Singular Perturbations and Ion Channel Problems

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Abstract

Ion channel problems concern macroscopic properties of ionic flow through nano-scale ion channels. It is no coincidence that singularly perturbed systems serve as suitable models for analyzing these multi-scale problems. The general framework of singular perturbations often reveals special structures (idealized physical situations) of multi-scale phenomena and allows one to extract concrete information for specific problems. This is the case for the Poisson-Nernst-Plank (PNP) systems as primitive models for ionic flows.

In this talk, we will describe the geometric singular perturbation framework for an analysis of PNP systems and report a number of concrete results that are directly relevant to central topics of ion channel problems. The talk is based on works with several collaborators.

OUTLINE

Part I: Background, models, and a specific GSP

– Ion channel problems and Poisson-Nernst-Planck (PNP) models

– A general framework of GSP + Special structures of PNP

$\Longrightarrow$ Singular orbits involving ALL physical parameters of the problem

Part II: A number of specific applications

– Reversal (Nernst) potential and reversal permanent charge

– Effects of permanent charges and channel shape

– Ion size effects via PNP w/ Hard-Sphere potentials

Part I

1. Ion channel structures: shape and permanent charge

   Ion channel functions: ionic flow and Poisson-Nernst-Planck models

2. A framework for analyzing PNP systems

– General theory of geometric singular perturbations (GSP)

– Special structures of PNP (most important ingredients for concrete information)

– Matching: yields (local) double-layers and brings (global) BC into picture

– Governing systems for singular orbits of BVP of PNP

1. Ion channel, ionic flow, PNP model

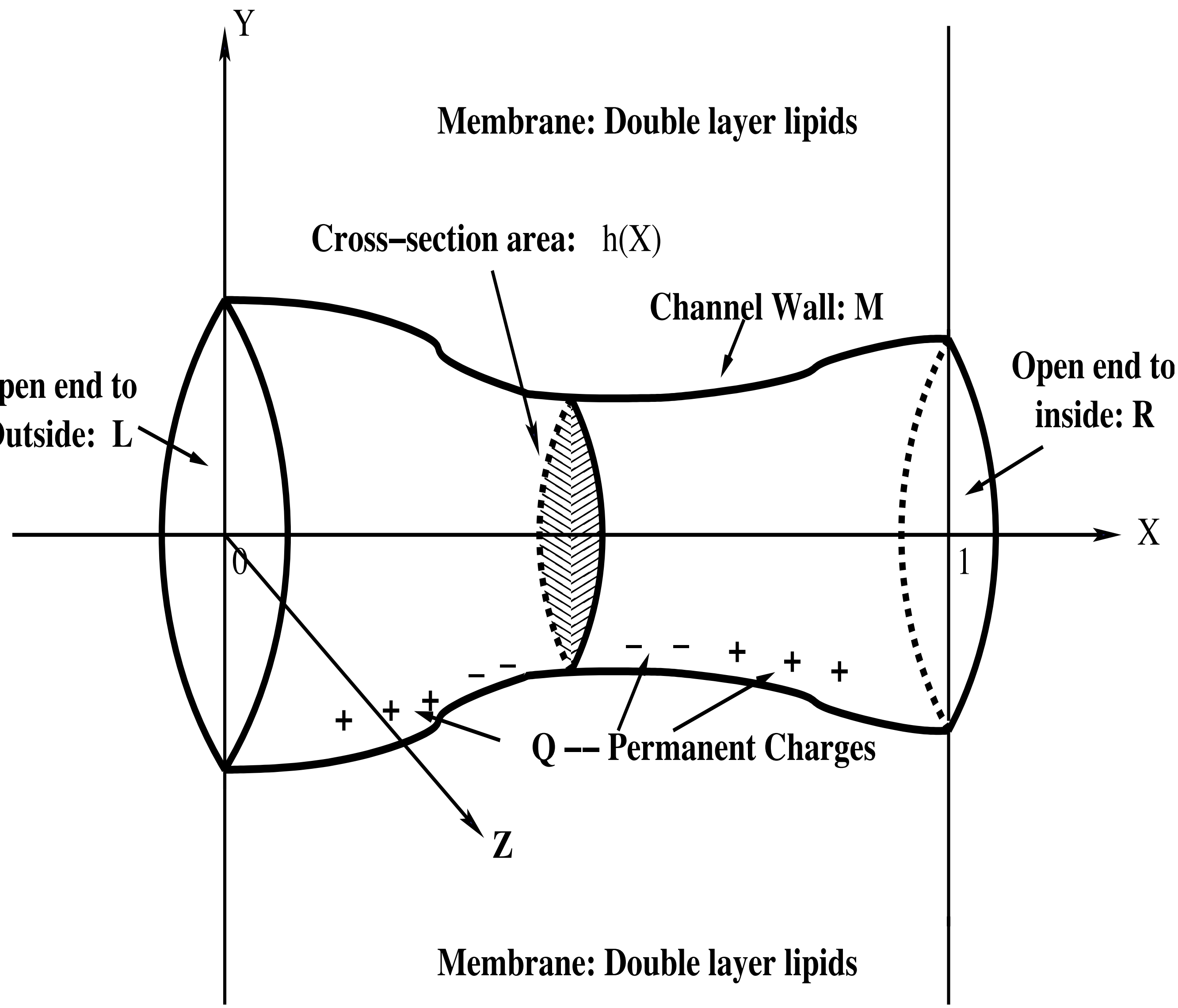

Figure 1: What Are Ion Channels: Shape and Permanent Charge

1.1. A quasi-one-dim PNP model for ionic flows of n types of ion species:

$$\text{Poisson:} \quad \frac{1}{h(x)}\frac{d}{dx}\Big(\epsilon^2 h(x)\frac{d\phi}{dx}\Big) = -e\Big(\sum z_s c_s + Q(x)\Big),$$

