# The dielectric boundary force in ion channels: the case of gramicidin

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## ABSTRACT

The dielectric boundary force (DBF) is the force that induced charges at dielectric boundaries exert on the charge that induced them. The DBF is present in any electrostatic problem with a non-uniform dielectric constant, and is important in the case of charged particles near dielectric boundaries. Yet, it is absent in common continuum theories of charge distribution and of charge transport, such as Poisson-Boltzmann and Poisson-Nernst-Planck. In this paper we define the DBF, formulate it as a solution of a partial differential equation, and present its crucial importance for ionic permeation through the gramicidin channel. The main permeation characteristics of gramicidin can be explained in terms of a delicate balance between the DBF and the force formed by the permanent charges of the gramicidin polypeptide. This balance, characteristic of a device, might suggest design principles for man-made nanopores.

***Keywords***: Dielectric forces, gramicidin, ion channels, continuum theories.

## 1 INTRODUCTION

Permeation through ion channels is one of the fundamental processes of life, and its understanding is one of the key problems in molecular biophysics and physiology of the cell [1]. At the crudest level of description, ionic permeation through a single protein channel embedded in a lipid membrane is an *electrostatic* problem, governed by the geometry of the pore, its permanent charge distribution and by the interactions of the mobile ions with the other mobile charges in the system.

One of the important features of this problem is the high spatial inhomogeneity of the dielectric coefficient. For an ion to pass through the channel, it has to move from an aqueous solution of high dielectric coefficient ($\varepsilon \approx 80$), through the narrow pore of the channel inside the membrane, which has a low dielectric coefficient ($\varepsilon \approx 2-5$).

In any electrostatic problem with a non-uniform dielectric constant, a charge $q$ in one dielectric region induces surface charges at all boundaries separating regions of different dielectric values. These induced surface charges, in turn, exert an often neglected force on the charge $q$ that induced them. Since most protein channels have a narrow pore or selectivity filter, this dielectric boundary force (DBF) is an important component in the overall forces acting on the mobile permeating ions, in addition to the familiar Coulombic interactions of the ions with all other fixed and mobile charges in the system.

In recent years, various continuum theories of charge distribution and of charge transport, such as Poisson-Boltzmann and Poisson-Nernst-Planck (PNP) have been applied to protein channels [2]–[9]. However, as shown both in simulations [8]–[13], and in theory [14], the DBF is not captured well in these theories. In [14], [15], we showed that a continuum description of charge transport in such nanoscale systems must include both the DBF and the excluded volume effects due to the finite size of ions. In [14], starting from a molecular model of interacting diffusing particles, an exact mathematical averaging procedure is presented that leads to a modified PNP type system of equations, explicitly containing the DBF and the finite size of ions.

In this paper we define the DBF and formulate it in a form useful for continuum theories, e.g., as a solution of a partial differential equation. We then present its crucial importance for ionic permeation through the gramicidin channel, widely studied in channology [16]. Analysis of the DBF provides a simple explanation of the main permeation characteristics of gramicidin in terms of a delicate balance between the DBF and the fixed charge force (FCF) formed by the permanent charges of the gramicidin polypeptide. For a monovalent positive ion, the DBF and the FCF almost cancel out, thus enabling permeation through the narrow pore of the gramicidin channel. For a negative ion or for a double charged positive ion, the two forces do not cancel out, yielding high insurmountable barriers that prevent these ions from crossing the channel. The remarkable fact that gramicidin, although overall neutral, produces an FCF that cancels out the DBF is characteristic of a device. This natural device might suggest design principles for man-made nanopores.

