Ionic Diffusion through Confined Regions: From Molecular Description to Continuum Equations

Boaz Nadler
Department of Mathematics
Yale University

boaz.nadler@yale.edu

Joint work with Zeev Schuss and Amit Singer (Tel-Aviv University) and Bob Eisenberg (Rush Medical Center, Chicago).

Ionic Diffusion Through Confined Regions

- Confined Regions in the context of Protein Channels
- Possible Levels of Modeling
- The problems with the standard continuity equations
- Nonequilibrium molecular model of ionic diffusion
- (Exact) Derivation of continuum-type equations
- Conclusion for diffusion through protein channels
- Applications to fuel cells (?)

What are Protein Channels ?

Protein channels are large macromolecules embedded in the membrane that encloses all living cells.

Channels play a crucial role in many of life's processes:

- Message signalling in the nervous system
- Regularization of ionic concentrations inside the cell
- The majority of medicines we take affect specific channels

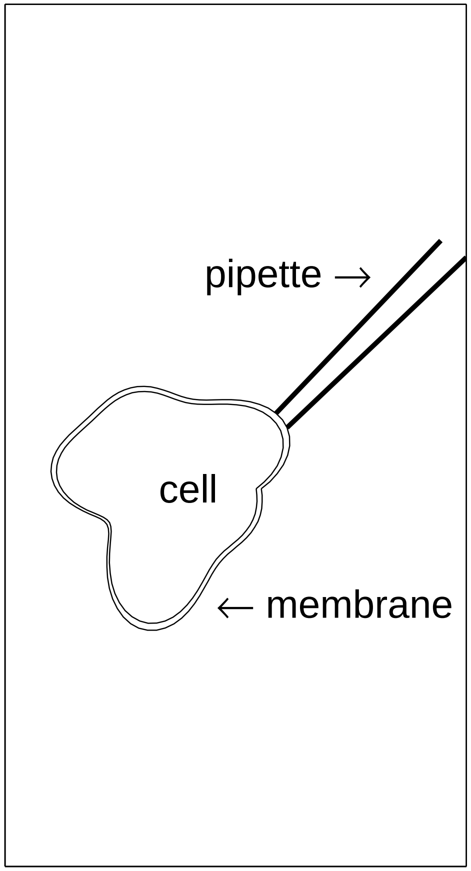
Thousands of different channels have been identified, and their sequence has been determined.

However, the 3-D structure of only five channels is known.

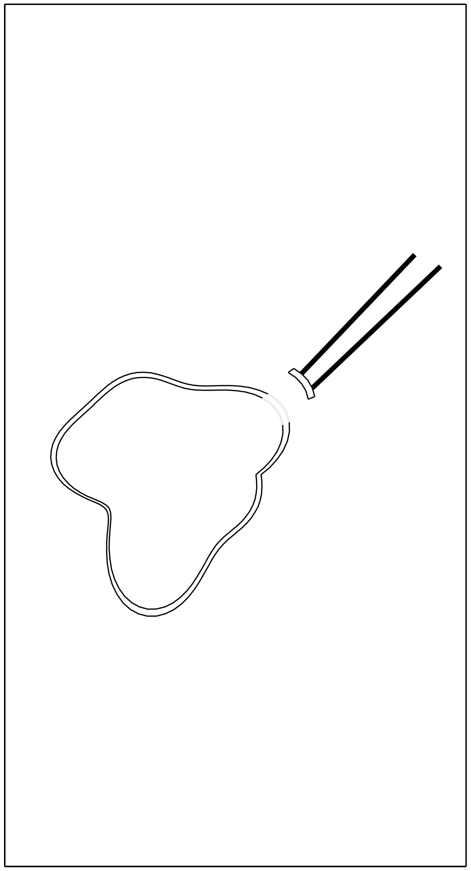
Channels have microscopic dimensions: diameter $d \approx 5\mathring{A} - 40\mathring{A}$, length $l \approx 25\mathring{A} - 50\mathring{A}$.

Modern Experimental Study of Channels

The Patch Clamp Experiment

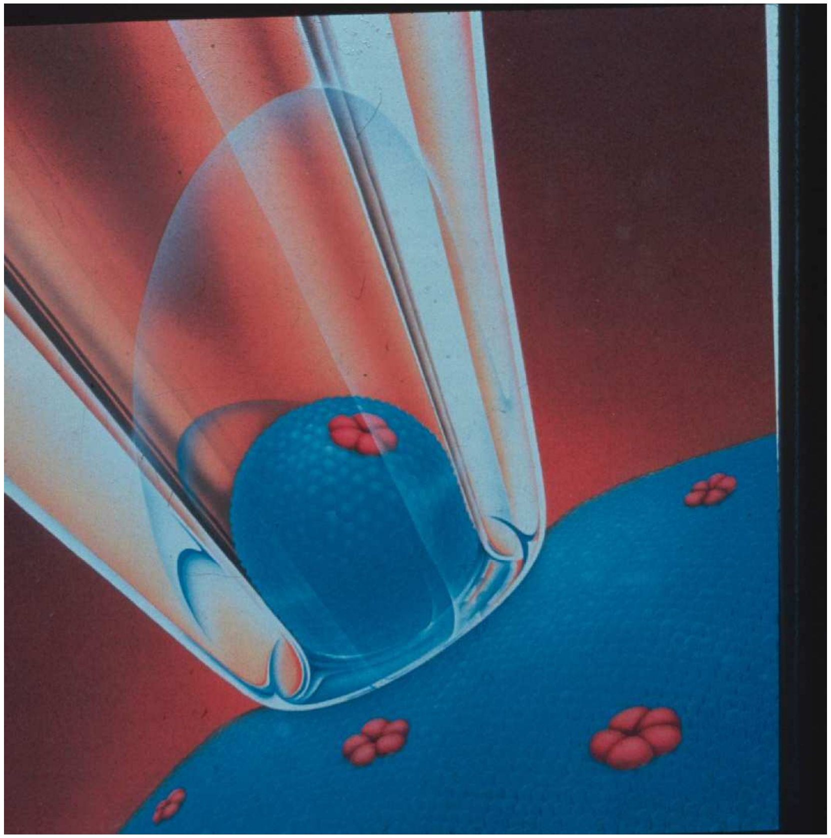


(a)

