Monte Carlo simulations of ion channels: dealing with dielectric boundaries and efficient phase space sampling

Dezső Boda

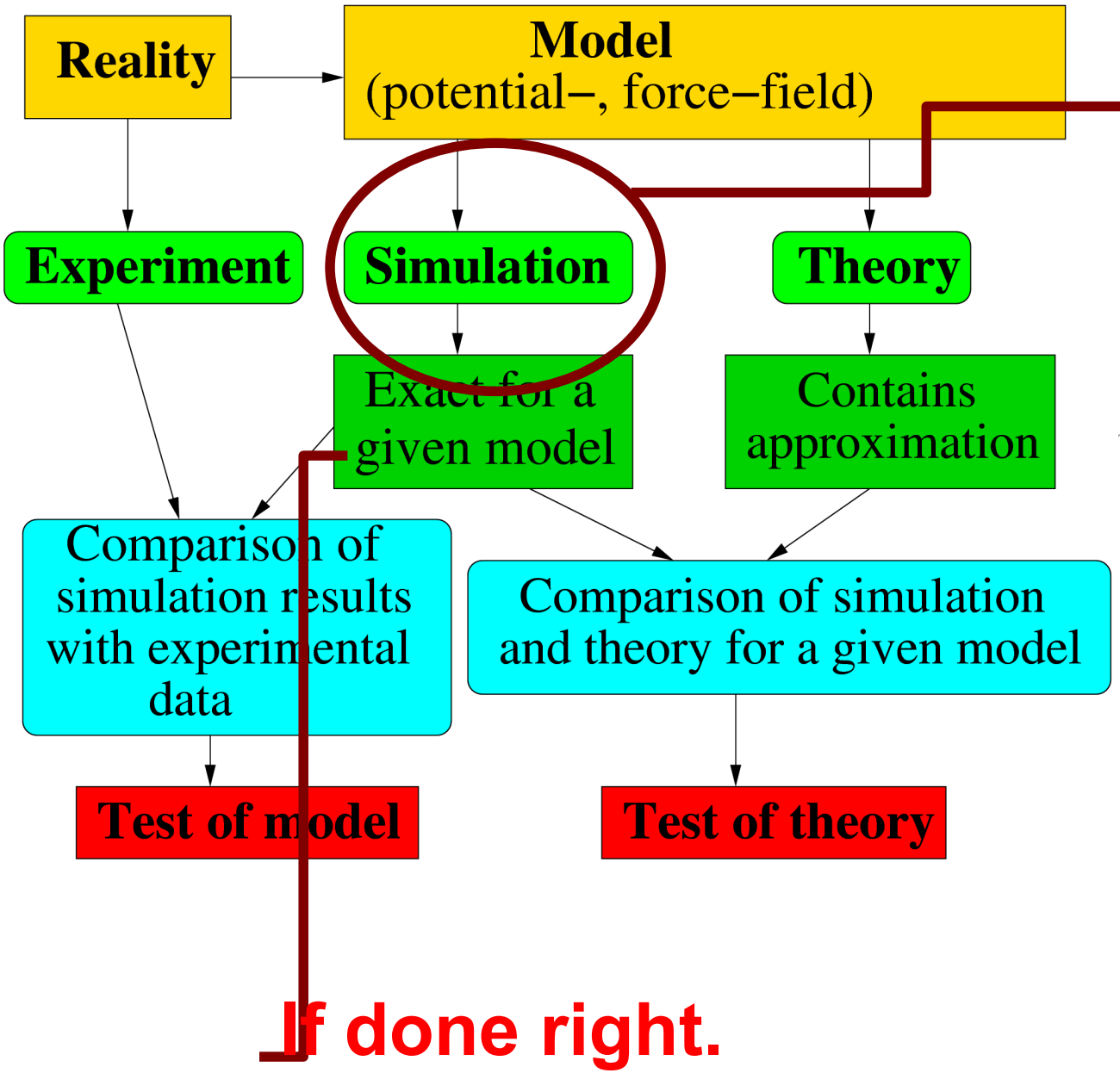
University of Pannonia, Veszprém, Hungary
Rush University Medical Center, Chicago, USA

Special Semester on Quantitative Biology analyzed by Mathematical Methods
Workshop on Ion Channels
October 8-12, 2007, Linz, Austria

Coworkers:

Bob Eisenberg
Doug Henderson
Wolfgang Nonner
Dirk Gillespie
Mónika Valiskó

Reality, model, and method



Calibration of simulations:

- **Is the simulation long enough?**
- **Is the system large enough?**
- **Is the energy (MC) or force (MD) computed right? (Poisson)**
- **Is the sampling efficient (MC)**
- **Is the integration of equations of motion right? (MD)**
- **Are sum rules, thermodynamic self-consistency etc. are obeyed?**
- **Are the results reproducable?**
- **What about bugs?**

Selectivity of ion channels

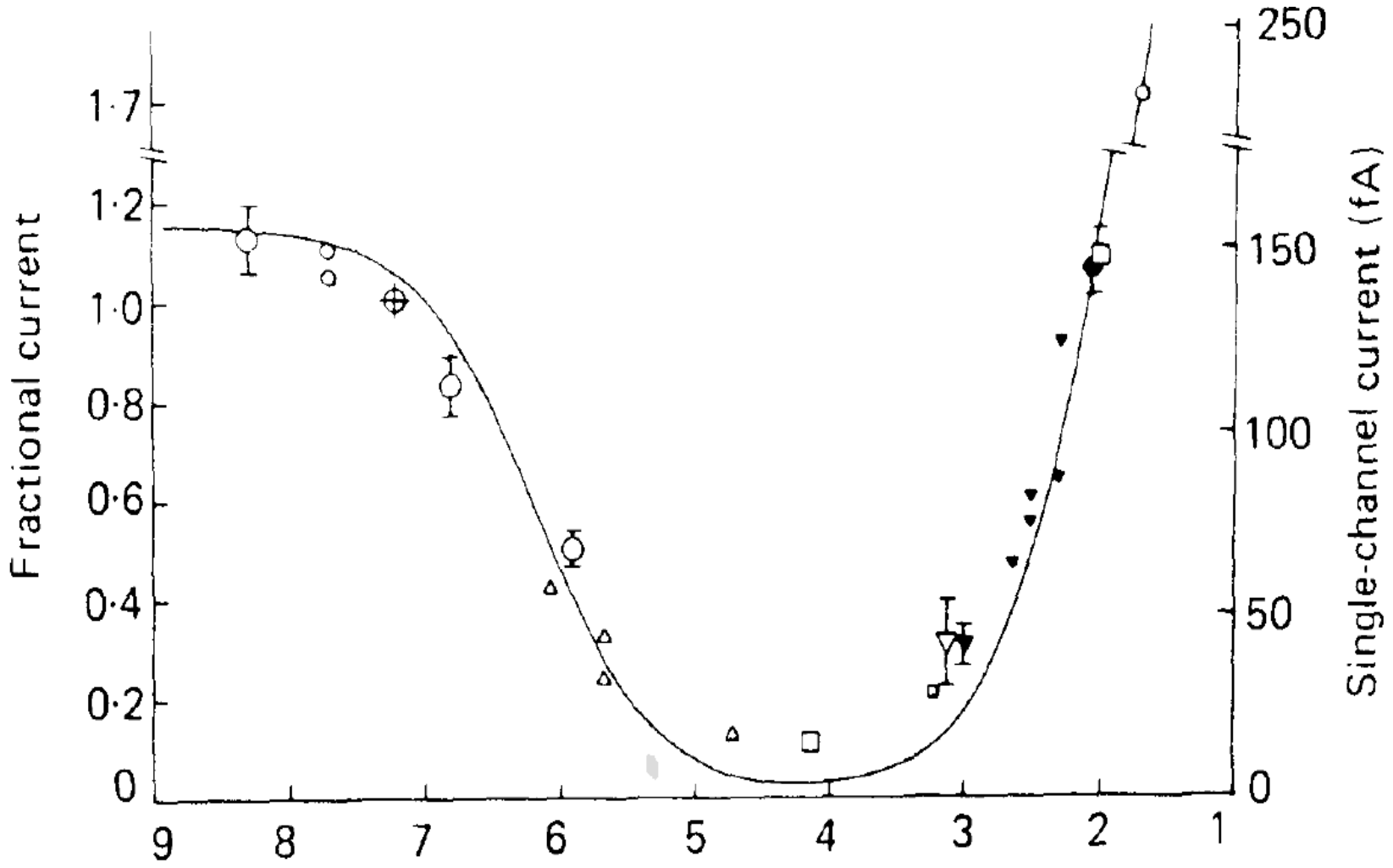
An ion channel that is **selective** for a given ion tends to conduct this ion with higher **probability** than other ions.

What is the **molecular mechanism** of this selectivity?

Statistical picture: the ion that stays in the selectivity filter with a higher probability (larger occupancy), will be conducted with higher probability (depends on ion concentrations).

Another approach: free energy differences between bulk and ”binding sites” (does not depend on ion concentrations).

A typical selectivity experiment



1 μM Ca^{2+} blocks Na^{+} current in the L-type Ca channel (Almers et al.)

Equilibrium simulations are performed

The system in the selectivity filter is **in equilibrium** with the bath where the concentration of the competing ionic species (eg. Na^{+} and Ca^{2+}) are changed.

The question: which ion enters the selectivity filter with higher probability as the bath [$CaCl_2$] is gradually increased?

The answer requires fairly correct treatment of the filter and the bath.

Challenges for the simulation

The electrolyte should be simulated at **micromolar concentrations**.

The **equilibration** of the small (crowded) selectivity filter with the large (dilute) bath.

Energy calculation: the solution of Possion's equation is required in every simulation step.

