

# Self-consistent analytic solution for the current and access resistance in open ionic channels.

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## ABSTRACT

Ionic motion in the bulk solution away from the mouth of a biological ion channel, and inside the channel, is analyzed using Poisson-Nernst-Planck (PNP) equation. The one-dimensional method allows us to connect in a self-consistent way ion dynamics in the bulk solution and inside the channel by taking into account access resistance to the channel. In order to glue the PNP solution in the bulk to that inside the channel, a continuity condition is used for the concentration and the current near the channel mouth at the surface of the hemisphere. The resulting one dimensional (1D) current-voltage characteristics are compared with the Kurnikova<sup>16</sup> results which are in good agreement with experimental measurement on the channel, by using a filling factor as the only fitting parameter. The filling factor compensates the fact that the radial charge distribution is non-uniform in a real channel as compared to the cylindrically symmetrical channel used in the 1D approximation.

**Keywords:** ionic channels, Poisson equation, Nernst-Planck equation, access resistance, self-consistent approach

## 1. INTRODUCTION

Ion channels in cellular membranes<sup>1,2</sup> control a vast range of biological functions in health and disease. Understanding their properties from the physical first principles is a long-standing fundamental and applied scientific problem of great interdisciplinary importance. Theoretical treatments of ion transport through channel proteins may be broadly classified as electro-diffusion models,<sup>3</sup> stochastic models<sup>4</sup> and molecular dynamical models.<sup>5</sup> Among these approaches, the first one has the advantage of providing analytic insight into the properties of ionic channels over a broad range of parameters. Analytic solutions are available for example for the electro-diffusion in the bulk in cylindrical symmetry, which can be used to estimate the access resistance to the channel mouth.<sup>6</sup> Some analytic approximations for the Poisson equation in the pore in one dimension were also derived.<sup>7,8</sup> However, we are not aware of an analytic solution that will connect in a self-consistent manner the ionic currents and electrostatic potentials in the bulk in the access resistance region and in the pore. If available, such a solution will allow one to set up boundary conditions for the Poisson-Nernst-Planck (PNP) equations in the pore in a self-consistent way and provide further analytic insight into the properties of open ionic channels.

In this paper we present such a self-consistent analytical solution of the access resistance problem, which is continuous in concentration, electrostatic potential, and electric field at the channel mouth, and satisfies given Dirichlet boundary conditions for the concentration and potential in the bulk at plus and minus infinity. This solution is found as follows. The permeation through a narrow cylindrical channel is obtained in one-dimensional approximation of the PNP theory<sup>6,7</sup> that satisfies given boundary conditions (concentrations and

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electrostatic potential) set in the bulk directly at the channel boundaries. We next obtain solutions of the Poisson-Boltzmann-Nernst-Planck (PBNP) equation in the linear approximation in the bulk at the left and right hand side of the channel. We then notice that the boundary conditions for the later solutions are set at infinity (bulk concentration and electrostatic potential) and the channel mouth at the distance of one pore radius from the pore. Importantly, at the channel mouth, boundary conditions are set as the gradients of concentration and the electrostatic potential. It is therefore, possible to find an quasi-analytic solution of the access resistance problem by method of successive approximations that adjusts boundary conditions for both of the analytic solutions at the channel mouth in a self-consistent manner.

The paper is organized as follows. We first present the solution of the 1D approximation of the Poisson-Nernst-Planck (PNP) equation in the cylindrical channel. In the next section, the solution of the Poisson-Boltzmann and Nernst-Planck (PBNP) equations in the bulk, away from the channel and near the hemisphere at the channel mouth is obtained. In the following section, the join solution of the two previous self-consistent solutions of the PNP and PBNP equations inside the channel and in the bulk solutions is obtained. This takes into account the access resistance to the channel and introduce the correction to the potential inside the channel and the current. The details of the algorithm for this calculation are also explained. Finally, we present the summary and conclusions.

## 2. 1D APPROXIMATION FOR THE DISTRIBUTION IN THE CHANNEL

### 2.1. The 1D solution of the Poisson equation

An analytical solution of Poisson's equation for the complex structure of a real ion channel is very difficult to derive. Only a few analytical solutions of Poisson's equation in three dimensional space for specific ion channel shapes have been reported in the literature.<sup>9</sup> In the particular case of the Gramicidin channel, good insight on its functions can be obtained from the one dimensional approximation of Poisson equation for the channel modelled as a tube with cylindrical symmetry. For the present study, we use the one-dimensional approximation derived by Barcion<sup>7,8</sup> for a long and narrow channel. In that approximation, the Poisson equation is written as:

$$-\varepsilon \frac{d^2 \tilde{\phi}}{d\tilde{x}^2} = z_p e \tilde{p}(\tilde{x}) + e \sum_{j=1}^2 z_j \tilde{c}_j(\tilde{x}) + \tilde{\varepsilon} \left[ \tilde{\Delta} \left( 1 - \frac{\tilde{x}}{d} \right) - \tilde{\phi} \right], \quad (1)$$

$$\tilde{\phi}(\tilde{x}_0) = \phi_0, \quad \tilde{\phi}(\tilde{x}_1) = \phi_1 = V_{app} = \tilde{\Delta}. \quad (2)$$