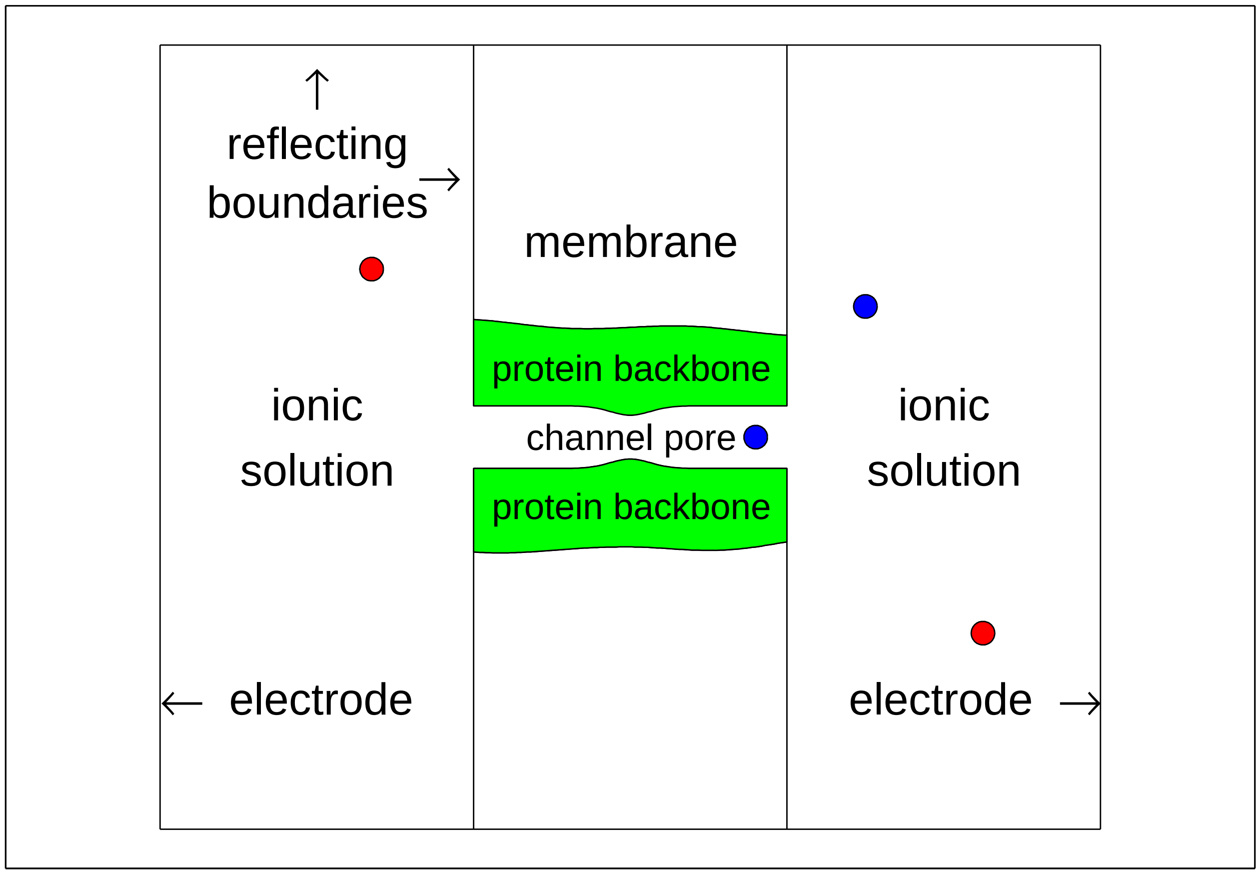


(b)

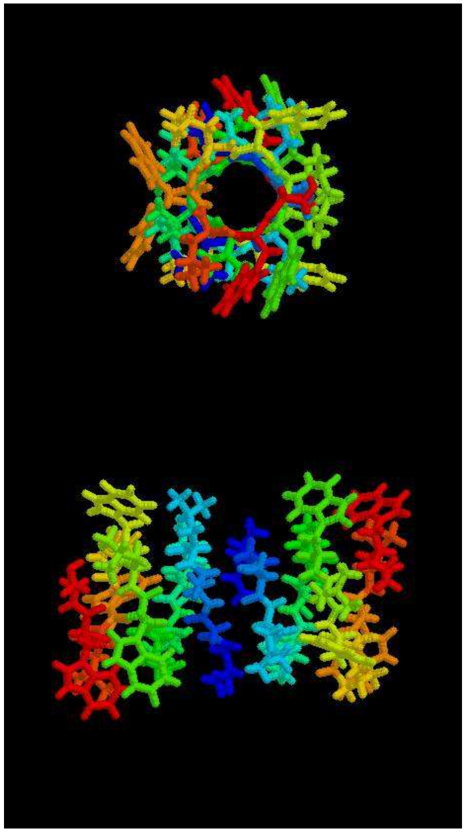
The Patch Clamp Experiment



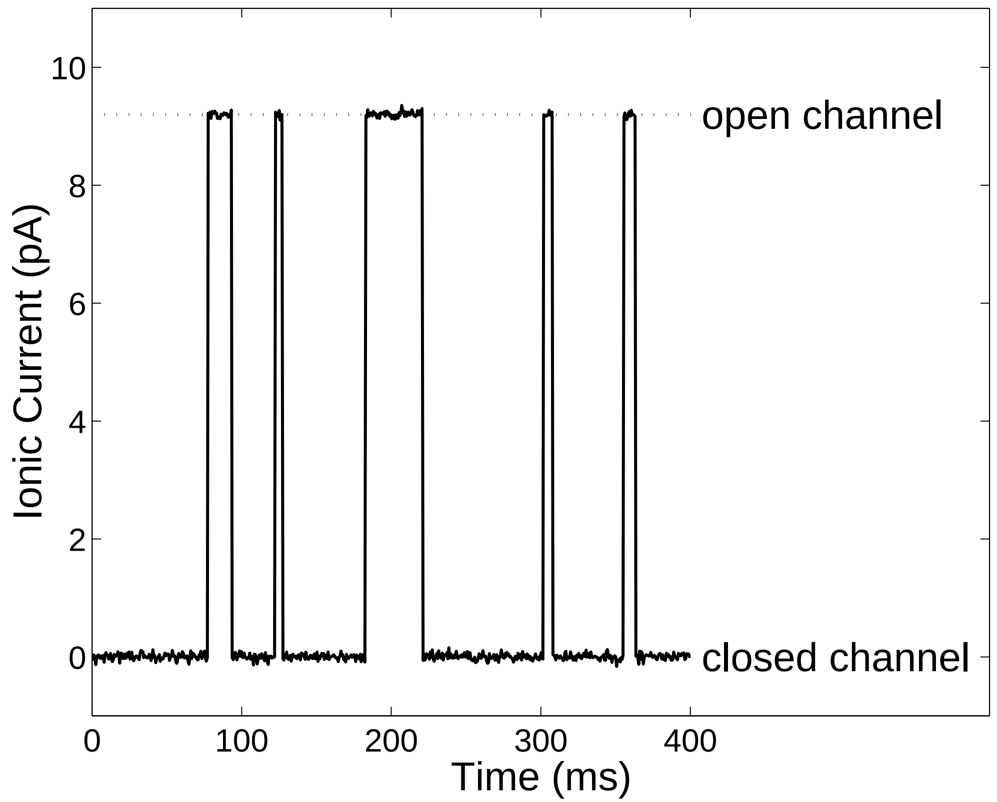
Permeation Through a Single Protein Channel



