Mathematical understanding of ionic flows through membrane channels via Poisson-Nernst-Planck models

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1. Ion channels

2. Mathematical modelings

3. Dynamical system framework: Geometric singular perturbation theory

4. Why mathematics important

5. Some interesting observations
Ion channels. When they are open, ions can pass through them, entering or leaving the cell.

**Figure:** Ion channels
Two most relevant biological properties of ion channels: permeation and selectivity.

How to characterize these two properties?

By current-voltage (I-V) relations measured experimentally under different ionic conditions.
Properties of ionic flows through ion channels rely further on

- **External driving forces**: boundary potentials and concentrations;
- **Specific structural characteristics**: the shape of its pore and the distribution of permanent charge along its interior wall.
Figure: A type of potassium channel
Why we care?

- Channels are responsible for the *initiation and continuation* of the electric signals in the nervous system;
- In muscle cells, a group of channels is responsible for the *timely delivery* of the Ca\(^{++}\) ions that initiate a contraction;
- Malfunctioning channels *cause cystic fibrosis, cholera, and many other diseases*. Neuronal disorders (such as Alzheimer’s disease and Parkinson’s disease) may result from dysfunction of voltage-gated sodium, potassium and calcium channels;
- A large number of *drugs* (including valium and PCP) act directly or indirectly on channels.
3D Poisson-Nernst-Planck model

For ionic solutions with $n$ ion species, the PNP system reads

$$
\nabla \cdot \left( \varepsilon_r(r) \varepsilon_0 \nabla \Phi \right) = -e \left( \sum_{s=1}^{n} z_s C_s + Q(r) \right),
$$

$$
\nabla \cdot J_k = 0, \quad J_k = \frac{1}{k_B T} D_k(r) C_k \nabla \mu_k, \quad k = 1, 2, \ldots, n,
$$

where $r \in \Omega$ with $\Omega$ being a three-dimensional cylindrical-like domain representing the channel, $Q(r)$ is the permanent charge density, $\varepsilon(r)$ is the relative dielectric coefficient, $\varepsilon_0$ is the vacuum permittivity, $e$ is the elementary charge, $k_B$ is the Boltzmann constant, $T$ is the absolute temperature; $\Phi$ is the electric potential. Also, for the $k$th ion species, $C_k$ is the concentration, $z_k$ is the valence (the number of charges per particle), $\mu_k$ is the electrochemical potential depending on $\Phi$ and $\{C_j\}$, $J_k$ is the flux density, and $D_k(r)$ is the diffusion coefficient.
1D PNP model

First proposed by R. S. Eisenberg and W. Nonner

\[
\frac{1}{A(X)} \frac{d}{dX} \left( \varepsilon_r(X) \varepsilon_0 A(X) \frac{d\Phi}{dX} \right) = -e \left( \sum_{j=1}^{n} z_j C_j(X) + Q(X) \right),
\]

\[
d\mathcal{J}_i = 0, \quad -\mathcal{J}_i = \frac{1}{k_B T} \mathcal{D}_i(X) A(X) C_i(X) \frac{d\mu_i}{dX}, \quad i = 1, 2, \cdots, n,
\]

and the boundary conditions are, for \( i = 1, 2, \cdots, n, \)

\[
\Phi(0) = \mathcal{V}, \quad C_i(0) = \mathcal{L}_i > 0; \quad \Phi(l) = 0, \quad C_i(l) = \mathcal{R}_i > 0.
\]
Outline
Ion channels
Mathematical modelings
Dynamical system framework: Geometric singular perturbation
Why mathematics important
Some interesting observations

Figure: A singular orbit connecting two boundaries: three transversal intersections
The study of ion channels in general consists of two related major topics: structure of ion channels and ionic flow properties.

Thanks to the advances of the cryo-electron microscopy recognized in 2017 Nobel Prize, which makes it possible to obtain the structure of a given ion channel.

However, the present experimental techniques allow measurements of mainly the I-V relation—far away from measurements of internal dynamics of ionic flows. Not knowing internal dynamics in any detail adds another level of difficulty for an understanding of ion channel properties.

Generally speaking, the best hope is to first understand key features and robust phenomena of ion channel problems for a certain extremal parameter values in simple biological setups. That is where mathematical analysis steps in.
Cubic-like feature of I-V relations

Expand the I-V relation along $\varepsilon = 0$

$$I(V) = I_0(V) + \varepsilon I_1(V) + \varepsilon^2 I_2(V) + \varepsilon^3 I_3(V) + \cdots$$

and obtain

**Theorem**

If $L \neq R$, for $\varepsilon > 0$ small, then, up to the order of $\varepsilon^3$, the I-V relation $I = I(V)$ is a cubic function with three distinct real roots.

Our result is consistent with the cubic-like features of the I-V relation adopted in the FitzHugh-Nagumo simplification of the famous Hodgkin-Huxley systems which describe the propagation of action potential of *an ensemble of channels* in a biological membrane.
Effects from finite ion sizes

In our study of ionic flows with finite size, we focus on, taking the individual flux for example,

\[ J_k(V; d) = J_{k0}(V) + dJ_{k1}(V) + o(d). \]

\( J_{k1}(V) \) is the leading term that contains finite ion size effects, and is our main interest term. For it, we find out that

- under electroneutrality boundary conditions, one \textbf{always} has
  \[ \frac{\partial J_{k1}}{\partial V} > 0, \]

- Critical potential \( V_{kc} \) such that \( J_{k1}(V_{kc}) = 0 \) that balance the finite ion size effects on the individual fluxes;

- Scaling laws, for any \( s > 0 \),

\[ J_{k0}(V; sL_k, sR_k) = sJ_{k0}(V; L_k, R_k) \text{ and } J_{k1}(V; sL_k, sR_k) = s^2 J_{k1}(V; L_k, R_k). \]
Effects from small permanent charges

For small positive $Q$, we consider

$$\mathcal{I}_k(V; Q) = \mathcal{I}_k(0) + Q\mathcal{I}_k(1) + o(Q).$$

It turns out that

- the channel filter to which the permanent charge is distributed should be short and narrow. This is consistent with the typical structure of an ion channel.
- for the PNP system with two oppositely charged ion species or three ion species having two cations with the same valence
  - can reduce the flux of cation and enhance that of anion;
  - can enhance the fluxes of both cation and anion;
  - can reduce the fluxes of both cation and anion;
  - but cannot enhance the flux of cation while reduce that of anion.
References


Thank You for Your Attention!