We have limited ourselves to only two types of ionic species. This approximation is valid as long as we are inside the channel. However, this is easily generalized to any number of species as will be seen in the next section when we consider ionic motion inside the bulk solution. The dielectric coefficient is taken as independent of time and space, for simplicity. In equation (1), the first term on the right hand side represents the permanent charge on the atoms of the protein, i.e. the charge that is independent of the electric field. Parameters of the associated distribution of the permanent charge  $\tilde{p}(x)$  and scaling factor  $z_p$  are fitting parameters for experiments. It gives the proportion of charge carried by the protein wall. The second term is the channel contents, made of free or mobile charge, carried by ions in the pore as they travel through the channel. The last term is the induced (sometimes called polarization) charge, in the pore and protein, created by the electric field; it is zero when the electric field is zero.<sup>10</sup> The concentrations  $\tilde{c}_j(x)$  are one-dimensional representations of number of ions per unit volume. The dielectric properties of the channel protein and its water-filled pore (radius  $r$ , length  $d$ ) are described by: the permittivity of free space  $\varepsilon_0$ ; (the dimensionless) dielectric constants  $\varepsilon_p$  and  $\varepsilon_{H_2O}$ , respectively; and the effective dielectric parameter

$$\tilde{\varepsilon} \equiv \frac{\varepsilon_p}{\varepsilon_{H_2O}} \cdot \frac{2\varepsilon_0}{a^2 \ln(d/a)}.$$

The constant  $\tilde{\Delta}$  is the potential difference across the channel,  $\tilde{\phi}$  is the electric potential,  $a$  is the channel radius, and  $e$  is the electronic charge. The permanent charge is modeled using a narrow Gaussian distribution, consistent with the fact that the charge is mainly concentrated in the central part of the channel<sup>11, 12</sup>:

$$p(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right). \quad (3)$$

Here  $\mu = 0.5$  is the mean value, taken to be the location of the channel center and  $\sigma = 0.1$  is the variance. To solve Poisson's equation we write it in dimensionless form using the following characteristic length, potential and concentration:

$$\tilde{p}_j = v_0^{-1}p_j, \quad \tilde{c}_j = v_0^{-1}c_j, \quad \tilde{\phi} = \Phi U_T, \quad \tilde{x} = xd, \quad U_T = \frac{k_B T}{e}. \quad (4)$$

The volume of the cylindrical ( $v_0 = \pi a^2 d$ ) channel is taken as the reference volume for the scaling of ion concentrations inside the channel. For the scaling of ion concentration in the bulk, we have to use a different reference volume. The dimensionless Poisson's equations are therefore given by:

$$\Phi''(x) - \beta\Phi(x) = -\beta\Delta(1-x) - z_p\alpha p(x) - \alpha \sum_{j=1}^2 z_j c_j(x), \quad \Phi(x_0) = \Phi_0, \quad \Phi(x_1) = \Phi_1 = \Delta. \quad (5)$$

After scaling, we are left with two dimensionless coefficients;  $\beta = \frac{d^2 \epsilon}{\epsilon_0 U_T}$  and  $\alpha = \kappa^2 d^2$  where  $\kappa^{-1} = \sqrt{\frac{\epsilon v_0 U_T}{e}}$  is known as the Debye length.  $U_T = \frac{k_B T}{Ze}$  is called the thermal voltage, and  $e$  is the electronic charge.  $k_B T$  is the thermal energy, where  $k_B$  is the Boltzmann's constant and  $T$  the absolute temperature.

By a linear transformation of the potential  $\Phi$ , the system of Eqs. (5) can be transformed into a zero boundary value problem. The resulting solution is given by the following equation:

$$\begin{aligned} \Phi(x) &= \frac{(\Phi_1 - \Phi_0)}{(x_1 - x_0)}(x - x_0) + \Phi_0 + \int_{x_0}^{x_1} G(x, s) f(s) ds, \\ f(s) &= \beta \left[ \frac{(\Phi_1 - \Phi_0)}{(x_1 - x_0)}(s - x_0) + \Phi_0 - \Delta(1 - s) \right] - \alpha z_p p(s) - \alpha \left[ z_1 c_1(s) + z_2 c_2(s) \right], \\ G(x, s) &= \begin{cases} A \sinh \sqrt{\beta}(s - x_1) \sinh \sqrt{\beta}(x - x_0), & x_0 \leq x \leq s. \\ A \sinh \sqrt{\beta}(s - x_0) \sinh \sqrt{\beta}(x - x_1), & s \leq x \leq x_1. \end{cases} \end{aligned} \quad (6)$$

$G(x, s)$  is the associated Green function and  $A = 1/(\sqrt{\beta} \sinh \sqrt{\beta}(x_1 - x_0))$ . Having estimated the solution of the Poisson's equation, we now focus on the Nernst-Planck equation for the determination of the current density as well as the concentrations of the two ion species.

