Journal of Applied Analysis and Computation
Volume 12, Number 3, June 2022, 932–951
Website:http://www.jaac-online.com
DOI:10.11948/20210003

STUDIES ON CURRENT-VOLTAGE RELATIONS VIA POISSON-NERNST-PLANCK SYSTEMS WITH MULTIPLE CATIONS AND PERMANENT CHARGES

Xijun Deng[1], Yusheng Jia[2,†] and Mingji Zhang[3]

Dedicated to Professor Jibin Li on the occasion of his 80th birthday.

Abstract We study a one-dimensional Poisson-Nernst-Planck system with multiple cations having the same valences and small permanent charges. Viewing the permanent charge as a small parameter, via regular perturbation analysis, approximations of the current-voltage (I-V) relations are derived explicitly, and this allows us to further study the qualitative properties of ionic flows through membrane channels. Our main interest are small permanent charge and channel geometry effects on the I-V relations, which additionally depend on the nonlinear interactions with other physical parameters involved in the model. Critical potentials are identified and their important roles played in the study of the property of ionic flows are characterized. We perform numerical simulations to provide more intuitive illustrations of our theoretical results. Those non-intuitive observations from analysis of the system provide better understandings of the mechanism of ionic flows through membrane channels, particularly the internal dynamics that is not able to be detected via current technology.

Keywords PNP, diffusion coefficients, permanent charges, channel geometry, electroneutrality conditions.

MSC(2010) 34A26, 34B16, 34D15, 37D10, 92C35.

1. Introduction

The study of electrodiffusion is an extraordinarily rich area for multidisciplinary research with numerous applications in different research fields, particularly, physics, chemistry and biology. To be specific, semiconductor technology controls the migration and diffusion of quasi-particles of charge in transistors and integrated circuits ([39,41]), chemical science deals with charged molecules in water ([3,7,8]), and biology occurs in plasma of ions and charged organic molecules in water ([1,9,21,42]).

[†]The corresponding author. Email: jiayusheng1982@tom.com(Y. Jia)
[1]College of Mathematics and Physics Science, Hunan University of Arts and Science, Changde, 415000, P.R. China
[2]The Institute of Complexity Science, Qingdao University, Qingdao, Shandong 266071, China
[3]Department of Mathematics, New Mexico Institution of Mining and Technology, Socorro, NM 87801, USA

The migration of ions through open ion channels is one of the most remarkable physical problems performed by living cells. Cells are enveloped by lipid membranes which are nearly impermeable to physiological ions (mainly Na^+, K^+, Ca^{++} and Cl^-). One mechanism for ions to go across these membranes is through ion channels, which are approximately cylindrical, hollow proteins with a hole down their middle that regulates the electro-diffusion of those ions, establishing communications among cells and the external environment ([13, 14, 18]). In this way, ion channels control a wide range of biological functions, in particular, many varied functions are necessary for life: channels are responsible for the initiation and continuation of the electrical signals in the nervous system; in muscle cells, a group of channels are responsible for the delivery ions that initiate a muscle contraction ([18]). Consequently, it is significant for one to explore the mechanism of ion channels.

The study of ion channels generally involves two related major topics: structures of ion channels and ionic flow properties. The physical structure of ion channels is defined by the channel shape and the spacial distribution of permanent charges and the polarity of these charges. For open channels with given structures, the main interest is on the study of its electrodiffusion property. A major challenge to examine properties of ionic flows through membrane channels lies in the nonlinear interplays among specific system parameters involved, particularly, the boundary concentrations and membrane potential, permanent charge distribution within the channel, channel geometry and diffusion coefficients. On the other hand, all present experimental measurements about ionic flow are of input-output type ([14]); that is, the internal dynamics within the channel cannot be measured with the current technology. Therefore, it is extremely difficult to extract coherent properties or to formulate specific characteristic quantities from the experimental measurements. Without knowing what to simulate among the potentially rich behavior presented by ion channel problems, it is also difficult for numerical simulations to conduct any systematic studies.

Mathematical analysis plays important and unique roles for generalizing and understanding the principles that allow control of electrodiffusion, explaining mechanics of observed biological phenomena and for discovering new ones, assuming a more or less explicit solution of the associated mathematical model can be obtained. Recently, there have been some successes in mathematical analysis of Poisson-Nernst-Planck (PNP) models for ionic flows through membrane channels. Particularly, for those ([4–6, 10, 11, 16, 17, 26, 27, 29–31, 33, 37, 46] etc.) that were studied under the dynamical system framework of geometric singular perturbation analysis, interesting phenomena of ionic flows were observed for relatively simple setups. To be specific, rich effect of permanent charge on cation flux and anion flux was discovered ([27, 47]), a mechanism of declining phenomenon − increasing of the transmembrane electrochemical potential of an ion species in a particular way leads to decreasing of the ionic flux, was revealed ([47]), and critical values for ionic flows were formulated ([4–6, 10, 17, 25, 27, 29, 32, 46]).

In current work, we analyze a PNP system with nonzero but small permanent charges. Our main interest is the effect on the I-V relation, which is the main tool to characterize the most two relevant properties of ion channels: permeation and selectivity. One is able to extract the I-V relation from solutions of the PNP system.

1.1. One-dimensional Poisson-Nernst-Planck models

PNP system is a basic macroscopic model for electrodiffusion of charges through ion channels ([9,12,15,19–21,24,35,36,38], etc.). Under various reasonable conditions, one can derive the PNP system as a reduced model from molecular dynamics, Boltzmann equations, and variational principles ([2,22,23,40]).

A quasi-one-dimensional *steady-state* PNP model for a mixtures of n charged particles though a single channel reads ([34])

$$\begin{aligned}
&\frac{1}{A(X)}\frac{d}{dX}\left(\varepsilon_r(X)\varepsilon_0 A(X)\frac{d\Phi}{dX}\right) = -e\left(\sum_{j=1}^{n} z_j C_j(X) + Q(X)\right),\\
&\frac{d\mathcal{J}_i}{dX} = 0, \quad -\mathcal{J}_i = \frac{1}{k_B T}\mathcal{D}_i(X)A(X)C_i(X)\frac{d\mu_i}{dX}, \quad i = 1, 2, \cdots, n,
\end{aligned} \tag{1.1}$$

where

- $e \approx 1.60 \times 10^{-19}$ (C=coulomb) is the elementary charge,
- $k_B \approx 1.38 \times 10^{-23}$ (JK^{-1}) is the Boltzmann constant,
- T is the absolute temperature (unit K (kelvin)), it is $T = 273.16$ (K),
- $\Phi(X)$ is the electric potential with the unit V=Volt=JC^{-1},
- $Q(X)$ is the permanent charge density of the channel (with unit 1/m^3),
- $\varepsilon_0(X)$ is the local dielectric coefficient (with unit Fm^{-1}),
- $\varepsilon_r(X)$ is the relative dielectric coefficient (with unit 1),
- $A(X)$ represents the area of the cross-section over the point X (with unit m^2),
- n is the number of distinct types of ion species (with unit 1),
- for the jth ion species,
  - C_j is the *number* density (with unit 1/m^3),
  - z_j is the valence (the number of charges per particle with unit 1),
  - μ_j is the electrochemical potential (with unit J=CV),
  - $\mathcal{J}_j$ is the *number* flux density (with unit 1/s) – the *number* of particles across each cross-section per unit time;
  - $\mathcal{D}_j(X)$ is the diffusion coefficient (with unit m^2/s).

The boundary conditions are, for $i = 1, 2, \cdots, n$,

$$\Phi(0) = \mathcal{V}, \quad C_i(0) = \mathcal{L}_i > 0; \quad \Phi(l) = 0, \quad C_i(l) = \mathcal{R}_i > 0. \tag{1.2}$$

1.2. Permanent charges

It is known that the spatial distribution of side chains in a specific channel defines the permanent charge of the channel. The permanent charge is the key to the PNP theory, and different channel types differ mainly in the distribution of permanent charge. Individual channels within a channel type have the same permanent charge since they are the same protein ([18]). Furthermore, the role of permanent charges in membrane channels is similar to the role of doping profiles in semiconductor devices ([39,44,48]).

Very often, one model the permanent charge $Q(X)$ through a piecewise constant function, that is, we assume, for a partition $X_0 = 0 < X_1 < \cdots < X_{m-1} < X_m = l$ of $[0, l]$ into m subintervals, $Q(X) = Q_j$ for $x \in (X_{j-1}, X_j)$ where Q_j's are constants with $Q_1 = Q_m = 0$ (the intervals $[X_0, X_1]$ and $[X_{m-1}, X_m]$ are viewed as the reservoirs where there is no permanent charge).

In [16], the authors established the existence and (local) uniqueness of solutions for the problem (1.1)-(1.2) with two ion species, and the permanent charge function is given by

$$Q(X) = \begin{cases} 0, & 0 < X < a, \\ Q_0, & a < X < b, \\ 0, & b < X < 1, \end{cases} \tag{1.3}$$

with Q_0 a constant. The authors in [27] extended the work done in [16] by further assuming Q_0 in (1.3) to be small, particularly, the work focus on the permanent charge and channel geometry effects on ionic flows. It turns out that the permanent charge plays a crucial role in the nature of ionic flows and introduces a new complicated interaction with other system parameters involved in the system, and the various ionic fluxes. In [10, 46], the authors extended the work done in [27] by considering the boundary layer effects on ionic flows under different setups, and gained better understandings of the mechanism of ionic flows through membrane channels. Recently, in [6,48], the authors considered the PNP system with multiple cations having the same valences, beyond the existence and local uniqueness results established via geometric singular perturbation theory, the competition between two cations due to the small permanent charges and nonlinear interplays with other system parameters is characterized in detail. Rich dynamics of ionic flows through membrane channels are observed, particularly, the internal dynamics, which cannot be detected via current technology. The studies in [6, 27, 48] provides better understandings of the qualitative properties of ionic flows through membrane channels.

