A flux ratio and a universal property of permanent charges effects on fluxes

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Abstract

In this work, we consider ionic flow through ion channels for an ionic mixture of a cation species (positively charged ions) and an anion species (negatively charged ions), and examine effects of a positive permanent charge on fluxes of the cation species and the anion species. For an ion species, and for any given boundary conditions and channel geometry, we introduce a ratio $\lambda(Q) = J(Q)/J(0)$ between the flux $J(Q)$ of the ion species associated with a permanent charge Q and the flux $J(0)$ associated with zero permanent charge. The flux ratio $\lambda(Q)$ is a suitable quantity for measuring an effect of the permanent charge Q: if $\lambda(Q) > 1$, then the flux is enhanced by Q; if $\lambda < 1$, then the flux is reduced by Q. Based on analysis of Poisson-Nernst-Planck models for ionic flows, a universal property of permanent charge effects is obtained: for a *positive* permanent charge Q, if $\lambda_1(Q)$ is the flux ratio for the cation species and $\lambda_2(Q)$ is the flux ratio for the anion species, then $\lambda_1(Q) < \lambda_2(Q)$, *independent of boundary conditions and channel geometry.* The statement is sharp in the sense that, at least for a given *small* positive Q, *depending on boundary conditions and channel geometry*, each of the followings indeed occurs:

$$(i)\ \lambda_1(Q) < 1 < \lambda_2(Q); \quad (ii)\ 1 < \lambda_1(Q) < \lambda_2(Q); \quad (iii)\ \lambda_1(Q) < \lambda_2(Q) < 1.$$

Analogous statements hold true for *negative* permanent charges with the inequalities reversed.

It is also shown that the quantity $\delta(Q) = |J(Q) - J(0)|$ may not be suitable for comparing the effects of permanent charges on cation flux and on anion flux. More precisely, for some *positive* permanent charge Q, if $\delta_1(Q)$ is associated with the cation species and $\delta_2(Q)$ is associated with the anion species, then, *depending on boundary conditions and channel geometry*, each of the followings is possible: (a) $\delta_1(Q) > \delta_2(Q)$; (b) $\delta_1(Q) < \delta_2(Q)$.

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1 Introduction

A central topic of physiology concerns functions of ion channels. Ion channels are large proteins embedded in cell membranes that have "holes" open to inside and outside of

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cells. Ion channels can open and close gated by various mechanisms (see, e.g. [8, 24]). During the open stage, ions flow through ion channels and produce electrical signals that control many biological functions (see, e.g. [14, 15]). Motions of ions are governed by general physical laws of electrodiffusion which relate rates of changes of interested quantities. The macroscopic properties of ionic flows through ion channels rely further on specific structural characteristics (permanent charges and channel geometry) of ion channels and external driving forces (boundary potentials and concentrations of ion species involved). The arguably most important quantity of ionic flows is the fluxes $\mathcal{J}_k$'s of individual ion species. The algebraic sum of fluxes with their valences z_k's as coefficients gives the total current $\mathcal{I} = \sum z_k\mathcal{J}_k$. Most experiments today measure the total current $\mathcal{I}$ based on electrical properties of the ionic mixture, from which one cannot separate the contributions of individual fluxes. To measure the fluxes of individual ions, radioactive isotopes of interested ion species are applied. For example, for sodium-chloride ($\mathrm{Na}^+\mathrm{Cl}^-$) solutions, one can add a tiny amount of a radioactive isotope of sodium. The flux of this isotope can be measured by its radioactivity. Flux of sodium can then be measured by measuring the flux of the isotope (see, for example, [25, 29, 62] for more details).

These measurements are input-output types, in particular, internal dynamics of ionic flows are beyond the limits of present experimental techniques of measurements. Mathematical analysis provides an alternative approach for the study of internal dynamics, has a flexibility to incorporate multi-parameters of the physical problem altogether, and has the potential to track the effects of different parameters on the physical properties. The basic primitive models for ionic flows are the Poisson-Nernst-Planck (PNP) type systems. PNP type systems are continuum models which miss many atomic level details and specifics (such as paths of individual ions, location of an ion with a finite size) but capture macroscopic/thermodynamic properties (such as fluxes, system energy, etc.) of ionic flows. The classical PNP model treats ions essentially as point charges. The classical model has been refined to include ion size effects, variable dielectric coefficients and side chains, and the efforts have shown great successes (see, for example, [7, 17, 21, 22, 23, 26, 27, 28, 30, 32, 33, 34, 36, 37, 38, 39, 40, 41, 42, 46, 50, 58, 63, 64, 65, 68, 69, 70]).

In this work, we will examine the effects of permanent charges on a mixture of a cation species and an anion species based on analysis of PNP type models. For an ion species, and for any given boundary conditions and channel geometry, we introduce a ratio $\lambda(Q) = J(Q)/J(0)$ between its flux $J(Q)$ associated with the permanent charge Q and the flux $J(0)$ associated with zero permanent charge. The flux ratio $\lambda(Q)$ turns out to be a suitable quantity for measuring the effect: if $\lambda(Q) > 1$, then the flux is enhanced by Q; if $\lambda < 1$, then the flux is reduced by Q. Our main result (Theorem 4.1) reveals a universal property for an effect of permanent charges on fluxes of ionic mixtures with a cation species and an anion species; that is, *for a positive permanent charge* Q*, if* $\lambda_1(Q)$ *is the ratio for the cation species and* $\lambda_2(Q)$ *is the ratio for the anion species, then* $\lambda_1(Q) < \lambda_2(Q)$*, independent of boundary conditions and channel shapes.* It follows from the results in [31] (summarized in Theorem 3.2) that the above statement is sharp. Analogous statements hold true for negative permanent charges with the inequalities reversed. We also show (Proposition 3.3) that the absolute difference $\delta(Q) = |J(Q) - J(0)|$ is not a suitable quantity for comparing the effects of permanent charges on the cation flux and the anion flux; that is, *for some positive permanent* *charge Q, if $\delta_1(Q)$ is associated with the cation species and $\delta_2(Q)$ is associated with the anion species, then, depending on boundary conditions and channel shapes, each of the followings is possible: (a) $\delta_1(Q) > \delta_2(Q)$; (b) $\delta_1(Q) < \delta_2(Q)$.*

