ION SIZE AND VALENCE EFFECTS ON IONIC FLOWS VIA POISSON-NERNST-PLANCK MODELS

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Abstract. We study boundary value problems of a quasi-one-dimensional steady-state Poisson-Nernst-Planck model with a local hard-sphere potential for ionic flows of two oppositely charged ion species through an ion channel, focusing on effects of ion sizes and ion valences. The flow properties of interest, *individual fluxes and total flow rates of the mixture*, depend on multiple physical parameters such as boundary conditions (boundary concentrations and boundary potentials) and diffusion coefficients, in addition to ion sizes and ion valences. For the relatively simple setting and assumptions of the model in this paper, we are able to characterize, almost completely, the distinct effects of the nonlinear interplay between these physical parameters. The boundaries of different parameter regions are identified through a number of critical values that are explicitly expressed in terms of the physical parameters. We believe our results will provide useful insights for numerical and even experimental studies of ionic flows through membrane channels.

Key words. Ionic flow, Poisson-Nernst-Planck models, ion size and valence effects

AMS subject classifications. 34A26, 34B16, 34D15, 37D10, 92C35.

1. Introduction

The dynamics of ionic flows through ion channels via a quasi-one-dimensional steady-state Poisson-Nernst-Planck (PNP) type system are studied. The PNP type systems are basic primitive models for electrodiffusion, which treat the medium as a dielectric continuum (see [6, 7, 10, 11, 13, 14, 15, 16, 17, 18, 24, 25, 26, 27, 34, 35, 38, 57], etc.). Under various reasonable conditions, the PNP system can be derived from more fundamental models such as the Langevin-Poisson system (see, for example, [12, 35, 47, 49, 57, 58]) or the Maxwell-Boltzmann equations (see, for example, [2, 34, 35, 57]), and from an energy variational analysis (see [31, 32, 33, 40, 62, 64]). The *classical* PNP (cPNP) system contains only the *ideal* component of electrochemical potential, which treats ions essentially as *point-charges*, and neglects ion size effects. It has been simulated (see, e.g., [8, 10, 11, 13, 24, 30]) and analyzed (see, e.g., [1, 3, 4, 19, 22, 37, 43, 41, 42, 51, 59, 60, 61, 63]) to a great extent. A major weak point of the cPNP model is that the treatment of ions as point charges is only reasonable in the extremely dilute setting. Furthermore, many extremely important properties of ion channels, such as *selectivity*, rely on ion sizes critically, in particular, for ions that have the *same* valence (number of charges per particle), such as sodium Na^+ and potassium K^+, the main difference is their ionic sizes.

The PNP type model considered in this paper contains an additional component, *an uncharged local hard-sphere* (LHS) potential, to partially account for *ion size effects*. Physically, this means that each ion is approximated as a hard-sphere with its charges at the center of the sphere. Both local and nonlocal models for hard-sphere potentials were introduced for this purpose. Nonlocal models give the hard-sphere potentials as *functionals* of ion concentrations while local models depend *pointwise* on ion concentrations. An early local model for hard-sphere potentials was proposed by Bik-

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erman ([5]), which is simple but unfortunately not ion specific (i.e., the hard-sphere potential is the same for different ion species). The Boublík-Mansoori-Carnahan-Starling-Leland local model is ion specific and has been shown to be accurate ([55, 56], etc.). Clearly, local models have the advantage of simplicity relative to nonlocal ones. The PNP type models with ion sizes have been investigated computationally for ion channels and have shown great success (see [23, 25, 26, 27, 29, 31, 32, 33, 38, 50, 64], etc.). Existence and uniqueness of minimizers and saddle points of the free-energy equilibrium formulation with ionic interaction have also been mathematically analyzed (see, for example, [20], [40]).

As expected, ionic flows through ion channels exhibit extremely rich phenomena, which is why ion channels are nano-scale valves for essentially all activities of living organisms. This is the very reason that it is a great challenge to understand the mechanisms of ion channel functions. For mathematical analysis, the challenge lies in the fact that specific dynamics depend on complicated nonlinear interplays of multiple physical parameters such as boundary conditions (boundary concentrations and boundary potentials), diffusion coefficients, ion sizes, permanent charge distributions, etc. There is no hope to have explicit solution formulae for such a complicated problem even with simple boundary values. The recent development in analyzing classical PNP models ([19, 41, 42]) sheds some lights on the voltage-current relationship in simplified settings. This development is based heavily on modern invariant manifold theory of nonlinear dynamical systems, particularly, the geometric theory of singular perturbations. But, most crucially, the advance reveals a *special structure* specific to PNP models. An upshot of this advance is that, far beyond the existence results, it allows a more or less explicit approximation formula for solutions from which one can extract concrete information directly related to biological measurements.

Recently, extending the approach in [19, 42], the authors of [36] provided an analytical treatment of a quasi-one-dimensional version of a PNP type system which involves two oppositely charged ions with zero permanent charge and a *nonlocal* hard-sphere potential. In particular, an approximation of the I-V relation was derived by considering the ion sizes to be small parameters, which is crucial for establishing the following results.

(i) There exists a critical potential V_c such that the current I increases (resp. decreases) with respect to ion size if the boundary potential V satisfies $V > V_c$ (resp. $V < V_c$);

(ii) There exists another critical potential V^c such that, the current I *increases* (resp. decreases) in $\lambda = d_2/d_1$ where d_1 and d_2 are, respectively, the diameters of the positively and negatively charged ions if $V > V^c$ (resp. $V < V^c$).

In [46], among other things, the authors successfully designed an algorithm for numerically detecting these critical potentials identified in [36] *without using any analytical formulas* from [36], even for the case with *nonzero* permanent charge.

In [44], the authors study a quasi-one-dimensional version of a PNP type system with a *local* model for the hard-sphere potential. Under electroneutrality (zero net charge) boundary conditions, the authors showed that the local hard-sphere model yields exactly the same results up to first order approximation (in the diameters of the ion species) for the I-V relation and the critical potentials V_c and V^c, as those of the nonlocal hard-sphere model in [36]. On the other hand, in the absence of electroneutrality, a rather surprising result was found; that is, effects of ion sizes exactly opposite to those in (i) and (ii) above can occur. Their results provide a concrete situation in which the important I-V relations can depend on boundary conditions sensitively. This is crucial since many biological processes are controlled by these ionic flows, which are in turn controlled through boundary conditions. The following scaling laws are also established:

(a) The contribution to the I-V relation from the ideal component of the electrochemical potential scales *linearly* in boundary concentrations;
(b) The contribution (up to the leading order in diameters of ion species) to the I-V relation from the hard-sphere component of the electrochemical potential scales *quadratically* in boundary concentrations;
(c) Both V_c and V^c scale *invariantly* in boundary concentrations.

Ion size effects on the *total flow rate of matter* are also analyzed in [44] and two critical potentials $\hat{V}_c$ and $\hat{V}^c$ are identified that characterize distinct effects of ion sizes on the total flow rate of matter.

In this paper, we study a quasi-one-dimensional PNP model with the same setting as in [44]. We focus on

(I) ion size effects on *individual* fluxes, in particular, on the first order terms (in diameter) of the individual fluxes;
(II) ion valence effects on *individual* fluxes, on the total flow rates of matter and charges. Here we vary the valance of the positively charged ion species while keeping its size fixed.

We take particular advantage of the work in [44] to provide a detailed explanation of how these physical parameters interact to produce a wide spectrum of behaviors for ionic flows. The main contribution of this paper is that we give explicit parameter ranges for qualitatively distinct effects on ionic fluxes. We emphasize that our results, for the relatively simple setting and assumptions of our model, are rigorous. *We believe these results will provide useful insights for numerical and even experimental studies of ionic flows through membrane channels.* It should be pointed out that the quasi-one-dimensional PNP model and the local hard-sphere model (see (2.7) below) adopted in [44] and in this paper are rather simple. Aside the trivial fact that they will miss the three-dimensional features of the problem, a major weakness is the missing of the excess electrostatic component in the excess potentials. Important phenomena such as charge inversion and layering may not be detected by this simple model.

The rest of the paper is organized as follows. In Section 2, we describe the quasi-one-dimensional PNP model of ion flows, a local model for hard-sphere (HS) potentials, the formulation of the boundary value problem of the singularly perturbed PNP-HS system, and the basic assumptions. Results from [44] are recalled, and these will be the starting point of our study.