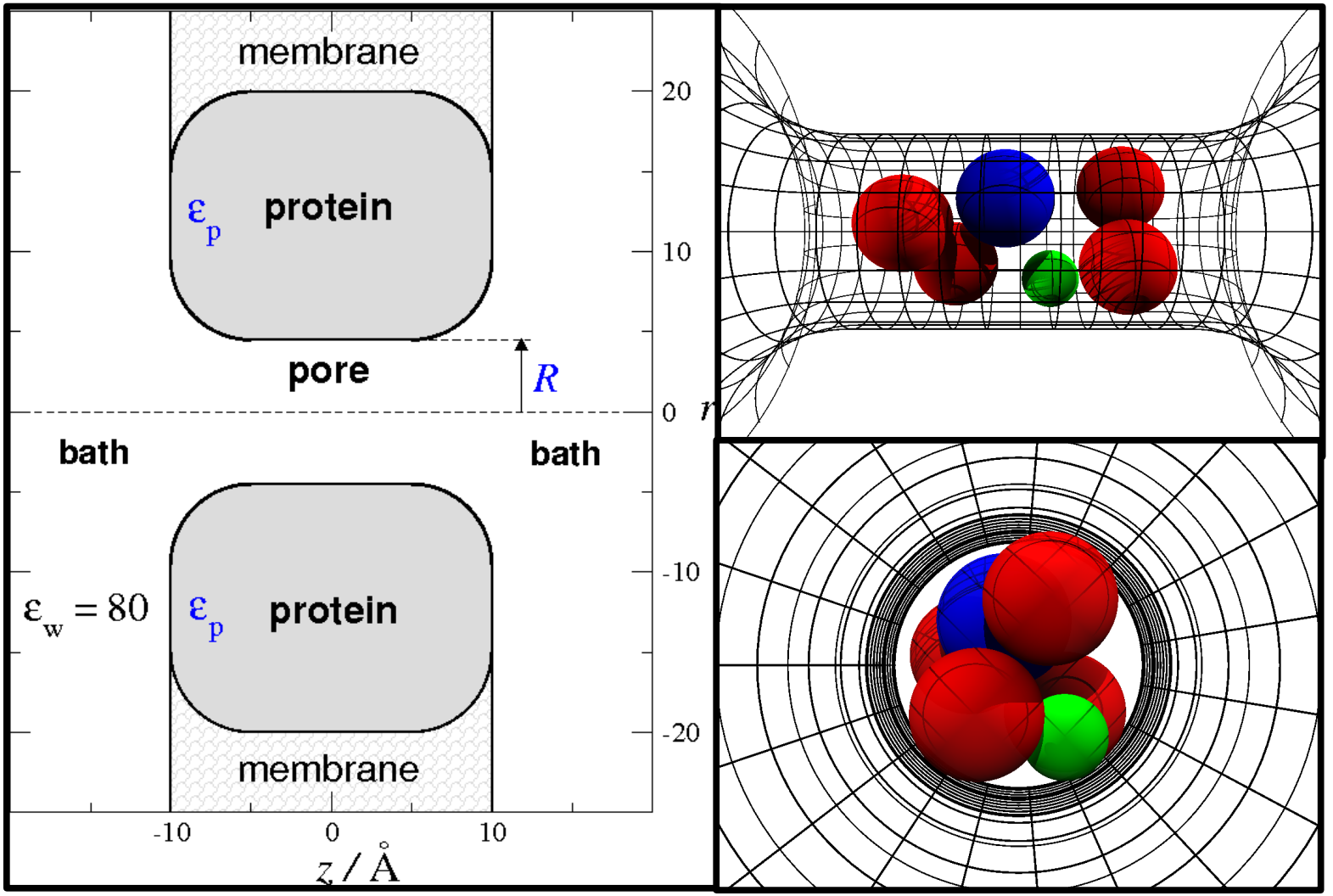
What model and what method can be used to cope with these challenges?

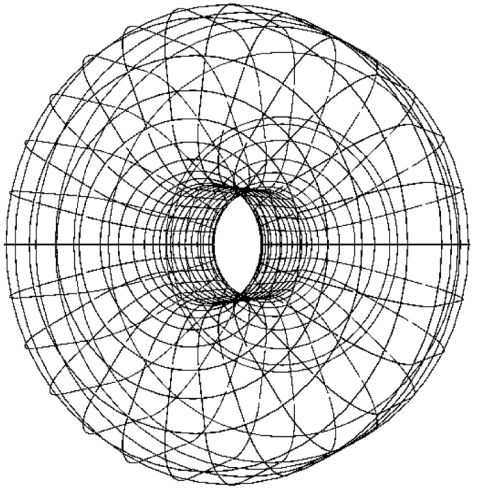
Model of solvent

The solvent has to be simulated as a dielectric **continuum**

(because of micromolar concentrations).

Model of channel

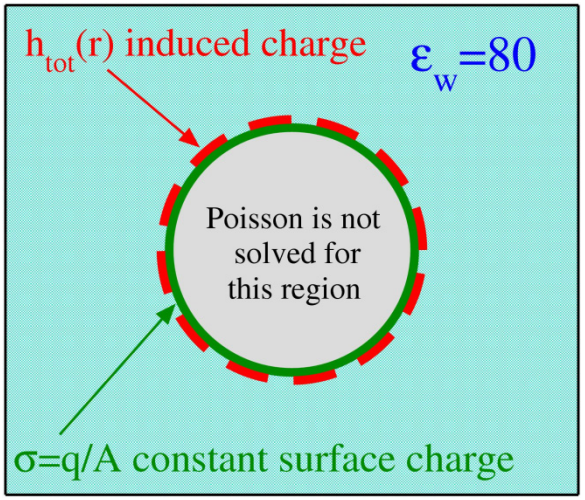




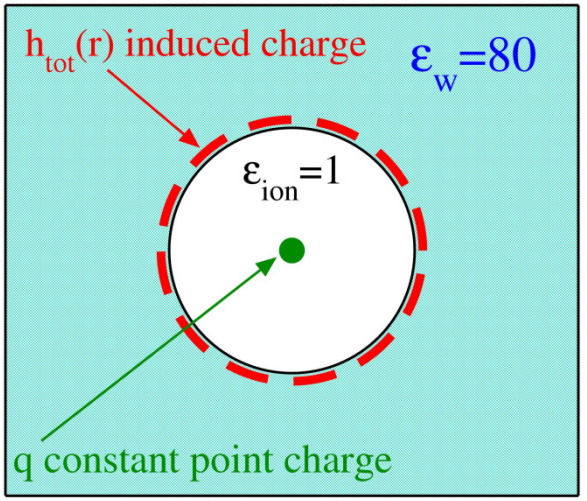
A **dielectric** continuum doughnut with hard walls forms the pore and provides **confinement**.
(ε and *R* are parameters of the model !!!)

Protein side chains **end-groups** modeled as **mobile** structural ions **confined** to the selectivity filter

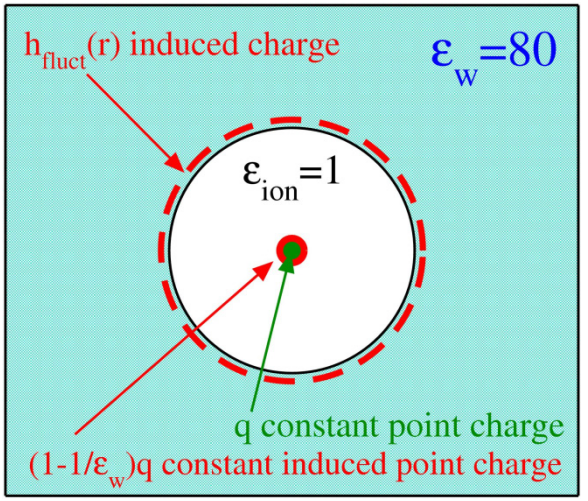
Model of ion



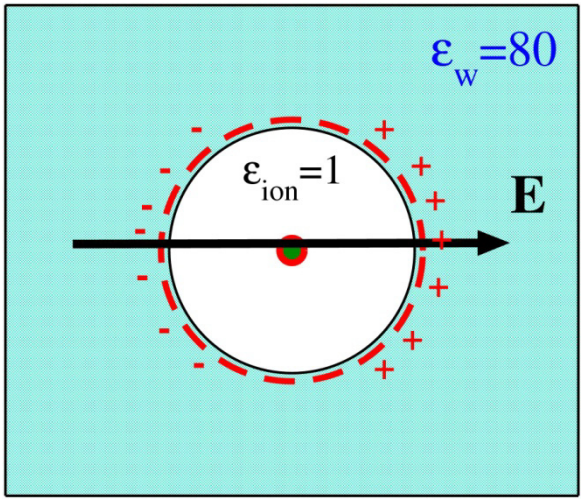
q/A fixed **surface charge** on the surface of the ion



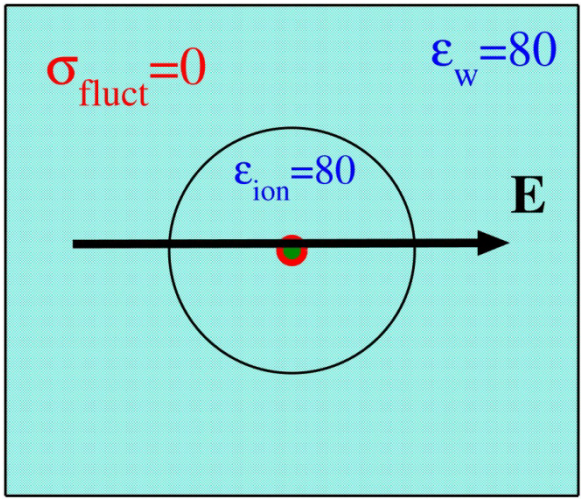
An equivalent: q **point charge** brought into the center



A **constant part** of induced charge is brought into the center



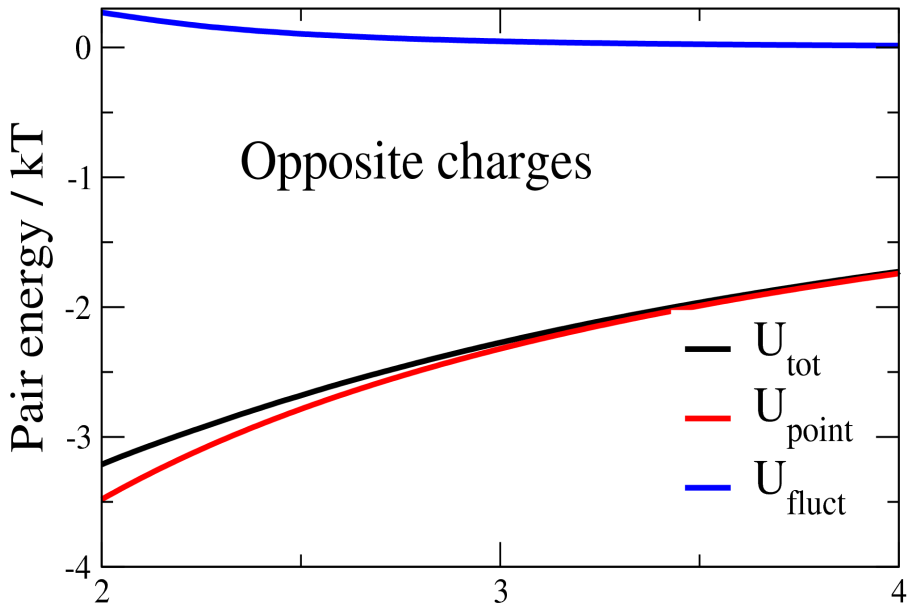
The remaining induced charge is **”dipole-like”**, its integral is zero