$$\text{Nernst-Planck:} \quad \frac{dJ_j}{dx} = 0, \quad -J_j = \frac{1}{k_B T} D_j h(x) c_j \frac{d\mu_j}{dx}.$$

$$\text{BV:} \quad \phi(0) = \mathcal{V},\ c_j(0) = L_j; \quad \phi(1) = 0,\ c_j(1) = R_j.$$

ϕ–electric potential, ϵ^2–dielectric, $h(x)$–area over x, $Q(x)$–permanent charge

c_j – concentration, J_j – flux density, z_j – valence, D_j – diffusion constant,

Electrochemical potential: $\mu_j(\phi, \{c_i\}) = \mu_j^{id} + \mu_j^{ex}$:

Ideal component $\mu_j^{id} = z_j e\phi + k_B T \ln c_j$; Excess potential μ_j^{ex} for ion size.

A key quantity: Current-Voltage (I-V) relation $\mathcal{I} = \sum z_j J_j(\mathcal{V}; L, R)$.

1.2 A brief background

- Nernst; Planck (1890s):
  - Nernst-Planck equation (study delayed due to lack of experimental data?)
  - Nernst equation for Reversal Potential (Goldman-Hodgkin-Katz equation)
- Gouy-Chapmann (1910s); O. Stern (1924): Double layer phenomena
- Debye-Hückel; Lars Onsager (1920s):
  - Electrolytic solutions based on Poisson-Boltzmann approximations
  - Corrected to some extent by Lars Onsager when he was less than 22.
- Hodgkin-Huxley (1952a-e):
  - "Voltage-Clamp" technique for recording action potentials in the squid giant axon (single cell w/ a population of channels)
  - Hodgkin-Huxley's phenomenological model describes how action potentials in neurons are initiated and propagated
- Katz-Miledi, Neher-Sakmann (1970s): Single-channel recording of current
- ⋯⋯:
  - permeation, selectivity, gating, layering, charge inversion, conductivity, etc.

2. GSP for cPNP w/ piecewise constant $Q(x)$: [Liu JDE 09]

2.1. Reformulate BVP to a connecting problem (after a rescaling)

Introduce $u = \varepsilon\dot{\phi}$ and $w = x$. cPNP becomes, for $k = 1, 2, \cdots, n$,

$$\varepsilon\dot{\phi} = u, \quad \varepsilon\dot{u} = -\sum_{s=1}^{n} z_s c_s - Q(w) - \varepsilon\frac{h'(w)}{h(w)}u,$$

$$\varepsilon\dot{c}_k = -z_k c_k u - \varepsilon J_k h^{-1}(w), \quad \dot{J} = 0, \quad \dot{w} = 1.$$

Associated to boundary conditions, introduce

$$B_L = \{(\phi, u, C, J, w) \in \mathbb{R}^{2n+3} : \phi = \mathcal{V},\ C = L,\ w = 0\},$$

$$B_R = \{(\phi, u, C, J, w) \in \mathbb{R}^{2n+3} : \phi = 0,\ C = R,\ w = 1\}.$$

BVP $\Longleftrightarrow$ A connecting orbit from B_L to B_R.

2.2. Construction of Singular Orbits over $[0, 1]$.

Pre-assign the values of ϕ, c_k's at jump point x_j of $Q(x)$ for $j = 1, 2, \cdots, m-1$,

$$\phi(x_j) = \phi^{[j]}, \quad c_k(x_j) = c_k^{[j]}, \quad k = 1, 2, \cdots, n \tag{1}$$

with given $\phi^{[0]} = \mathcal{V}$ and $c_k^{[0]} = L_k$ at $x_0 = 0$, $\phi^{[m]} = 0$ and $c_k^{[m]} = R_k$ at $x_m = 1$, and introduce the set, for $j = 0, 1, \cdots, m$,

$$B_j = \{(\phi, u, C, J, w):\ \phi = \phi^{[j]}, C = C^{[j]}, w = x_j\}. \tag{2}$$

Two main steps for a construction of a singular orbits over $[0, 1]$

- Singular orbits on $[x_{j-1}, x_j]$ between B_{j-1} and B_j with $Q(x) = Q_j$.
- Matching them at jump points $x = x_j$'s to form a singular orbit on $[0, 1]$.

