To Whom It May Concern:

This is Mingji Zhang, an Assistant Professor at the Department of Mathematics. I would like to nominate Daniel Acheampong, a graduate from the Department of Mathematics for the Langmuir Award.

He worked with me on a research project since last November, and we submitted our research result, "*Effects on ionic flows from finite ion sizes via Poisson-Nernst-Planck models with non-local excess chemical potentials*", this March to a top mathematical journal, *the Journal of Dynamics and Differential Equations*.

In the work, we study a quasi-one-dimensional steady-state Poisson-Nernst-Planck model for ionic flows through membrane channels. Excess chemical potentials are included in this work to account for finite ion size effects. In addition to ion sizes, our result shows that the qualitative properties of ionic flows, in terms of *individual fluxes and total flow rates of mixture*, depend on multiple physical parameters such as boundary concentrations and potentials, diffusion coefficients, 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 potential values that are explicitly expressed in terms of the physical parameters. *We believe our results will provide some useful insights for numerical and even experimental studies of ionic flows through membrane channels*.

For any further questions and concerns, please let me know.

Sincerely,

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Effects on ionic flows from finite ion sizes via Poisson-Nernst-Planck models with non-local excess chemical potentials

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Abstract

We study a quasi-one-dimensional steady-state Poisson-Nernst-Planck model for ionic flows through membrane channels. Excess chemical potentials are included in this work to account for finite ion size effects. This is the main difference from the classical Poisson-Nernst-Planck models, which treat ion species as point charges and neglect ion-to-ion interactions. In addition to ion sizes, the qualitative properties of ionic flows, in terms of *individual fluxes and total flow rates of mixture*, depend on multiple physical parameters such as boundary concentrations and potentials, diffusion coefficients, 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 potential values that are explicitly expressed in terms of the physical parameters. We believe our results will provide some useful insights for numerical and even experimental studies of ionic flows through membrane channels.

Key Words. Ionic flows, PNP, hard-sphere, individual fluxes, I-V relations, flow rate of matter, critical potentials

AMS subject classification 34A26, 34B16, 34D15, 37D10, 92C35

1 Introduction

In this work, we study the qualitative properties of ionic flows through ion channels via a quasi-one-dimensional steady-state Poisson-Nernst-Planck (PNP) type system. PNP systems are basic primitive models for electrodiffusion that treat the medium as a dielectric continuum (see [6, 7, 9, 10, 12, 13, 14, 15, 16, 17, 23, 24, 25, 26, 33, 34, 38, 56], etc.). Under various reasonable conditions, the PNP system can be

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derived from more fundamental models such as the Langevin-Poisson system (see, for example, [11, 34, 49, 51, 56, 61]) or the Maxwell-Boltzmann equations (see, for example, [2, 33, 34, 56]), and from an energy variational analysis (see [29, 30, 32, 40, 65, 67]). 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, 9, 10, 12, 23, 28]) and analyzed (see, e.g., [1, 3, 4, 18, 21, 36, 43, 41, 42, 47, 53, 62, 63, 64, 66]) 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 non-local hard-sphere* potential (an approximation to the excess chemical potential defined in (2.6)), 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 Bikerman ([5]), which is simple but unfortunately not ion specific. The Boublík-Mansoori-Carnahan-Starling-Leland local model is ion specific and has been shown to be accurate ([58, 59], etc.). The PNP models with ion sizes have been investigated computationally for ion channels and have shown great success (see [22, 24, 25, 26, 27, 29, 30, 32, 37, 38, 44, 46, 52, 67], 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, [19] and [40]).

As expected, ionic flows through membrane channels exhibit extremely rich phenomena. This is why ion channels are nano-scale valves for essentially all activities of living organisms. This is also the very reason that it is a great challenge to understand the mechanisms of ion channel functions. The challenge in mathematical analysis is due to the fact that, very often, 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 almost no hope to have explicit solution formulae for such a complicated problem even with simple boundary values. Fortunately, the recent development in analyzing classical PNP models ([18, 41, 42]) sheds some lights on the I-V (voltage-current) relations in simplified settings. This development is based heavily on modern invariant manifold theory of nonlinear dynamical systems, in particular, 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 [18, 42], the authors of [35] 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 *non-local* 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 $\lambda = r_2/r_1$ where r_1 and r_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 (V_c and V^c) identified in [35] *without using any analytical formulas* from [35], even for the case with *nonzero* permanent charge.

In this work, we study a quasi-one-dimensional PNP model with the same setting as in [35]. We focus on ion size effects on *individual* fluxes and the *total flow rate of matter*, in particular, on the first order terms (in radius) of the individual fluxes and the total flow rate of matter.

We take particular advantage of the work in [35] 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 the quasi-one-dimensional PNP model and the non-local hard-sphere model (see (2.7) below) adopted in [35] 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 following scaling laws are also established (see Propositions 2.4 and 3.9):

(a) The contribution to the individual fluxes, the I-V relations and the total flow rate of matter from the ideal component of the electrochemical potential scales *linearly* in boundary concentrations;

(b) The contribution (up to the leading order in radii of ion species) to the individual fluxes, the I-V relations and the total flow rate of matter from the non-local hard-sphere component of the electrochemical potential scales *quadratically* in boundary concentrations;

(c) All critical potentials (V_c and V^c from [35], $\hat{V}_c$, $\hat{V}^c$, V_{1v}, V_{2c}, V_1^c and V_2^c identified in this work) scale *invariantly* in boundary concentrations.

The rest of the paper is organized as follows. In Section 2, we describe the quasi-one-dimensional PNP model of ion flows, a non-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 [35] are recalled, and these will be the starting point of our study.