## 2.2. Quasi-analytical solution of the Nernst-Planck equation in the channel

The problem to be discussed is the one described by Schuss.<sup>13</sup> The local concentration of ions of species  $j$  is denoted as  $\tilde{c}_j(x)$ , in the reaction region located on the axis between  $\tilde{x}_0 = 0$  and  $\tilde{x}_1 = d$ , satisfies the Nernst-Planck equation in the Stratonovich form<sup>14</sup>

$$\frac{d}{d\tilde{x}} z_j F D_j(\tilde{x}) \left[ \frac{d\tilde{c}_j(\tilde{x})}{d\tilde{x}} + \frac{z_j e}{k_B T} \tilde{c}_j(\tilde{x}) \frac{d\tilde{\phi}}{d\tilde{x}} \right] = 0 \quad \text{for } \tilde{x}_0 \leq \tilde{x} \leq \tilde{x}_1. \quad (7)$$

The Nernst-Planck equation is the sum of the molar fluxes due to local concentration and potential multiplied by  $z_j F$  (the charge on a mole of atom of valence  $z_j$ ).  $F = N_A e$  is the Faraday constant, where  $N_A$  and  $e$  are respectively the Avogadro number and the elementary charge. The channel length is given by  $d$ . For simplicity,

the diffusion coefficient  $D_j(\tilde{x})$  is taken to be a function of the position of the ion on the channel axis. The concentration is assumed to be constant in the bath regions on both sides of the channel to avoid having to solve the Nernst-Planck equation in all three domains. Therefore, the boundary conditions for Eq. (7) are given by:

$$\tilde{c}_j(\tilde{x} = \tilde{x}_0) = \tilde{c}_{jL} \quad \tilde{c}_j(\tilde{x} = \tilde{x}_1) = \tilde{c}_{jR} \quad (8)$$

Integrating Eq. (7) once, we obtain:

$$\tilde{J}_j = -z_j F D_j(\tilde{x}) \left[ \frac{d\tilde{c}_j(\tilde{x})}{d\tilde{x}} + \frac{z_j e}{k_B T} \tilde{c}_j(\tilde{x}) \frac{d\tilde{\phi}}{d\tilde{x}} \right], \quad (9)$$

where  $\tilde{J}_j$  is the current density carried by ions  $j$  (current per unit area; corresponding to the flux of ions  $j$  through the channel). We can now write this equation in dimensionless variables. Using the scaling factors from Eq. (4), the dimensionless Nernst-Planck equation is therefore given by:

$$J_j = \frac{\tilde{J}_j v_0 d}{z_j F} = -D_j(x) \left[ \frac{dc_j(x)}{dx} + c_j(x) \frac{dz_j \Phi}{dx} \right], \quad c_j(x = x_0) = c_{jL} \quad c_j(x = x_1) = c_{jR}. \quad (10)$$

Integrating the system of Eq. (10), the analytical flux and concentration can be calculated as follows:

$$J = \frac{c_{jL} \exp(z_j \Phi(x_0)) - c_{jR} \exp(z_j \Phi(x_1))}{\int_{x_0}^{x_1} \exp(z_j \Phi(s)) \frac{ds}{D(s)}}, \quad c_j(x) = \exp(-z_j \Phi(x)) \left[ c_{jL} \exp(z_j \Phi(x_0)) - J_j \int_{x_0}^x \exp(z_j \Phi(s)) \frac{ds}{D(s)} \right]. \quad (11)$$

Solution of the Poisson equation and the current density coupled to the ionic concentrations may now be calculated simultaneously in a self-consistent manner.