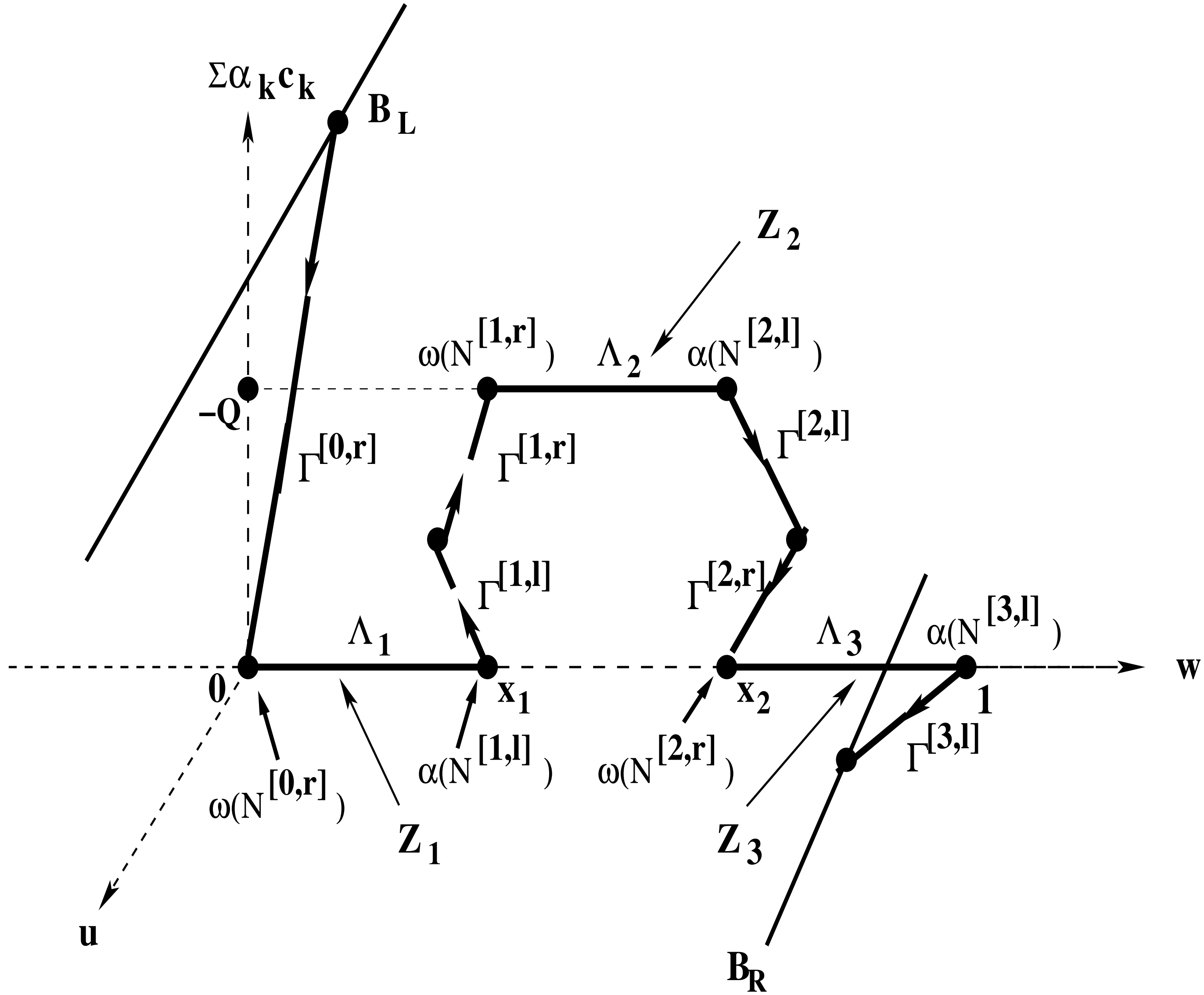

Figure 2: A singular orbit: double-layer at each x_j

2.2.1. Singular orbit over $[x_{j-1}, x_j]$ between B_{j-1} and B_j with $Q(x) = Q_j$.

Each such an orbit will consist of two singular layers $\Gamma^{[j-1,r]}$ at $x = x_{j-1}$, and $\Gamma^{[j,l]}$ at $x = x_j$, and a regular layer Λ_j over the interval $[x_{j-1}, x_j]$.

