Asymptotic Expansions of I-V Relations via a Poisson–Nernst–Planck System[*]

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Abstract. We investigate higher order matched asymptotic expansions of a steady-state Poisson–Nernst–Planck (PNP) system with particular attention to the I-V relations of ion channels. Assuming that the Debye length is small relative to the diameter of the narrow channel, the PNP system can be viewed as a singularly perturbed system. Special structures of the zeroth order inner and outer systems make it possible to provide an *explicit* derivation of higher order terms in the asymptotic expansions. For the case of zero permanent charge, our results concerning the I-V relation for two oppositely charged ion species are (i) the first order correction to the zeroth order linear I-V relation is generally *quadratic* in V; (ii) when the electro-neutrality condition is enforced at both ends of the channel, there is NO first order correction, but the second order correction is *cubic* in V. Furthermore (Theorem 3.4), up to the second order, the cubic I-V relation has (except for a very degenerate case) three distinct real roots that correspond to the bistable structure in the FitzHugh–Nagumo simplification of the Hodgkin–Huxley model.

Key words. singular perturbation, matched asymptotic expansion, I-V relations

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1. Introduction. The Poisson–Nernst–Planck (PNP) systems are basic electro-diffusion equations modeling, for example, ion flow through membrane channels and transport of holes and electrons in semiconductors (see, for example, [3, 4, 5, 10, 21, 32, 39, 18, 19, 34, 35]). In the context of ion flow through a membrane channel, the flow of ions is driven by their concentration gradients and by the electric field modeled together by the Nernst–Planck continuity equations, and the electric field is in turn determined by the concentrations through the Poisson equation. The PNP system describes the current flow at low resolution; that is, it is an approximate description of the transport process [3] appropriate when channel selectivity (between different chemical species of ions) is not of importance, as, for example, in the numerous classical studies of the *gramicidin channel* [51] most recently reviewed in [1, 2] (see also [16, 36, 37, 11, 25, 51, 17, 20]). Derivation from a Langevin model of ionic diffusion [42] shows how correlations are approximated in PNP systems and suggests extensions of the PNP approach to deal with selectivity arising from excess chemical potentials [13, 14, 6]. The bio-

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logical properties of a channel called *permeation* can be described by the PNP equations. The biological properties called *selectivity* can be described by the extended PNP equations. Both permeation and selectivity are characterized by the current-voltage (I-V) relation measured experimentally under different ionic conditions.

The domain for the PNP system is a three-dimensional region including both the channel in the middle and the two baths at the ends of the tube. Thus there are some specifics regarding the domain geometry: the middle part of the domain representing the channel is much more narrow than the two ends that represent the two baths. A reasonable model of the domain would be a tubular-like region for the channel and two widely open conical regions for the baths. Another structure of the channel is its permanent charge, which is highly concentrated at the neck (center) of the channel. To capture the essence of the three-dimensional dynamics, one-dimensional PNP systems have been introduced with the key geometry ($h(x)$ in (1.1)) of the three-dimensional domain encoded in the equations. In particular, the following one-dimensional (steady-state) PNP system for n types of ion species was suggested by Nonner and Eisenberg in [32] and is derived in [42] and analyzed in [29] under the assumption that the characteristic radius of the channel is much smaller than its length:

(1.1)
$$\frac{\epsilon^2}{h(x)}\frac{d}{dx}\left(h(x)\frac{d}{dx}\phi\right) = -\sum_{j=1}^{n}\alpha_j c_j - Q(x),$$
$$\frac{dJ_k}{dx} = 0, \quad h(x)\frac{dc_k}{dx} + \alpha_k c_k h(x)\frac{d\phi}{dx} = -J_k, \quad k = 1, 2, \ldots, n.$$

Here the channel is normalized from $x = 0$ to $x = 1$; $h(x)$ is the scaled area function of the cross section of the channel at location x; $Q(x)$ is the permanent charge density; $\epsilon^2 = \lambda/r$, where λ is the Debye length and r is the characteristic radius of the channel; ϕ is the electric potential; and, for each $k = 1, 2, \ldots, n$, c_k is the concentration, α_k is the valence, and J_k is the flux density (scaled by the diffusion constant) of the kth ion species. Note that J_k's are constant since we are considering the steady-state PNP system. The Debye length is customarily computed from the concentrations of ions on one side of the channel or the other, but we note for completeness that in some conditions the concentration of ions in the channel itself is quite different from that in the baths, and so the "local" Debye length (describing the inside of the channel) is quite different as well.

The baths are macroscopic regions in which the concentration of charges is nearly constant (because the dimensions of the reservoirs are macroscopic and so the total number of charges is hardly changed by the flows) and electrical potentials are nearly constant too. It is then natural to impose the following boundary conditions:

(1.2) $\phi(0) = V, \quad c_k(0) = L_k > 0; \quad \phi(1) = 0, \quad c_k(1) = R_k > 0.$

Here V is the electric potential in the bath at the left end relative to that at the right end, and, for $k = 1, 2, \ldots, n$, L_k and R_k are the concentrations of the kth ion species in the left and right baths, respectively.

In our one-dimensional setting, we model the region by a finite interval (normalized to $[0, 1]$). In this way, the interval can be partitioned into several subintervals so that the permanent charge takes large (in magnitude) values in the middle subintervals and small values away

from middle (zero near 0 and 1). There are other choices for the one-dimensional domain. For example, in [44], the whole real line is taken instead of a finite interval, and the boundary conditions are imposed at infinity. These two scalings correspond to different interpretations of relative ratios of different lengths involved in the biological problem. The mathematical treatment would be the same except at the boundaries. At this moment, it is not clear to us which interprets the biology better. Since the types of channels are so rich, we suspect that one scaling is better for certain types of channels and the other is better for other types.

With the setting in (1.1) and (1.2), the *I-V relation* means the dependence of the current $I = \sum \alpha_k J_k$ on the voltage V for fixed L_k's and R_k's. We remark that, in general, the I-V relation is NOT unique (see [30, 38, 39, 45, 46, 10] for $Q \neq 0$ and see [28] even for $Q = 0$). Understanding the nonuniqueness issue is critical for ion channels because nonuniqueness might explain the gating behavior of single channels, which switch suddenly and stochastically from one current level to another [16, 40, 31, 15]. Nonuniqueness is directly related to the stability of the corresponding steady states. The study of the stability problem is beyond the scope of this work. In section 3, we will consider special cases where the I-V relation is indeed unique.

System (1.1) together with the boundary condition (1.2) will be treated as a singular boundary value problem with $\epsilon \ll 1$ as the singular parameter. In, e.g., [5, 12, 27], the zeroth order I-V relation is explicitly obtained for two types of ion species and $Q = 0$ (see [10, 28] for a treatment of general situations and [44, 43] for a treatment using a three-dimensional PNP model). The zeroth order I-V relation, in this case, is linear. Experimental data show clearly a nonlinear I-V relation. But there is not much discussion on the nature of the nonlinearity except the famous Goldman–Hodgkin–Katz (GHK) I-V equation, which has been used to analyze experimental data for nearly 60 years but does not include such useful and necessary parameters as the charge of the channel protein.

It is our goal in this paper to examine higher order asymptotic expansions of the I-V relation. In particular, we are interested in higher order corrections to the zeroth order I-V relation. To obtain higher order asymptotic expansions of the I-V relation requires higher order asymptotic expansion of ϕ and c_k's. Both the classical matched asymptotic expansion method and the geometric singular perturbation method work well for the zeroth order term (see [5, 12, 27]) at least for the special case mentioned above. An advantage of the geometric method is that it also provides a rigorous justification directly of the validity of the zeroth order terms. But, for higher order terms, a direct application of the geometric singular perturbation theory seems not to work. Roughly speaking, it is not clear how to fully incorporate the information on the zeroth order terms in deriving systems for higher order terms. In fact, some natural approaches for higher order terms result in singularly perturbed systems that do not have the so-called *slow manifolds*. We therefore take the classical matched asymptotic expansion approach for higher order terms.

