
Selectivity and conduction of a model calcium channel studied by the NP+LEMC method

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Combinations

Coupling DIRECT simulation with control cells: MD+DCV and DMC+DCV - well established techniques

Coupling DIRECT simulation with LEMC: DMC+LEMC – newly proposed:

- The poster of Ható, Boda, and Kristóf
- Z. Ható, D. Boda, T. Kristóf: Simulation of Steady-State Diffusion: Driving Force Ensured by Dual Control Volumes or Local Equilibrium Monte Carlo. *J. Chem. Phys.*, N:054109, 2012.

Coupling a transport equation with LEMC : NP+LEMC – freshly proposed:

- D. Boda, D. Gillespie: Steady state electrodiffusion from the Nernst-Planck equation coupled to Local Equilibrium Monte Carlo simulations. *J. Chem. Theory Comp.*, **8**: 824-829, 2012.

Coupling a transport equation with control cells : not possible

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Motivation

Purpose: computing the **steady-state diffusion** of particles through membranes/pores/channels on the basis of a molecular model.

This implies: simulation

Two things should be provided to study steady-state transport :

1. Treating dynamics:

- A simulation method (direct): *Molecular Dynamics* (MD) or *Dynamic Monte Carlo* (DMC) – see the poster of Ható et al.
- A transport equation (indirect): *Nernst-Planck* (NP) equation – this talk

2. Providing the steady-state driving force:

- Control cells: *Dual Control Volumes* (DCV) – the poster of Ható et al.
- *Local Equilibrium Monte Carlo* (LEMC) – this talk

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Electrodiffusion: the Nernst-Planck equation

$$\mathbf{j}^\alpha(\mathbf{r}) = -\frac{1}{kT} D^\alpha(\mathbf{r}) c^\alpha(\mathbf{r}) \nabla \mu^\alpha(\mathbf{r})$$

- $\mathbf{j}^\alpha(\mathbf{r})$ – flux density
- $D^\alpha(\mathbf{r})$ – diffusion coefficient profile (input)
- $c^\alpha(\mathbf{r})$ – density (concentration) profile
- $\mu^\alpha(\mathbf{r}) = \mu_c^\alpha(\mathbf{r}) + z^\alpha e \Phi(\mathbf{r})$ – electrochemical potential, where
 - $\mu_c^\alpha(\mathbf{r})$ – chemical work (chemical potential)
 - $z^\alpha e \Phi(\mathbf{r})$ – electrical work
- z^α – valence, e – elementary charge
- $\Phi(\mathbf{r})$ – mean electrical potential
- T – temperature, k – Boltzmann's constant

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Dynamics and driving force

- **Dynamics:** hidden in $D^\alpha(\mathbf{r})$
- **Driving force:** $\nabla\mu^\alpha(\mathbf{r})$
- **Task:** find $c^\alpha(\mathbf{r})$ and $\mu^\alpha(\mathbf{r})$ that
 - are computed on the basis of a molecular model
 - consistent with steady-state statistical mechanics – we need a closure between $c^\alpha(\mathbf{r})$ and $\mu^\alpha(\mathbf{r})$
 - together with $D^\alpha(\mathbf{r})$, they provide a flux that satisfy the continuity equation (conservation of mass):

$$\nabla \cdot \mathbf{j}^\alpha(\mathbf{r}) = 0$$

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Local Equilibrium Monte Carlo

- We divide the system into **elementary cells** $\mathcal{B}_i$ of volumes V_i
- Assume **local equilibrium** (LE) in the cells
- Assign electrochemical potential μ_i^α to them
- Perform independent **Grand Canonical Monte Carlo** (GCMC) simulations (fixed μ_i^α, V_i, T) for the cells
 - Assumption of LE is needed only if we strictly identify μ_i^α with the electrochemical potential.
 - Otherwise, μ_i^α is just the function driving the transport and the GCMC formalism is used by analogy.
- **Output:** c_i^α
- The **input** (μ_i^α) must be **iterated** until the resulting flux satisfy the continuity equation.