The rest of the paper is organized as follows. In Section 2, we recall the three-dimensional and a quasi-one-dimensional PNP type models for ionic flows and a dimensionless form of the quasi-one-dimensional model. A statement of our result is provided. In Section 3, some relevant results from [31] are recalled that also serve as a part of motivations for our study in this paper and the above stated claim on the quantity $\delta(Q)$ is established. Section 4 contains proofs of our main results on $\lambda(Q)$. In Section 5, concluding remarks and further related problems are provided.

2 Poisson-Nernst-Planck type models and the main result

Permanent charges and *channel shapes* are the key structures of ion channels. Their effects on ionic flows are the main concern of ion channel functions. We will study the effects based on analysis of PNP type models.

2.1 Three-dimensional and quasi-one-dimensional PNP models

Taking the structural characteristics into considerations, PNP type systems are primitive models for ionic flows that treat the aqueous medium (in which salts are dissolved to free ions and ions are migrating) as dielectric continuum. PNP systems can be derived as reduced continuum models from molecular dynamic Langevin models ([55]), from Boltzmann equations ([4]), and from variational principles ([26, 27, 28, 60]), etc.

For an ionic mixture with n ion species, PNP reads

$$\begin{aligned}
&\nabla\cdot\Big(\varepsilon_r(\mathbf{r})\varepsilon_0\nabla\Phi\Big) = -e_0\Big(\sum_{s=1}^{n} z_sC_s + \mathcal{Q}(\mathbf{r})\Big),\\
&\nabla\cdot\vec{\mathcal{J}}_k = 0, \quad -\vec{\mathcal{J}}_k = \frac{1}{k_BT}\mathcal{D}_k(\mathbf{r})C_k\nabla\mu_k, \quad k=1,2,\cdots,n
\end{aligned}\tag{2.1}$$

where $\mathbf{r}\in\Omega$ with Ω being a three-dimensional cylindrical-like domain representing the channel, $\mathcal{Q}(\mathbf{r})$ is the permanent charge density, $\varepsilon_r(\mathbf{r})$ is the relative dielectric coefficient, ε_0 is the vacuum permittivity, e_0 is the elementary charge, k_B is the Boltzmann constant, T is the absolute temperature; Φ is the electric potential, and, for the kth ion species, C_k is the concentration, z_k is the valence (the number of charges per particle), μ_k is the electrochemical potential depending on Φ and $\{C_j\}$, $\vec{\mathcal{J}}_k$ is the flux density vector, and $\mathcal{D}_k(\mathbf{r})$ is the diffusion coefficient.

Reduction of three-dimensional PNP systems (2.1) to quasi-one-dimensional models was first proposed in [48] based on the fact that ion channels have narrow cross-sections relative to their lengths, and was partially justified in [45] for special cases. A quasi-one-dimensional PNP model is

$$\begin{aligned}
&\frac{1}{A(X)}\frac{d}{dX}\Big(\varepsilon_r(X)\varepsilon_0A(X)\frac{d}{dX}\Phi\Big) = -e_0\Big(\sum_{s=1}^{n} z_sC_s + \mathcal{Q}(X)\Big),\\
&\frac{d}{dX}\mathcal{J}_k = 0, \quad -\mathcal{J}_k = \frac{1}{k_BT}\mathcal{D}_k(X)A(X)C_k\frac{d}{dX}\mu_k, \quad k=1,2,\cdots,n
\end{aligned}\tag{2.2}$$

where $X \in [0,l]$ is the coordinate along the axis of the channel, $A(X)$ is the area of cross-section of the channel over the location X. Equipped with system (2.2), we impose the following boundary conditions (see, [16] for a reasoning), for $k = 1, 2, \cdots, n$,

$$\Phi(0) = \mathcal{V}, \quad C_k(0) = L_k > 0; \quad \Phi(l) = 0, \quad C_k(l) = R_k > 0. \tag{2.3}$$

For a solution of BVP (2.2) and (2.3), the *current* $\mathcal{I}$ is

$$\mathcal{I} = \sum_{j=1}^{n} z_j \mathcal{J}_j. \tag{2.4}$$

For fixed L_k's and R_k's, $\mathcal{J}_k$'s depend on $\mathcal{V}$ only and formula (2.4) defines the *I-V (current-voltage) relation* – an important characteristic of an ion channel.