It is known that higher order terms satisfy linear but nonautonomous and nonhomogeneous systems. The homogeneous parts of the linear systems are the same and are nothing but the linearizations of the zeroth order nonlinear system along the zeroth order (inner and outer) solutions. Also known is the fact that it is generally impossible to get explicit solutions of a linear nonautonomous system. A special feature of the problem at hand is that the zeroth order nonlinear system possesses a complete set of integrals, and each integral provides an

integral for the linearization (see Propositions 2.1 and 2.2). It is this feature that allows us to carry out a detailed asymptotic analysis. Theoretically, any order of the asymptotic expansion can be found. But there are several technical difficulties even for obtaining the zeroth order terms; that is, one has to solve some nonlinear algebraic systems that are too complicated to expect explicit solutions in general. As a starting point, we will restrict ourselves to the simplest case where $n = 2$, $h = 1$, $Q = 0$, $\alpha_1 = -\alpha_2 = 1$. From the biological point of view, the most restrictive part of this constraint is $Q = 0$, since many channels have significant permanent charge. However, many channels are analyzed without consideration of permanent charge. The classical channel gramicidin, which has been simulated much more than any other channel we know of, has often been approximated that way [2, 51, 36, 37]. Maltoporin—one of the few channels with known high resolution crystallographic structure—has insignificant permanent charge [50, 24, 7, 49, 41]. Mathematically, this simplification allows us to obtain exact asymptotic expansions and, from those, explicit qualitative properties of I-V relations can be derived. Furthermore, a perturbation argument will allow one to generalize the result to cases where Q is small. Also, as mentioned above, we believe that the approach will work for general cases, say, a piecewise constant Q for quantitative results, particularly with the help of numerics. (This is a project that we will pursue in the future.) It should be clearly understood that some biological phenomena of importance—e.g., selectivity between cations— will not appear until three ions are considered, perhaps with different diffusion coefficients for each ionic type. Readers interested in more general cases may carry out the analysis along the lines of this paper with some extra analysis (see remarks in section 4).

For the special case where $n = 2$, $\alpha_1 = -\alpha_2 = 1$, $h = 1$, and $Q = 0$, our results give a *definite* nonlinear characterization of the I-V relations up to the second order $(O(\epsilon^2))$. More precisely, the first order correction to the zeroth order linear I-V relation is generally *quadratic* in V given in (3.20), but, when the electro-neutrality condition is imposed at both ends of the channel, the first order correction is *zero*. The second order correction is *cubic* in V even with the electro-neutrality condition (see formula (3.26)). Furthermore, the coefficient of the cubic term is always *negative* except for a highly degenerate case (see Theorem 3.4). The importance of this negative sign is that, up to the second order, the cubic I-V function has three distinct real roots—this agrees qualitatively with the I-V relation adopted in the FitzHugh–Nagumo simplification of the Hodgkin–Huxley systems. The existence of three roots of the I-V relation is responsible for the bistable structure in the FitzHugh–Nagumo system and may be related to the instabilities in biological channels called single channel gating [16, 40, 31, 15] and to the instabilities seen by [47, 48] in abiotic nanopores that have fixed structure. It should be pointed out that our analysis via the PNP system describes current flow through a single channel, and the FitzHugh–Nagumo equations (like the Hodgkin–Huxley system) describe an ensemble of channels in a biological membrane. The current through an ensemble of channels is determined by the current through a single channel and the gating process that determines the number of open channels. The FitzHugh–Nagumo equations have not yet been applied to abiotic channels of fixed structure [47, 48] as far as we know.

This paper is organized as follows. In section 2, we derive outer and inner systems for each order in the asymptotic expansions for a general situation. Starting in section 3, we restrict ourselves to the special case and examine the outer and inner expansions and matching. A treatment for the zeroth order is included in subsection 3.1 for completeness, and the first order

expansions and matching are detailed in subsection 3.2. In subsection 3.3, the analysis for the second order is carried out under the electro-neutrality assumption. Possible generalizations of our analysis and some general remarks are discussed in section 4.

For the reader's convenience, we provide a table of some notation to be used in this paper:

$x = 0$: the left end of the channel;
$x = 1$: the right end of the channel;
$\phi(x)$: the electric potential over the channel;
$0 = \phi(1)$: the reference of the potential set at the right end;
$V = \phi(0)$: the relative potential at the left end;
$c_k(x)$: the concentration of the kth ion species over the channel;
$L_k = c_k(0)$: the concentration of the kth ion species at the left end;
$R_k = c_k(1)$: the concentration of the kth ion species at the right end;
$Q(x)$: the permanent charge of the channel;
ε: the singular parameter related to the Debye length;
J_{kj}: the jth order in ε of the kth flux density;
$J_k = \sum_j \varepsilon^j J_{kj}$: the flux density of the kth ion species;
$T_j = \sum_k J_{kj}$: the jth order in ε of the diffusion flux density;
$I_j = \sum_k \alpha_k J_{kj}$: the jth order in ε of the current density;
$T = \sum_j \varepsilon^j T_j$: the diffusion flux density;
$I = \sum_j \varepsilon^j I_j$: the current density;
I-V relation: the dependence of I on V for fixed L_k, R_k, and Q.

2. Systems for asymptotic expansions.
In this section, we derive the outer and inner systems for the asymptotic expansions and describe the matching principle to be employed. The outer systems govern the dynamics of ion flows within the channel, and the inner systems determine the potential boundary layers representing the effects of boundary conditions coming from the bath conditions. The matching principle then provides the interaction between the boundary conditions and the internal dynamics. In this sense, the boundary layers model the channel-bath interfaces. The process is standard but we will point out two special structures, (2.4) and Proposition 2.1, that allow us to obtain explicit information.

2.1. Outer systems for each order.
We assume Q is constant and look for outer expansion of the form, for $k = 1, 2, \ldots, n$,

$$
\begin{aligned}
\phi(x; \epsilon) &= \phi_0(x) + \epsilon \phi_1(x) + \epsilon^2 \phi_2(x) + \cdots, \\
c_k(x; \epsilon) &= c_{k0}(x) + \epsilon c_{k1}(x) + \epsilon^2 c_{k2}(x) + \cdots, \\
J_k &= J_{k0} + \epsilon J_{k1} + \epsilon^2 J_{k2} + \cdots.
\end{aligned}
$$
(2.1)

Substituting (2.1) into (1.1) and denoting the derivatives with respect to x by overdots, with the convention that $\phi_{-1} = \phi_{-2} = 0$, $\delta_0 = 1$, and $\delta_j = 0$ for $j \neq 0$, the jth order system is

$$
\begin{aligned}
\ddot{\phi}_{j-2} + h^{-1}(x) h_x(x) \dot{\phi}_{j-2} &= -\sum_{l=1}^{n} \alpha_l c_{lj} - \delta_j Q, \\
\dot{c}_{kj} &= -\sum_{p+q=j} \alpha_k c_{kp} \dot{\phi}_q - h^{-1}(x) J_{kj}.
\end{aligned}
$$
(2.2)

Upon introducing $u_j = h(x)\dot{\phi}_j$, system (2.2) becomes

$$\dot{\phi}_{j-2} = h^{-1}(x)u_{j-2},$$

(2.3)
$$\dot{u}_{j-2} = -h(x)\sum_{l=1}^{n}\alpha_l c_{lj} - \delta_j h(x)Q,$$

$$\dot{c}_{kj} = -h^{-1}(x)\sum_{p+q=j}\alpha_k c_{kp}u_q - h^{-1}(x)J_{kj}.$$

An observation is that the homogeneous part for $\mathcal{C}_j = (c_{1j}, \ldots, c_{nj})^T$ is

(2.4)
$$\dot{\mathcal{C}}_j = -\frac{u_0(x)}{h(x)}\mathcal{D}\mathcal{C}_j = -\dot{\phi}_0(x)\mathcal{D}\mathcal{C}_j,$$

where $\mathcal{D} = \text{diag}\{\alpha_1, \ldots, \alpha_n\}$ is a diagonal matrix. Once $\phi_0(x)$ is found, system (2.4) can be simply integrated:

$$\mathcal{C}_j(x) = \text{diag}\left\{e^{-\alpha_1(\phi_0(x)-\phi_0(0))}, \ldots, e^{-\alpha_n(\phi_0(x)-\phi_0(0))}\right\}\mathcal{C}_j(0).$$

Hence, system (2.3) can be solved by the method of variation of parameters.