In Section 3, we study ion size effects on individual fluxes and the total flow rate of matter. *Six* critical potentials V_{jc}, V_j^c for $j = 1, 2$, $\hat{V}_c$ and $\hat{V}^c$ 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 (resp. the total flow rate of matter) are different and are rigorously analyzed (Section 3.1). The relations between the six critical potentials and those of V_c, V^c identified in [35] 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).

The paper ends with a concluding remark provided in Section 4.

2 Models and two critical potentials

In this section, we briefly recall the model of PNP systems with non-local hard sphere potentials for ion sizes and the main result obtained in [35], which characterizes ion size effects on the I-V relations.

2.1 A one-dimensional PNP-type system

We assume the channel is narrow so that it can be effectively viewed as a one-dimensional channel that connects the interior and the exterior of the channel. A quasi-one-dimensional *steady-state* PNP model for ion flows of n ion species though a single channel is (see [45, 50])

$$\begin{aligned}
&\frac{1}{A(X)}\frac{d}{dX}\left(\varepsilon_r(X)\varepsilon_0 A(X)\frac{d\Phi}{dX}\right) = -e\Big(\sum_{j=1}^n z_j C_j(X) + Q(X)\Big),\\
&\frac{d\mathcal{J}_i}{dX} = 0, \quad -\mathcal{J}_i = \frac{1}{k_BT}\mathcal{D}_i(X)A(X)C_i(X)\frac{d\mu_i}{dX}, \quad i = 1, 2, \cdots, n,
\end{aligned} \tag{2.1}$$

where $X \in [0, l]$, 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 of the channel, $\varepsilon_r(X)$ is the relative dielectric coefficient, ε_0 is the vacuum permittivity; $A(X)$ is the area of the cross-section of the channel over the point $X \in [0, l]$; for the ith ion species, C_i is the concentration (number of ith ions per volume), z_i is the valence (number of charges per particle) that is positive for cations and negative for anions, μ_i is the electrochemical potential, $\mathcal{J}_i$ is the flux density, and $\mathcal{D}_i(X)$ is the diffusion coefficient.

For system (2.1), we impose the following boundary conditions (see, [18] for justification), for $k = 1, 2, \cdots, n$,

$$\Phi(0) = V, \quad C_i(0) = \mathcal{L}_i > 0; \quad \Phi(l) = 0, \quad C_i(l) = \mathcal{R}_i > 0. \tag{2.2}$$

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

$$\sum_{j=1}^{n} z_j\mathcal{L}_j = \sum_{j=1}^{n} z_j\mathcal{R}_j = 0 \tag{2.3}$$

are typically maintained.

Remark 2.1. *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 [18, 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 ion channels, an important characteristic is the so-called *I-V relations* (current-voltage relations). For a solution of the *steady-state* boundary value problem (2.1)-(2.2), the *rate of flow of charge through a cross-section* or *current* $\mathcal{I}$ is

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

For fixed boundary concentrations $\mathcal{L}_i$'s and $\mathcal{R}_i$'s, $\mathcal{J}_j$'s depend on V only and formula (2.4) provides a relation of the current $\mathcal{I}$ on the voltage V. This relation is the *I-V relation.*

The electrochemical potential μ_i for the ith ion species consists of the concentration-independent component $\mu_i^0(x)$ (e.g. a hard-well potential), the ideal component $\mu_i^{id}(x)$, and the excess component $\mu_i^{ex}(x)$:

$$\mu_i(x) = \mu_i^0(x) + \mu_i^{id}(x) + \mu_i^{ex}(x)$$

where

$$\mu_i^{id}(x) = z_i e\phi(x) + kT\ln\frac{c_i(x)}{c_0} \tag{2.5}$$

with some characteristic number density c_0. The excess chemical potential $\mu_i^{ex}(x)$ to account for the finite size effect of charges consists of two components: the hard-sphere component μ_i^{HS} and the electrostatic component μ_i^{ES}([57, 58]); that is,

$$\mu_i^{ex} = \mu_i^{HS} + \mu_i^{ES}. \tag{2.6}$$

The Density Functional Theory (DFT) ([31, 39, 48], etc.) states that $\mu_i^{ex}(x)$ is actually a functional of the *concentrations*, $\{c_j(x)\}$. But no explicit formula for the functional dependence is available.

For the hard-sphere component μ_i^{HS} with two ion species, one has ([20, 54, 55, 60, 57, 58])

$$\mu_i^{HS} = \frac{\delta\Omega(\{c_j\})}{\delta c_i}, \tag{2.7}$$

where

$$\begin{aligned}\Omega(\{c_j\}) =& -\int n_0(x;c_1,c_2)\ln(1-n_1(x;c_1,c_2))dx,\\ n_l(x;c_1,c_2) =& \sum_{j=1}^{2}\int c_j(x')\omega_l^j(x-x')dx', \quad (l=0,1),\\ \omega_0^j(x) =& \frac{\delta(x-r_j)+\delta(x+r_j)}{2}, \quad \omega_1^j(x)=\Theta(r_j-|x|),\end{aligned} \tag{2.8}$$

where δ is the Dirac delta function, Θ is the Heaviside function, and r_j is the radius of the jth ion species.

2.2 The steady-state boundary value problem and assumptions

The main goal of this paper is to examine the qualitative properties of the ion size effect on ionic flows via the steady-state PNP system (2.1)-(2.2).

For definiteness, we will take essentially the same setting as that in [35], that is,

(A1). We consider two ion species ($n=2$) with $z_1>0$ and $z_2<0$.

(A2). We assume the permanent charge $Q(X)$ to be zero.

