Multiscale modeling of ion transport through nanopores: the case study of a rectifying bipolar nanofluidic diode

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Hybrid Methods in Molecular Simulation

Cagliari, Italy

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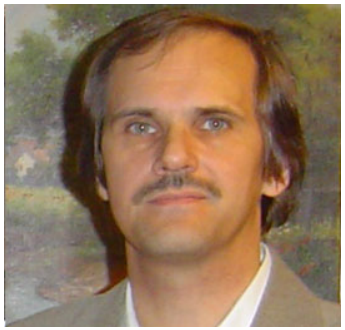
Cagliari, 2017.04.03-04.

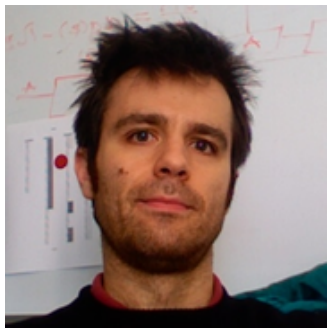
People on board: international multiscale modeling network

The University of Pannonia / iASK team: Dezső Boda, Tamás Kristóf, Mónika Valiskó, Zoltán Ható

The Chicago wizard: Dirk Gillespie

The Italian connection: Simone Furini, Claudio Berti



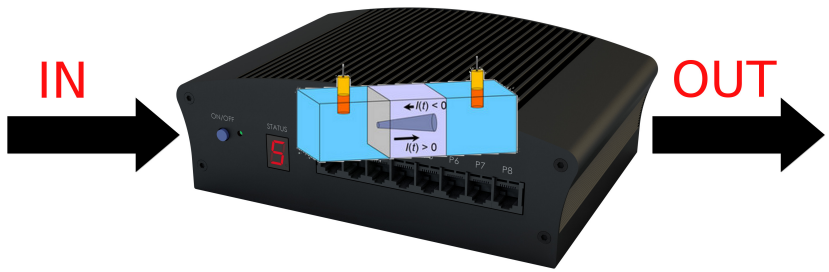

The Mathematicians:
Bart Matejczyk, M.-T. Wolfram, Jan Pietschmann



The Carloni Group (Jülich):
Paolo Carloni, Justin Finnerty

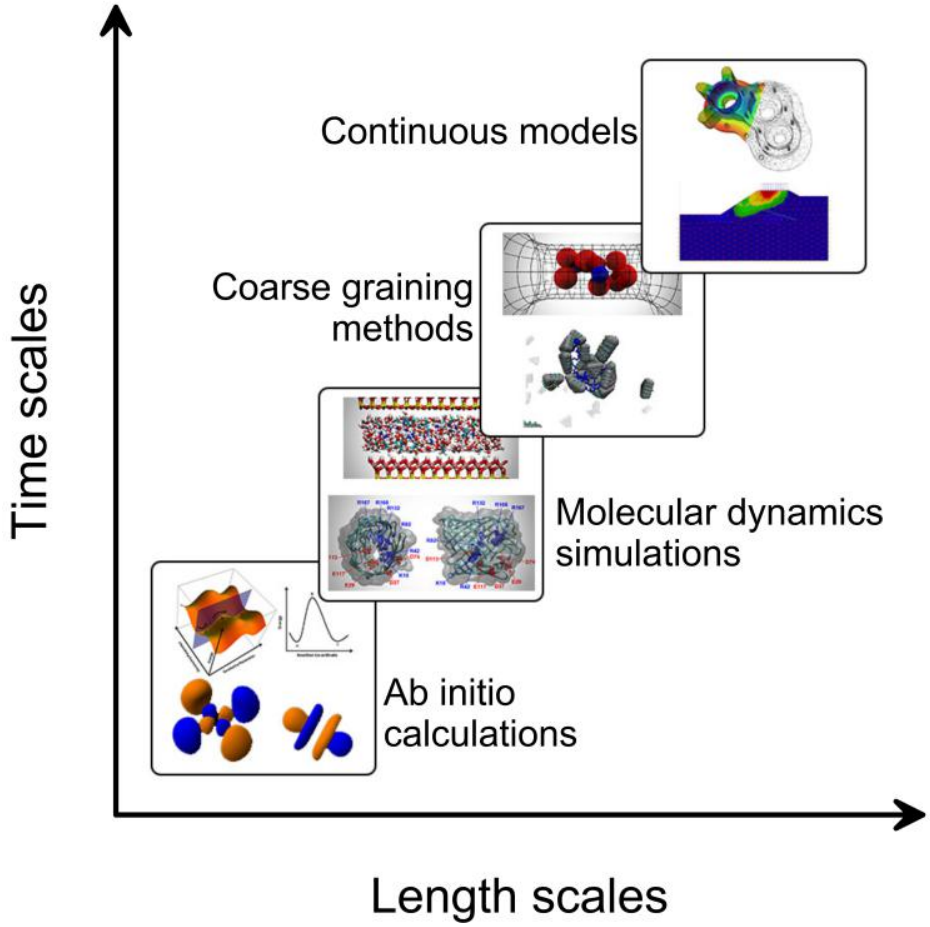

Study nanodevices and peek into the black box

- Many devices are **black boxes**, in the sense that **input-output** relations (response functions) are known, but we know much less about their internal structures.
- Their inner mechanisms are usually studied with continuum theories (for example, PNP for semiconductor devices)
- Dimensions of the devices, however, continuously shrink (nanodevices)
- The **molecular behavior** of the *core unit* of the device (that can be very different from bulk behavior) determines **device behavior**
- We need to study the *core unit* on the molecular level with **modeling** and **computation**

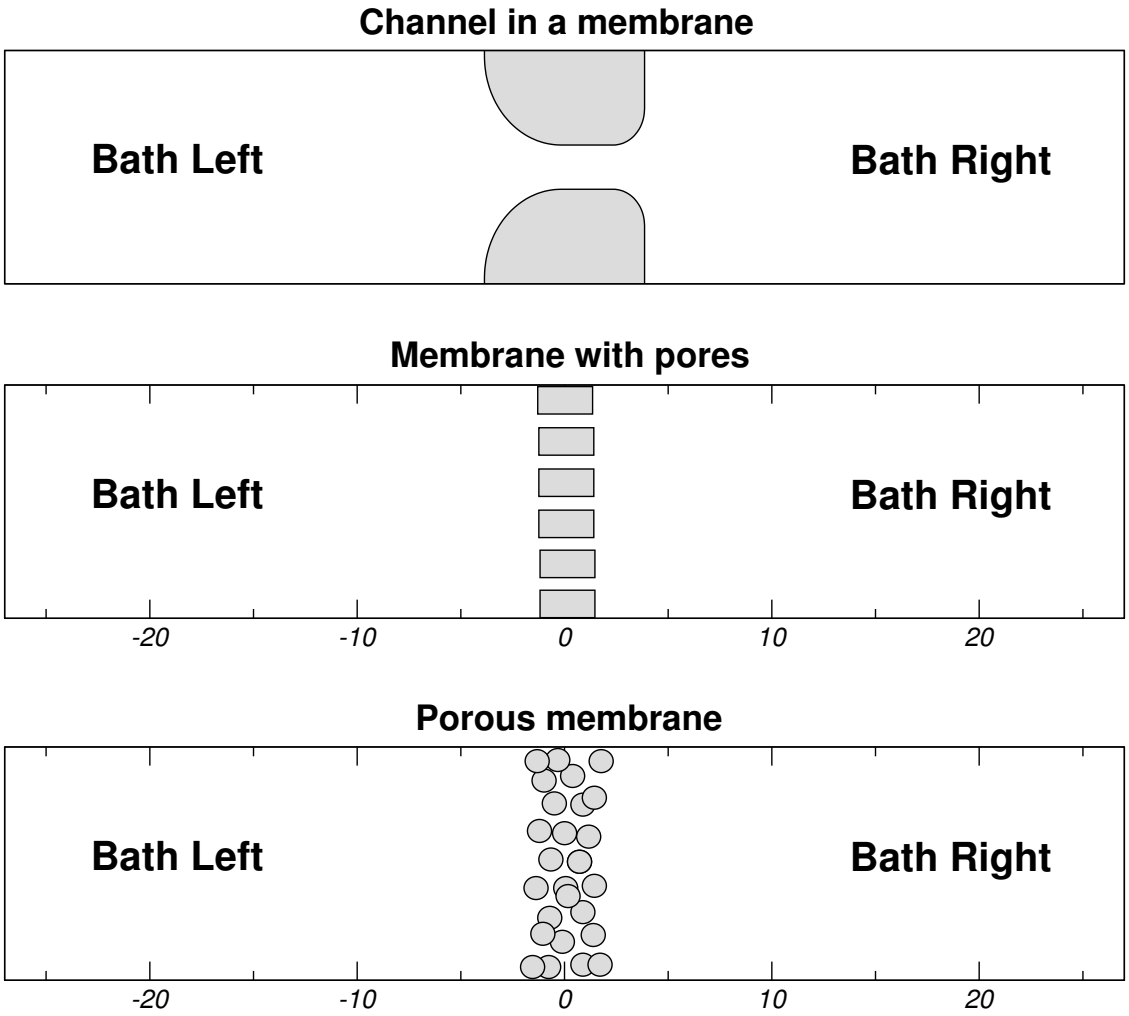


Core units and the devices „around” them have different length/time scales

- Different length and time scales
- Different techniques to deal with them
- What is the relation of the different levels?



In our studes, the core units are porous materials



Examples: ion channels in biological membranes, synthetic nanopores, silicate membranes (zeolite, silicalite, kaolinite)

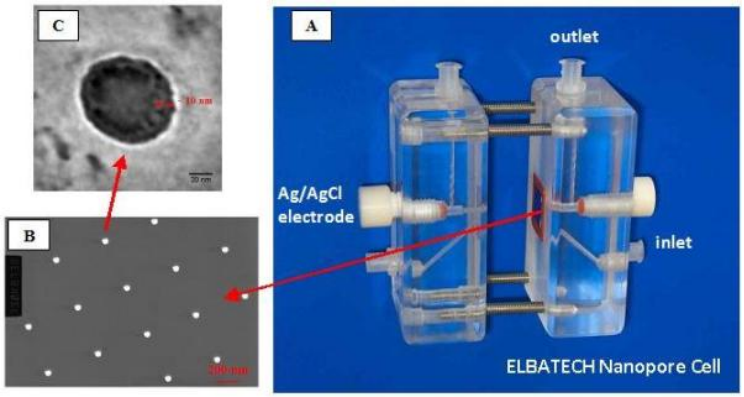
Phenomena of interest: selectivity, permeation, rectification

Models: from all-atom to coarse-grained (reduced)