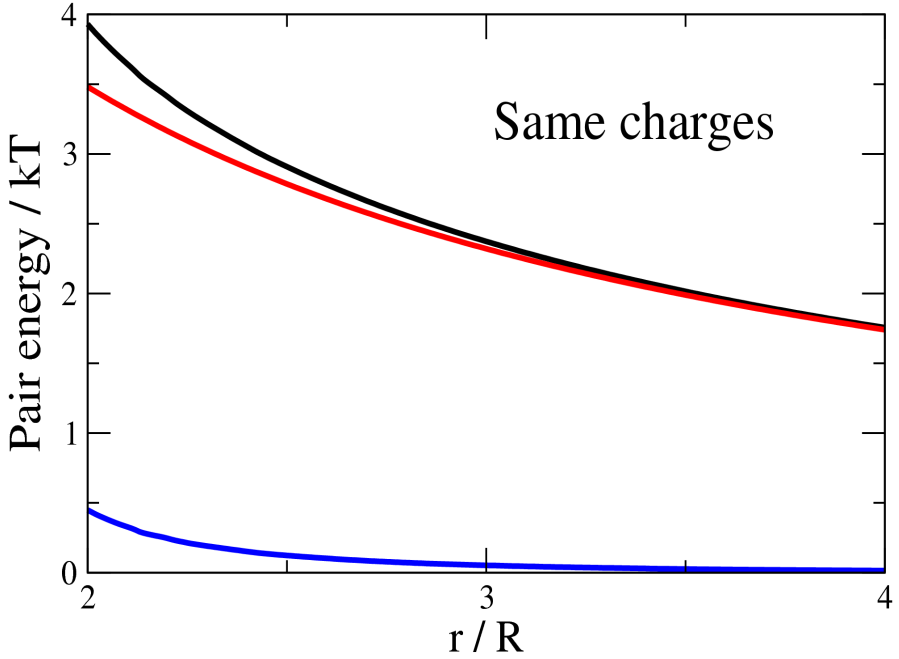


Approximation used in our present simulations: the ”dipole-like” induced charge is omitted

This approximation can be used *self-consistently* in our model because ions do not cross dielectric boundaries and do not overlap with them.

Interaction between two ions





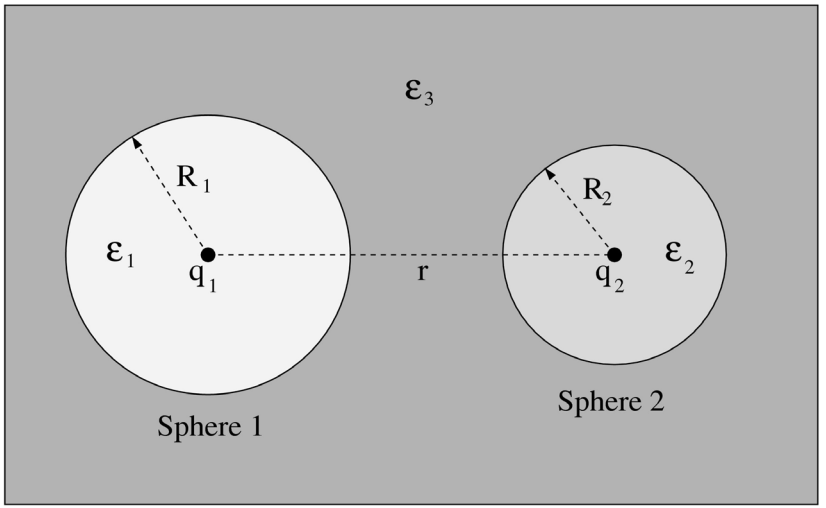
Pair interaction energy = total energy – self terms

Self term: interaction energy of an ion with its own induced charge

U_{point}: interaction between two q/ε point charges

U_{tot}: total interaction energy

U_{fluct}: interaction energy between a q/ε charge and the ”dipole-like” induced charge of the other ion



Monte Carlo simulations

- A **stochastic sampling** of the phase space
- The **model** of the system is fixed: the interparticle potentials, external forces, mechanical constraints (walls), etc.
- We fix the **Hamiltonian** (*H*) of the system
- The MC simulation produces **ensemble averages** of physical quantities.
- In equilibrium, these equal the **time averages** given by MD simulations.

Monte Carlo basics

Uniform sampling (NVT ensemble average):

$$\langle B \rangle_{NVT} \approx \frac{\sum_i B(\Gamma_i) \exp[-H(\Gamma_i)/kT]}{\sum_i \exp[-H(\Gamma_i)/kT]}$$

Sampling with a $\xi(\Gamma)$ distribution function:

$$\langle B \rangle_{NVT} \approx \frac{\sum_i B(\Gamma_i) \frac{\exp[-H(\Gamma_i)/kT]}{\xi(\Gamma_i)}}{\sum_i \frac{\exp[-H(\Gamma_i)/kT]}{\xi(\Gamma_i)}}$$

If $\xi(\Gamma) = \frac{\exp[-H(\Gamma)/kT]}{\sum_i \exp[-H(\Gamma_i)/kT]}$ **(Boltzmann sampling)**

then $\langle B \rangle_{NVT} \approx \frac{\sum_{i=1}^{K} B(\Gamma_i)}{K}$

Monte Carlo basics

- We generate sample configurations as members of a Markov chain governed by a π **transition matrix**, for which: $\sum_i \xi_i \pi_{ij} = \xi_j$ and $\sum_j \pi_{ij} = 1 \qquad \forall i$
- **Microscopic reversibility:** $\pi_{ij}\xi_i = \pi_{ji}\xi_j$
- It is constructed as: $\pi_{ij} = \alpha_{ij} P_{ij}$
- where
  - α_{ij} is the **probability of selecting** state *j* after state *i* in the simulation and
  - P_{ij} is the **acceptance probability** of the MC move

Monte Carlo basics

- Example: **random particle displacement**
- α_{ij} matrix is symmetric
- Then: $\frac{P_{ij}}{P_{ji}} = \frac{\xi_j}{\xi_i}$
- **Metropolis sampling:**

$$P_{ij} = \frac{\xi_j}{\xi_i} \quad \text{if} \quad \xi_i > \xi_j$$

$$P_{ij} = 1 \quad \text{if} \quad \xi_j > \xi_i$$

- **Acceptance probability**: $P_{ij} = \frac{\xi_j}{\xi_i} = \exp[-\Delta H_{ij}/kT]$
- It depends on the energy change of the MC move.
- The **heart** of the MC simulation is the energy calculation.

Biased ion exchange between channel and bath

- MC displacements between the channel and bath are **rare**, because:
- 1. **number of particles in channel is small**, so the probability of selecting an ion in the channel is small
- 2. **volume of the channel is small**, so the probability of putting an ion into the channel is small
- **Consequence**: convergence of average number of ions in the channel (our main interest) is slow.
- Solution: **preference sampling**
- We prefer ion moves between channel and bath: if the selected ion is in the channel, we move it into the bath and vice versa.

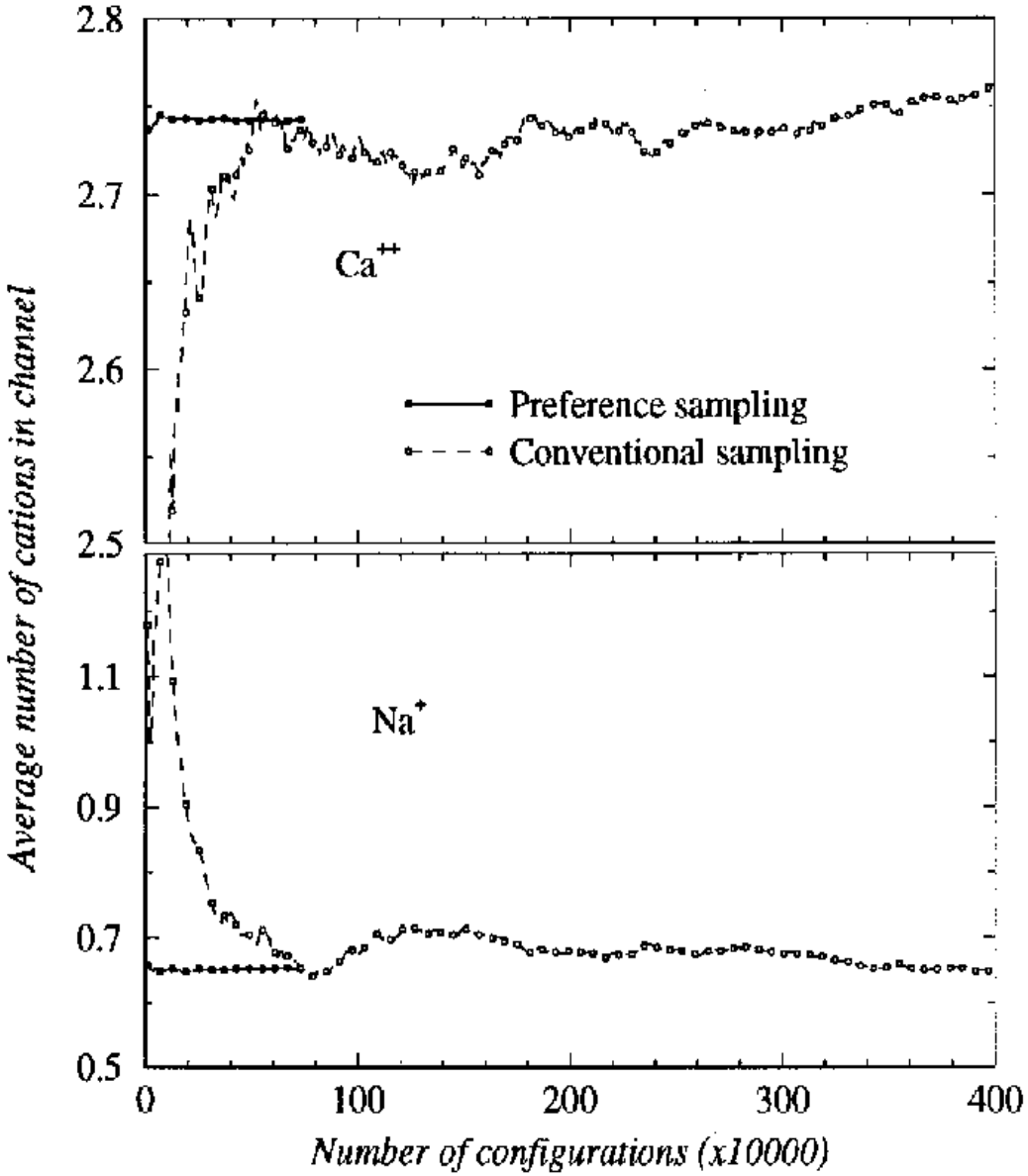
Biased ion exchange between channel and bath