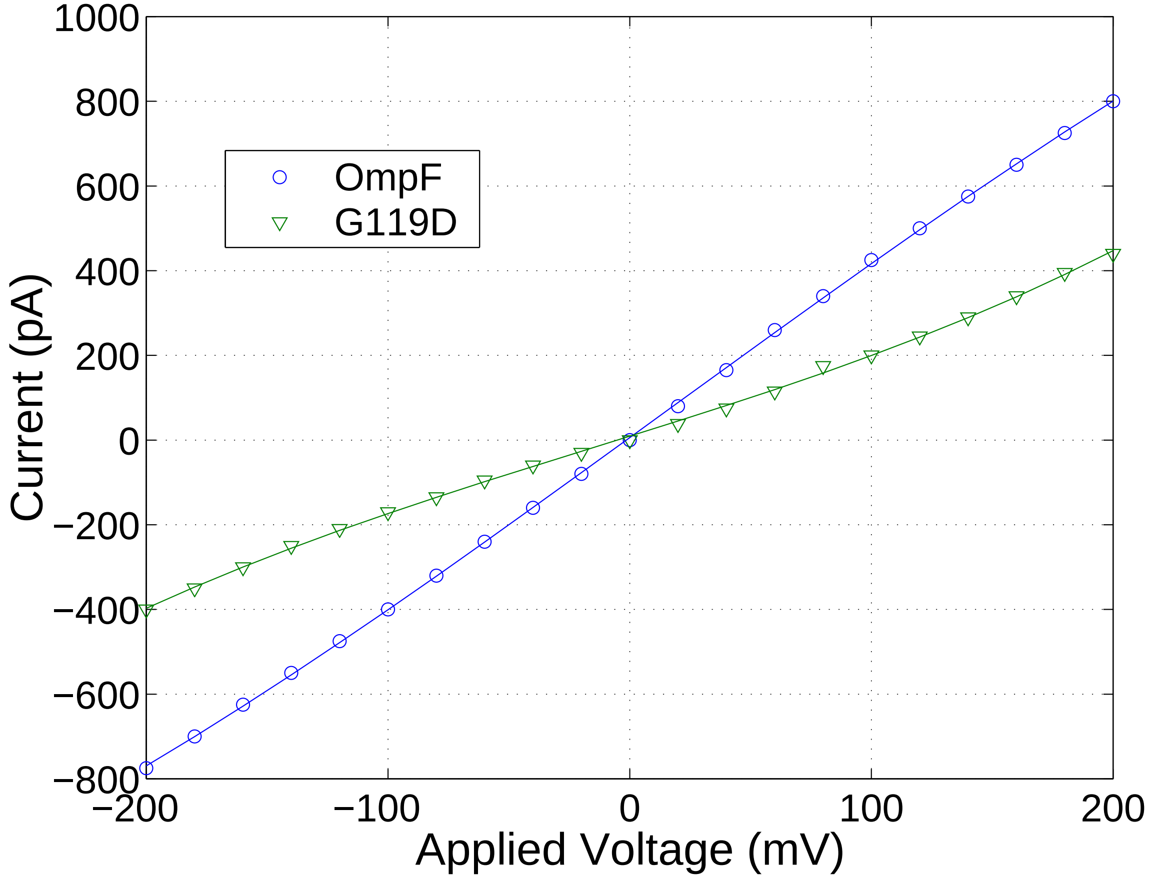
The Structure of a Protein Channel



Experimental Results of a Patch Clamp Experiment



Experimental Results: I-V curves

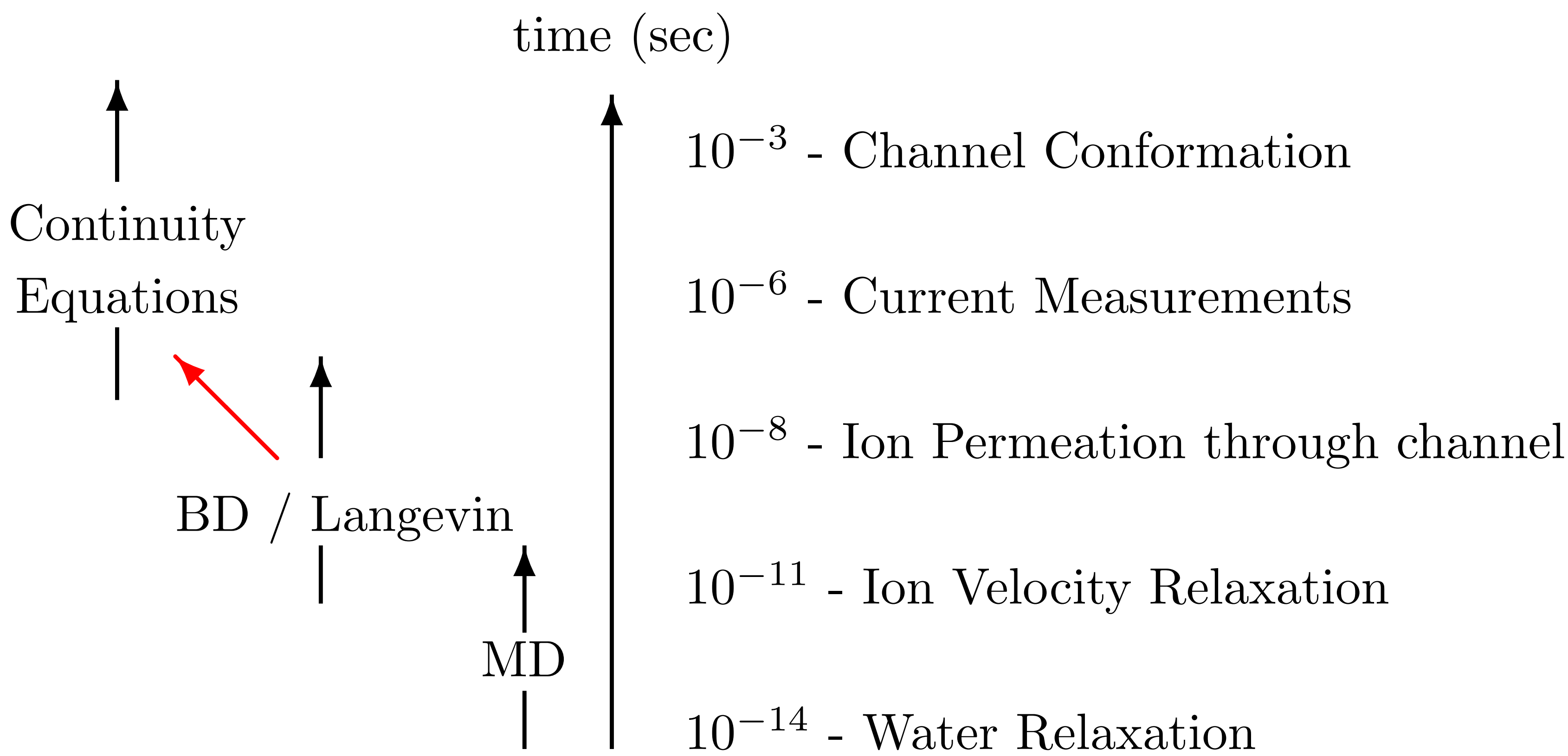


Theoretical Study of Protein Channels

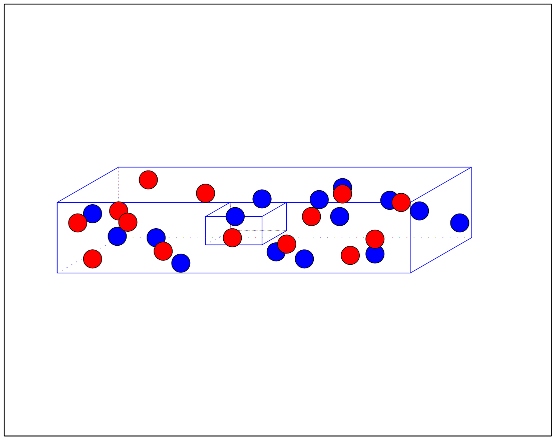
- Protein channels are natural biological *devices*.
- Each channel has a specific function, or input-output response.
- Inputs: bath concentrations, applied voltage.
- Output: Current (Selectivity, Gating characteristics).
- Channels function in *non-equilibrium*.

Goal: Predict Function (e.g. current) from Structure

Characteristic Time Scales and Models for Ion Permeation



Continuity Equations - The PNP System

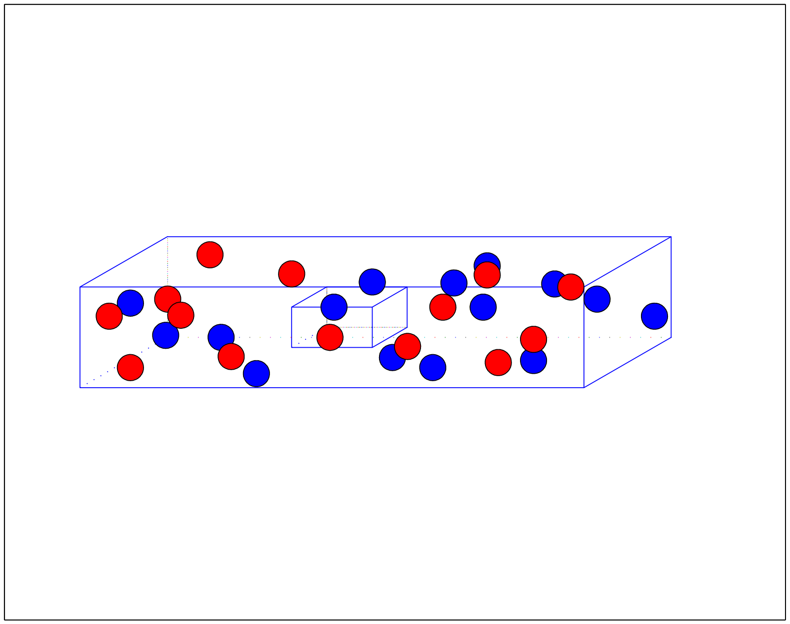


Macroscopic Treatment:

Assume constitutive relations, ionic flux J_p of species p is

$$\boldsymbol{J}_p(\boldsymbol{x}) = -D_p\left(\nabla c_p(\boldsymbol{x}) + c_p(\boldsymbol{x})\frac{ez_p}{kT}\nabla\psi(\boldsymbol{x})\right)$$

The Nernst-Planck Equation



Conservation laws of mass & momentum:

$$
\begin{aligned}
0 &= -\nabla \cdot \boldsymbol{J}_p(\boldsymbol{x}) \\
&= D_p \left[\Delta c_p(\boldsymbol{x}) + \nabla \left(c_p(\boldsymbol{x}) \frac{e z_p}{kT} \nabla \psi(\boldsymbol{x}) \right) \right]
\end{aligned}
$$

Nernst-Planck / Drift-diffusion equation

The Poisson-Nernst-Planck System

PNP = coupling of the NP equations to Poisson's equation.

Macroscopic variables are:

$c_p(\boldsymbol{x}), c_n(\boldsymbol{x})$ - positive & negative concentrations

$\psi(\boldsymbol{x})$ - potential of mean field.