(A3). For the electrochemical potential μ_i, in addition to the ideal component μ_i^{id} defined in (2.5), we also include non-local hard sphere potential (2.7) to approximate the excess component μ^{ex}.

(A4). The relative dielectric coefficient and the diffusion coefficient are constants, that is, $\varepsilon_r(X)=\varepsilon_r$ and $D_i(X)=D_i$.

In the sequel, we will assume (A1)–(A4). We first make a dimensionless rescaling following ([21]). Set $C_0=\max\{\mathcal{L}_i,\mathcal{R}_i : i=1,2\}$ and let

$$\begin{aligned}\varepsilon^2 =& \frac{\varepsilon_r\varepsilon_0k_BT}{e^2l^2C_0}, \quad x=\frac{X}{l}, \quad h(x)=\frac{A(X)}{l^2}, \quad D_i=lC_0\mathcal{D}_i;\\ \phi(x) =& \frac{e}{k_BT}\Phi(X), \quad c_i(x)=\frac{C_i(X)}{C_0}, \quad J_i=\frac{\mathcal{J}_i}{D_i};\\ \bar{V} =& \frac{e}{k_BT}V, \quad L_i=\frac{\mathcal{L}_i}{C_0}; \quad R_i=\frac{\mathcal{R}_i}{C_0}.\end{aligned} \tag{2.9}$$

The BVP (2.1)-(2.2) then becomes

$$\begin{aligned}&\frac{\varepsilon^2}{h(x)}\frac{d}{dx}\left(h(x)\frac{d}{dx}\phi\right)=-z_1c_1-z_2c_2,\\ &\frac{dc_1}{dx}+z_1c_1\frac{d\phi}{dx}+\frac{c_1(x)}{k_BT}\frac{d}{dx}\mu_1^{HS}(x)=-\frac{J_1}{h(x)},\\ &\frac{dc_2}{dx}+z_2c_2\frac{d\phi}{dx}+\frac{c_2(x)}{k_BT}\frac{d}{dx}\mu_2^{HS}(x)=-\frac{J_2}{h(x)},\\ &\frac{dJ_1}{dx}=\frac{dJ_2}{dx}=0,\end{aligned} \tag{2.10}$$

with the boundary conditions

$$\phi(0)=\bar{V},\quad c_i(0)=L_i;\quad \phi(1)=0,\quad c_i(1)=R_i. \tag{2.11}$$

We now recall some results obtained in [35], which are crucial for our study and which will be frequently used. In [35], assuming $h(x)=1$ over the whole interval $[0,1]$ and treating ε and $r=r_1$ as small parameters, the authors derive approximations for the current (total flow rate of charge) I expanded in r with $\lambda=\frac{r_2}{r}$:

$$\mathcal{I}(V;\varepsilon,r)=ez_1\mathcal{J}_1+ez_2\mathcal{J}_2=ez_1D_1J_1+ez_2D_2J_2=I_0(V;\varepsilon)+I_1(V;\varepsilon)r+o(r),$$

where

$$\begin{aligned}I_0(V;0)=&ez_1D_1J_{10}(V;0)+ez_2D_2J_{20}(V;0),\\ I_1(V;0)=&ez_1D_1J_{11}(V;0)+ez_2D_2J_{21}(V;0),\end{aligned}$$

Under electroneutrality conditions, one has

$$\begin{aligned}J_{10}=&\frac{L-R}{z_1}+f_0(L,R)\frac{e}{k_BT}V,\\ J_{20}=&-\frac{L-R}{z_2}-f_0(L,R)\frac{e}{k_BT}V,\\ J_{11}=&\frac{2}{z_1z_2}\bigg((\lambda-1)(L-R)f_0(L,R)-\frac{(z_1\lambda-z_2)(L^2-R^2)}{z_1}\\ &-(z_1\lambda-z_2)f_1(L,R)\frac{e}{k_BT}V\bigg),\\ J_{21}=&\frac{2}{z_1z_2}\bigg(-(\lambda-1)(L-R)f_0(L,R)+\frac{(z_1\lambda-z_2)(L^2-R^2)}{z_2}\\ &+(z_1\lambda-z_2)f_1(L,R)\frac{e}{k_BT}V\bigg).\end{aligned} \tag{2.12}$$

In particular,

$$\begin{aligned}I_0(V;0)=&e(D_1-D_2)(L-R)+\frac{e^2(z_1D_1-z_2D_2)}{k_BT}f_0(L,R)V,\\ I_1(V;0)=&-\frac{2e(D_1-D_2)(z_1\lambda-z_2)(L^2-R^2)}{z_1z_2}+\frac{2e(z_1D_1-z_2D_2)(\lambda-1)(L-R)}{z_1z_2}f_0(L,R)\\ &-\frac{2e^2(z_1D_1-z_2D_2)(z_1\lambda-z_2)}{z_1z_2k_BT}f_1(L,R)V,\end{aligned} \tag{2.13}$$

where

$$\begin{aligned}f_0(L,R)=&\frac{L-R}{\ln L-\ln R},\\ f_1(L,R)=&\frac{(L^2-R^2)(\ln L-\ln R)-2(L-R)^2}{(\ln L-\ln R)^2}\\ =&-2f_0(L,R)\left(f_0(L,R)-\frac{L+R}{2}\right).\end{aligned} \tag{2.14}$$

The explicit approximation in (2.13) allows the authors of [35] to realize the existence of two critical potential values V_c and V^c defined, respectively, by

$$I_1(V_c;0)=0,\quad \frac{d}{d\lambda}I_1(V^c;0)=0. \tag{2.15}$$

They are given, in this setting, by

$$\begin{aligned}V_c=&\frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)}\left(\frac{\lambda-1}{z_1\lambda-z_2}\frac{f_0(L,R)}{L+R}-\frac{D_1-D_2}{z_1D_1-z_2D_2}\right),\\ V^c=&\frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)}\left(\frac{1}{z_1}\frac{f_0(L,R)}{L+R}-\frac{D_1-D_2}{z_1D_1-z_2D_2}\right).\end{aligned} \tag{2.16}$$

The importance of V_c and V^c is evident and we summarize it here ([35]).