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The statistical mechanical closure

- EXISTING METHODS:
 - **Poisson-Nernst-Planck (PNP)** theory: the closure is Poisson-Boltzmann (PB) – huge literature (works fine for semiconductor devices, for example)
Disadvantage: mean field theory – works only for ideal solutions:
$$\mu^\alpha(\mathbf{r}) = kT \ln c^\alpha(\mathbf{r}) + z^\alpha e \Phi(\mathbf{r})$$
 - **Density Functional Theory** (DFT) – D. Gillespie, W. Nonner, B. Eisenberg: Coupling Poisson–Nernst–Planck and density functional theory to calculate ion flux, *J. Phys.: Condens. Matter*, **14**, 12129, 2002.
Disadvantage: works only in 1D

- OUR SUGGESTION: **Local Equilibrium Monte Carlo (LEMC)**

D. Boda, D. Gillespie: Steady state electrodiffusion from the Nernst-Planck equation coupled to Local Equilibrium Monte Carlo simulations. *J. Chem. Theory Comp.*, **8**: 824-829, 2012.

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Iteration algorithm

- **Divergence theorem:**

$$0 = \int_{\mathcal{D}_i} \nabla \cdot \mathbf{j}^\alpha(\mathbf{r}) dV = \oint_{\mathcal{S}_i} \mathbf{j}^\alpha(\mathbf{r}) \cdot d\mathbf{a}$$

$\mathcal{S}_i$ is the closed surface of $\mathcal{D}_i$

- Substituting the NP equation:

$$0 = \oint_{\mathcal{S}_i} D^\alpha c^\alpha[n] \nabla \mu^\alpha[n+1] \cdot d\mathbf{a}$$

- The **electrochemical potentials** for the next, $[n+1]$ th iteration are computed from the **concentrations** obtained in the $[n]$ th iteration.
- After **discretization** of the surface $\mathcal{S}_i$, a linear system of equations (a matrix equation) is obtained.
- **Boundary conditions** (concentrations and electrical potentials in the left and right hand side bulk regions) are naturally built in.

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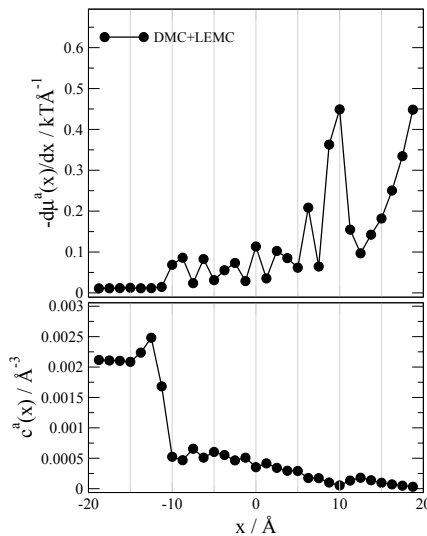
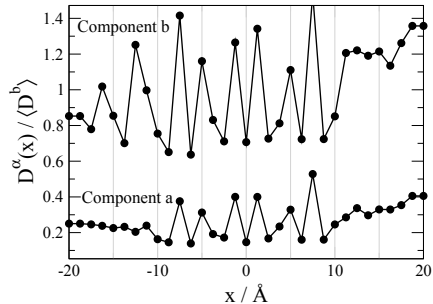
Pros and cons

- **Advantage over PNP:** it is beyond mean field (ionic correlations are naturally built in – simulation)
- **Advantage over DFT:** works for 3D and complex potential models
- **Advantage over DMC+LEMC:** it is fast
- **Disadvantage:**
 - dynamics is treated indirectly by a transport equation
 - particles' mobility is hidden in the auxiliary variable $D^\alpha(\mathbf{r})$
- **Where do we get $D^\alpha(\mathbf{r})$ from?**
 - Fit it **to experiments** as Gillespie did.
 - In model calculations, we fit it **to dynamical simulations** (DMC, MD).

