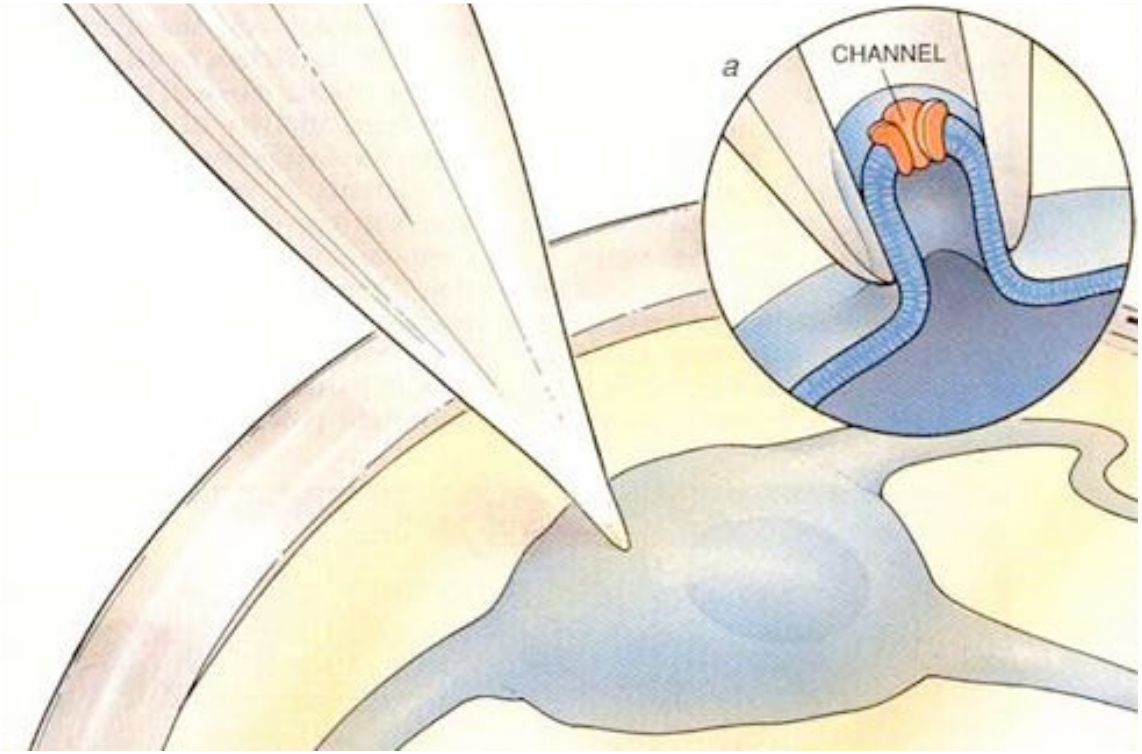
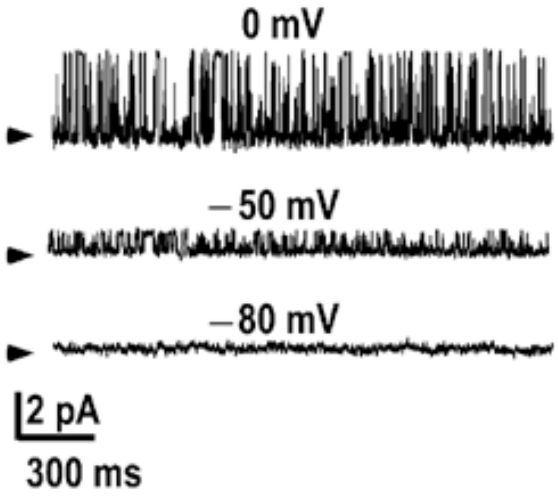
Analyzing Ion channel Simulations



(Neher and Sakmann, Scientific American 1992)

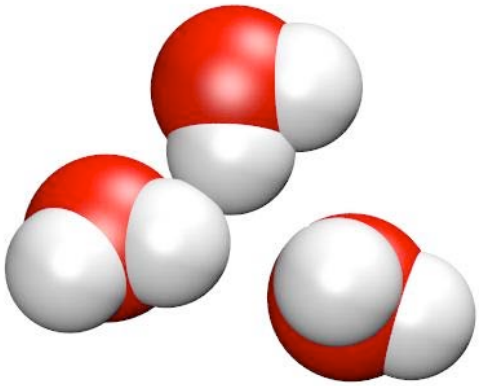


Single channel current

(Heurteaux et al, EMBO 2004)