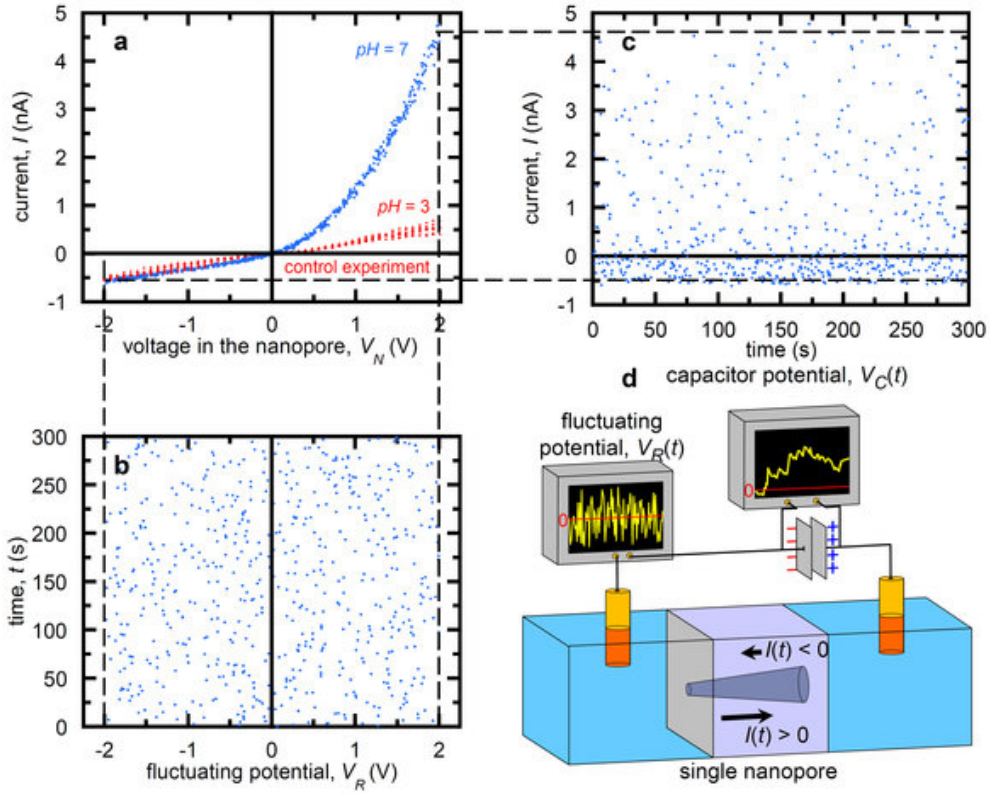
Motivation: technology, biology

Nanopore as a device – a rectifying diode

- Pore etched into plastic foil
- Dimensions: μm length, nm radius
- **Input**: voltage
- **Output**: current
- Engineering point of view: voltage-current relation

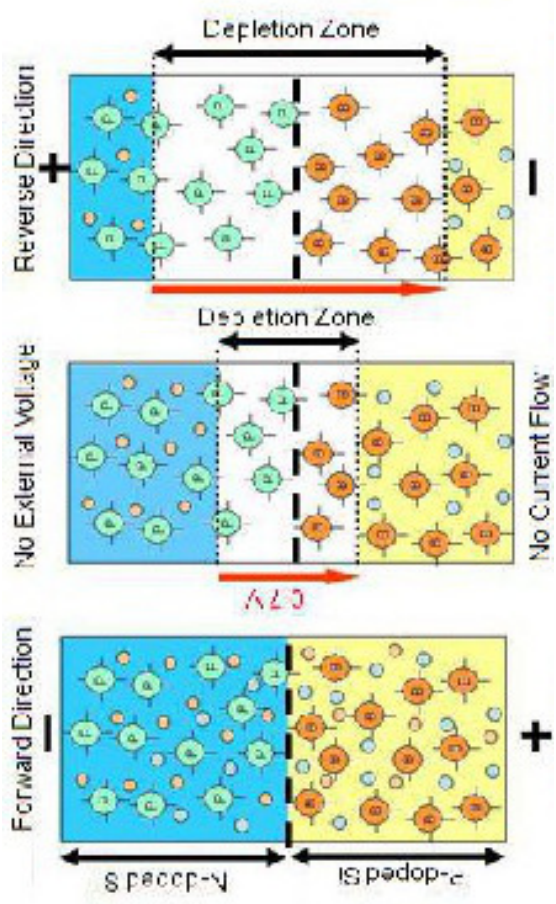


- Black box response function
- **But what is in the black box?**

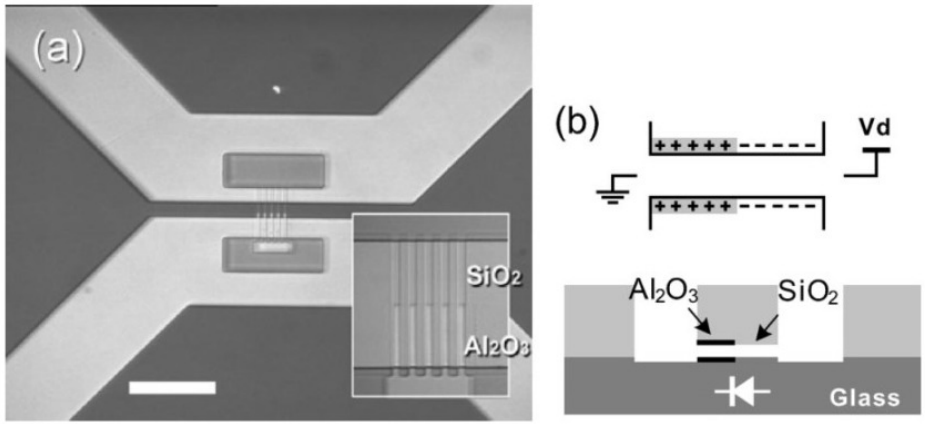


Nanopore fabrication

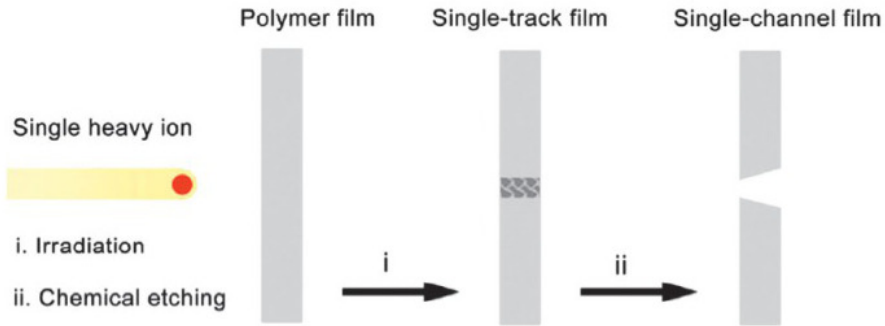
- Motivation: semiconductor p-n junctions



- PDMS or PET nanopores

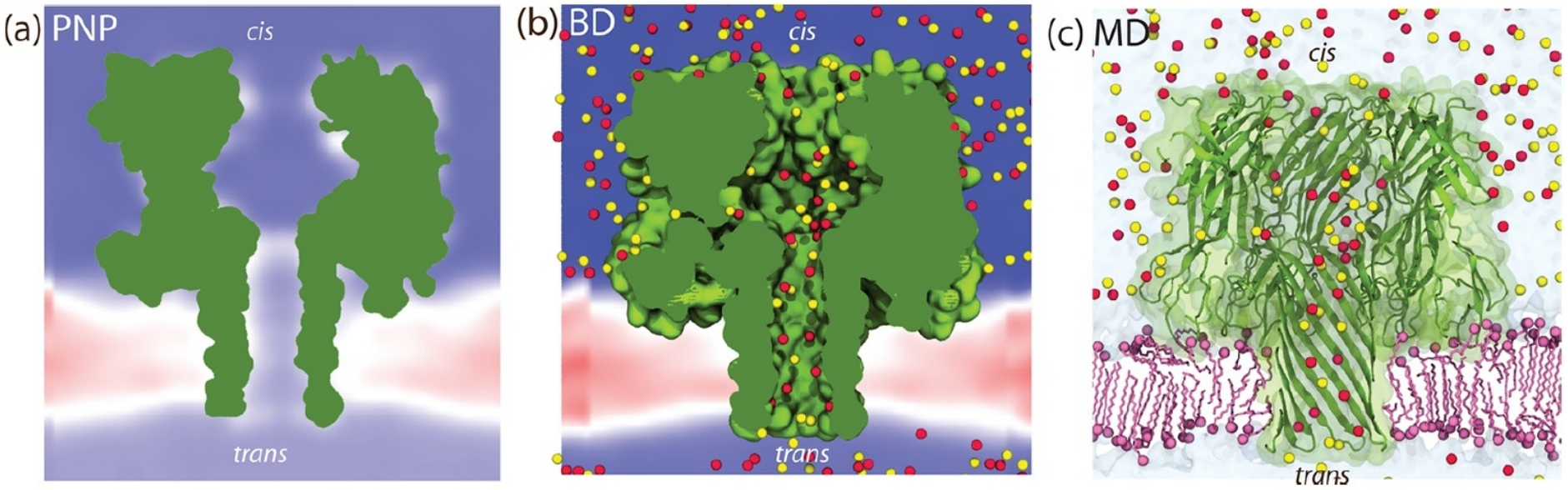


(a) Ion-track-etching technique



Resolution of the microscopic model – multiscaling

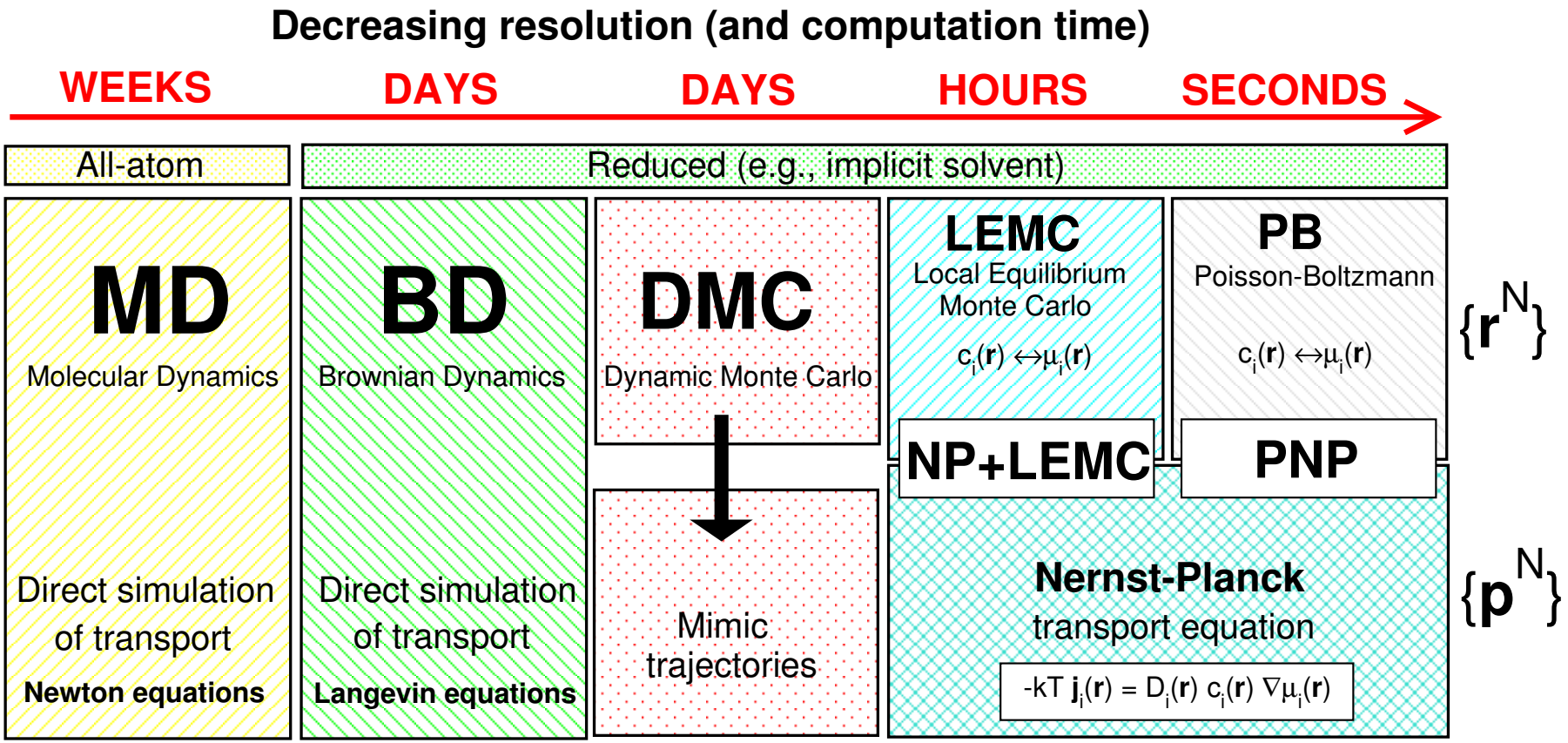
- Detailed model vs. reduced model to handle subsystems with different scales
- Advantages/disadvantages (too many details vs. too much approximation)
- Reduced models for large-scale device properties, all-atom models for molecular details
- The challenge is to link the various modeling levels



1 Z. Ható, D. Boda, D. Gillepie, J. Vrabec, G. Rutkai, and T. Kristóf. Simulation study of a rectifying bipolar ion channel: detailed model versus reduced model. *Cond. Matt. Phys.*, **19**(1):13802, 2016.