### 2.3. Self-consistent solution of Poisson-Nernst-Planck (PNP) equations in the channel

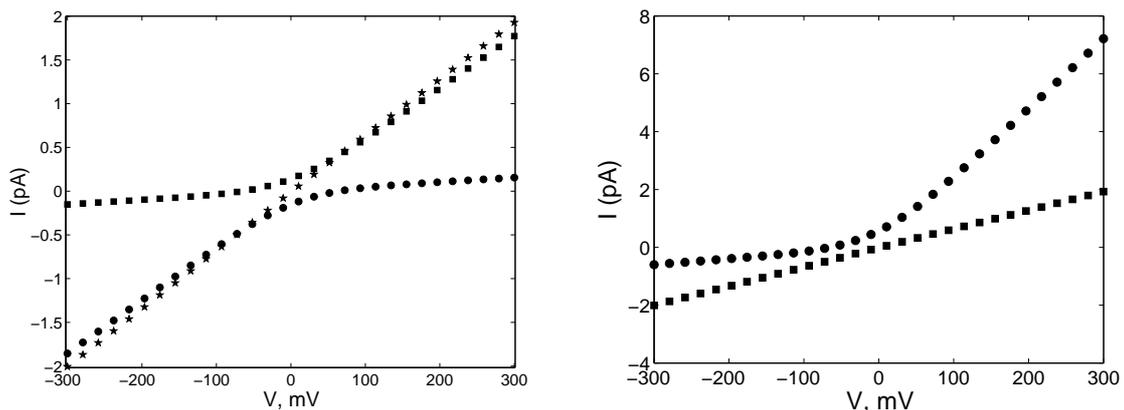
A self-consistent solution of the PNP equation means that the potential used to determine the flux is calculated from the solution of Poisson equation and not assumed. The solution is obtained by combining equations (6) and (11). The potential in Eq. (6) depends on the concentration  $c_j$  and the concentration in Eq. (11) also depend on the potential  $\Phi$ . The well known Gummel iteration of semiconductor physics is used to solve the 1D PNP equation, ensuring that Poisson's equation and far field boundary conditions are always satisfied.<sup>2</sup> The current is therefore calculated by using an initial guess for the potential. The linear part of the potential

$$\Phi(x; \text{initial guess}) = \frac{(\Phi_1 - \Phi_0)}{(x_1 - x_0)}(x - x_0) + \Phi_0, \quad (12)$$

can be seen as a reasonable initial guess. It is used to determine the concentration and then use the estimated concentration to calculate the potential. This procedure can be repeated to obtain higher order accuracy of the solution. This numerical procedure was used earlier by Eisenberg.<sup>15</sup> The only difference from the present calculation is that we included permanent charges on the wall with a Gaussian distribution and solved Poisson's equation analytically.

In Fig. 1(a), we present the calculation of the resulting current voltage characteristic for an uncharged channel. It can be seen that, in the absence of a net charge on the wall, the current voltage characteristic is linear. The effect of a net charge on the current is analyzed in Fig. 1(b) where we compare the current voltage characteristic for an uncharged and a charged channel. The net negative charge used for this calculation is equal to  $-0.02e$ . As was already stressed by Kurnikova,<sup>16</sup> the large difference between the current for the charged and uncharged channel demonstrates that the embedded charge distribution in the channel significantly influences current through the channel.

A filling factor of 0.155 is used in the calculation of the current-voltage characteristics. The filling factor is closely related to how ions distribute themselves inside the channel. In particular, the ionic radial distribution



**Figure 1.** (a) Current-voltage characteristics for the uncharged Gramicidin A (GA) channel. The stars show the total current, the squares represent positive ion current, the circles represent negative ion current. Ionic strengths in the lower (or left) and upper (or right) reservoirs are  $c_L = 500$  mMol and  $c_R = 40$  mMol, respectively. Diffusion constants are  $D_+ = D_- = 1.27 \times 10^{-10}$  m<sup>2</sup>/s. To fit the result, we used a channel of radius = 4 Å, length = 30 Å with a filling factor of 0.155. (b) the corresponding current-voltage characteristics for charged GA (circles) and uncharged GA (squares).

inside the channel is not uniform. This is due to the fact that the shape of the channel as measured experimentally is not uniform. In the 1D approximation, the channel is assumed to be a cylindrical tube of uniform radius. Therefore, the filling factor is used to compensate the fact that the radial charge distribution is non-uniform in the real channel as compared to the cylindrical symmetrical channel used in the 1D approximation. This adjustment of parameter is necessary since we use an approximation of Poisson's equation on the channel axis to determine the potential. This allows us to obtain good agreement with Kurnikova<sup>16</sup> whose results fit experiments. It is therefore interesting to notice that even a simple approximation of a one dimensional continuous theory can fit experiment, provided that fitting parameter is suitably chosen. The filling factor may have broad physical significance and can also be related to the fact that the dielectric coefficient is spatially inhomogeneous. Its spatial inhomogeneity is related on one hand to the ions' passage from water (a high polarizable medium) into the protein surrounded by lipid bilayer (a low polarity medium). On the other hand, the constant fluctuations of the atoms forming the protein wall may induce changes in the spatial distribution of the dielectric coefficient of the wall. Moreover, in a real channel experiment, both the protein which is embedded in the lipid bilayer and the lipid bilayer dielectric coefficients are taken into account.