2.2. Inner systems for each order. There will be two sets of inner systems, one at the boundary $x = 0$ and the other at the boundary $x = 1$.

2.2.1. Inner systems at the boundary $x = 0$. At the boundary $x = 0$, in terms of the inner variable $\xi = x/\epsilon$, let $\Phi(\xi; \epsilon) = \phi(\epsilon\xi; \epsilon)$, $C_k(\xi; \epsilon) = c_k(\epsilon\xi; \epsilon)$. System (1.1) becomes, for $k = 1, 2, \ldots, n$,

(2.5)
$$h^{-1}(\epsilon\xi)\frac{d}{d\xi}\left(h(\epsilon\xi)\frac{d}{d\xi}\Phi\right) = -\sum_{l=1}^{n}\alpha_l C_l - Q, \quad \frac{dJ_k}{d\xi} = 0,$$

$$h(\epsilon\xi)\frac{dC_k}{d\xi} + \alpha_k C_k h(\epsilon\xi)\frac{d\Phi}{d\xi} = -\epsilon J_k.$$

We look for the inner expansion of the form

(2.6)
$$\Phi(\xi; \epsilon) = \Phi_0(\xi) + \epsilon\Phi_1(\xi) + \epsilon^2\Phi_2(\xi) + \cdots,$$
$$C_k(\xi; \epsilon) = C_{k0}(\xi) + \epsilon C_{k1}(\xi) + \epsilon^2 C_{k2}(\xi) + \cdots,$$
$$J_k = J_{k0} + \epsilon J_{k1} + \epsilon^2 J_{k2} + \cdots.$$

Set

$$h(\epsilon\xi) = \sum_{p=0}\epsilon^p r_p^0\xi^p, \quad h^{-1}(\epsilon\xi) = \sum_{p=0}\epsilon^p s_p^0\xi^p,$$

where

$$r_p^0 = \frac{1}{p!}\frac{d^p h}{dx^p}(0) \quad \text{and} \quad s_p^0 = \frac{1}{p!}\frac{d^p h^{-1}}{dx^p}(0).$$

Denote by primes the derivatives with respect to ξ, and substitute (2.6) into (2.5) to get, for each $j = 0, 1, \ldots,$

(2.7)
$$\sum_{p+q+l=j} s_p^0 \xi^p (r_q^0 \xi^q \Phi_l')' = -\sum_{l=1}^n \alpha_l C_{lj} - \delta_j Q,$$
$$C_{kj}' = -\sum_{p+q=j} \alpha_k C_{kp} \Phi_q' - \sum_{p+q=j-1} s_p^0 \xi^p J_{kq}.$$

By introducing $U_j = a_0 \Phi_j'$, we recast system (2.7) as

(2.8)
$$\Phi_j' = s_0^0 U_j, \quad U_j' = -r_0^0 \sum_{l=1}^n \alpha_l C_{lj} - \delta_j r_0^0 Q,$$
$$C_{kj}' = -s_0^0 \sum_{p+q=j} \alpha_k C_{kp} U_q - \sum_{p+q=j-1} s_p^0 \xi^p J_{kq}.$$

For $j = 0$, the system is

(2.9)
$$\Phi_0' = s_0^0 U_0, \quad U_0' = -r_0^0 \sum_{l=1}^n \alpha_l C_{l0} - r_0^0 Q, \quad C_{k0}' = -s_0^0 \alpha_k C_{k0} U_0,$$

and, for all $j \geq 1$, system (2.8) has the same homogeneous part that is the linearization of the zeroth order system (2.9).

A specific structure of system (2.9) is revealed in the following.

Proposition 2.1. *The zeroth order inner system* (2.9) *has a complete set of* $(n+1)$ *first integrals given by, for* $k = 1, 2, \ldots, n,$

$$H_k = C_{k0} e^{\alpha_k \Phi_0}, \quad H_{n+1} = \frac{s_0^0}{2r_0^0} U_0^2 - \sum_{l=1}^n C_{l0} + Q \Phi_0.$$

Proof. This can be verified directly (see also [28]). ∎

A crucial result is given below. We believe it is known but did not find a reference in the literature.

Proposition 2.2. *Consider an autonomous system*

(2.10)
$$z' = f(z), \quad z \in \mathbf{R}^m.$$

For a solution $z_0(t)$ of (2.10)*, consider the linearization along $z_0(t)$:*

(2.11)
$$Z' = Df(z_0(t))Z, \quad Z \in \mathbf{R}^m.$$

If a C^2 function $H : \mathbf{R}^m \to \mathbf{R}$ is an integral of system (2.10) *(that is, $H(z(t))$ is independent of t for any solution $z(t)$ of* (2.10)*), then $G(Z, t) = \langle \nabla H(z_0(t)), Z \rangle$ is an integral of the linear system* (2.11) *(that is, $G(Z(t), t)$ is independent of t for any solution $Z(t)$ of* (2.11)*).*

Proof. Since H is an integral of (2.10), $\frac{d}{dt}H(z(t)) = 0$ for all t, or

$$\langle \nabla H(z), f(z) \rangle = \sum_j \partial_j H(z) f_j(z) = 0$$

for all $z \in \mathbf{R}^m$. For any $k = 1, 2, \ldots, m$, take the partial derivative with respect to z_k to get

$$(2.12) \qquad \sum_j \left(\partial^2_{kj} H(z) f_j(z) + \partial_j H(z) \partial_k f_j(z) \right) = 0.$$

As a consequence of (2.12), a computation gives that $\frac{d}{dt}G(Z(t), t) = 0$. ∎

As noted, the homogeneous part of (2.8) for $j \geq 1$ is the linearization of the zeroth order system (2.9); one can combine Propositions 2.1 and 2.2 to derive a complete set of integrals for the homogeneous part of (2.8). An application of variation of parameters allows one to get a closed form for the solutions of (2.8). For the general case presented in this section, certain technical difficulties arise in evaluating integrals explicitly. This is the main reason that, in section 3, we will restrict our analysis to a simple case.

