Particle-Based Simulation of Bio-Electronic Systems

Alex Smolyanitsky, and Marco Saraniti

Center for Computational Nanoscience

Arizona State University

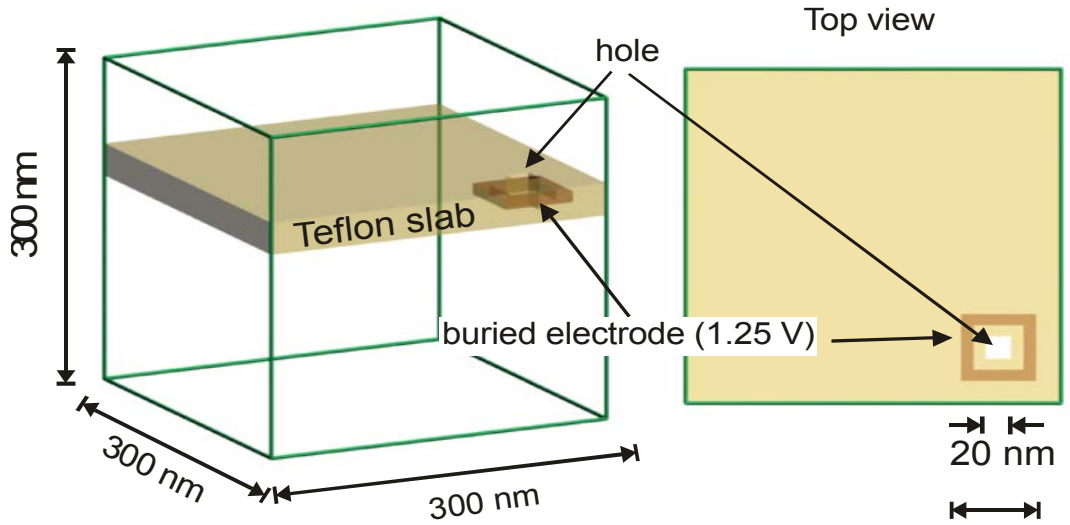
Outline

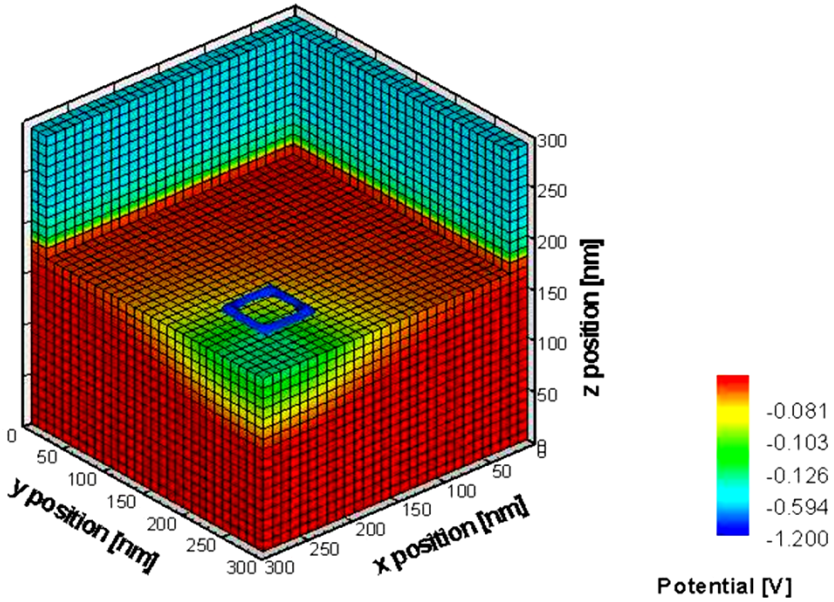
Particle-based Brownian dynamics simulations for bioelectronic systems

- Complex-field DC-electrophoresis of charged proteins
- Simulations of molecule: constraints and general computational framework
- SHAKE and LINCS algorithms
- RATTLE and general velocity correction
- Results and discussion for ***OmpF*** ion channel
- Preliminary results for ***Kv1.2*** ion channel
- Visualization of simple protein folding

Conclusions and future work

Complex field electrophoresis: system description





- ***α-Hemolysin*** protein molecules are driven by DC electrophoresis.

- Protein modeled as charged rigid sphere (r = 5 nm) suspended in water (ε = 78.0).
- External field, stokesian drag, stochastic contribution explicitly included in the simulation.

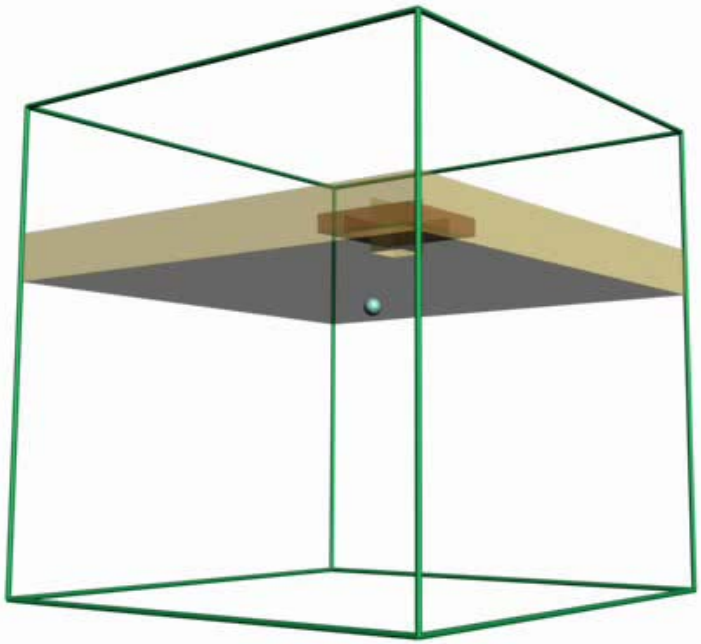
- Driving fields obtained via application of constant potentials, not constant fields.

- Electric charge calculated from protonation states of individual residues in α-Hemolysin at a given pH value.

- *T = 300K, q = +65|e|* at pH = 5.0; diffusion coefficient, mobility, and settling time used in simulation, respectively:

The simulation setup is a *300 nm x 300 nm x 300 nm* water-filled box split by a 30 nm thick teflon membrane (ε = 2.0).

Complex field electrophoresis: visualization

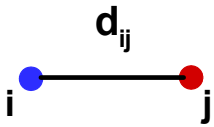


•The distance from the protein's initial position is calculated at approx. *115 nm.*

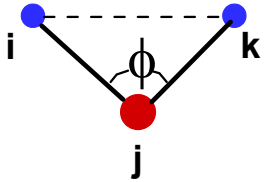
•Total focusing time is about 4 microseconds.

•The protein with effective diameter of *10 nm* is successfully focused into a *20 nm x 20 nm* hole.