Hierarchy of models and methods

- Explicit water (MD) → implicit water (BD, LEMC, PNP)
- Direct simulation of tranport (BD) → transport equation (NP)
- Particle simulation (LEMC) → continuum method (PNP)



Electrodiffusion: the Nernst-Planck equation

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

- **Flux**: output of the calculation – $\mathbf{j}^{\alpha}(\mathbf{r})$
- **Concentration**: availability of the transported particles – $c^{\alpha}(\mathbf{r})$
- **Diffusion coefficient**: mobility of the transported particles – $D^{\alpha}(\mathbf{r})$
- **Driving force**: difference/gradient of the electrochemical potential – $\mu^{\alpha}(\mathbf{r})$
- What is the relation of $c^{\alpha}(\mathbf{r})$ and $\mu^{\alpha}(\mathbf{r})$ in the transport (non-equilibrium) region?
- Non-equilibrium statistical mechanics is needed. Not well-established.
- General solution: divide the system into volume elements and assume **local equilibrium** (LE) in them.
- **Use the procedures of equilibrium statistical mechanics in the volume elements.**

2 D. Boda, D. Gillespie. Steady state electrodiffusion from the Nernst-Planck equation coupled to Local Equilibrium Monte Carlo simulations. *J. Chem. Theory Comp.*, **8**(3):824-829, 2012.

Statistical mechanical methods that can be used

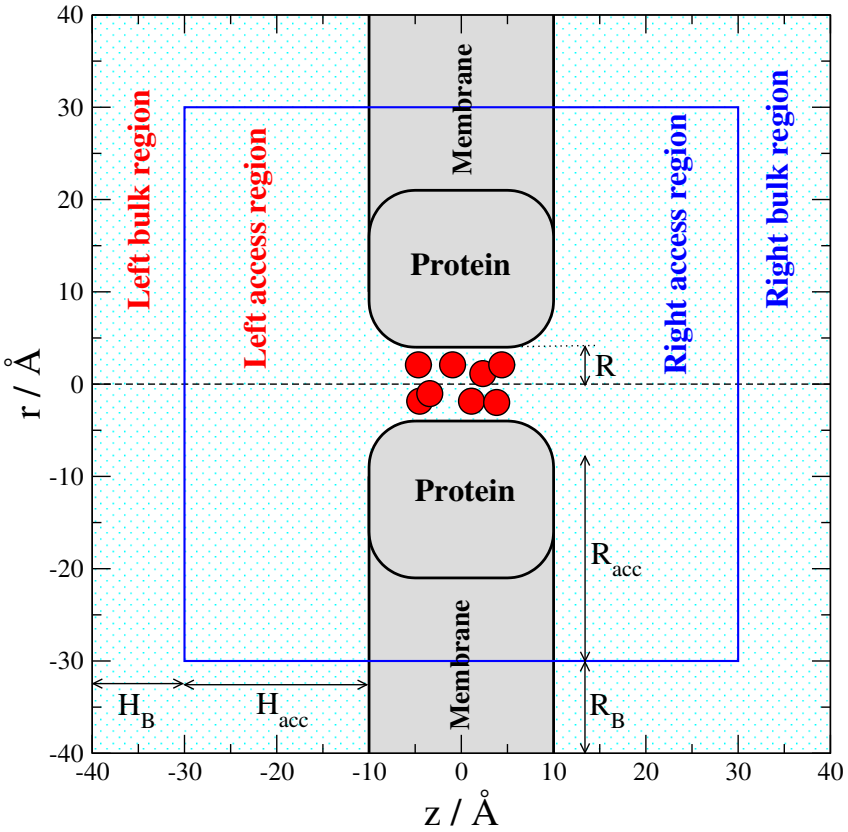
The electrochemical potential:

$$\mu^\alpha(\mathbf{r}) = \mu_0^\alpha + kT \ln c^\alpha(\mathbf{r}) + \mu_{\mathrm{EX}}^\alpha + z^\alpha e\Phi(\mathbf{r})$$

- **Poisson-Boltzmann**: used for the ideal solution ($\mu_{\mathrm{EX}}^\alpha(\mathbf{r}) = 0$) – NP+PB (traditionally called Poisson-Nernst-Planck (PNP) theory)
- **Density Functional Theory** (Tarazona, Gillespie) – NP+DFT (1D)
- **Simulation (our suggestion)**: perform GCMC simulation using different electrochemical potentials in the volume elements (each element is an open system in the GC ensemble) – **Local Equilibrium Monte Carlo** (LEMC)

2. D. Boda, D. Gillespie. Steady state electrodiffusion from the Nernst-Planck equation coupled to Local Equilibrium Monte Carlo simulations. *J. Chem. Theory Comp.*, **8**(3):824-829, 2012.
3. D. Boda, R. Kovács, D. Gillespie, T. Kristóf. Selective transport through a model calcium channel studied by Local Equilibrium Monte Carlo simulations coupled to the Nernst-Planck equation *J. Mol. Liq.*, **189**:100, 2014.
4. D. Boda. Monte Carlo simulation of electrolyte solutions in biology: In and out of equilibrium. *Annual Reports in Computational Chemistry*, **10**, Chapter 5, Pages 127–163, Elsevier, 2014.

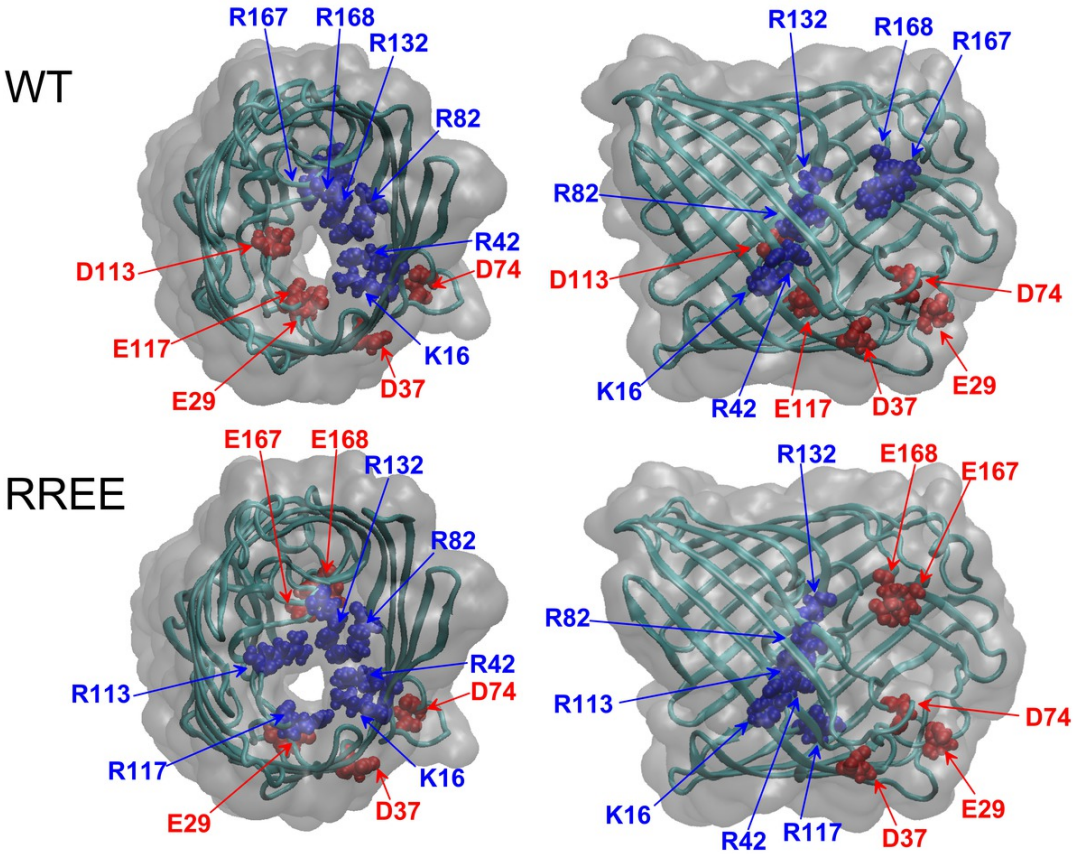
Local Equilibrium Monte Carlo (LEMC)

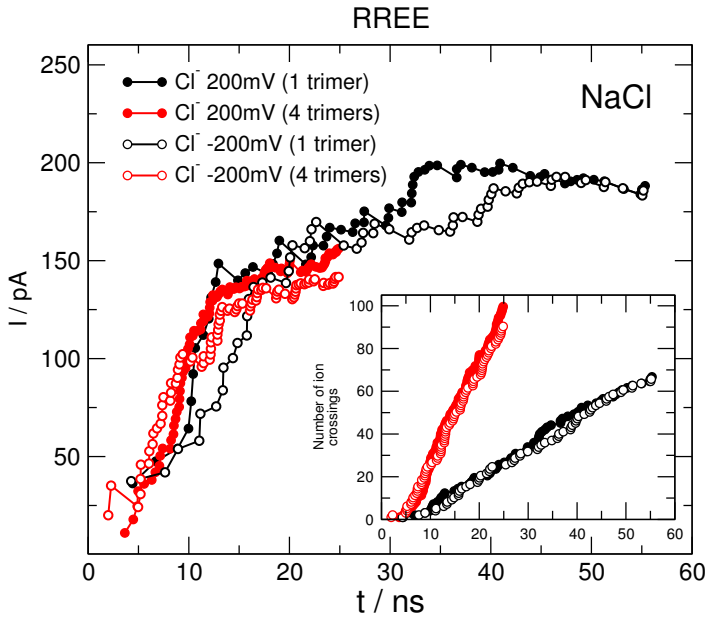


- Solution domain (pore + acess regions) is divided into volume elements (V_i)
- **Input**: $\mu^\alpha(\mathbf{r}_i)$, **Output**: $c^\alpha(\mathbf{r}_i)$
- **Acceptance probability** for inserting ($\chi = 1$) or deleting ($\chi = -1$) an ion in a volume element (below).
- N_i^α is the number of ions in V_i **before** insertion/deletion
- The energy contains the interactions with **everything** in the whole simulation cell including the applied field ($\mathbf{r} \in V_i$).

