Simulating Ion Transport through Selective and Rectifying Ion Channels Using Local Equilibrium Monte Carlo

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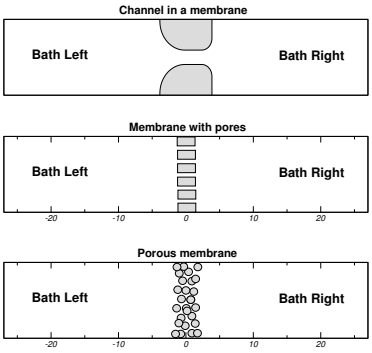
Motivation



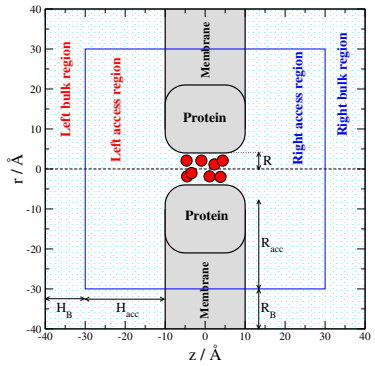
Systems of interest:
- ion channels in biological membranes
- synthetic nanopores
- silicate membranes

Phenomena of interest:
- Selective transport and/or adsorption
- Rectification

Models:
- Molecular models – coarse grained to some degree

Methods:
- Simulations – combined with transport equation

Model



- **Ions:** charged hard spheres
- **Water:** dielectric continuum
- **Protein & membrane:** pore confined by hard walls containing the side chains of the "important" amino acids
- **Simulation cell:** contains
  - the pore embedded in a membrane
  - access regions
  - bulk regions (control cells)
- **Boundary conditions:** voltage and concentrations are prescribed in the baths

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
- $c^\alpha(\mathbf{r})$ – concentration profile
- $\mu^\alpha(\mathbf{r})$ – electrochemical potential profile (contains the external electric field)
- We need a statistical mechanically correct relation between $c^\alpha(\mathbf{r})$ and $\mu^\alpha(\mathbf{r})$.

Local Equilibrium Monte Carlo

- **Suggestion**: divide the domain of solution (blue line) into volume elements, V_i.
- Perform Grand Canonical Monte Carlo simulation using the local μ_i^α in V_i.
- **Key**: assume **LOCAL EQUILIBRIUM** in V_i [1-3].
- **Acceptance probability:** ($\chi = \pm 1$ for insertion/deletion)

$$p_{i,\chi}^\alpha(\mathbf{r}) = \frac{N_i^\alpha! V_i^\chi}{(N_i^\alpha + \chi)!} \exp\left(-\frac{\Delta U(\mathbf{r}) - \chi \mu_i^\alpha}{kT}\right)$$

NP+LEMC [1-3]

- An iteration procedure is needed to make the system self consistent [1-3], namely, the flux satisfies the **continuity equation** (conservation of mass):

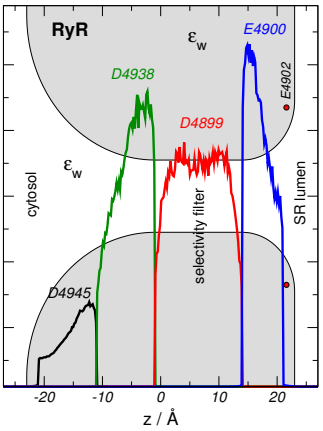
$$\nabla \cdot \mathbf{j}^\alpha(\mathbf{r}) = 0$$

- $\mu^\alpha(\mathbf{r})$ is iterated until convergence is reached
- **Diffusion coefficients** are
  - Experimental values in the baths
  - Fitted to experiments in the pore

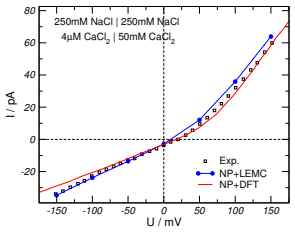
The algorithm:

$$\mu_i^\alpha[n] \xrightarrow{\text{LEMC}} c_i^\alpha[n] \xrightarrow{\text{NP}} \mathbf{j}_i^\alpha[n] \xrightarrow{\nabla \cdot \mathbf{j}^\alpha = 0} \mu_i^\alpha[n+1]$$