1.3. Problem set-up

For definiteness, we will take the following setting in this work:

(A1) We consider three ion species with $z_1 = z_2 = z > 0$ and $z_3 < 0$ under the electroneutrality boundary conditions given by

$$\sum_{k=1}^{n} z_k \mathcal{L}_k = \sum_{k=1}^{n} z_k \mathcal{R}_k = 0. \tag{1.4}$$

(A2) The permanent charge is defined by (1.3).

(A3) For the electrochemical potential μ_i, we only consider the ideal component μ_i^{id} modeled by

$$\mu_k^{id}(X) = z_k e\Phi(X) + k_B T \ln \frac{C_k(X)}{C_0}, \tag{1.5}$$

with some characteristic number density C_0 defined by

$$C_0 = \max_{1 \le i \le n} \Big\{ \mathcal{L}_i, \mathcal{R}_i, \sup_{X \in [0,l]} |Q(X)| \Big\}. \tag{1.6}$$

(A4) We assume $\varepsilon_r(X) = 1$ and $D_i(X) = D_i$, where D_i is some positive constant.

In the sequel, we will assume (A1)–(A4). We first make a dimensionless rescaling following [18]. With C_0 given in (1.6), let

$$\begin{aligned} &\varepsilon^2 = \frac{\varepsilon_r\varepsilon_0 k_B T}{e^2 l^2 C_0}, \quad x = \frac{X}{l}, \quad h(x) = \frac{A(X)}{l^2}, \quad D_i = lC_0\mathcal{D}_i, \\ &\phi(x) = \frac{e}{k_B T}\Phi(X), \quad c_i(x) = \frac{C_i(X)}{C_0}, \quad J_i = \frac{\mathcal{J}_i}{D_i}, \\ &V = \frac{e}{k_B T}\mathcal{V}, \quad L_i = \frac{\mathcal{L}_i}{C_0}, \quad R_i = \frac{\mathcal{R}_i}{C_0}. \end{aligned} \tag{1.7}$$

The BVP (1.1)-(1.2) then becomes (noting that $z_1 = z_2 = z$)

$$\begin{aligned} &\frac{\varepsilon^2}{h(x)}\frac{d}{dx}\left(h(x)\frac{d}{dx}\phi\right) = -zc_1 - zc_2 - z_3c_3 - Q(x), \\ &\frac{dc_1}{dx} + zc_1\frac{d\phi}{dx} = -\frac{J_1}{h(x)}, \quad \frac{dc_2}{dx} + zc_2\frac{d\phi}{dx} = -\frac{J_2}{h(x)}, \\ &\frac{dc_3}{dx} + z_3c_3\frac{d\phi}{dx} = -\frac{J_3}{h(x)}, \quad \frac{dJ_k}{dx} = 0, \end{aligned} \tag{1.8}$$

with the boundary conditions, for $i = 1, 2, 3$,

$$\phi(0) = V, \quad c_i(0) = L_i > 0; \quad \phi(1) = 0, \quad c_i(1) = R_i > 0. \tag{1.9}$$

The electroneutrality boundary conditions (1.4) correspondingly reads

$$z(L_1 + L_2) + z_3L_3 = 0, \quad z(R_1 + R_2) + z_3R_3 = 0. \tag{1.10}$$

2. Brief description of the dynamical system framework

Our analysis is based on the so-called geometric singular perturbation theory. One may refer to [48] for details. Here, we just briefly describe the process. To get started, we rewrite system (1.1) into a standard form for singularly perturbed systems and convert the boundary value problem (1.8)-(1.9) to a connection problem.

Upon introducing $u = \varepsilon\dot\phi$ and $\tau = x$. System (1.1) becomes

$$\begin{aligned} &\varepsilon\dot\phi = u, \quad \varepsilon\dot u = -zc_1 - zc_2 - z_3c_3 - Q(x) - \varepsilon\frac{h_\tau(\tau)}{h(\tau)}u, \\ &\varepsilon\dot c_1 = -zc_1u - \frac{\varepsilon}{h(\tau)}J_1, \quad \varepsilon\dot c_2 = -zc_2u - \frac{\varepsilon}{h(\tau)}J_2, \quad \varepsilon\dot c_3 = -z_3c_3u - \frac{\varepsilon}{h(\tau)}J_3, \\ &\dot J_1 = \dot J_2 = \dot J_3 = 0, \quad \dot\tau = 1, \end{aligned} \tag{2.1}$$

where overdot denotes the derivative with respect to the variable x.

Viewing ε as a small parameter, we treat the system (2.1) to be a singularly perturbed one with state variables $(\phi, u, c_1, c_2, c_3, J_1, J_2, J_3, \tau)$ in the phase space $\mathbb{R}^9$.

For $\varepsilon > 0$, the rescaling $x = \varepsilon\xi$ of the independent variable x gives rise to

$$\begin{aligned}
&\phi' = u, \quad u' = -zc_1 - zc_2 - z_3c_3 - Q(x) - \varepsilon\frac{h_\tau(\tau)}{h(\tau)}u,\\
&c_1' = -zc_1u - \frac{\varepsilon}{h(\tau)}J_1, \quad c_2' = -zc_2u - \frac{\varepsilon}{h(\tau)}J_2, \quad c_3' = -z_3c_3u - \frac{\varepsilon}{h(\tau)}J_3,\\
&J_1' = J_2' = J_3' = 0,\ \tau' = \varepsilon,
\end{aligned} \tag{2.2}$$

where prime denotes the derivative with respect to the variable ξ.

Let B_L and B_R be the subsets of the phase space $\mathbb{R}^9$ defined by

$$\begin{aligned}
B_L =& \{(V, u, L_1, L_2, L_3, J_1, J_2, J_3, 0) \in \mathbb{R}^9 : \text{arbitrary } u, J_1, J_2, J_3\},\\
B_R =& \{(0, u, R_1, R_2, R_3, J_1, J_2, J_3, 1) \in \mathbb{R}^9 : \text{arbitrary } u, J_1, J_2, J_3\}.
\end{aligned} \tag{2.3}$$

Then the original boundary value problem is equivalent to a connecting problem: finding a solution of (2.1) or (2.2) from B_L to B_R (refer to [28] for more details).

Considering the jumps of the function (1.3) at $x = a$ and $x = b$, we divide the interval $[0, 1]$ into three subintervals $[0, a]$, $[a, b]$ and $[b, 1]$, where the intervals $[0, a]$ and $[b, 1]$ represent the reservoirs, and the interval $[a, b]$ represents the channel. To construct a singular orbit over the whole interval $[0, 1]$, we first construct a singular orbit on each of the subintervals. We first preassign the values of ϕ, c_1, c_2 and c_3 at $x = a$ and $x = b$:

$$\phi(a) = \phi^{[a]},\ c_k(a) = c_k^{[a]}; \quad \phi(b) = \phi^{[b]},\ c_k(b) = c_k^{[b]}, \quad k = 1, 2, 3. \tag{2.4}$$

These eight unknown values will be determined along our construction of a singular orbit on the whole interval $[0, 1]$ (See Figure 1 adopted from [48] for a more intuitive illustration).

(i) The singular orbit on $[0, a]$ consists of two boundary layers Γ_l^0 and Γ_l^a and one regular layer Λ_l with $(\phi, c_1, c_2, c_3, \tau)$ being

$$(V, L_1, L_2, L_3, 0) \text{ at } x = 0 \text{ and } (\phi^{[a]}, c_1^{[a]}, c_2^{[a]}, c_3^{[a]}, a) \text{ at } x = a.$$

Once $(\phi^{[a]}, c_1^{[a]}, c_2^{[a]}, c_3^{[a]})$ is given, the flux densities J_k^l and the value $u_l(a)$ are uniquely determined.

(ii) The singular orbit on $[a, b]$ consists of two boundary layers Γ_m^a and Γ_m^b and one regular layer Λ_m with $(\phi, c_1, c_2, c_3, \tau)$ being

$$(\phi^{[a]}, c_1^{[a]}, c_2^{[a]}, c_3^{[a]}, a) \text{ at } x = a \text{ and } (\phi^{[b]}, c_1^{[b]}, c_2^{[b]}, c_3^{[b]}, b) \text{ at } x = b.$$

Once $(\phi^{[a]}, c_1^{[a]}, c_2^{[a]}, c_3^{[a]})$ and $(\phi^{[b]}, c_1^{[b]}, c_2^{[b]}, c_3^{[b]})$ are given, the flux densities J_k^m and the value $u_m(a)$ and $u_m(b)$ are uniquely determined.

(iii) The singular orbit on $[b, 1]$ consists of two boundary layers Γ_r^b and Γ_r^1 and one regular layer Λ_r with $(\phi, c_1, c_2, c_3, \tau)$ being

$$(\phi^{[b]}, c_1^{[b]}, c_2^{[b]}, c_3^{[b]}, b) \text{ at } x = b \text{ and } (0, R_1, R_2, R_3, 1) \text{ at } x = 1.$$

Once $(\phi^{[b]}, c_1^{[b]}, c_2^{[b]}, c_3^{[b]})$ is given, the flux densities J_k^r and the value $u_r(b)$ are uniquely determined.

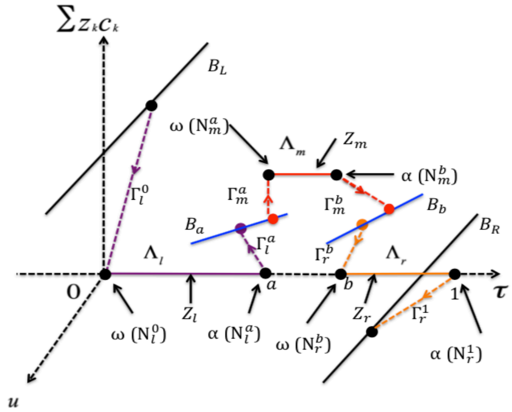

Figure 1. Illustration of a singular orbit projected to the space of $(u, \sum z_k c_k, \tau)$ under current setup.