Computational Patch Clamp (Molecular Dynamics)

Atoms move according to classical mechanics



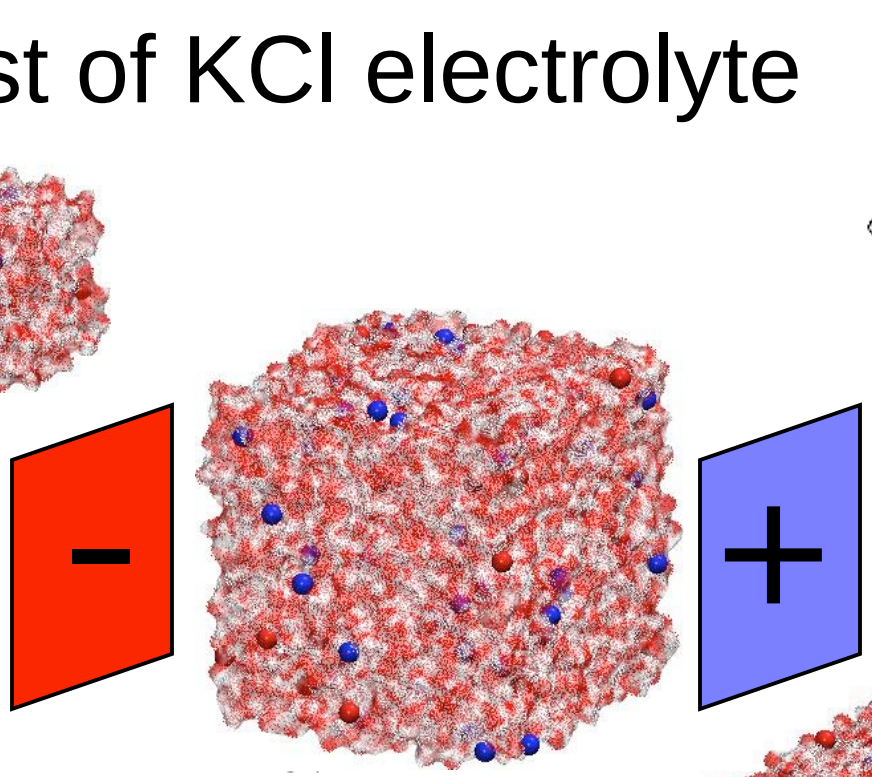
Interaction between atoms is defined by molecular force field (AMBER95, CHARMM27)