In Section 3, we study ion size effects on individual fluxes. *Four* critical potentials V_{jc} and V_j^c, for $j=1,2$, are identified. Each of these critical potentials depends on other physical parameters, and hence, divides the space of all parameters into two regions. The physical parameter space is thus decomposed by these critical potentials into different regions and, over different regions, the ion size effects on individual fluxes are different and are rigorously analyzed (Section 3.1). The relations between the four critical potentials and those of V_c, V^c, $\hat{V}_c$, $\hat{V}^c$ identified in [44] are established; moreover, partial orders and total orders among all critical potentials are provided in terms of conditions on other parameters (Section 3.2). A rather striking result on the sensitive dependence of these critical potentials on boundary concentrations for nearly equal left and right boundary concentrations is obtained (Section 3.3).

In Section 4, ion valence effects on the ionic flows are analyzed. For simplicity, we only present the results on the effects of ion valence z_1 of the positively charge ion species. For individual fluxes, *two* critical potentials V_1 and V_2 and *one* critical value z_1^* are identified which divide the parameter space into different regions exhibiting different effects from ion valence z_1 (Section 4.1). For the total flow rates, *one* critical potential V^m and *two* critical values z_1^m and z_1^c are identified which characterize different z_1 effects on the total flow rate $\mathcal{T}$ of matter and the total flow rate $\mathcal{I}$ of charge (Section 4.2).

A concluding remark is provided in Section 5.

2. Models and critical potentials

We briefly recall the PNP model with LHS potential and some results obtained in [44] for ion size effects on the *total* flow rates of charge (I-V relations) and matter.

We assume the channel to be narrow so that it can be effectively viewed as a one-dimensional channel and normalize it as the interval $[0,1]$ that connects the interior and the exterior of the cell. A quasi-one-dimensional steady-state PNP model for ion flows of n ion species is (see [45, 48]), for $i=1,2,\cdots,n$,

$$\begin{aligned}&\frac{1}{h(x)}\frac{\partial}{\partial x}\left(\varepsilon_r(x)\varepsilon_0 h(x)\frac{\partial\Phi}{\partial x}\right)=-e\left(\sum_{j=1}^{n} z_jc_j+Q(x)\right),\\&\frac{\partial\mathcal{J}_i}{\partial x}=0,\quad -\mathcal{J}_i=\frac{1}{k_BT}D_i(x)h(x)c_i\frac{\partial\mu_i}{\partial x},\end{aligned}\tag{2.1}$$

where e is the elementary charge, k_B is the Boltzmann constant, T is the absolute temperature; Φ is the electric potential, $Q(x)$ is the permanent charge distributed in the channel wall, $\varepsilon_r(x)$ is the relative dielectric coefficient, ε_0 is the vacuum permittivity; $h(x)$ is the area of cross-section of the channel at the point x; for the ith ion species, c_i is the concentration, z_i is the valence (the number of charges per particle), μ_i is the electrochemical potential, $\mathcal{J}_i$ is the flux density, and $D_i(x)$ is the diffusion coefficient. The boundary conditions are, for $i=1,2,\cdots,n$,

$$\Phi(0)=V,\, c_i(0)=L_i;\quad \Phi(1)=0,\, c_i(1)=R_i.\tag{2.2}$$

Ion channels link macroscopic reservoirs. The boundaries are treated as the macroscopic reservoirs in which the electroneutrality conditions

$$\sum_{j=1}^{n} z_jL_j=\sum_{j=1}^{n} z_jR_j=0\tag{2.3}$$

are typically maintained. On the other hand, without electroneutrality boundary conditions, there will be boundary layers, one at each boundary. In this case, say, for the boundary layer at the left boundary $x=0$, the values Φ^L and c_i^L's of the potential and concentrations of the limiting points of the boundary layer can be determined uniquely from the boundary condition V and L_i's *alone* and the electroneutrality conditions hold for $\{c_i^L\}$ (see [19, 42]). One can then replace the boundary condition (V,L_i) at $x=0$ with (Φ^L,c_i^L) to perform the analysis. For simplicity, throughout this paper, we will assume the electroneutrality boundary conditions (2.3).

For a solution of the steady-state boundary value problem (2.1)-(2.2), the *flow rate of charge through a cross-section* or *current* $\mathcal{I}$ is

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

For fixed boundary concentrations L_i and R_i, $\mathcal{J}_j$ depends on V only and (2.4) provides the relation between the current $\mathcal{I}$ and the voltage V, which is the so-called *I-V relation.* The *total flow rate of matter* $\mathcal{T}$ through a cross-section is given by

$$\mathcal{T} = \sum_{j=1}^{n} \mathcal{J}_j. \tag{2.5}$$

Note that $z_i \mathcal{J}_i$ represents the individual flow rate of charge through a cross-section for the ith ion species and $\mathcal{J}_i$ represents the individual flow rate of matter through a cross-section for the ith ion species.

The electrochemical potential $\mu_i(x) = \mu_i^{id}(x) + \mu_i^{ex}(x)$ for the ith ion species consists of the ideal component

$$\mu_i^{id}(x) = z_i e\Phi(x) + k_BT \ln \frac{c_i(x)}{c_0} \tag{2.6}$$

with some characteristic c_0, and the excess component $\mu_i^{ex}(x)$. The excess chemical potential $\mu_i^{ex}(x)$ accounts for the finite sizes of charges (see, e.g., [21, 52, 53, 54, 55]).

In [44], the authors considered the local hard-sphere potential with μ_i^{LHS} for μ_i^{ex} with two ion species ($n = 2$) of opposite charges ($z_1 > 0$ and $z_2 < 0$) and $Q = 0$. The local hard sphere potential is given by

$$\mu_i^{LHS}(x) = -k_BT \ln\left(1 - \sum_{j=1}^{n} d_j c_j(x)\right) + k_BT \frac{d_i \sum_{j=1}^{n} c_j(x)}{1 - \sum_{j=1}^{n} d_j c_j(x)}, \tag{2.7}$$

where d_j is the diameter of the jth ion species.

The local hard-sphere potential in (2.7), without the second term on the right-hand side, was first proposed by Bikerman ([5]) and has been adopted by several authors (see, e.g., [9, 28, 39]). It is not ion specific since it is the same for all ion species. The local hard-sphere potential in (2.7) is ion specific (i.e. potentials for ion species with the same valence but with different sizes are different) due to the second term on the right-hand side. This is crucial for many functions of ion channels since, for example, K^+ and Na^+ are different for many biological functions mainly due to their different sizes.

The authors also assumed that $\varepsilon_r(x) = \varepsilon_r$ and $D_i(x) = D_i$ are constants.

We now recall some results obtained in [44], which are crucial for our study and which will be frequently used. We first recall a dimensionless parameter ε defined as

$$\varepsilon = \frac{1}{l}\sqrt{\frac{\varepsilon_r \varepsilon_0 k_BT}{e^2 c_0}}$$

where l is the length of the channel that is normalized to 1 in model (2.1) and (2.2) and c_0 is a characteristic concentration. The parameter ε is typically small and is directly related to the ratio κ_D/l where

$$\kappa_D = \sqrt{\frac{\varepsilon_r \varepsilon_0 k_BT}{\sum_j (z_j e)^2 c_j}}$$

is the Debye length; in particular, $\varepsilon = \kappa_D/l$ when $z_j^2 = 1$ and $c_j = c_0$.

In [44], with $n=2$ and under electroneutrality conditions (2.3), the authors treat ε and $d=d_1$ as small parameters and derive approximations for the current $\mathcal{I}$ and $\mathcal{T}$ expanded in d with $\lambda=d_2/d$:

$$\begin{aligned}\mathcal{I}(V;\varepsilon,d)=&z_1D_1J_1+z_2D_2J_2=I_0(V;\varepsilon)+I_1(V;\lambda,\varepsilon)d+o(d),\\ \mathcal{T}(V;\varepsilon,d)=&D_1J_1+D_2J_2=T_0(V;\varepsilon)+T_1(V;\lambda,\varepsilon)d+o(d),\end{aligned}\tag{2.8}$$

where, with $\mathcal{J}_{k0}=D_kJ_{k0}$ and $\mathcal{J}_{k1}=D_kJ_{k1},k=1,2,$

$$\begin{aligned}&I_0(V;0)=z_1\mathcal{J}_{10}+z_2\mathcal{J}_{20},\ T_0(V;0)=\mathcal{J}_{10}+\mathcal{J}_{20},\\ &I_1(V;\lambda,0)=z_1\mathcal{J}_{11}+z_2\mathcal{J}_{21},\ T_1(V;\lambda,0)=\mathcal{J}_{11}+\mathcal{J}_{21}.\end{aligned}$$