The PNP solution as presented so far is incomplete. It does not take into account the bulk solution away from the channel mouth. Taking into account the concentration and potential variation away from and particularly near the channel mouth will introduce a correction to the current. This can be done by solving Poisson's equation for the determination of the potential coupled to the Nernst-Planck equation for the determination of ions' flux and concentration in the bulk.

### 3. SOLUTION OF THE POISSON-BOLTZMANN AND THE NERNST-PLANCK (PNBP) EQUATIONS IN THE 3D BULK SOLUTION WITH SPHERICAL SYMMETRY.

In order to introduce the correction to the current, we now consider the solution of Poisson and Nernst-Planck equations in the 3D bulk solution with spherical symmetry. The solution in the bulk in both ends of the channel spans from infinity to an imaginary hemisphere at the channel mouth, with a radius equal to that of the channel. The flux density of the  $j$ th ion  $\tilde{J}_j$  (ions m<sup>2</sup>s<sup>-1</sup>) is related to its concentration  $\tilde{c}_j$  (mol m<sup>-3</sup>), and the potential  $\tilde{\phi}$  (V) by the Nernst-Planck equation,

$$\tilde{J}_j = -z_j F D_j(\tilde{r}) \left[ \frac{d\tilde{c}_j(\tilde{r})}{d\tilde{r}} + \frac{z_j e}{k_B T} \tilde{c}_j(\tilde{r}) \frac{d\tilde{\phi}}{d\tilde{r}} \right], \quad (13)$$

where  $D_j$  ( $\text{m}^2 \text{s}^{-1}$ ) is the diffusion coefficient,  $z_j$  is the ion valence,  $F$  (C/mol) is the Faraday constant and  $\tilde{r}$  (m) is the radial distance measured from the center of the hemisphere at the mouth of the channel. Spherical symmetry is assumed in the bulk; therefore, ion density is independent of the angular coordinate. Ion densities are known at infinity and are written as follows:

$$\tilde{c}_j(\tilde{r} = \infty) = \tilde{c}_j^\infty. \quad (14)$$

The ion density is not known on the surface of the hemisphere. A simple integration of Eq. (13) with the boundary condition (14) is given by:

$$\tilde{c}_j(\tilde{r}) = \left[ \tilde{c}_j^\infty + \int_{\tilde{r}}^{\infty} \frac{\tilde{J}_j}{z_j F D_j(\tilde{s})} \exp\left(\frac{z_j e \tilde{\phi}(\tilde{s})}{k_B T}\right) d\tilde{s} \right] \exp\left(-\frac{z_j e \tilde{\phi}(\tilde{r})}{k_B T}\right). \quad (15)$$

We assume that all ions species are permeable to the channel's mouth, and we therefore write

$$\tilde{J}_j = -\frac{q_j}{2\pi\tilde{r}^2}, \quad (16)$$

where  $q_j$  is the current of the  $j$ th ion entering the channel at the mouth. By substituting Eq. (16) in Eq. (15), we arrive at the following relation for each ion density:

$$\tilde{c}_j(\tilde{r}) = \tilde{c}_j^\infty \left[ 1 - \int_{\tilde{r}}^{\infty} \frac{\tilde{q}_j}{2\pi z_j F D_j(\tilde{s}) \tilde{c}_j^\infty \tilde{s}^2} \exp\left(\frac{z_j e \tilde{\phi}(\tilde{s})}{k_B T}\right) d\tilde{s} \right] \exp\left(-\frac{z_j e \tilde{\phi}(\tilde{r})}{k_B T}\right). \quad (17)$$

This solution was obtained by assuming that the potential at infinity, far away from the channel mouth is equal to zero. Near the channel mouth, on the surface of the hemisphere, the gradient of the bulk potential is taken to be equal to the gradient of the electric potential inside the channel. The electric potential is determined by solving the Poisson equation in radial coordinates with only radial dependence:

$$\varepsilon \frac{1}{\tilde{r}} \frac{d^2}{d\tilde{r}^2} (\tilde{r} \tilde{\phi}) = -e \sum_j z_j \tilde{c}_j, \quad (18)$$

$$\tilde{\phi}(\tilde{r} = \infty) = 0, \quad \nabla \tilde{\phi}(\tilde{r} = a) = \nabla \tilde{\phi}^{PNP}(\tilde{r} = 0). \quad (19)$$