To obtain a singular orbit on the whole interval $[0, 1]$, one need

$$J_k^l = J_k^m = J_k^r, \quad u_l(a) = u_m(a), \quad u_m(b) = u_r(b), \; k = 1, 2, 3. \tag{2.5}$$

This consists of eight conditions. The number of conditions is exactly the same as the number of unknowns in (2.4).

The singular orbit constructed above consists of nine pieces $\Gamma_l^0 \cup \Lambda_l \cup \Gamma_l^a \cup \Gamma_m^a \cup \Lambda_m \cup \Gamma_m^b \cup \Gamma_r^b \cup \Lambda_r \cup \Gamma_r^1$. Once a singular orbit is constructed, one then can apply Exchange Lemma, to show that, for $\varepsilon > 0$ small, there is a unique solution close to the singular orbit (see Theorem 1 in [48] for details).

3. Effects on I-V relations from small permanent charges

We first recall some results from [48], and our discussion will take great advantage of them. In [48], the matching conditions (2.5) leads to the set of nonlinear algebraic equations, for $k = 1, 2$, which eventually determines the existence and local unique of singular orbits,

$$\begin{aligned}
0 &= C^{[a]}\left(e^{z(\phi^{[a]}-\phi^{[a,m]})} - e^{z(\phi^{[a]}-\phi^{[a,l]})}\right) + c_3^{[a]}\left(e^{z_3(\phi^{[a]}-\phi^{[a,m]})} - e^{z_3(\phi^{[a]}-\phi^{[a,l]})}\right)\\
&\quad + Q_0(\phi^{[a]} - \phi^{[a,m]}),\\
0 &= C^{[b]}\left(e^{z(\phi^{[b]}-\phi^{[b,r]})} - e^{z(\phi^{[b]}-\phi^{[b,m]})}\right) + c_3^{[b]}\left(e^{z_3(\phi^{[b]}-\phi^{[b,r]})} - e^{z_3(\phi^{[b]}-\phi^{[b,m]})}\right)\\
&\quad - Q_0(\phi^{[b]} - \phi^{[b,m]}),\\
0 &= zc_1^{[a]} e^{z(\phi^{[a]}-\phi^{[a,m]})} + zc_2^{[a]} e^{z(\phi^{[a]}-\phi^{[a,m]})} + z_3 c_3^{[a]} e^{z_3(\phi^{[a]}-\phi^{[a,m]})} + Q_0,\\
0 &= zc_1^{[b]} e^{z(\phi^{[b]}-\phi^{[b,m]})} + zc_2^{[b]} e^{z(\phi^{[b]}-\phi^{[b,m]})} + z_3 c_3^{[b]} e^{z_3(\phi^{[b]}-\phi^{[b,m]})} + Q_0,\\
J_k &= \mathcal{A}_1\mathcal{B}_1 \frac{L_k - c_k^{[a,l]} e^{z(\phi^{a,l} - V)}}{H(a)} = \mathcal{A}_2\mathcal{B}_2 \frac{c_k^{[b,r]} - R_k e^{-z\phi^{[b,r]}}}{H(1) - H(b)},
\end{aligned}$$

$$
\begin{aligned}
&J_3=-\frac{z}{z_3}\mathcal{A}_1\frac{\ln L-\ln C^{[a,l]}e^{z_3(\phi^{a,l}-V)}}{H(a)}=-\frac{z}{z_3}\mathcal{A}_2\frac{\ln C^{[b,r]}-\ln Re^{-z_3\phi^{[b,r]}}}{H(1)-H(b)},\\
&\phi^{[b,m]}=\phi^{[a,m]}-T^cy_0,\quad c_1^{[b,m]}=\frac{J_2c_1^{[a,m]}-J_1c_2^{[a,m]}}{J_1+J_2}e^{zT^cy_0}-J_1\cdot\mathcal{A}_3(y_0),\\
&c_2^{[b,m]}=\frac{J_1c_2^{[a,m]}-J_2c_1^{[a,m]}}{J_1+J_2}e^{zT^cy_0}-J_2\cdot\mathcal{A}_3(y_0),\\
&T^m=\frac{(z-z_3)(C^{[b,m]}-C^{[a,m]})+z_3Q_0(\phi^{[b,m]}-\phi^{[a,m]})}{z_3(H(b)-H(a))}.
\end{aligned}\tag{3.1}
$$

where, for $k=1,2$,

$$
\begin{aligned}
&\phi^L=V,\ c_1^L=L_1,\ c_2^L=L_2,\ c_3^L=L_3,\ \phi^{[a,l]}=\phi^{[a]}-\frac{1}{z-z_3}\ln\frac{-z_3c_3^{[a]}}{zC^{[a]}},\\
&c_k^{[a,l]}=c_k^{[a]}\Big(\frac{-z_3c_3^{[a]}}{zC^{[a]}}\Big)^{\frac{z}{z-z_3}},\ c_3^{[a,l]}=c_3^{[a]}\Big(\frac{-z_3c_3^{[a]}}{zC^{[a]}}\Big)^{\frac{z_3}{z-z_3}},\\
&c_k^{[b,r]}=c_k^{[b]}\Big(\frac{-z_3c_3^{[b]}}{zC^{[b]}}\Big)^{\frac{z}{z-z_3}},\ c_3^{b,r}=c_3^{[b]}\Big(\frac{-z_3c_3^{[b]}}{zC^{[b]}}\Big)^{\frac{z_3}{z-z_3}},\\
&\phi^{[b,r]}=\phi^{[b]}-\frac{1}{z-z_3}\ln\frac{-z_3c_3^{[b]}}{zC^{[b]}},\ \phi^R=0,\ c_1^R=R_1,\ c_2^R=R_2,\ c_3^R=R_3,\\
&c_k^{[a,m]}=c_k^{[a]}e^{z(\phi^{[a]}-\phi^{[a,m]})},\ c_3^{[a,m]}=c_3^{[a]}e^{z_3(\phi^{[a]}-\phi^{[a,m]})},\\
&c_k^{[b,m]}=c_k^{[b]}e^{z(\phi^{[b]}-\phi^{[b,m]})},\ c_3^{[b,m]}=c_3^{[b]}e^{z_3(\phi^{[b]}-\phi^{[b,m]})},\\
&\mathcal{A}_1=\frac{L-C^{[a,l]}}{\ln L-\ln C^{[a,l]}},\ \mathcal{B}_1=\frac{\ln L-\ln C^{[a,l]}e^{z(\phi^{[a,l]}-V)}}{L-C^{[a,l]}e^{z(\phi^{[a,l]}-V)}},\\
&\mathcal{A}_2=\frac{C^{[b,r]}-R}{\ln C^{[b,r]}-\ln R},\ \mathcal{B}_2=\frac{\ln C^{[b,r]}-\ln Re^{-z\phi^{[b,r]}}}{C^{[b,r]}-Re^{-z\phi^{[b,r]}}},\\
&\mathcal{A}_3(y)=\frac{Q_0}{zT^m}\big(1-e^{zz_3T^my}\big)-\frac{C^{[a,m]}}{J_1+J_2}e^{zz_3T^my}.
\end{aligned}\tag{3.2}
$$

Here,

$$
\begin{aligned}
&T^m=J_1+J_2+J_3,\ T^c=z(J_1+J_2)+z_3J_3,\ L=L_1+L_2,\ R=R_1+R_2,\\
&C^{[a]}=c_1^{[a]}+c_2^{[a]},\ C^{[b]}=c_1^{[b]}+c_2^{[b]},\ C^{[a,l]}=c_1^{[a,l]}+c_2^{[a,l]},\\
&C^{[a,m]}=c_1^{[a,m]}+c_2^{[a,m]},\quad C^{[b,r]}=c_1^{[b,r]}+c_2^{[b,r]}.
\end{aligned}\tag{3.3}
$$

Assuming $|Q_0|$ is small, the author in [48] employed regular perturbation analysis to expand all unknown quantities in (3.1)-(3.2) in Q_0, for example, for $k=1,2,3$,

$$
\begin{aligned}
&\phi^{[a]}=\phi_0^{[a]}+\phi_1^{[a]}Q_0+\phi_2^{[a]}Q_0^2+o(Q_0^2),\ \phi^{[b]}=\phi_0^{[b]}+\phi_1^{[b]}Q_0+\phi_2^{[b]}Q_0^2+o(Q_0^2),\\
&c_k^{[a]}=c_{k0}^{[a]}+c_{k1}^{[a]}Q_0+c_{k2}^{[a]}Q_0^2+o(Q_0^2),\ c_k^{[b]}=c_{k0}^{[b]}+c_{k1}^{[b]}Q_0+c_{k2}^{[b]}Q_0^2+o(Q_0^2),\\
&y_0=y_{00}+y_{01}Q_0+y_{02}Q_0^2+o(Q_0^2),\ J_k=J_{k0}+J_{k1}Q_0+J_{k2}Q_0^2+o(Q_0^2).
\end{aligned}\tag{3.4}
$$

Upon introducing

$$
\alpha=H(a)/H(1),\ \beta=H(b)/H(1),\tag{3.5}
$$

and, corresponding to (3.3),

$$T_0^m = J_{10} + J_{20} + J_{30}, \quad C_i^{[a]} = c_{1i}^{[a]} + c_{2i}^{[a]},\ C_i^b = c_{1i}^{[b]} + c_{2i}^{[b]},\ i = 0, 1, \tag{3.6}$$

the following result is established in [48], which is the starting point of current work.