Nernst-Planck equations:

$$0 = -\nabla \cdot \boldsymbol{J}_p(\boldsymbol{x}) = \Delta c_p(\boldsymbol{x}) + \nabla \left(c_p(\boldsymbol{x}) \frac{e}{kT} \nabla \psi(\boldsymbol{x}) \right)$$

$$0 = -\nabla \cdot \boldsymbol{J}_n(\boldsymbol{x}) = \Delta c_n(\boldsymbol{x}) - \nabla \left(c_n(\boldsymbol{x}) \frac{e}{kT} \nabla \psi(\boldsymbol{x}) \right)$$

Poisson Equation for mean field potential ψ:

$$\nabla \left[\varepsilon \cdot \nabla \psi(\boldsymbol{x}) \right] = - \left[c_p(\boldsymbol{x}) - c_n(\boldsymbol{x}) + \rho_{\text{fixed}}(\boldsymbol{x}) \right]$$

All three equations are non-linearly coupled.

Applications of the PNP system

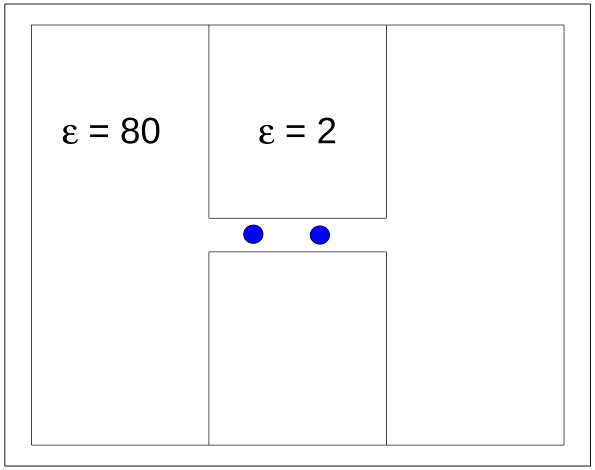
- Transport in Ionic Solution (1900's).
- Semiconductor Device Modeling, electron & hole transport (1950's).
- Plasma Physics
- Ionic Transport through narrow protein channels

▷ 1-D: Eisenberg & Chen 92', Nonner & al. 98'.
▷ 3-D: Kurnikova & al, 99', Hollerbach & al, 00'.

Advantage over MD / BD :

- Computationally efficient
- PNP equations are amenable to analysis

Are continuum equations valid in confined geometries ?



In a narrow protein channel:

- *Single Filing* - size of moving ions is comparable to channel diameter.
- *Selectivity - Is it due to the finite size of ions ?*
- *Non-Linear Phenomena in mixtures and unidirectional currents*

Improved PNP ?

Application of standard PNP to channel permeation is *problematic* (Corry & al 00', Schuss & al 01').

Two main problems:

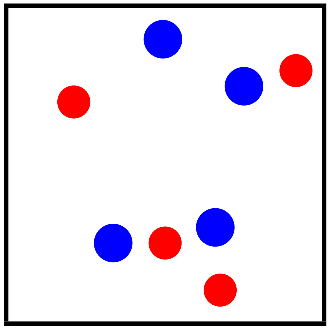
- In the PNP equations there are no discrete ions with finite size.
- Missing derivation from a molecular model.

Indeed the PNP equations fit only some of the experimental data for only some channels.

Question: How to derive "continuum type equations" that include microscopic structure ?

Equilibrium Statistical Physics

The theory of Equilibrium Statistical Physics describes microscopic features of systems *in equilibrium* by continuum type equations.

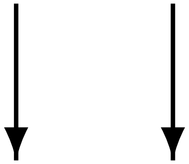


I) Ensemble of Configurations

II) Boltzmann Distribution

$$\Pr\{configuration\} \propto \exp(-Energy/kT)$$

III) Limit $\quad N, V \to \infty$ with $N/V = \rho$



A set of continuum Equations (BBGKY)

Marginal Densities

The *marginal* pdf of the first n particles is

$$p_N^{(n)}(\boldsymbol{r}_1, ..., \boldsymbol{r}_n) = \int p(\boldsymbol{r}_1, ...\boldsymbol{r}_N) d\boldsymbol{r}_{n+1} \cdots d\boldsymbol{r}_N$$

The *marginal* density for indistinguishable particles is

$$\rho_N^{(n)}(\boldsymbol{r}_1, ..., \boldsymbol{r}_n) = \frac{N!}{(N-n)!} p_N^{(n)}(\boldsymbol{r}_1, ..., \boldsymbol{r}_n)$$

This is the n-th order physical concentration.

BBGKY Equation for Equilibrium Density (n=1)

Example: Physical density

$$\rho(\boldsymbol{x}_1) = N \int p(\boldsymbol{x}_1, ..., \boldsymbol{x}_N) d\boldsymbol{x}_2 ... d\boldsymbol{x}_N$$

In the case of pairwise interactions,

$$U(\boldsymbol{x}_1, ..., \boldsymbol{x}_N) = \sum_{i<j} U_{1,2}(\boldsymbol{x}_i - \boldsymbol{x}_j)$$

in the limit $N, |V| \to \infty$, $\rho(\boldsymbol{r})$ satisfies the BBGKY equation

$$\nabla \rho(\boldsymbol{x}) + \rho(\boldsymbol{x}) \int \frac{e}{kT} \nabla_{\boldsymbol{x}} U_{1,2}(\boldsymbol{x} - \boldsymbol{y}) \rho(\boldsymbol{y} \,|\, \boldsymbol{x}) d\boldsymbol{y} = 0$$

Equilibrium as Flux = 0

Note that equation for $\rho(\boldsymbol{x})$ can be written as

$$\nabla \rho(\boldsymbol{x}) - \rho(\boldsymbol{x}) \frac{\bar{\boldsymbol{f}}(\boldsymbol{x})}{kT} = 0,$$

