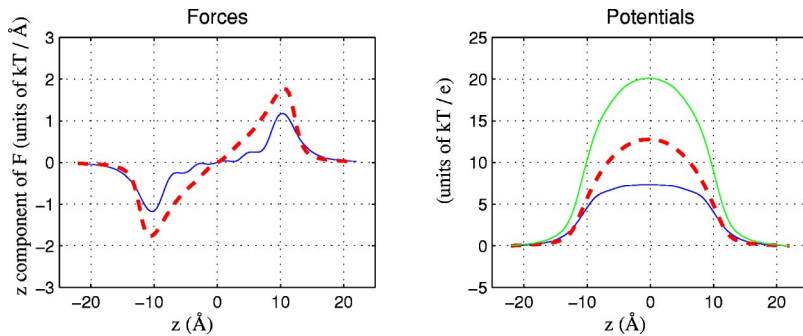
FIG. 4. (Color online) The DBF and corresponding potential on a negative ion on the channel axis of gramicidin, compared to the corresponding FCF and potential due to the gramicidin fixed charges.

with no protein with fixed charges in it, would be impermeable to passage of single positive ions. Since the dielectric boundary force is proportional to q^2 (see Sec. II), the dielectric boundary force on a negative ion is the same as on a positive ion, while the force on a doubly charged ion (such as Ca^{2+}) is four times as large. Therefore, a noncharged pore opening in the membrane would be impermeable not only to a positive ion but also to a negative ion or a double charged ion. Note that this analysis applies only to the movement of a single ion, and not to the coupled motion of a pair of say anion cation. This analysis also neglects the possible shielding of this force by mobile ions in the surrounding electrolytic solutions. While the Brownian dynamics simulation results of Corry *et al.* [16] show that for a long and narrow channel, this shielding is negligible (see, for example, their Fig. 4 of Ref. [16] on page 2355), in general these two issues require further investigation.

The gramicidin channel, however, differs from an idealized noncharged pore. Although the gramicidin protein is overall neutral, there are nonvanishing partial charges along its atom groups that create a nonvanishing electrostatic potential. In Fig. 3 (left), the FCF, on an ion due to the gramicidin fixed charges, is compared to the dielectric boundary force. As seen from this figure, the two forces are nearly opposite, yielding a much smaller net force on a positive ion, with a corresponding potential barrier of about $5kT$, see Fig. 3 (right).

For a negative ion, however, the situation is quite different. While the dielectric boundary force remains the same, the force due to the Gramicidin channel is inverted with respect to the case of a positive ion because it is proportional to q. Therefore, as shown in Fig. 4, now the two forces do not cancel each other, but rather add up to produce a high insurmountable barrier of more than $20kT$.

Finally, consider the case of a double charged ion such as Ca^{2+}. Since the FCF is proportional to q while the DBF is proportional to q^2, the first is multiplied by two while the latter by four, in comparison to the case of a positive ion. Therefore, as shown in Fig. 5, the dielectric boundary force dominates, and the DBF is not canceled by the interaction with the gramicidin fixed charges. This leads to a potential barrier more than $30kT$ high.

Therefore, the cation selectivity of gramicidin can be explained by a simple continuum-type analysis of the balance between the different forces acting on an ion inside a rigid channel. Recently, similar results have been independently obtained by Edwards *et al.* [23], who also state that such a simplistic approach is not valid for quantitative results such as computation of the net current through the channel. We stress that indeed the development of a quantitative theory requires the computation of diffusion, friction, and dielectric coefficients inside and near the channel, using more refined theories or molecular dynamics simulations that can give the dependence of these parameters on location, time, and experimental conditions. In addition, the assumption that the channel is rigid needs to be reconsidered as well. For a study of the effective potential profile inside a nonrigid gramicidin channel, see, for example, the recent paper by Mamonov *et al.* [20]. Finally, in the broader context of permeation through protein channels, while the effects of single filing and finite size of ions are easily modeled in simulations [16,17,24,25], their inclusion into macroscopic theories is a formidable theoretical challenge [26–31].

It is instructive to have another look at the striking near cancellation between the dielectric boundary force and the electrostatic interactions with the gramicidin fixed charges, for a positive ion (Fig. 3). It is our claim that the fact that these two forces nearly cancel each other cannot be purely coincidental. While the dielectric boundary force is a property of the geometry and dielectric coefficients of the problem, independent of the fixed charges of the protein, the electrostatic potential of the protein depends directly on its fixed
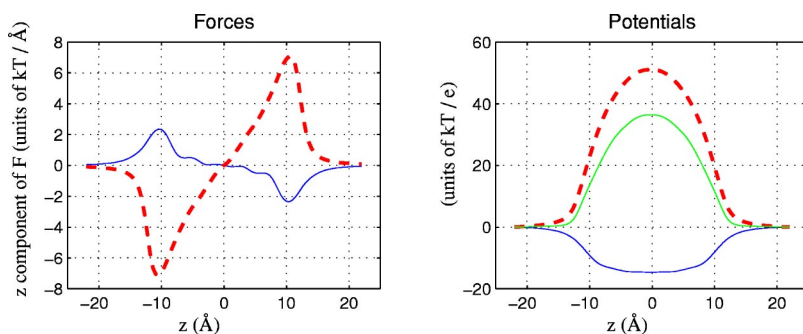