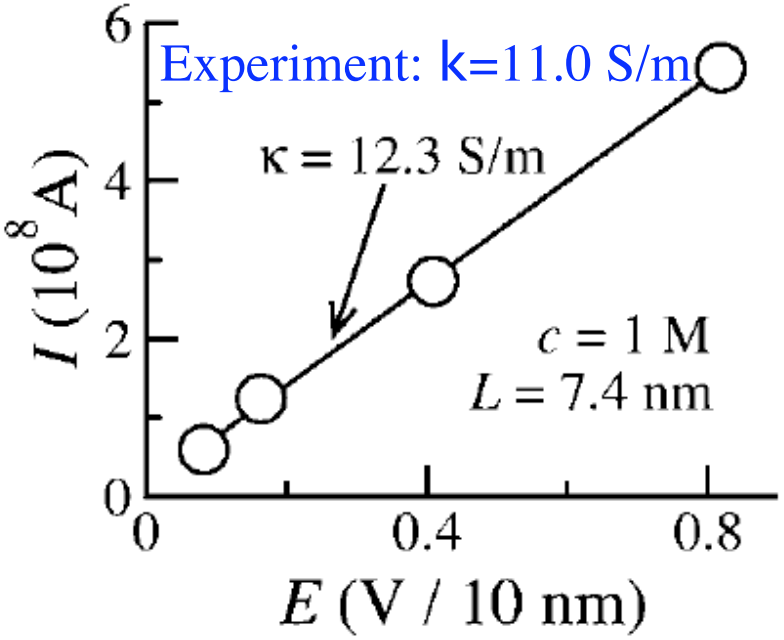
Time scale: up to 100ns

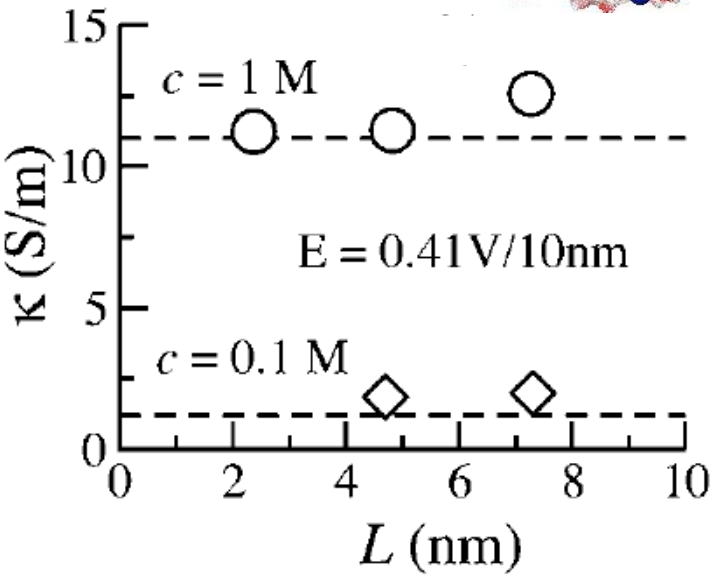
Length scale: up to 1,000,000 atoms or $(< 20\text{nm})^3$

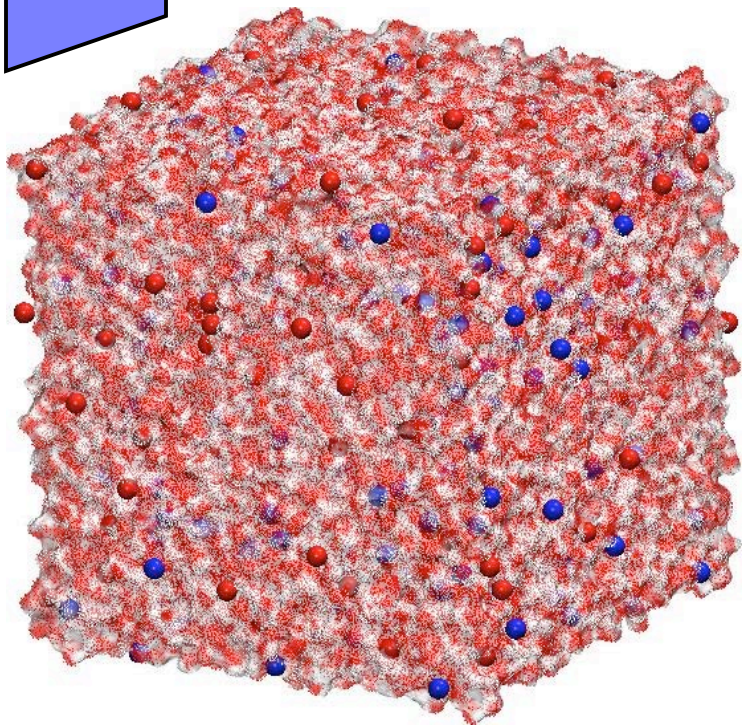
Massive parallel computer (PSC Lemieux)