2.2.2. Inner systems at the boundary $x = 1$. At the boundary $x = 1$, we use the inner variable $\xi = (-1 + x)/\epsilon$. Set $\Psi(\xi; \epsilon) = \phi(1 + \epsilon\xi; \epsilon)$ and $D_k(\xi; \epsilon) = c_k(1 + \epsilon\xi; \epsilon)$. We will then look for the inner expansion of the form:

$$(2.13) \qquad \begin{aligned} \Psi(\xi; \epsilon) &= \Psi_0(\xi) + \epsilon\Psi_1(\xi) + \epsilon^2\Psi_2(\xi) + \cdots, \\ D_k(\xi; \epsilon) &= D_{k0}(\xi) + \epsilon D_{k1}(\xi) + \epsilon^2 D_{k2}(\xi) + \cdots, \\ J_k &= J_{k0} + \epsilon J_{k1} + \epsilon^2 J_{k2} + \cdots. \end{aligned}$$

In the same way as that for the boundary $x = 0$, one has, for each j,

$$(2.14) \qquad \begin{aligned} \sum_{p+q+l=j} s_p^1 \xi^p (r_q^1 \xi^q \Psi_l')' &= -\sum_{l=1}^n \alpha_l D_{lj} - \delta_j Q, \\ D_{kj}' &= -\sum_{p+q=j} \alpha_k D_{kp} \Psi_q' - \sum_{p+q=j-1} s_p^1 \xi^p J_{kq}, \end{aligned}$$

where

$$r_p^1 = \frac{1}{p!} \frac{d^p h}{dx^p}(1) \quad \text{and} \quad s_p^1 = \frac{1}{p!} \frac{d^p h^{-1}}{dx^p}(1).$$

By introducing $V_j = r_0^1 \Psi_j'$, we get

$$(2.15) \qquad \begin{aligned} \Psi_j' &= s_0^1 V_j, \quad V_j' = -r_0^1 \sum_{l=1}^n \alpha_l D_{lj} - \delta_j r_0^1 Q, \\ D_{kj}' &= -s_0^1 \sum_{p+q=j} \alpha_k D_{kp} V_q - \sum_{p+q=j-1} s_p^1 \xi^p J_{kq}. \end{aligned}$$

2.3. Asymptotic matching principle. To piece together the inner solution and outer solution, one needs matching principles. There are two mainstreams in matching. One is the method of *intermediate matching* of Kaplun and Lagerstrom and the other is the *asymptotic matching principle* of Van Dyke (see [8, 9, 22, 23, 26]). The method of intermediate matching is based rigorously on the so-called *extension theorems*, but in general the implementation is more complicated than that of the asymptotic matching principle. The asymptotic matching principle, with a suitable hypothesis, can be also rigorously justified. It turns out that, for the problem handled in this paper, the so-called *outer manifold* is normally hyperbolic [10, 27], and Van Dyke's principle of asymptotic matching is justified (see, for example, [33]). We will thus use the asymptotic matching principle for our matching purpose.

To state the principle of asymptotic matching, we recall the notion of *kth order expansion operators* E_x^k and E_ξ^k in [26]: if, in terms of the outer variable x, $g(x;\epsilon) = \sum_{j=0}^\infty \epsilon^j g_j(x)$ and, in terms of the inner variable $\xi = x/\epsilon$, $f(\xi;\epsilon) = \sum_{j=0}^\infty \epsilon^j f_j(\xi)$, then

$$E_x^k(g(x;\epsilon)) = \sum_{j=0}^k \epsilon^j g_j(x), \quad E_\xi^k(f(\xi;\epsilon)) = \sum_{j=0}^k \epsilon^j f_j(\xi).$$

To match f and g up to the kth order at $x = 0$, one needs to express both $E_x^k(g(x;\epsilon))$ and $E_\xi^k(f(\xi;\epsilon))$ in the same variable. For example, to express $E_x^k(g(x;\epsilon)) = \sum_{j=0}^k \epsilon^j g_j(x)$ in terms of ξ, one replaces x by $\epsilon\xi$ in $g_j(x)$ and rewrites the expansion, say,

$$E_x^k(g(x;\epsilon)) = \sum_{j=0}^k \epsilon^j g_j(\epsilon\xi) = \sum_{j=0}^\infty \epsilon^j h_j(\xi);$$

in particular,

$$E_\xi^k E_x^k(g(x;\epsilon)) = \sum_{j=0}^k \epsilon^j h_j(\xi).$$

The kth order asymptotic matching principle for f and g at $x = 0$ is (see, for example, [8, 26]), in terms of the inner variable ξ,

(2.16) $$E_\xi^k(f) = E_\xi^k E_x^k(g); \quad \text{that is,} \quad f_j(\xi) = h_j(\xi) \ \text{for} \ j = 0, 1, \ldots, k.$$

3. Matched asymptotic expansion: Case study. In this section, we will derive the matched asymptotic expansions for the case where $n = 2$, $\alpha_1 = -\alpha_2 = 1$, $Q = 0$, and $h = 1$. The zeroth order I-V relation turns out to be linear in V. While the first order correction is quadratic in V in general, it is zero when both ends are electro-neutral ($L_1 = L_2$ and $R_1 = R_2$). For this reason, we also carried out the analysis for the second order terms of the I-V relation under the electro-neutrality conditions and found that the I-V relation is a cubic in V.

For convenience, we set

(3.1) $$I_j = \sum \alpha_k J_{kj} \quad \text{and} \quad T_j = \sum J_{kj}.$$

We point out that our main interest in the I-V relation is to derive the asymptotic expansion $I = I_0 + \epsilon I_1 + \epsilon^2 I_2 + \cdots$.

3.1. Zeroth order I-V relation. The zeroth order has been obtained in [5] using the asymptotic expansion method and in [27] using the geometric singular perturbation method. Here we rederive the zeroth order terms explicitly. This is crucial for an explicit formulation of higher order terms in the asymptotic expansions.

3.1.1. Zeroth order outer solution. From (2.3), the zeroth order outer system reads

$$(3.2) \qquad 0 = c_{10} - c_{20}, \quad \dot{c}_{10} = -c_{10}\dot{\phi}_0 - J_{10}, \quad \dot{c}_{20} = c_{20}\dot{\phi}_0 - J_{20}.$$

It is easy to solve system (3.2) to deduce

$$(3.3) \qquad c_{10}(x) = c_{20}(x) = \frac{a_0 - T_0 x}{2}, \quad \phi_0(x) = b_0 + \frac{I_0}{T_0} \ln|a_0 - T_0 x|$$

for some constants a_0 and b_0 to be determined through matching. Here $I_0 = J_{10} - J_{20}$ and $T_0 = J_{10} + J_{20}$ from (3.1).

3.1.2. Zeroth order inner solution. At the boundary $x = 0$, the zeroth order inner system (2.8) is

$$(3.4) \qquad \begin{aligned} \Phi_0'(\xi) &= U_0, \quad U_0'(\xi) = -C_{10} + C_{20}, \\ C_{10}'(\xi) &= -C_{10}U_0, \quad C_{20}'(\xi) = C_{20}U_0. \end{aligned}$$

In this case, Proposition 2.1 reads as follows.