where  $\varepsilon = \varepsilon_{H_2O} \varepsilon_0$  is the product of the water dielectric constant and the dielectric constant of empty space.  $a$  is the channel radius and  $\tilde{\phi}^{PNP}$  is the PNP solution obtained inside the channel as calculated in section 2. The solution of Poisson's equation require knowledge of the ion density. Substituting the ion density from Eq. (17) into Poisson's equation gives the following integro-differential equation:

$$\begin{aligned} \varepsilon \frac{1}{\tilde{r}} \frac{d^2}{d\tilde{r}^2} (\tilde{r} \tilde{\phi}) &= -e \sum_j z_j \tilde{c}_j^\infty \exp\left(-\frac{z_j e \tilde{\phi}(\tilde{r})}{k_B T}\right) \\ + e \sum_j z_j \tilde{c}_j^\infty \int_{\tilde{r}}^{\infty} &\frac{\tilde{q}_j}{2\pi z_j F D_j(\tilde{s}) \tilde{c}_j^\infty \tilde{s}^2} \exp\left(\frac{z_j e \tilde{\phi}(\tilde{s})}{k_B T}\right) d\tilde{s} \exp\left(-\frac{z_j e \tilde{\phi}(\tilde{r})}{k_B T}\right). \end{aligned} \quad (20)$$

Before solving the coupled Nernst-Planck equations in the bulk, we write them in dimensionless form. We use the following scaling factors for the electric potential, the radial coordinate and the ion density

$$\tilde{\phi} = \phi U_T, \quad \tilde{r} = xa, \quad \tilde{c}_j = c_j \tilde{c}_2^\infty, \quad U_T = \frac{k_B T}{e}, \quad (21)$$

For simplicity, we choose three ion species and scale the ion densities relative to the bulk value of the density of the second ion type taken away from the channel mouth. The problem can be generalized to any number of ion species. At infinity, away from the channel mouth, the solution is assumed to be charge neutral. A straightforward solution of Poisson's equation is obtained if the charge neutral condition applies to the whole space by setting the right hand side of Eq. (18) equal to zero. Using the charge neutrality condition away from the channel mouth ( $\sum_j z_j \tilde{c}_j^\infty = 0$ ), we obtained the following dimensionless ion densities and Poisson equation:

$$c_j(x) = \frac{\tilde{c}_j^\infty}{\tilde{c}_2^\infty} \left[ 1 - 2\beta_j \int_x^\infty \frac{\exp(z_j \phi(s))}{s^2} ds \right] \exp(-z_j \phi(x)), \quad (22)$$

$$\sinh \phi(x) + \sum_j z_j c_j \beta_j \exp(-z_j \phi(x)) \int_x^\infty \frac{\exp(z_j \phi(s))}{s^2} ds = \frac{1}{\alpha^2 x} \frac{d^2}{dx^2} (x\phi) = \quad (23)$$

The following parameters have also been introduced for simplicity:

$$\beta_j = \frac{\delta_j}{2a}, \quad \delta_j = \frac{q_j}{2\pi z_j \tilde{c}_j^\infty F D_j}. \quad (24)$$

The parameter  $\delta_j$  have the dimensions of distance. Therefore,  $\beta_j$  is a dimensionless constant. We have assumed that the diffusion coefficients are not space dependent. The Debye length is given by:

$$\lambda = \left( \frac{\varepsilon k_B T}{2\tilde{c}_2^\infty e^2} \right)^{1/2}, \quad (25)$$

and the dimensionless length:

$$\alpha = \frac{a}{\lambda}. \quad (26)$$

The solution of the integrodifferential equation is not trivial. It can be solved numerically to determine the electrostatic potential. However, it was shown by Peskoff<sup>6</sup> that the linear approximation agrees well with the exact solution under most physiological conditions. Therefore, we linearized the Poisson equation when the potential decreases across the bulk. For small values of the electrostatic potential, Equations (22) and (23) are reduced respectively to:

$$c_j(x) = \frac{\tilde{c}_j^\infty}{\tilde{c}_2^\infty} \left[ 1 - \frac{2\beta_j}{x} \right], \quad (27)$$

$$\frac{1}{\alpha^2 x} \frac{d^2}{dx^2} (x\phi) = \phi + \frac{\beta}{x}. \quad (28)$$

In the case of the linear approximation, The charge density is identical to that obtained for an electro-neutral solution in the absence of any external field. The corresponding current for each ion species at the hemisphere near the channel mouth can be deduced by considering the hemisphere as a sink. Therefore, the ionic concentration at the surface of the hemisphere is equal to zero. This condition leads to the current  $q_j = 2\pi z_j \tilde{c}_j^\infty F D_j a$ . In the presence of the electric field, this value of the current is increased.<sup>6</sup>