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

Failure for a mutant rectifying ion channel with MD simulations



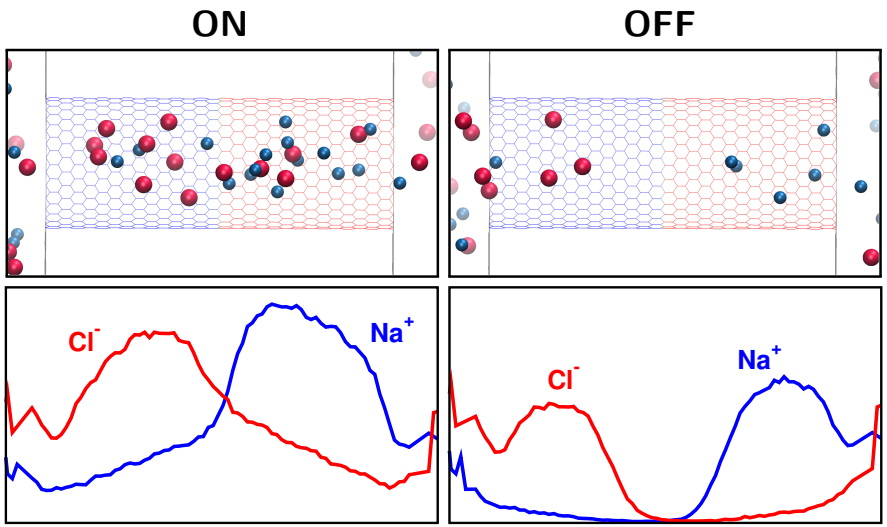


- Experiments (Miedema et al. *Nano Lett.*, **7**, 2886, 2007.) showed rectification for the RREE mutant
- Our large-scale all-atom MD simulations did not

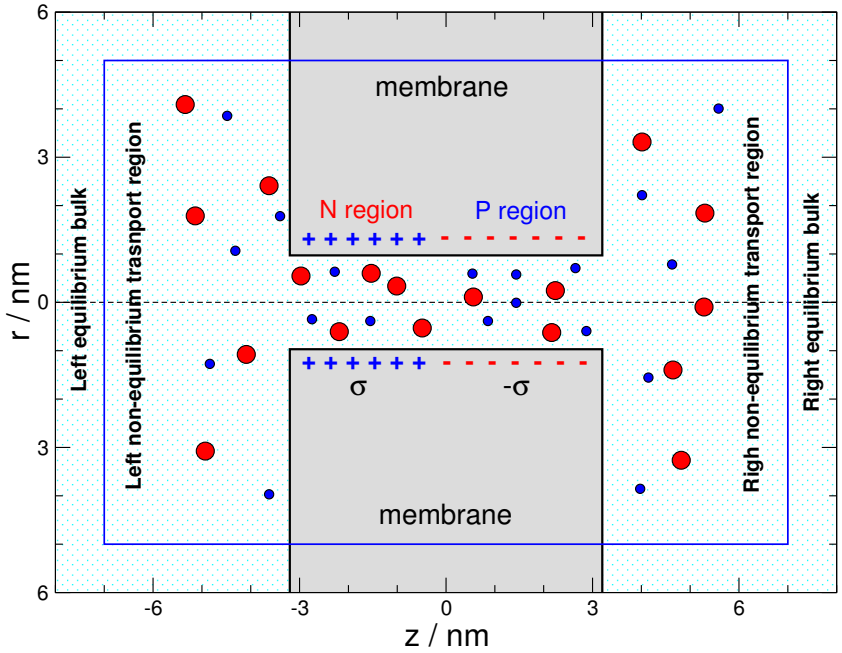
1. Z. Ható, D. Boda, D. Gillepie, J. Vrabec, G. Rutkai, and T. Kristóf. Simulation study of a rectifying bipolar ion channel: detailed model versus reduced model. *Cond. Matt. Phys.*, **19**(1):13802, 2016.

Bipolar nanopore models

- Nanopore is CNT, membrane is CNS
- MD: GROMACS, CHARMM27
- **Explicit water**: SPC



- Nanopore and membrane walls are hard walls
- Ions: charged hard spheres
- **Implicit water**: $\epsilon = 78.5$

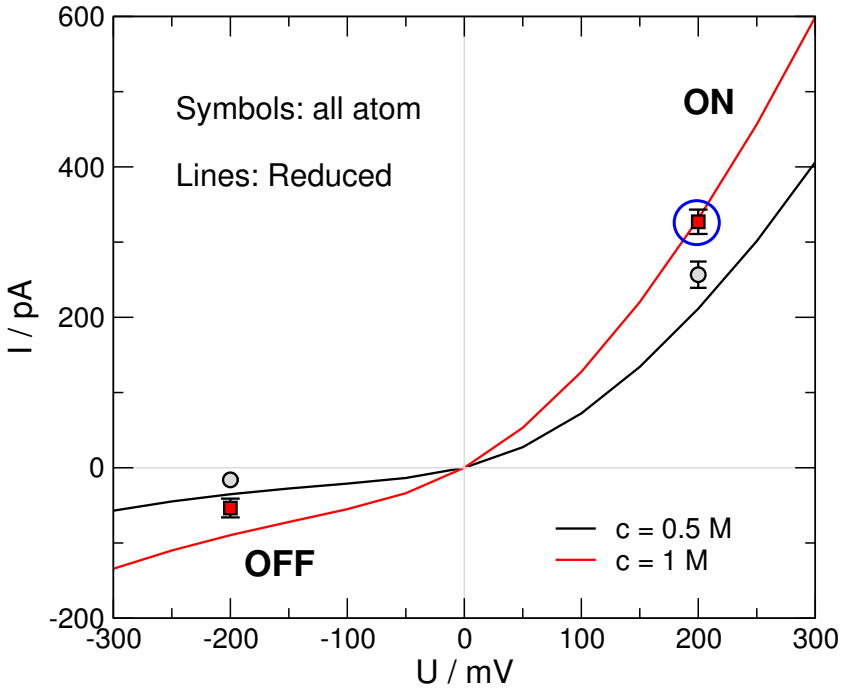


[5] Z. Ható, M. Valiskó, T. Kristóf, D. Gillespie, D. Boda. Multiscale modeling of a rectifying bipolar nanopore: explicit-water versus implicit-water simulations. *PCCP* submitted, 2017.

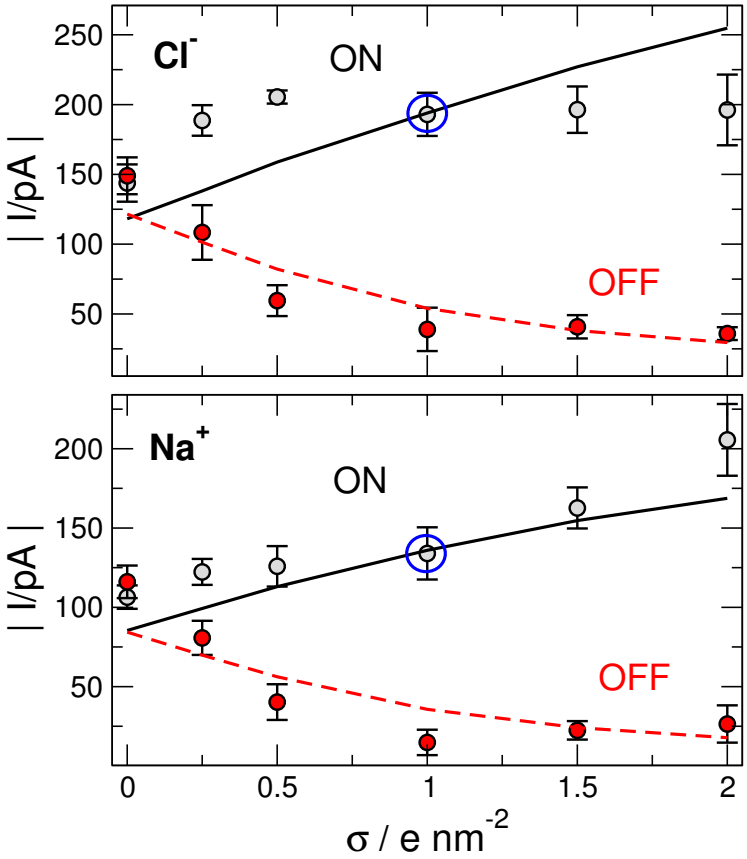
Explicit vs. implicit water comparison (MD vs. NP+LEMC)

Results for device function - qualitative agreement

- **Current vs. voltage**



- **Current vs. pore charge**

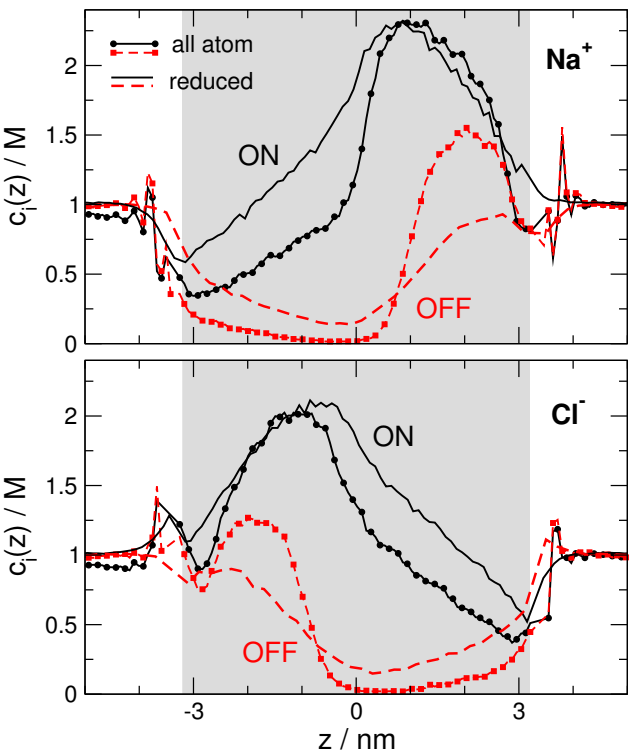


5 Z. Ható, M. Valiskó, T. Kristóf, D. Gillespie, D. Boda. Multiscale modeling of a rectifying bipolar nanopore: explicit-water versus implicit-water simulations. *PCCP* submitted, 2017.