where

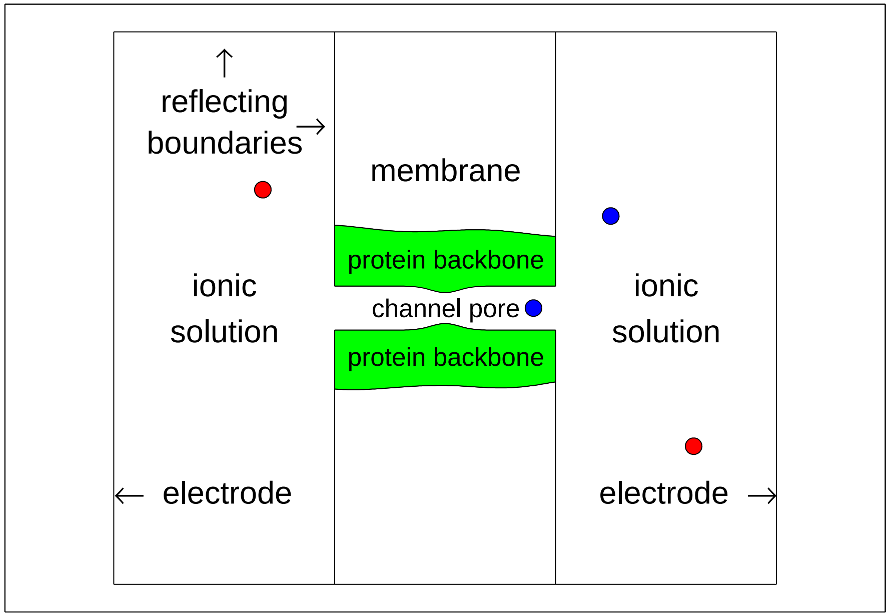
$$\bar{\boldsymbol{f}}(\boldsymbol{x}) = - \int e \nabla_{\boldsymbol{x}} U_{1,2}(\boldsymbol{x} - \boldsymbol{y}) \rho(\boldsymbol{y} \,|\, \boldsymbol{x}) d\boldsymbol{y}$$

Expression on LHS very similar to flux $\boldsymbol{J}$.

Recall that in equilibrium $\boldsymbol{J} \equiv 0$.

Can we derive a corresponding equation in non-equilibrium ?

Permeation Through a Protein Channel
A Non-Equilibrium problem



Cannot apply the tools of equilibrium stat. mech. :

- Different concentrations
- Externally Applied Voltage
- Stationary non-zero flux (current)

Equilibrium vs. Non-Equilibrium

Equilibrium	Non-Equilibrium
Configurations	Configurations
Boltzmann Distribution	?????
Static, no dynamics, flux=0	Net Particle Flow

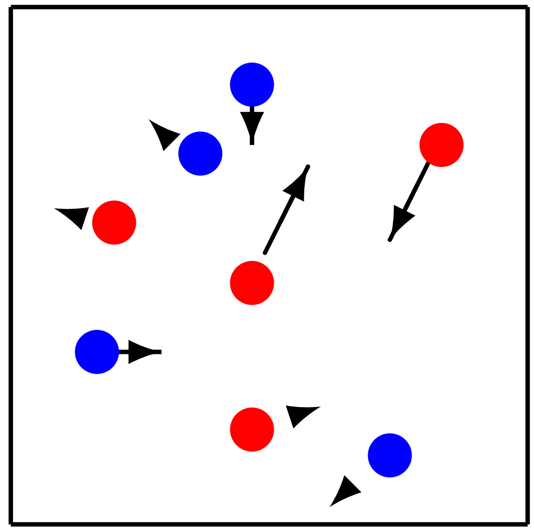
Description of Dynamics

Particle Trajectories

Predict Flux by Counting Trajectories

Trajectories Formulation

Finite region Ω
connected to an
external feedback



N positive ions

N negative ions

Langevin Model: system of $2N$ coupled stochastic equations

$$\ddot{\boldsymbol{x}}_k^p - \frac{\boldsymbol{f}_k^p(\tilde{\boldsymbol{x}})}{m} = -\gamma \dot{\boldsymbol{x}}_k^p + \sqrt{\frac{2\gamma kT}{m}}\,\dot{\boldsymbol{w}}_k^p$$

$$\underbrace{\ddot{\boldsymbol{x}}_k^n - \frac{\boldsymbol{f}_k^n(\tilde{\boldsymbol{x}})}{m}}_{\text{Newton's law}} = \underbrace{-\gamma \dot{\boldsymbol{x}}_k^n + \sqrt{\frac{2\gamma kT}{m}}\,\dot{\boldsymbol{w}}_k^n}_{\text{Friction \& Noise}},$$

From Trajectories to Probabilities

The stationary probability density function of *both* positions and velocities

$$p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) = \Pr\left\{ \{\boldsymbol{x}_j, \boldsymbol{v}_j\}_{j=1}^{2N} \right\}$$

satisfies the FPE (Fokker-Planck equation)

$$0 = \sum_j \mathcal{L}_j^p p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) + \sum_j \mathcal{L}_j^n p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}})$$

in $6N$-dimensional phase-space of all particles positions and velocities, with

$$\begin{aligned} \mathcal{L}_j^c p &= -\boldsymbol{v}_j^c \cdot \nabla_{\boldsymbol{x}_j^c} p + \nabla_{\boldsymbol{v}_j^c} \cdot \left(\gamma \boldsymbol{v}_j^c - \frac{\boldsymbol{f}_j^c}{m} \right) p + \\ & +\Delta_{\boldsymbol{v}_j^c} \frac{\gamma k T}{m} p \quad (c = p, n), \end{aligned}$$

Deriving Continuum Equations

Equilibrium

Configurations

Boltzmann Distribution

Limit $N, V \to \infty$

Continuum Equations

Non-Equilibrium

Configurations

Fokker-Planck Equation

Finite System

External feedback mechanism

??????

Marginal Densities

The Fokker-Planck equation provides the analogue of the Boltzmann distribution. Its solution gives the probability of configurations in non-equilibrium.

Now we follow the steps of equilibrium stat. mech: Marginal density of first particle

$$p_1(\boldsymbol{x}_1, \boldsymbol{v}_1) = \int p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}}) d\boldsymbol{x}_2 \cdots d\boldsymbol{x}_{2N}\, d\boldsymbol{v}_2 \cdots d\boldsymbol{v}_{2N}$$

and physical particle concentration at location $\boldsymbol{x}$ is

$$\rho(\boldsymbol{x}) = N p_1(\boldsymbol{x}_1) = N \int p_1(\boldsymbol{x}_1, \boldsymbol{v}_1) d\boldsymbol{v}_1.$$

In equilibrium statistical mechanics, $\rho(\boldsymbol{x})$ satisfies the BBGKY equation.

What happens in non-equilibrium ?

Equation for $p_1(\boldsymbol{x}, \boldsymbol{v})$

In equilibrium stat. mech. $p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}})$ is known explicitly from the Boltzmann distribution. Integrations can be performed directly.

In our case p is not known explicitly. However, it satisfies a Fokker-Planck equation.

Therefore: Integrate the full FPE for $p(\tilde{\boldsymbol{x}}, \tilde{\boldsymbol{v}})$

$$0 = \sum_j \mathcal{L}_j^p p + \sum_j \mathcal{L}_j^n p$$

over all phase space variables except $(\boldsymbol{x}_1, \boldsymbol{v}_1)$.