The special feature of this approach is that the linearized Poisson equation is given in terms of the total current through  $\beta = \sum_j c_j \beta_j$  and the ion density is also a function of the electrostatic potential. The integration of Eq. (28) yields the following expression for the electrostatic potential:

$$\phi(x) = \frac{\left( \frac{\beta}{x_a} - \nabla \phi^{PNP}(x_0) \right) x_a^2 \exp(\alpha(x_a - x))}{(1 + \alpha x_a)x} - \frac{\beta}{x}. \quad (29)$$

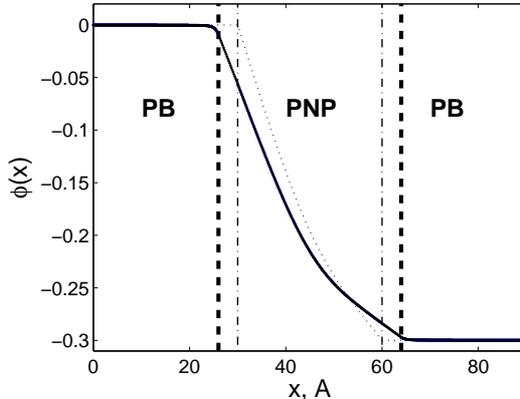
Where  $x_0$  and  $x_a$  are respectively the origin at the channel mouth and a point on the semi-sphere at the channel's mouth.

#### 4. JOINT SELF-CONSISTENT SOLUTION OF THE 1D PNP IN THE CHANNEL AND THE 3D PBNP IN THE BULK

In order to complete the calculation of ion density and electrostatic potential everywhere in the space, we coupled the solutions of the Poisson-Nernst-Planck obtained in the channel and in the bulk spanning from infinity to the hemisphere near the channel mouth. One particular thing to notice is that neither solution gives us knowledge of the electrostatic potential and concentrations for all the species involved inside the hemisphere. The important thing to notice about these boundary conditions is the fact that the given values of the bulk concentrations and electric potential are set at infinity, while near the channel mouth at the surface of the hemisphere, the boundary conditions are given by the continuity condition for the electric field and the current. Therefore, the electrostatic potential and the concentrations obtained by solving PNP equations in the channel can be used to determine the corresponding electric field and current at the boundary on the hemisphere. The algorithm can be summarized as follows

1. Initialization: The following boundary conditions  $c_{L\infty}$ ,  $c_{R\infty}$ ,  $\phi_{L\infty}$ ,  $\phi_{R\infty}$  as defined in Fig. 2 are used both at infinity for the PBNP in the bulk and at the channel mouth for the PNP inside the channel. The initial guess for potential (see Eq. 12) as linear function of the position in the channel. The corresponding concentration is then deduced
2. PNP solution in the channel.
  - Choose an initial guess for the potential
  - Calculate the corresponding concentration from the analytic formula
  - Use the concentration obtained at the zero iteration to calculate the new potential from its analytical formula.
  - Use the second iteration of the potential to deduce the concentration
  - Repeat the operation until both potential and concentration converge.
  - Determine the current inside the channel for the given applied voltage
3. Substitute the current through the channel into the boundary conditions for the PBNP equation. Solve the PBNP in the bulk.

4. Calculate new boundary conditions at the channel mouth and go back to item 2 (PNP solution in the channel)



**Figure 2.** Electrostatic potential obtained with the following boundary conditions:  $\phi(-\infty) = 0$ ;  $\phi(\infty) = -300$  mV;  $C(-\infty) = 500$  mMol;  $C(\infty) = 40$  mMol;  $\text{Na}^+$  80%,  $\text{K}^+$  20%; fixed charge  $-0.2e$  in the middle of the channel normally distributed with standard deviation  $\sigma = 0.2$ . The initial solution for the PNP equations in the channel is shown by the thin dashed line. The result of the self-consistent calculations of the potential in the bathing solutions and in the pore is shown by the thick solid line. The vertical thin dashed-dotted lines indicate the position of the channel entrances. The vertical thick dashed lines show the boundaries for the calculations of the access resistance.

The solution obtained in the previous section for the current and potential gradient in the pore is therefore used to set up boundary conditions for Eqs. (13) and (18) in the bath. In turn, the solutions Eqs. (29) and (22) can be used to set up the boundary conditions for the Eqs. (1) and (7) in the pore. The convergence of the successive approximations is guaranteed by the fact that in the zero approximation the current through the channel and the electric field at the channel mouth have maximum possible values. This leads to the maximum possible reduction of the concentration and the potential at the channel mouth. In turn this reduces the current and the electric field in the channel, which leads to a smaller correction. I.e. the scheme is converging and the resulting solution is shown in the Fig. 2. Note that in the two regions of thickness  $a$  (radius of the channel) at the left and right hand sides of the channel, the gradient of the electric potential is assumed to be constant.