Proposition 3.1. *System* (3.4) *has three first integrals given by*

$$H_1 = C_{10}e^{\Phi_0}, \quad H_2 = C_{20}e^{-\Phi_0}, \quad H_3 = \frac{1}{2}U_0^2 - C_{10} - C_{20}.$$

One can then solve system (3.4) explicitly (see [5, 27]) to get

$$(3.5) \qquad \begin{aligned} \Phi_0 &= V + \frac{1}{2}\ln\frac{L_1}{L_2} + \ln\left(\frac{1 + le^{-\sqrt{M}\xi}}{1 - le^{-\sqrt{M}\xi}}\right)^2, \qquad U_0 = -\frac{4l\sqrt{M}e^{-\sqrt{M}\xi}}{1 - l^2 e^{-2\sqrt{M}\xi}}, \\ C_{10} &= \sqrt{L_1 L_2}\left(\frac{1 - le^{-\sqrt{M}\xi}}{1 + le^{-\sqrt{M}\xi}}\right)^2, \qquad C_{20} = \sqrt{L_1 L_2}\left(\frac{1 + le^{-\sqrt{M}\xi}}{1 - le^{-\sqrt{M}\xi}}\right)^2, \end{aligned}$$

where

$$M = 2\sqrt{L_1 L_2}, \quad l = \frac{L_2^{1/4} - L_1^{1/4}}{L_2^{1/4} + L_1^{1/4}}.$$

Similarly, at the boundary $x = 1$ with $\xi = (x - 1)/\epsilon$, we have

$$(3.6) \qquad \begin{aligned} \Psi_0(\xi) &= \frac{1}{2}\ln\frac{R_1}{R_2} + \ln\left(\frac{1 + re^{\sqrt{N}\xi}}{1 - re^{\sqrt{N}\xi}}\right)^2, \qquad V_0(\xi) = \frac{4r\sqrt{N}e^{\sqrt{N}\xi}}{1 - r^2 e^{2\sqrt{N}\xi}}, \\ D_{10}(\xi) &= \sqrt{R_1 R_2}\left(\frac{1 - re^{\sqrt{N}\xi}}{1 + re^{\sqrt{N}\xi}}\right)^2, \qquad D_{20}(\xi) = \sqrt{R_1 R_2}\left(\frac{1 + re^{\sqrt{N}\xi}}{1 - re^{\sqrt{N}\xi}}\right)^2, \end{aligned}$$

where

$$N = 2\sqrt{R_1 R_2}, \quad r = \frac{R_2^{1/4} - R_1^{1/4}}{R_2^{1/4} + R_1^{1/4}}.$$

3.1.3. Zeroth order matching.
In view of the matching principle (2.16), the matching conditions at the boundary $x = 0$ are

$$E_\xi^0 E_x^0(c_k) = E_\xi^0(C_k) \quad \text{and} \quad E_\xi^0 E_x^0(\phi) = E_\xi^0(\Phi).$$

From (3.3) and (3.5), we get

$$E_\xi^0 E_x^0(c_k) = \frac{a_0}{2}, \quad E_\xi^0 E_x^0(\phi) = b_0 + \frac{I_0}{T_0} \ln a_0,$$

$$E_\xi^0(C_k) = \sqrt{L_1 L_2}, \quad E_\xi^0(\Phi) = V + \frac{1}{2} \ln \frac{L_1}{L_2}.$$

The matching gives

(3.7) $$a_0 = 2\sqrt{L_1 L_2} \quad \text{and} \quad b_0 = V + \frac{1}{2} \ln \frac{L_1}{L_2} - \frac{I_0}{T_0} \ln(2\sqrt{L_1 L_2}).$$

Similarly, the matching at the boundary $x = 1$ requires

(3.8) $$a_0 - T_0 = 2\sqrt{R_1 R_2} \quad \text{and} \quad b_0 + \frac{I_0}{T_0} \ln(a_0 - T_0) = \frac{1}{2} \ln \frac{R_1}{R_2}.$$

We deduce, from (3.7) and (3.8), that

(3.9)
$$T_0 = 2\sqrt{L_1 L_2} - 2\sqrt{R_1 R_2},$$
$$I_0 = \frac{2(\sqrt{L_1 L_2} - \sqrt{R_1 R_2})(2V + \ln(L_1 R_2) - \ln(L_2 R_1))}{\ln(L_1 L_2) - \ln(R_1 R_2)}.$$

In particular, at the zeroth order, the I-V relation $I_0 = I_0(V)$ is *linear* in V. When $L_1 = L_2 = L$ and $R_1 = R_2 = R$ (electro-neutrality condition at both ends of the channel) hold, we have

(3.10) $$T_0 = 2(L - R), \quad I_0 = \frac{2(L - R)}{\ln L - \ln R} V.$$

Note also that, as $L \to R$, we have $T_0 \to 0$ and $I_0 \to 2RV$.

3.2. First order I-V relation.
Since the higher order outer systems (2.3) and inner systems (2.8) and (2.15) are nonautonomous, one cannot solve them explicitly in general. The upshot for our problem is that they can actually be solved explicitly. For inner systems, the solvability is due to Propositions 2.2 and 3.1.

3.2.1. First order outer solution.
From (2.3), the first order outer system is

(3.11) $$c_{11} = c_{21}, \quad \dot{c}_{11} = -(c_{10}\dot\phi_1 + c_{11}\dot\phi_0) - J_{11}, \quad \dot{c}_{21} = (c_{20}\dot\phi_1 + c_{21}\dot\phi_0) - J_{21}.$$

Recall, from (3.1), that $T_1 = J_{11} + J_{21}$ and $I_1 = J_{11} - J_{21}$. Using (3.3) for $(\phi_0(x), c_{10}(x), c_{20}(x))$, one solves system (3.11) to get

$$c_{11}(x) = c_{21}(x) = \frac{a_1 - T_1 x}{2},$$

$$\phi_1(x) = b_1 + \frac{T_0 I_1 - I_0 T_1}{T_0^2} \ln|a_0 - T_0 x| + \frac{I_0(a_1 T_0 - a_0 T_1)}{T_0^2(a_0 - T_0 x)}$$

for some unknown constants a_1 and b_1.

3.2.2. First order inner solution. The first order inner system (2.8) at $x = 0$ is

$$(3.12) \qquad \begin{aligned} \Phi_1' &= U_1, \quad U_1' = -(C_{11} - C_{21}), \\ C_{11}' &= -(C_{10}U_1 + C_{11}U_0) - J_{10}, \quad C_{21}' = (C_{20}U_1 + C_{21}U_0) - J_{20}. \end{aligned}$$

As an application of Propositions 2.2 and 3.1, we have the next result.

  Proposition 3.2. The homogeneous part of (3.12) *has the following integrals:*

$$\begin{aligned} G_1^h &= C_{11}e^{\Phi_0} + C_{10}e^{\Phi_0}\Phi_1, \\ G_2^h &= C_{21}e^{-\Phi_0} - C_{20}e^{-\Phi_0}\Phi_1, \\ G_3^h &= U_0U_1 - C_{11} - C_{21}. \end{aligned}$$

The full system (3.12) *has the following integrals:*

$$\begin{aligned} G_1 &= C_{11}e^{\Phi_0} + C_{10}e^{\Phi_0}\Phi_1 + J_{10}F_1(\xi), \\ G_2 &= C_{21}e^{-\Phi_0} - C_{20}e^{-\Phi_0}\Phi_1 + J_{20}F_2(\xi), \\ G_3 &= U_0U_1 - C_{11} - C_{21} - T_0\xi, \end{aligned}$$

where

$$\begin{aligned} F_1(\xi) &= \int_0^\xi e^{\Phi_0(s)}ds = -\sqrt{\frac{L_1}{L_2}}\frac{e^V}{\sqrt{M}}\left(\frac{4}{1 - le^{-\sqrt{M}\xi}} - \frac{4}{1 - l} - \sqrt{M}\xi\right), \\ F_2(\xi) &= \int_0^\xi e^{-\Phi_0(s)}ds = -\sqrt{\frac{L_2}{L_1}}\frac{e^{-V}}{\sqrt{M}}\left(\frac{4}{1 + le^{-\sqrt{M}\xi}} - \frac{4}{1 + l} - \sqrt{M}\xi\right). \end{aligned}$$

  Proof. The first statement for the homogeneous part of system (3.12) follows from Propositions 2.2 and 3.1. The extra terms in the second statement are obtained by adding trial functions and forcing the resulting functions to be integrals of (3.12). This leads to

$$F_1(\xi) = \int_0^\xi e^{\Phi_0(s)}ds \quad \text{and} \quad F_2(\xi) = \int_0^\xi e^{-\Phi_0(s)}ds.$$