The electrochemical potential $\mu_k = \mu_k^{id}(X) + \mu_k^{ex}(X)$ consists of the ideal component $\mu_k^{id}(X)$ and the excess component $\mu_k^{ex}(X)$. The ideal component $\mu_k^{id}(X)$, given by

$$\mu_k^{id}(X) = z_k e_0 \Phi(X) + k_B T \ln \frac{C_k(X)}{C_0} \tag{2.5}$$

with a fixed reference concentration C_0, reflects the point-charge component of ions. PNP models including only ideal components are referred to as *classical* PNP models. Dynamics of classical PNP models has been analyzed by using asymptotic expansion methods ([1, 4, 5, 6, 35, 49, 56, 57, 59, 61]) and geometric singular perturbation (GSP) approaches ([2, 3, 16, 18, 31, 32, 43, 44, 47]). The excess component $\mu_k^{ex}(X)$ accounts for ion sizes, which is crucial for many important properties of ion channels such as selectivity. Modeling of the excess component $\mu_k^{ex}(X)$ is extremely challenging and is not completely understood. A great deal of efforts has been attributed to approximations of $\mu_k^{ex}(X)$ based on mean-spherical approximations, fundamental measure theory, and density functional theory (e.g., [9, 10, 51, 52, 53]). Numerical simulations of PNP with approximated models of $\mu_k^{ex}(X)$ have been conducted for ion channel problems in comparison with experimental data and have shown great successes for properties such as ion permeation and ion selectivity (e.g., [11, 12, 20, 21, 22, 23]). Other important phenomena involving $\mu_k^{ex}(X)$ such as steric effects, layering, charge inversions, and critical potentials have also been studied [7, 26, 27, 28, 30, 33, 34, 36, 38, 46, 54, 70].

We point out that BVP (2.2) and (2.3) is generally well-posed if the excess potentials $\mu_k^{ex}(X)$ are local models, that is, for any X, $\mu_k^{ex}(X)$ depends on $\{C_j(X)\}$ at the given location X. In general, the excess potentials $\mu_k^{ex}(X)$ are nonlocal and, in this case, the boundary value problem with boundary conditions (2.3) is severely under determined. We refer the readers to [58] for more detailed discussion and for a correct formulation of the boundary conditions for PNP with nonlocal excess potentials.

2.2 Rescaling of the quasi-one-dimensional model problem

We make a dimensionless rescaling following [19]. Let C_0 be a characteristic concentration of the problems, for example,

$$C_0 = \max_{1 \le k \le n} \big\{ L_k, R_k, \sup_{X \in [0,l]} |\mathcal{Q}(X)| \big\}.$$

Set

$$\mathcal{D}_0 = \max_{1\le k\le n}\{\sup_{X\in[0,l]}\mathcal{D}_k(X)\} \text{ and } \bar{\varepsilon}_r = \sup_{X\in[0,l]}\varepsilon_r(X).$$

Let

$$\begin{aligned}
&\varepsilon^2 = \frac{\bar{\varepsilon}_r\varepsilon_0 k_BT}{e_0^2 l^2 C_0}, \quad \hat{\varepsilon}_r(x) = \frac{\varepsilon_r(X)}{\bar{\varepsilon}_r}, \quad x = \frac{X}{l}, \quad h(x) = \frac{A(X)}{l^2},\\
&D_k(x) = \frac{\mathcal{D}_k(X)}{\mathcal{D}_0}, \quad Q(x) = \frac{\mathcal{Q}(X)}{C_0}, \quad \phi(x) = \frac{e_0}{k_BT}\Phi(X),\\
&c_k(x) = \frac{C_k(X)}{C_0}, \quad \hat{\mu}_k = \frac{1}{k_BT}\mu_k, \quad J_k = \frac{\mathcal{J}_k}{lC_0\mathcal{D}_0}.
\end{aligned} \tag{2.6}$$

In terms of the new variables, BVP (2.2) and (2.3) becomes

$$\begin{aligned}
&\frac{\varepsilon^2}{h(x)}\frac{d}{dx}\left(\hat{\varepsilon}_r(x)h(x)\frac{d\phi}{dx}\right) = -\sum_{s=1}^{n} z_s c_s - Q(x),\\
&\frac{dJ_k}{dx} = 0, \quad -J_k = D_k(x)h(x)c_k\frac{d\hat{\mu}_k}{dx},
\end{aligned} \tag{2.7}$$

with boundary conditions at $x = 0$ and $x = 1$

$$\phi(0) = \mathcal{V}_0 := \frac{e_0}{k_BT}\mathcal{V}, \ c_k(0) = l_k := \frac{L_k}{C_0}; \quad \phi(1) = 0, \ c_k(1) = r_k := \frac{R_k}{C_0}. \tag{2.8}$$

Our analysis is based on the scaled quasi-one-dimensional BVP (2.7) and (2.8). All results can be transformed easily back to BVP (2.2) and (2.3). In the following, we assume $\varepsilon > 0$ is small and examine BVP (2.7) and (2.8) as a singularly perturbed BVP. We comment that if the distance between the boundary points is $l = 2.5(nm)$ and the characteristic concentration is $C_0 = 10(M)$, then ε is of order 10^{-3} (see, for example, [17]).

For fixed boundary conditions, we denote any solution of BVP (2.7) and (2.8) by

$$\big(\phi(x; Q, \varepsilon), c_1(x; Q, \varepsilon), c_2(x; Q, \varepsilon), J_1(Q, \varepsilon), J_2(Q, \varepsilon)\big),$$

and often its zeroth order approximation in ε by

$$\big(\phi(x; Q), c_1(x; Q), c_2(x; Q), J_1(Q), J_2(Q)\big). \tag{2.9}$$

We indicate the dependence of solutions on Q but, of course, all these quantities depend on other parameters of the problem too such as the boundary conditions, the diffusion coefficients and the channel geometry. We will also use the notation $D_k(x; Q)$ to indicate the dependence of diffusion coefficients on the environment with the presence of $Q(x)$.