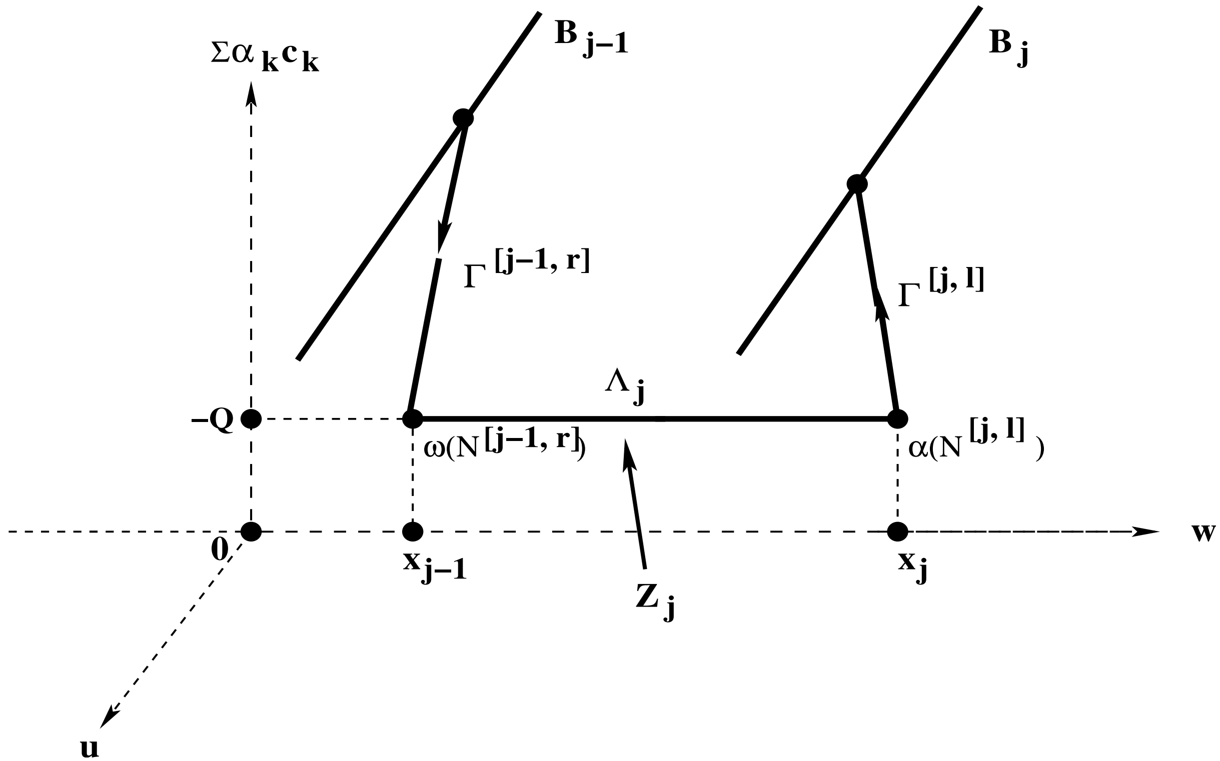

Figure 3: Singular orbit over $[x_{j-1}, x_j]$

– Fast dynamics and bdry/internal layers.

The slow manifold is $\mathcal{Z}_j = \{u = 0,\ \sum_{s=1}^{n} z_s c_s + Q_j = 0\}$.

Note that $\dim \mathcal{Z}_j = 2n + 1$ – co-dim two.

In terms of the independent variable $\xi = x/\epsilon$, we obtain the fast system,

$$\phi' = u, \quad u' = -\sum_{s=1}^{n} z_s c_s - Q_j - \varepsilon \frac{h'(w)}{h(w)} u,$$

$$c_k' = -z_k c_k u - \varepsilon J_k h^{-1}(w), \quad J' = 0, \quad w' = \varepsilon.$$

The limiting fast system is, for $k = 1, 2, \cdots, n$,

$$\phi' = u, \quad u' = -\sum_{s=1}^{n} z_s c_s - Q_j,$$

$$c_k' = -z_k c_k u, \quad J' = 0, \quad w' = 0.$$

Two e-values normal to $\mathcal{Z}_j$ are $\pm\sqrt{\sum z_s^2 c_s}$ (Debye length)$^{-1}$ $\Longrightarrow$ $\mathcal{Z}_j$ is NH.

Special structure of the limiting fast system:

Proposition. *The limiting fast system has a complete set of $(2n+2)$ first integrals given by, for $k = 1, 2, \cdots, n$,*

$$G_k = \ln c_k + z_k \phi, \quad G_{n+1} = \frac{1}{2}u^2 - \sum_{s=1}^{n} c_s + Q_j \phi,$$

$$G_{n+1+k} = J_k \text{ and } G_{2n+2} = w.$$

Consequences:

One can determine $u^{[j-1,+]}$ and $u^{[j,-]}$, and $\omega(B_{j-1})$ and $\alpha(B_j)$ up to J.

– Slow dynamics to connect $\omega(B_{j-1})$ and $\alpha(B_j)$.

Introduce $u = \varepsilon p, \quad z_n c_n = -\sum_{s=1}^{n-1} z_s c_s - Q_j - \varepsilon q.$

In replacing u with p and c_n with q, slow system becomes, for $k = 1, \cdots, n-1$,

$$\dot{\phi} = p, \quad \varepsilon \dot{p} = q - \varepsilon \frac{h'(w)}{h(w)} p,$$

$$\varepsilon \dot{q} = \Big(\sum_{s=1}^{n-1} (z_s - z_n) z_s c_s - z_n Q_j - \varepsilon z_n q \Big) p + h^{-1}(w) \sum_{s=1}^{n} z_s J_s,$$

$$\dot{c}_k = -z_k p c_k - J_k h^{-1}(w), \quad \dot{J} = 0, \quad \dot{w} = 1.$$

When $\varepsilon = 0$, it is

$$\dot{\phi} = p, \quad 0 = q,$$

$$0 = \Big(\sum_{s=1}^{n-1} (z_s - z_n) z_s c_s - z_n Q_j \Big) p + h^{-1}(w) \sum_{s=1}^{n} z_s J_s,$$

$$\dot{c}_k = -z_k p c_k - J_k h^{-1}(w), \quad \dot{J} = 0, \quad \dot{w} = 1.$$