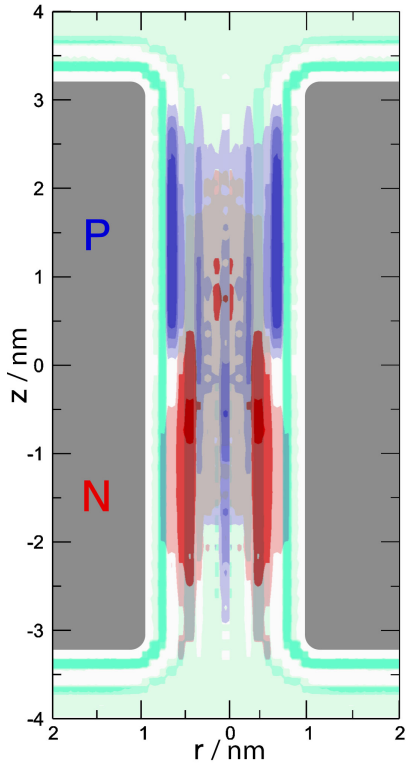
Explicit vs. implicit water comparison (MD vs. NP+LEMC)

Concentration profiles - different agreement in z and r dimensions

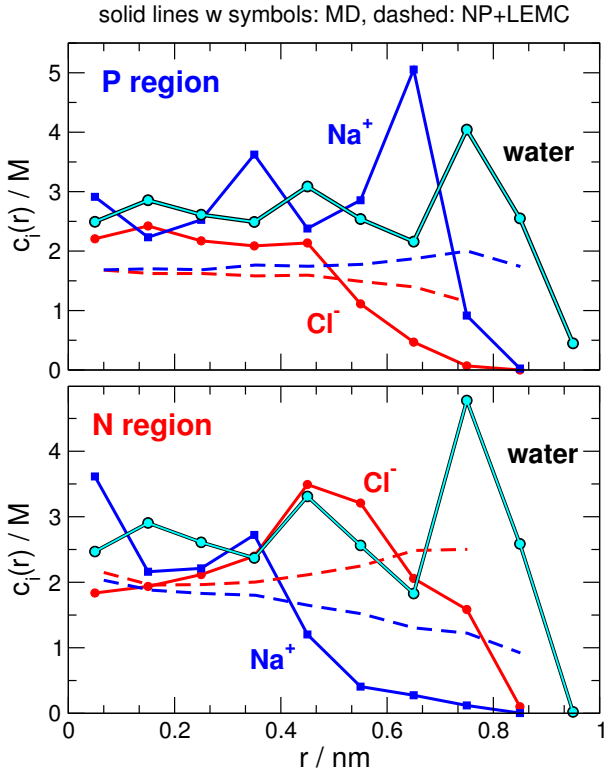
- **Axial profiles** – agree
- Relevant for device function



- **Radial profiles** – disagree
- Irrelevant for device function



(A)

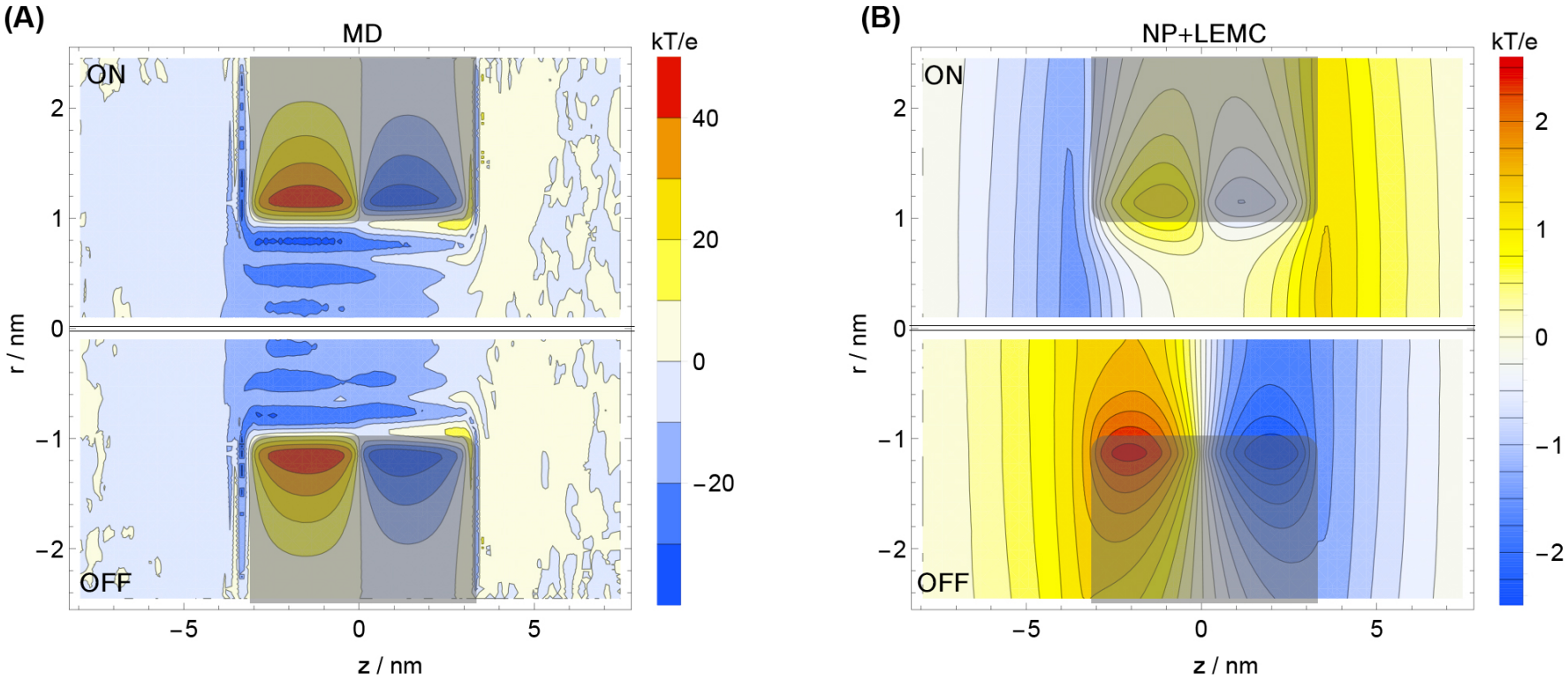


(B)

5 Z. Ható, M. Valiskó, T. Kristóf, D. Gillespie, D. Boda. Multiscale modeling of a rectifying bipolar nanopore: explicit-water versus implicit-water simulations. *PCCP* submitted, 2017.

Explicit vs. implicit water comparison (MD vs. NP+LEMC)

Potential profiles - not even close



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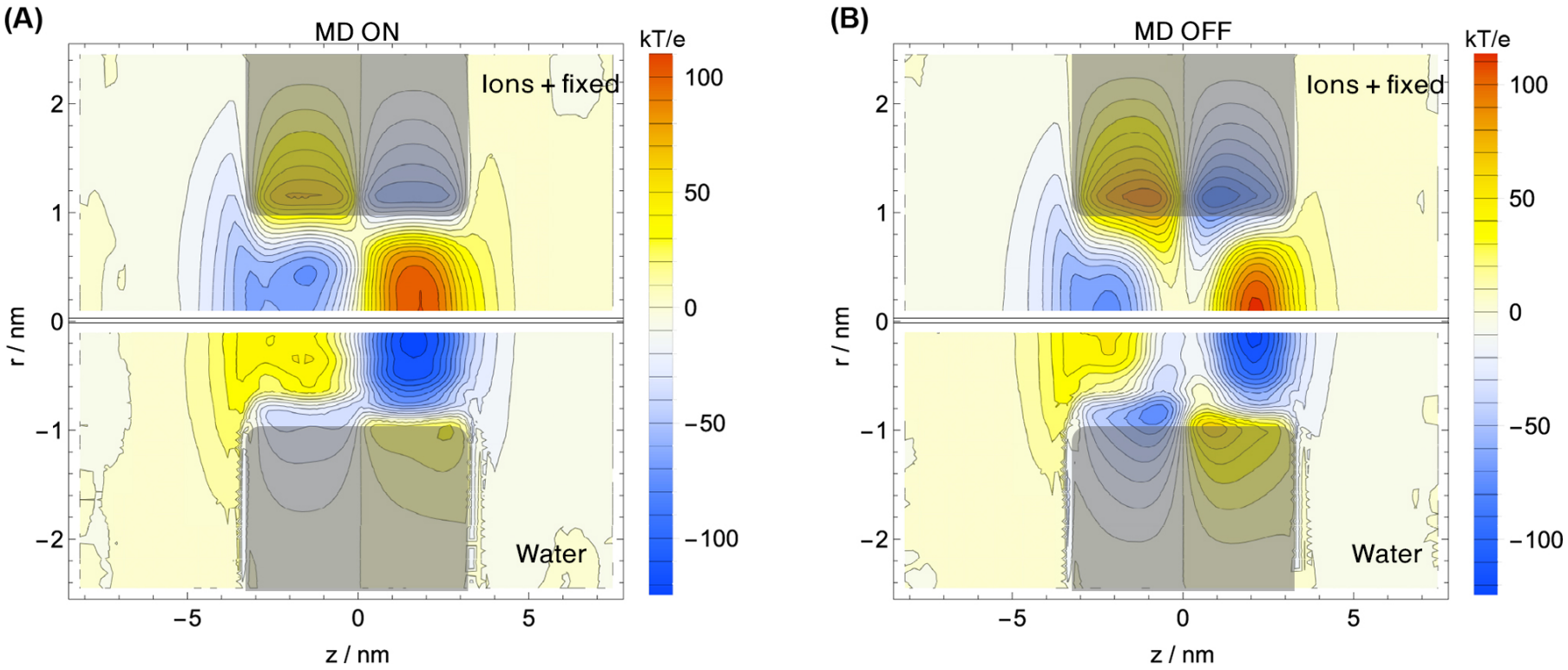
Screening in the explicit solvent model

Potential profiles of ions and water are opposite



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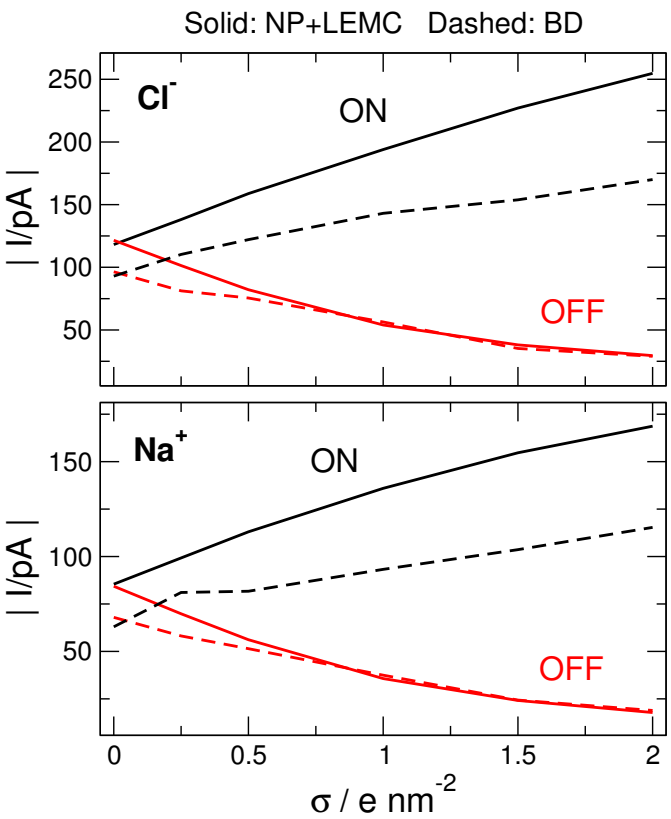
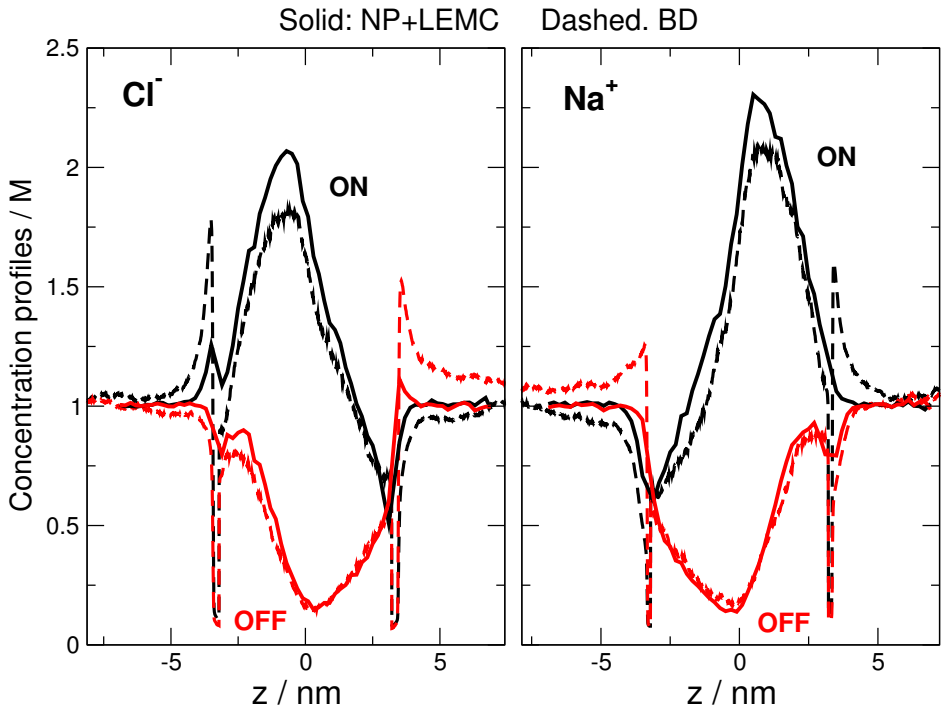
Direct dynamics vs. transport equation (BD vs. NP+LEMC)