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Example 1: diffusion of LJ particles through a Powles-membrane

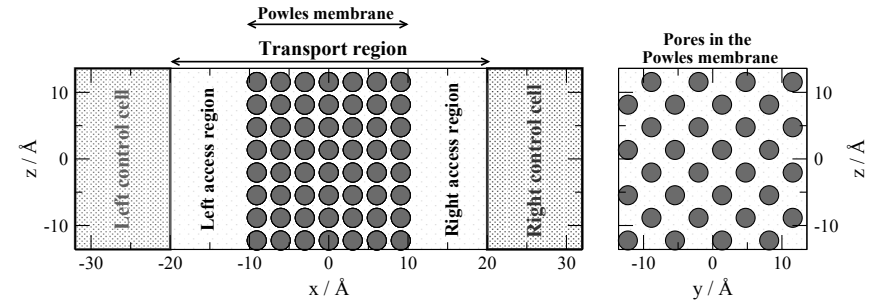
- Solving inverse problem from DMC+LEMC simulations:
- Computing $D^\alpha(x)$ profiles (left side) from the results of the DMC+LEMC simulation (right side).
- It is strongly fluctuating.



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Example 1: diffusion of LJ particles through a Powles-membrane

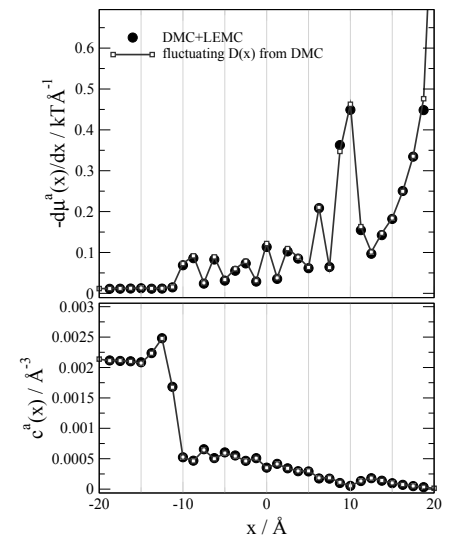
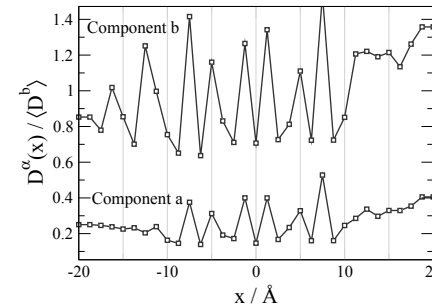
- **Powles-membrane:** cut&shifted LJ particles at fixed positions
- **Diffusing particles:** mixtures of cut&shifted LJ particles
- **Driving force:** concentration difference (simple diffusion)



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Example 1: diffusion of LJ particles through a Powles-membrane

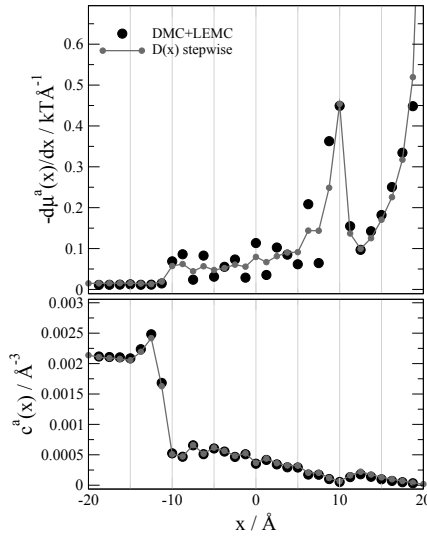
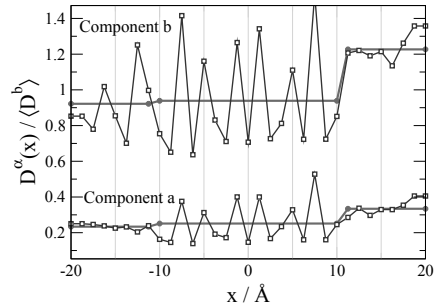
- Using this $D^\alpha(x)$ in the NP+LEMC calculation
- $d\mu^\alpha/dx$ and c^α profiles are reproduced.
- Not surprising!