Theorem 2.2. *Let V_c and V^c be defined by (2.15). For $\varepsilon>0$ small and $r>0$ small, one has*

(i) *If $V>V_c$ (resp. $V<V_c$), then $I(V;\varepsilon,r)>I(V;\varepsilon,0)$ (resp. $I(V;\varepsilon,r)<I(V;\varepsilon,0)$);*

(ii) *If $V>V^c$ (resp. $V<V^c$), then the current I is increasing (resp. decreasing) in λ.*

We next state a result that will be used frequently in the following sections, whose proof is straightforward and will be omitted.

Lemma 2.3. *Assume $L\neq R$. 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* (2.14). *With $R>0$ being fixed,*

$$\lim_{L\to R}f_0(L,R)=R\quad\textit{and}\quad\lim_{L\to R}f_1(L,R)=0.$$

As a by-product, we study the so-called *total flow rate of matter* defined as follows:

$$T(V;\lambda,\varepsilon)=eD_1J_1(V;\lambda,\varepsilon)+eD_2J_2(V;\lambda,\varepsilon). \tag{2.17}$$

Similarly, approximations for the total flow rate of charge $\mathcal{T}$ expanded in r with $\lambda=\frac{r_2}{r}$ can be obtained

$$\mathcal{T}(V;\varepsilon,r)=e\mathcal{J}_1+e\mathcal{J}_2=eD_1J_1+eD_2J_2=T_0(V;\varepsilon)+T_1(V;\varepsilon)r+o(r),$$

where

$$\begin{aligned}T_0(V;0)=&eD_1J_{10}(V;0)+eD_2J_{20}(V;0),\\ T_1(V;0)=&eD_1J_{11}(V;0)+eD_2J_{21}(V;0).\end{aligned}$$

Together with (2.12), one has

$$\begin{aligned}T_0(V;0)=&\frac{e(z_2D_1-z_1D_2)(L-R)}{z_1z_2}+(D_1-D_2)f_0(L,R)\frac{e^2}{k_BT}V,\\ T_1(V;0)=&\frac{2e(z_1D_2-z_2D_1)(z_1\lambda-z_2)(L^2-R^2)}{z_1^2z_2^2}+\frac{2e(D_1-D_2)(\lambda-1)(L-R)}{z_1z_2}f_0(L,R)\\ &-\frac{2e^2(D_1-D_2)(z_1\lambda-z_2)f_1(L,R)}{z_1z_2k_BT}V.\end{aligned} \tag{2.18}$$

We end this section with a very interesting observation from (2.12), (2.13) and (2.18).

Proposition 2.4. *Viewing* $J_{i0},\ J_{i1},\ I_0,\ I_1,\ T_0$ *and* T_1 *as functions of* (L,R), *one has*

(i) $J_{i0},\ I_0$ *and* T_0 *are homogeneous of degree one in* (L,R), *that is, for any* $s>0$,

$$J_{i0}(V;sL,sR)=sJ_{i0}(V;L,R),\quad I_0(V;sL,sR)=sI_0(V;L,R)$$

and

$$T_0(V;sL,sR)=sT_0(V;L,R).$$

(ii) $J_{i1},\ I_1$ *and* T_1 *are homogeneous of degree two in* (L,R), *that is, for any* $s>0$,

$$J_{i1}(V;sL,sR)=s^2J_{i1}(V;L,R),\quad I_1(V;sL,sR)=s^2I_0(V;L,R)$$

and

$$T_1(V;sL,sR)=s^2T_1(V;L,R).$$

3 Ion size effects on ionic flows

In this section, our main focus is to provide a detailed analysis of ion size effects on *individual fluxes* and the *total flow rate of matter.*

3.1 Critical potentials for the total flow rate of matter and individual fluxes

Notice that ion sizes do not play roles for D_iJ_{10}. We will focus on D_iJ_{i1} (and hence, $z_iD_iJ_{i1}$) and $T_1=eD_1J_{11}+eD_2J_{21}$, the leading terms containing ion size effects.

For the individual flux, we observe

(i) the sign of $\mathcal{J}_{i1}$ determines whether ion sizes enhance (i.e. $\mathcal{J}_{i1}(V;\varepsilon,r)>\mathcal{J}_{i1}(V;\varepsilon,0)$) or reduce (i.e. $\mathcal{J}_{i1}(V;\varepsilon,r)<\mathcal{J}_{i1}(V;\varepsilon,0)$) the flux of the ith ion species;

(ii) the sign of $d\mathcal{J}_{i1}/d\lambda$ determines if the flux of ith ion species is increasing or decreasing in λ.

Remark 3.1. *Similar arguments can be applied to the total flow rate of matter in terms of the leading term* $T_1(V;\varepsilon,r)$.

We therefore introduce six critical potentials (four for individual fluxes and two for the total flow rate of matter)– zeros of these quantities– that separate the signs of these quantities.