Lemma 3.1. *Assume the conditions* (1.10). *For* $k = 1, 2$, *one has*

$$\begin{aligned}
J_{k0} &= \frac{f_0(L,R) f_1(L,R;V)}{H(1)} \big(L_k - R_k e^{-zV}\big),\\
J_{30} &= -\frac{z}{z_3} \frac{f_0(L,R)}{H(1)} \left(\ln L - \ln R + z_3 V\right),\\
J_{k1} &= f_1(L,R;V) \frac{A\left(z_3(1-B)V + \ln L - \ln R\right)}{(z - z_3) H(1) \left(\ln L - \ln R\right)^2} \big(L_k - R_k e^{-zV}\big),\\
J_{31} &= \frac{A\left(z_3 V + \ln L - \ln R\right)\left(z(1-B)V + \ln L - \ln R\right)}{(z_3 - z) H(1) \left(\ln L - \ln R\right)^2},
\end{aligned} \tag{3.7}$$

where

$$\begin{aligned}
f_0(L,R) &= \frac{L - R}{\ln L - \ln R}, \quad f_1(L,R;V) = \frac{\ln L - \ln R + zV}{L - Re^{-zV}},\\
A &= \frac{(\alpha - \beta)\left(L - R\right) f_0(L,R)}{\omega(\alpha)\omega(\beta)}, \quad B = \frac{\ln \omega(\beta) - \ln \omega(\alpha)}{A}
\end{aligned}$$

with $\omega(s) = (1-s)L + sR$.

For later discussion, we recall the function $\gamma(t)$ for $t > 0$ from [48] with

$$\gamma(t) = \frac{t \ln t - t + 1}{(t-1)\ln t}, \text{ for } t \neq 1, \text{ and } \gamma(1) = \frac{1}{2}. \tag{3.8}$$

Some related results (corresponding to Lemmas 6, 7 and 8 in [48]) are restated as follows:

Lemma 3.2. *For* $t > 0$, *one has* $0 < \gamma(t) < 1$, $\gamma'(t) > 0$, $\lim_{t\to 0} \gamma(t) = 0$ *and* $\lim\limits_{t\to\infty} \gamma(t) = 1$.

Lemma 3.3. *Set* $t = L/R$. *A has the same sign with that of* $R - L$, *that is, if* $t > 1$, *then* $A < 0$, *and if* $t < 1$, *then* $A > 0$.

We comment that for the analysis in Section 3.1, the sign of $A(1-B)$ is crucial. Since the sign of A has been handled in Lemma 3.3, we next characterize the sign of $1 - B$.

Lemma 3.4. *Suppose* $t = L/R > 1$ *and* $\gamma(t)$ *is given in (3.8). One has* $B > 0$, *and* $1 - B \to 0$ *as* $t \to 1$. *Moreover,*

(i) *if* $\gamma(t) \le \alpha$, *then* $\frac{z}{z_3} < 0 < 1 - B$ *and* $V_1 < 0 < V_2$;

(ii) *if* $\alpha < \gamma(t) < \alpha - \frac{z}{z_3 \ln t}$, *then, there exists a unique* $\beta_1 \in (\alpha, 1)$ *such that*

  (ii1) $\frac{z}{z_3} < 1 - B < 0$ *and* $V_2 < V_1 < 0$, *for* $\beta \in (\alpha, \beta_1)$;

  (ii2) $\frac{z}{z_3} < 1 - B = 0$, *for* $\beta = \beta_1$;

  (ii3) $\frac{z}{z_3} < 0 < 1 - B$ *and* $V_1 < 0 < V_2$, *for* $\beta \in (\beta_1, 1)$.

(iii) *if* $\gamma(t) > \alpha - \frac{z}{z_3 \ln t}$, *then, there exists a unique* $\beta_1^* \in (\alpha, \beta_1)$ *such that*

(iii1) $1 - B < \frac{z}{z_3} < 0$ *and* $V_1 < V_2 < 0$, *for* $\beta \in (\alpha, \beta_1^*)$;

(iii2) $1 - B = \frac{z}{z_3} < 0$ *and* $V_2 = V_1 < 0$, *for* $\beta = \beta_1^*$;

(iii3) $\frac{z}{z_3} < 1 - B < 0$ *and* $V_2 < V_1 < 0$, *for* $\beta \in (\beta_1^*, \beta_1)$;

(iii4) $\frac{z}{z_3} < 1 - B = 0$, *for* $\beta = \beta_1$;

(iii5) $\frac{z}{z_3} < 0 < 1 - B$ *and* $V_1 < 0 < V_2$, *for* $\beta \in (\beta_1, 1)$.

3.1. Effects on I-V relations from small permanent charge

We are interested in studying the effect on the I-V relations from nonzero but small permanent charge, which additionally depends on nonlinear interaction with other physical parameters. To be specific, we consider the I-V relations of the form

$$\mathcal{I}(V) = \mathcal{I}_0(V) + Q_0\mathcal{I}_1(V) + o(Q_0),$$

where, from Lemma 3.1 with $L_d^* = D_1L_1 + D_2L_2$ and $R_d^* = D_1R_1 + D_2R_2$, one has

$$\begin{aligned}
\mathcal{I}_0(V) &= zD_1J_{10} + zD_2J_{20} + z_3D_3J_{30}\\
&= \frac{zf_0(L,R)}{H(1)}\bigg(f_1(L,R;V)\big(L_d^* - R_d^*e^{-zV}\big) - D_3\left(\ln L - \ln R + z_3V\right)\bigg),\\
\mathcal{I}_1 &= zD_1J_{11} + zD_2J_{21} + z_3D_3J_{31}\\
&= \frac{Azz_3(1-B)}{(z-z_3)H(1)\left(\ln L - \ln R\right)^2}\bigg(\frac{z\left(V-V_1\right)\left(V-V_2\right)}{L-Re^{-zV}}\left(L_d^* - R_d^*e^{-zV}\right)\\
&\quad - z_3D_3\Big(V - \frac{z}{z_3}V_1\Big)\Big(V - \frac{z_3}{z}V_2\Big)\bigg),
\end{aligned} \tag{3.9}$$

where

$$V_1 = \frac{1}{z}\ln\frac{R}{L}, \quad V_2 = \frac{1}{z_3(1-B)}\ln\frac{R}{L}. \tag{3.10}$$

The leading term $\mathcal{I}_1$ that contains the small permanent charge effects is our main concern, and the sign of $A(1-B)$ characterized by Lemmas 3.3 and 3.4 is crucial in our following discussion. For simplicity, we will focus on the case with $A(1-B) > 0$, and similar arguments can be applied to the case with $A(1-B) < 0$.

For convenience, we introduce some functions of the potential V, viewing L, R, L_d^*, R_d^*, V_1, V_2, D_3, z and z_3 as fixed parameters, $f_{t1}(V)$ and $g_{t1}(V)$ as follows:

$$\begin{aligned}
f_{t1}(V) =& z\left(2V - V_1 - V_2\right)\big(L - Re^{-zV}\big)\big(L_d^*e^{zV} - R_d^*\big) + z^2\big(R_d^*L - L_d^*R\big)\left(V - V_1\right)\left(V - V_2\right)\\
&- z_3D_3\left(2V - \frac{z}{z_3}V_1 - \frac{z_3}{z}V_2\right)\left(L - Re^{-zV}\right)^2e^{zV},\\
g_{t1}(V) =& z\Big[2\big(L_d^* - R_d^*e^{-zV}\big) + z\left(2V - V_1 - V_2\right)\left(L_d^* + R_d^*e^{-zV}\right)\Big]\\
&- z_3D_3\Big[2\big(L - Re^{-zV}\big) + z\Big(2V - \frac{z}{z_3}V_1 - \frac{z_3}{z}V_2\Big)\big(L + Re^{-zV}\big)\Big].
\end{aligned} \tag{3.11}$$

For the leading term $\mathcal{I}_1$ as a function of the membrane potential V, one has

$$\frac{d\mathcal{I}_1}{dV} = \frac{zz_3A(1-B)}{(z-z_3)H(1)\left(\ln L - \ln R\right)^2}\frac{e^{-zV}}{\left(L - Re^{-zV}\right)^2}f_{t1}(V),$$

and

$$f'_{t1}(V)=\frac{df_{t1}}{dV}=e^{zV}\big(L-Re^{-zV}\big)g_{t1}(V).$$

Straightforward calculations give the following results and we skip their proofs.

Lemma 3.5. *$V=V_{t0}$ is the unique inflection point of $g_{t1}(V)$ given by*

$$V_{t0}=\frac{6\big(zR_d^*-z_3D_3R\big)+z^2R_d^*(V_1+V_2)-zz_3D_3R\big(\frac{z}{z_3}V_1+\frac{z_3}{z}V_2\big)}{2z\big(zR_d^*-z_3D_3R\big)}.$$

Furthermore, $g'_{t1}(V)$ attains its global minimum at $V=V_{t0}$, and

$$g'_{t1}(V_{t0})=2z\Big(zL_d^*-z_3D_3L-\big(zR_d^*-z_3D_3R\big)e^{-zV_{t0}}\Big).$$