## 5. SUMMARY AND CONCLUSIONS

We have suggested an analytic self-consistent solution for the problem of calculating the access resistance, potential and charge distribution in the channel. The obtained solution allows one to set boundary conditions for the PNP solution in the bulk in a self-consistent way. A particular feature of this approach is that it does not assume that only one type of ion is permeating the channel's mouth. It calculates the total current as the sum of the current produced by each ion species. The current-voltage characteristics of a Gramicidin A channel is presented using the 1D approximation of the PNP equation. The obtained results are in very good agreement with the Kurnikova<sup>16</sup> 3D result with a good fit to experimental results for the Gramicidin A channel. The agreement with experiment is made in the case of the 1D approximation by using a filling factor as a fitting parameter.

We have shown that 1D PNP can provide a good tool for ion channels current-voltage characteristics calculation. Despite its success, it is used under the assumption that water is a continuum, with no ion-ion interaction and the membrane considered as a rigid structure. Protein flexibility is not taken into account in the Poisson-Nernst-Planck model which describes water and protein as a continuum by using their average structure. Moreover,

our technique as proposed does not determine the field inside the hemisphere near the channel mouth. Another correction can be introduced into this model by solving Poisson's equation numerically in the entire space. This way, the potential inside the hemisphere will be explicitly calculated numerically and not extrapolated from the converged tails and heads of the electrostatic solution in the bulk and inside the pore. The solution of Poisson's equation will incorporate the dielectric self-energy acting on the ion as it crossed the channel.

## ACKNOWLEDGMENTS

The work was supported by the Engineering and Physical Sciences Research Council (UK), RFBR (The Russian Foundation for Basic Research) , INTAS, and ESF.

## REFERENCES

1. B. Hille, *Ionic Channel Of Excitable Membranes*, Sinauer Associates, Sunderland, MA, 1992.
2. R. S. Eisenberg, "Ionic channels in biological membranes - electrostatic analysis of a natural nanotube," *Contemporary Physics* **39**(6), pp. 447–466, 1998.
3. D. P. Chen, J. Lear, and R. S. Eisenberg, "Permeation through an open channel: Poisson-Nernst-Planck theory of a synthetic ionic channel," *Biophys. J.* **72**, pp. 97–116, 1997.
4. B. Corry, T. W. Allen, S. Kuyucak, and S.-H. Chung, "Mechanisms of permeation and selectivity in Calcium channels," *Biophys. J.* **80**(1), pp. 195–214, 2001.
5. B. Roux, "Valence selectivity of the Gramicidin channel: A molecular dynamics free energy perturbation study," *Biophys. J.* **71**, pp. 3177–3185, 1996.
6. A. Peskoff and D. M. Bers, "Electrodifusion of ions approaching the mouth of a conducting membrane channel," *Biophys. J.* **53**, pp. 863–875, 1988.
7. V. Barcilon, "Ion flow through narrow membrane channels: Part I," *SIAM J. Appl. Math.* **52**, pp. 1391–1404, 1992.
8. V. Barcilon, D. P. Chen, and R. S. Eisenberg, "Ion flow through narrow membrane channels: Part II," *SIAM J. Appl. Math.* **52**, pp. 1405–1425, 1992.
9. S. Kuyucak, M. Hoyles, and S.-H. Chung, "Analytical solutions of Poisson's equation for realistic geometrical shapes of membrane ion channels," *Biophys. J.* **74**, pp. 22–36, 1998.
10. D. P. Chen and R. S. Eisenberg, "Charges, currents, and potentials in ionic channels of one conformation," *Biophys. J.* **64**(5), pp. 1405–1421, 1993.
11. S. McLaughlin, "The electrostatic properties of membranes," *Annu. Rev. Biophys. Biophys. Chem* **18**, pp. 113–136, 1989.
12. D. P. Chen, J. Tang, and R. S. Eisenberg, "Structure-function study of Porins," *Nanotech* **2**, pp. 64–67, 2002.
13. R. S. Eisenberg, M. M. Klosek, and Z. Schuss, "Diffusion as a chemical-reaction - stochastic trajectories between fixed concentrations," *J. Chem. Phys.* **102**, pp. 1767–1780, 1995.
14. C. Gardiner, *Handbook of Stochastic methods for Physics and Chemistry, Number 13 in Springer series in Synergetics*, Springer, New York, 1996.
15. R. S. Eisenberg, "Computing the field in proteins and channels," *J. Membrane Biol.* **150**, pp. 1–25, 1996.
16. A. E. Cardenas, R. D. Coalson, and M. G. Kurnikova, "Three-dimensional Poisson-Nernst-Planck theory studies: Influence of membrane electrostatics on Gramicidin A channel conductance," *Biophys. J.* **79**, pp. 80–93, 2000.