For this system, the slow manifold is

$$\mathcal{S}_j = \left\{ p = -\frac{h^{-1}(w)\sum_{s=1}^{n} z_s J_s}{\sum_{s=1}^{n-1}(z_s - z_n) z_s c_s - z_n Q_j},\ q = 0 \right\}.$$

The limiting slow dynamics on $\mathcal{S}_j$ is, with $\mathcal{I} = \sum_{s=1}^{n} z_s J_s$,

$$\begin{aligned}
\dot\phi &= -\frac{h^{-1}(w)\mathcal{I}}{\sum_{s=1}^{n-1}(z_s - z_n) z_s c_s - z_n Q_j},\\
\dot c_k &= \frac{h^{-1}(w)\mathcal{I}}{\sum_{s=1}^{n-1}(z_s - z_n) z_s c_s - z_n Q_j} z_k c_k - h^{-1}(w) J_k,\\
\dot J &= 0, \quad \dot w = 1.
\end{aligned}$$

Special structure of limiting slow dynamics: On slow manifold $\mathcal{S}_j$,

$$\sum_{s=1}^{n-1} z_s c_s + Q_j = -z_n c_n \Longrightarrow \sum_{s=1}^{n-1}(z_s - z_n) z_s c_s - z_n Q_j = \sum_{s=1}^{n} z_s^2 c_s > 0.$$

Multiply $h(w)\sum_{s=1}^{n} z_s^2 c_s$ on the RHS to get

$$\frac{d}{d\tau}\phi = -\mathcal{I}, \quad \frac{d}{d\tau}C = D(J)C, \quad \sum_{s=1}^{n} z_s c_s + Q_j = 0,$$

$$\frac{d}{d\tau}J = 0, \quad \frac{d}{d\tau}w = h(w)\sum_{s=1}^{n} z_s^2 c_s,$$

where $D(J) = \Gamma - Jb^T$ with $\Gamma = \mathcal{I}$ diag$(z_1, \cdots, z_n)$ and $b^T = (z_1^2, \cdots, z_n^2)$.

Solving this system from $\omega(B_{j-1})$ to $\alpha(B_j)$, one gets $J^{[j]}$ over $[x_{j-1}, x_j]$.

2.2.2. Global matching: $u^{[j,-]} = u^{[j,+]}$ and $J^{[1]} = J^{[2]} = \cdots = J^{[m]}$.

$m - 1 + n(m-1) = (n+1)(m-1) =$ the number of preassigned unknowns.

The result gives the governing system for singular orbits of the BVP.

Theorem [L-Xu JDE 15]. For $Q = 0$ and general n, there is a unique solution.

From Eisenberg-L. 07 SIMA for $n = 2$ and three-piece-one-nonzero Q:

$$z_1 c_1^a e^{z_1(\phi^a - \phi^{a,m})} + z_2 c_2^a e^{z_2(\phi^a - \phi^{a,m})} + Q = 0,$$

$$z_1 c_1^b e^{z_1(\phi^b - \phi^{b,m})} + z_2 c_2^b e^{z_2(\phi^b - \phi^{b,m})} + Q = 0,$$

$$\frac{z_2 - z_1}{z_2} c_1^{a,l} = c_1^a e^{z_1(\phi^a - \phi^{a,m})} + c_2^a e^{z_2(\phi^a - \phi^{a,m})} + Q(\phi^a - \phi^{a,m}),$$

$$\frac{z_2 - z_1}{z_2} c_1^{b,r} = c_1^b e^{z_1(\phi^b - \phi^{b,m})} + c_2^b e^{z_2(\phi^b - \phi^{b,m})} + Q(\phi^b - \phi^{b,m}),$$

$$J_1 = \frac{c_1^L - c_1^{a,l}}{H(a)}\left(1 + \frac{z_1(\phi^L - \phi^{a,l})}{\ln c_1^L - \ln c_1^{a,l}}\right) = \frac{c_1^{b,r} - c_1^R}{H(1) - H(b)}\left(1 + \frac{z_1(\phi^{b,r} - \phi^R)}{\ln c_1^{b,r} - \ln c_1^R}\right),$$

$$J_2 = \frac{c_2^L - c_2^{a,l}}{H(a)}\left(1 + \frac{z_2(\phi^L - \phi^{a,l})}{\ln c_2^L - \ln c_2^{a,l}}\right) = \frac{c_2^{b,r} - c_2^R}{H(1) - H(b)}\left(1 + \frac{z_2(\phi^{b,r} - \phi^R)}{\ln c_2^{b,r} - \ln c_2^R}\right),$$

$$\phi^{b,m} = \phi^{a,m} - (z_1 J_1 + z_2 J_2)y,$$

$$c_1^{b,m} = e^{z_1 z_2 (J_1 + J_2)y} c_1^{a,m} - \frac{Q J_1}{z_1(J_1 + J_2)}\left(1 - e^{z_1 z_2 (J_1 + J_2)y}\right),$$

$$J_1 + J_2 = -\frac{(z_1 - z_2)(c_1^{a,m} - c_1^{b,m}) + z_2 Q(\phi^{a,m} - \phi^{b,m})}{z_2(H(b) - H(a))}.$$

Part II

1. Reversal potential and reversal permanent charge

2. Effects of permanent charges and channel geometry

3. Ion size effects via PNP w/ Hard-Sphere potentials

1. Reversal charge and potential: Eisenberg-L.-Xu (Nonlinearity 15)

- From NP: $J_k \int_0^1 \frac{1}{h(x)D_k c_k(x)} dx = \mu_k(0) - \mu_k(1) = \frac{e}{k_B T} z_k \mathcal{V}_0 + \ln \frac{L_k}{R_k}$.