- It is a nonuniform, **biased** sampling (the matrix α is not symmetric), so it has to be **unbiased** in the acceptance probability:

$$P_{ij} = \frac{V_{to}}{V_{from}} \exp[-\Delta H_{ij}/kT]$$

- where V_{from} is the volume **from which** we move the ion and
- V_{to} is the volume **to which** we move the ion

Efficiency of the preference sampling



Grand Canonical simulations

- The system is **open**,
- the number of particles **fluctuates**,
- the concentrations are **outputs**,
- the **chemical potentials** of the ionic species are **fixed**,
- the system is connected to an **external bath** with given electrolyte concentrations.
- Additional MC moves have to be introduced:
  particle insertions and deletions

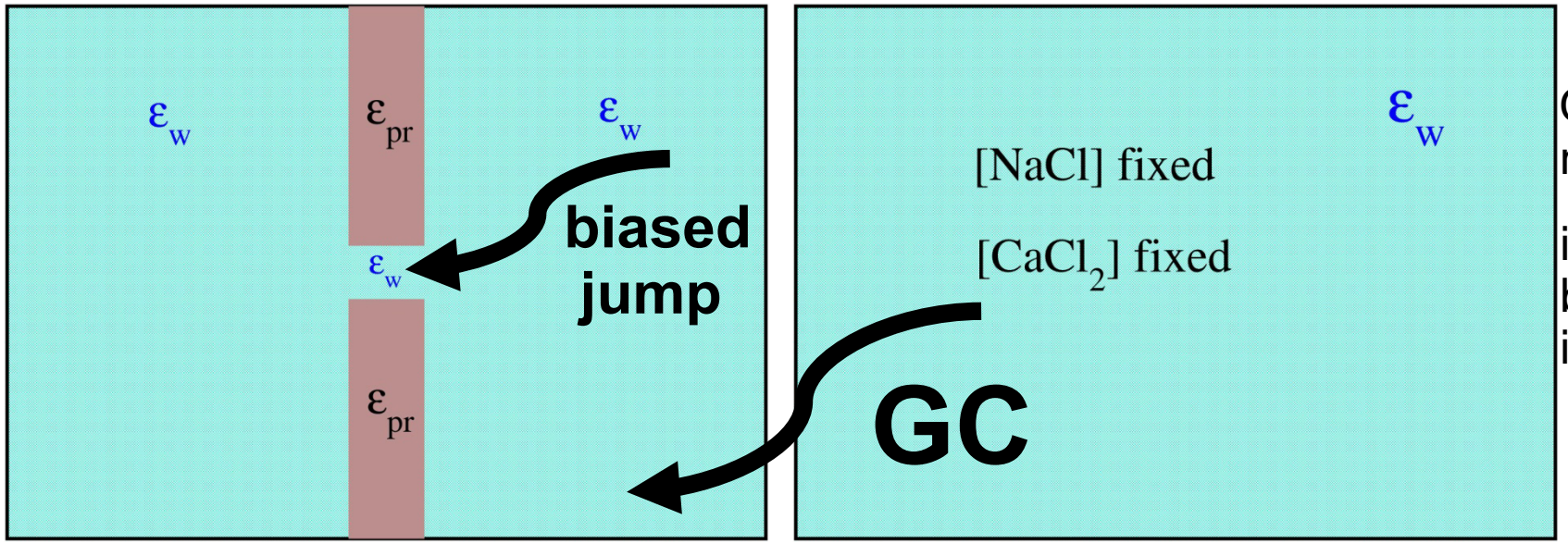
Grand Canonical simulations

- **Neutral groups** of NaCl or $CaCl_2$ are inserted / deleted into random positions in the simulation cell.
- **Acceptance probabilities** for $CaCl_2$:

$$P_{insert} = \frac{V_+ V_-^2}{(N_+ + 1)(N_- + 1)(N_- + 2)} \exp \frac{-\Delta H + (\mu_+ + 2\mu_-)}{kT}$$

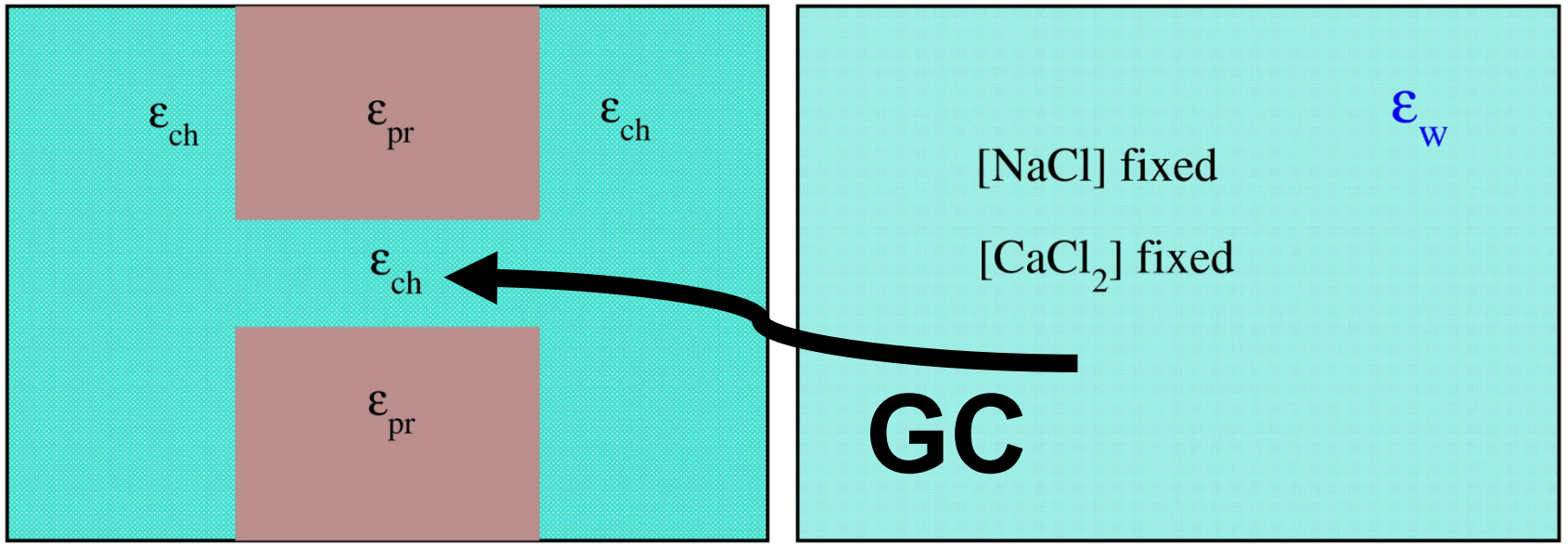
$$P_{delete} = \frac{(N_+)(N_-)(N_- - 1)}{V_+ V_-^2} \exp \frac{-\Delta H - (\mu_+ + 2\mu_-)}{kT}$$

Improved GCMC sampling



Original method:

ions go from bulk to channel in **two steps**



Ions are inserted **directly** into the channel.