Direct integrations with Φ_0 in (3.5) give the explicit expressions for $F_1(\xi)$ and $F_2(\xi)$ as claimed. ■

  One can then use the integrals to solve system (3.12). Note that we have the initial conditions $\Phi_1(0) = 0$ and $C_{11}(0) = C_{21}(0) = 0$, but $U_1(0)$ has to be determined via matching. One finds, after careful integrations,

$$\begin{aligned} U_1(\xi) &= \frac{U_0(0)U_1(0) - (C_{10} - C_{20})\Phi_1 - J_{10}e^{-\Phi_0}F_1 - J_{20}e^{\Phi_0}F_2 + T_0\xi}{U_0}, \\ (3.13) \qquad \Phi_1(\xi) &= -\frac{4l(T_0 + lI_0)}{M^{3/2}(1 + l)(1 - l)} - \frac{I_0}{M}\xi \\ &\quad + \frac{1}{2\sqrt{M}}\left(U_1(0) + \frac{I_0 + lT_0}{(1 + l)(1 - l)M}\right)e^{\sqrt{M}\xi} + o(e^{-\sqrt{M}\xi}). \end{aligned}$$

The term involving $e^{\sqrt{M}\xi}$ should disappear due to matching. Thus,

$$U_1(0) = -\frac{I_0 + lT_0}{(1+l)(1-l)M}.$$

In summary, we have

$$(3.14) \qquad \begin{aligned} \Phi_1(\xi) &= -\frac{4l(T_0 + lI_0)}{M^{3/2}(1+l)(1-l)} - \frac{I_0}{M}\xi + o(e^{-\sqrt{M}\xi}), \\ C_{11}(\xi) &= -\frac{2l(I_0 + lT_0)}{\sqrt{M}(1+l)(1-l)} - \frac{T_0}{2}\xi + o(e^{-\sqrt{M}\xi}), \\ C_{21}(\xi) &= -\frac{2l(I_0 + lT_0)}{\sqrt{M}(1+l)(1-l)} - \frac{T_0}{2}\xi + o(e^{-\sqrt{M}\xi}). \end{aligned}$$

Similarly, at $x = 1$ with $x - 1 = \epsilon\xi$, we have

$$(3.15) \qquad \begin{aligned} \Psi_1(\xi) &= -\frac{4r(T_0 + rI_0)}{N^{3/2}(1+r)(1-r)} - \frac{I_0}{N}\xi + o(e^{-\sqrt{N}\xi}), \\ D_{11}(\xi) &= -\frac{2r(I_0 + rT_0)}{\sqrt{N}(1+r)(1-r)} - \frac{T_0}{2}\xi + o(e^{-\sqrt{N}\xi}), \\ D_{21}(\xi) &= -\frac{2r(I_0 + rT_0)}{\sqrt{N}(1+r)(1-r)} - \frac{T_0}{2}\xi + o(e^{-\sqrt{N}\xi}). \end{aligned}$$

3.2.3. First order matching. We first consider the matching near $x = 0$. For the inner expansion, we have, from (3.5) and (3.14), for $k = 1, 2$,

$$(3.16) \qquad \begin{aligned} E_\xi^1(\Phi) &= E_\xi^1(\Phi_0(\xi) + \epsilon\Phi_1(\xi)) \\ &= V + \frac{1}{2}\ln\frac{L_1}{L_2} - \epsilon\left(\frac{4l(T_0 + lI_0)}{M^{3/2}(1+l)(1-l)} + \frac{I_0}{M}\xi\right), \\ E_\xi^1(C_k) &= E_\xi^1(C_{k0}(\xi) + \epsilon C_{k1}(\xi)) \\ &= \sqrt{L_1 L_2} - \epsilon\left(\frac{2l(I_0 + lT_0)}{\sqrt{M}(1+l)(1-l)} + \frac{T_0}{2}\xi\right). \end{aligned}$$

On the other hand, for the outer expansion, we have

$$\begin{aligned} E_x^1(\phi) &= E_x^1(\phi_0(x) + \epsilon\phi_1(x)) = b_0 + \frac{I_0}{T_0}\ln a_0 - \frac{I_0}{a_0}x \\ &\quad + \epsilon\left(b_1 + \frac{T_0 I_1 - I_0 T_1}{T_0^2}\ln a_0 + \frac{I_0(a_1 T_0 - a_0 T_1)}{T_0^2 a_0} + O(x)\right), \\ E_x^1(c_k) &= E_x^1(c_{k0}(x) + \epsilon c_{k1}(x)) = \left(\frac{a_0}{2} - \frac{T_0}{2}x\right) + \epsilon\left(\frac{a_1}{2} - \frac{T_1}{2}x\right). \end{aligned}$$

Therefore, in terms of the inner variable ξ,

$$
\begin{aligned}
E_\xi^1 E_x^1(\phi) &= b_0 + \frac{I_0}{T_0} \ln a_0 \\
&+ \epsilon \left(b_1 + \frac{T_0 I_1 - I_0 T_1}{T_0^2} \ln a_0 + \frac{I_0(a_1 T_0 - a_0 T_1)}{T_0^2 a_0} - \frac{I_0}{a_0} \xi \right),
\end{aligned}
$$

$$
E_\xi^1 E_x^1(c_k) = \frac{a_0}{2} + \epsilon \left(\frac{a_1}{2} - \frac{T_0}{2} \xi \right).
$$

(3.17)

The matchings $E_\xi^1(\Phi) = E_\xi^1 E_x^1(\phi)$ and $E_\xi^1(C_k) = E_\xi^1 E_x^1(c_k)$ imply, from (3.16) and (3.17),

$$
a_0 = M = 2\sqrt{L_1 L_2}, \qquad b_0 = V + \frac{1}{2} \ln \frac{L_1}{L_2} - \frac{I_0}{T_0} \ln a_0,
$$

$$
a_1 = -\frac{4l(I_0 + lT_0)}{\sqrt{M}(1+l)(1-l)},
$$

(3.18)

$$
\begin{aligned}
b_1 &= -\frac{I_0(a_1 T_0 - a_0 T_1)}{T_0^2 a_0} - \frac{T_0 I_1 - I_0 T_1}{T_0^2} \ln a_0 \\
&\quad - \frac{4l(T_0 + lI_0)}{M^{3/2}(1+l)(1-l)}.
\end{aligned}
$$

Note that the relation for a_0 in (3.18) is consistent since $M = 2\sqrt{L_1 L_2}$.

Similarly, the matching near $x = 1$ gives

$$
a_0 = N + T_0 = 2\sqrt{R_1 R_2} + T_0, \qquad b_0 = \frac{1}{2} \ln \frac{R_1}{R_2} - \frac{I_0}{T_0} \ln(a_0 - T_0),
$$

$$
a_1 = T_1 - \frac{4r(I_0 + rT_0)}{\sqrt{N}(1+r)(1-r)},
$$

(3.19)

$$
\begin{aligned}
b_1 &= -\frac{I_0(a_1 T_0 - a_0 T_1)}{2\sqrt{R_1 R_2} T_0^2} - \frac{T_0 I_1 - I_0 T_1}{T_0^2} \ln(2\sqrt{R_1 R_2}) \\
&\quad - \frac{4r(T_0 + rI_0)}{N^{3/2}(1+r)(1-r)}.
\end{aligned}
$$

As expected, one recovers (3.9) for T_0 and I_0 from the two expressions in (3.18) and (3.19) for a_0 and b_0. Using the two expressions for a_1 and b_1, we get

$$
T_1 = \frac{4r(I_0 + rT_0)}{\sqrt{N}(1+r)(1-r)} - \frac{4l(I_0 + lT_0)}{\sqrt{M}(1+l)(1-l)},
$$

(3.20)

$$
\begin{aligned}
I_1 &= T_0^{-1} I_0 T_1 - \frac{T_0^{-1} I_0(a_1 T_0 - a_0 T_1)}{\ln(R_1 R_2) - \ln(L_1 L_2)} \left(\frac{1}{\sqrt{R_1 R_2}} - \frac{1}{\sqrt{L_1 L_2}} \right) \\
&\quad - \frac{4r T_0(T_0 + rI_0)}{\sqrt{R_1 R_2 N}(1+r)(1-r)} + \frac{4l T_0(T_0 + lI_0)}{\sqrt{L_1 L_2 M}(1+l)(1-l)}.
\end{aligned}
$$

Note that T_1 is linear in I_0 and hence is linear in V; I_1 is quadratic in I_0 and hence is also quadratic in V. That is, the first order correction to the zeroth order linear I-V relation is *quadratic* in V in general.