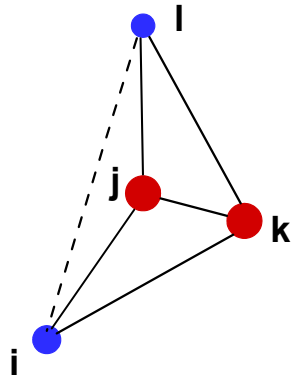
Constrained dynamics: basic constraints



a) simple linear bond



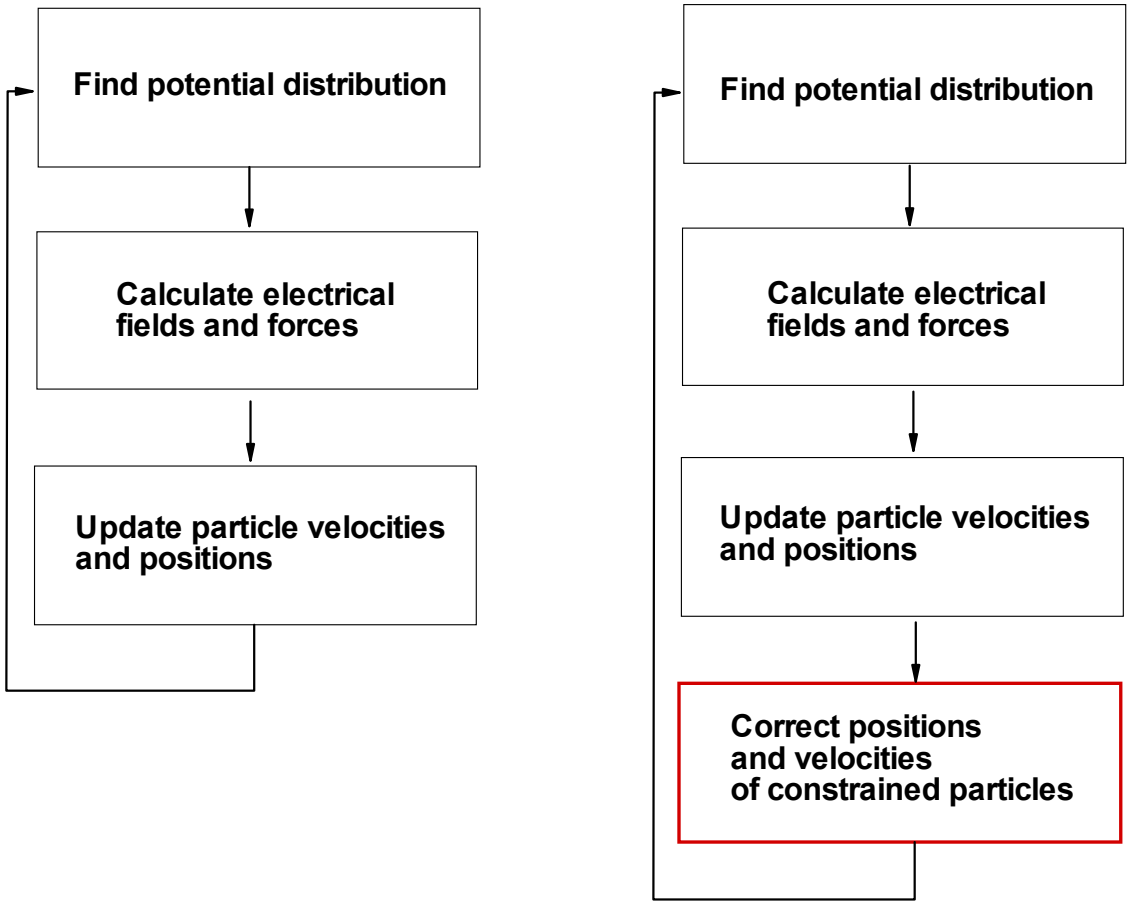
b) 2-D bond angle



c) 3-D dihedral angle

Constrained dynamics: flowchart

Flowchart of the Brownian dynamics simulation tool without (left) and with (right) the constrained dynamics corrections.



Constraint algorithm review

General Framework

- Based on Lagrange multiplier method
- For a system containing ***N*** particles requires inversion of ***N*** x ***N*** matrix at every timestep

SHAKE algorithm

- Approximate iterative method to avoid direct matrix inversion
- Guaranteed to converge within 50 iterations with timesteps up to 10 fs

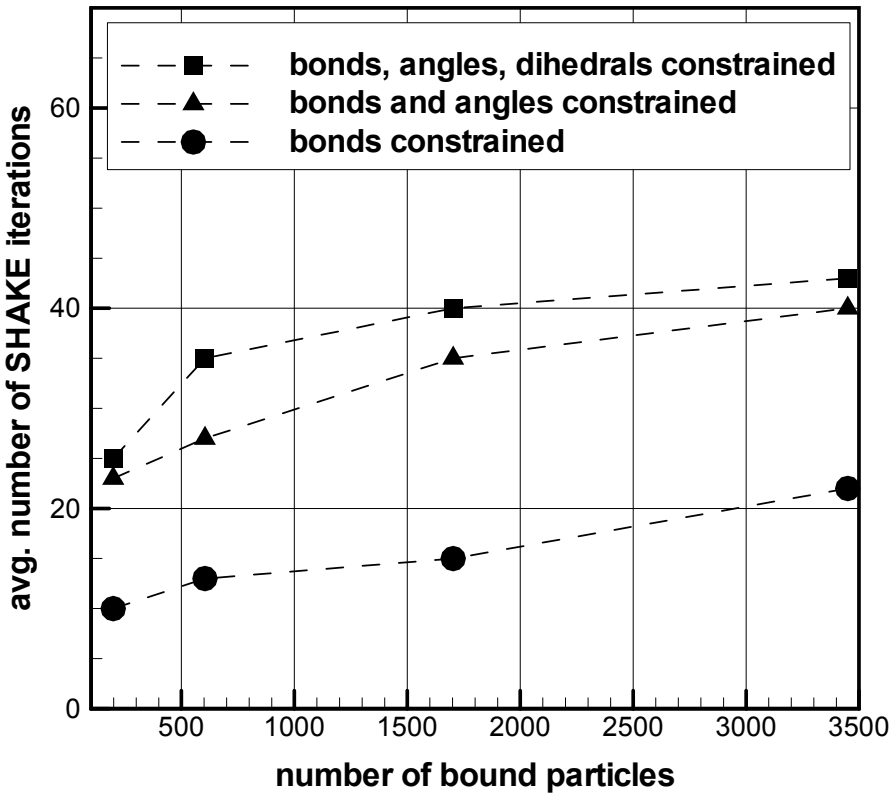
LINCS algorithm

- Non-iterative, uses matrix form of Taylor expansion to avoid direct matrix inversion
- Timesteps up to 20 fs, twice as large compared to SHAKE
- Applicable only to systems with low connectivity, limiting use for constraining the angles using artificial bonds and demanding use of angle-constraining potentials rather than artificial bonds