Upon introducing $L=z_1L_1=-z_2L_2$ and $R=z_1R_1=-z_2R_2$, one has

$$\begin{aligned}J_{10}=&\frac{f_0(L,R)}{z_1H(1)}\left(\frac{e}{k_BT}z_1V+\ln L-\ln R\right),\\ J_{20}=&-\frac{f_0(L,R)}{z_2H(1)}\left(\frac{e}{k_BT}z_2V+\ln L-\ln R\right);\\ J_{11}=&\frac{2(\lambda z_1-z_2)f_0(L,R)f_1(L,R)}{z_1z_2H(1)}\left(\frac{e}{k_BT}V-\frac{(1-\lambda)(L-R)}{2(\lambda z_1-z_2)f_1(L,R)}\right.\\ &\left.-\frac{L^2-R^2}{2z_1f_0(L,R)f_1(L,R)}\right),\\ J_{21}=&-\frac{2(\lambda z_1-z_2)f_0(L,R)f_1(L,R)}{z_1z_2H(1)}\left(\frac{e}{k_BT}V-\frac{(1-\lambda)(L-R)}{2(\lambda z_1-z_2)f_1(L,R)}\right.\\ &\left.-\frac{L^2-R^2}{2z_2f_0(L,R)f_1(L,R)}\right),\end{aligned}\tag{2.9}$$

where

$$\begin{aligned}f_0(L,R)=&\frac{L-R}{\ln L-\ln R},\quad f_1(L,R)=f_0^2(L,R)-f_0(L,R)\frac{L+R}{2},\\ H(1)=&\int_0^1h^{-1}(s)ds.\end{aligned}\tag{2.10}$$

In particular,

$$
\begin{aligned}
I_0(V;0) &= \frac{(z_1D_1-z_2D_2)f_0(L,R)}{H(1)}\left(\frac{e}{k_BT}V+\frac{D_1-D_2}{z_1D_1-z_2D_2}(\ln L-\ln R)\right),\\
I_1(V;\lambda,0) &= \frac{2(z_1D_1-z_2D_2)(\lambda z_1-z_2)f_0(L,R)f_1(L,R)}{z_1z_2H(1)}\frac{e}{k_BT}V\\
&\quad -\frac{(z_1D_1-z_2D_2)(1-\lambda)(L-R)f_0(L,R)}{z_1z_2H(1)}\\
&\quad -\frac{(D_1-D_2)(\lambda z_1-z_2)(L^2-R^2)}{z_1z_2H(1)},\\
T_0(V;0) &= \frac{f_0(L,R)}{H(1)}\left((D_1-D_2)\frac{e}{k_BT}V+\frac{z_2D_1-z_1D_2}{z_1z_2}(\ln L-\ln R)\right),\\
T_1(V;\lambda,0) &= \frac{2(D_1-D_2)(\lambda z_1-z_2)f_0(L,R)f_1(L,R)}{z_1z_2H(1)}\frac{e}{k_BT}V\\
&\quad -\frac{(D_1-D_2)(1-\lambda)(L-R)f_0(L,R)}{z_1z_2H(1)}\\
&\quad -\frac{(z_2D_1-z_1D_2)(\lambda z_1-z_2)(L^2-R^2)}{z_1^2z_2^2H(1)}.
\end{aligned}
\tag{2.11}
$$

Four critical potentials V_c, V^c, $\hat{V}_c$ and $\hat{V}^c$ are identified by $I_1(V_c;\lambda,0)=0$, $\frac{d}{d\lambda}I_1(V^c;\lambda,0)=0$, $T_1(\hat{V}_c;\lambda,0)=0$, and $\frac{d}{d\lambda}T_1(\hat{V}^c;\lambda,0)=0$, respectively. They are given by

$$
\begin{aligned}
V_c &= \frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\Big(\frac{D_1-D_2}{z_1D_1-z_2D_2}+\frac{1-\lambda}{\lambda z_1-z_2}\frac{f_0(L,R)}{L+R}\Big),\\
V^c &= \frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\Big(\frac{D_1-D_2}{z_1D_1-z_2D_2}-\frac{f_0(L,R)}{z_1(L+R)}\Big),\\
\hat{V}_c &= \frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\Big(\frac{z_2D_1-z_1D_2}{z_1z_2(D_1-D_2)}+\frac{1-\lambda}{\lambda z_1-z_2}\frac{f_0(L,R)}{L+R}\Big),\\
\hat{V}^c &= \frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\Big(\frac{z_2D_1-z_1D_2}{z_1z_2(D_1-D_2)}-\frac{f_0(L,R)}{z_1(L+R)}\Big).
\end{aligned}
\tag{2.12}
$$

We comment that, when $D_1=D_2$, it follows from (2.11) that $\hat{V}_c$ and $\hat{V}^c$ do not exist. In this case, T_1 and $dT_1/d\lambda$ have the same sign as that of $L-R$.

The roles of these four critical potentials in characterizing ion size effects on the I-V relations and the total flow rate of matter are discussed. We have:

THEOREM 2.1. *([44]) Suppose $L>R$. For small $\varepsilon>0$ and $d>0$,*

- (i) *if $V>V_c$ (resp. $V<V_c$), then $\mathcal{I}(V;\varepsilon,d)>\mathcal{I}(V;\varepsilon,0)$ (resp. $\mathcal{I}(V;\varepsilon,d)<\mathcal{I}(V;\varepsilon,0)$);*
- (ii) *if $V>V^c$ (resp. $V<V^c$), then the current $\mathcal{I}$ is increasing (resp. decreasing) in λ;*
- (iii) *if $V>\hat{V}_c$ (resp. $V<\hat{V}_c$), then $\mathcal{T}(V;\varepsilon,d)>\mathcal{T}(V;\varepsilon,0)$ (resp. $\mathcal{T}(V;\varepsilon,d)>\mathcal{T}(V;\varepsilon,0)$);*
- (iv) *if $V>\hat{V}^c$ (resp. $V<\hat{V}^c$), then the flow rate of matter $\mathcal{T}$ increases (resp. decreases) in λ.*

To end this section, we state the following result which helps the analyses in Sections 3 and 4, whose proof is elementary and will be omitted.

Lemma 2.1. *For $L\neq R$, one has $f_0(L,R)>0$ and $f_1(L,R)<0$, where $f_0(L,R)$ and $f_1(L,R)$ are defined in* (2.10). *With $R>0$ being fixed,*

$$\lim_{L\to R} f_0(L,R)=R \text{ and } \lim_{L\to R}\frac{f_1(L,R)}{(L-R)^2}=-\frac{1}{12R}.$$

3. Ion size effects on ionic flows

Our interest in this section is to provide a detailed analysis of ion size effects on *individual* fluxes.

3.1. Critical potentials for individual fluxes

It is clear that ion sizes do not play roles for $\mathcal{J}_{i0}=D_iJ_{i0}$. We will focus on $\mathcal{J}_{i1}=D_iJ_{i1}$ (and hence, $z_i\mathcal{J}_{i1}=z_iD_iJ_{i1}$), the leading terms containing ion size effects.

The sign of J_{i1} determines if ion sizes enhance (i.e. $J_{i1}(V;\varepsilon,d)>J_{i1}(V;\varepsilon,0)$) or reduce (i.e. $J_{i1}(V;\varepsilon,d)>J_{i1}(V;\varepsilon,0)$) the flux of ith ion species and the sign of $dJ_{i1}/d\lambda$ determines if the flux of ith ion species is increasing or decreasing in λ. We therefore introduce four critical potentials – zeros of these quantities– that separate the signs of these quantities.