2.3 Statement of results for $n = 2$ with $z_1 > 0 > z_2$

A simple but important observation was made explicitly in [18], that is, the Nernst-Planck equation in (2.7) for the flux J_k gives

$$J_k(Q, \varepsilon)F_k(Q, \varepsilon) = \hat{\mu}_k(0) - \hat{\mu}_k(1). \tag{2.10}$$

where

$$F_k(Q,\varepsilon)=\int_0^1 \frac{1}{D_k(x;Q)h(x)c_k(x;Q,\varepsilon)}dx>0.$$

An immediate consequence is that the *sign* of $J_k(Q,\varepsilon)$ is determined solely by the transmembrane electrochemical potential $\hat{\mu}_k(0)-\hat{\mu}_k(1)$: *under the same boundary conditions, the sign of $J_k(Q,\varepsilon)$ is the same as that of $J_k(0,\varepsilon)$, independent of the permanent charge $Q(x)$.* However, the permanent charge $Q(x)$ influences *magnitudes* of $J_k(Q,\varepsilon)$'s. To measure this effect for kth ion species, we introduce a flux ratio

$$\lambda_k(Q,\varepsilon):=\frac{J_k(Q,\varepsilon)}{J_k(0,\varepsilon)}. \tag{2.11}$$

From (2.10), for any permanent charge $Q(x)$, one has $\lambda_k(Q,\varepsilon)>0$. In particular, if $\lambda_k(Q,\varepsilon)>1$, then $|J_k(Q,\varepsilon)|>|J_k(0,\varepsilon)|$; that is the magnitude of the flux $J_k(Q,\varepsilon)$, relative to that of the flux $J_k(0,\varepsilon)$, is *enhanced* by the permanent charge Q; if $\lambda_k(Q,\varepsilon)<1$, then the magnitude of the flux $J_k(Q,\varepsilon)$, relative to that of the flux $J_k(0,\varepsilon)$, is *reduced* by the permanent charge Q.

Remark 2.1. *We comment on the flux ratio $\lambda_k(Q;\varepsilon)$ when $J_k(0,\varepsilon)=0$. Note that, from (2.10), $J_k(0,\varepsilon)=0$ if and only if $\hat{\mu}_k(0)-\hat{\mu}_k(1)=0$, and hence, $J_k(Q,\varepsilon)=0$. In this case, one would say that the permanent charge has no effect on the flux and attempt to set $\lambda_k(Q;\varepsilon)=1$ as a convention. A closer examination provides a correct meaning and definition of $\lambda_k(Q;\varepsilon)$ for this case. In fact, in this case, $\lambda_k(Q;\varepsilon)$ is given by a ratio of $0/0$-type – a case occurs in calculus where one uses L'Hoptial rule to determine if the ratio is well-defined as a limit. Indeed, treating the ratio as a limit as $\hat{\mu}_k^\delta=\hat{\mu}_k(0)-\hat{\mu}_k(1)\to 0$, it follows from (2.10) that*

$$\lambda_k(Q;\varepsilon)=\lim_{\hat{\mu}_k^\delta\to 0}\frac{F_k(0,\varepsilon)\hat{\mu}_k^\delta}{F_k(Q,\varepsilon)\hat{\mu}_k^\delta}=\frac{F_k(0,\varepsilon)}{F_k(Q,\varepsilon)}. \tag{2.12}$$

The latter ratio is well-defined, independent of whether or not $\hat{\mu}_k^\delta=0$. In general, thought, the ratio does not equal to 1 (see Remark 3.1, for example). In case that $\lambda_k(Q;\varepsilon)\neq 1$, say $\lambda_k(Q;\varepsilon)>1$, it is still consistent with the statement that the permanent charge enhances the flux $J_k(Q;\varepsilon)=\lambda_k(Q;\varepsilon)J_k(0,\varepsilon)$ but the enhancement is annihilated by $J_k(0,\varepsilon)=0$.

Thus, the definition of $\lambda_k(Q;\varepsilon)$ in the case that $\hat{\mu}_k^\delta=0$ should be understood as that in (2.12). It is worthwhile to mention a technical reason for this definition. The flux ratio $\lambda_k(Q;\varepsilon)$ depends also on $(\mathcal{V}_0,L,R)$. If one uses the convention that $\lambda_k=1$ for $\hat{\mu}_k^\delta=0$, then, viewing λ_k as a function of $(\mathcal{V}_0,L,R,Q)$, it would have (removable) discontinuity at parameters where $\hat{\mu}_k^\delta=0$. The definition of λ_k in (2.12) for the case $\hat{\mu}_k^\delta=0$ removes the discontinuity, and hence, is of advantage. ◇

We consider ionic flows of ionic mixtures consisting of two ion species ($n=2$), one cation species with valence $z_1>0$ and one anion species with valence $z_2<0$. We will show that (Theorem 4.1):

$$\text{If }\ Q(x)\geq 0,\ Q(x)\neq 0,\ \text{ then }\ \lambda_1(Q,\varepsilon)<\lambda_2(Q,\varepsilon)\ \text{ when }\ \varepsilon\ \text{ is small enough.} \tag{2.13}$$

Furthermore, combining with results from [31] (recalled in Section 3 for reader's convenience), this result is *optimal* or *sharp*.

In general, the quantity $\delta_k(Q) = |J_k(Q;\varepsilon) - J_k(0;\varepsilon)|$ is not suitable for comparing the effects of permanent charges on cation flux and anion flux. This is discussed in Proposition 3.3 in Section 3.