Ryanodine Receptor (RyR) Ca^{2+}-release calcium channel

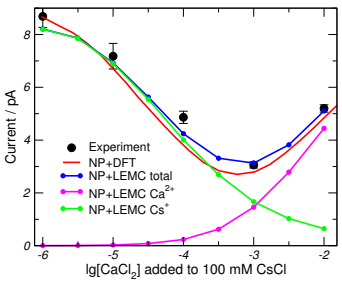


- 3D model [3] contains amino acid side chains based on experimental facts and the 1D model of Dirk Gillespie [4-5].
- Output: current-voltage curves for various compositions of electrolytes on the two sides of the membrane:

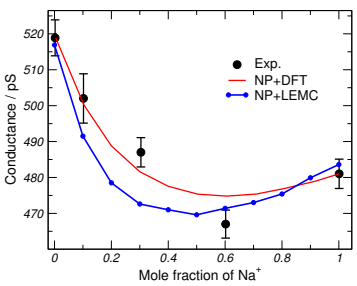


Anomalous mole fraction experiment: voltage is fixed, electrolyte composition is varied

$CaCl_2$ is added to 100 mM CsCl on the SR side at -20 mV.



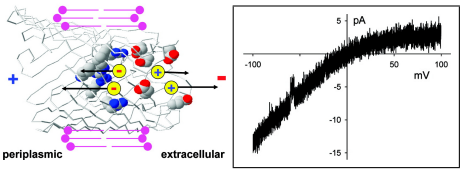
CsCl+NaCl mixture at 250 mM total concentration (both sides).



Experimental data and NP+DFT results of Gillespie are from Refs. [4-5].

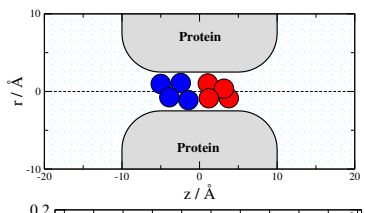
Rectifying ion channel motivated by a mutated OmpF porin

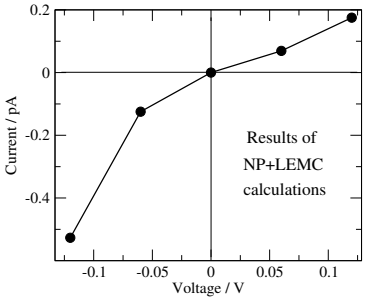
Motivation: experiments of Miedema et al. [6] for an OmpF porin ion channel.

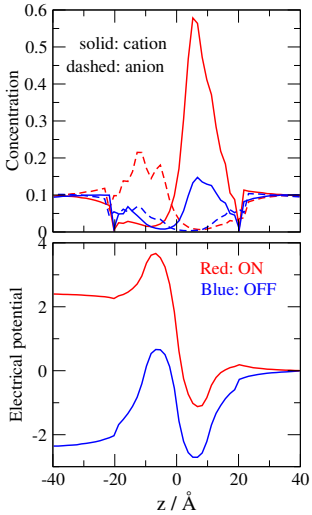


- The wild-type OmpF porin has been mutated (RREE) into a rectifying channel.
- All-atom molecular dynamics simulations failed to reproduce this behavior.

Let us try a reduced model! It contains the positive & negative amino acids in order to mimic the PN junction of a rectifying diode.







Conclusion

- NP+LEMC is an efficient combined transport equation & simulation method that is able to compute steady state diffusion through pores.
- **Advantage**: fast and it gives correct relation between $c^\alpha(\mathbf{r})$ and $\mu^\alpha(\mathbf{r})$.
- **Disadvantage**: dynamics is hidden in $D^\alpha(\mathbf{r})$
- **Solution**: a dynamical simulation method can be used instead of NP [7].

References

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