Definition 3.1. *Let V_{1c}, V_{2c}, V_1^c, and V_2^c be defined, respectively, through*

$$J_{11}(V_{1c};\lambda,0)=0,\ J_{21}(V_{2c};\lambda,0)=0,\ \frac{d}{d\lambda}J_{11}(V_1^c;\lambda,0)=0,\ \frac{d}{d\lambda}J_{21}(V_2^c;\lambda,0)=0.$$

From (2.9), a direct calculation gives

Lemma 3.2. *Suppose $L\neq R$. Then,*

$$\begin{aligned}
V_{1c}&=\frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\left(\frac{1}{z_1}+\frac{1-\lambda}{\lambda z_1-z_2}\frac{f_0(L,R)}{L+R}\right),\\
V_{2c}&=\frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\left(\frac{1}{z_2}+\frac{1-\lambda}{\lambda z_1-z_2}\frac{f_0(L,R)}{L+R}\right),\\
V_1^c&=\frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\left(\frac{1}{z_1}-\frac{1}{z_1}\frac{f_0(L,R)}{L+R}\right),\\
V_2^c&=\frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\left(\frac{1}{z_2}-\frac{1}{z_1}\frac{f_0(L,R)}{L+R}\right).
\end{aligned}$$

Remark 3.1. *Observe that V_{1c} and V_{2c} depend on λ, z_1 and z_2. For Na^+Cl^- and K^+Cl^-, since Na^+ and K^+ have the same valence but different ion sizes, the values of V_{1c} and V_{2c} are different due to the ion size effect. For Na^+Cl^- and $Ca^{++}Cl^-$, since Na^+ and Ca^{++} have essentially the same size but different valences, the values of V_{1c} and V_{2c} are different due to the ion valence effect.*

Note that V_1^c and V_2^c do not depend on λ, which is important for the result in Theorem 3.4 below. We also comment that V_1^c depends on z_1 but not on z_2, and V_2^c depends on both z_1 and z_2. This asymmetric dependence on valences is due to the asymmetric appearance of λ in (2.9).

Corollary 3.2. *Suppose $L\neq R$. Then,*

$$\frac{d}{d\lambda}V_{1c}=\frac{d}{d\lambda}V_{2c}=\frac{k_BT}{e}\frac{L^2-R^2}{2f_1(L,R)}\frac{z_2-z_1}{(\lambda z_1-z_2)^2}.$$

In particular, $\frac{d}{d\lambda}V_{1c}=\frac{d}{d\lambda}V_{2c}$ has the same sign as that of $L-R$.

The significance of the four critical potentials is apparent from their definitions. The values V_{1c} and V_{2c} are the potentials that balance the ion size effects on individual fluxes, and the values V_1^c and V_2^c are the potentials that separate the relative size effects on individual fluxes. The precise statements are collected in two theorems below, the first one for V_{1c} and V_{2c} and the other for V_1^c and V_2^c. First of all, from (2.9), we have

LEMMA 3.3. *Suppose $L\neq R$. One has, for $j=1,2$, $\partial_V J_{j1}>0$ and $\partial^2_{V\lambda}J_{j1}>0$, and*

$$\lim_{L\to R}\partial_V J_{j1}=\lim_{L\to R}\partial^2_{V\lambda}J_{j1}=0.$$

The next two results follow directly from (2.9), Definition 3.1 and Lemma 3.3. Their proofs are omitted.

THEOREM 3.3. *One has, for $\varepsilon>0$ small and $d>0$ small,*

- (i) *if $V<V_{1c}$ (resp. $V>V_{1c}$), then $\mathcal{J}_1(V;\varepsilon,d)<\mathcal{J}_1(V;\varepsilon,0)$ (resp. $\mathcal{J}_1(V;\varepsilon,d)>\mathcal{J}_1(V;\varepsilon,0)$);*
- (ii) *if $V<V_{2c}$ (resp. $V>V_{2c}$), then $\mathcal{J}_2(V;\varepsilon,d)>\mathcal{J}_2(V;\varepsilon,0)$ (resp. $\mathcal{J}_2(V;\varepsilon,d)<\mathcal{J}_2(V;\varepsilon,0)$).*

Recall, from Lemma 3.2 and Remark 3.1, that V_1^c and V_2^c are independent of λ.

THEOREM 3.4. *One has, for $\varepsilon>0$ small and $d>0$ small,*

- (i) *if $V<V_1^c$ (resp. $V>V_1^c$), then $\mathcal{J}_1$ is decreasing (resp. increasing) in λ;*
- (ii) *if $V<V_2^c$ (resp. $V>V_2^c$), then $\mathcal{J}_2$ is increasing (resp. decreasing) in λ.*

Theorems 3.3 and 3.4, together with Theorem 2.1, provide the roles of those critical potentials in the classification of ion sizes effects on flows of individual ion species and the total flows of the mixture.

3.2. Relations among critical potentials

In view of the above results, to understand how boundary conditions and diffusion coefficients interact with the ion sizes and valences to affect ionic flows, we will study the dependence of critical potentials on these parameters. The relations among the critical potentials discussed in this subsection will provide detailed insight for ion size effects and have not been described previously, to the best of our knowledge.

We will discuss the roles of each of these critical potentials V_{1c}, V_{2c}, V_1^c, V_2^c, V_c, V^c, $\hat{V}_c$ and $\hat{V}^c$, and (partial) orders among them.

We start with a scaling law on these critical potentials, which can be easily verified from (2.9).

PROPOSITION 3.5. *Viewing J_{i0},J_{i1},V_{ic} and V_i^c as functions of (L,R), one has*

- (i) *J_{i0} is homogeneous of degree one in (L,R), that is, for any $s>0$, $J_{i0}(V;sL,sR)=sJ_{i0}(V;L,R)$.*
- (ii) *J_{i1} is homogeneous of degree two in (L,R), that is, for any $s>0$, $J_{i1}(V;sL,sR)=s^2J_{i1}(V;L,R)$.*
- (iii) *Both V_{ic} and V_i^c are homogeneous of degree zero in (L,R), that is, for any $s>0$, $V_{ic}(sL,sR)=V_{ic}(L,R)$ and $V_i^c(sL,sR)=V_i^c(L,R)$.*

On the basis of the physical meanings of the critical potentials, it is expected that V_c and $\hat{V}_c$ depend on V_{1c} and V_{2c}, and V^c and $\hat{V}^c$ depend on V_1^c and V_2^c. The explicit relations follow from (2.12) and Lemma 3.2 and are provided in the next result.

PROPOSITION 3.6. *Suppose $L\neq R$. One has*

$$V_c=\frac{z_1D_1V_{1c}-z_2D_2V_{2c}}{z_1D_1-z_2D_2},\quad V^c=\frac{z_1D_1V_1^c-z_2D_2V_2^c}{z_1D_1-z_2D_2}, \tag{3.1}$$

and, for $D_1 \neq D_2$,

$$\hat{V}_c = \frac{D_1 V_{1c} - D_2 V_{2c}}{D_1 - D_2}, \quad \hat{V}^c = \frac{D_1 V_1^c - D_2 V_2^c}{D_1 - D_2}. \tag{3.2}$$

Furthermore,

$$\begin{aligned} V_{1c} - V_{2c} =& V_1^c - V_2^c = \frac{k_B T}{e} \frac{z_2 - z_1}{z_1 z_2} \frac{L^2 - R^2}{2 f_1(L,R)}, \\ V_{1c} - V_1^c =& V_{2c} - V_2^c = V_c - V^c = \hat{V}_c - \hat{V}^c \\ =& \frac{k_B T}{e} \frac{z_1 - z_2}{z_1(\lambda z_1 - z_2)} \frac{(L-R) f_0(L,R)}{2 f_1(L,R)}, \\ V_c - \hat{V}_c =& V^c - \hat{V}^c \\ =& \frac{k_B T}{e} \frac{(z_1 - z_2)^2 D_1 D_2}{z_1 z_2 (D_1 - D_2)(z_1 D_1 - z_2 D_2)} \frac{L^2 - R^2}{2 f_1(L,R)}. \end{aligned} \tag{3.3}$$

We comment that the above relations (3.1) and (3.2) among the critical potentials are independent of L and R although the values of the differences in (3.3) do depend on L and R. Furthermore, certain relations like (3.1) and (3.2) are expected for the relevant critical potentials; on the other hand, relations in (3.3) are not immediately intuitive and have important consequences in studies below.

Next, we examine further relations – *orders or partial orders* – among these critical potentials. These relations are more sophisticated and, very importantly, reveal detailed interplays between electric potentials and other system parameters: boundary concentrations (L,R) and diffusion coefficients (D_1,D_2).

PROPOSITION 3.7. *One has the following partial orders among the critical potentials.*

(i) *If* $L > R$, *then*

$$V_{1c} < V_1^c < 0 < V_{2c} < V_2^c, \quad V_c < V^c, \quad \hat{V}_c < \hat{V}^c, \quad V_{1c} < V_c < V_{2c}, \quad V_1^c < V^c < V_2^c;$$

In addition, if $D_1 > D_2$, *then* $\hat{V}_c < V_{1c}$ *and* $\hat{V}^c < V_1^c$; *if* $D_1 < D_2$, *then* $V_{2c} < \hat{V}_c$ *and* $V_2^c < \hat{V}^c$.