The sign of J_k is determined by bdry electrochemical potentials.

Permanent charges cannot do anything about the sign of J_k BUT

do affect the magnitude of J_k.

Can $Q(x)$ change the sign of $\mathcal{I} = \sum z_k J_k$?.

- Reversal permanent charge Q is defined to be the one that makes $\mathcal{I} = 0$.

- Reversal potential $\mathcal{V}_0$ is defined to be the one that makes $\mathcal{I} = 0$.

- Consider $Q(x) = Q^*$ for $x \in [x_1, x_2]$ and $Q(x) = 0$ for $x \notin [x_1, x_2]$.

Let $$g(V, \mathcal{V}_0) := \sum_{s=1}^{n} \frac{z_s(L_s e^{z_s \mathcal{V}_0} - R_s)}{1 - x_2 + x_1 e^{z_s \mathcal{V}_0} + (x_2 - x_1)e^{z_s V}}.$$

Theorem. *(i) Fix $\mathcal{V}_0$. If V^* is a real root of $g(V, \mathcal{V}_0) = 0$, then*

$$Q^* = f(V, \mathcal{V}_0) := -\sum_{s=1}^{n} z_s e^{z_s(\mathcal{V}_0 - V^*)} \frac{[1 - x_2 + (x_2 - x_1)e^{z_s V^*}]L_s + x_1 R_s}{1 - x_2 + x_1 e^{z_s \mathcal{V}_0} + (x_2 - x_1)e^{z_s V^*}},$$

is a reversal permanent charge.

(ii) Fix Q^*. There is a unique solution $(V, \mathcal{V}_0)$ of the system

$$g(V, \mathcal{V}_0) = 0 \;\; \text{and} \;\; f(V, \mathcal{V}_0) = Q^*,$$

and the corresponding $\mathcal{V}_0$ is the reversal (Nernst) potential.

Theorem. *(i) For $n = 2$, $\exists$ a reversal charge Q^* if and only if*

$$(L_1 e^{z_1 \mathcal{V}_0} - R_1)(L_2 e^{z_2 \mathcal{V}_0} - R_2) > 0.$$

If exists, the reversal charge Q^* is unique.

(ii) For $n = 3$ with $z_1 = 1$, $z_2 = 2$ and $z_3 = -1$, and for some bdry conditions, there are at least TWO reversal permanent charges.

Theorem. *For $n = 2$ with $z_1 = 1 = -z_2$ ($L_j = L$ and $R_j = R$).*

For some $(\mathcal{V}_0, L, R)$, the reversal permanent charge Q^* exists and

$$J_1(0) > J_2(0) > J_1(Q^*) = J_2(Q^*).$$

[Somewhat counterintuitive, if not, nobody seems to know before.]

2. Effects of small $Q(x)$ and channel geometry: Ji-L.-Zhang SIAP 15

Consider $Q(x) = Q_0$ over $[x_1, x_2]$ w/ $n = 2$;

Electroneutrality: $z_1 L_1 = -z_2 L_2 = L$ and $z_1 R_1 = -z_2 R_2 = R$.

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

2.1. Effects of channel geometry on fluxes of zeroth order in Q_0

$$J_{10} = \frac{L - R}{z_1 H(1)(\ln L - \ln R)} \mu_1^\delta, \quad J_{20} = \frac{R - L}{z_2 H(1)(\ln L - \ln R)} \mu_2^\delta;$$

$$\mu_k^\delta := \mu_k(0) - \mu_k(1) = z_k \mathcal{V}_0 + \ln L - \ln R \text{ and } H(1) = \int_0^1 A^{-1}(x)\,dx.$$

J_{10} doesn't depend on 2nd ion species and J_{20} doesn't depend on 1st ion species.

Effects of channel geometry for zeroth order in Q_0 are simple.

2.2. Effects of $Q(x)$ and channel geometry on 1st order fluxes

$$J_{11} = \frac{A(\mu_2^\delta - z_2 BV)}{(z_1 - z_2)H(1)(\ln L - \ln R)^2}\mu_1^\delta,$$
$$J_{21} = \frac{A(\mu_1^\delta - z_1 BV)}{(z_2 - z_1)H(1)(\ln L - \ln R)^2}\mu_2^\delta,$$

where, in terms of $\alpha = H(x_1)/H(1)$ and $\beta = H(x_2)/H(1)$,

$$A = A(L,R) = -\frac{(\beta-\alpha)(L-R)^2}{((1-\alpha)L+\alpha R)((1-\beta)L+\beta R)(\ln L - \ln R)},$$
$$B = B(L,R) = \frac{\ln((1-\beta)L+\beta R) - \ln((1-\alpha)L+\alpha R)}{A}.$$

J_{11} depends on 2nd ion species and J_{20} depends on 1st ion species.

More detailed channel geometry presents in 1st order J_{k1}.