Lemma 3.6. *For the function $g_{t1}(V)$, one has*

- (i) *if $g'_{t1}(V_{t0})\geq 0$, then $g'_{t1}(V)\geq 0$ for all V. Furthermore, $g_{t1}(V)$ has a unique zero V_{t1};*
- (ii) *if $g'_{t1}(V_{t0})<0$, then there exist two zeros of $g'_{t1}(V)$, say V_{t2} and V_{t3} with $V_{t2}<V_{t3}$ for convenience. $g_{t1}(V)$ increases on $(-\infty,V_{t2})$, decreases on (V_{t2},V_{t3}), and increases on (V_{t3},∞). $g_{t1}(V)$ attains its local maximum at $V=V_{t2}$ and its local minimum at $V=V_{t3}$. Furthermore,*
  - (ii1) *if $g_{t1}(V_{t2})>0$ and $g_{t1}(V_{t3})=0$, then $g_{t1}(V)$ has two zeros V_{t3} and V_{t4}.*
  - (ii2) *if $g_{t1}(V_{t2})>0$ and $g_{t1}(V_{t3})<0$, then $g_{t1}(V)$ has three zeros V_{t5}, V_{t6} and V_{t7}, for convenience, we assume that $V_{t5}<V_{t6}<V_{t7}$.*
  - (ii3) *if $g_{t1}(V_{t2})>0$ and $g_{t1}(V_{t3})>0$, then $g_{t1}(V)$ has a unique zero V_{t8}.*
  - (ii4) *if $g_{t1}(V_{t2})<0$ and $g_{t1}(V_{t3})<0$, then $g_{t1}(V)$ has a unique zero V_{t9}.*
  - (ii5) *if $g_{t1}(V_{t2})=0$ and $g_{t1}(V_{t3})<0$, then $g_{t1}(V)$ has two zeros V_{t2} and V_{t10}.*

Theorem 3.1. *Assume $B\neq 1$, $A(1-B)>0$ and $Q_0>0$ small. For the leading term $\mathcal{I}_1$ containing the small permanent charge effects, one has*

- (i) *if one of the following conditions holds,*
  - (a) $g'_{t1}(V_{t0})\geq 0$*;*
  - (b) $g'_{t1}(V_{t0})<0$, $g_{t1}(V_{t2})>0$, *and* $g_{t1}(V_{t3})\geq 0$*;*
  - (c) $g'_{t1}(V_{t0})<0$, $g_{t1}(V_{t2})\leq 0$, *and* $g_{t1}(V_{t3})<0$*;*
  - (d) $g'_{t1}(V_{t0})<0$, $g_{t1}(V_{t2})>0$, $g_{t1}(V_{t3})<0$, $f_{t1}(V_{t6})\leq 0$*; and* $f_{t1}(V_{t7})<0$*;*
  - (e) $g'_{t1}(V_{t0})<0$, $g_{t1}(V_{t2})>0$, $g_{t1}(V_{t3})<0$, $f_{t1}(V_{t6})>0$*; and* $f_{t1}(V_{t7})\geq 0$*;*

  where some notations are introduced in the proof, then, there exists a critical V_{g1}^c such that $\mathcal{I}_1$ increases on $\big(-\infty,V_{g1}^c\big)$ and decreases on $\big(V_{g1}^c,+\infty\big)$. Furthermore,
  - (i1) *if $\mathcal{I}_1(V_{g1}^c)>0$, then, $\mathcal{I}_1$ has two zeros V_{g1}^z and V_{g2}^z with $V_{g1}^z<V_{g2}^z$, such that, if $V<V_{g1}^z$ or $V>V_{g2}^z$ (resp. $V_{g1}^z<V<V_{g2}^z$), then $\mathcal{I}_1<0$ (resp. $\mathcal{I}_1>0$);*
  - (i2) *if $\mathcal{I}_1(V_{g1}^c)=0$, then, $\mathcal{I}_1$ has a unique zero V_{g3}^z, in fact, $V_{g3}^z=V_g^{1c}$, such that, if $V<V_{g3}^z$ or $V>V_{g3}^z$, then $\mathcal{I}_1<0$;*
  - (i3) *if $\mathcal{I}_1(V_{g1}^c)<0$, then, for any V, $\mathcal{I}_1<0$.*

(ii) *If* $g'_{t1}(V_{t0})<0$, $g_{t1}(V_{t2})>0$, $g_{t1}(V_{t3})<0$, $f_{t1}(V_{t6})>0$; *and* $f_{t1}(V_{t7})<0$, *then, there exists three critical potentials* V^c_{g2}, V^c_{g3} *and* V^c_{g4}, *such that* $\mathcal{I}_1$ *increases on* $\big(-\infty,V^c_{g2}\big)$, *decreases on* $\big(V^c_{g2},V^c_{g3}\big)$, *increases on* $\big(V^c_{g3},V^c_{g4}\big)$, *and decreases on* $\big(V^c_{g4},+\infty\big)$. *Furthermore,*

(ii1) *if* $\mathcal{I}_1(V^c_{g2})<0$ *and* $\mathcal{I}_1(V^c_{g4})<0$, *then, for any* V, $\mathcal{I}_1<0$;

(ii2) *if* $\mathcal{I}_1(V^c_{g2})<0$ *and* $\mathcal{I}_1(V^c_{g4})=0$, *then,* $\mathcal{I}_1$ *has a unique zero* V^z_{g4}, *in fact,* $V^z_{g4}=V^c_{g4}$, *such that, if* $V\neq V^z_{g4}$, *then* $\mathcal{I}_1<0$;

(ii3) *if* $\mathcal{I}_1(V^c_{g2})<0$ *and* $\mathcal{I}_1(V^c_{g4})>0$, *then,* $\mathcal{I}_1$ *has two zeros* V^z_{g5} *and* V^z_{g6} *with* $V^z_{g5}<V^z_{g6}$, *such that, if* $V<V^z_{g5}$ *or* $V>V^z_{g6}$ *(resp.* $V^z_{g5}<V<V^z_{g6}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*);*

(ii4) *if* $\mathcal{I}_1(V^c_{g2})=0$ *and* $\mathcal{I}_1(V^c_{g4})<0$, *then,* $\mathcal{I}_1$ *has a unique zero* V^z_{g7}, *in fact,* $V^z_{g7}=V^c_{g2}$, *such that, if* $V\neq V^z_{g7}$, *then* $\mathcal{I}_1<0$;

(ii5) *if* $\mathcal{I}_1(V^c_{g2})=0$ *and* $\mathcal{I}_1(V^c_{g4})=0$, *then,* $\mathcal{I}_1$ *has two zeros* V^z_{g8} *and* V^z_{g8} *with* $V^z_{g8}<V^z_{g9}$, *such that, if* $V<V^z_{g8}$ *or* $V>V^z_{g9}$ *or* $V^z_{g8}<V<V^z_{g9}$, *then,* $\mathcal{I}_1<0$;

(ii6) *if* $\mathcal{I}_1(V^c_{g2})=0$ *and* $\mathcal{I}_1(V^c_{g4})>0$, *then,* $\mathcal{I}_1$ *has three zeros* V^z_{g10}, V^z_{g11} *and* V^z_{g12} *with* $V^z_{g10}<V^z_{g11}<V^z_{g12}$, *in fact,* $V^z_{g10}=V^c_{g2}$, *such that, if* $V<V^z_{g10}$ *or* $V>V^z_{g12}$ *or* $V^z_{g10}<V<V^z_{g11}$ *(resp.* $V^z_{g11}<V<V^z_{g12}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*);*

(ii7) *if* $\mathcal{I}_1(V^c_{g2})>0$ *and* $\mathcal{I}_1(V^c_{g4})<0$, *then,* $\mathcal{I}_1$ *has two zeros* V^z_{g13} *and* V^z_{g14} *with* $V^z_{g13}<V^z_{g14}$, *such that, if* $V<V^z_{g13}$ *or* $V>V^z_{g14}$ *(resp.* $V^z_{g13}<V<V^z_{g14}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*);*

(ii8) *if* $\mathcal{I}_1(V^c_{g2})>0$ *and* $\mathcal{I}_1(V^c_{g4})=0$, *then,* $\mathcal{I}_1$ *has three zeros* V^z_{g15}, V^z_{g16} *and* V^z_{g17} *with* $V^z_{g15}<V^z_{g16}<V^z_{g17}$, *in fact,* $V^z_{g17}=V^c_{g4}$, *such that, if* $V<V^z_{g15}$ *or* $V>V^z_{g17}$ *or* $V^z_{g16}<V^z_{g17}$ *(resp.* $V^z_{g15}<V<V^z_{g16}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*);*

(ii9) *if* $\mathcal{I}_1(V^c_{g2})>0$ *and* $\mathcal{I}_1(V^c_{g4})>0$, *then,* $\mathcal{I}_1$ *has four zeros* V^z_{g18}, V^z_{g19}, V^z_{g20}, *and* V^z_{g21} *with* $V^z_{g18}<V^z_{g19}<V^z_{g20}<V^z_{g21}$, *such that, if* $V<V^z_{g18}$ *or* $V>V^z_{g21}$ *or* $V^z_{g19}<V<V^z_{g20}$ *(resp.* $V^z_{g18}<V<V^z_{g19}$ *or* $V^z_{g20}<V<V^z_{g21}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*);*

(ii10) *if* $\mathcal{I}_1(V^c_{g2})>0$ *and* $\mathcal{I}_1(V^c_{g3})=0$, *then,* $\mathcal{I}_1$ *has three zeros* V^z_{g22}, V^z_{g23} *and* V^z_{g24} *with* $V^z_{g22}<V^z_{g23}<V^z_{g24}$, *in fact,* $V^z_{g23}=V^c_{g3}$, *such that, if* $V<V^z_{g22}$ *or* $V>V^z_{g24}$ *(resp.* $V^z_{g22}<V<V^z_{g23}$ *or* $V^z_{g23}<V^z_{g24}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*);*

(ii11) *if* $\mathcal{I}_1(V^c_{g2})>0$ *and* $\mathcal{I}_1(V^c_{g3})>0$, *then,* $\mathcal{I}_1$ *has two zeros* V^z_{g25} *and* V^z_{g26} *with* $V^z_{g25}<V^z_{g26}$, *such that, if* $V<V^z_{g25}$ *or* $V>V^z_{g26}$ *(resp.* $V^z_{g25}<V<V^z_{g26}$*), then,* $\mathcal{I}_1<0$ *(resp.* $\mathcal{I}_1>0$*).*

Proof. The discussion is based on Lemma 3.5 and Lemma 3.6, which consists of two parts. Part one deals with the monotone results for statements (i) and (ii). More precisely, treating $\mathcal{I}_1$ as a function of the potential V, we identify the critical points of $\mathcal{I}$ and study the sign of $\frac{d\mathcal{I}}{dV}$, from which one gets the information of the monotonicity of $\mathcal{I}$. In the second part, we examine the zeroes of $\mathcal{I}$ and its sign.