(ii) *If* $L < R$, *then*

$$V_{1c} > V_1^c > 0 > V_{2c} > V_2^c, \quad V_c > V^c, \quad \hat{V}_c > \hat{V}^c, \quad V_{1c} > V_c > V_{2c}, \quad V_1^c > V^c > V_2^c;$$

In addition, if $D_1 > D_2$, *then* $\hat{V}_c > V_{1c}$ *and* $\hat{V}^c > V_1^c$; *if* $D_1 < D_2$, *then* $V_{2c} > \hat{V}_c$ *and* $V_2^c > \hat{V}^c$.

The above partial orders rely on simple conditions on (L,R) and (D_1,D_2). Further details depend on more complicated conditions between (L,R) and (D_1,D_2). We will consider the sub-case where $L > R$ and $D_1 > D_2$.

Our next result follows from (2.12), Lemmas 2.1 and 3.2, and Proposition 3.7 directly. We omit the proof.

PROPOSITION 3.8. *Suppose* $L > R$ *and* $D_1 > D_2$. *One has*

(a) *If* $\frac{(\lambda z_1 - z_2) D_2}{z_1 D_1 - z_2 D_2} < \frac{f_0(L,R)}{L+R} < \frac{z_2 - \lambda z_1}{z_2} \min\left\{\frac{D_2}{D_1 - D_2}, \frac{z_1 D_1}{z_1 D_1 - z_2 D_2}\right\}$, *then*

$$\hat{V}_c < \hat{V}^c < V_{1c} < V_c < V_1^c < V^c < V_{2c} < V_2^c.$$

(b) *If* $\frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)} < \frac{f_0(L,R)}{L+R} < \frac{(z_2-\lambda z_1)D_2}{z_2(D_1-D_2)}$, *and this holds if* $\frac{z_1-\sqrt{z_1(z_1-z_2)}}{z_2} < \frac{D_2}{D_1}$, *then*

$$\hat{V}_c < \hat{V}^c < V_{1c} < V_c < V_1^c < V_{2c} < V^c < V_2^c.$$

(c) *If* $\frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)} < \frac{f_0(L,R)}{L+R} < \frac{z_2-\lambda z_1}{z_2}\min\left\{\frac{-z_2D_2}{z_1D_1-z_2D_2},\ \frac{D_2}{D_1-D_2}\right\}$, *then*

$$\hat{V}_c < \hat{V}^c < V_{1c} < V_1^c < V_c < V_{2c} < V^c < V_2^c.$$

(d) *If* $\frac{f_0(L,R)}{L+R} < \frac{z_2-\lambda z_1}{z_2}\min\left\{\frac{D_2}{D_1-D_2},\ \frac{z_1D_1}{z_1D_1-z_2D_2},\ \frac{-z_2D_2}{z_1D_1-z_2D_2}\right\}$, *then*

$$\hat{V}_c < \hat{V}^c < V_{1c} < V_1^c < V_c < V^c < V_{2c} < V_2^c.$$

(e) *If* $\frac{z_2-\lambda z_1}{z_2}\max\left\{\frac{D_2}{D_1-D_2},\ \frac{-z_2D_2}{z_1D_1-z_2D_2}\right\} < \frac{f_0(L,R)}{L+R} < \frac{z_2-\lambda z_1}{z_2}\min\left\{\frac{z_1D_1}{z_1D_1-z_2D_2},\ \frac{(z_1-z_2)D_1D_2}{(D_1-D_2)(z_1D_1-z_2D_2)}\right\}$, *then*

$$\hat{V}_c < V_{1c} < \hat{V}^c < V_c < V_1^c < V^c < V_{2c} < V_2^c.$$

(f) *If* $\frac{z_2-\lambda z_1}{z_2}\max\left\{\frac{D_2}{D_1-D_2},\ \frac{-z_2D_2}{z_1D_1-Z_2D_2},\ \frac{z_1D_1}{z_1D_1-z_2D_2}\right\} < \frac{f_0(L,R)}{L+R} < \frac{(z_2-\lambda z_1)(z_1-z_2)D_1D_2}{z_2(D_1-D_2)(z_1D_1-z_2D_2)}$, *then*

$$\hat{V}_c < V_{1c} < \hat{V}^c < V_c < V_1^c < V_{2c} < V^c < V_2^c.$$

(g) *If* $\frac{(z_2-\lambda z_1)D_2}{z_2(D_1-D_2)} < \frac{f_0(L,R)}{L+R} < \min\left\{\frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)},\ \frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2}\right\}$, *then*

$$\hat{V}_c < V_{1c} < \hat{V}^c < V_1^c < V_c < V^c < V_{2c} < V_2^c.$$

(h) *If* $\frac{z_2-\lambda z_1}{z_2}\max\left\{\frac{D_2}{D_1-D_2},\ \frac{z_1D_1}{z_1D_1-z_2D_2}\right\} < \frac{f_0(L,R)}{L+R} < \frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2}$, *then*

$$\hat{V}_c < V_{1c} < \hat{V}^c < V_1^c < V_c < V_{2c} < V^c < V_2^c.$$

(i) *If* $\frac{(z_2-\lambda z_1)(z_1-z_2)D_1D_2}{z_2(D_1-D_2)(z_1D_1-z_2D_2)} < \frac{f_0(L,R)}{L+R} < \frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)}$, *and this holds if* $\frac{D_2}{D_1} < \frac{z_1}{2z_1-z_2}$, *then*

$$\hat{V}_c < V_{1c} < V_c < \hat{V}^c < V_1^c < V^c < V_{2c} < V_2^c.$$

(j) *If* $\frac{z_2-\lambda z_1}{z_2}\max\left\{\frac{(z_1-z_2)D_1D_2}{(D_1-D_2)(z_1D_1-z_2D_2)},\ \frac{z_1D_1}{z_1D_1-z_2D_2}\right\} < \frac{f_0(L,R)}{L+R}$, *then*

$$\hat{V}_c < V_{1c} < V_c < \hat{V}^c < V_1^c < V_{2c} < V^c < V_2^c.$$

Remark 3.9. *In Proposition 3.8, we try to provide a complete classification of the potential regions based on the critical potentials identified in* (2.12) *and Definition 3.1 for the sub-cases where* $L > R$ *and* $D_1 > D_2$*. From this the distinct effects of the nonlinearity and the interplay among the physical parameters, such as the boundary potential, boundary concentration, ion size, ion valence and diffusion coefficients can be characterized. Except cases (b) and (i), all the other cases consist of sub-cases, for example, in case (a), one has the following two sub-cases:*

V region	$\mathcal{J}_1$	$\mathcal{J}_2$	$\mathcal{T}=\mathcal{J}_1+\mathcal{J}_2$	$\mathcal{I}=z_1\mathcal{J}_1+z_2\mathcal{J}_2$
$(-\infty,\hat{V}_c)$	$\mathcal{J}_1(d)<\mathcal{J}_1(0)$	$\mathcal{J}_2(d)>\mathcal{J}_2(0)$	$\mathcal{T}(d)<\mathcal{T}(0)$	$\mathcal{I}(d)<\mathcal{I}(0)$
$(\hat{V}_c,V_{1c})$	$\mathcal{J}_1(d)<\mathcal{J}_1(0)$	$\mathcal{J}_2(d)>\mathcal{J}_2(0)$	$\mathcal{T}(d)>\mathcal{T}(0)$	$\mathcal{I}(d)<\mathcal{I}(0)$
(V_{1c},V_c)	$\mathcal{J}_1(d)>\mathcal{J}_1(0)$	$\mathcal{J}_2(d)>\mathcal{J}_2(0)$	$\mathcal{T}(d)>\mathcal{T}(0)$	$\mathcal{I}(d)<\mathcal{I}(0)$
(V_c,V_{2c})	$\mathcal{J}_1(d)>\mathcal{J}_1(0)$	$\mathcal{J}_2(d)>\mathcal{J}_2(0)$	$\mathcal{T}(d)>\mathcal{T}(0)$	$\mathcal{I}(d)>\mathcal{I}(0)$
(V_{2c},∞)	$\mathcal{J}_1(d)>\mathcal{J}_1(0)$	$\mathcal{J}_2(d)<\mathcal{J}_2(0)$	$\mathcal{T}(d)>\mathcal{T}(0)$	$\mathcal{I}(d)>\mathcal{I}(0)$

TABLE 3.1. *For convenience, we rewrite $\mathcal{J}_1(V;\varepsilon,d)$ as $\mathcal{J}_1(d)$, and so on. Ion size effects on both the individual fluxes and total flux over different potential regions separated by the critical potentials are characterized. For example, over the interval $(-\infty,\hat{V}_c)$, the ion size reduces $\mathcal{J}_1$, enhances $\mathcal{J}_2$, but reduces both the total flux of matter $\mathcal{T}$ and the current $\mathcal{I}$; while in $(\hat{V}_{2c},\infty)$, the ion size enhances $\mathcal{J}_1$, reduces $\mathcal{J}_2$, but enhances both $\mathcal{T}$ and the current $\mathcal{I}$.*

(a1) $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2}<\frac{f_0(L,R)}{L+R}<\frac{(z_2-\lambda z_1)D_2}{z_2(D_1-D_2)}$, *and this holds if* $\frac{z_1+z_2}{2z_2}<\frac{D_2}{D_1}<\frac{z_1-\sqrt{z_1(z_1-z_2)}}{z_2}$, *which is only possible if* $\frac{z_1}{z_2}<-\frac{1}{3}$;

(a2) $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2}<\frac{f_0(L,R)}{L+R}<\frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)}$, *and this holds if* $\frac{z_1-\sqrt{z_1(z_1-z_2)}}{z_2}<\frac{D_2}{D_1}<-\frac{z_1}{z_2}$, *which is only possible if* $\frac{z_1}{z_2}<-\frac{1}{3}$.