3 Relevant results from [31] and the quantity $\delta_k(Q)$

3.1 Specifics of flux ratios for small positive permanent charges

In [31], the authors considered a setting of *classical* PNP models with $n = 2$, $\hat{\varepsilon}_r = 1$, constant diffusion coefficients $D_k(x)$'s, and $Q(x)$ as

$$Q(x) = \begin{cases} 0, & 0 < x < a, \\ Q_0, & a < x < b, \\ 0, & b < x < 1, \end{cases} \tag{3.1}$$

where Q_0 is a constant with $|Q_0|$ *small* relative to the boundary concentrations l_k's and r_k's. For the zeroth order approximation in ε of BVP (2.7) and (2.8), one can write

$$J_k(Q_0) = J_{k0} + J_{k1}Q_0 + O(Q_0^2). \tag{3.2}$$

For kth ion species, denote the difference of its boundary electrochemical potentials by

$$\hat{\mu}_k^\delta := \hat{\mu}_k^\delta(\mathcal{V}_0; l_k, r_k) = \hat{\mu}_k(0) - \hat{\mu}_k(1) = z_k\mathcal{V}_0 + \ln l_k - \ln r_k.$$

Applying the methods in [16, 44] to the study of BVP (2.7) and (2.8), the following results were obtained in [31] (see [31] for details and for other results).

Under the electroneutrality boundary conditions $z_1 l_1 = -z_2 l_2 = L$ and $z_1 r_1 = -z_2 r_2 = R$, it is derived in [31] that

$$J_{10} = \frac{L - R}{z_1 H(1)(\ln L - \ln R)}\hat{\mu}_1^\delta, \quad J_{20} = \frac{R - L}{z_2 H(1)(\ln L - \ln R)}\hat{\mu}_2^\delta, \tag{3.3}$$

and

$$\begin{aligned} J_{11} =& \frac{A(z_2(1-B)\mathcal{V}_0 + \ln L - \ln R)}{(z_1 - z_2)H(1)(\ln L - \ln R)^2}\hat{\mu}_1^\delta, \\ J_{21} =& \frac{A(z_1(1-B)\mathcal{V}_0 + \ln L - \ln R)}{(z_2 - z_1)H(1)(\ln L - \ln R)^2}\hat{\mu}_2^\delta, \end{aligned} \tag{3.4}$$

where,

$$H(x) = \int_0^x h^{-1}(s)ds, \quad \alpha = \frac{H(a)}{H(1)}, \quad \beta = \frac{H(b)}{H(1)},$$

$$\begin{aligned} A =& A(L,R) = -\frac{(\beta - \alpha)(L - R)^2}{((1-\alpha)L + \alpha R)((1-\beta)L + \beta R)(\ln L - \ln R)}, \\ B =& B(L,R) = \frac{\ln((1-\beta)L + \beta R) - \ln((1-\alpha)L + \alpha R)}{A}. \end{aligned} \tag{3.5}$$

Therefore, for $|Q_0|$ small,

$$\begin{aligned}\lambda_1(Q;0) =&\frac{J_1(Q_0)}{J_1(0)} = \frac{J_{10}+J_{11}Q_0+O(Q_0^2)}{J_{10}} = 1+\frac{J_{11}}{J_{10}}Q_0+O(Q_0^2)\\ =&1+\frac{z_1A(z_2(1-B)\mathcal{V}_0+\ln L-\ln R)}{(z_1-z_2)(\ln L-\ln R)(L-R)}Q_0+O(Q_0^2),\\ \lambda_2(Q;0) =&\frac{J_2(Q_0)}{J_2(0)} = \frac{J_{20}+J_{21}Q_0+O(Q_0^2)}{J_{20}} = 1+\frac{J_{21}}{J_{20}}Q_0+O(Q_0^2)\\ =&1+\frac{z_2A(z_1(1-B)\mathcal{V}_0+\ln L-\ln R)}{(z_2-z_1)(\ln L-\ln R)(R-L)}Q_0+O(Q_0^2).\end{aligned}$$

Remark 3.1. *We provide a discussion directly related to Remark 2.1. Consider the case, say $\hat{\mu}_1^\delta = z_1\mathcal{V}_0+\ln L-\ln R=0$ but $L\neq R$ so $\mathcal{V}_0\neq 0$. Then, for small $|Q_0|$ and up to $O(Q_0)$,*

$$\lambda_1(Q;0)=1+\frac{z_1A(z_2(1-B)\mathcal{V}_0+\ln L-\ln R)}{(z_1-z_2)(\ln L-\ln R)(L-R)}Q_0.$$

If the coefficient of Q_0 on the right-hand side of above is not zero, then $\lambda_k(Q;0)\neq 1$ for small $|Q_0|\neq 0$. On the other hand, the coefficient of Q_0 equals to zero if either $A=0$ or $z_2(1-B)\mathcal{V}_0+\ln L-\ln R=0$. The assumption that $L\neq R$ implies that $A\neq 0$. Thus, $z_2(1-B)\mathcal{V}_0+\ln L-\ln R=0$, which together with $\hat{\mu}_1^\delta=0$ give $B=(z_2-z_1)/z_2$. The latter does not hold in general, and hence, $\lambda_1(Q;0)\neq 1$ even if $\hat{\mu}_1^\delta=0$. ◇

A complete classification of properties of J_{k1}'s as consequences of interplay between boundary concentrations, boundary potential, channel geometry, and permanent charges $Q(x)$ with small $|Q_0|$ is obtained. The following is a summary of Theorems 4.7 and 4.8 in [31] in terms of the flux ratios $\lambda_k(Q,\varepsilon)$.