FIG. 5. (Color online) The dielectric boundary force and potential on a Ca^{2+} on the channel axis of gramicidin (dashed red line), compared to the corresponding force and potential due to the gramicidin fixed charges (solid blue line). The thin green line is the net effective potential.

charge distribution. The fact that the dielectric boundary force and the gramicidin force due to its fixed charges have extremal points (maxima and minima) at almost the same locations with almost the same heights (see Fig. 4) is characteristic of a *device*, not a manmade one in our case, but rather a natural biological device, designed or evolved to "have a purpose," i.e., to have a simple reasonably robust input/output relation. It seems that the fixed charges of gramicidin have been optimized, by the course of evolution, to almost cancel out the dielectric boundary force, and thus allow the permeation of monovalent positive ions through the channel.

IV. SUMMARY AND DISCUSSION

In an inhomogeneous system, charges *always* interact with (induced) dielectric boundary charges and with fixed charges if these are present near the boundary (as is usually the case). Then, the forces between charged particles depend as much on their distance to the boundary, and the shape and dielectric properties (and fixed charge) of the boundary, as on the distance between them.

In this paper, we took a step in the analysis of such problems by considering the dielectric boundary force on a single particle and its crucial role in the determination of the permeation through a long and narrow protein channel such as gramicidin. We confined our analysis to the computation of the net force on a single mobile charge, due only to the dielectric boundary force and to the fixed charges of the protein, neglecting the effects of other mobile charges either inside the channel or in the surrounding electrolyte solutions.

Even though approximate and limited by our simplifying assumptions, our results show a striking cancellation between the dielectric boundary force and the force due to the fixed charges of the gramicidin channel. This kind of cancellation is characteristic of a *device*, in which the free parameters, e.g., the fixed charges of the protein in our case, have been optimized to perform a certain function. The role of the dielectric boundary force, and cancellation of forces, needs to be investigated in other channels, and proteins as well, before conclusions can be reached about its general importance.

Obviously, in multiparticle systems, one has to consider the overall effect of all other mobile charges. It is a well known and central result of equilibrium statistical mechanics that in a homogeneous system composed of an infinite number of charged particles, the shielding is perfect [32,33]. For inhomogeneous systems, either at equilibrium or at nonequilibrium, similar analytical results are unknown. Indeed, shielding cannot be the whole story in inhomogeneous systems. Ionic solutions within (nearly) insulating cylinders

conduct dc potentials at macroscopic distances, thereby producing the well-known cable properties (i.e., transmission line behavior) of nerve fibers. Only recently has the simple case of an electrolyte solution near an infinite dielectric wall been analyzed theoretically by Aqua and Cornu [34]. Their results show that due to the shielding of the electrolyte solution, the dielectric boundary force decreases exponentially instead of the long range inverse distance squared decay calculated for a single charge. Thus, the dielectric boundary force might not play a crucial role in the study of the properties of planar membranes. The DBF might well be important, however, in the study of binding sites of enzymes, due to its dependence on the geometry of the binding site. All in all, the role of the dielectric boundary force may be significant in the binding of molecules (and macromolecules) to active sites of proteins.

For more complex systems, such as narrow pores or highly charged binding sites of enzymes, the theoretical analysis of the interplay between the dielectric boundary force and electrostatic shielding still awaits investigation. The papers of Corry *et al.* [16,17] reporting Brownian dynamics simulation studies, clearly show that shielding effects are important as the radii of the pores become wider. As discussed in the Introduction, continuum theories such as PB or PNP replace discrete charges with continuum distributions composed of infinitely small charges, and thus discard the discrete polarization surface charges, and replace them with the effective polarization due to the continuum charge. This means that the dielectric boundary force is immediately lost in this description [5]. In addition, the non-Coulombic part of interactions between two discrete ions, which are non-negligible near dielectric interfaces (see Sec. III as well as Ref. [12]), are also lost and thus may lead to incorrect results. As shown in a mathematically rigorous manner in Ref. [5], a Brownian (Langevin) model for the motion of the mobile ions is equivalent to a hierarchy of Poisson-Nernst-Planck-type equations containing conditional and unconditional densities, which explicitly contain the dielectric boundary force. The derivation is similar to that of equilibrium statistical mechanics, where Monte Carlo simulations sampling according to the Boltzmann distribution are equivalent to the infinite Bogolyubov-Born-Green-Kirkwood-Yvon equations containing continuum averaged densities [2]. Thus, to pursue further the analysis of shielding and the role of the dielectric boundary force from a theoretical approach, closure relations and/or other approximations that are valid near dielectric interfaces need to be developed and checked against simulations. This presents new challenges in the study of microscopic equilibrium and nonequilibrium systems, most common in molecular biology.

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