RATTLE and general velocity correction

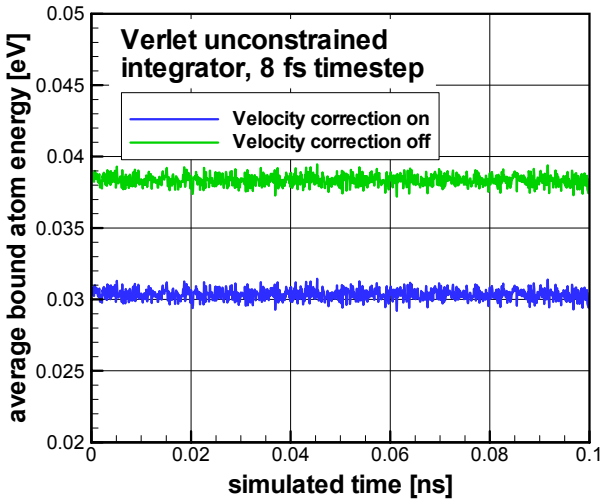
- Removes bond strain by minimizing relative velocity along the constraint
- Applied sequentially
- Improves SHAKE convergence

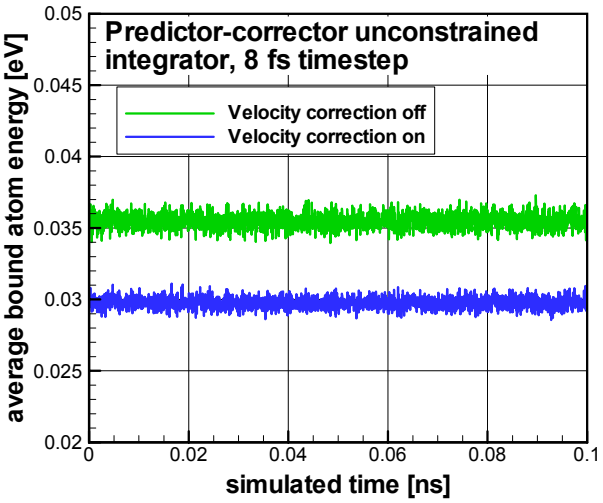
Constrained dynamics: SHAKE algorithm

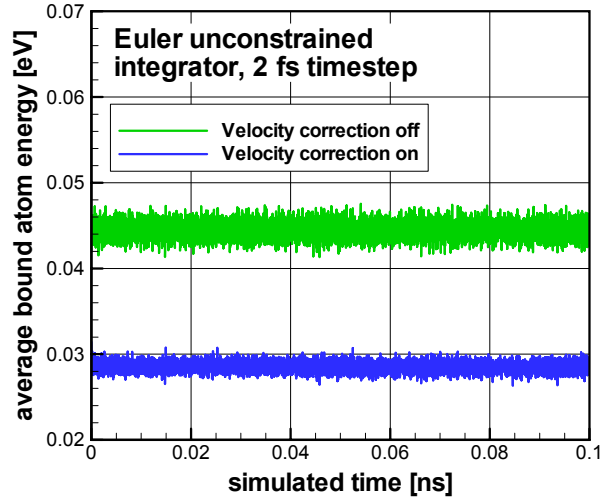


Average number of SHAKE iterations vs. number of bound particles required for convergence to relative SHAKE tolerance of 0.001 for various types of constraints. Verlet unconstrained integrator with free flight timestep of 8 fs used.

Constrained dynamics: velocity correction





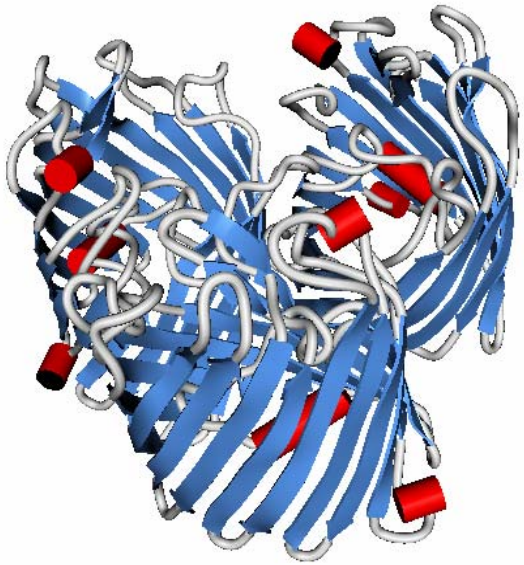


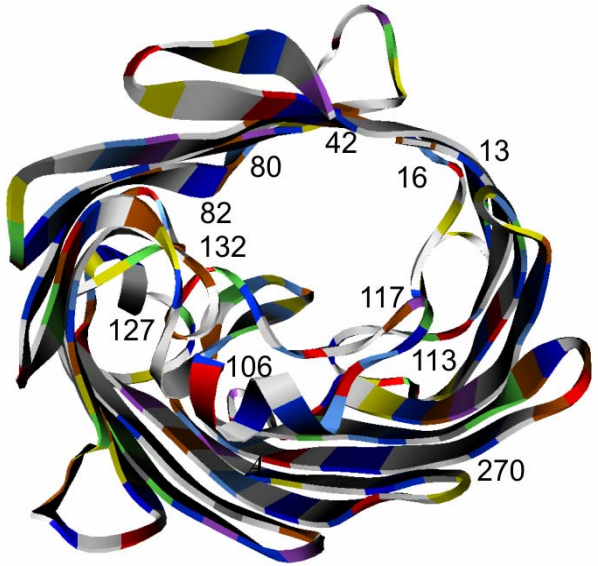
Time evolution of the average energy of the bound atoms for various unconstrained integrator algorithms.

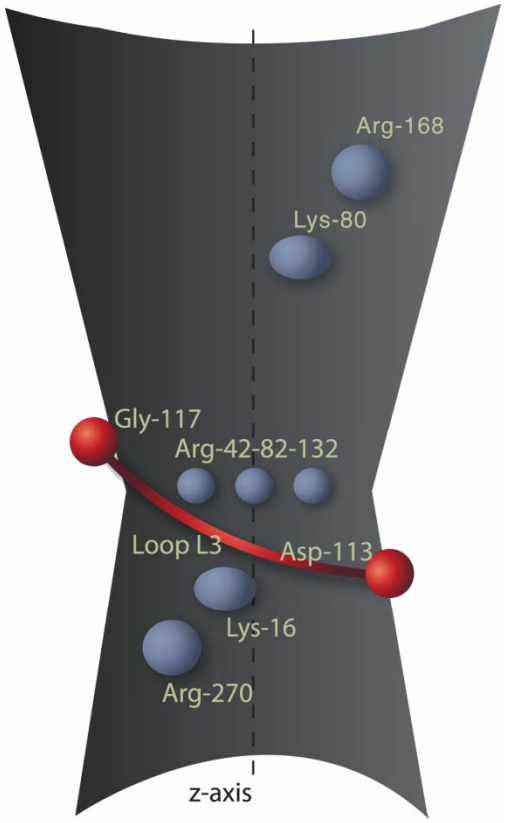
After velocity correction, avg. kinetic energy around 30meV for all algorithms.