Part I: Critical potentials and Monotonicity of $\mathcal{I}$. We first focus on the conditions (a)-(e) in (i).

(a) If $g'_{t1}(V_{t0})\geq 0$, from Lemma 3.6, $f'_{t1}(V)$ has two zeros V_1 and V_{t1}. Furthermore, $V_1>V_{t1}$ if $g_{t1}(V_1)>0$; $V_1=V_{t1}$ if $g_{t1}(V_1)=0$; and $V_1<V_{t1}$ if $g_{t1}(V_1)<0$.

For $V_1 < V_{t1}$, one has $f_{t1}(V)$ increases on $(-\infty, V_1)$, decreases on (V_1, V_{t1}), and increases on (V_{t1}, ∞). Note that $f_{t1}(V)$ attains its local maximum at $V = V_1$ and $f_{t1}(V_1) = 0$. Together with $\lim_{V\to-\infty} f_{t1}(V) = -\infty$ and $\lim_{V\to\infty} f_{t1}(V) = \infty$. $f_{t1}(V)$ has an additional zero, say V_g^{1c} with $V_g^{1c} > V_1$. Note also that $g_{t1}(V)$ increases on $(-\infty, V_{t1})$ and $V_1 < V_{t1}$. We have $g_{t1}(V_1) < g_{t1}(V_{t1}) = 0$. Therefore, as $V \to V_1$,

$$\frac{d\mathcal{I}_1}{dV} = \frac{z_3 A(1-B)e^{zV_1} g_{t1}(V_1)}{2(z-z_3)H(1)\left(\ln L - \ln R\right)^2 R} > 0.$$

We conclude that $\frac{d\mathcal{I}_1}{dV} < 0$ for $V > V_g^{1c}$, and $\frac{d\mathcal{I}_1}{dV} > 0$ for $V < V_g^{1c}$. The result also holds for the case with $V_1 \geq V_{t1}$, which can be discussed similarly.

The discussion for (b): $g'_{t1}(V_{t0}) < 0$, $g_{t1}(V_{t2}) > 0$, and $g_{t1}(V_{t3}) \geq 0$; and (c): $g'_{t1}(V_{t0}) < 0$, $g_{t1}(V_{t2}) \leq 0$, and $g_{t1}(V_{t3}) < 0$ follows exactly the same as this in (a).

As for other cases, one has if $g'_{t1}(V_{t0}) < 0$, $g_{t1}(V_{t2}) > 0$ and $g_{t1}(V_{t3}) < 0$, then it follows from Lemma 3.6 that $f'_{t1}(V)$ has four zeros V_1, V_{t5}, V_{t6} and V_{t7}. Without loss of generality, we assume $V_1 < V_{t5} < V_{t6} < V_{t7}$ (other cases can be argued similarly). Then, $f_{t1}(V)$ increases on $(-\infty, V_1)$, decreases on (V_1, V_{t5}), increases on (V_{t5}, V_{t6}), decreases on (V_{t6}, V_{t7}), and increases on (V_{t7}, ∞). Note that f_{t1} attains its local maximum at $V = V_1$, and $f_{t1}(V_1) = 0$. One immediately has $f_{t1}(V_{t5}) < 0$. For the values of $f_{t1}(V_{t6})$ and $f_{t1}(V_{t7})$, one has the following three cases

- $f_{t1}(V_{t6}) \leq 0$ and $f_{t1}(V_{t7}) < 0$ corresponding to case (d) of (i);
- $f_{t1}(V_{t6}) > 0$ and $f_{t1}(V_{t7}) \geq 0$ corresponding to case (e) of (i);
- $f_{t1}(V_{t6}) > 0$ and $f_{t1}(V_{t7}) < 0$ corresponding to the statement (ii).

The discussion for those cases is similar, we take $f_{t1}(V_{t6}) < 0$ and $f_{t1}(V_{t7}) < 0$ for example. It is easy to see that if $f_{t1}(V_{t6}) < 0$ and $f_{t1}(V_{t7}) < 0$, then $f_{t1}(V)$ has two zeros V_1 and V_g^{1c}, from the fact the $f_{t1}(V) \to +\infty$ as $V \to +\infty$. Note that $\frac{d\mathcal{I}_1}{dV} > 0$ as $V \to V_1$, one then has, $\frac{d\mathcal{I}_1}{dV} < 0$ if $V > V_g^{1c}$, and $\frac{d\mathcal{I}_1}{dV} > 0$ if $V < V_g^{1c}$.

Part II: Sign of $\mathcal{I}_1$. Together with the arguments in our first step, the results of the sign of $\mathcal{I}_1$ follow directly from the observation that $\mathcal{I}_1(V) \to -\infty$ as $V \to \pm\infty$. □

Remark 3.1. In Theorem 3.1,

(i) To clarify the notations introduced in this work, we emphasize that for the notation V_{gk}^c and V_{gk}^z in Theorem 3.1, g stands for "general"; c stands for "critical", which corresponds to the critical point of the term $\mathcal{I}_1(V)$; while z stands for "zero", which corresponds to the zero of $\mathcal{I}_1(V) = 0$.

(ii) The critical potentials identified in current work further depend on the nonlinear interaction with other physical parameters involved in the system, which has been analyzed in great details (Lemmas 3.3, 3.4, 3.5, 3.6 and Theorem 3.1). Because of the complexity and the nonlinearity, although explicit expressions of these critical potentials, except some special ones, cannot be obtained, we would like to point out that, for V_{gk}^z, the zeros of $\mathcal{I}_1(V)$, identified in Theorem 3.1, one is able to take an experimental I-V relation as $I(V; Q_0)$ and numerically (or analytically) compute $I_0(V; 0)$ for ideal case which allows one to obtain an estimate of V_{gk}^z by examing the zeros of $I(V; Q_0) - I_0(V; 0)$. The characterization of these critical potentials provides better understanding of the ionic flow properties of interest, and could stimulate further studies on related ion channel problems.

(iii) Our discussion in Theorem 3.1 focuses on the case with $A < 0$ and $1 - B < 0$. Similar discussions can be applied to other cases, such as $A < 0$ and $1-B > 0$, which has been studied in [45] with A replaced by M and B replaced by N.

We finally point out that compared to the work done in [27] for the PNP system with two oppositely charged particles, the qualitative properties of ionic flows studied in current work is more complicated and more rich, and new phenomena are observed (one may also refer to [5] for more details). Take the leading term $\mathcal{I}_1$ that contains the permanent charge effects for example, in [27], it is a quadratic function in the potential V, which has at most two critical potentials $V_q^{\pm}$ such that $\mathcal{I}_1(V_q^{\pm}) = 0$ (the third statement in Theorem 4.15 in [27]), however, in this paper, from (3.9), the following factors is involved in $\mathcal{I}_1(V)$

$$\frac{z\,(V-V_1)\,(V-V_2)}{L-Re^{-zV}}\big(L_d^* - R_d^* e^{-zV}\big) - z_3 D_3\Big(V - \frac{z}{z_3}V_1\Big)\Big(V - \frac{z_3}{z}V_2\Big),$$

from which one is able to obtain *four* zeros ((ii9) in Theorem 3.1). This is not surprising because much more ion interactions are involved in our current system. Both works demonstrate the key role of the permanent charge in the study of ionic flows through membrane channels.

4. Numerical simulations

To better understand the analytical results obtained in current work, we further perform numerical simulations to provide a more intuitive illustrations. To get started, the system (1.1)-(1.9) is rewritten as a system of first order ordinary differential equations. We introduce $u = \varepsilon\dot{\phi}$, it then follows that

$$\begin{aligned}
&\varepsilon\dot{\phi} = u, \quad \varepsilon\dot{u} = -z_1c_1 - z_2c_2 - z_3c_3 - Q(x) - \varepsilon\frac{h_x(x)}{h(x)}u,\\
&\varepsilon\dot{c}_1 = -z_1c_1u - \varepsilon\frac{J_1}{h(x)}, \quad \varepsilon\dot{c}_2 = -z_2c_2u - \varepsilon\frac{J_2}{h(x)}, \quad \varepsilon\dot{c}_3 = -z_3c_3u - \varepsilon\frac{J_3}{h(x)},\\
&\dot{J}_1 = \dot{J}_2 = \dot{J}_3 = 0
\end{aligned} \tag{4.1}$$

with boundary conditions

$$\phi(0) = V,\ c_k(0) = L_k; \quad \phi(1) = 0,\ c_k(1) = R_k,\ k = 1, 2, 3. \tag{4.2}$$

For our simulation to (4.1)-(4.2), we further choose $z_1 = z_2 = -z_3 = 1,\ D_1 = 2,$ $D_2 = 8,\ D_3 = 10,\ a = 0.475,\ b = 0.6266,\ \varepsilon = 0.01,\ Q_0 = 0.01, r_0 = 0.5$

$$Q(x) = \begin{cases} 0, & 0 < x < a,\\ Q_0, & a < x < b,\\ 0, & b < x < 1, \end{cases} \quad \text{and} \quad h(x) = \begin{cases} \pi\big(-x + r_0 + a\big)^2, & 0 \le x < a,\\ \pi r_0^2, & a \le x < b,\\ \pi\big(x + r_0 - b\big)^2, & b \le x < 1. \end{cases} \tag{4.3}$$

For the choice of $h(x)$, please refer to [48] for explanations. Recall that

$$L = L_1 + L_2,\ R = R_1 + R_2,\ L_d^* = D_1L_1 + D_2L_2,\ R_d^* = D_1R_1 + D_2R_2,$$

$$\alpha = \frac{H(a)}{H(1)},\ \beta = \frac{H(b)}{H(1)},\ t = \frac{L}{R}.$$

It follows from $h(x)$ defined in (4.3) that $\alpha = 0.4$ and $\beta = 0.649$.