What is interesting and potentially important is that, when $L_1 = L_2$ and $R_1 = R_2$ (electro-neutrality), one deduces that $T_1 = I_1 = 0$. That is, under the electro-neutrality condition at both ends, there is NO first order correction for the I-V relation.

3.3. Second order I-V relation with electro-neutrality. We now assume the electro-neutrality condition $L_1 = L_2$ and $R_1 = R_2$ and examine the I-V correction at the second order $O(\epsilon^2)$.

3.3.1. Second order outer expansion. The second order outer system (2.3) is

$$\ddot{\phi}_0 = -c_{12} + c_{22},$$
(3.21)
$$\dot{c}_{12} = -(c_{12}\dot{\phi}_0 + c_{11}\dot{\phi}_1 + c_{10}\dot{\phi}_2) - J_{12},$$
$$\dot{c}_{22} = (c_{22}\dot{\phi}_0 + c_{21}\dot{\phi}_1 + c_{20}\dot{\phi}_2) - J_{22}.$$

Note that, under the assumption $L_1 = L_2$ and $R_1 = R_2$, we have

$$a_1 = b_1 = T_1 = I_1 = c_{11}(x) = c_{21}(x) = \phi_1(x) = 0.$$

Upon using (3.3), one solves system (3.21) to get

$$c_{12}(x) = \frac{a_2 - T_2 x}{2} + \frac{I_0^2 + 2I_0 T_0}{4(a_0 - T_0 x)^2},$$

$$c_{22}(x) = \frac{a_2 - T_2 x}{2} + \frac{I_0^2 - 2I_0 T_0}{4(a_0 - T_0 x)^2},$$
(3.22)
$$\phi_2(x) = b_2 - \frac{2I_0 T_0}{3(a_0 - T_0 x)^3} + \frac{I_0^3}{6T_0(a_0 - T_0 x)^3} + \frac{I_0(a_2 T_0 - a_0 T_2)}{T_0^2(a_0 - T_0 x)}$$
$$- \frac{I_0 T_2}{T_0^2} \ln|a_0 - T_0 x| + \frac{I_2}{T_0} \ln|a_0 - T_0 x|,$$

where a_2 and b_2 are unknown constants.

3.3.2. Second order inner expansion. The second order inner system (2.8) at $x = 0$ is

$$\Phi_2' = U_2, \quad U_2' = -(C_{12} - C_{22}),$$
(3.23)
$$C_{12}' = -(C_{10}U_2 + C_{11}U_1 + C_{12}U_0) - J_{11},$$
$$C_{22}' = (C_{20}U_2 + C_{21}U_1 + C_{22}U_0) - J_{21}.$$

Similarly to the first order inner system, we have the following claim.

Proposition 3.3. *System* (3.23) *has the following integrals:*

$$G_1 = C_{12}e^{\Phi_0} + C_{10}e^{\Phi_0}\Phi_2 + J_{11}F_1(\xi) + F_{12}(\xi),$$
$$G_2 = C_{22}e^{-\Phi_0} - C_{20}e^{-\Phi_0}\Phi_2 + J_{21}F_2(\xi) - F_{22}(\xi),$$
$$G_3 = U_0 U_2 - C_{12} - C_{22} - T_1\xi + \frac{1}{2}U_1^2,$$

where $F_1(\xi)$ and $F_2(\xi)$ are given in Proposition 3.2 *and*

$$F_{12}(\xi) = \int_0^\xi C_{11}(s)U_1(s)e^{\Phi_0(s)}ds, \qquad F_{22}(\xi) = \int_0^\xi C_{21}(s)U_1(s)e^{-\Phi_0(s)}ds.$$

Using $L_1 = L_2 = L$ and $R_1 = R_2 = R$, we have, from (3.5) and (3.6), that

$$\Phi_0(\xi) = V, \quad U_0(\xi) = 0, \quad C_{10}(\xi) = C_{20}(\xi) = L,$$
$$\Psi_0(\xi) = 0, \quad V_0(\xi) = 0, \quad D_{10}(\xi) = D_{20}(\xi) = R,$$

and, from (3.14) and (3.15), that

$$\Phi_1(\xi) = -\frac{I_0}{2L}\xi, \quad U_1(\xi) = -\frac{I_0}{2L}, \quad C_{11}(\xi) = C_{21}(\xi) = -\frac{T_0}{2}\xi,$$
$$\Psi_1(\xi) = -\frac{I_0}{2R}\xi, \quad V_1(\xi) = -\frac{I_0}{2R}, \quad D_{11}(\xi) = D_{21}(\xi) = -\frac{T_0}{2}\xi.$$

Also,

$$J_{11} = J_{21} = 0, \quad F_{12}(\xi) = \frac{I_0 T_0}{8L} e^V \xi^2, \quad F_{22}(\xi) = \frac{I_0 T_0}{8L} e^{-V} \xi^2.$$

Applying the integrals in Proposition 3.3, we can solve (3.23) with $\Phi_2(0) = C_{12}(0) = C_{22}(0) = 0$ to get

$$\Phi_2(\xi) = \left(\frac{I_0 T_0}{8L^3} - A\right) e^{-\sqrt{2L}\xi} + A e^{\sqrt{2L}\xi} - \frac{I_0 T_0}{8L^3} - \frac{I_0 T_0}{8L^2}\xi^2.$$

The matching will force $A = 0$. Thus, for $\xi \geq 0$,

(3.24)
$$\Phi_2(\xi) = \frac{I_0 T_0}{8L^3}\left(e^{-\sqrt{2L}\xi} - 1\right) - \frac{I_0 T_0}{8L^2}\xi^2,$$
$$C_{12}(\xi) = -\frac{I_0 T_0}{8L^2}\left(e^{-\sqrt{2L}\xi} - 1\right), \quad C_{22}(\xi) = \frac{I_0 T_0}{8L^2}\left(e^{-\sqrt{2L}\xi} - 1\right).$$

Similarly, at $x = 1$, the second order inner solution is, for $\xi \leq 0$,

(3.25)
$$\Psi_2(\xi) = \frac{I_0 T_0}{8R^3}\left(e^{\sqrt{2R}\xi} - 1\right) - \frac{I_0 T_0}{8R^2}\xi^2,$$
$$D_{12}(\xi) = -\frac{I_0 T_0}{8R^2}\left(e^{\sqrt{2R}\xi} - 1\right), \quad D_{22}(\xi) = \frac{I_0 T_0}{8R^2}\left(e^{\sqrt{2R}\xi} - 1\right).$$