No spurious heating/cooling of molecule.

OmpF ion channel simulation: general structure

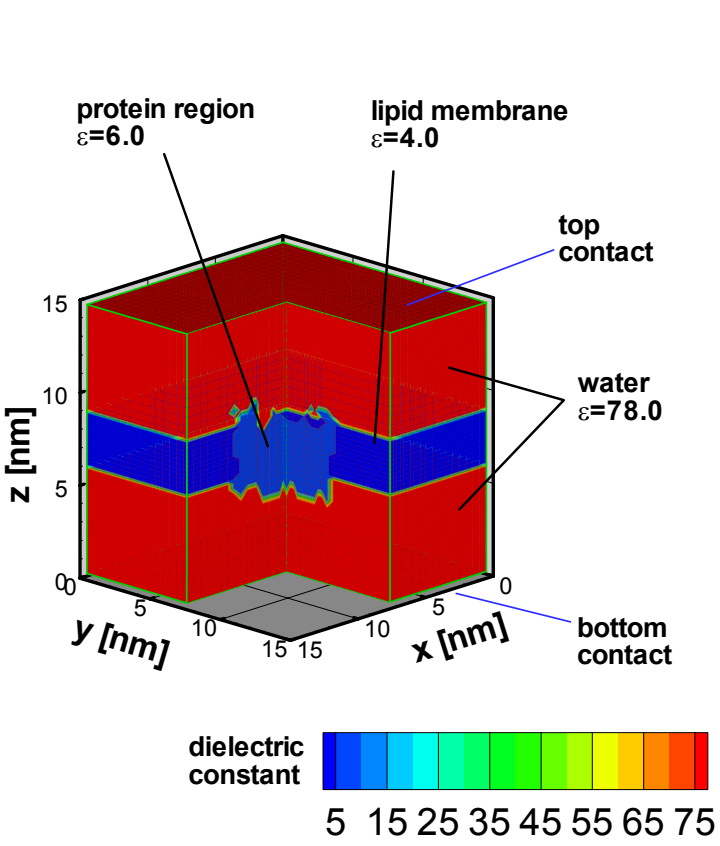


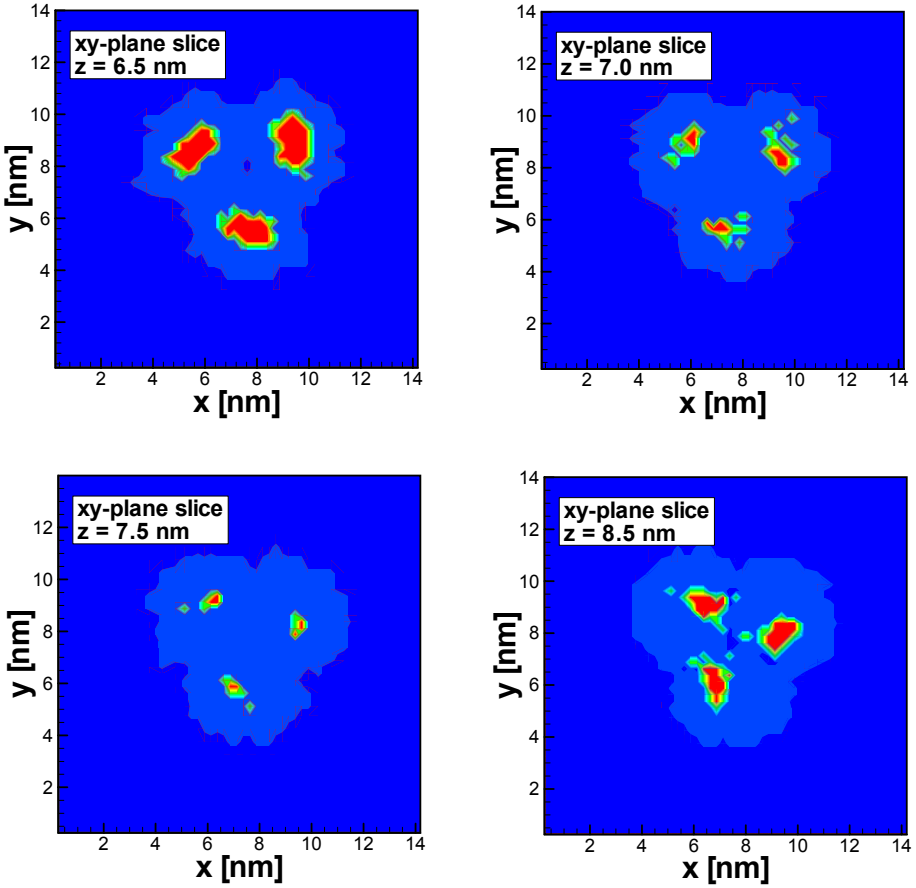




- Three 16-strand barrel subunits (340 residues each)
- Permeation region constricted to 7 x 11 Å
- Transverse fields in permeation region due to charged residues
- Cation-selective, depending on salt concentration selectivity ratio 1.5 to 2.5

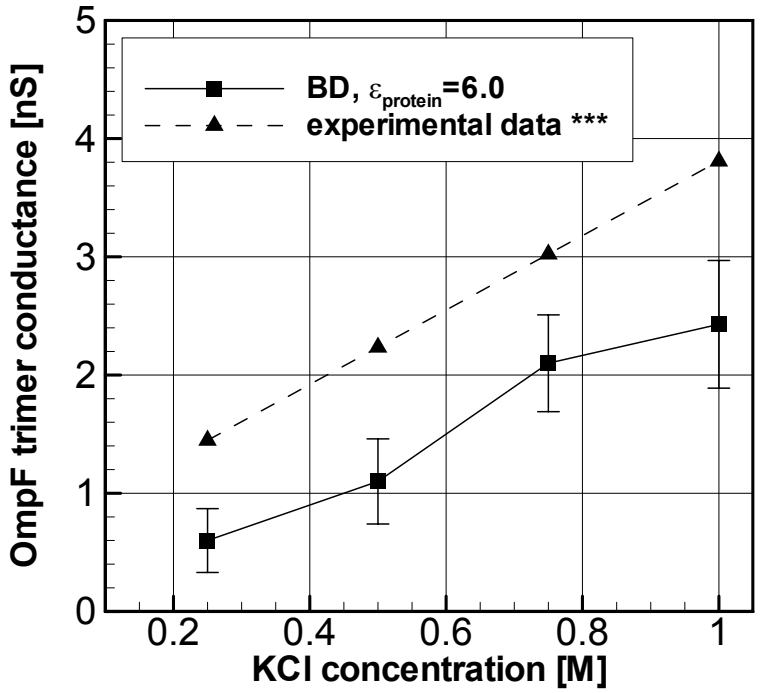
OmpF ion channel simulation: system description