We point our that our numerical simulations under the above setups are consistent with our analytical results. More precisely, we conduct the following six experiments by choosing different values for L_k and R_k for $k = 1, 2$:

(c1) $L_1 = 24,\ L_2 = 6,\ R_1 = 9$ and $R_2 = 2$,

(c2) $L_1 = 16,\ L_2 = 5,\ R_1 = 1$ and $R_2 = 5$,

(c3) $L_1 = 14.4866,\ L_2 = 3.14,\ R_1 = 1$ and $R_2 = 9$,

(c4) $L_1 = 16.4,\ L_2 = 1,\ R_1 = 1$ and $R_2 = 9$,

(c5) $L_1 = 14.11315,\ L_2 = 1,\ R_1 = 1$ and $R_2 = 9$,

(c6) $L_1 = 15,\ L_2 = 1,\ R_1 = 1$ and $R_2 = 9$.

Our main interest is $\mathcal{I}_1(V;\varepsilon)$, approximation of $\mathcal{I}_1(V;0)$ defined in (3.9) given by

$$\mathcal{I}_1(V;\varepsilon) = \mathcal{I}(V;Q_0;\varepsilon) - \mathcal{I}(V;0;\varepsilon).$$

Our numerical simulations show that

(e1) Case (c1) corresponds to (i1) in Theorem 3.1, see Figure 2;

(e2) Case (c2) corresponds to (ii1) in Theorem 3.1, see Figure 3;

(e3) Case (c3) corresponds to (ii2) in Theorem 3.1, see Figure 4;

(e4) Case (c4) corresponds to (ii3) in Theorem 3.1, see Figure 5;

(e5) Case (c5) corresponds to (ii10) in Theorem 3.1, see Figure 6;

(e6) Case (c6) corresponds to (ii9) in Theorem 3.1, see Figure 7.

The monotonicity and the sign of $\mathcal{I}_1(V;\varepsilon)$ can be seen clearly from the graphs in Figures 2-7.

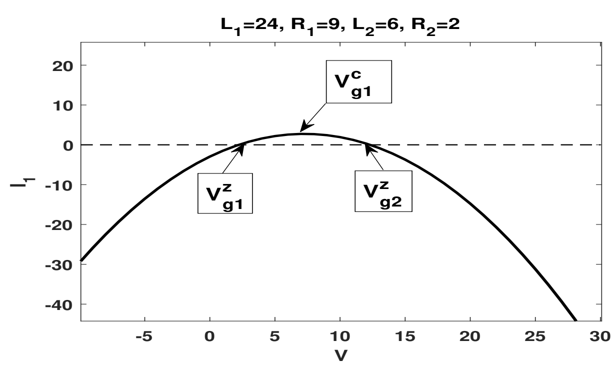

Figure 2. $\mathcal{I}_1(V;\varepsilon)$, the approximation of $\mathcal{I}_1(V)$, has two zeros V^z_{g1} and V^z_{g2}, and a critical point V^c_{g1} with $V^z_{g1} < V^c_{g1} < V^z_{g2}$.

We comment that other cases in Theorem 3.1 can be tested numerically by choosing different boundary concentrations.

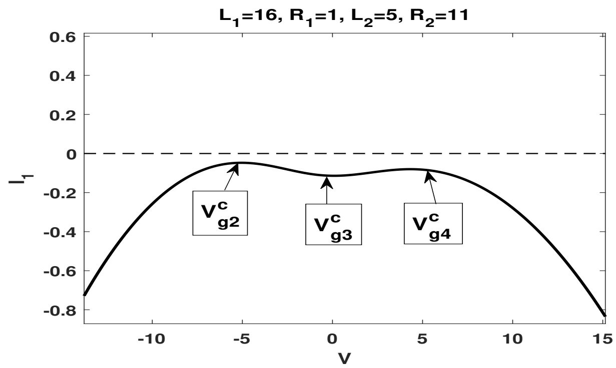

Figure 3. $\mathcal{I}_1(V;\varepsilon)$, the approximation of $\mathcal{I}_1(V)$, has no zeros, but has three critical point V^c_{g2}, V^c_{g3} and V^c_{g4} with $V^c_{g2} < V^c_{g3} < V^c_{g4}$.

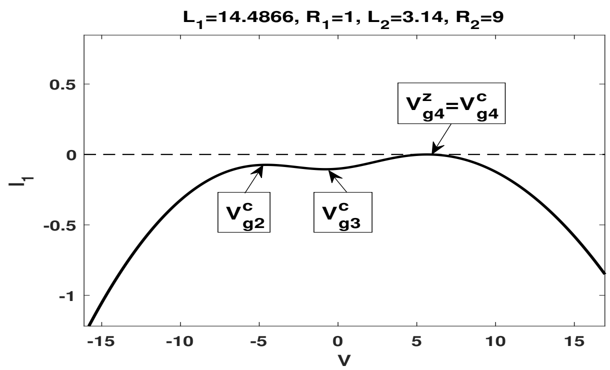

Figure 4. $\mathcal{I}_1(V;\varepsilon)$, the approximation of $\mathcal{I}_1(V)$, has a unique zero V^z_{g4}, and three critical point V^c_{g2}, V^c_{g3} and V^c_{g4} with $V^c_{g2} < V^c_{g3} < V^c_{g4} = V^z_{g4}$.

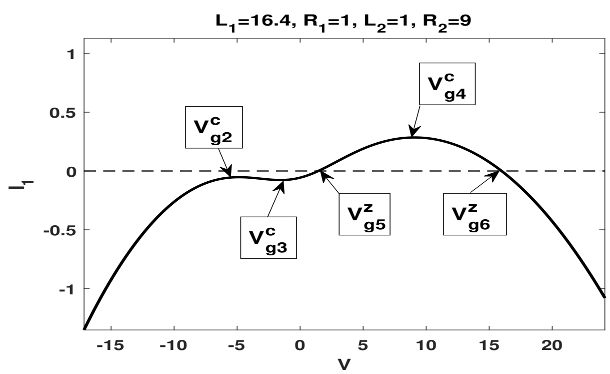

Figure 5. $\mathcal{I}_1(V;\varepsilon)$, the approximation of $\mathcal{I}_1(V)$, has two zeros V^z_{g5} and V^z_{g6} and three critical point V^c_{g2}, V^c_{g3} and V^c_{g4} with $V^c_{g2} < V^c_{g3} < V^z_{g5} < V^c_{g4} < V^z_{g6}$.

5. Concluding remarks

We analyze the Poisson-Nernst-Planck system with two cations having the same valences and one anion, which include small permanent charges. Particularly, we

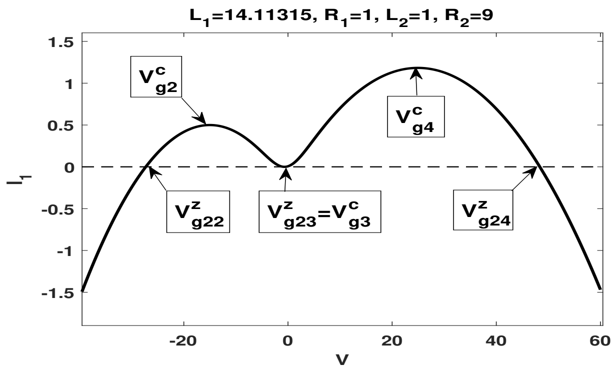

Figure 6. $\mathcal{I}_1(V;\varepsilon)$, the approximation of $\mathcal{I}_1(V)$, has three zeros $V^z_{g22},\ V^z_{g23},\ V^z_{g24}$, and three critical point V^c_{g2}, V^c_{g3} and V^c_{g4} with $V^z_{g22} < V^c_{g2} < V^c_{g3} = V^z_{g23} < V^c_{g4} < V^z_{g24}$.

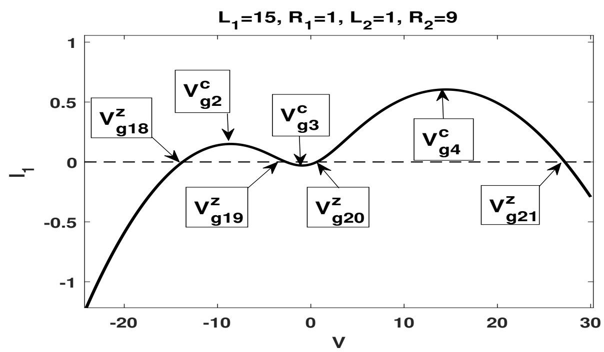

Figure 7. $\mathcal{I}_1(V;\varepsilon)$, the approximation of $\mathcal{I}_1(V)$, has four zeros $V^z_{g18},\ V^z_{g19},\ V^z_{g20},\ V^z_{g21}$ and three critical point V^c_{g2}, V^c_{g3} and V^c_{g4} with $V^z_{g18} < V^c_{g2} < V^z_{g19} < V^c_{g3} < V^z_{g20} < V^c_{g4} < V^z_{g21}$.

study the effects on the I-V relations from the small permanent charge. Detailed analysis is provided, from which one can better understand the dynamics of ionic flows, particularly the internal dynamics, which are non-intuitive and cannot be detected by current technology. The leading term $\mathcal{I}_1(V)$ of the I-V relations that contains small permanent charge effects is analyzed; critical potentials that balance the small permanent charge effects on the I-V relations are identified, and their critical roles played in the study of ionic flow properties are characterized. Numerical simulations are performed to provide more intuitive illustrations of the analytical results, and they are consistent.