3.3.3. Second order matching. From (3.22), in terms of $\xi = x/\epsilon$, the outer expansion at $x = 0$ is

$$E_\xi^2 E_x^2(\phi) = b_0 + \frac{I_0}{T_0}\ln a_0 - \epsilon\frac{I_0}{a_0}\xi$$
$$+ \epsilon^2\left(b_2 - \frac{I_0(2T_0 - I_0)(2T_0 + I_0)}{6T_0 a_0^3} + \frac{I_0(a_2 T_0 - a_0 T_2)}{T_0^2 a_0}\right.$$
$$\left. + \frac{T_0 I_2 - I_0 T_2}{T_0^2}\ln a_0 - \frac{I_0 T_0}{2a_0^2}\xi^2\right),$$
$$E_\xi^2 E_x^2(c_1) = \frac{a_0}{2} - \epsilon\frac{T_0}{2}\xi + \epsilon^2\left(\frac{a_2}{2} + \frac{I_0^2 + 2T_0 I_0}{4a_0^2}\right),$$
$$E_\xi^2 E_x^2(c_2) = \frac{a_0}{2} - \epsilon\frac{T_0}{2}\xi + \epsilon^2\left(\frac{a_2}{2} + \frac{I_0^2 - 2T_0 I_0}{4a_0^2}\right),$$

and, in terms of $\xi = (x-1)/\epsilon$, the outer expansion at $x = 1$ is

$$E_\xi^2 E_x^2(\phi) = b_0 + \frac{I_0}{T_0}\ln(a_0 - T_0) - \epsilon\frac{I_0}{a_0 - T_0}\xi$$
$$+ \epsilon^2\left(b_2 - \frac{I_0(2T_0 - I_0)(2T_0 + I_0)}{6T_0(a_0 - T_0)^3} + \frac{I_0(a_2 T_0 - a_0 T_2)}{T_0^2(a_0 - T_0)}\right.$$
$$+ \left.\frac{T_0 I_2 - I_0 T_2}{T_0^2}\ln(a_0 - T_0) - \frac{I_0 T_0}{2(a_0 - T_0)^2}\xi^2\right),$$

$$E_\xi^2 E_x^2(c_1) = \frac{a_0 - T_0}{2} - \epsilon\frac{T_0}{2}\xi + \epsilon^2\left(\frac{a_2 - T_2}{2} + \frac{I_0^2 + 2T_0 I_0}{4(a_0 - T_0)^2}\right),$$

$$E_\xi^2 E_x^2(c_2) = \frac{a_0 - T_0}{2} - \epsilon\frac{T_0}{2}\xi + \epsilon^2\left(\frac{a_2 - T_2}{2} + \frac{I_0^2 - 2T_0 I_0}{4(a_0 - T_0)^2}\right).$$

From (3.24) and (3.25), the inner expansion at $x = 0$ is

$$E_\xi^2(\Phi) = V - \epsilon\frac{I_0}{2L}\xi - \epsilon^2\left(\frac{I_0 T_0}{8L^3} + \frac{I_0 T_0}{8L^2}\xi^2\right),$$

$$E_\xi^2(C_1) = L - \epsilon\frac{T_0}{2}\xi + \epsilon^2\frac{I_0 T_0}{8L^2}, \quad E_\xi^2(C_2) = L - \epsilon\frac{T_0}{2}\xi - \epsilon^2\frac{I_0 T_0}{8L^2},$$

and the inner expansion at $x = 1$ is

$$E_\xi^2(\Psi) = -\epsilon\frac{I_0}{2R}\xi - \epsilon^2\left(\frac{I_0 T_0}{8R^3} + \frac{I_0 T_0}{8R^2}\xi^2\right),$$

$$E_\xi^2(D_1) = R - \epsilon\frac{T_0}{2}\xi + \epsilon^2\frac{I_0 T_0}{8R^2}, \quad E_\xi^2(D_2) = R - \epsilon\frac{T_0}{2}\xi - \epsilon^2\frac{I_0 T_0}{8R^2}.$$

The matchings at $x = 0$ and at $x = 1$ then give

$$T_2 = \frac{(L - R)^3(L + R)}{2L^2 R^2(\ln L - \ln R)^2},$$

(3.26)
$$I_2 = \frac{(L - R)^4(L^2 + LR + R^2)}{3L^3 R^3(\ln L - \ln R)^2}V - \frac{(L - R)^3(L^3 - R^3)}{3L^3 R^3(\ln L - \ln R)^4}\nu_0^3$$
$$+ \frac{(L - R)^2(L^2 - R^2)}{2L^2 R^2(\ln L - \ln R)^3}V^3.$$

In particular, the second order correction $I_2(V)$ to the zeroth order I-V relation $I_0(V)$ is *cubic* in V. Note also that, as $L \to R$, one finds that $T_2 \to 0$ and $I_2 \to 0$.

Theorem 3.4. *If $L \neq R$, then, up to the order of ϵ^2, the I-V relation $I = I(V)$ in (3.26) is a cubic function with three distinct real roots.*

Proof. From (3.10) and (3.26), up to $O(\epsilon^2)$, $I = f(L, R; \epsilon)V - \epsilon^2 g(L, R)V^3$, where

$$f(L, R; \epsilon) = \frac{2(L - R)}{\ln L - \ln R} + \epsilon^2\frac{(L - R)^4(L^2 + LR + R^2)}{3L^3 R^3(\ln L - \ln R)^2},$$

$$g(L, R) = \frac{(L - R)^3(L^3 - R^3)}{3L^3 R^3(\ln L - \ln R)^4} - \frac{(L - R)^2(L^2 - R^2)}{2L^2 R^2(\ln L - \ln R)^3}.$$

It is easy to see that $f(L, R; \epsilon) > 0$ for $L \neq R$ (and $f(R, R; \epsilon) = 2R$). It remains to show that $g(L, R) > 0$ for $L \neq R$. Note that $g(L, R) = g(R, L)$. Thus, it suffices to show $g(L, R) > 0$ for $L > R$. Assume now $L > R$ and rewrite $g(L, R)$ as

$$g(L, R) = \frac{(L - R)^3}{6L^3 R^3 (\ln L - \ln R)^4} h(L, R),$$

where $h(L, R) = 2(L^3 - R^3) - 3LR(L + R)(\ln L - \ln R)$. To show $h(L, R) > 0$ for $L > R$, we fix R and treat $h(L) = h(L, R)$ as a function of L. Then, a direct computation gives $h(R) = h'(R) = h''(R) = 0$ but $h'''(L) > 0$ for all L. Therefore, $h(L) > 0$ for $L > R$. ∎

4. Some remarks. We investigated higher order asymptotic expansion of the I-V relation for biological channels via a one-dimensional steady-state Poisson–Nernst–Planck system. For the case of two oppositely charged ion species and zero permanent charge, we obtained explicit information on the I-V relation up to the second order. In particular, we found that the zeroth order I-V relation is *linear*, the first order correction to the zeroth order I-V relation is generally *quadratic*, and, with the electro-neutrality condition at both ends of the channel, there is NO first order correction but the second order correction is *cubic*. Furthermore, up to the second order, the cubic I-V relation has three real roots (Theorem 3.4), which is potentially related to the cubic-like feature of the average I-V relation of a population of channels in the FitzHugh–Nagumo simplification of the Hodgkin–Huxley model.

For second order terms, we only treated the electro-neutrality case because this is a natural biological assumption and the first order correction to the zeroth order linear I-V relation is zero. This occurs in the special case when the permanent charge Q is zero. In general, a realistic assumption is that Q is piecewise constant. To treat this general situation of Q, one can follow our approach to first work on each subinterval where Q is constant (see [10] for the zeroth order case). In doing so, one cannot assume the electro-neutrality condition since it is known to hold only at the two baths ($x = 0$ and $x = 1$). Another direction to be further explored is the case where three or more ion species are involved in the channel. We believe our analysis can be extended to those cases.

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