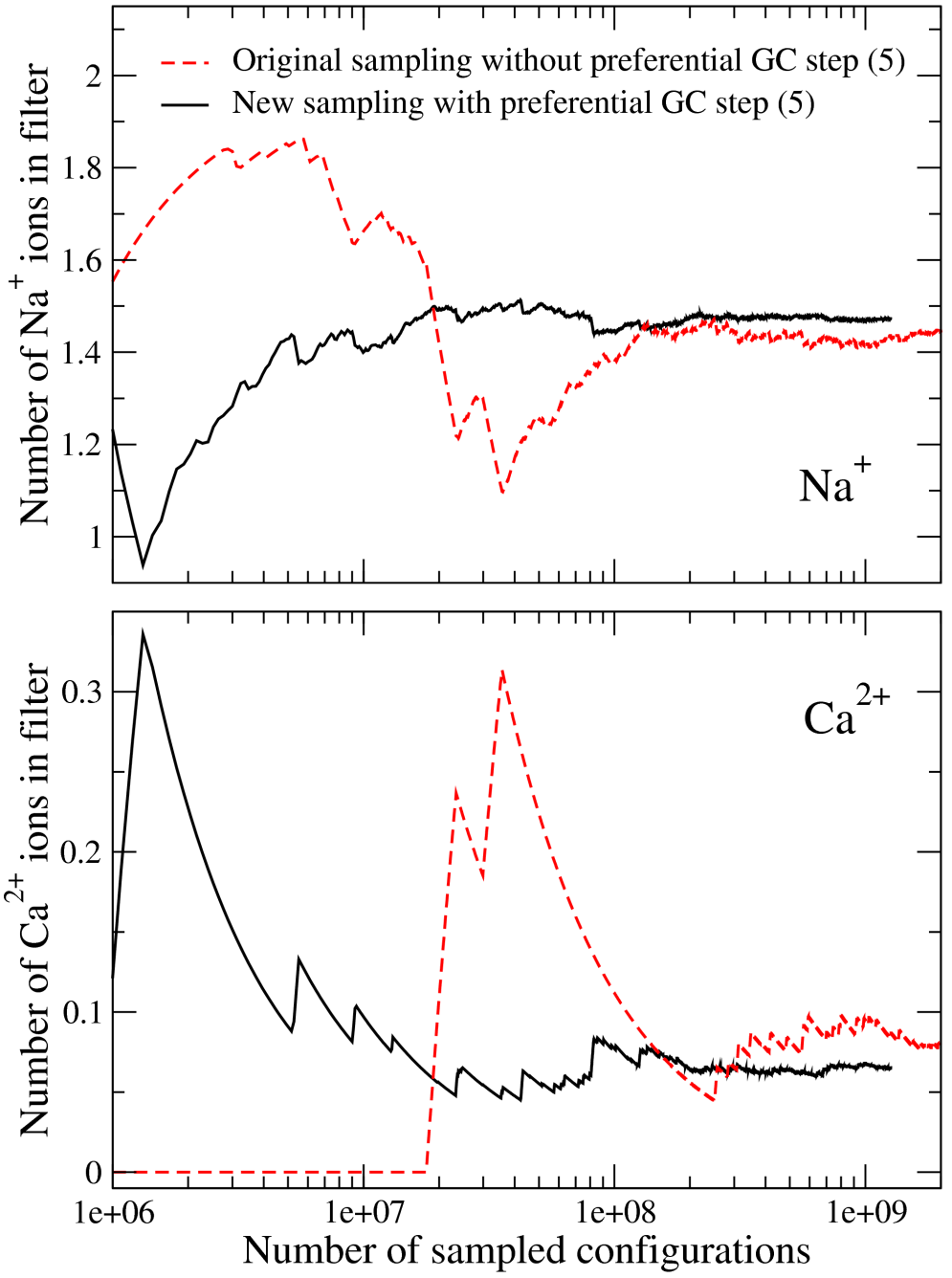
Simulation box **External bulk**

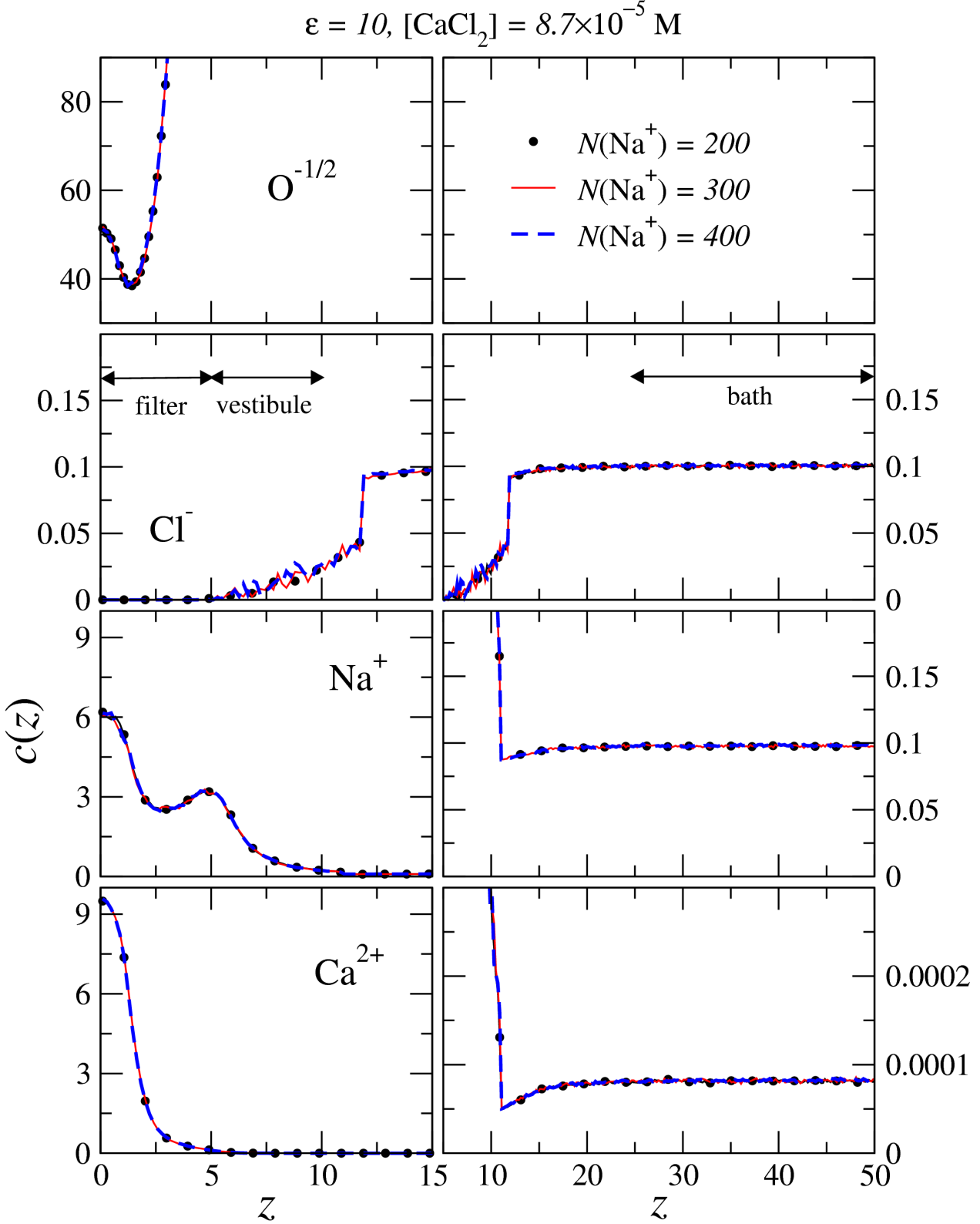
Improved GCMC sampling

In the preferential GC insertion/deletion we insert/delete the **cation** into the channel/filter, while we insert **anion(s)** into the whole simulation cell.

In the acceptance probability V_+ is the **volume** of the channel/filter and N_+ is the **number of cations** in the channel/filter.

This GCMC step considerably **accelerates the convergence** of the number of ions in the filter (beware the logarithmic scale of abscissa!)





Check on system-size dependence.

Energy calculation

- The simulation box is **finite**, it is confined by a **hard wall**, outer boundary conditions set in **infinity** (ε=80 outside the cell too).
- In the **absence** of **dielectric boundaries**, the solution of Poisson's equation is **trivial**: the energy is the sum of **Coulomb** interactions
- When the interior of the protein has a **different** dielectric coefficient than the solution, the problem becomes **challenging**.

Energy calculation

- The **differential equation**

$$\epsilon_0 \nabla \epsilon(\mathbf{r}) \nabla \cdot \mathrm{E}(\mathbf{r}) = \rho(\mathbf{r})$$

  with the **boundary condition**

$$\begin{aligned} \epsilon_1 \mathrm{E}_1 \cdot \mathbf{n} &= \epsilon_2 \mathrm{E}_2 \cdot \mathbf{n} \\ \mathrm{E}_1 \times \mathbf{n} &= \mathrm{E}_2 \times \mathbf{n} \end{aligned}$$

  at the dielectric boundary is transformed into an **integral equation**.

- Its variable is the **induced charge** instead of the **electric field**.
- It self-contains the boundary condition.

Energy calculation

- **The integral equation**:

$$h(\mathbf{s}) + \frac{\Delta\epsilon(\mathbf{s})}{4\pi\bar{\epsilon}(\mathbf{s})}\mathbf{n}(\mathbf{s}) \cdot \int_{\mathcal{B}} \frac{\mathbf{s}-\mathbf{s}'}{|\mathbf{s}-\mathbf{s}'|^3} h(\mathbf{s}') = -\frac{\Delta\epsilon(\mathbf{s})}{4\pi\bar{\epsilon}(\mathbf{s})}\mathbf{n}(\mathbf{s}) \cdot \sum_k \frac{q_k}{\epsilon(\mathbf{r}_k)} \frac{\mathbf{s}-\mathbf{r}_k}{|\mathbf{s}-\mathbf{r}_k|^3}$$

- The solution is performed numerically
- The surface is divided into **surface elements** (boundary element methods).
- Writing the equation for **tile centers**, we get

$$\sum_\beta h_\beta \left[\delta_{\alpha\beta} + \frac{\Delta\epsilon_\alpha}{4\pi\bar{\epsilon}_\alpha} I_{\alpha\beta}\right] = -\frac{\Delta\epsilon_\alpha}{4\pi\bar{\epsilon}_\alpha} \sum_k \frac{q_k}{\epsilon(\mathbf{r}_k)} \frac{(\mathbf{s}_\alpha - \mathbf{r}_k)}{|\mathbf{s}_\alpha - \mathbf{r}_k|^3} \cdot \mathbf{n}_\alpha$$

with $$I_{\alpha\beta} = \int_{\mathcal{B}_\beta} \frac{(\mathbf{s}_\alpha - \mathbf{s}') \cdot \mathbf{n}_\alpha}{|\mathbf{s}_\alpha - \mathbf{s}'|^3} d\mathbf{s}'$$

Energy calculation

$$\sum_\beta h_\beta \left[\delta_{\alpha\beta} + \frac{\Delta\epsilon_\alpha}{4\pi\bar{\epsilon}_\alpha} I_{\alpha\beta}\right] = -\frac{\Delta\epsilon_\alpha}{4\pi\bar{\epsilon}_\alpha} \sum_k \frac{q_k}{\epsilon(\mathbf{r}_k)} \frac{(\mathbf{s}_\alpha - \mathbf{r}_k)}{|\mathbf{s}_\alpha - \mathbf{r}_k|^3} \cdot \mathbf{n}_\alpha$$

can be turned into a **matrix equation**

$$\boxed{\mathbb{A}\mathbf{h} = \mathbf{c}}$$

where the matrix can be **precalculated** at the beginning of the simulation.

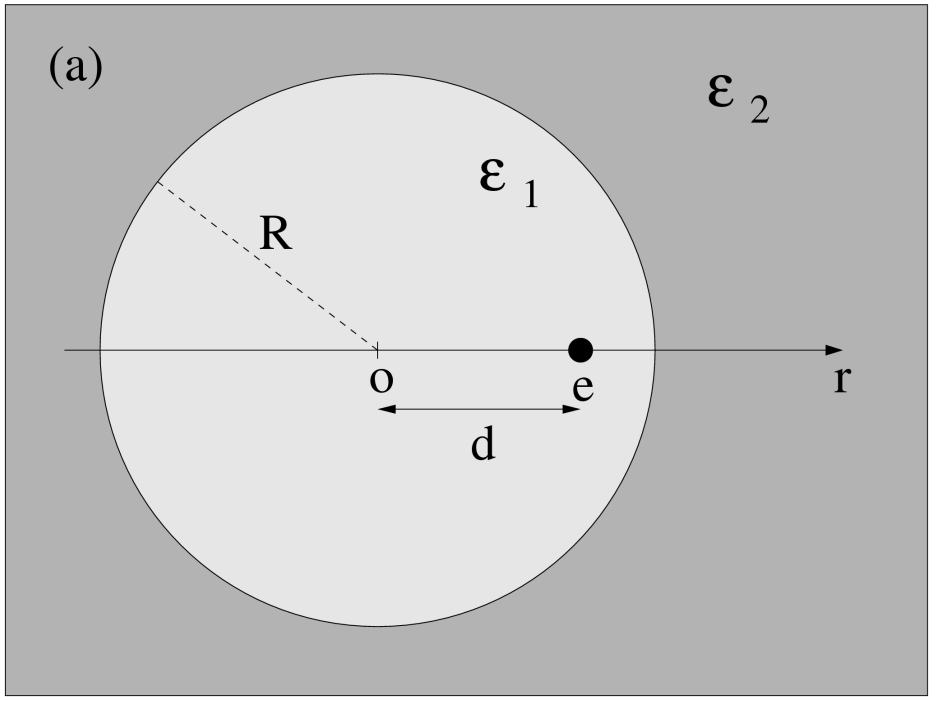
Vector **c** (the **electric field** at the surface) changes as ions move, and the **induced charge** can be computed from the matrix equation.

We compute the potential only where it is interesting.