Test of KCl electrolyte



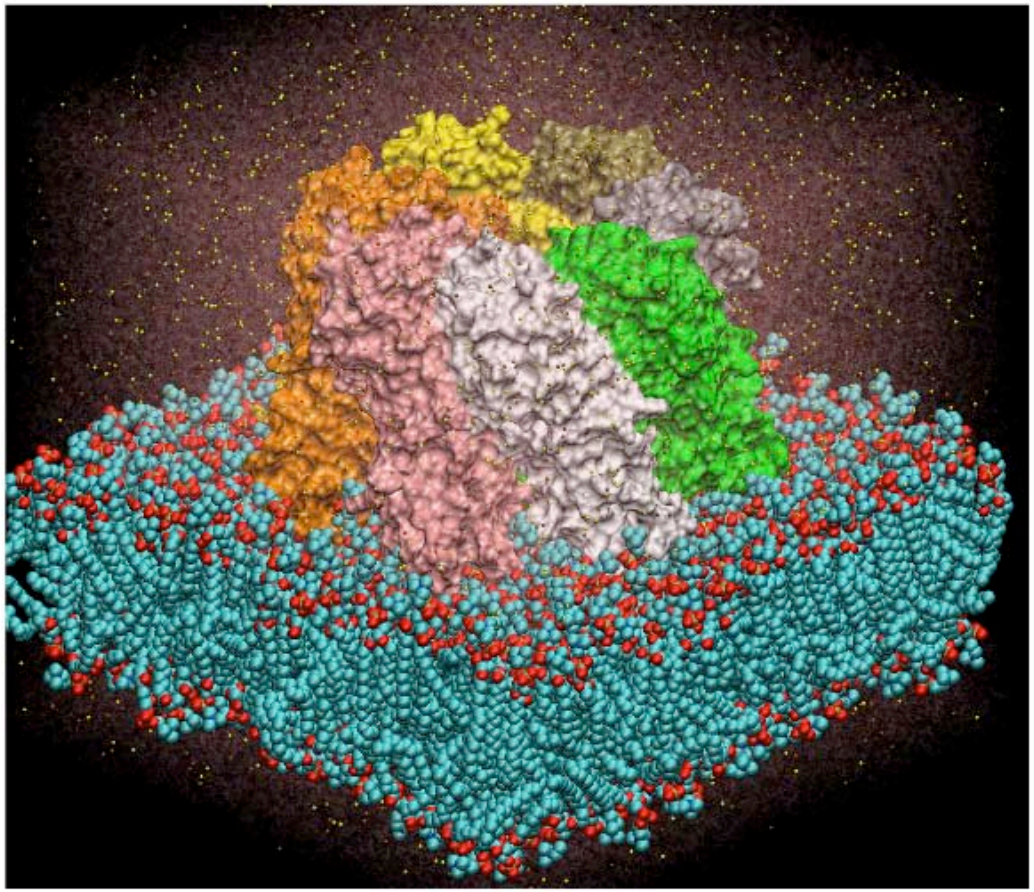


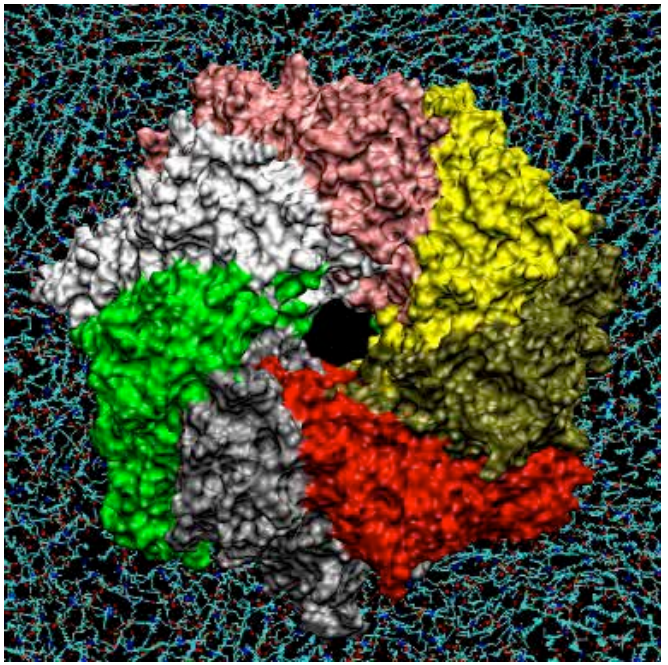




α-Hemolysin Channel