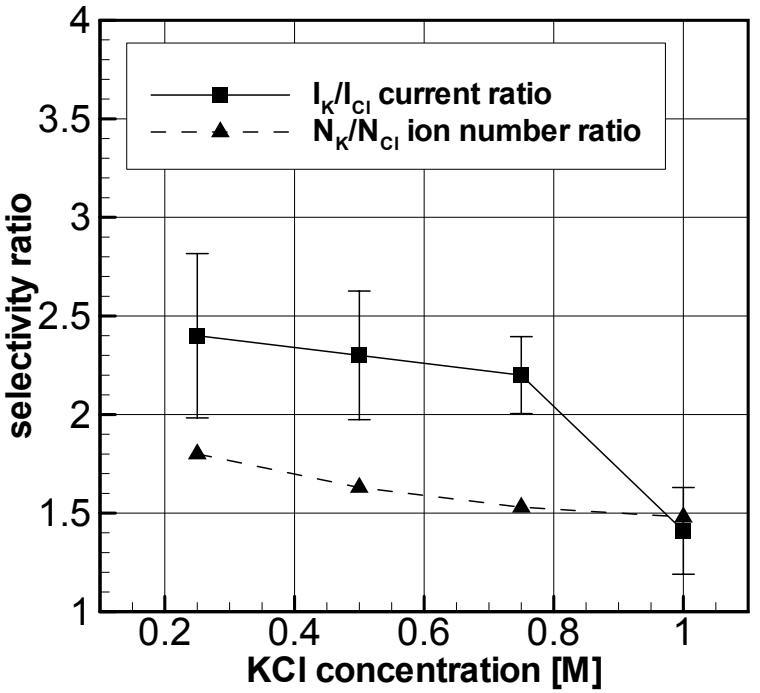




3-D dielectric map of the system (left) and
dielectric contour planes at various z-coordinates (right).

OmpF ion channel simulation: conductance and selectivity

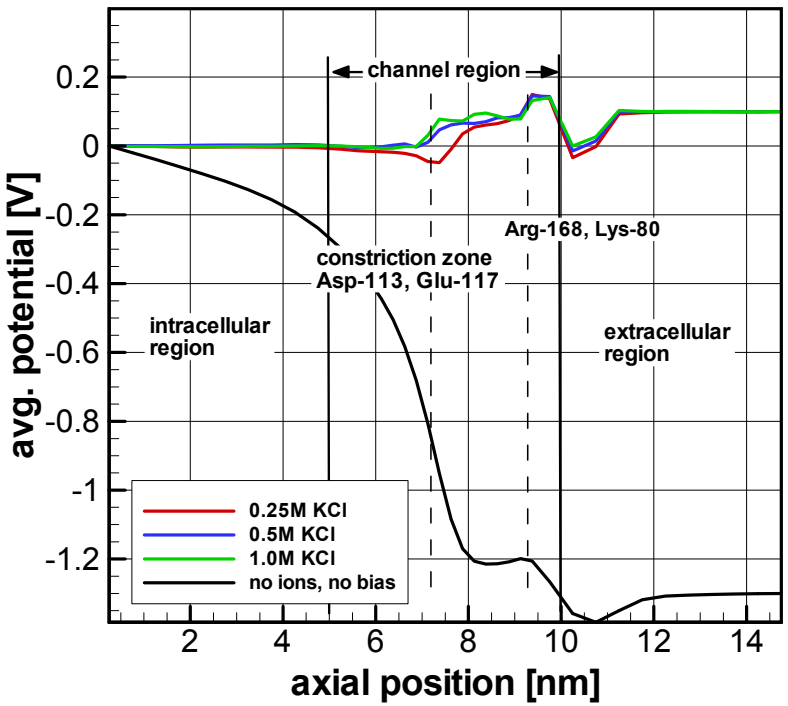


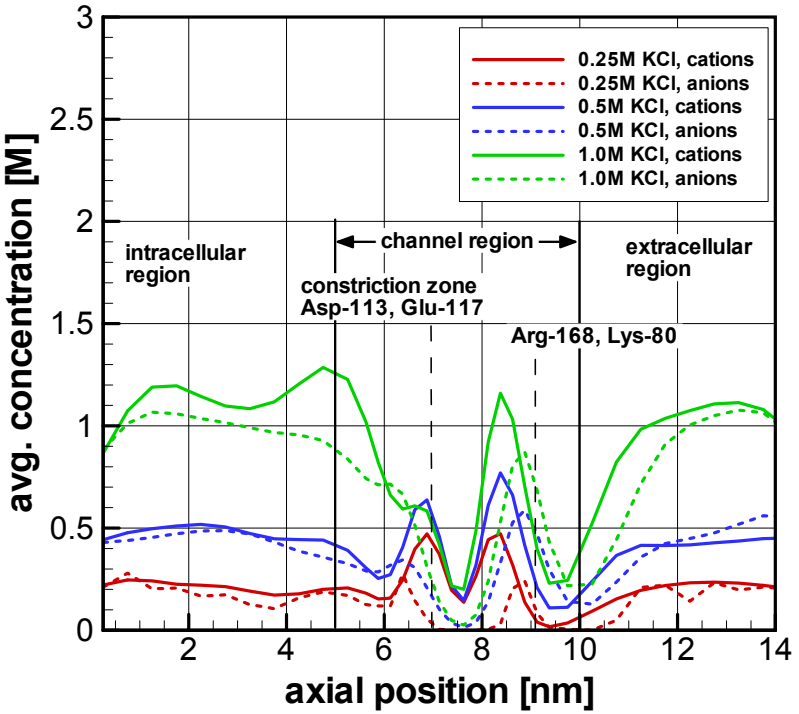


Simulated ***OmpF*** conductance vs. ***KCl*** concentration compared to experimental data, and simulated ionic selectivity based on currents and ion numbers (right).

*** S. J. Wilk, S. Aboud, L. Petrossian, M. Goryll, J. M. Tang, R. S. Eisenberg, M.Saraniti, S. M. Goodnick, and T. J. Thornton. Ion channel conductance measurements on a silicon-based platform. *Journal of Physics Conference Series*, 37(1):21-24, 2006.