... some math ...

Results - An NP-type equation

In the overdamped limit $\gamma \gg 1$,

$$0 = -\nabla \cdot \boldsymbol{J}^p_{\text{non-eq}}(\boldsymbol{x})$$

where

$$\boldsymbol{J}^p_{\text{non-eq}}(\boldsymbol{x}) = -D_p \left[\nabla c_p(\boldsymbol{x}) - \frac{\bar{\boldsymbol{f}}^p(\boldsymbol{x})}{kT} c_p(\boldsymbol{x}) \right]$$

$\boldsymbol{J}^p_{\text{non-eq}}(\boldsymbol{x})$ - non-equilibrium physical flux of positive particles at $\boldsymbol{x}$.

This is a Nernst-Planck type equation defined in a finite domain Ω.

The average force $\bar{f}$

$$\bar{\boldsymbol{f}}^p(\boldsymbol{x}) = \boldsymbol{f}_{ed}(\boldsymbol{x}) + \bar{\boldsymbol{f}}_{sr}(\boldsymbol{x}) - e\nabla_{\boldsymbol{y}}\phi(\boldsymbol{y}|\boldsymbol{x})\Big|_{\boldsymbol{y}=\boldsymbol{x}}$$

where

- $\boldsymbol{f}_{ed}(\boldsymbol{x})$ - external and dielectric force on single ion
- $\boldsymbol{f}_{sr}(\boldsymbol{x})$ - average short range force due to all other ions

$$\bar{\boldsymbol{f}}_{sr}(\boldsymbol{x}) = \sum_{\text{species } j} \int \boldsymbol{f}_{sr}^{p,j}(\boldsymbol{x},\boldsymbol{y}) c^{j|p}(\boldsymbol{y}|\boldsymbol{x}) d\boldsymbol{y}$$

- $\phi^p(\boldsymbol{y}|\boldsymbol{x})$ - conditional potential satisfies conditional Poisson equation

$$\nabla \cdot [\varepsilon(\boldsymbol{x})\nabla\phi^p(\boldsymbol{y}|\boldsymbol{x})] = -\left[c^{p|p}(\boldsymbol{y}|\boldsymbol{x}) - c^{n|p}(\boldsymbol{y}|\boldsymbol{x}) + \rho_{fixed}(\boldsymbol{y})\right]$$

Main Result: Conditional PNP system

A stationary non-equilibrium system is described by a conditional PNP system of equations with conditional and unconditional densities and potentials defined in a finite domain Ω.

The average force $\bar{\boldsymbol{f}}$ in the Nernst-Planck equation depends on $c^{j|p}(\boldsymbol{y}|\boldsymbol{x})$ = conditional concentration of species j at $\boldsymbol{y}$ given particle of species p at $\boldsymbol{x}$.

Two important features:

- Finite size effects (Single Filing / Excluded Volume).
- Dielectric boundary force on a single ion due to its discrete charge.

Equation for the pair density

Equation for single ion density of species i depends on $\bar{\boldsymbol{f}}^i$ which depends on $c^{j|i}(\boldsymbol{y}|\boldsymbol{x})$.

By definition

$$c^{j|i}(\boldsymbol{y}|\boldsymbol{x}) = \frac{c^{i,j}(\boldsymbol{x},\boldsymbol{y})}{c^i(\boldsymbol{x})}$$

By similar methods $c^{i,j}(\boldsymbol{x},\boldsymbol{y})$ satisfies an equation of the form

$$\nabla_{\boldsymbol{x}} \boldsymbol{J}^{i,j}_{\boldsymbol{x}}(\boldsymbol{x},\boldsymbol{y}) + \nabla_{\boldsymbol{y}} \boldsymbol{J}^{i,j}_{\boldsymbol{y}}(\boldsymbol{x},\boldsymbol{y}) = 0,$$

defined in the 6-D domain $\Omega \times \Omega$.

Similar to the single ion density, the two dimensional fluxes contain average forces $\bar{\boldsymbol{f}}(\boldsymbol{x},\boldsymbol{y})$ that depend on the higher dimensional conditional densities $c^{k|i,j}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y})$.

Conditional Poisson-Nernst-Planck Hierarchy

The bulk concentrations $c_j(\boldsymbol{x})$ for species j satisfy Nernst-Planck equations with average forces $\bar{\boldsymbol{f}}^j(\boldsymbol{x})$.

Average force $\bar{\boldsymbol{f}}^j(\boldsymbol{x})$ depends on conditional densities $c_{i|j}(\boldsymbol{y}|\boldsymbol{x})$.

Second order densities satisfy Nernst-Planck equations with average forces that depend on higher order densities $c_{i|j,k}(\boldsymbol{z}|\boldsymbol{x},\boldsymbol{y})$, etc, etc.

Result: Conditional PNP Hierarchy of equations defined in finite domains.

Similar time dependent equations defined in infinite domains have been formulated from hydrodynamic continuity considerations in the study of transport coefficients of electrolytes (Ebeling 78', Bernard, Turq, Dufreche, 99'-02').

Missing Ingredients

Needed:

- A closure relation, to close the system.

  Example:

$$c_{i,j,k}(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{z}) = \frac{c_{i,j}(\boldsymbol{x}, \boldsymbol{y}) c_{j,k}(\boldsymbol{y}, \boldsymbol{z}) c_{i,k}(\boldsymbol{x}, \boldsymbol{z})}{c_i(\boldsymbol{x}) c_j(\boldsymbol{y}) c_k(\boldsymbol{z})}$$

- Boundary Conditions.

Back to Equilibrium

In equilibrium there is no flux. Therefore

$$\nabla \cdot \boldsymbol{J} = 0,$$

with boundary conditions $\boldsymbol{J}(\boldsymbol{x}) \cdot \boldsymbol{n} = 0$ for $\boldsymbol{x} \in \partial\Omega$.

In this case we recover the equilibrium equation

$$\boldsymbol{J}(\boldsymbol{x}) \equiv 0.$$

Thus the C-PNP equations are a non-equilibrium generalization of the BBGKY hierarchy.

The boundary conditions drive the system away from equilibrium.

The PNP system revisited

The approximation $c_{i|j}(\boldsymbol{y}|\boldsymbol{x}) = c_i(\boldsymbol{y})$ closes the system, and there is no need for b.c. for $c_{i|j}(\boldsymbol{y}|\boldsymbol{x})$.