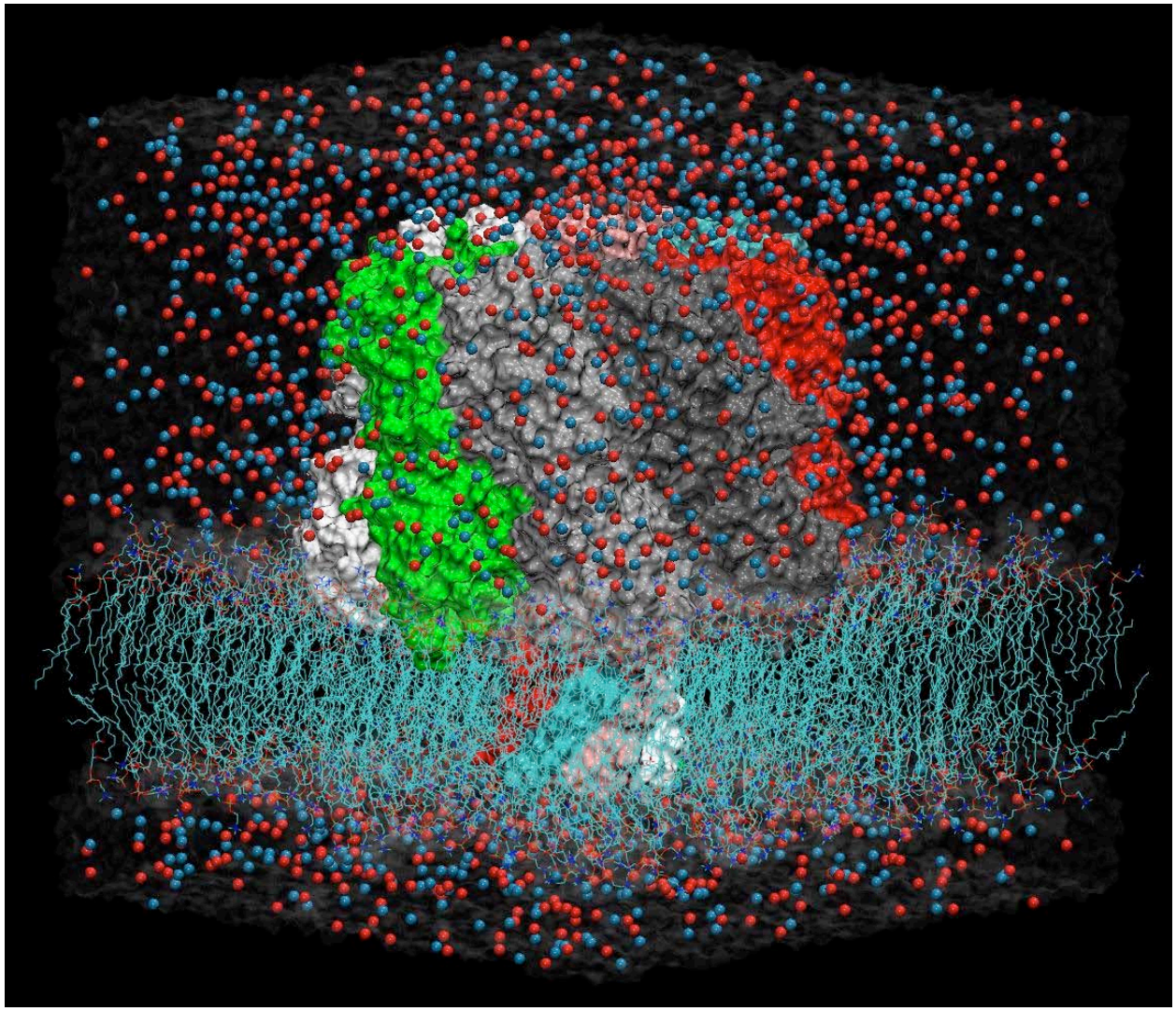
of *Staphylococcus aureus*



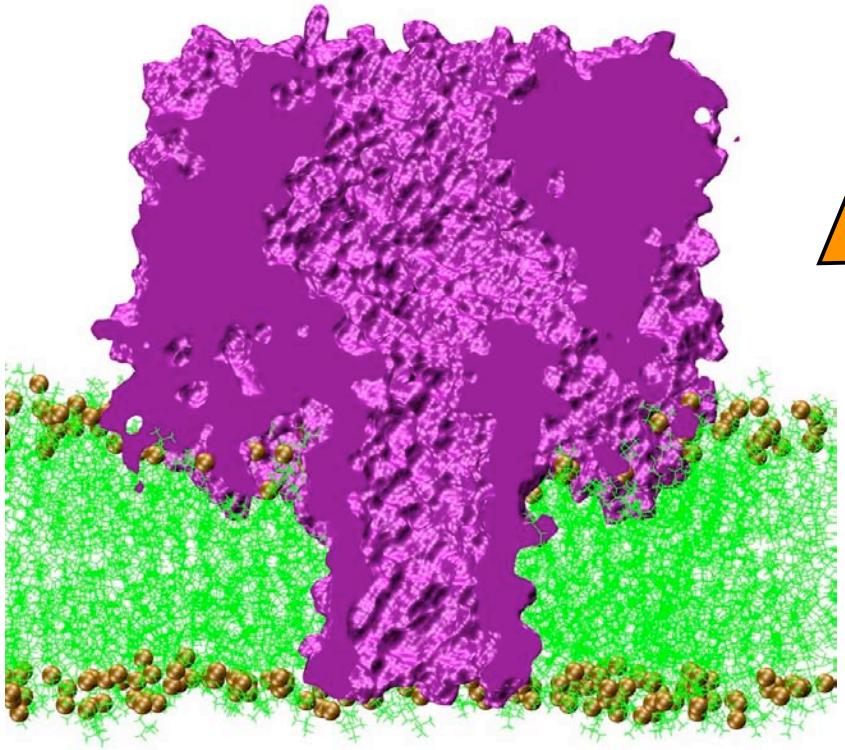


- Self-assembles from soluble monomers to form a transmembrane channel
- Stable over wide pH and temperature range
- Pore diameter: 1.3-2.6 nm