## 2 DIELECTRIC BOUNDARY FORCE

Consider a physical system consisting of charged particles in a non-homogeneous dielectric medium composed of an arbitrary number of regions of arbitrary shapes, denoted $\Omega_i$. Further assume that in each region $\Omega_i$ the dielectric coefficient is constant with value $\varepsilon_i$. Now consider the electrostatic force on a single charge $q_1$ located, for example, at $\boldsymbol{r}_1$ inside the region $\Omega_1$. One component of this force includes all Coulombic interactions of $q_1$ with all other charges in the system. This force component, denoted $\boldsymbol{F}_c$, is given by $-q_1\nabla\phi_c(\boldsymbol{r}_1)$, where $\phi_c(\boldsymbol{r})$ is the potential at $\boldsymbol{r}$ created by all *other* charges in the system, except $q_1$. It is the solution of Poisson's equation

$$\nabla\cdot[\varepsilon(\boldsymbol{r})\phi_c(\boldsymbol{r})] = -\frac{1}{\varepsilon_0}\sum_{j\neq 1} q_j\delta(\boldsymbol{r}-\boldsymbol{r}_j) \qquad (1)$$

with the standard jump conditions at dielectric boundaries,

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

where $\varepsilon(\boldsymbol{r})$ is the relative dielectric coefficient at $\boldsymbol{r}$, $\boldsymbol{n}$ 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 variable enclosed within them, between the value outside the region $\Omega_i$ and inside it.

Note that the potential $\phi_c$ does not include the charge $q_1$ explicitly, but rather treats it as an imaginary test charge. The physical presence of the charge $q_1$, however, induces surface charges at all boundaries between regions of different polarizability. Assuming a linear response of the dielectric mediums, this leads to additional induced surface charges, other than those induced surface charges produced by the other charges in the system, which are taken into account by the potential $\phi_c$, through eqs. (1) and (2) .

While most standard textbooks on electrostatics explicitly write formulas for the induced surface charges due to a single charge, as gradients of the electrostatic potential, an important point usually not discussed explicitly, is that these induced surface charges, in turn, exert a force on the single charge itself. We denote this force by $\boldsymbol{F}_d$, and refer to it as the *dielectric boundary force* (DBF). In an electrostatic problem with a non-homogeneous dielectric coefficient, the total electrostatic force on the charge $q_1$ is given by

$$\boldsymbol{F} = \boldsymbol{F}_c(\boldsymbol{r}_1) + \boldsymbol{F}_d(\boldsymbol{r}_1)$$

while in a homogeneous system $\boldsymbol{F}_d = 0$.

In [17] some properties concerning the DBF are proven.

***Property 1:*** The DBF on a point charge $q$ can be computed from the potential $\phi_0$ created by the charge, by the following formula,

$$\boldsymbol{F}_d(\boldsymbol{r}_1) = -q\,\nabla_{\boldsymbol{r}}\left(\phi_0(\boldsymbol{r}) - \frac{q}{4\pi\varepsilon_0\varepsilon_1|\boldsymbol{r}-\boldsymbol{r}_1|}\right)\Big|_{\boldsymbol{r}=\boldsymbol{r}_1} \qquad (3)$$

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

***Property 2:*** The DBF is size-independent. The dielectric boundary force on a point charge of strength $q$ is equal to the DBF on a uniform sphere of same strength and arbitrary radius $a$ (as long as $a$ is less than the distance from $\boldsymbol{r}_1$ to the boundary $\partial\Omega_1$). Moreover, for a charged sphere, the DBF can simply be computed as

$$\boldsymbol{F}_d(\boldsymbol{r}_1) = -q\nabla\phi_a(\boldsymbol{r})\Big|_{\boldsymbol{r}=\boldsymbol{r}_1}. \qquad (4)$$

where $\phi_a$ is the electric potential created by a sphere of radius $a$. The potential of a uniform sphere is smooth everywhere, so there is no need to subtract a singular term as in the case of a point charge, eq. (3).

***Property 3:*** The DBF is proportional to $q^2$. It has the same direction and magnitude for a positive or negative charge of same strength $\pm q$.

## 3 THE DBF 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 [16]. Despite the absence of the DBF in continuum theories such as PNP, these theories have been used to study ionic permeation through gramicidin [4], [6]. Various authors noticed this error in the context of simulations [5], [11], [13]. The need for the inclusion of the DBF in a continuum description, derived from an underlying molecular model has been shown in a mathematical rigorous manner by Schuss & al. [14]. Recently various groups have studied the effects of the inclusion of the DBF in modified Poisson-Boltzmann and Poisson-Nernst-Planck equations applied to gramicidin and other channel-like geometries [7]–[9], [12], reporting that explicit inclusion of the dielectric boundary force in a continuum formulation yields better results than the standard theories that omit this force term.