Dielectric sphere

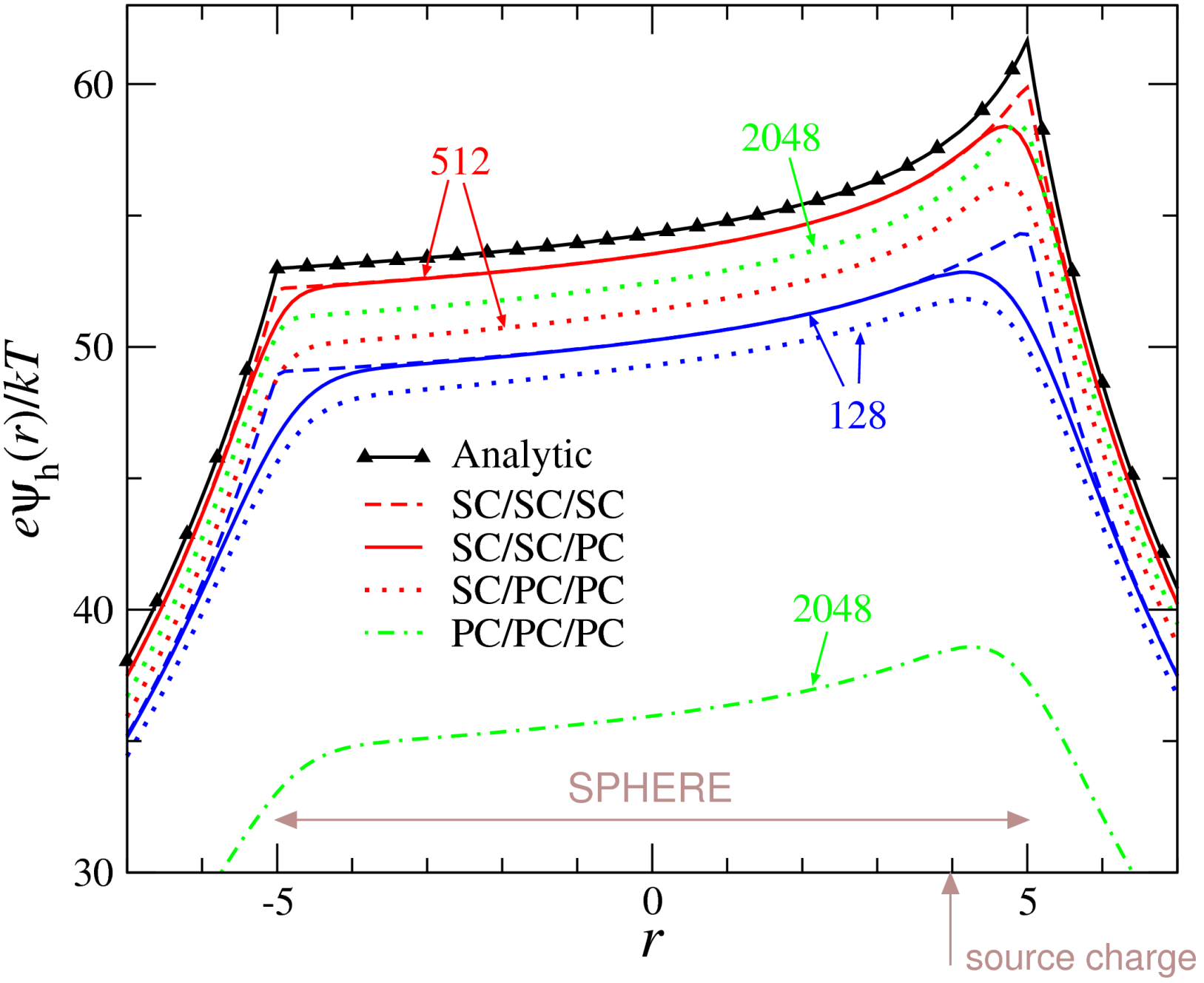
Computation of the **integral** $I_{\alpha\beta}$ is very important in the case of **curved** dielectric boundaries.

Toy-problem: the **dielectric sphere**:

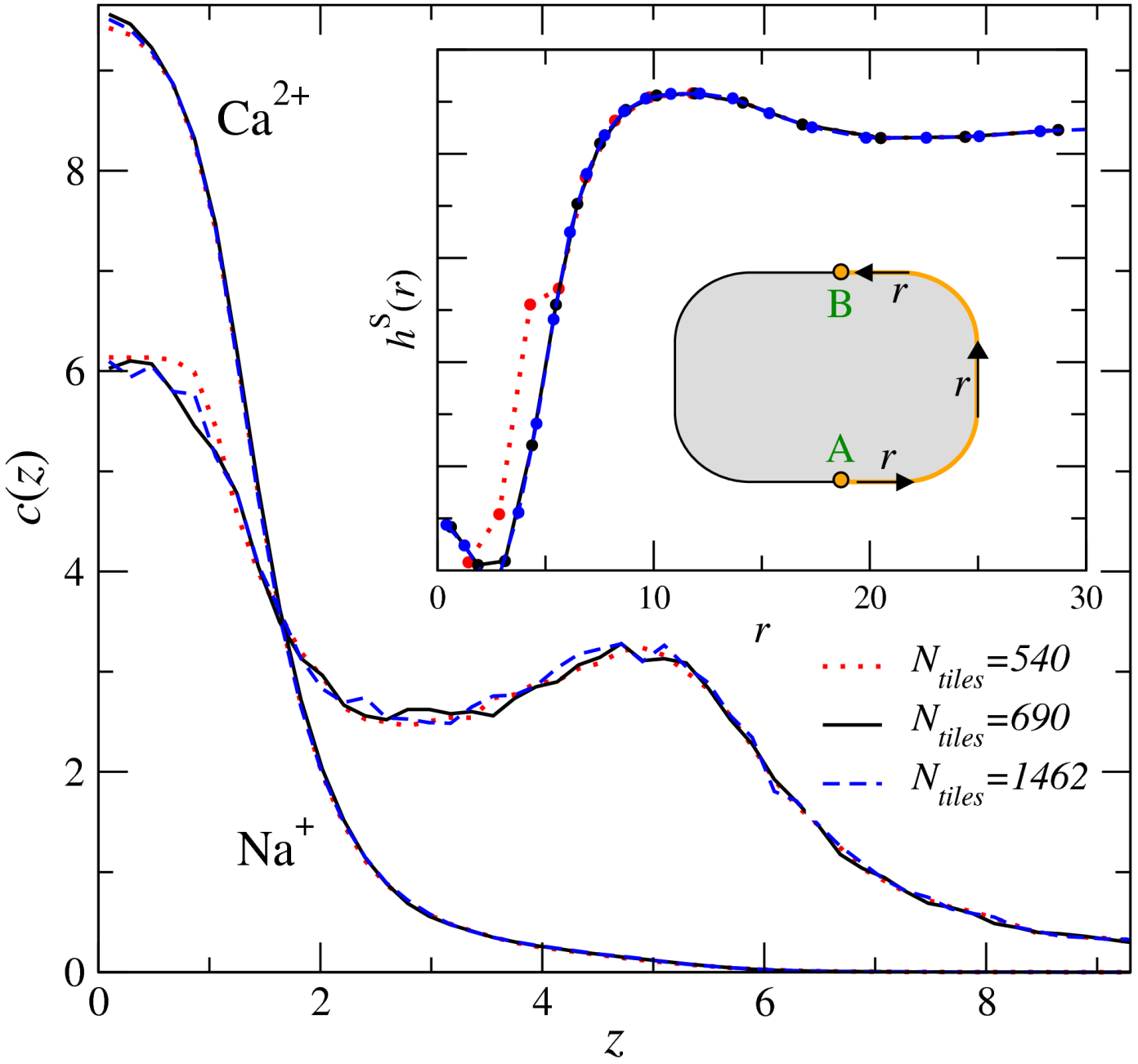


We calculate **potential** along the axis.