Setting up an α-hemolysin simulation

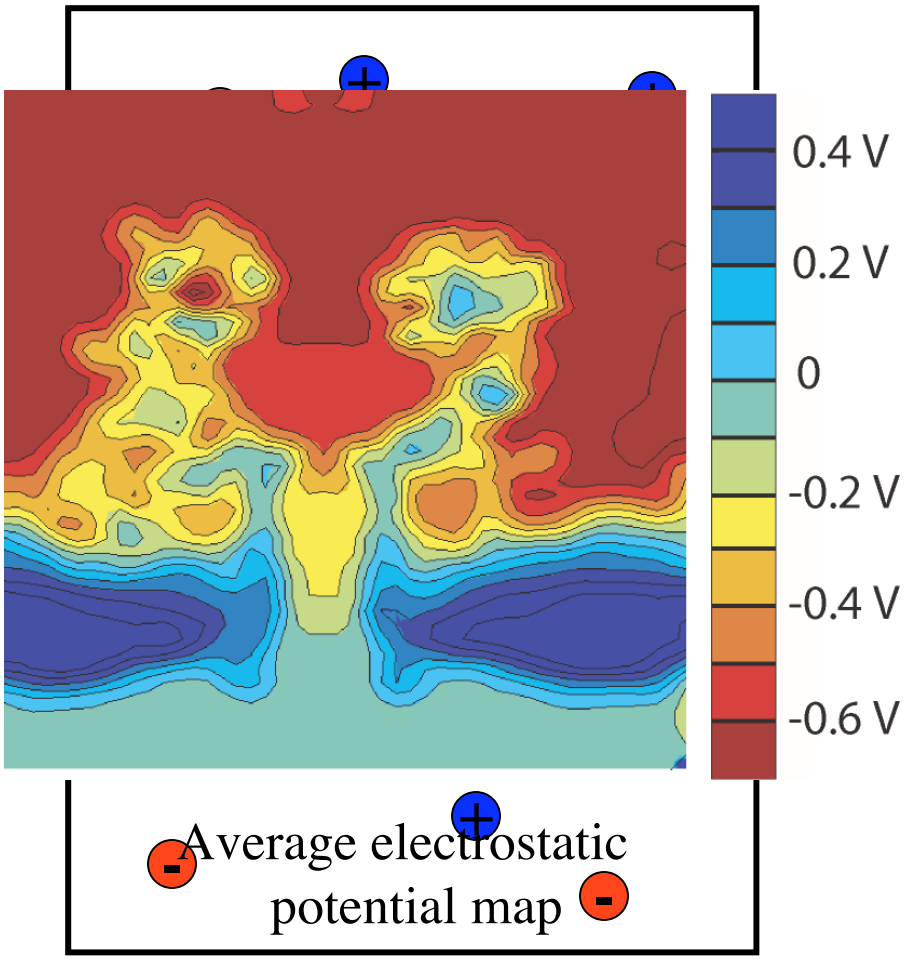


Computing conductance of α-hemolysin with molecular dynamics



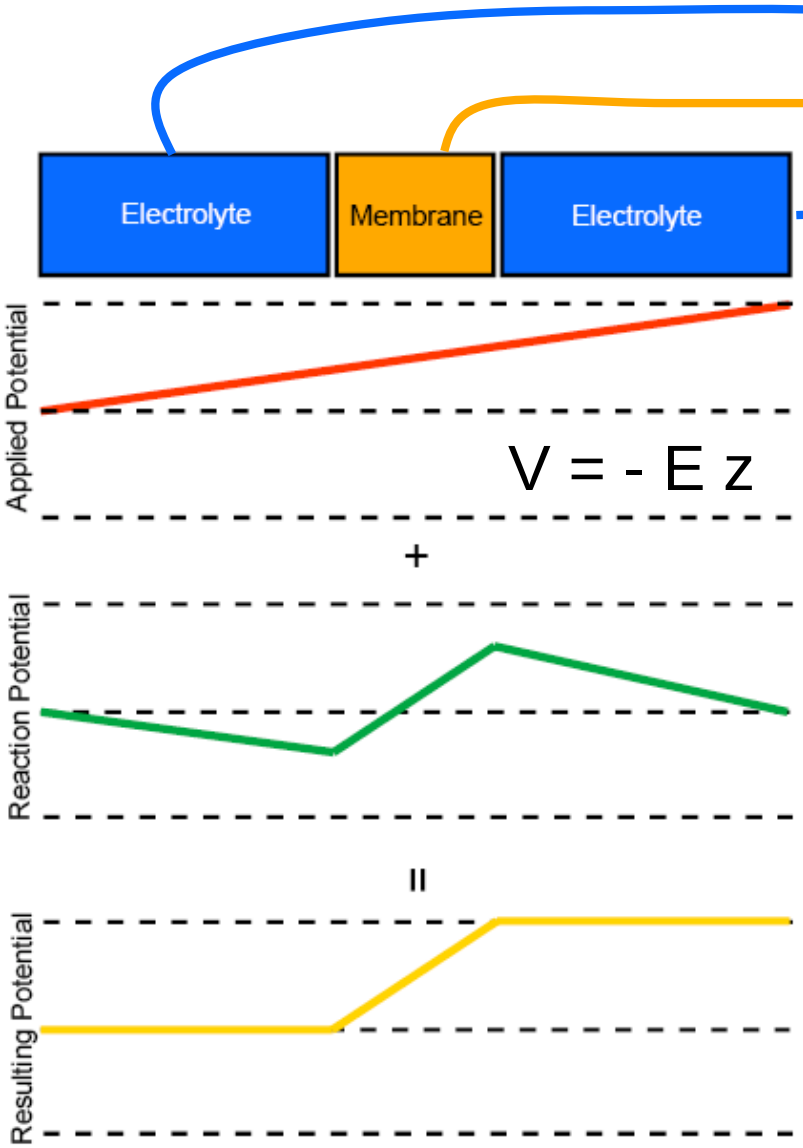
Protein + DPPC lipid membrane + 1M water solution of KCl = 300,000 atoms