Theorem 3.2. *Suppose $\varepsilon>0$ is small enough. Then, depending on the boundary condition $(\mathcal{V}_0,L,R)$ and the characteristic (α,β) of the channel geometry, a* small positive *Q_0 can*

- *(i) reduce the flux of cations and enhance that of anions: $\lambda_1(Q,\varepsilon)<1<\lambda_2(Q,\varepsilon)$;*
- *(ii) enhance the fluxes of both cations and anions: $\lambda_1(Q,\varepsilon)>1$ and $\lambda_2(Q,\varepsilon)>1$;*
- *(iii) reduce the fluxes of both cations and anions: $\lambda_1(Q,\varepsilon)<1$ and $\lambda_2(Q,\varepsilon)<1$;*
- *(iv) but cannot enhance the flux of cations while reduce that of anions.*

To complement the above results, we comment that, in [67], it is shown that, for values of $(\mathcal{V}_0,L,R)$ in a bounded region, if $Q_0>0$ is large enough, then $\lambda_1(Q,\varepsilon)<1$; but, either $\lambda_2(Q,\varepsilon)<1$ or $\lambda_2(Q,\varepsilon)>1$ may occur, depending on the specifics of $(\mathcal{V}_0,L,R)$. For moderate values of Q_0, a numerical study in [66], focusing on parameter values of $(\mathcal{V}_0,Q_0)$ for which $\lambda_k=1$, reveals a rich behavior of the flux ratios.

Nevertheless, in Theorem 4.1, we will establish a universal property, that is, for $Q(x)\geq 0$ and $Q(x)\neq 0$ (not necessarily a piecewise constant $Q(x)$) and for $\varepsilon>0$ small, one always has $\lambda_1(Q,\varepsilon)<\lambda_2(Q,\varepsilon)$.

3.2 On the quantities $\delta_k(Q;\varepsilon)$

To end this section, we present a result to indicate that the quantity $\delta_k(Q,\varepsilon) = |J_k(Q,\varepsilon) - J_k(0,\varepsilon)|$ is not a suitable quantity for comparing the effects of permanent charges on fluxes of cations and anions.

Proposition 3.3. *Assume the setup in Subsection 3.1 with $z_1 = 1$ and $z_2 = -1$. For $Q_0 > 0$ small and $\varepsilon > 0$ small, depending on specifics of $(\mathcal{V}_0, L, R, \alpha, \beta)$, each of the following inequalities is possible*

$$\text{(a) } \delta_1(Q;\varepsilon) > \delta_2(Q;\varepsilon); \quad \text{(b) } \delta_1(Q;\varepsilon) < \delta_2(Q;\varepsilon).$$

Proof. It suffices to establish the statement for $\delta_k(Q;0)$. Note that, for $k = 1, 2$, if $Q_0 > 0$ is small, $\delta_k(Q;0) = |J_k(Q_0) - J_k(0)| = |J_{k1}Q_0 + O(Q_0^2)|$, and hence, inequality (a) is equivalent to $|J_{11}|/|J_{21}| > 1$ and inequality (b) is equivalent to $|J_{11}|/|J_{21}| < 1$. It follows from (3.4) that

$$\begin{aligned} \frac{|J_{11}|}{|J_{21}|} &= \left| \frac{-(1-B)\mathcal{V}_0 + \ln(L/R)}{(1-B)\mathcal{V}_0 + \ln(L/R)} \cdot \frac{\mathcal{V}_0 + \ln(L/R)}{-\mathcal{V}_0 + \ln(L/R)} \right| \\ &= \left| \frac{(B-1)\mathcal{V}_0^2 + B\mathcal{V}_0 \ln(L/R) + (\ln(L/R))^2}{(B-1)\mathcal{V}_0^2 - B\mathcal{V}_0 \ln(L/R) + (\ln(L/R))^2} \right|. \end{aligned}$$

Consider $L > R$. It has been shown that one can choose (α, β), depending on L and R but independent of $\mathcal{V}_0$, so that $B > 1$ (Case (i) in Lemma 4.6 of [31]). Assume this is the case. Note that, in the above expression inside the absolute value sign, the numerator

$$\mathcal{N} := (B-1)\mathcal{V}_0^2 + B\mathcal{V}_0 \ln\frac{L}{R} + \left(\ln\frac{L}{R}\right)^2$$

and the denominator

$$\mathcal{D} := (B-1)\mathcal{V}_0^2 - B\mathcal{V}_0 \ln\frac{L}{R} + \left(\ln\frac{L}{R}\right)^2$$

can be viewed as quadratic polynomials in $\mathcal{V}_0$. Recall that we take $L > R$ and $B > 1$. The numerator $\mathcal{N}$ has two zeros given by

$$-\ln\frac{L}{R} < 0 \quad \text{and} \quad -\frac{1}{B-1}\ln\frac{L}{R} < 0,$$

and the denominator $\mathcal{D}$ has two zeros given by

$$\ln\frac{L}{R} > 0 \quad \text{and} \quad \frac{1}{B-1}\ln\frac{L}{R} > 0.$$

If we choose $\mathcal{V}_0$ so that

$$\min\left\{\ln\frac{L}{R}, \frac{1}{B-1}\ln\frac{L}{R}\right\} > \mathcal{V}_0 > 0,$$

then $\mathcal{N} > 0$ and $\mathcal{D} > 0$, and $\mathcal{N} - \mathcal{D} = 2B\mathcal{V}_0 \ln(L/R) > 0$, and hence, $|J_{11}| > |J_{21}|$, which implies inequality (a).