2.2.1. Channel geometry for optimal permanent charge effects on fluxes

Theorem. $|J_{11}|$ *and* $|J_{21}|$ *attain their maximums for* $(\alpha, \beta) = (0, 1)$.

Recall that $\alpha = H(x_1)/H(1)$, $\beta = H(x_2)/H(1)$, $H(x) = \int_0^x h^{-1}(s)ds$.

Striking Consequences

A short and narrow neck " > " A long and wide neck.

Short and Narrow : $x_2 - x_1 \ll 1$ and $h(x)$ is much smaller for $x \in (x_1, x_2)$.

Long and Wide: $x_2 - x_1 \approx 1$ and $h(x)$ is more uniform with more charges

Ion channels prefer short and narrow necks.

2.2.2. Charge effects on fluxes of positively charged and negatively charged ions

For $t > 0$, set

$$\gamma(t) = \frac{t \ln t - t + 1}{(t-1)\ln t}.$$

Lemma. *For* $t > 0$, $0 < \gamma(t) < 1$, $\gamma'(t) > 0$, $\gamma(t) + \gamma(1/t) = 1$,

$$\lim_{t \to 0} \gamma(t) = 0, \quad \lim_{t \to 1} \gamma(t) = 1/2, \quad \lim_{t \to \infty} \gamma(t) = 1.$$

Theorem. *Let V_q^1 and V_q^2 be as*

$$V_q^1 = V_q^1(L,R) = -\frac{\ln L - \ln R}{z_2(1-B)} \text{ and } V_q^2 = V_q^2(L,R) = -\frac{\ln L - \ln R}{z_1(1-B)}.$$

Then, for $t = L/R > 1$, one has

(i) if $\alpha < \gamma(t)$ and $\beta \in (\alpha, \beta_1)$, then $V_q^1 < 0 < V_q^2$; and,

(i1) for $V \in (V_q^1, V_q^2)$, small positive Q_0 reduces both $|J_1|$ and $|J_2|$;
(i2) for $V < V_q^1$, small positive Q_0 strengthens $|J_1|$ but reduces $|J_2|$;
(i3) for $V > V_q^2$, small positive Q_0 reduces $|J_1|$ but strengthens $|J_2|$;

(ii) if either $\alpha < \gamma(t)$ and $\beta \in (\beta_1, 1)$ or $\alpha \geq \gamma(t)$, then $V_q^1 > 0 > V_q^2$; and,

(ii1) for $V \in (V_q^2, V_q^1)$, small positive Q_0 strengthens both $|J_1|$ and $|J_2|$;
(ii2) for $V > V_q^1$, small positive Q_0 strengthens $|J_1|$ but reduces $|J_2|$;
(ii3) for $V < V_q^2$, small positive Q_0 reduces $|J_1|$ but strengthens $|J_2|$.

SMALL positive permanent charge can do anything but strengthening the flux of positively charged ions while reducing that of negatively charged ions.

In general, for $k = 1, 2$ with $z_1 > 0 > z_2$, set $\lambda_k(Q, \varepsilon) = \dfrac{J_k(Q, \varepsilon)}{J_k(0, \varepsilon)}$.

Since Q does not change the sign of $J_k(Q, \varepsilon)$, one has $\lambda_k(Q, \varepsilon) > 0$.

If $\lambda_k(Q, \varepsilon) > 1$, then $|J_k(Q, \varepsilon)| > |J_k(0, \varepsilon)|$; that is,

the flux J_k is strengthened by the permanent charge Q.

Theorem. *For positive permanent charge $Q(x)$, one has, for $\varepsilon > 0$ small,*

$$\lambda_2(Q, \varepsilon) > \lambda_1(Q, \varepsilon) \quad \text{— } \quad \textit{A Universal Effect}$$

and each of the following is possible:

(i) $\lambda_2(Q, \varepsilon) > 1 > \lambda_1(Q, \varepsilon)$;

(ii) $\lambda_2(Q, \varepsilon) > \lambda_1(Q, \varepsilon) > 1$;

(iii) $1 > \lambda_2(Q, \varepsilon) > \lambda_1(Q, \varepsilon)$.

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

(i) the flux of anion is enhanced while that of cation is reduced;

(ii) the fluxes of both anion and cation are enhanced and, in this case,

$$\frac{J_2(Q) - J_2(0)}{J_2(0)} > \frac{J_1(Q) - J_1(0)}{J_1(0)} > 0,$$

i.e, the relative amount of flux increased for anion is greater than that for cation;

(iii) the fluxes of both anion and cation are reduced and, in this case,

$$0 < \frac{J_2(0) - J_2(Q)}{J_2(0)} < \frac{J_1(0) - J_1(Q)}{J_1(0)},$$

i.e., the relative amount of flux reduced for anion is smaller than that for cation.

3. PNP with hard-sphere potentials (HS)

3.1. Why do we care about ion sizes

Serious weakness of cPNP: treating $Na^+ = K^+$

In real world, $Na^+ \neq K^+$ significantly

Key difference: $Na^+ < K^+$ in ion size

Na^+-channels v.s. K^+-channels - (Protein Structure: MacKinnon 2003 Nobel)

Excess potential μ_i^{ex} accounts for finite size of ions
to distinguish ions with same valence but different sizes.