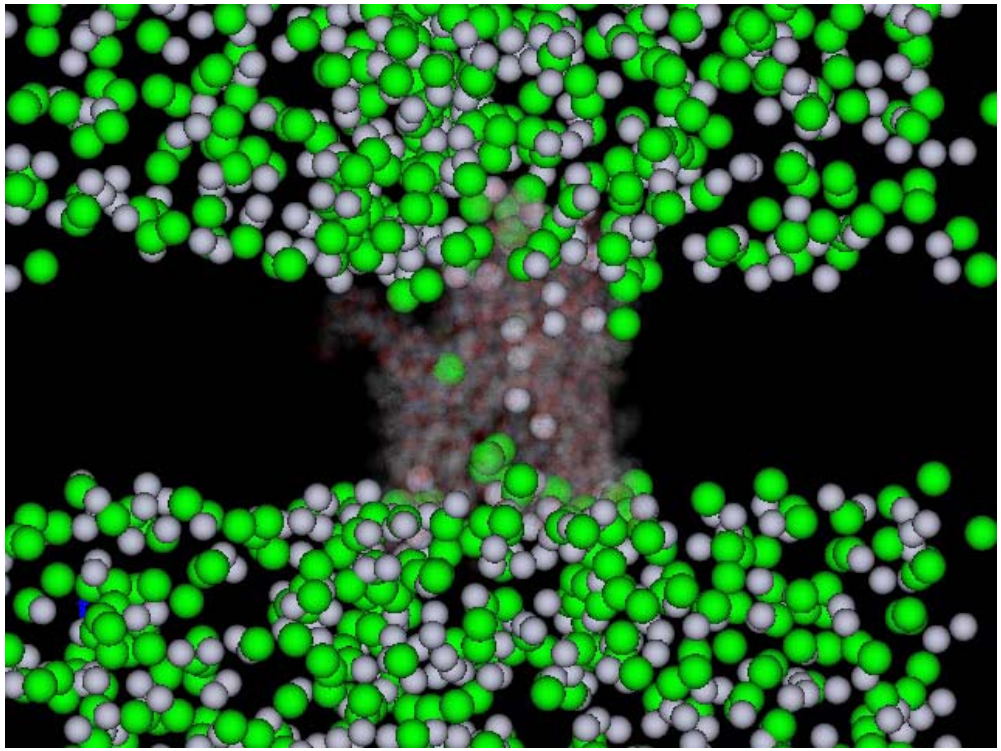
OmpF ion channel simulation: axial potential and ion distribution profiles





Simulated distributions of potential (left) and ionic concentration (right) along the axis of an ***OmpF*** monomer for various ***KCl*** concentrations.

OmpF ion channel simulation: visualization of conduction through isolated monomer

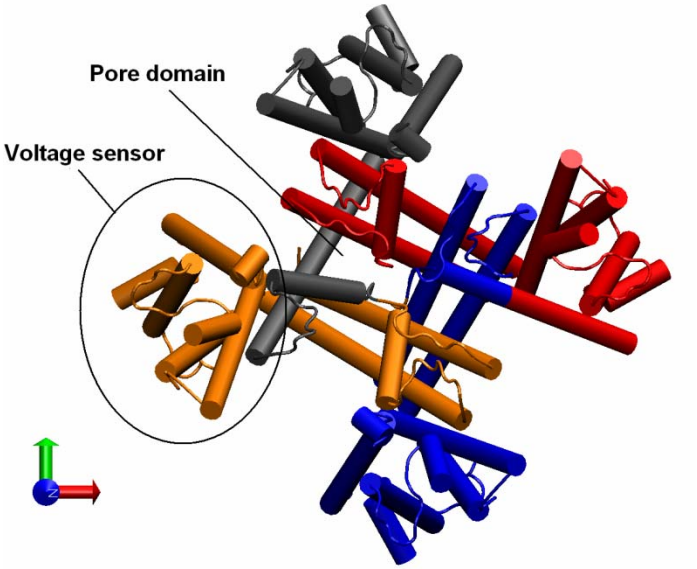


The potassium and chlorine ions are shown in grey and green, respectively. The ***OmpF*** monomer is shown as semi-transparent, inserted in lipid membrane (impermeable dielectric slab, not shown). The transmembrane potential is 100mV.

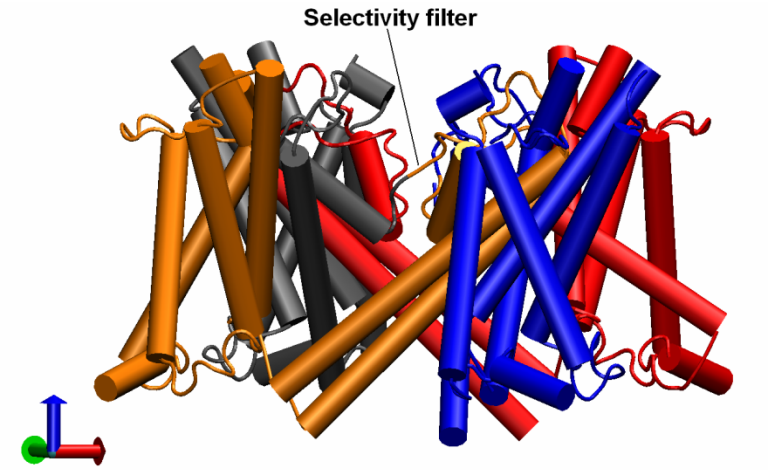
Kv1.2 voltage-dependent potassium channel

- Belongs to large family of voltage-dependent potassium channels
- Regulates potassium flow across cell membrane in neuron synapse of mammals
- Transmembrane portion is a tetramer, each subunit consisting of six helices ***S1-S6*** forming voltage sensor (***S1-S4***) and pore domain (***S5*** and ***S6***)
- Channel can be in open and closed conformations, depending on transmembrane voltage, the exact electromechanical process still unknown
- Conformation transition on millisecond timescale

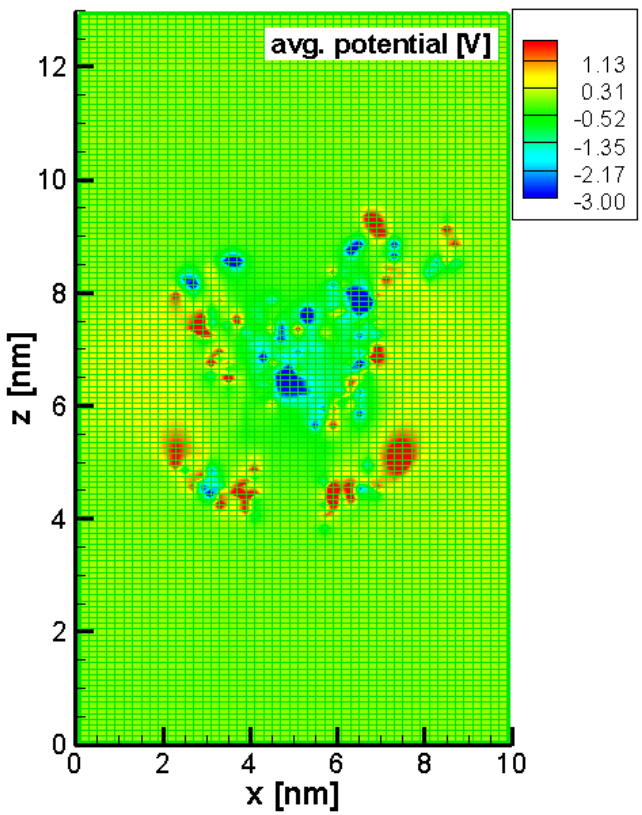
Top view (RCSB code *2R9R*)