To further illustrate Proposition 3.8, we consider several examples

(i) $z_1=-z_2=1$

  (i1) *Taking the positively charged ion species as K^+, the negatively charged one as Cl^-, and $\lambda=1.382$, $L=0.005$, $R=0.2$, $D_1=2$, and $D_2=10$. For this set-up, we have $\frac{f_0(L,R)}{L+R}=0.2579$, $\frac{(z_2-\lambda z_1)D_2}{z_2(D_1-D_2)}=-2.9775$, $\frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)}=0.397$, and $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2}=1.985$. This satisfies case (g) in Proposition 3.8 with $\mathcal{J}_1:=\mathcal{J}_{Na}$ and $\mathcal{J}_2:=\mathcal{J}_{Cl}$. Based on Theorems 2.1, 3.3 and 3.4, one has Tables* 3.1 *and* 3.2.

  (i2) *Taking the positively charged ion species as Na^+, the negatively charged one as Cl^-, and $\lambda=1.885$, $L=0.2$, $R=0.02$, $D_1=1$, and $D_2=10$. For this set-up, we have $\frac{f_0(L,R)}{L+R}=0.3553$, $\frac{(z_2-\lambda z_1)z_1D_1}{z_2(z_1D_1-z_2D_2)}=0.2623$, $\frac{(z_2-\lambda z_1)D_2}{z_2(D_1-D_2)}=-3.2056$, and $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2}=2.6227$. This satisfies case (h) in Proposition 3.8. Similar tables can be obtained, we leave these to the readers.*

(ii) $z_1=2$, $z_2=-1$, *taking the positively charged ion species as Ca^{++}, the negatively charged one as Cl^-, and $\lambda=1.382$, $L=0.002$, $R=0.000002$, $D_1=0.1$, and $D_2=10$. For this set-up, we have $\frac{f_0(L,R)}{L+R}=6.8940$, $\frac{(z_2-\lambda z_1)(z_1-z_2)D_1D_2}{z_2(D_1-D_2)(z_1D_1-z_2D_2)}=-0.1118$, and $\frac{z_1(z_2-\lambda z_1)D_1}{z_2(z_1D_1-z_2D_2)}=0.0738$. This satisfies case (j) in Proposition 3.8.*

3.3. Sensitivity of ion size effects near $L=R$. We carefully examine the situation for L and R close to each other. It turns out, in this situation, the properties of the critical potentials are extremely sensitive to whether $L>R$ or $L<R$.

V region	$\mathcal{J}_1$	$\mathcal{J}_2$	$\mathcal{T}$	$\mathcal{I}$
$(-\infty,\hat{V}^c)$	$\mathcal{J}_1$ decreases in λ	$\mathcal{J}_2$ increases in λ	$\mathcal{T}$ decreases in λ	$\mathcal{I}$ decreases in λ
$(\hat{V}^c,V_1^c)$	$\mathcal{J}_1$ decreases in λ	$\mathcal{J}_2$ increases in λ	$\mathcal{T}$ increases in λ	$\mathcal{I}$ decreases in λ
(V_1^c,V^c)	$\mathcal{J}_1$ increases in λ	$\mathcal{J}_2$ increases in λ	$\mathcal{T}$ increases in λ	$\mathcal{I}$ decreases in λ
(V^c,V_2^c)	$\mathcal{J}_1$ increases in λ	$\mathcal{J}_2$ increases in λ	$\mathcal{T}$ increases in λ	$\mathcal{I}$ increases in λ
(V_2^c,∞)	$\mathcal{J}_1$ increases in λ	$\mathcal{J}_2$ decreases in λ	$\mathcal{T}$ increases in λ	$\mathcal{I}$ increases in λ

Table 3.2. *For convenience, we rewrite $\mathcal{J}_1(V;d,\varepsilon,\lambda)=\mathcal{J}_1$, and so on. Relative ion size effects (in terms of $\lambda:=\frac{d_1}{d_2}$, where d_1, the diameter of the positively charged ion species, and d_2 is the diameter of the negatively charged one) on both individual fluxes and total fluxes over different potential regions are characterized.*

Proposition 3.10. *One has,*

$$\lim_{L\to R^+} V_{1c}=\lim_{L\to R^+} V_1^c=\lim_{L\to R^-} V_{2c}=\lim_{L\to R^-} V_2^c=-\infty,$$
$$\lim_{L\to R^-} V_{1c}=\lim_{L\to R^-} V_1^c=\lim_{L\to R^+} V_{2c}=\lim_{L\to R^+} V_2^c=+\infty.$$

Proof: The second factors in formulas for V_{1c}, V_{2c}, V_1^c, and V_2^c in Lemma 3.2 satisfy

$$\lim_{L\to R}\Big(\frac{1}{z_1}+\frac{1-\lambda}{\lambda z_1-z_2}\frac{f_0(L,R)}{L+R}\Big)=\frac{(1+\lambda)z_1-2z_2}{2z_1(\lambda z_1-z_2)}>0,$$
$$\lim_{L\to R}\Big(\frac{1}{z_2}+\frac{1-\lambda}{\lambda z_1-z_2}\frac{f_0(L,R)}{L+R}\Big)=\frac{2\lambda z_1-(1+\lambda)z_2}{2z_2(\lambda z_1-z_2)}<0,$$
$$\lim_{L\to R}\Big(\frac{1}{z_1}-\frac{1}{z_1}\frac{f_0(L,R)}{L+R}\Big)=\frac{1}{2z_1}>0,$$
$$\lim_{L\to R}\Big(\frac{1}{z_2}-\frac{1}{z_1}\frac{f_0(L,R)}{L+R}\Big)=\frac{1}{z_2}-\frac{1}{2z_1}<0.$$

The results then follow from Lemma 2.1.

The significance of the above result is discussed in the next remark.

Remark 3.11. *Combining this result with Theorems 3.3 and 3.4, one concludes that the effects on computed ionic flows by including the LHS potential are sensitive to whether $L>R$ or $L<R$ for L and R close. More precisely, on one hand, as $L\to R^+$, one has $V_{1c}<V<V_{2c}$ for any fixed potential V, and hence, $\mathcal{J}_i(V;\varepsilon;d)>\mathcal{J}_i(V;\varepsilon;0)$, $i=1,2$ (see, (ii) and (iii) in Theorem 3.3); and on the other hand, as $L\to R^-$, exactly the opposite occurs, that is, one has $V_{1c}>V>V_{2c}$ for any fixed potential V, and hence, $\mathcal{J}_i(V;\varepsilon;d)<\mathcal{J}_i(V;\varepsilon;0)$, $i=1,2$ (see, (i) and (iv) in Theorem 3.3). A similar conclusion applies to results in Theorem 3.4. This sensitive dependence of ion size effects on individual fluxes near $L=R$ is rather striking, and perhaps could be observed experimentally.*

Similar sensitive dependence of ion size effects on total fluxes near $L=R$ is examined below. The result depends naturally on D_1 and D_2 as well as λ.

Recall that $z_1>0>z_2$ and $\lambda>0$. Set

$$\beta_1=\frac{2\lambda z_1-(\lambda+1)z_2}{(\lambda+1)z_1-2z_2} \text{ and } \beta_2=\frac{2z_1-z_2}{z_1}.$$

Note that $0<\beta_1<\beta_2$.