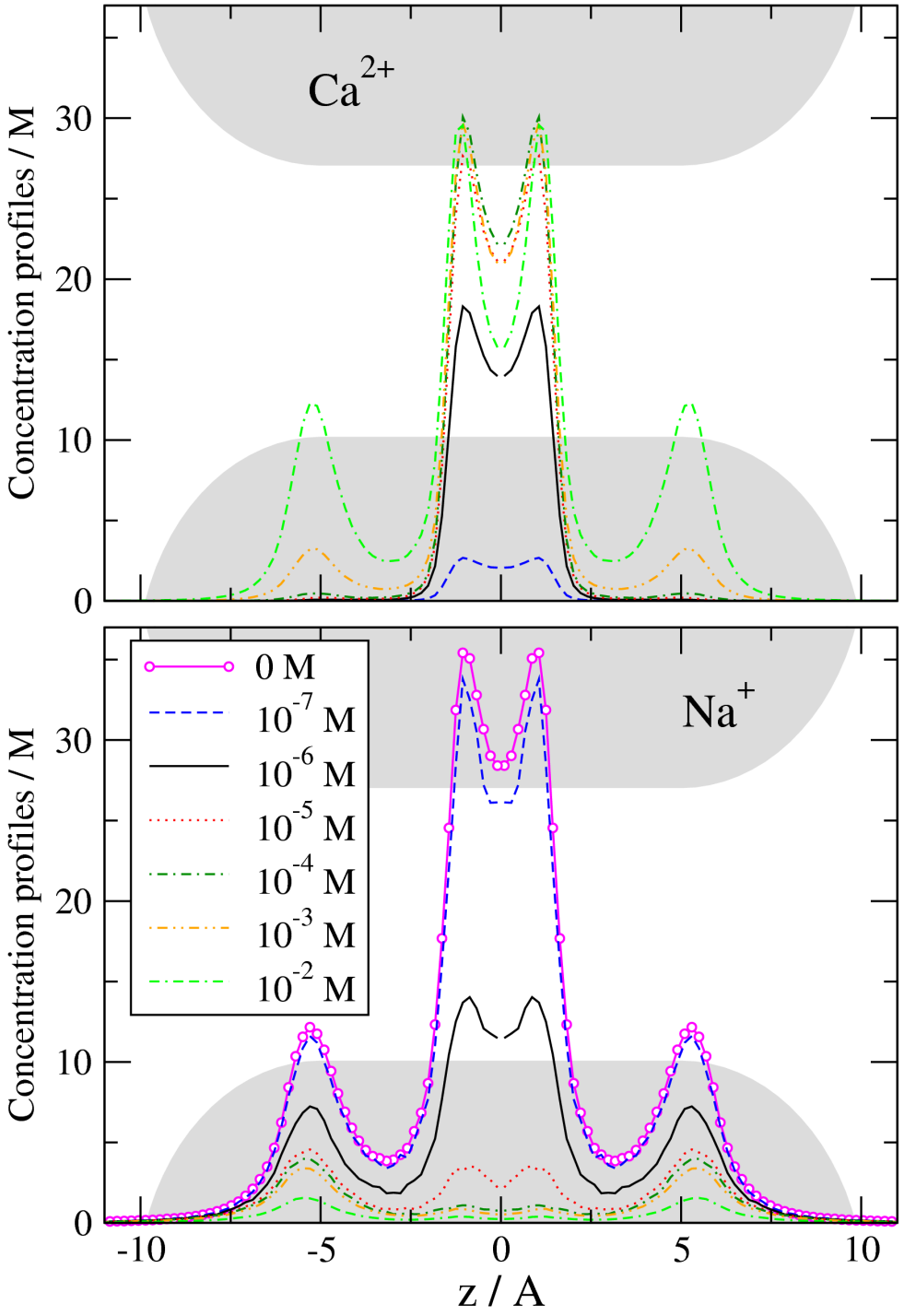
Dielectric sphere



Check on grid-resolution

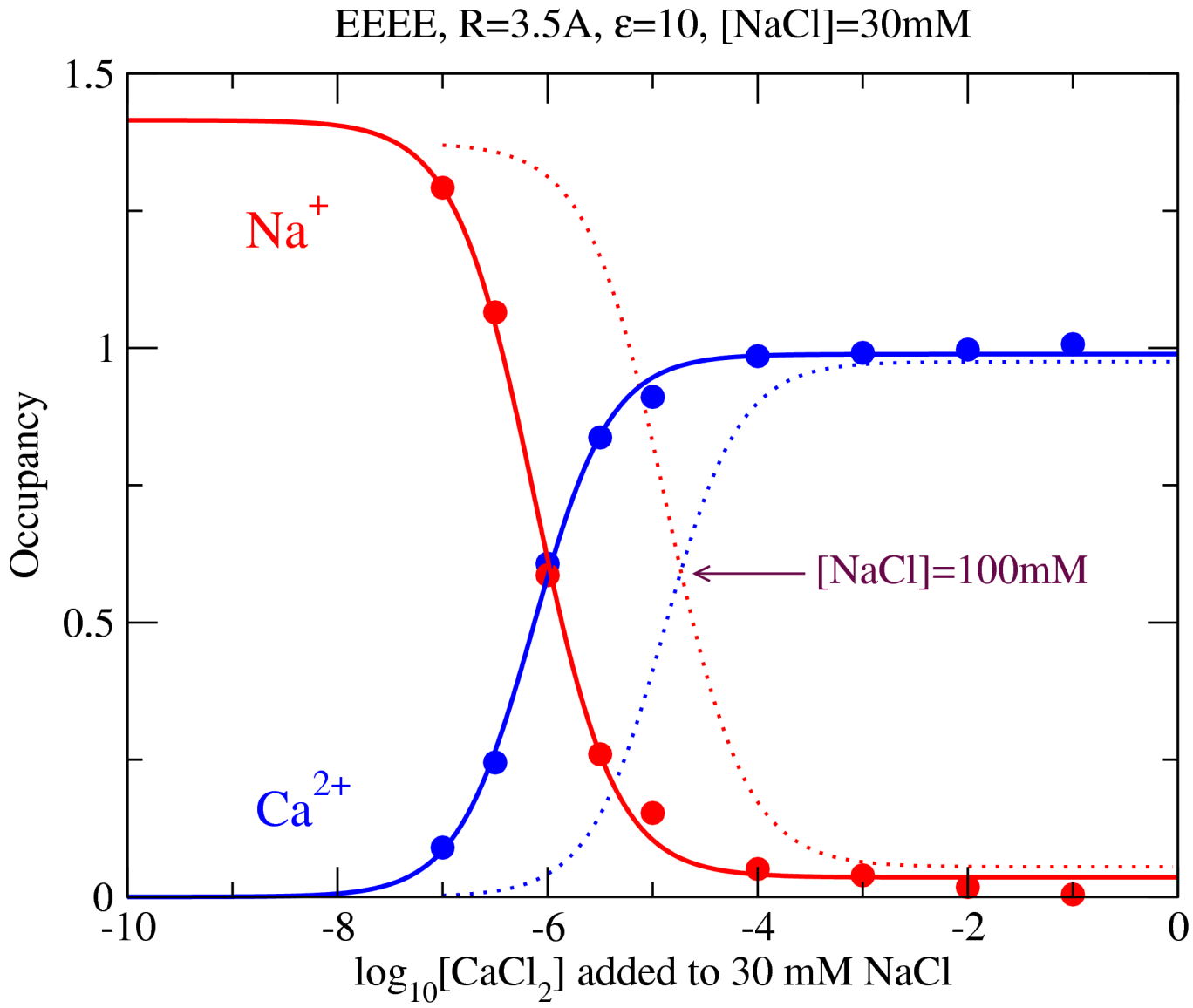


Some typical results for the Ca channel



- $CaCl_2$ is added to 30 mM NaCl.
- Na^+ peak is considerably reduced when **micromolar** Ca^{2+} is present.
- Above **millimolar** Ca^{2+} level, Ca^{2+} starts to conduct.
- ε_p=10, R=3.5Å

Some typical results for the Ca channel



Selectivity curve for the equilibrium competition of Na^+ against Ca^{2+}

Integrated Nernst-Planck equation

1-D Nernst-Planck equation: $J_i = -\frac{1}{kT} D_i(x) A(x) \rho_i(x) \frac{d\mu_i}{dx}$

Integrated: $$\boxed{J_i \int \frac{dx}{D_i(x) A(x) \rho_i(x)} = \frac{\Delta \mu_i}{kT} = \frac{z_i e}{kT} V}$$

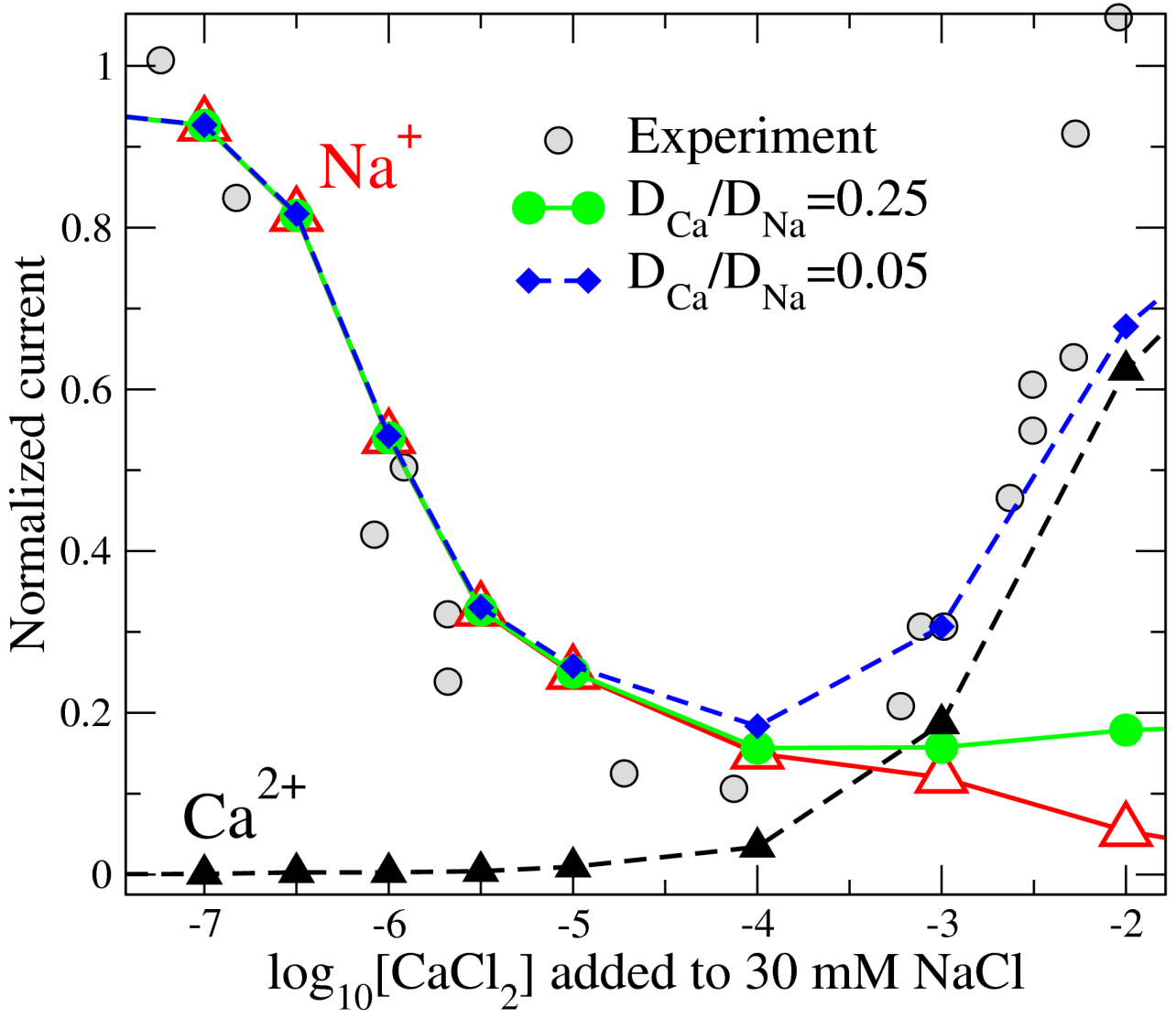
Channel conductance:

$$g = \frac{e}{V} \sum_i z_i J_i = \frac{e^2}{kT} \sum_i \frac{z_i^2}{\int [D_i(x) A(x) \rho_i(x)]^{-1} dx}$$