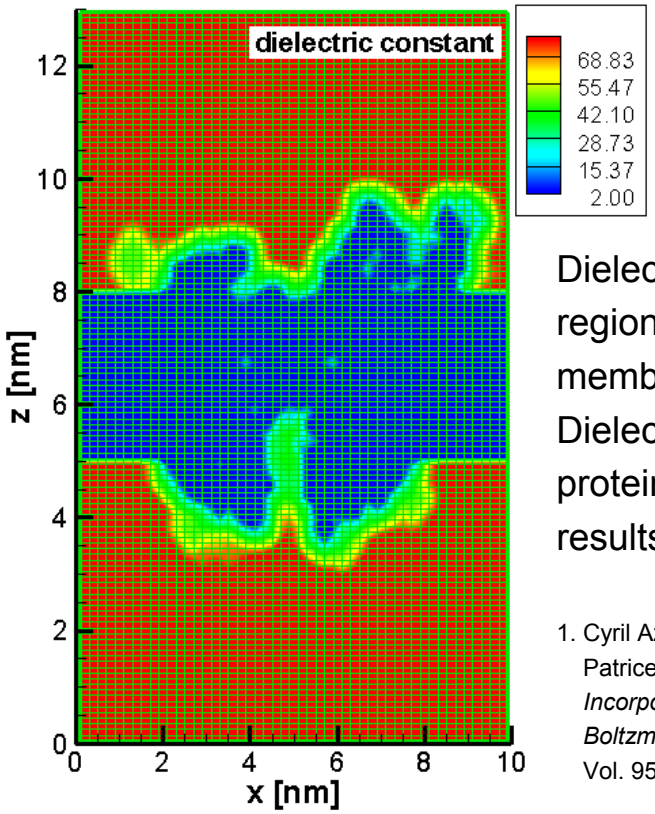


Side view



Kv1.2 potential profile (side)



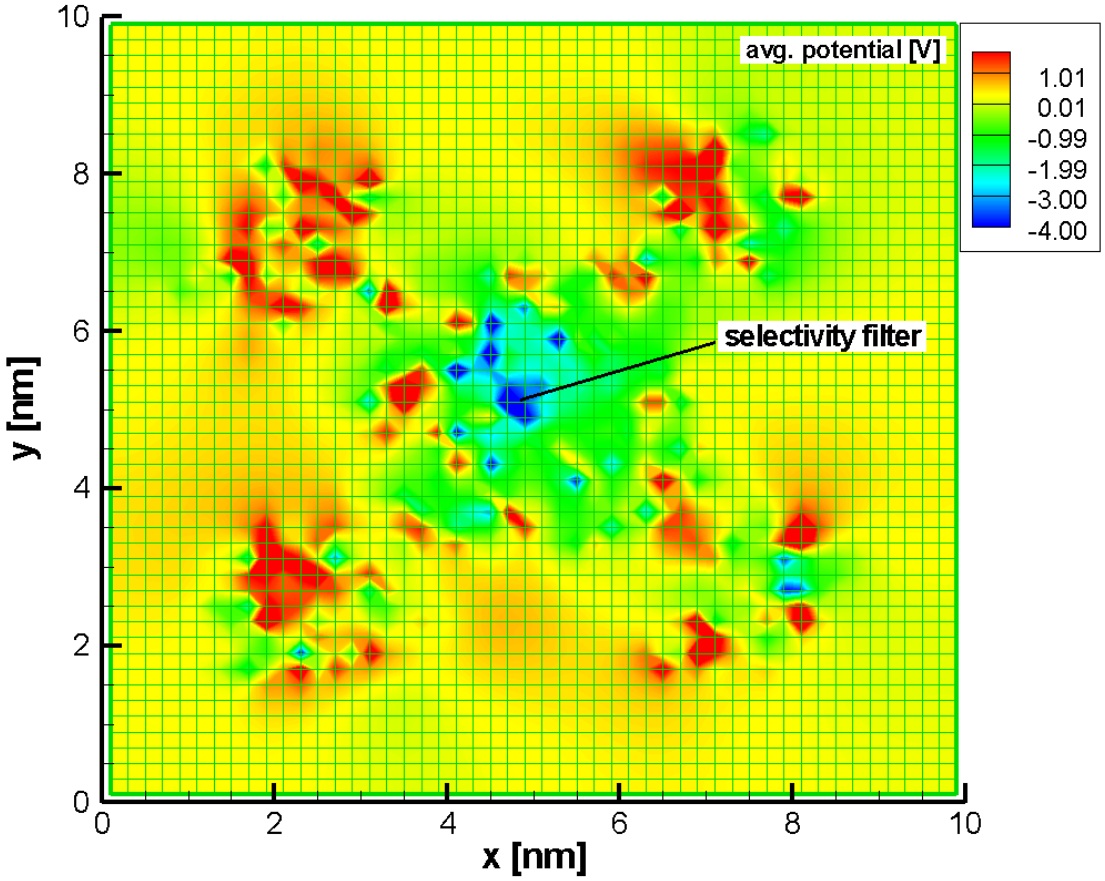


Dielectric constant of protein region and implicit lipid membrane set to 2.0. Dielectric smoothing of the protein-water contact using the results in [1].

1. Cyril Azuara, Henri Orland, Michael Bon, Patrice Koehl, and Marc Delarus, *Incorporating Dipolar Solvents in Poisson-Boltzmann Electrostatics*, Biophysical Journal, Vol. 95, Dec. 2008.

XZ-plane slices at y = 5.0 nm of simulated distributions of potential (left) and dielectric constant (right). No added ***KCl***, single Poisson step.