Proposition 3.12. *One has,*

(i) *if $D_1/D_2<\beta_1$, then*

$$\lim_{L\to R^+} V_c=\lim_{L\to R^+} V^c=\infty, \lim_{L\to R^-} V_c=\lim_{L\to R^-} V^c=-\infty;$$

(ii) *if $\beta_1<D_1/D_2<\beta_2$, then*

$$\lim_{L\to R^+} V_c=\lim_{L\to R^-} V^c=-\infty, \lim_{L\to R^-} V_c=\lim_{L\to R^+} V^c=\infty;$$

(iii) *if $D_1/D_2>\beta_2$, then*

$$\lim_{L\to R^+} V_c=\lim_{L\to R^+} V^c=-\infty, \lim_{L\to R^-} V_c=\lim_{L\to R^-} V^c=\infty.$$

Proof: Direct calculations give

$$\lim_{L\to R^+} V_c=\frac{k_BT}{e}g_1(y)\cdot(-\infty), \lim_{L\to R^+} V^c=\frac{k_BT}{e}g_2(y)\cdot(-\infty)$$

and

$$\lim_{L\to R^-} V_c=\frac{k_BT}{e}g_1(y)\cdot\infty, \quad \lim_{L\to R^-} V^c=\frac{k_BT}{e}g_2(y)\cdot\infty,$$

where

$$g_1(y)=\frac{y-1}{z_1y-z_2}+\frac{1-\lambda}{2(\lambda z_1-z_2)}, \ g_2(y)=\frac{y-1}{z_1y-z_2}-\frac{1}{2z_1}$$

with $y=\frac{D_1}{D_2}$. Note that $g_1(y)=0$ if and only if $y=y_c:=\frac{D_{1c}}{D_{2c}}$, and $g_2(y)=0$ if and only if $y=y^c:=\frac{D_1^c}{D_2^c}$. In addition, one has $y_c<y^c$. Note also that

$$g_1'(y)=\frac{z_1-z_2}{(z_1y-z_2)^2}>0 \quad \text{and} \quad g_2'(y)=\frac{z_1-z_2}{(z_1y-z_2)^2}>0$$

for all $y>0$. Therefore, we have (i) $g_1(y)<0$ and $g_2(y)<0$ if $y<y_c$; (ii) $g_1(y)>0$ and $g_2(y)<0$ if $y_c<y<y^c$; and (iii) $g_1(y)>0$ and $g_2(y)>0$ if $y>y^c$. Our results then follow directly.

Remark 3.13. *(a) Similar to Remark 3.11, when combining Proposition 3.12 with Theorem 2.1, one concludes sensitive dependence of ion size effects on the current $\mathcal{I}$ near $L=R$. The precise dependence further involves the quantities D_1/D_2 relative to β_1 and β_2; for example, if $D_1/D_2<\beta_1$, on one hand, as $L\to R^+$, one has $V<V_c$ and $V<V^c$ for any fixed potential V, and hence, $\mathcal{I}(V;\varepsilon;d)<\mathcal{I}(V;\varepsilon;0)$ (see, (i) in Theorem 2.1) and the current $\mathcal{I}$ is always decreasing in λ (see, (ii) in Theorem 2.1); on the other hand, as $L\to R^-$, exactly the opposite effect occurs. For the other cases, the ion size effects as $L\to R^-$ are always opposite to those as $L\to R^+$.*

(b) Comparing consequences from results in Proposition 3.10 and in Proposition 3.12, we note that the sensitive dependences of ion size on individual fluxes $\mathcal{J}_1$ *and* $\mathcal{J}_2$ *do not depend on* D_1 *and* D_2 *but those on the current* $\mathcal{I}$ *do depend on* $\frac{D_1}{D_2}$*, simply because* $\mathcal{I}=z_1\mathcal{J}_1+z_2\mathcal{J}_2=z_1D_1J_1+z_2D_2J_2$ *with* $z_1>0>z_2$ *(see (2.8)). Generally, one cannot make conclusions about ion size effects on* $\mathcal{I}$ *based on those on* $\mathcal{J}_1$ *and* $\mathcal{J}_2$*; indeed, one cannot make conclusions about ion size effects on* $\mathcal{I}$*; but the effect on* $\mathcal{I}$ *can go either way.*

Similarly, for the critical potentials $\hat{V}^c$ and $\hat{V}_c$, the following result holds.

PROPOSITION 3.14. *One has*

$$\lim_{L\to R^+}\hat{V}_c=\lim_{L\to R^+}\hat{V}^c=\infty,\ \lim_{L\to R^-}\hat{V}_c=\lim_{L\to R^-}\hat{V}^c=-\infty.$$

4. Ion valence effects on ionic flows

In addition to the effect of ion size, we will consider ion valence effects on ionic flows. For simplicity, we will only examine the effects of z_1 – the valence of the positively charged ion species – on ionic flows when ion sizes are fixed (e.g. Na^+ and Ca^{++} have approximately the same size but different valences).

For convenience, we treat z_1 as a real number (*even though* z_1 *is an integer*). We will be interested in effects of z_1 on $\mathcal{J}_1$ (*self-effect*) and on $\mathcal{J}_2$ (*cross-effect*), and on $\mathcal{T}$ and $\mathcal{I}$. We will fix $L=-z_2L_2$ and $R=-z_2R_2$, the boundary concentrations of the negatively charged ion species, and require the electroneutrality boundary conditions $z_1L_1=-z_2L_2=L$ and $z_1R_1=-z_2R_2=R$. Thus, as z_1 varies, L_1 and R_1 will vary accordingly.

4.1. Effects of ion valence z_1 on individual fluxes

We begin with the effects of z_1 on individual fluxes.

The effects of z_1 on the zeroth order fluxes are simple and can be readily obtained from (2.9).

PROPOSITION 4.1. *One has*

(i) J_{10} *is strictly increasing in* z_1 *if* $L<R$ *and strictly decreasing in* z_1 *if* $L>R$*, and* $J_{10}=0$ *exactly when*

$$V=-\frac{k_BT}{z_1e}(\ln L-\ln R).$$

(ii) J_{20} *is independent of* z_1*.*

REMARK 4.2. *The statement (ii) implies that the zeroth order flux of one ion species is independent of the other. This is consistent with physical intuition since the zeroth order fluxes* J_{10} *and* J_{20} *capture only the point-charge contribution of ion species and, statistically, there is no ion-ion interaction for point-charges.*

The first order terms J_{11} and J_{21} should involve interactions between the two ion species; in particular, z_1 will contribute to J_{21} and is expected to also have a more complicated effect on J_{11} compared to that on J_{10} in (i) of Proposition 4.1. Conditions for the signs of J_{11} and J_{21} have been examined in the previous section (Theorem 3.3 and Theorem 3.4) focusing on ion size effects. The results there can be easily transformed to conditions treating z_1 as the key variable. We will thus study the monotonicity of J_{11} and J_{21} in z_1.

Direct calculations from (2.9) give

$$\begin{aligned}\frac{\partial J_{11}}{\partial z_1}=&\frac{e}{k_BT}\frac{2f_1(L,R)}{z_1^2H(1)}(V-V_1)-\frac{2(L^2-R^2)}{z_1^3H(1)},\\ \frac{\partial J_{21}}{\partial z_1}=&-\frac{e}{k_BT}\frac{2f_1(L,R)}{z_1^2H(1)}(V-V_2),\end{aligned}\tag{4.1}$$

where

$$\begin{aligned}V_1=&\frac{k_BT}{e}\frac{L^2-R^2}{2z_2f_1(L,R)}\Big((\lambda-1)\frac{f_0(L,R)}{L+R}-\lambda\Big),\\ V_2=&\frac{k_BT}{e}\frac{L^2-R^2}{2z_2f_1(L,R)}\Big((\lambda-1)\frac{f_0(L,R)}{L+R}+1\Big).\end{aligned}\tag{4.2}$$

We remark that both V_1 and V_2 are independent of z_1. Note that, for $V\neq V_1$, $\partial J_{11}/\partial z_1=0$ has a unique root $z_1=z_1^*$ given by

$$z_1^*=\frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)(V-V_1)}.\tag{4.3}$$

Remark 4.3. *Note that, for z_1^* in (4.3) to be positive, one requires $(L-R)(V-V_1)<0$. In particular, as $L\to R$, z_1^* does not exist.*

We first examine some properties of V_1 and V_2.

Lemma 4.1. *If $L>R$, then $V_1<0<V_2$; if $L<R$, then $V_1>0>V_2$; and*

$$\lim_{L\to R^+}V_1=\lim_{L\to R^-}V_2=-\infty,\quad \lim_{L\to R^-}V_1=\lim_{L\to R^+}V_2=\infty.$$

Proof: Note that $0<f_0(L,R)<L+R$. Thus,

$$(\lambda-1)\frac{f_0(L,R)}{L+R}-\lambda<0 \text{ and } (\lambda-1)\frac{f_0(L,R)}{L+R}+1>0.$$

The results then follows from Lemma 2.1.