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Example 1: diffusion of LJ particles through a Powles-membrane

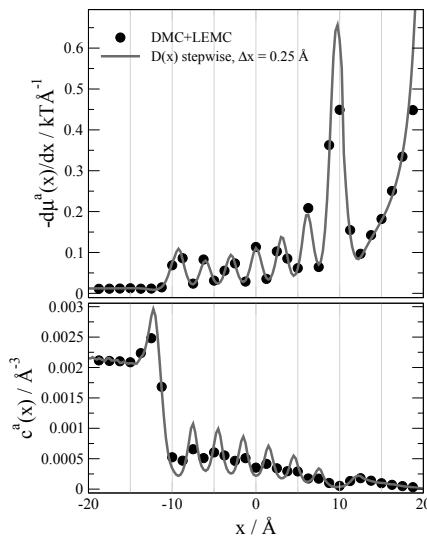
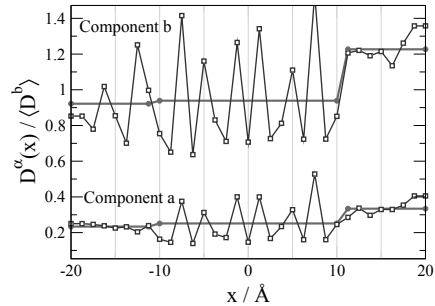
- Let us assign different constant D^α values to regions different conductivity (left bulk, membrane, right bulk)!
- Fine details of $d\mu^\alpha/dx$ and c^α profiles are not reproduced.



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Example 1: diffusion of LJ particles through a Powles-membrane

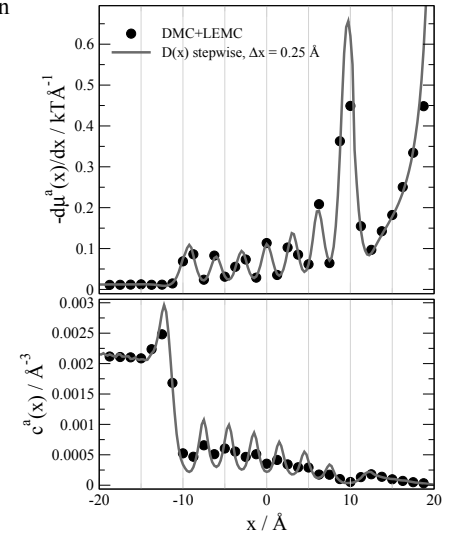
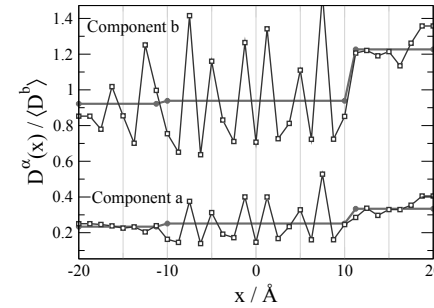
- Fine details of $d\mu^\alpha/dx$ and c^α profiles are **determined by the intermolecular forces**, NOT by the diffusion coefficient profiles.
- It is a **good approximation** to use stepwise constant $D^\alpha(x)$ profiles.



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Example 1: diffusion of LJ particles through a Powles-membrane

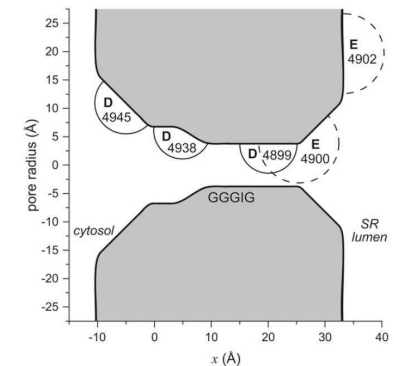
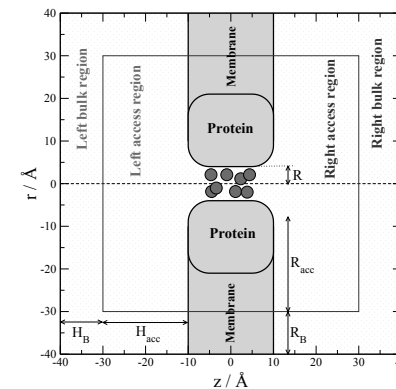
- Using the same stepwise $D^\alpha(x)$ function in an NP+LEMC with finer resolution.
- Fine details of $d\mu^\alpha/dx$ and c^α profiles are reproduced.