Finally, we would like to point out that that the setup in this work is relatively simple, but it is reasonable for synthetic channels, and it is a starting point for further study of more realistic models. The simple model studied allows us to obtain a more explicit expression of the I-V relations in terms of physical parameters of the problem so that we are able to extract concrete information of the effects from nonzero but small permanent charges, which further depends on the nonlinear interaction with other physical parameters. Moreover, the discussion in this simpler setting provides better understanding of the qualitative properties of ionic flows through membrane channels, and detailed characterization of the interplay among different physical parameters involved in the model.

References

[1] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts and D. J. Watson, *Molecular Biology of the Cell,* 3rd ed., Garland, New York, 1994.

[2] V. Barcilon, *Ion flow through narrow membrane channels: Part I*, SIAM J. Appl. Math., 1992, 52, 1391–1404.

[3] J. Barthel, H. Krienke and W. Kunz, *Physical Chemistry of Electrolyte Solutions: Modern Aspects,* Springer-Verlag, New York, 1998.

[4] P. W. Bates, J. Chen and M. Zhang, *Dynamics of ionic flows via Poisson-Nernst-Planck systems with local hard-sphere potentials: Competition between cations,* Math. Biosci. Eng., 2020, 17, 3736–3766.

[5] P. W. Bates, Y. Jia, G. Lin, H. Lu and M. Zhang, *Individual flux study via steady-state Poisson-Nernst-Planck systems: Effects from boundary conditions,* SIAM J. on Appl. Dyn. Syst., 2017, 16, 410–430.

[6] P. W. Bates, Z. Wen and M. Zhang, *Small permanent charge effects on individual fluxes via Poisson-Nernst-Planck models with multiple cations,* J. Nonlinear Sci., 2021, 31, 1–62.

[7] M. Bazant, K. Thornton and A. Ajdari, *Diffuse-charge dynamics in electrochemical systems,* Phys. Review E, 2004, 70, 1–24.

[8] M. Z. Bazant, K. Chu and B. J. Bayly, *Current-voltage relations for electrochemical thin films,* SIAM J. Appl. Math., 2005, 65, 1463–1484.

[9] D. Chen and R. S. Eisenberg, *Charges, currents and potentials in ionic channels of one conformation,* Biophys. J., 1993, 64, 1405–1421.

[10] J. Chen, Y. Wang, L. Zhang and M. Zhang, *Mathematical analysis of Poisson-Nernst-Planck models with permanent charges and boundary layers: Studies on individual fluxes,* Nonlinearity, 2021, 34, 3879–3906.

[11] J. Chen and M. Zhang, *Boundary layer effects on ionic flows via Poisson-Nernst-Planck systems with nonuniform ion sizes,* Discrete Contin. Dyn. Syst., Series B, doi:10.3934/dcdsb.2021312.

[12] B. Eisenberg, *Proteins, Channels, and Crowded Ions,* Biophys. Chem., 2003, 100, 507–517.

[13] B. Eisenberg, *Ions in Fluctuating Channels: Transistors Alive,* Fluctuation and Noise Letters, 2012, 11, 76–96.

[14] B. Eisenberg, *Crowded charges in ion channels,* In Advances in Chemical Physics; Rice, S. A. Ed., John Wiley & Sons: Hoboken, NJ, USA, 2011, 77–223.

[15] R. S. Eisenberg, *From Structure to Function in Open Ionic Channels,* J. Memb. Biol., 1999, 71, 1–24.

[16] B. Eisenberg and W. Liu, *Poisson-Nernst-Planck systems for ion channels with permanent charges,* SIAM J. Math. Anal., 2007, 38, 1932–1966.

[17] B. Eisenberg, W. Liu and H. Xu, *Reversal charge and reversal potential: case studies via classical Poisson-Nernst-Planck models,* Nonlinearity, 2015, 28, 103–128.

[18] D. Gillespie, *A singular perturbation analysis of the Poisson-Nernst-Planck system: Applications to Ionic Channels,* Ph.D Thesis, Rush University at Chicago, Chicago, IL, USA, 1999.

[19] D. Gillespie and R. S. Eisenberg, *Physical descriptions of experimental selectivity measurements in ion channels,* European Biophys. J., 2002, 31, 454–466.

[20] D. Gillespie, W. Nonner and R. S. *Eisenberg, Coupling Poisson-Nernst-Planck and density functional theory to calculate ion flux,* J. Phys. Condens. Matter, 2002, 14, 12129–12145.

[21] L. J. Henderson, *The Fitness of the Environment: an Inquiry Into the Biological Significance of the Properties of Matter,* Macmillan, New York, 1927.

[22] Y. Hyon, B. Eisenberg and C. Liu, *A mathematical model for the hard sphere repulsion in ionic solutions,* Commun. Math. Sci., 2010, 9, 459–475.

[23] Y. Hyon, J. Fonseca, B. Eisenberg and C. Liu, *A new Poisson-Nernst-Planck equation (PNP-FS-IF) for charge inversion near walls,* Biophys. J., 2011, 100, 578a.

[24] W. Im and B. Roux, *Ion permeation and selectivity of OmpF porin: a theoretical study based on molecular dynamics, Brownian dynamics, and continuum electrodiffusion theory,* J. Mol. Biol., 2002, 322, 851–869.

[25] S. Ji and W. Liu, *Poisson-Nernst-Planck Systems for Ion Flow with Density Functional Theory for Hard-Sphere Potential: I-V relations and Critical Potentials. Part I: Analysis,* J. Dyn. Diff. Equat., 2012, 24, 955–983.

[26] S. Ji and W. Liu, *Flux ratios and channel structures,* J. Dynam. Differ. Equations, 2019, 31, 1141–1183.

[27] S. Ji, W. Liu and M. Zhang, *Effects of (small) permanent charges and channel geometry on ionic flows via classical Poisson-Nernst-Planck models,* SIAM J. on Appl. Math., 2015, 75, 114–135.

[28] C. Jones, *Geometric singular perturbation theory,* Dynamical systems (Montecatini Terme, 1994, 44–118. Lect. Notes in Math., 1609. Springer, Berlin, 1995.

[29] G. Lin, W. Liu, Y. Yi and M. Zhang, *Poisson-Nernst-Planck systems for ion flow with density functional theory for local hard-sphere potential,* SIAM J. on Appl. Dyn. Syst., 2013, 12, 1613–1648.

[30] W. Liu, *Geometric singular perturbation approach to steady-state Poisson-Nernst-Planck systems,* SIAM J. Appl. Math., 2005, 65, 754–766.

[31] W. Liu, *One-dimensional steady-state Poisson-Nernst-Planck systems for ion channels with multiple ion species,* J. Differential Equations, 2009, 246, 428–451.

[32] W. Liu, *A flux ratio and a universal property of permanent charges effects on fluxes,* Comput. Math. Biophys., 2018, 6, 28–40.

[33] W. Liu and H. Xu, *A complete analysis of a classical Poisson-Nernst-Planck model for ionic flow,* J. Differential Equations, 2015, 258, 1192–1228.

[34] W. Nonner and R. S. Eisenberg, *Ion permeation and glutamate residues linked by Poisson-Nernst-Planck theory in L-type Calcium channels,* Biophys. J., 1998, 75, 1287–1305.

[35] S. Y. Noskov, S. Berneche and B. Roux, *Control of ion selectivity in potassium channels by electrostatic and dynamic properties of carbonyl ligands.* Nature, 2004, 431 , 830–834.

[36] S. Y. Noskov and B. Roux, *Ion selectivity in potassium channels,* Biophys. Chem., 2006, 124, 279–291.

[37] J. K. Park and J. W. Jerome, *Qualitative properties of steady-state Poisson-Nernst-Planck systems: Mathematical study,* SIAM J. Appl. Math., 1997, 57, 609–630.

[38] B. Roux, T. W. Allen, S. Berneche and W. Im, *Theoretical and computational models of biological ion channels,* Quat. Rev. Biophys., 2004, 37, 15–103.

[39] D. J. Rouston, *Bipolar Semiconductor Devices*, McGraw-Hill, New York, 1990.

[40] Z. Schuss, B. Nadler and R. S. Eisenberg, *Derivation of Poisson and Nernst-Planck equations in a bath and channel from a molecular model,* Phys. Rev. E, 2001, 64, 1–14.

[41] B. G. Streetman, *Solid State Electronic Devices*, 4th ed., Prentice-Hall, Englewood Cliffs, NJ, 1972.

[42] C. Tanford, *Reynolds, J. Nature's Robots: A History of Proteins*, Oxford University Press, New York, 2001.

[43] Y. Wang, L. Zhang and M. Zhang, *Studies on individual fluxes via Poisson-Nernst-Planck models with small permanent charges and partial electroneutrality conditions,* J. Appl. Anal. Comput., doi: 10.11948/20210045.

[44] J. R. M. Warner, *Microelectronics: Its unusual origin and personality,* IEEE Trans. Electron. Devices, 2001, 48, 2457–2467.

[45] Z. Wen, P. W. Bates and M. Zhang, *Effects on I-V relations from small permanent charge and channel geometry via classical Poisson-Nernst-Planck equations with multiple cations,* Nonlinearity, 2021, 34, 4464–4502.

[46] Z. Wen, L. Zhang and M. Zhang, *Dynamics of classical Poisson-Nernst-Planck systems with multiple cations and boundary layers,* J. Dyn. Diff. Equat., 2021, 33, 211–234.

[47] L. Zhang, B. Eisenberg and W. Liu, *An effect of large permanent charge: Decreasing flux with increasing transmembrane potential,* Eur. Phys. J. Special Topics, 2019, 227, 2575–2601.

[48] M. Zhang, *Competition between cations via Poisson-Nernst-Planck systems with nonzero but small permanent charges,* Membranes, 2021, 11, 236.