Treating z_1^*, V_1, V_2 as functions of (L,R), one has

Lemma 4.2. *The quantities z_1^*, V_1 and V_2 are homogeneous of degree zero in (L,R).*

We now state the results on effects of z_1.

Proposition 4.4. *For self-effects, one has,*

(i) *if $V<V_1$, then, for $L>R$, J_{11} is decreasing in z_1 for $z_1<z_1^*$ and is increasing in z_1 for $z_1>z_1^*$.*

(ii) *if $V=V_1$, then J_{11} is decreasing in z_1 for $L>R$ and is increasing in z_1 for $L<R$.*

(iii) *if $V>V_1$, then, for $L<R$, J_{11} is increasing in z_1 for $z_1<z_1^*$ and is decreasing in z_1 for $z_1>z_1^*$.*

For cross-effects, one has, J_{21} is increasing in z_1 for $V>V_2$ and is decreasing in z_1 for $V<V_2$.

4.2. Effects of z_1 on total flow rates We first study the effects of z_1 on the total flow rate of matter $\mathcal{T}$ in (2.8).

For the effects of z_1 on T_0, from (2.11) one can deduce

Lemma 4.3. *If $L<R$, then T_0 is strictly increasing in z_1; if $L>R$, then T_0 is strictly decreasing in z_1; and $T_0=0$ exactly when $D_1\neq D_2$ and*

$$V=\frac{k_BT}{e}\frac{(z_1D_2-z_2D_1)(L-R)}{z_1z_2(D_1-D_2)f_0(L,R)}.$$

For the first order term T_1, a direct calculation from (2.11) gives that

$$\frac{\partial T_1}{\partial z_1}=\frac{e}{k_BT}\frac{2(D_1-D_2)f_1(L,R)}{z_1^2H(1)}(V-V^m)-\frac{2D_1(L^2-R^2)}{z_1^3H(1)}, \tag{4.4}$$

where

$$V^m=\frac{k_BT}{e}\frac{L^2-R^2}{2z_2f_1(L,R)}\Big(\frac{D_2+\lambda D_1}{D_1-D_2}-(\lambda-1)\frac{f_0(L,R)}{L+R}\Big). \tag{4.5}$$

Note that V^m is independent of z_1 and, for $V\neq V^m$, $\partial T_1/\partial z_1=0$ has a unique root $z_1=z_1^m$ given by

$$z_1^m=\frac{k_BT}{e}\frac{D_1(L^2-R^2)}{(D_1-D_2)f_1(L,R)(V-V^m)}. \tag{4.6}$$

Remark 4.5. *Note that, for z_1^m in (4.6) to be positive, one requires $(L-R)(V-V^m)<0$.*

We now examine some properties of V^m and z_1^m.

Lemma 4.4. *Assume $D_1>D_2$. One has if $L>R$, then $V^m>0$; if $L<R$, then $V^m<0$; and*

$$\lim_{L\to R^+}V^m=\infty,\quad \lim_{L\to R^-}V^m=-\infty.$$

Treating z_1^m and V^m as functions of (L,R), one has

Proposition 4.6. *The quantities z_1^m and V^m are homogeneous of degree zero in (L,R).*

We now state a result on the effect of z_1 on T_1.

Proposition 4.7. *Assume $D_1>D_2$. One has*

- (i) *If $V<V^m$, then, for $L>R$, T_1 is decreasing in z_1 for $z_1<z_1^m$ and increasing in z_1 for $z_1>z_1^m$;*
- (ii) *If $V=V^m$, then, T_1 is increasing in z_1 for $L<R$ and decreasing in z_1 for $L>R$;*
- (iii) *If $V>V^m$, then, for $L<R$, T_1 is increasing in z_1 for $z_1<z_1^m$ and decreasing in z_1 for $z_1>z_1^m$.*

We next examine the effect of z_1 on the current $\mathcal{I}$. First we study the effects of z_1 on I_0. It follows from (2.11) that

Lemma 4.5. *I_0 is strictly increasing in z_1 if $V>0$ and strictly decreasing in z_1 if $V<0$, and $I_0=0$ exactly when*

$$V=-\frac{k_BT}{e}\frac{D_1-D_2}{z_1D_1-z_2D_2}(\ln L-\ln R).$$

For the first order term I_1, it follows from (2.11) that

$$\begin{aligned}\frac{\partial I_1}{\partial z_1}=&\frac{2\lambda D_1f_1(L,R)}{z_1^2z_2H(1)}\Big[z_1^2\frac{e}{k_BT}V-\frac{z_2^2D_2}{\lambda D_1}\frac{e}{k_BT}V\\&+\frac{z_2D_2(L^2-R^2)}{2\lambda D_1f_1(L,R)}\Big((\lambda-1)\frac{f_0(L,R)}{L+R}+\frac{D_2-D_1}{D_2}\Big)\Big].\end{aligned}$$

The following results establish the existence of a unique root of $\partial I_1/\partial z_1=0$.

LEMMA 4.6. *The equation $\partial I_1/\partial z_1=0$ has a unique root $z_1=z_1^c$ given by*

$$z_1^c=\left[\frac{z_2^2D_2}{\lambda D_1}-\frac{k_BT}{e}\frac{z_2D_2(L^2-R^2)}{2\lambda D_1f_1(L,R)V}\left((\lambda-1)\frac{f_0(L,R)}{L+R}+\frac{D_2-D_1}{D_2}\right)\right]^{\frac{1}{2}}.$$

This holds if one of the following conditions is satisfied

(i) $\frac{D_1}{D_2}\geq\frac{\lambda+1}{2}$ *and* $(L-R)V>0$;

(ii) $\frac{D_1}{D_2}<\frac{\lambda+1}{2}$, $R<L<L^*$ *and* $V<0$ *for some critical* L^* *determined uniquely by* $(\lambda-1)\frac{f_0(L,R)}{L+R}+\frac{D_2-D_1}{D_2}=0$;

(iii) $\frac{D_1}{D_2}<\frac{\lambda+1}{2}$, $L>L^*$ *and* $V>0$.

From Lemma 4.6, we have the following result of effect from z_1 on I_1.

LEMMA 4.7. *One has*

(i) *For* $\frac{D_1}{D_2}\geq\frac{\lambda+1}{2}$
  (i1) I_1 *is decreasing in* z_1 *if* $z_1>z_1^c$ *and increasing in* z_1 *if* $0<z_1<z_1^c$ *for* $V<0$ *and* $L<R$;
  (i2) I_1 *is increasing in* z_1 *if* $z_1>z_1^c$ *and decreasing in* z_1 *if* $0<z_1<z_1^c$ *for* $V>0$ *and* $L>R$.

(ii) *For* $\frac{D_1}{D_2}<\frac{\lambda+1}{2}$
  (ii1) I_1 *is decreasing in* z_1 *if* $z_1>z_1^c$ *and increasing in* z_1 *if* $0<z_1<z_1^c$ *for* $V<0$ *and* $R<L<L^*$;
  (ii2) I_1 *is increasing in* z_1 *if* $z_1>z_1^c$ *and decreasing in* z_1 *if* $0<z_1<z_1^c$ *for* $V>0$ *and* $L>L^*$.

Finally, treating z_1^c as a function of (L,R), one has

PROPOSITION 4.8. z_1^c *is homogeneous of degree zero in* (L,R).

5. Concluding remarks

Based on a quasi-one-dimensional PNP model for ionic flows through ion channels, we investigated ion size and ion valence effects on *individual* fluxes and on *total flow rates* of matter and charge of ionic mixtures. A unique feature of this work is its ability to provide a detailed characterization of complicated interactions among multiple and physically crucial parameters for ionic flows. These parameters include boundary concentrations and potentials, diffusion coefficients, ion sizes and ion valences. The results, although established for simple biological settings (two types of ion species without permanent charge in the channel) and with only uncharged hard-sphere potentials, have demonstrated extremely rich behaviors of ionic flows and sensitive dependence of flow properties on all these parameters. We expect more complex phenomena for more realistic ion channel models and for general electrolyte solutions. We believe that this work will be useful for numerical studies and stimulate further analytical studies of ionic flows through membrane channels. It is also our hope that this work may provide meaningful insights or a fundamental understanding of mechanisms for controlling ionic flows.

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