Both are for implicit water

- **Current vs. pore charge**



- **Axial concentration profiles**

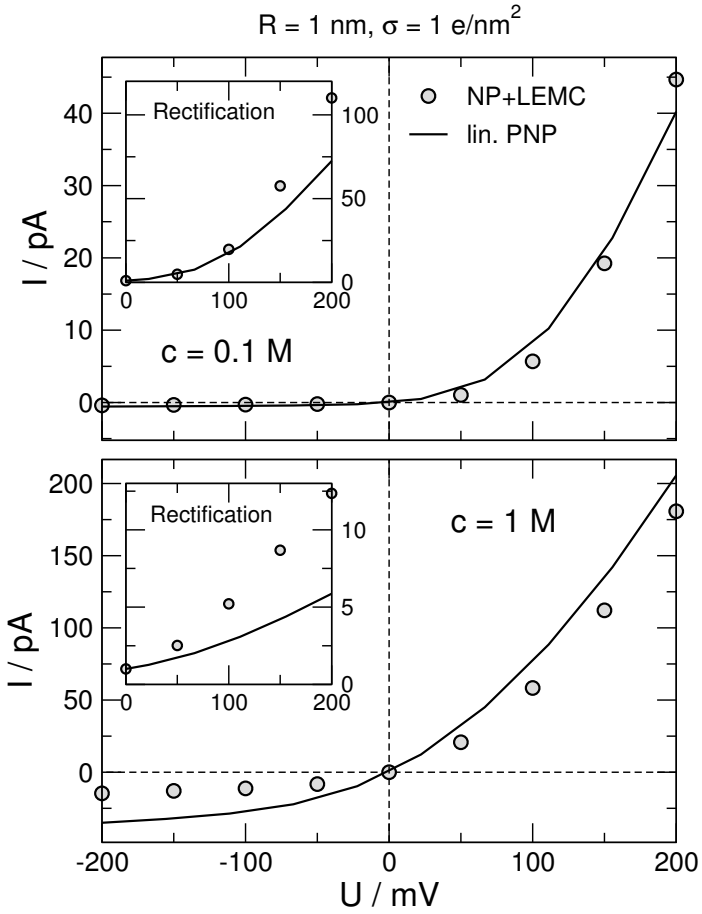


- Using the same diffusion coefficient in the pore in the two cases
- Currents are different: D_i has different meanings in BD and NP

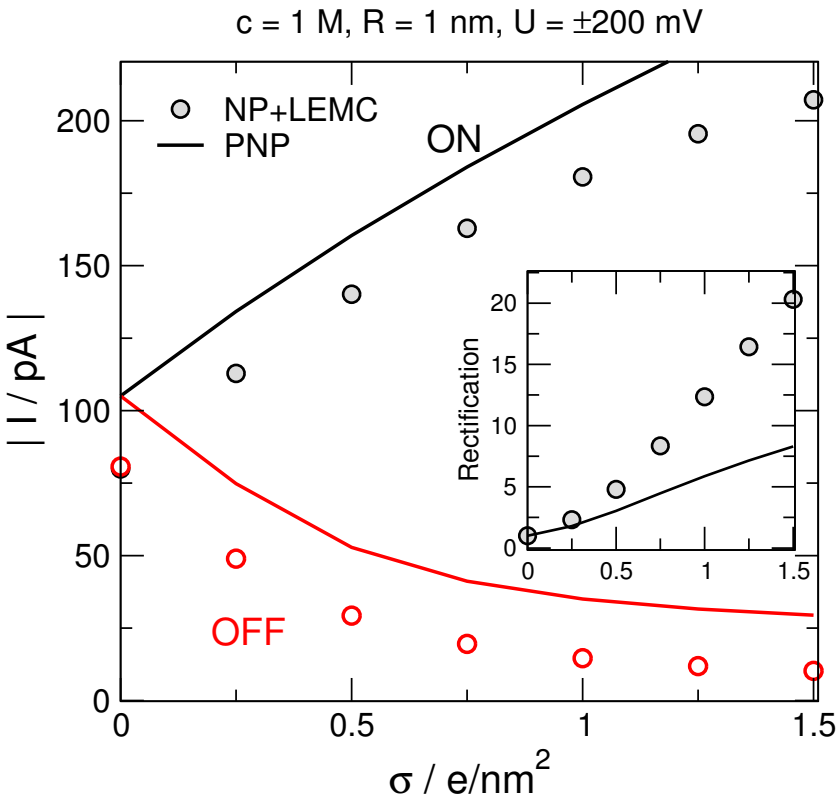
Molecular simulation vs. continuum theory (LEMC vs. PNP)

Device properties

- **Current vs. voltage**



- **Current vs. pore charge**

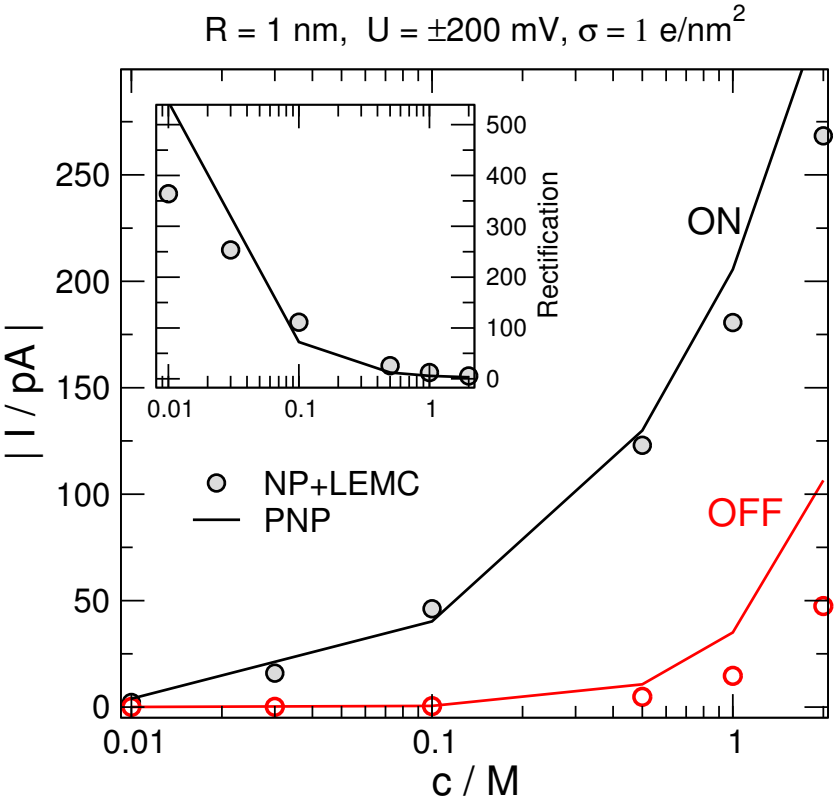


6 B. Matejczyk, M. Valiskó, M.-T. Wolfram, J.-F. Pietschmannn, D. Boda. Multiscale modeling of a rectifying bipolar nanopore: Comparing Poisson-Nernst-Planck to Monte Carlo. *J. Chem. Phys.* 146, 124125, 2017.

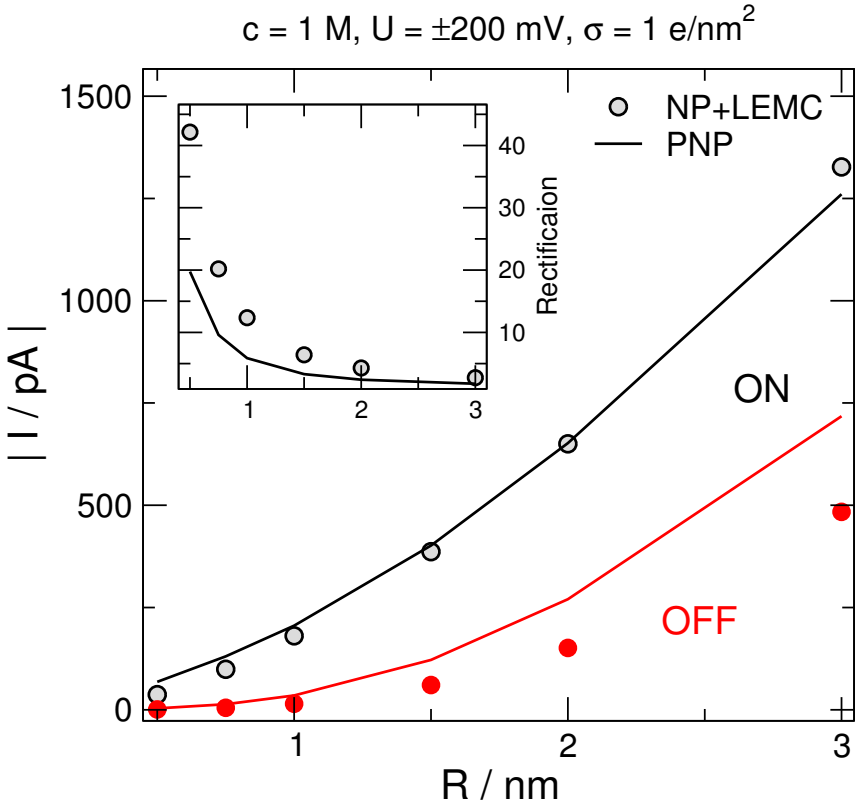
Molecular simulation vs. continuum theory (LEMC vs. PNP)