Definition 3.2. *Let* $V_{1c},\ V_{2c},\ V_1^c,\ V_2^c,\ \hat{V}_c$, *and* $\hat{V}^c$ *be defined, respectively, through*

$$\begin{aligned}
&J_{11}(V_{1c};\lambda,0)=0,\quad J_{21}(V_{2c};\lambda,0)=0,\\
&\frac{d}{d\lambda}J_{11}(V_1^c;\lambda,0)=0,\quad \frac{d}{d\lambda}J_{21}(V_2^c;\lambda,0)=0,\\
&T_1(\hat{V}_c;\lambda,0)=0,\quad \frac{d}{d\lambda}T_1(\hat{V}^c;\lambda,0)=0.
\end{aligned}$$

From (2.12) and (2.18), a direct calculation gives

Lemma 3.3. *Suppose $L \neq R$. One has, for $i = 1, 2$,*

$$
\begin{aligned}
V_{ic} =& -\frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)}\left(\frac{1}{z_i}+\frac{1-\lambda}{\lambda z_1 - z_2}\frac{f_0(L,R)}{L+R}\right),\\
V_i^c =& -\frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)}\left(\frac{1}{z_i}-\frac{1}{z_1}\frac{f_0(L,R)}{L+R}\right),\\
\hat V_c =& \frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)}\left(\frac{z_1D_2-z_2D_1}{z_1z_2(D_1-D_2)}+\frac{\lambda-1}{z_1\lambda - z_2}\frac{f_0(L,R)}{L+R}\right),\\
\hat V^c =& \frac{k_BT}{e}\frac{L^2-R^2}{f_1(L,R)}\left(\frac{1}{z_1}\frac{f_0(L,R)}{L+R}+\frac{z_1D_2-z_2D_1}{z_1z_2(D_1-D_2)}\right).
\end{aligned}
$$

We would like to point out the following interesting but reasonable observation related to the individual flux from Lemma 3.3:

(i) V_{1c} and V_{2c} depend on λ, z_1 and z_2. Take $\mathrm{Na^+Cl^-}$ and $\mathrm{K^+Cl^-}$ for example, since $\mathrm{Na^+}$ and $\mathrm{K^+}$ 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 $\mathrm{Na^+Cl^-}$ and $\mathrm{Ca^{++}Cl^-}$, since $\mathrm{Na^+}$ and $\mathrm{Ca^{++}}$ have essentially the same size but different valences, the values of V_{1c} and V_{2c} are different due to the ion valence effect.

(ii) V_1^c and V_2^c do not depend on λ. 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 (2.12).

Remark 3.4. *Similar arguments can be obtained for $\hat V_c$ and $\hat V^c$.*

The significance of the six critical potentials is apparent from their definitions. The values V_{1c} and V_{2c} (resp. $\hat V_c$) are the potentials that balance the ion size effects on individual fluxes (resp. the total flow rate of matter), and the values V_1^c and V_2^c (resp. $\hat V^c$) are the potentials that separate the relative size effects on individual fluxes (resp. the total flow rate of matter). The precise statements are collected in two theorems below, the first one for V_{1c}, V_{2c} and $\hat V_c$, the other one for V_1^c, V_2^c and $\hat V^c$.

It first follows from (2.12) and (2.18) that

Lemma 3.5. *Suppose $L \neq R$. One has,*

(i) $\partial_V J_{11} > 0$ *and* $\partial^2_{V\lambda} J_{11} > 0$*;*

(ii) $\partial_V J_{21} < 0$ *and* $\partial^2_{V\lambda} J_{21} < 0$*;*

(iii) $\partial_V T_1 > 0$ *(resp.* $\partial_V T_1 > 0$*), if* $D_1 > D_2$ *(resp.* $D_1 < D_2$*);* $\partial^2_{V\lambda} T_1 > 0$ *(resp.* $\partial^2_{V\lambda} T_1 > 0$*), if* $D_1 > D_2$ *(resp.* $D_1 < D_2$*).*

In addition, with $R > 0$ fixed,

$$\lim_{L\to R}\partial_V J_{j1} = \lim_{L\to R}\partial^2_{V\lambda} J_{j1} = \lim_{L\to R}\partial_V T_1 = \lim_{L\to R}\partial^2_{V\lambda} T_1 = 0.$$

The next two results follow directly from (2.12), Definition 3.2 and Lemma 3.5. Their proofs are omitted.

Theorem 3.6. *Assume $D_1 < D_2$. One has, for $\varepsilon > 0$ small and $r > 0$ 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. $\mathcal{J}_2(V;\varepsilon,d) < \mathcal{J}_2(V;\varepsilon,0)$);*

(iii) *if $V < \hat{V}_c$ (resp. $V > \hat{V}_c$), then $\mathcal{T}(V;\varepsilon,d) > \mathcal{T}(V;\varepsilon,0)$ (resp. $\mathcal{T}(V;\varepsilon,d) < \mathcal{T}(V;\varepsilon,0)$).*

Recall from Lemma 3.3 that V_1^c, V_2^c and $\hat{V}^c$ are independent of λ.

Theorem 3.7. *Assume $D_1 < D_2$. One has, for $\varepsilon > 0$ small and $r > 0$ 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,*

(iii) *if $V < \hat{V}^c$ (resp. $V > \hat{V}^c$), then $\mathcal{T}(V;\varepsilon,d)$ is increasing in (resp. decreasing) in λ.*

Remark 3.8. *Similar arguments for the total flow rate of matter can be obtained for the case with $D_1 > D_2$.*

Theorems 3.6 and 3.7, together with Theorem 2.2, provide the roles of those critical potentials in the classification of ion sizes effects on ionic flows of individual fluxes, the current, and the total flow rate of matter.

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 (2.16) and (3.3).