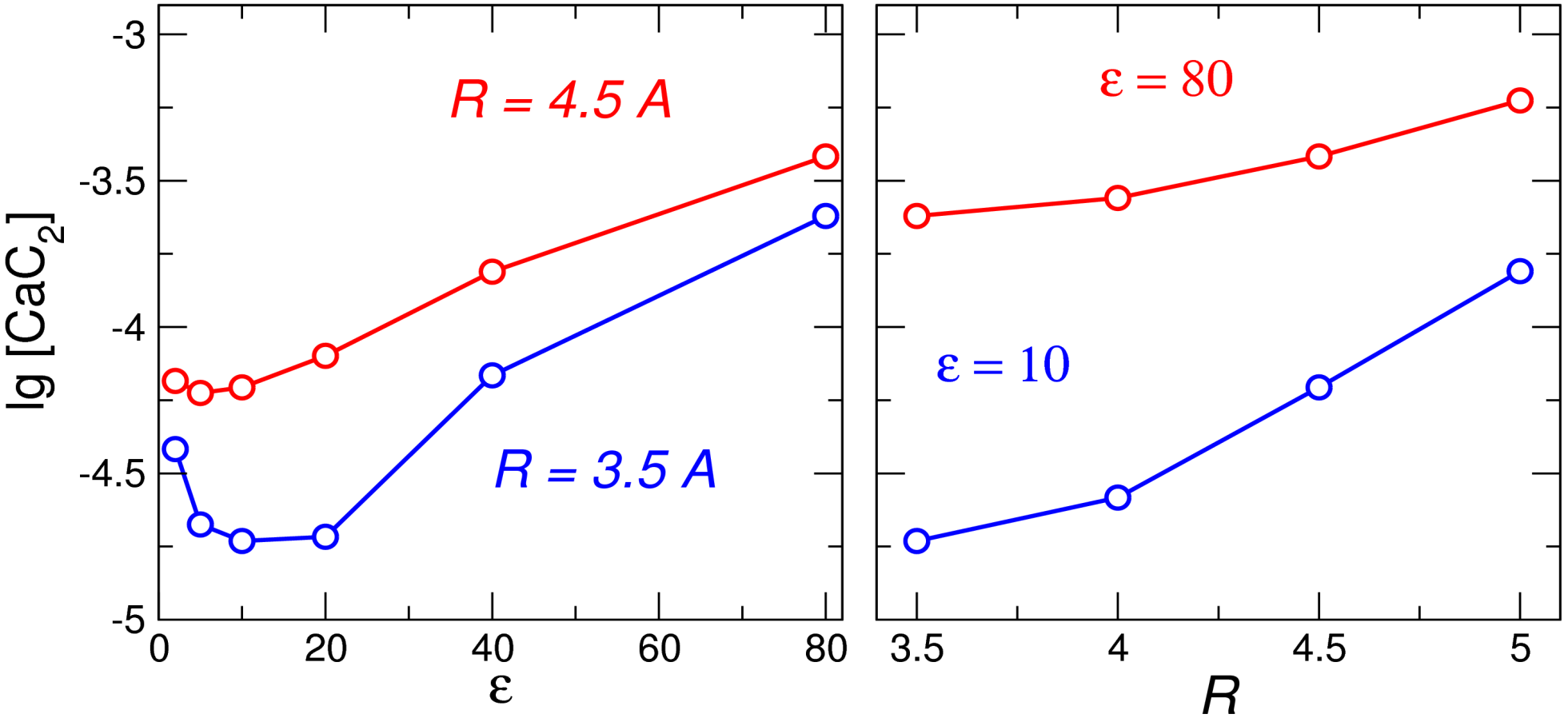
Assumptions: (1) Symmetric system, (2) *V* is small (linear *J-V* range), (3) bulk is low resistance (*A* and *D* is large: wire), (4) the channel is the low resistance element: we integrate for this part: A_i and D_i are constant, (5) the only adjustable parameter: D_{Ca}/D_{Na} (we compute normalized current)

Some typical results for the Ca channel

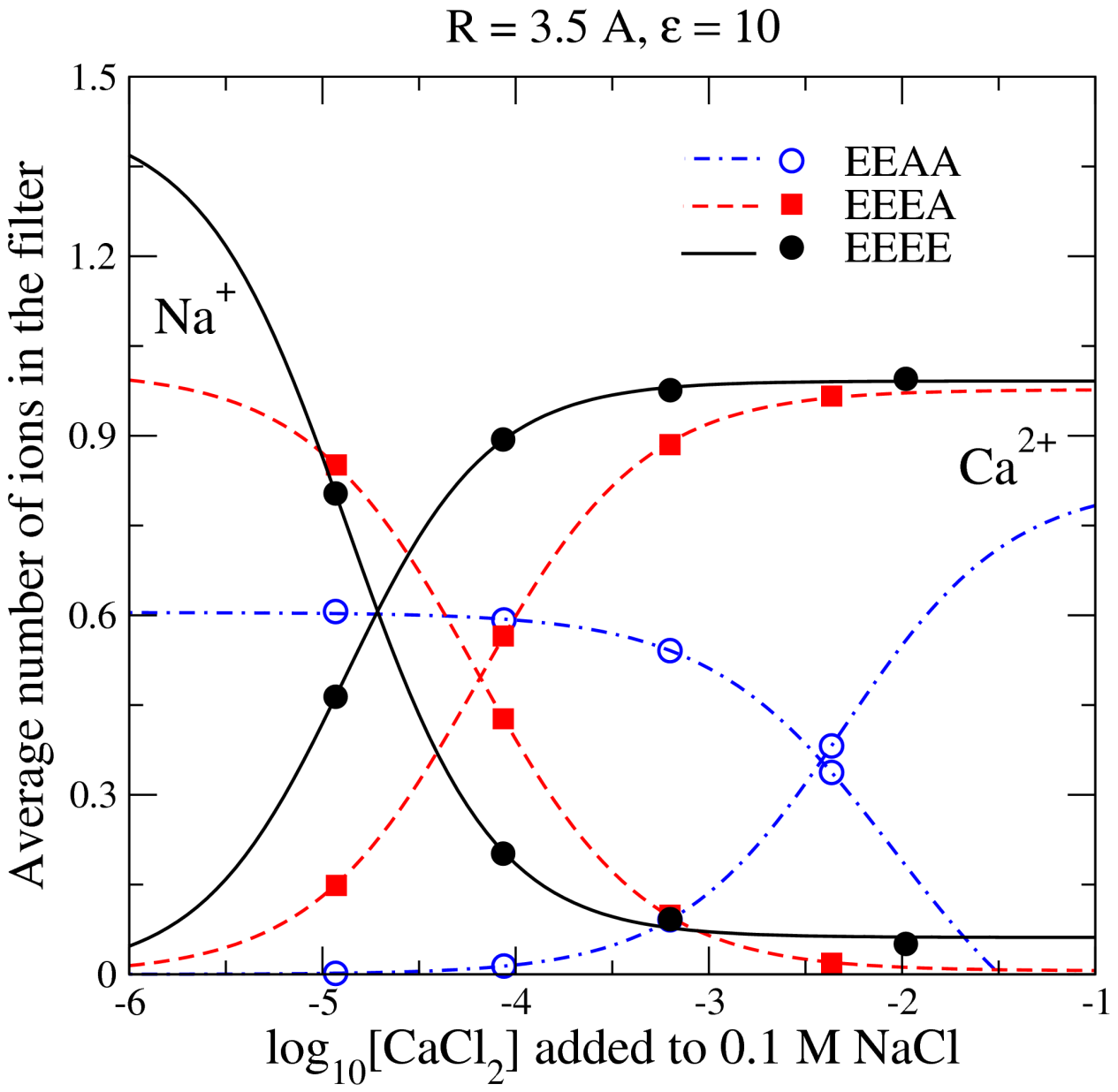
Using the integrated Nernst-Planck equation, normalized currents can be computed from the equilibrium concentration profiles:



How can we tune selectivity between micromolar and millimolar?

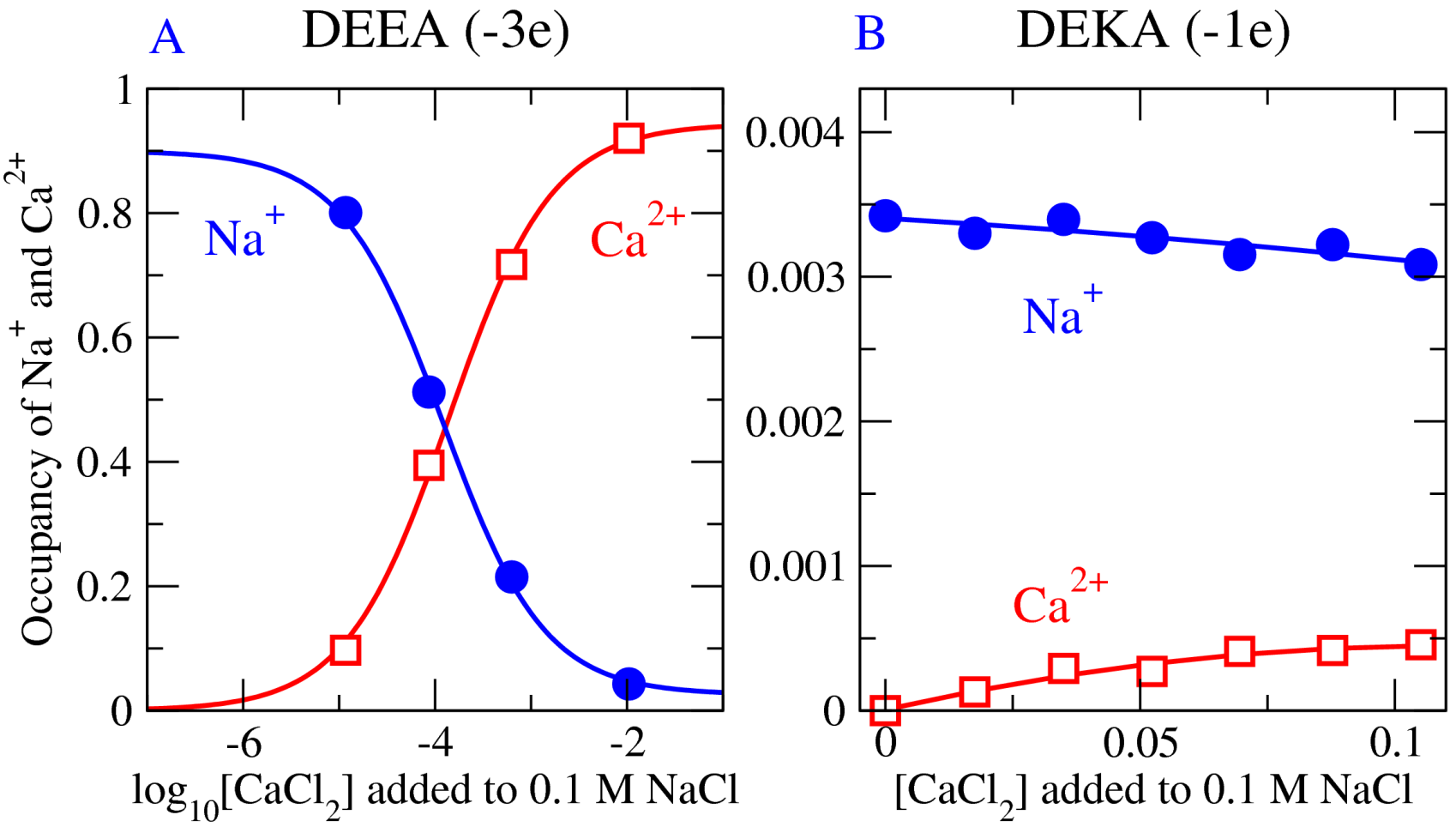


Gene mutation experiment in the computer



The amount of negative amino acids is changed

Gene mutation experiment in the computer



The Na channel (DEKA) is turned into a Ca channel (DEEA) with a K <-----> E mutation (Eisenmann experiment).

Some conclusions

- Ca^{2+} vs. Na^{+} selectivity **becomes better** when

  1. The **dielectric constant** of the protein is decreased
  2. The **radius** of the pore is decreased
  3. The **concentration of NaCl** is decreased
  4. The amount of negative **structural charge** in the filter is increased

- Importance of **depletion zones** in explaining Ca^{2+}-block and AMFE experiments.
- Only **physical forces** were used (electrostatics and hard sphere excluded volume).