Device properties

- **Current vs. concentration**



- **Current vs. pore radius**



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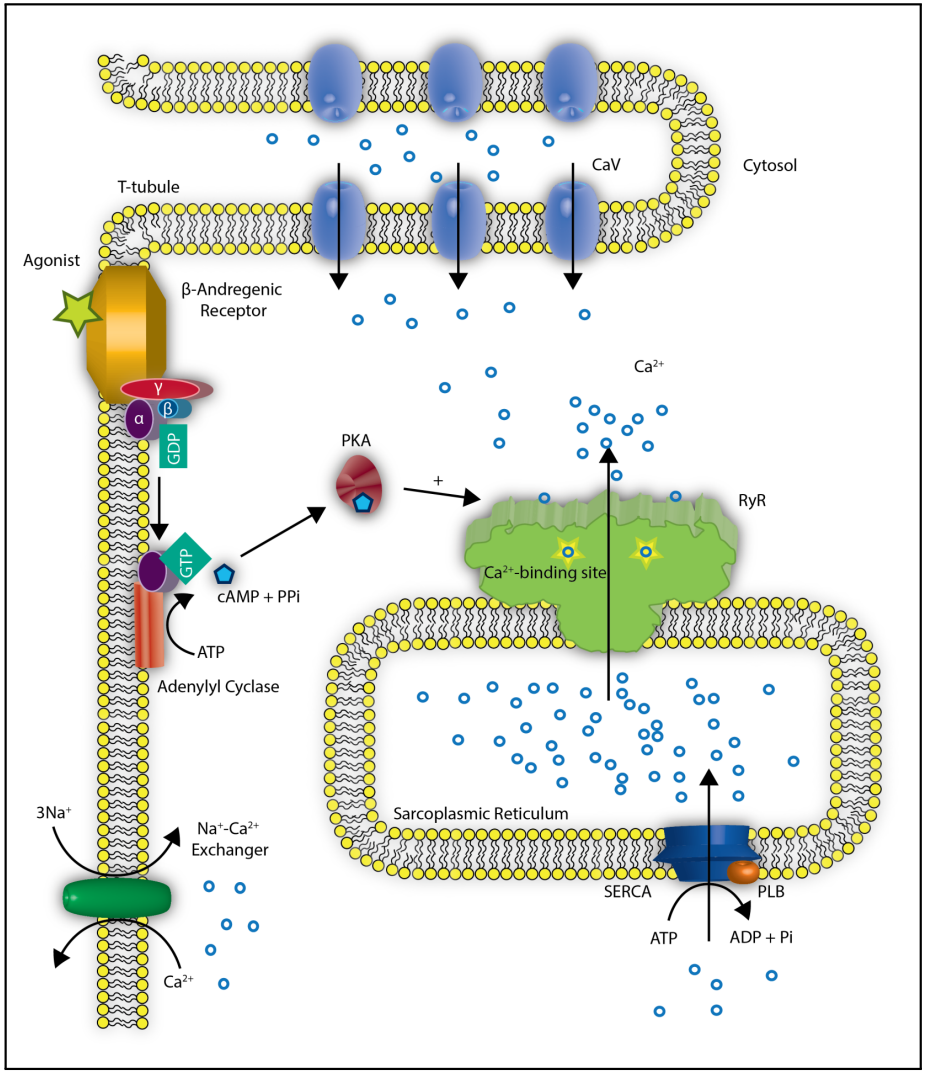
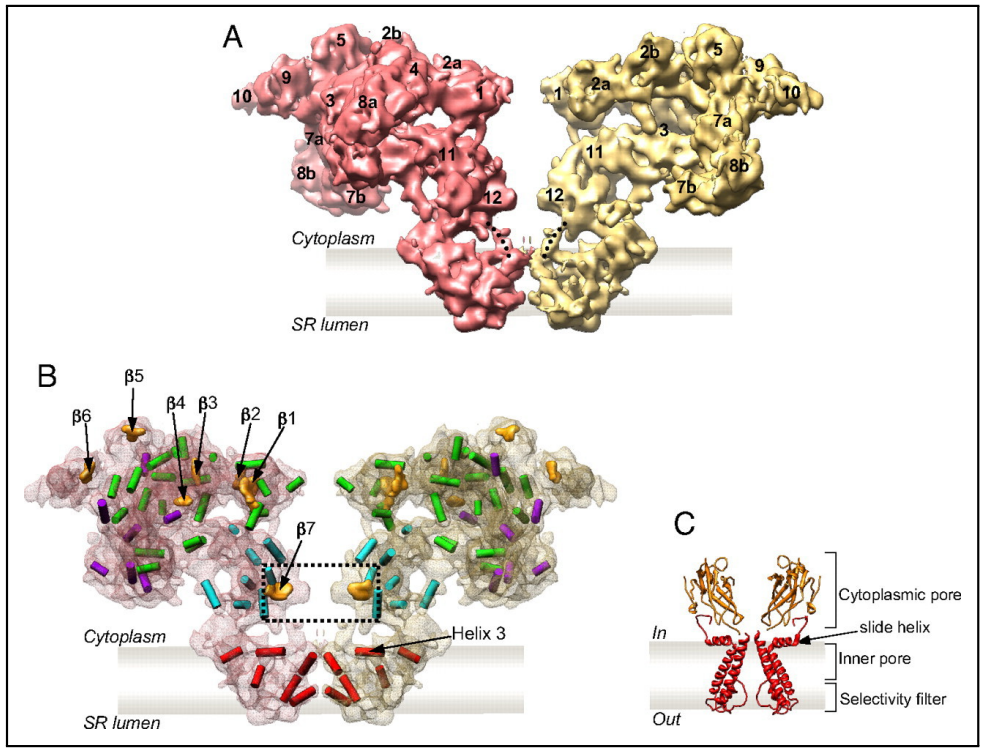
RyR calcium-release ion channel



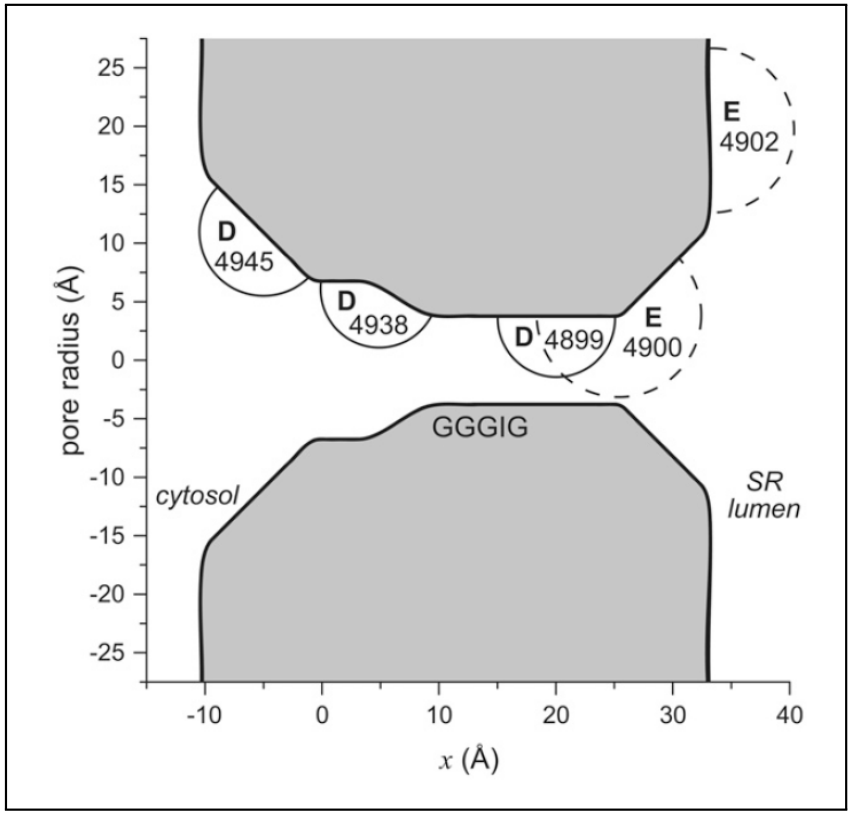
- Ca^{2+}-release Ryanodine Receptor (RyR) calcium channel channel
- The released Ca^{2+} initiates muscle contraction



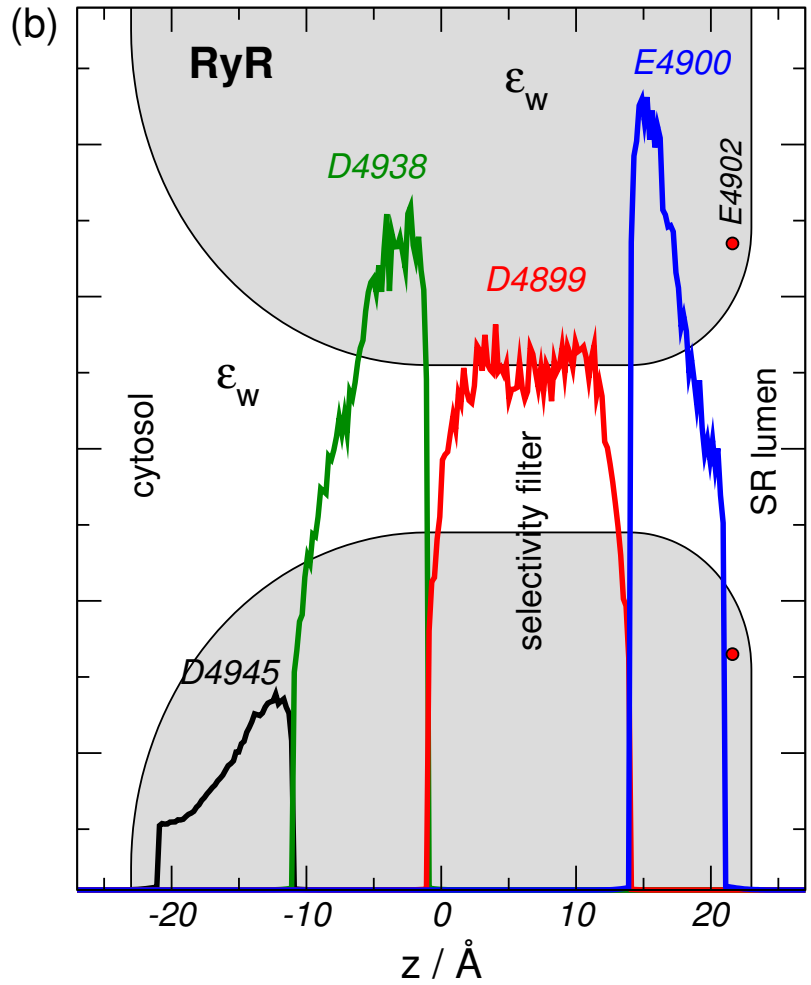
Models of the RyR Ca^{2+}-release channel

1-D model of Dirk Gillespie for NP+DFT

JPCB **109**, 15598, *BJ*, **94**, 1169, 2008; *BJ*, **97**, 2212, 2009.