Proposition 3.9. *Viewing V_c, V^c, V_{ic}, V_i^c, $\hat{V}_c$ and $\hat{V}^c$ as functions of (L,R), one has V_c, V^c, V_{ic}, V_i^c, $\hat{V}_c$ and $\hat{V}^c$ are all homogeneous of degree zero in (L,R), that is, for any $s > 0$,*

$$V_c(sL,sR) = V_c(L,R),\ V^c(sL,sR) = V^c(L,R),\ V_{ic}(sL,sR) = V_{ic}(L,R),$$

$$V_i^c(sL,sR) = V_i^c(L,R),\ \hat{V}_c(sL,sR) = \hat{V}_c(L,R),\ \hat{V}^c(sL,sR) = \hat{V}^c(L,R).$$

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 (2.16), (3.3) and Lemma 3.3 and are provided in the next result.

Proposition 3.10. *Assume $L \neq R$. Then,*

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

and, for $D_1 \neq D_2$,

$$\hat{V}_c = \frac{D_1V_{1c} - D_2V_{2c}}{D_1 - D_2}, \quad \hat{V}^c = \frac{D_1V_1^c - D_2V_2^c}{D_1 - D_2}. \tag{3.2}$$

Furthermore,

$$\begin{aligned} V_{1c} - V_{2c} =& V_1^c - V_2^c = \frac{k_BT}{e}\frac{L^2 - R^2}{f_1(L,R)}\frac{z_1 - z_2}{z_1z_2}, \\ V_{1c} - V_1^c =& V_{2c} - V_2^c = V_c - V^c = \hat{V}_c - \hat{V}^c \\ =& -\frac{k_BT}{e}\frac{L^2 - R^2}{f_1(L,R)}\frac{f_0(L,R)}{L+R}\frac{z_1 - z_2}{z_1(\lambda z_1 - z_2)}, \\ V_c - \hat{V}_c =& V^c - \hat{V}^c = \frac{k_BT}{e}\frac{L^2 - R^2}{f_1(L,R)}\frac{(z_1 - z_2)^2D_1D_2}{z_1z_2(D_1 - D_2)(z_1D_1 - z_2D_2)}. \end{aligned} \tag{3.3}$$

Remark 3.11. *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. Moreover, 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 our following studies.*

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

Proposition 3.12. *One has the following partial orders among the critical potentials.*

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

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

Furthermore, 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*

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

Furthermore, 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 study the sub-case with $L < R$ and $D_1 < D_2$. Other cases, such as $L < R,\ D_1 > D_2$, $L > R,\ D_1 > D_2$ and $L > R,\ D_1 < D_2$ can be analyzed similarly, and we leave it to readers.

From (2.16), (3.3), Lemmas 2.3 and 3.3, and Proposition 3.12, one has

Proposition 3.13. *Suppose $L < R$ and $D_1 < D_2$. Then,*

(a) *If* $\frac{(z_1\lambda - z_2)D_2}{z_1D_1 - z_2D_2} < \frac{f_0(L,R)}{L+R} < \frac{(z_1\lambda - z_2)D_1}{z_2(D_1 - D_2)}$, *and this holds if* $1 < \frac{D_2}{D_1} < 1 - \frac{\sqrt{z_2(z_2 - z_1)}}{z_2}$, *then*

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

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

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

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

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

(d) *If* $\frac{f_0(L,R)}{L+R} > \frac{(z_1\lambda - z_2)D_1}{z_2(D_1 - D_2)}$, *then*

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

(e) *If* $\frac{(z_1\lambda - z_2)D_1}{z_2(D_1 - D_2)} < \frac{f_0(L,R)}{L+R} < \frac{z_1\lambda - z_2}{z_2} \min\left\{-\frac{z_1D_1}{z_1D_1 - z_2D_2}, \frac{z_2D_2}{z_1D_1 - z_2D_2}\right\}$, *and this holds if* $\frac{D_2}{D_1} > \max\left\{1 - \frac{\sqrt{z_2(z_2 - z_1)}}{z_2}, \frac{2z_1}{z_1 + z_2}\right\}$, *which is only possible if* $z_1 > -z_2$, *then*

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

(f) *If* $\frac{z_1\lambda - z_2}{z_2} \max\left\{-\frac{z_1D_1}{z_1D_1 - z_2D_2}, \frac{z_2D_2}{z_1D_1 - z_2D_2}, \frac{D_1}{D_1 - D_2}\right\} < \frac{f_0(L,R)}{L+R} < \frac{(z_1 - z_2)(z_1\lambda - z_2)D_1D_2}{z_2(D_1 - D_2)(z_1D_1 - z_2D_2)}$, *and this holds if* $1 < \frac{D_2}{D_1} < 2 - \frac{z_1}{z_2}$, *then*

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

(g) *If* $\frac{z_1\lambda - z_2}{z_2} \max\left\{\frac{z_2D_2}{z_1D_1 - z_2D_2}, \frac{D_1}{D_1 - D_2}\right\} < \frac{f_0(L,R)}{L+R} < -\frac{z_1(z_1\lambda - z_2)D_1}{z_2(z_1D_1 - z_2D_2)}$, *and this holds if* $\frac{2z_1}{z_1 + z_2} < \frac{D_2}{D_1} < -\frac{z_1}{z_2}$, *which is only possible if* $\frac{z_1}{z_2} < -1$, *then*