In this paper we do not attempt to compute currents through gramicidin, but rather only present some interesting observations concenrning the role of the DBF in this channel. 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 aqueous baths have dielectric constant $\varepsilon = 80$. Since gramicidin is a long and narrow channel, we present the various forces only along the one dimensional channel axis, where the mobile ions are most likely to be. All numerical computations were performed with the "gramicidin" model described in [18].

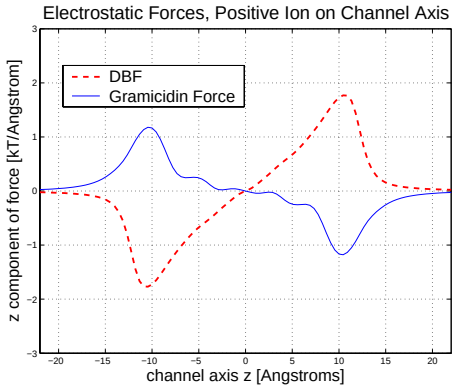


Figure 1: Gramicidin FCF (blue) and DBF (red) on a monovalent positive ion.

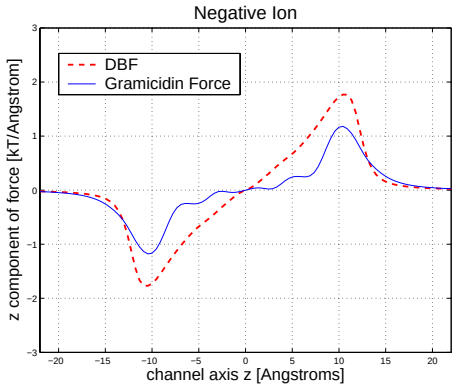


Figure 2: FCF and DBF on a monovalent negative ion.

In Fig. 1 the red dashed curve is the dielectric boundary force on a positive (or negative) ion as a function of position along the channel axis. Since the narrow pore is embedded in a region of low dielectric coefficient, surrounded by two aqueous solutions of high dielectric coefficient, the DBF is repulsive, and it 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 $25\mathring{A}$ and diameter of about $4\mathring{A}$, but 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 Section 2), such a non-charged pore opening in the membrane would be impermeable 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, and also neglects the possible shielding of this force by mobile ions in the surrounding electrolytic solutions.

The gramicidin channel, however, differs from an idealized non-charged pore. Although gramicidin is overall neutral, there are non-vanishing partial charges along its atom groups, that create a non-vanishing electrostatic

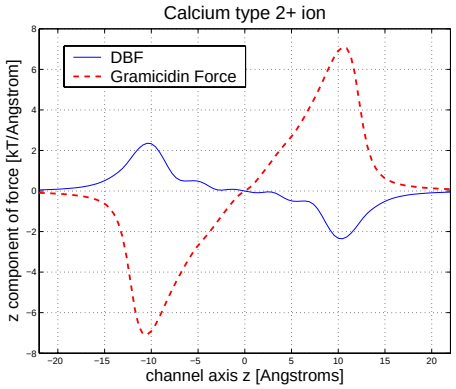


Figure 3: FCF and DBF on a Calcium type ion.

potential. The fixed charge force (FCF) on a positive ion, due to the gramicidin fixed charges is shown as the blue curve in Fig. 1. For a positive ion, the DBF and the FCF are nearly opposite, yielding a much smaller net force and a decreased potential barrier of about $5kT$.

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 $q$. Now, the two forces do not cancel each other, but rather add up to produce a high insurmountable barrier of more than $20kT$ (see Fig. 2).

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. The dielectric boundary force dominates, and it is not cancelled by the interaction with the gramicidin fixed charges (Fig. 3). This leads to a potential barrier more than $30kT$ high.

The cation selectivity of gramicidin can now 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 & al. [19], 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 provide estimates of these parameters. In addition, the assumption that the channel is rigid needs to be reconsidered as well. For a study of the effective potential profile in a non-rigid gramicidin channel, see for example [7], [20].