Kv1.2 potential profile (top)

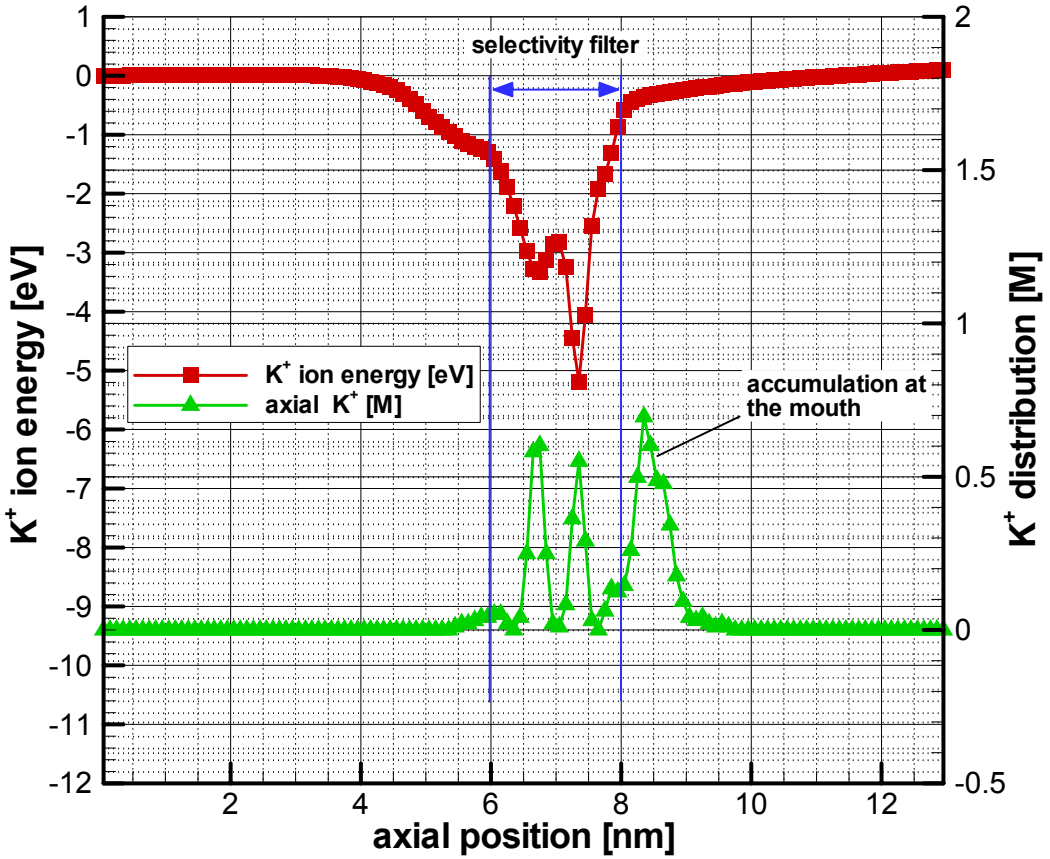


4eV-deep potential well in the selectivity filter.
Considerable positive charge in the voltage sensor domains.

XY-plane slice at z = 6.5 nm of simulated distribution of potential.

No added ***KCl***, single Poisson step.

Kv1.2 axial energy and potassium distribution



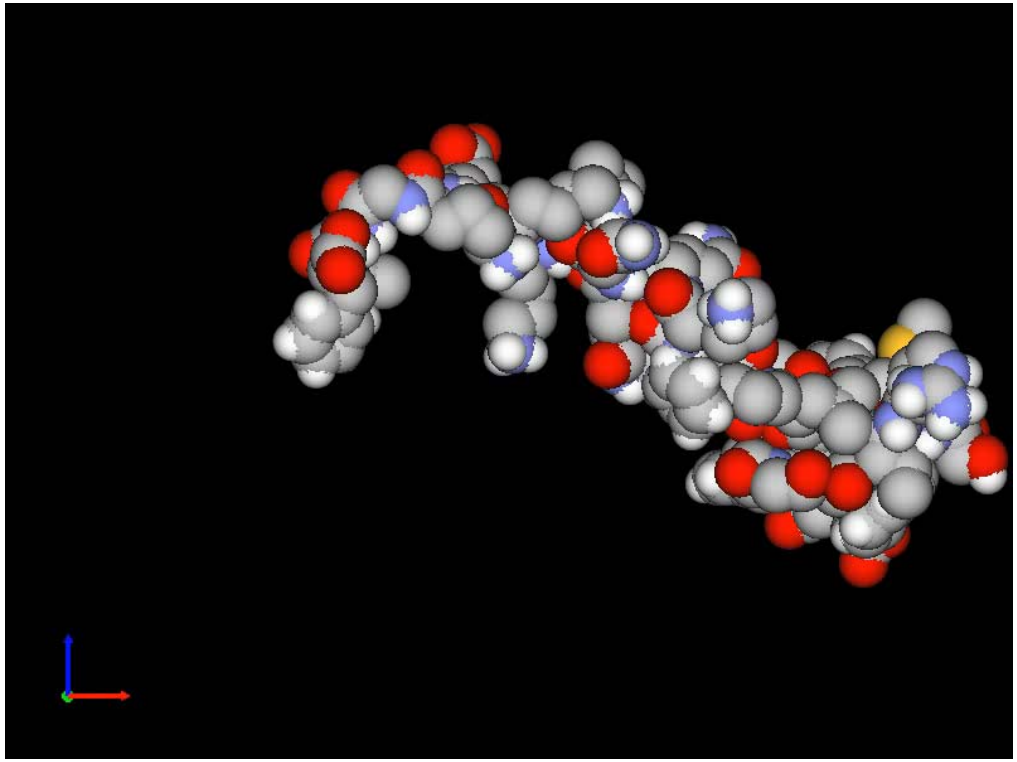
Potential energy of a potassium ion and potassium ion distribution along the channel axis. Bulk ***KCl*** concentration 1mM, 40 ns simulation, results averaged over the last 20 ns.

Ion distribution consistent with molecular dynamics simulation results revealing two potassium ions inside the selectivity filter and one at the mouth of ***KcsA*** channel with similar selectivity filter [2].

Peaks in ion distribution spatially coincide with near-zero axial field regions.

2. Simon Berneche and Benoit Roux, *Molecular Dynamics of the KcsA K+ Channel in a Bilayer Membrane*, Biophysical Journal, Vol 78, June 2000.

Visualization: Chicken Villin Headpiece folding



One of the few protein subdomains obtaining stable conformation within microseconds (see, for example, RCSB code ***1VII***).

200 ns simulated, starting from thermally unstable linear conformation. ***LINCS*** bond constraint algorithm with angle-constraining potentials used.

Conclusions and future work

- Constrained dynamics with velocity correction implemented
- Conduction in ***OmpF*** ion channel studied, good agreement with experiment
- ***OmpF*** selectivity reveals combination of electrostatic and steric effects
- Preliminary data on ***Kv1.2*** voltage-dependent potassium channel obtained, consistent with experimental data and MD simulations

Future work

- Developing a Monte-Carlo based mechanism mimicking ion adsorption by chemically active solid surfaces in aqueous environment
- Moving closer to MD and electrically polarizable forcefield
- Modeling ionic conduction in nanostructures, including man-made and biological structures