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

(h) *If* $\frac{z_1\lambda - z_2}{z_2} \max\left\{\frac{-z_1D_1}{z_1D_1 - z_2D_2}, \frac{D_1}{D_1 - D_2}\right\} < \frac{f_0(L,R)}{L+R} < \frac{(z_1\lambda - z_2)D_2}{z_2(z_1D_1 - z_2D_2)} \min\left\{z_2, \frac{(z_1 - z_2)D_1}{D_1 - D_2}\right\}$, *and this holds if* $\frac{D_2}{D_1} > \max\left\{-\frac{z_1}{z_2}, 1 - \frac{\sqrt{z_2(z_2 - z_1)}}{2z_2}\right\}$, *then*

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

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

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

(j) *If* $\frac{z_1\lambda-z_2}{z_2}\max\left\{\frac{-z_1D_1}{z_1D_1-z_2D_2},\ \frac{D_1}{D_1-D_2},\ \frac{(z_1-z_2)D_1D_2}{(D_1-D_2)(z_1D_1-z_2D_2)}\right\} < \frac{f_0(L,R)}{L+R} < \frac{(z_1\lambda-z_2)D_2}{z_1D_1-z_2D_2}$, *and this holds if* $\frac{D_2}{D_1} > \max\left\{2-\frac{z_1}{z_2},\ -\frac{z_1}{z_2},\ 1-\frac{\sqrt{z_2(z_2-z_1)}}{2z_2}\right\}$, *then*

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

Proof. The proof is elementary and we omit it here. □

Remark 3.14. *Our main purpose in Proposition 3.13 is to provide a complete classification of the potential regions based on the critical potentials identified in* (2.16), (3.3) *and Definition 3.2 for the sub-case where* $L < R$ *and* $D_1 < D_2$. *From this, the distinct effects of the nonlinearity and the interplay among the physical parameter, such as boundary potentials, boundary concentrations, ion sizes, ion valences and diffusion coefficients can be characterized. Except cases (a) and (d), all the other cases consist of sub-cases, for example, in case (b), one has the following two sub-cases:*

(b1) $\frac{f_0(L,R)}{L+R} > \frac{(z_1\lambda-z_2)D_1}{z_2(D_1-D_2)}$, *and this holds if* $1 < \frac{D_2}{D_1} < 1-\frac{\sqrt{z_2(z_2-z_1)}}{z_2}$;

(b2) $\frac{f_0(L,R)}{L+R} > \frac{(z_1\lambda-z_2)D_2}{z_1D_1-z_2D_2}$, *and this holds if* $\frac{D_2}{D_1} > 1-\frac{\sqrt{z_2(z_2-z_1)}}{z_2}$.

To further illustrate Proposition 3.13, we consider the following 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* $\frac{f_0(L,R)}{L+R} = 0.2579$, $\frac{(z_1\lambda-z_2)D_1}{z_2(D_1-D_2)} = 0.5955$ *and* $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2} = 1.985$. *This satisfies case (a) in Proposition 3.13 with* $J_1 := J_{Na}$ *and* $J_2 := J_{Cl}$. *Based on Theorems 2.2, 3.6 and 3.7, one has Tables* 3.1 *and* 3.2.

  (i2) *Taking the positively charged ion species as* Na^+, *the negatively charged one as* Cl^-, *and* $\lambda = 1.885,\ L = 0.02,\ R = 0.2,\ D_1 = 2$, *and* $D_2 = 10$. *For this set-up, we have* $\frac{f_0(L,R)}{L+R} = 0.3553$, $\frac{(z_1\lambda-z_2)D_1}{z_2(D_1-D_2)} = 0.7213$, *and* $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2} = 2.4041$. *This satisfies case (c) in Proposition 3.13. 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* $\lambda = 1.382,\ L = 0.000002,\ R = 0.002,\ D_1 = 0.1$, *and* $D_2 = 10$. *For this set-up, we have* $\frac{f_0(L,R)}{L+R} = 6.8940$, $\frac{(z_1\lambda-z_2)D_1}{z_2(D_1-D_2)} = 0.0241$, *and* $\frac{(\lambda z_1-z_2)D_2}{z_1D_1-z_2D_2} = 2.3584$. *This satisfies case (b) in Proposition 3.13.*

3.3 Sensitivity of ion size effects near $L = R$.

We carefully examine the situation when L and R close to each other. It turns out that the properties of the critical potentials are extremely sensitive to whether $L > R$ or $L < R$.

V region	$\mathcal{J}_1$	$\mathcal{J}_2$	$\mathcal{T} = e\mathcal{J}_1 + e\mathcal{J}_2$	$\mathcal{I} = z_1 e\mathcal{J}_1 + z_2 e\mathcal{J}_2$
$(-\infty, \hat{V}_c)$	$J_1(r) < J_1(0)$	$J_2(r) > J_2(0)$	$T(r) < T(0)$	$I(r) < I(0)$
$(\hat{V}_c, V_{2c})$	$J_1(r) < J_1(0)$	$J_2(r) > J_2(0)$	$T(r) > T(0)$	$I(r) < I(0)$
(V_{2c}, V_c)	$J_1(r) < J_1(0)$	$J_2(r) > J_2(0)$	$T(r) > T(0)$	$I(r) < I(0)$
(V_c, V_{1c})	$J_1(r) < J_1(0)$	$J_2(r) > J_2(0)$	$T(r) > T(0)$	$I(r) > I(0)$
(V_{1c}, ∞)	$J_1(r) > J_1(0)$	$J_2(r) < J_2(0)$	$T(r) > T(0)$	$I(r) > I(0)$

Table 1: For convenience, we rewrite $\mathcal{J}_1(V;\varepsilon,r)$ as $\mathcal{J}_1(r)$, 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 (V_{1c}, ∞), the ion size enhances $\mathcal{J}_1$, reduces $\mathcal{J}_2$, but enhances both $\mathcal{T}$ and the current $\mathcal{I}$.