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Example 2: ionic transport through a model Ca channel Models

- Selectivity filter of Ca channel: COO^- rich region
- Crude model for model calculations - $R = 4 \text{ Angstroms}$
- Fine tuned model for the RyR ca channel by Dirk Gillespie, *Biophys. J.* **94**, 1169, 2008.
- Experimental current-voltage data are reproduced

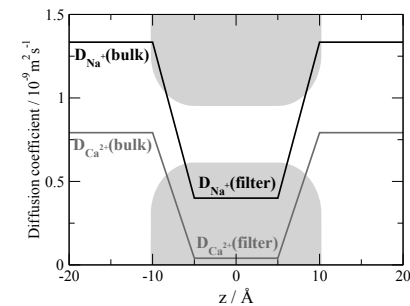


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Example 2: ionic transport through a model Ca channel

Diffusion coefficients

- Diffusion coefficients in the **bulk**: experimental values
- Diffusion coefficients in the **filter**: fitted values



$$\frac{D_{\text{Na}^+}(\text{bulk})}{D_{\text{Na}^+}(\text{filter})} = 34$$

from Gillespie's work

$$\frac{D_{\text{Na}^+}(\text{filter})}{D_{\text{Ca}^{2+}}(\text{filter})} = 7.89$$

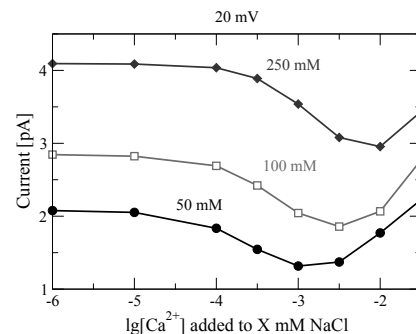
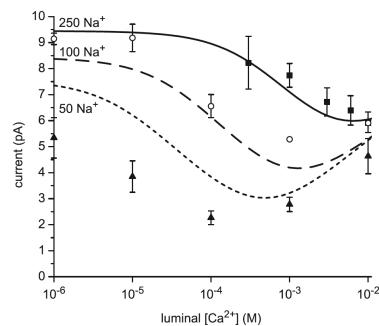
fitted to DMC simulation of Tamás Kristóf

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Example 2: ionic transport through a model Ca channel

Anomalous mole fraction effect: [NaCl]-dependence

- [NaCl] is changed, voltage is fixed 20 mV
- **Symbols**: experiments, **lines**: NP+DFT data obtained with the refined model
- NP+LEMC results obtained with the crude model
- Qualitative behavior is reproduced



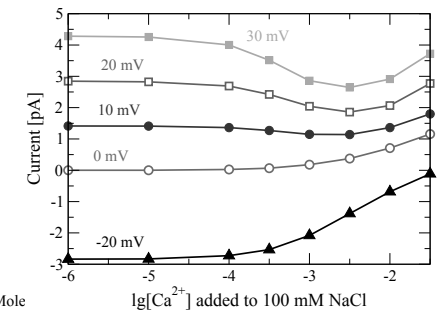
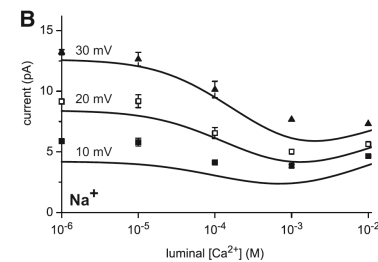
D. Gillespie, J. Giri, M. Fill: Reinterpreting the Anomalous Mole Fraction Effect: The Ryanodine Receptor Case Study, *Biophys. J.* **97**, 2212, 2009