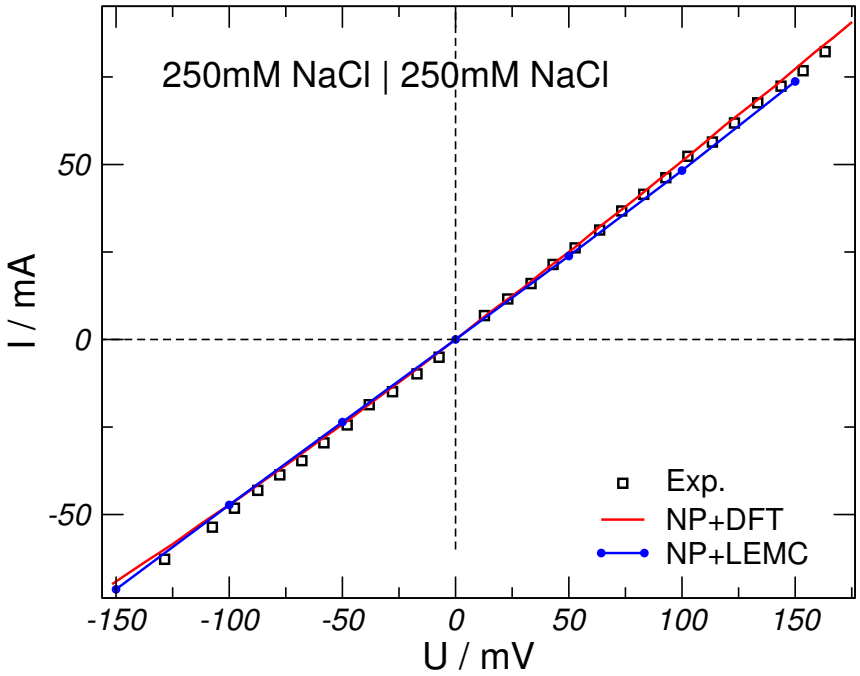


Our 3-D model for NP+LEMC based on Dirk's model

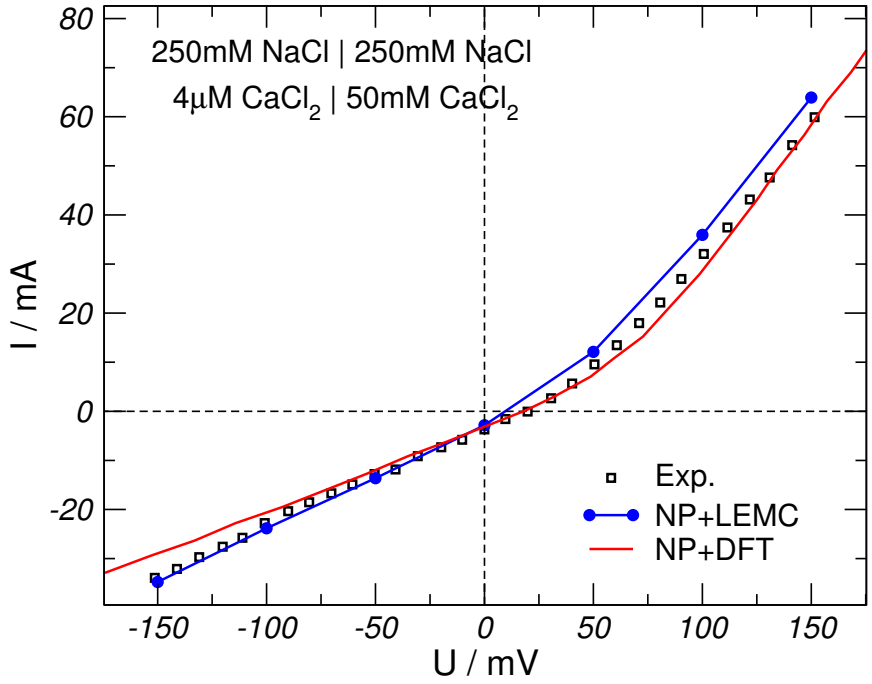


I-V curves for NaCl and NaCl-$CaCl_2$

Symmetric 250 mM NaCl (basis of fit of D^{α} in the channel).



$NaCl$-$CaCl_2$ mixture - non-symmetric I-V curve.

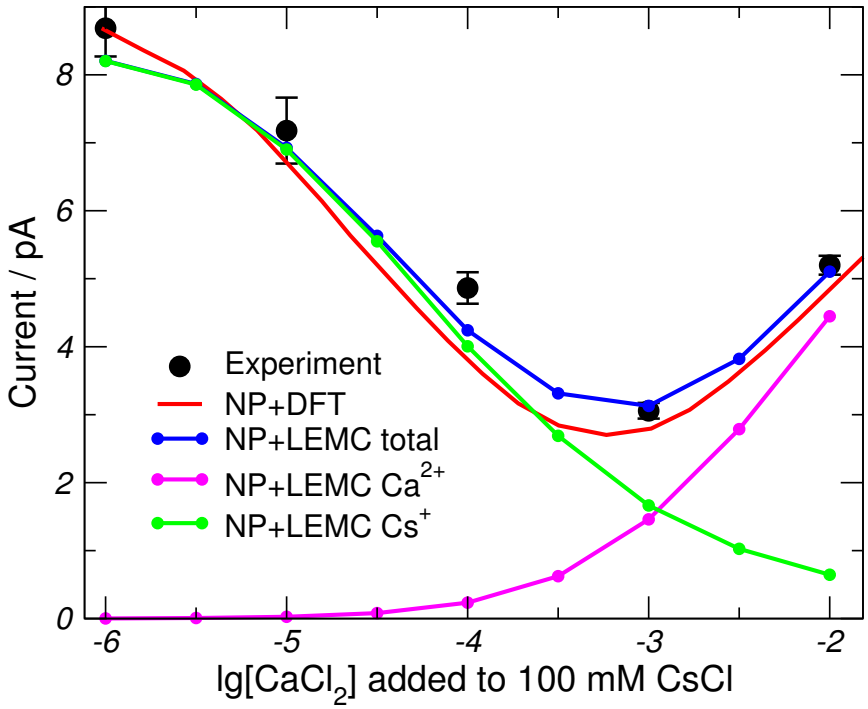


DFT: Gillespie et al. *JPCB* **109**, 15598, *BJ*, **94**, 1169, 2008; *BJ*, **97**, 2212, 2009.

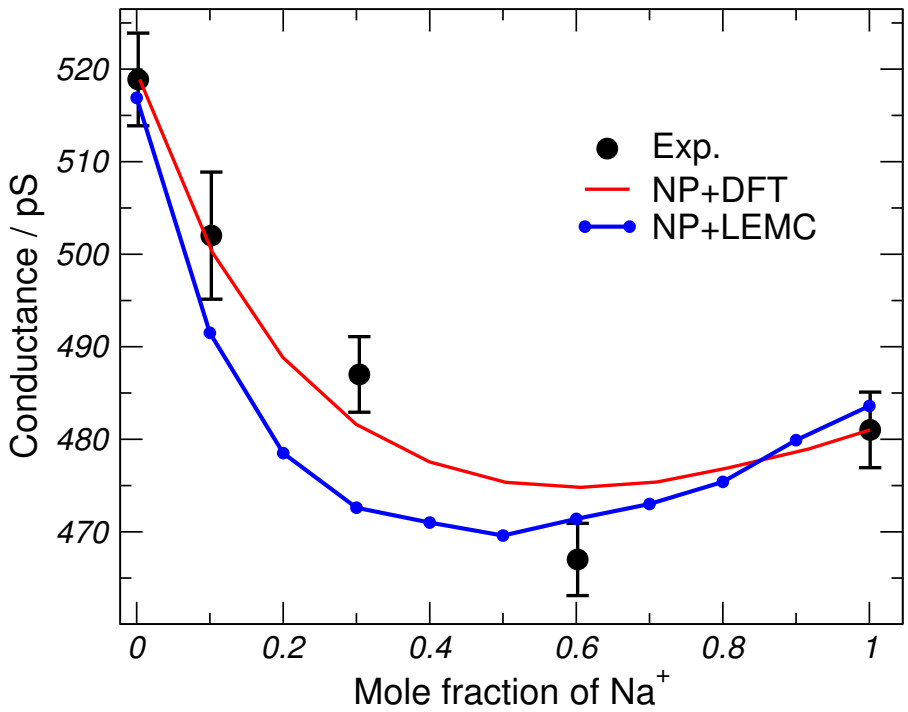
4 D. Boda. Monte Carlo simulation of electrolyte solutions in biology: In and out of equilibrium. *Annual Reports in Computational Chemistry*, Volume **10**, Chapter 5, Pages 127–163, Elsevier, 2014.

Anomalous mole fraction effects for the RyR channel

$CaCl_2$ is added to 100 mM CsCl



NaCl-CsCl mole fraction experiment



DFT: Gillespie et al. *JPCB* **109**, 15598, *BJ*, **94**, 1169, 2008; *BJ*, **97**, 2212, 2009.

4 D. Boda. Monte Carlo simulation of electrolyte solutions in biology: In and out of equilibrium. *Annual Reports in Computational Chemistry*, Volume **10**, Chapter 5, Pages 127–163, Elsevier, 2014.

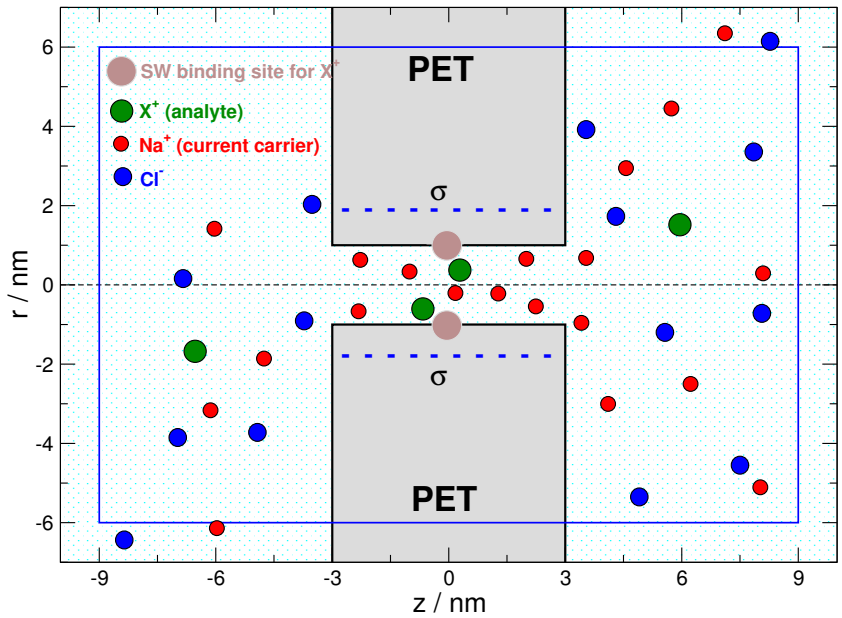
Reduced models reproduce experimental data for device behavior properly.

- Why is that?
- How can reduced models work while they ignore seemingly important molecular details (water, for example)?
- Our answer is that they work, because they get those properties right that are important for device behavior.
- In the case of nanopores/channels, it is the axial behavior of concentration profiles.

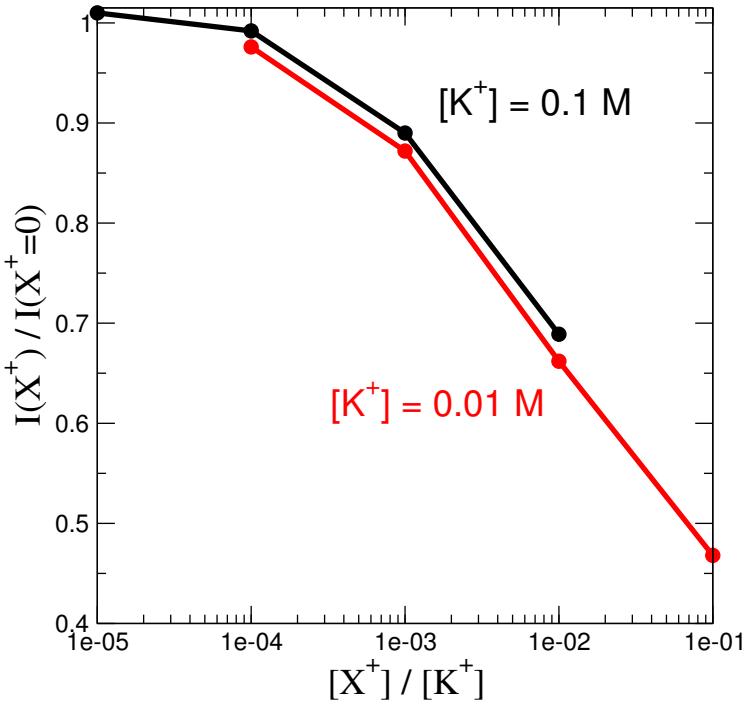
- When we build a reduced model by ignoring certain degrees of freedom, we can ignore the „unimportant" ones and we must include the „important" ones in the model.
- How do you distinguish „important" and „uniportant" details is the art of multiscaling. Sometimes, it is obvious. Sometimes, it is not.

Nanopore sensor of biomolecules – preliminary NP+LEMC results

- Pore contains selective **square-well** binding sites for the analyte molecule (X^+) that is present in the sample in small (possibly trace) concentration
- X^+ ions continuously replace Na^+ ions as $[X^+]$ increases



- **Calibration curves:** Current reducement vs. $[X^+]$
- Small $[X^+]$ can be detected
- Noise/sign relation is important



Possibility for multiscaling: connect reduced model of binding site to MD or QM simulations

Thanks for your attention!