If we choose $\mathcal{V}_0$ so that

$$\max\left\{-\ln\frac{L}{R},\ -\frac{1}{B-1}\ln\frac{L}{R}\right\} < \mathcal{V}_0 < 0,$$

then $\mathcal{N} > 0$ and $\mathcal{D} > 0$, and $\mathcal{N} - \mathcal{D} = 2B\mathcal{V}_0\ln(L/R) < 0$, and hence, $|J_{11}| < |J_{21}|$, which implies inequality (b). □

4 A universal property of permanent charge effects

We will establish our main result on the flux ratios for cations and anions.

4.1 Basic assumptions

For our result, we will consider $n = 2$ with $z_1 > 0 > z_2$ and make the following general assumptions for PNP type system (2.7).

(A1) The dimensionless quantity $\varepsilon > 0$ defined in (2.6) is small.

(A2) The permanent charge $Q(x)$ satisfies that $Q(x) \geq 0$, $Q(x) \neq 0$ and $Q(x)$ may have jump discontinuity.

(A3) The diffusion coefficients satisfy

$$\frac{D_2(x;Q)}{D_1(x;Q)} = \sigma$$

for a constant $\sigma > 0$ independent of x and $Q(x)$.

(A4) For a solution $(\phi(x;Q,\varepsilon), c_1(x;Q,\varepsilon), c_2(x;Q,\varepsilon), J_1(Q,\varepsilon), J_2(Q,\varepsilon))$ of BVP (2.7) and (2.8), the zeroth order approximation in ε

$$(c_1(x;Q), c_2(x;Q)) = (c_1(x;Q,0), c_2(x;Q,0))$$

satisfies electroneutrality condition

$$z_1c_1(x;Q) + z_2c_2(x;Q) + Q(x) = 0$$

for every x except possible jump points of $Q(x)$.

We comment that (A3) and (A4) are assumed to be true also for $Q = 0$.

Before a statement of our main claim, we briefly comment on assumptions (A3) and (A4). In general, the nature of diffusion coefficients $D_k(x;Q)$'s is not completely understood. They are though not constants and vary from environment to environment. In (A3), we do not assume *specifics* on individual diffusion coefficients but assume a *relation* among them. (A3) roughly means that, as the environment varies from location to location, its influences on the two diffusion coefficients at the same location x are assumed to be the same; that is, the two diffusion coefficients vary from one common environment to another common environment in a way so that their ratio is independent of locations. This is clearly not a justification of this assumption but only an explanation of what it reflects.

The identity in (A4) is nothing but, up to the zeroth order approximation in ε, the *pointwise-electroneutrality* condition. Global electroneutrality is widely accepted while, in general, it is reasonable to assume only *approximate* pointwise-electroneutrality. Our assumption of "approximate" is specific: pointwise-electroneutrality is assumed to be exact only at the zeroth order approximation in ε. Mathematically, the zeroth order pointwise-electroneutrality condition has been rigorously justified for classical PNP models ([16, 44]) and PNP with hard-sphere potentials ([30, 38]).

We emphasize that, in the following, we do not assume PNP system (2.7) to be classical; that is, the electrochemical potential μ_k can include any local excess components to account for the finite sizes of ions. Also, from the proof of Theorem 4.1 below, we only need to assume the excess components to be local at $x = 0$ and $x = 1$. Away from these two points, the models for the excess potentials could be nonlocal.

4.2 Statement of the main result and its proof

We are ready to show the following result.

Theorem 4.1. *Consider ionic flow for two ion species with* $z_1 > 0 > z_2$. *Assume (A1)–(A4). Then, for any solution of BVP (2.7) and (2.8), one has*

$$\lambda_1(Q,\varepsilon) = \frac{J_1(Q,\varepsilon)}{J_1(0,\varepsilon)} < \lambda_2(Q,\varepsilon) = \frac{J_2(Q,\varepsilon)}{J_2(0,\varepsilon)}.$$

Proof. Without loss of generality, we assume the positive permanent charge $Q(x)$ has the following property: for some $0 < a < b < 1$, $Q(x) = 0$ for $x \in [0,a] \cup]b,1]$ and $Q(x) > 0$ for $x \in (a,b)$. Due to the assumption (A1), it suffices to show the result for the zeroth order approximation in ε, that is,

$$\frac{J_1(Q,0)}{J_1(0,0)} < \lambda_2(Q,0) = \frac{J_2(Q,0)}{J_2(0,0)}.$$

In the following, we will denote $J_k(Q,0)$ and $J_k(0,0)$ for $\varepsilon = 0$ by $J_k(Q)$ and $J_k(0)$, respectively. Set, for $k = 1,2$,

$$F_k(Q) = \int_0^1 \frac{1}{D_k(x;Q)h(x)c_k(x;Q)}dx.$$

Note that $F_k(Q) > 0$. Then, display (2.10) gives

$$J_k(0)F_k(0) = J_k(Q)F_k(Q) = \hat{\mu}_k(0) - \hat{\mu}_k(1),$$

and hence,

$$\frac{J_k(Q)}{J_k(0)} = \frac{F_k(0)}{F_k(Q)}. \tag{4.1}$$

It follows from (A3) that

$$F_2(0) = \int_0^1 \frac{1}{D_2(x;0)h(x)c_2(x;0)}dx = \frac{1}{\sigma}\int_0^1 \frac{1}{D_1(x;0)h(x)c_2(x;0)}dx.$$