Percus-Yevick (70s) and Rosenfeld (93) model: (exact)

$$\mu_j^{HS} = \frac{\delta \Omega(\{c_i\})}{\delta c_j},$$

where

$$\Omega(\{c_i\}) = -\int n_0(x; \{c_i\}) \ln(1 - n_1(x; \{c_i\}))dx,$$

$$n_l(x; \{c_i\}) = \sum_i \int c_i(x')\omega_l^i(x - x')dx', \quad l = 0, 1$$

$$\omega_0^i(x) = \frac{\delta(x - r_i) + \delta(x + r_i)}{2}, \quad \omega_1^i(x) = \Theta(r_i - |x|).$$

δ: Dirac function; Θ: Heaviside function; r_i: radius of ith ions.

3.3. A local HS potential μ_j^{LHS} for 3-dim

Bikerman's model (42):

$$\mu_j^{LHS}(x) = -\ln\left(1 - \frac{4\pi}{3}\sum_i r_i^3 c_i(x)\right) - \text{not ion specific.}$$

Many refined models $\cdots\cdots$

Boublik-Mansoori-Carnahan-Starling-Leland model (70-71):

Very accurate and more sophisticate, up to lowest order in radii,

$$\mu_j^{LHS}(x) = 8\sum_i (r_j + r_i)^3 c_i(x) + O(r^6) - \text{ion specific.}$$

Quasi-one-dim'l PNP with HS potential

$$\frac{1}{h(x)}\frac{d}{dx}\Big(\varepsilon^2 h(x)\frac{d\phi}{dx}\Big) = -\sum_{s=1}^{n} z_s c_s - Q(x),$$

$$\frac{dJ_j}{dx} = 0, \quad -J_j = D_j h(x)\Big(\frac{dc_j}{dx} + z_j c_j \frac{d\phi}{dx} + \underline{c_j \frac{d\mu_j^{HS}}{dx}}\Big)$$

with the boundary conditions

$$\phi(0) = V, \ \ c_j(0) = L_j; \quad \phi(1) = 0, \ \ c_j(1) = R_j.$$

3.4. Electroneutrality, $n=2$: $L := z_1L_1 = -z_2L_2$, $R := z_1R_1 = -z_2R_2$

Ji-L. JDDE 12 (for PNP w/ 1d nonlocal HS & $Q=0$)

Lin-L.-Yi-Zhang SIADS 13 (for PNP w/ 1d local HS & $Q=0$)

Let $r = r_1$ (ionic radius of 1st ion species) and $\lambda = r_2/r_1$, and let

$$V_c = \frac{(\lambda-1)(L-R)(\ln L - \ln R)}{(z_1\lambda - z_2)((L+R)(\ln L - \ln R) - 2(L-R))} - \frac{(D_1-D_2)(L+R)(\ln L - \ln R)^2}{(z_1D_1 - z_2D_2)((L+R)(\ln L - \ln R) - 2(L-R))};$$

$$V^c = \frac{(L-R)(\ln L - \ln R)}{z_1((L+R)(\ln L - \ln R) - 2(L-R))} - \frac{(D_1-D_2)(L+R)(\ln L - \ln R)^2}{(z_1D_1 - z_2D_2)((L+R)(\ln L - \ln R) - 2(L-R))}.$$

Theorem. [Size-Balance-Voltage V_c]

For $\varepsilon > 0$ small and $r > 0$ small,

(i) if $V > V_c$, then ion sizes enhance *current: $I(V;\varepsilon,r) > I(V;\varepsilon,0)$;*

(ii) if $V < V_c$, then ion sizes reduce *current: $I(V;\varepsilon,r) < I(V;\varepsilon,0)$.*

Theorem. [Size-Selectivity-Voltage V^c – independent of λ]

For $\varepsilon > 0$ small and $r > 0$ small,

(i) if $V > V^c$, the current I is increasing *in λ*

*(*smaller *positive ion species is* 'preferred'*, say, Na^+ over K^+);*

(ii) if $V < V^c$, the current I is decreasing *in λ*

*(*larger *positive ion species is* 'preferred'*, say, K^+ over Na^+).*

Scaling Properties in Boundary Concentrations

Write $I(V;\varepsilon,r) = I_0(V;\varepsilon) + I_1(V;\varepsilon)r + o(r)$.

$I_0(V;0) = I_0(V;L_j,R_j)$ – point-charge contribution;

$I_1(V;0) = I_1(V;L_j,R_j)$ – ion size component;

$V_c = V_c(L_j,R_j), \quad V^c = V^c(L_j,R_j)$ – two critical voltages.

Theorem. [Scaling Laws in Bdry Concentrations]

(i) I_0 *scales* linearly *in* (L_j,R_j)*:* $I_0(V;\sigma L_j,\sigma R_j) = \sigma I_0(V;L_j,R_j)$*;*

(ii) I_1 *scales* quadratically *in* (L_j,R_j)*:* $I_1(V;\sigma L_j,\sigma R_j) = \sigma^2 I_1(V;L_j,R_j)$*;*

(iii) V_c *and* V^c *scale* invariantly *in* (L_j,R_j)*:* $V_c^c(\sigma L_j,\sigma R_j) = V_c^c(L_j,R_j)$.

Many other important applications of GSP to PNP to Ion channel problems !!!

Thank You !