V region	$\mathcal{J}_1$	$\mathcal{J}_2$	$\mathcal{T}$	$\mathcal{I}$
$(-\infty, \hat{V}^c)$	J_1 decreases in λ	J_2 decreases in λ	T decreases in λ	I decreases in λ
$(\hat{V}^c, V_2^c)$	J_1 decreases in λ	J_2 decreases in λ	T increases in λ	I decreases in λ
(V_2^c, V^c)	J_1 decreases in λ	J_2 increases in λ	T increases in λ	I decreases in λ
(V^c, V_1^c)	J_1 decreases in λ	J_2 increases in λ	T increases in λ	I increases in λ
(V_1^c, ∞)	J_1 increases in λ	J_2 decreases in λ	T increases in λ	I increases in λ

Table 2: For convenience, we rewrite $\mathcal{J}_1(V;r,\varepsilon,\lambda) = \mathcal{J}_1$, and so on. Relative ion size effects (in terms of $\lambda := \frac{r_1}{r_2}$, where r_1, the diameter of the positively charged ion species, and r_2 is the diameter of the negatively charged one) on both individual fluxes and total fluxes over different potential regions are characterized.

Proposition 3.15. *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 3.3 satisfy

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

The results then follow from Lemma 2.3.

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

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

Note that $0 < \gamma < \sigma$.

Proposition 3.16. *One has,*

(i) *if $D_1/D_2 < \gamma$, 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 $\gamma < D_1/D_2 < \sigma$, 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 $D_1/D_2 > \sigma$, 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: A careful calculation gives

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

and

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

where, with $x = \frac{D_1}{D_2}$,

$$g_1(x) = \frac{x-1}{z_1x - z_2} + \frac{1-\lambda}{2(\lambda z_1 - z_2)} \text{ and } g_2(x) = \frac{x-1}{z_1x - z_2} - \frac{1}{2z_1}.$$

Notice that

$$g_1(x) = 0 \Longleftrightarrow x = x_c := \frac{D_{1c}}{D_{2c}} \text{ and } g_2(x) = 0 \Longleftrightarrow x = x^c := \frac{D_1^c}{D_2^c}.$$

In addition, one has $x_c < x^c$. Note also that

$$g_1'(x) = \frac{z_1 - z_2}{(z_1x - z_2)^2} > 0 \quad \text{and} \quad g_2'(x) = \frac{z_1 - z_2}{(z_1x - z_2)^2} > 0 \text{ for all } x > 0.$$

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

The significance of Propositions 3.15 and 3.16 is discussed in the following remark.

Remark 3.17. (i) *Combining Proposition 3.15 with Theorems 3.6 and 3.7, we conclude that the effects on computed ionic flows by including the nonlocal HS potential are sensitive to whether $L > R$ or $L < R$ when 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, $\mathcal{J}_i(V;\varepsilon;r) > \mathcal{J}_i(V;\varepsilon;0)$, $i = 1,2$; and on the other hand, as $L \to R^-$, exactly the opposite occurs, that is, one has $V_{2c} < V < V_{1c}$ for any fixed potential V, and hence, $\mathcal{J}_i(V;\varepsilon;r) < \mathcal{J}_i(V;\varepsilon;0)$, $i = 1,2$ (see, (i) and (ii) in Theorem 3.6). A similar conclusion applies to results in Theorem 3.7. This sensitive dependence of ion size effects on individual fluxes near $L = R$ is rather striking, and possibly could be observed experimentally.*

(ii) *Similarly, when combining Proposition 3.16 with Theorem 2.2, 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 γ and σ; for example, if $D_1/D_2 < \gamma$, on one hand, as $L \to R^+$, one has $V < V_c$ and $V < V^c$ for any fixed potential V, and hence, $\mathcal{I}(V;\varepsilon;r) < \mathcal{I}(V;\varepsilon;0)$ (see, (i) in Theorem 2.2) and the current $\mathcal{I}$ is always decreasing in λ (see, (ii) in Theorem 2.2); 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 $L \to R^+$.*

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

Proposition 3.18. *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 Concluding remarks

In this work, we consider a quasi-one-dimensional PNP model for ionic flows through membrane channels. Ion size effects on *individual* fluxes and on *total flow rates* of matter and charge of ionic mixtures are carefully analyzed. 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, one positively charged and one negatively charge, with zero permanent charge in the channel) and with only uncharged nonlocal 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 ion channels. We also hope that this work may provide meaningful insights or a fundamental understanding of mechanisms for controlling ionic flows.

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Support Letter for Daniel Acheampong

Daniel Acheampong, a graduate student at the Department of Mathematics, began to become interested in my research since last March during my on-campus interview. Last semester, I gave two seminar talks and introduced several interesting topics related to my research, *dynamics of Poisson-Nernst-Planck theory for ionic flows through membrane channels.* He immediately talked with me and wanted to do some research with me. We began to get started in November 2015.

Daniel works very hard, and I am surprised by his ability to learn new materials and solve some complicated nonlinear differential equations. He finished all the complicated calculations and obtained very interesting results. He will give a talk on April 22nd to introduce our results in our department seminar.

I invited Bob Eisenberg, a famous expert who proposed the Poisson-Nernst-Planck model to visit New Mexico between March 9th and 12th. I discussed our results with him, and he is very surprised with our results and gave high evaluation of our work. He agreed that our results will provide useful insights for numerical and even experimental studies of ionic flows through membrane channels. He also encouraged us to perform some numerical simulations to further support our analytical results, and currently, we are working on that.

I would really appreciate your kind consideration of our case!

Sincerely,

Mingji Zhang