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Example 2: ionic transport through a model Ca channel

Anomalous mole fraction effect: voltage dependence

- $[\text{NaCl}] = 10^{-2} \text{ M}$ on both sides
- $[\text{CaCl}_2] = 10^{-6} \text{ M}$ on the left CaCl_2 is added to the other side
- **Symbols**: experiments, **lines**: NP+DFT data obtained with the refined model
- NP+LEMC results obtained with the crude model
- Qualitative behavior is reproduced



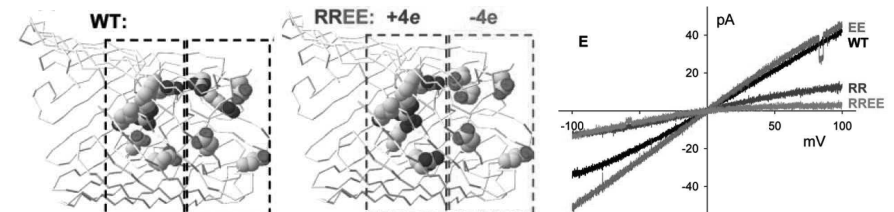
D. Gillespie, J. Giri, M. Fill: Reinterpreting the Anomalous Mole Fraction Effect: The Ryanodine Receptor Case Study, *Biophys. J.* **97**, 2212, 2009

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Example 3: a rectifying ion channel

Motivation: point mutation experiment of Miedema et al.

- Non-rectifying biological ion channel (wild-type (WT) OmpF porin) is engineered into a rectifying nanofluidic diode.
- Acidic and basic side chains are rearranged by point mutations to form a p-n junction (RREE).
- Electrolyte: 0.1 M NaCl



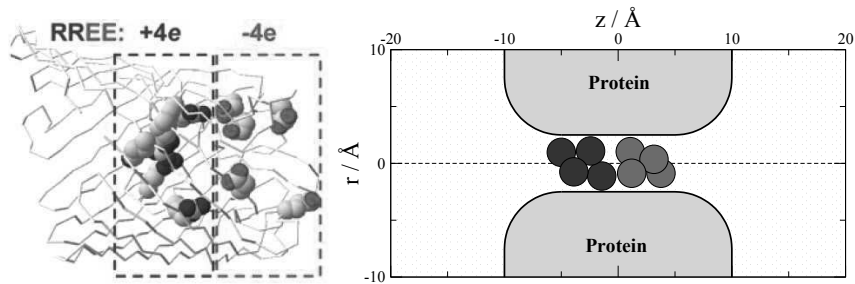
H. Miedema, M. Vroenenraets, J. Wierenga, W. Meijberg, G. Robillard, B. Eisenberg: A Biological Porin Engineered into a Molecular, Nanofluidic Diode, *Nano Letters*, **7**, 2886, 2007

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Example 3: a rectifying ion channel

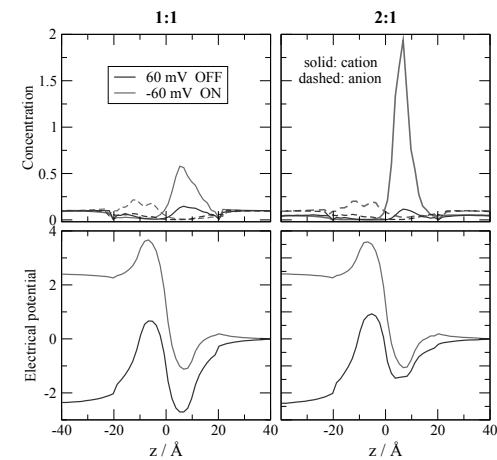
Reduced model of the rectifying pore

- **Positive** structural charges on the **left** and **negative** structural charges on the **right** side
- They are free to move, but confined to their respective regions.
- Both 1:1 and 2:1 electrolytes were tested.



Example 3: a rectifying ion channel

Results of NP+LEMC calculations



- Experimental results are reproduced qualitatively
- Rectifying is better for 2:1 electrolytes