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. 1). 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 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. 2), is characteristic of a *device*, designed or evolved to "have a purpose". 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.

## 4 DISCUSSION

In an inhomogeneous system, charges *always* interact with (induced) dielectric boundary charges and with fixed charges if these are present near the boundary. In such cases, the induced surface charges and the corresponding DBF must be explicitly included in the computations.

In this paper we presented a simple example of the importance of the inclusion of the DBF in such computations, in the context of the gramicidin channel. 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 DBF 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. This working hypothesis and the role of the dielectric boundary force should be investigated in other proteins as well.

While analysis of the DBF can explain why gramicidin is permeable mostly to monovalent positive ions, the DBF is not directly responsible for selectivity amongst different such ions, because the DBF on a spherical ion is independent of the radius of the ion [17].

In our analysis, we considered the force on a single ion, neglecting its interactions with the other mobile ions in the system. Obviously, in multi-particle systems, one has to consider the overall effect of all other mobile charges. A correct computation of these interactions is also required in continuum theories that attempt to compute currents, such as PNP. Standard PNP replaces discrete charges by continuum distributions composed of infinitely small charges. Thus, both the dielectric boundary force and the finite size of the ions are lost in this description. As shown in [14], 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. Thus, to pursue further the analysis of shielding and the role of the dielectric boundary force from a theoretical approach, closure relations that are valid near dielectric interfaces need to be developed and checked against simulations.

## REFERENCES


[1] Hille, B., *Ionic Channels of Excitable Membranes*, 2nd edition, Sinauer, 1992.

[2] Chen, D.P., Eisenberg, R.S., *Biophys. J.* 64:1405-1421, 1993.

[3] Chen, D.P., Lear, J., Eisenberg, R.S., *Biophys. J.* 72:97-116, 1997.

[4] A. Cardenas, R. Coalson and M. Kurnikova, *Biophys. J.* 79(1):80-93, 2000.

[5] M. Kurnikova, R. Coalson, P.Graf, and A.Nitzan, *Biophys. J.* 76:642-656, 1999.

[6] Hollerbach,U., Chen, D.P., Busath, D., Eisenberg, R.S., *Langmuir*, 16(13):5509-5514, 2000.

[7] A. Mamonov, R. Coalson, A. Nitzan and M. Kurnikova, *Biophys. J.*, 84:3646-3661, 2003.

[8] W. Im and B. Roux, *J. Mol. Biol.* 319(5):1177-97, 2002.

[9] W. Im, and B. Roux, *J. Mol. Biol.* 322(4):851-69, 2002.

[10] G. Moy, B. Corry, S. Kuyucak and S. Chung, *Biophys. J.* 78:2349-2363, 2000.

[11] B. Corry, S. Kuyucak and S. Chung, *Biophys. J.* 78:2364-2381, 2000.

[12] B. Corry, S. Kuyucak and S. Chung, *Biophys. J.*, 84:3594-3606, 2003.

[13] P. Graf P, A. Nitzan, M. Kurnikova and R. Coalson, *J. Phys. Chem. B*, 104:12324-12338 (2000).

[14] Z. Schuss, B. Nadler and R.S. Eisenberg, *Phys. Rev. E.* 64(3), 036116, 2001.

[15] B. Nadler, Z. Schuss, A. Singer and R.S. Eisenberg, *Nanotech 2003 technical conference proceedings,* Volume 3, pages 439 - 442.

[16] Wallace, B. A., (editor), *Gramicidin and related ion channel forming peptides*, Wiley, New York, 1999.

[17] B. Nadler, U. Hollerbach and R.S. Eisenberg, *Phys. Rev. E.* 68, 021905, 2003.

[18] Elber, R., D. Chen, D. Rojewska, and R. S. Eisenberg, *Biophys. J.*, 68:906-924, 1995.

[19] Edwards S., Corry B., Kuyucak S., Chung S., *Biophys. J.* 83:1348-1360, (2002).

[20] T. Allen, O. Andersen and B. Roux, *J. Am. Chem. Soc.* 125(32):9868-77, 2003.