Result: Closed Poisson-Nernst-Planck system with unconditional variables, with additional dielectric self force term $\boldsymbol{f}_{ed}(\boldsymbol{x})$

This term present only near dielectric interfaces. Without this term, the standard PNP system is recovered.

Conclusion: This approximation neglects all finite size effects, and leads to the PNP system but with an additional dielectric force term. Therefore, standard PNP is not valid in narrow channels or near dielectric interfaces.

Equilibrium vs. Non-Equilibrium

	Equilibrium	**Non-Eq.**
start point	static configurations Canonical Ensemble	dynamical description trajectories
$p(\boldsymbol{r}_1, ..., \boldsymbol{r}_N)$	Boltzmann	Fokker-Planck Eq.
Region	infinite	finite
b.c. for $\rho(\boldsymbol{x}, \boldsymbol{y})$	none/simple	feedback mechanism non-equilibrium b.c.
Closures	assumed simple cases	need derivation need general
Solutions	homogeneous solutions simple geometry	non-hom. systems complex geometry

Summary

Main Results:

1. Derivation of continuum equations for ion transport, from non-equilibrium molecular model. The result is a conditional PNP Hierarchy, which contains finite size & ion-ion electrostatic effects.

Conclusion: Standard PNP is valid only in bulk. Not valid in confined geometries or near interfaces.

2. C-PNP Hierarchy is the non-equilibrium generalization of the well known BBGKY Hierarchy of equilibrium statistical physics.

Summary

The study of stationary non-equilibrium systems of diffusing interacting particles requires three main ingredients:

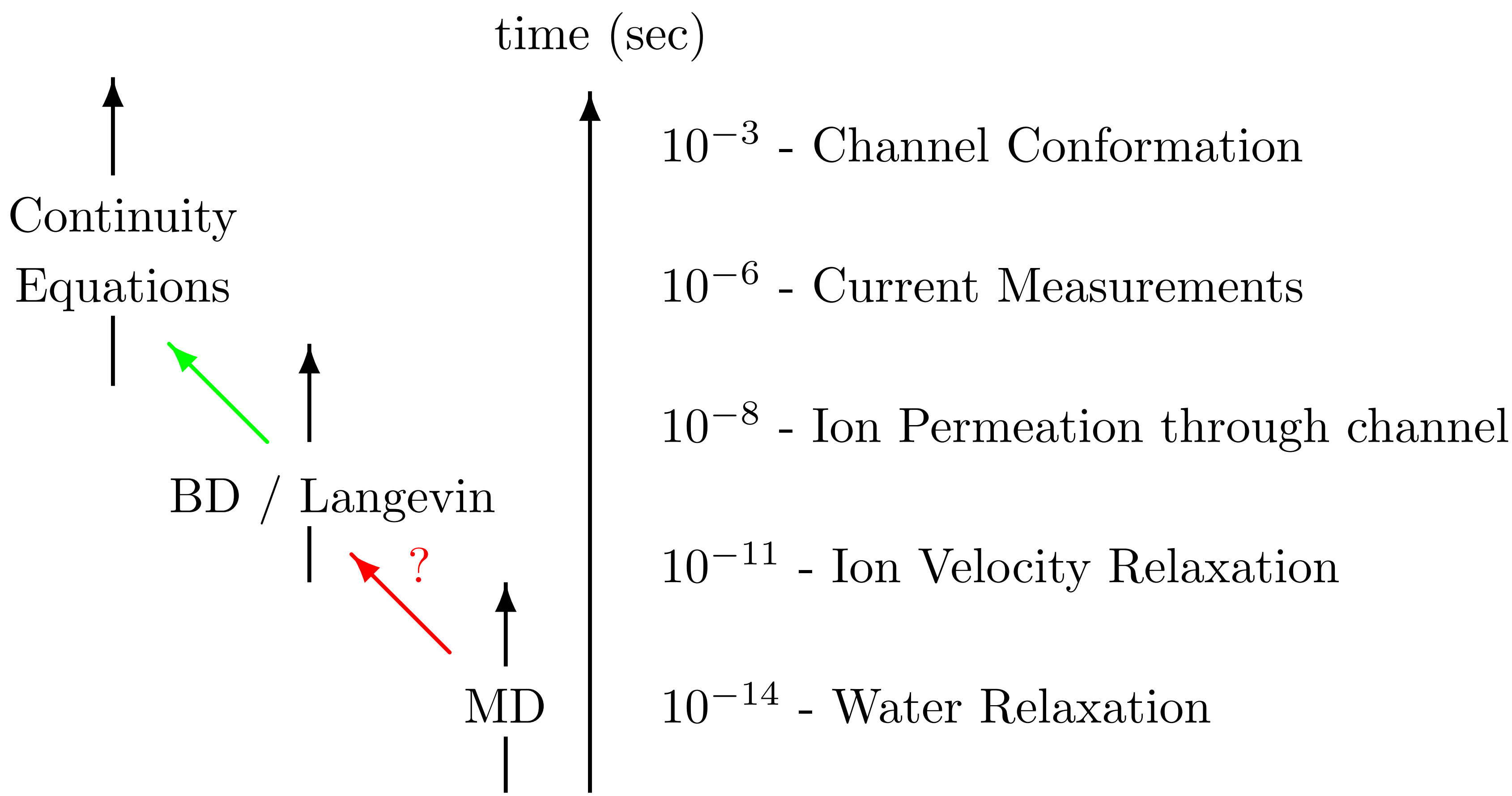
$\surd$ - ***A non-equilibrium molecular model (trajectories).***

$\surd$ - ***Boundary Conditions. - (separate talk)***

? - ***Non-Eq. Closure Relations / Smart Simulations***

Reference: Schuss, Nadler, Eisenberg, *Phys. Rev. E.* (64), 036116, 2001.

Open Research Problems
From MD to BD to continuum - a multiscale approach



Open Problems & Further Research

Physics

• Find the role of water in confined geometries (can it be described by noise and a dielectric coefficient?)

Mathematical Analysis

• Derive non-equilibrium closure relations for the C-PNP hierarchy of PDEs

• Find Criteria for a good closure / Error Analysis for a given closure

• Find lower dimensional approximations to solutions of higher dimensional PDEs

Numerical/Computational Analysis

• Develop efficient solvers for C-PNP in 6D

• Smart MD simulations