The assumption (A4) with $Q = 0$ then gives $z_1 c_1(x;0) + z_2 c_2(x;0) = 0$, and hence,

$$F_2(0) = -\frac{z_2}{z_1\sigma}\int_0^1 \frac{1}{D_1(x;0)h(x)c_1(x;0)}dx = -\frac{z_2}{z_1\sigma}F_1(0). \tag{4.2}$$

On the other hand, it follows from (A3) and (A4) that

$$\begin{aligned}F_2(Q) =& \int_0^a \frac{1}{D_2(x;Q)h(x)c_2(x;Q)}dx + \int_b^1 \frac{1}{D_2(x;Q)h(x)c_2(x;Q)}dx\\ &+ \int_a^b \frac{1}{D_2(x;Q)h(x)c_2(x;Q)}dx\\ =& -\frac{z_2}{z_1\sigma}\int_0^a \frac{1}{D_1(x;Q)h(x)c_1(x;Q)}dx - \frac{z_2}{z_1\sigma}\int_b^1 \frac{1}{D_1(x;Q)h(x)c_1(x;Q)}dx \\ &- \frac{z_2}{z_1\sigma}\int_a^b \frac{1}{D_1(x;Q)h(x)[z_1^{-1}Q(x) + c_1(x;Q)]}dx\\ =& -\frac{z_2}{z_1\sigma}\left(F_1(Q) + \Delta(Q)\right),\end{aligned} \tag{4.3}$$

where

$$\Delta(Q) = \int_a^b \frac{1}{D_1(x;Q)h(x)[z_1^{-1}Q(x) + c_1(x;Q)]}dx - \int_a^b \frac{1}{D_1(x;Q)h(x)c_1(x;Q)}dx.$$

The assumption (A2) and $z_1 > 0$ imply that, for $x \in (a,b)$,

$$\frac{1}{z_1^{-1}Q(x) + c_1(x;Q)} < \frac{1}{c_1(x;Q)},$$

and hence, $\Delta(Q) < 0$. One has, from (4.1), (4.2), (4.3) and $F_k(Q) > 0$, that

$$\frac{J_2(Q)}{J_2(0)} = \frac{F_2(0)}{F_2(Q)} = \frac{F_1(0)}{F_1(Q) + \Delta(Q)} > \frac{F_1(0)}{F_1(Q)} = \frac{J_1(Q)}{J_1(0)}.$$

This completes the proof. □

Corollary 4.2. *Given a positive permanent charge $Q(x)$, it is possible that*

(i) $\dfrac{J_2(Q)}{J_2(0)} > \dfrac{J_1(Q)}{J_1(0)} > 1$*, and hence,* $\dfrac{J_2(Q) - J_2(0)}{J_2(0)} > \dfrac{J_1(Q) - J_1(0)}{J_1(0)} > 0$*; that is, the fluxes of both anion and cation are enhanced and, in this case, the relative amount of flux increased for anion is greater than that for cation.*

(ii) $1 > \dfrac{J_2(Q)}{J_2(0)} > \dfrac{J_1(Q)}{J_1(0)}$*, and hence,* $0 < \dfrac{J_2(0) - J_2(Q)}{J_2(0)} < \dfrac{J_1(0) - J_1(Q)}{J_1(0)}$*; that is, the fluxes of both anion and cation are reduced and, in this case, the relative amount of flux reduced for anion is smaller than that for cation.*

(iii) $\dfrac{J_2(Q)}{J_2(0)} > 1 > \dfrac{J_1(Q)}{J_1(0)}$ *so that the flux of anion is enhanced and that of cation is reduced.*

Remark 4.3. *A numerical study on flux ratios $\lambda_k(Q)$ was recently conducted in [66] based on the classical PNP model and a PNP model with a Hard-Sphere component (PNP-HS). The permanent charge $Q(x)$ was taken as in display (3.1) and the quantity Q_0 was increased from 0 to a large value. The numerical results for both the classical PNP and the PNP-HS models verify the property $\lambda_1(Q;\varepsilon) < \lambda_2(Q;\varepsilon)$ in Theorem 4.1. Furthermore, for small Q_0, the numerical results on the boundary conditions for each of the cases (i), (ii) and (iii) in Theorem 3.2 agree perfectly with the analytical results in [31].* □

5 Concluding remarks and further related problems

In this work, we discover a universal property of positive permanent charge effects on fluxes of cations and anions. Combining with the results in [31], a fairly global picture is obtained: A positive permanent charge can enhance the fluxes of both cations and anions, can reduce the fluxes of both cations and anions, can reduce the flux of cations while enhance that of anions, but cannot enhance the flux of cations while reduce that of anions. Furthermore, in case both fluxes are enhanced, the relative amount of flux increased for cations is smaller than that for anions; in case both fluxes are reduced, the relative amount of flux decreased for cations is greater than that for anions. It is straightforward to state the results of the effects of negative permanent charges on fluxes of cations and anions.

The assumptions (A1) and (A4) are not independent: Without (A1), the pointwise electroneutrality in (A4) may not be a good approximation. It would be interesting to know if the claim of Theorem 4.1 is still true without assuming ε to be particularly small. Other problems that are worthwhile to examine include

(P1) the effect of a positive permanent charge on fluxes of three and more ionic species;

(P2) the effect of sign changing permanent charges (e.g. piecewise constant with different signs) on fluxes of ionic mixtures.

We have used a quasi-one-dimensional PNP model for the study of the present topic. For three-dimensional channels, the permanent charge may not be ring-like so its effective one-dimensional version is not clear. This is an interesting problem to study. Of course, it is important to study the topics discussed in this paper and the above mentioned related problems for three-dimensional PNP type models.

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