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

Mingji Zhang

Department of Mathematics
New Mexico Tech

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

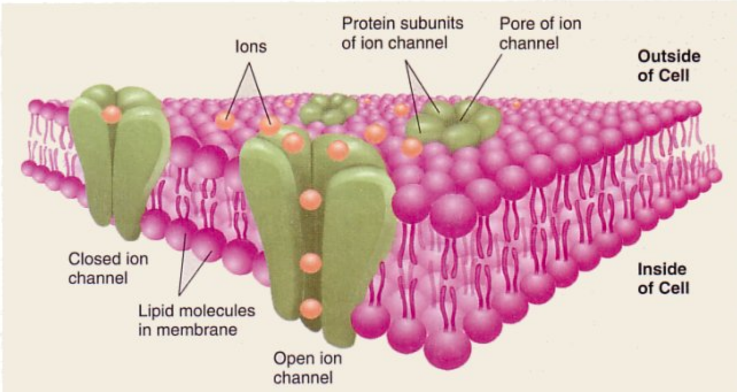

Figure: Ion channels

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.

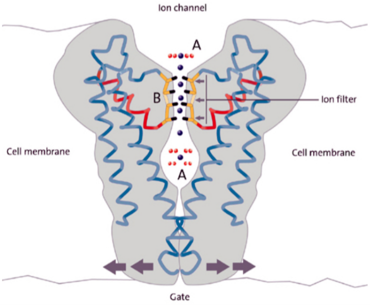

Figure: A type of potassium channel

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

$$\begin{aligned} &\nabla\cdot\Big(\varepsilon_r(\mathbf{r})\varepsilon_0\nabla\Phi\Big) = -e\Big(\sum_{s=1}^{n} z_s C_s + \mathcal{Q}(\mathbf{r})\Big), \\ &\nabla\cdot\mathcal{J}_k = 0, \quad -\mathcal{J}_k = \frac{1}{k_B T}\mathcal{D}_k(\mathbf{r})C_k\nabla\mu_k, \quad k = 1, 2, \cdots, n, \end{aligned} \tag{1}$$

where $\mathbf{r} \in \Omega$ with Ω being a three-dimensional cylindrical-like domain representing the channel, $\mathcal{Q}(\mathbf{r})$ is the permanent charge density, $\varepsilon(\mathbf{r})$ is the relative dielectric coefficient, ε_0 is the vacuum permittivity, e is the elementary charge, k_B is the Boltzmann constant, T is the absolute temperature; Φ is the electric potential. Also, for the kth ion species, C_k is the concentration, z_k is the valence (the number of charges per particle), μ_k is the electrochemical potential depending on Φ and $\{C_j\}$, $\mathcal{J}_k$ is the flux density, and $\mathcal{D}_k(\mathbf{r})$ is the diffusion coefficient.

1D PNP model

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

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

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

$$\Phi(0) = \mathcal{V}, \quad C_i(0) = \mathcal{L}_i > 0; \quad \Phi(l) = 0, \quad C_i(l) = \mathcal{R}_i > 0. \tag{3}$$

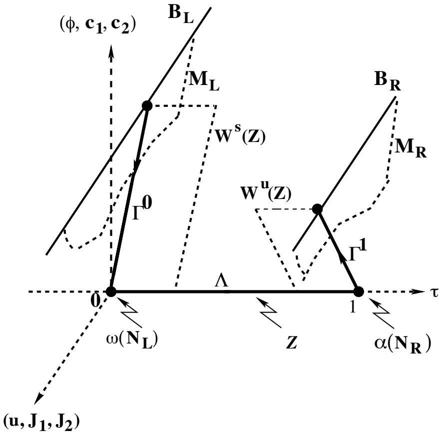

Figure: A singular orbit connecting two boundaries: three transversal intersections

- 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 ε^3, the I-V relation $\mathcal{I} = \mathcal{I}(V)$ 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,

$$\mathcal{J}_k(V;d) = \mathcal{J}_{k0}(V) + d\mathcal{J}_{k1}(V) + o(d).$$

$\mathcal{J}_{k1}(V)$ 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 always has

$$\frac{\partial \mathcal{J}_{k1}}{\partial V} > 0,$$

- Critical potential V_{kc} such that $\mathcal{J}_{k1}(V_{kc}) = 0$ that balance the finite ion size effects on the individual fluxes;
- Scaling laws, for any $s > 0$,

$$\mathcal{J}_{k0}(V; sL_k, sR_k) = s\mathcal{J}_{k0}(V; L_k, R_k) \text{ and } \mathcal{J}_{k1}(V; sL_k, sR_k) = s^2\mathcal{J}_{k1}(V; L_k, R_k).$$

Effects from small permanent charges

For small positive Q, we consider

$$\mathcal{J}_k(V;Q) = \mathcal{J}_{k0}(V) + Q\mathcal{J}_{k1}(V) + o(Q).$$

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.

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Thank You for Your Attention!