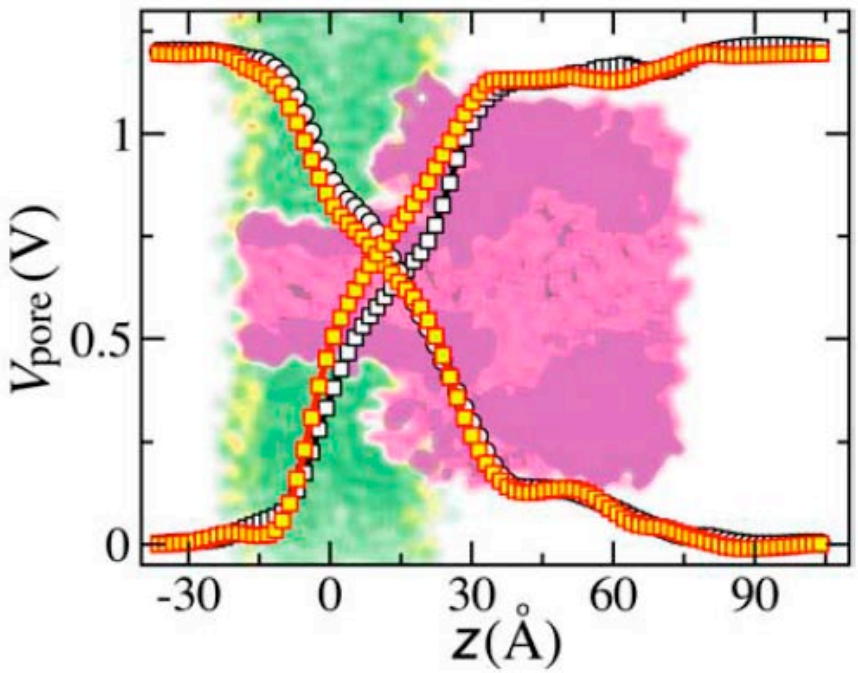
Electric field



Average electrostatic potential map

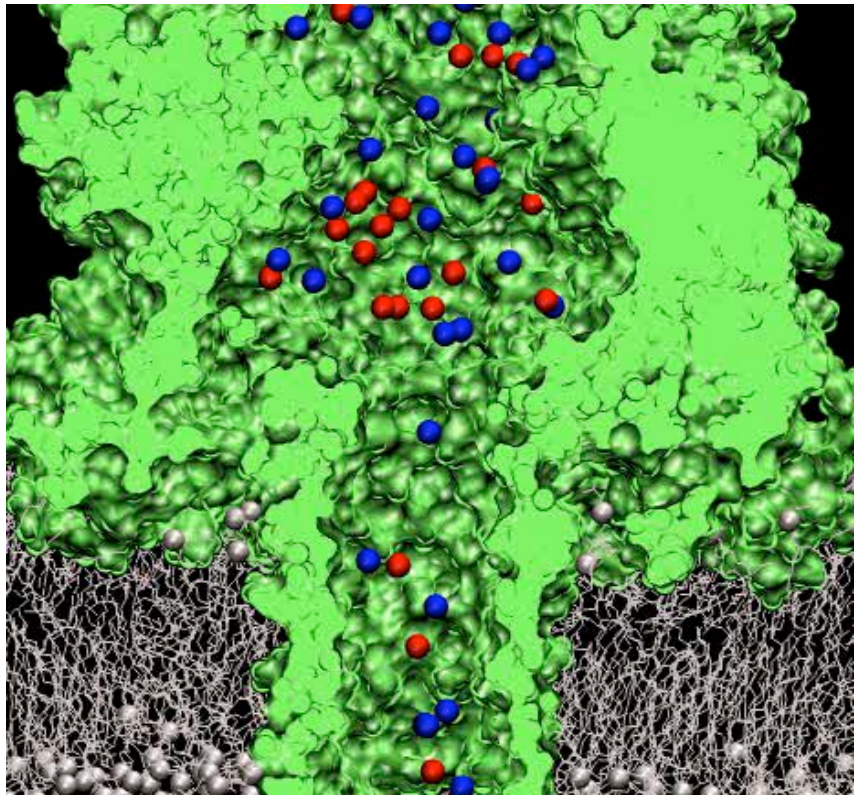
Electrostatic potential

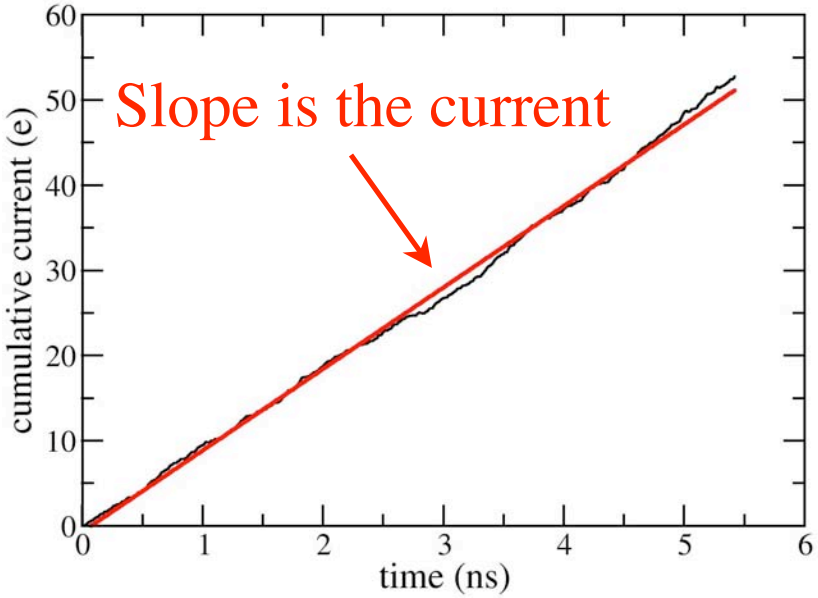




Average electrostatic potential map

Current-Voltage curve: excellent agreement with experiment

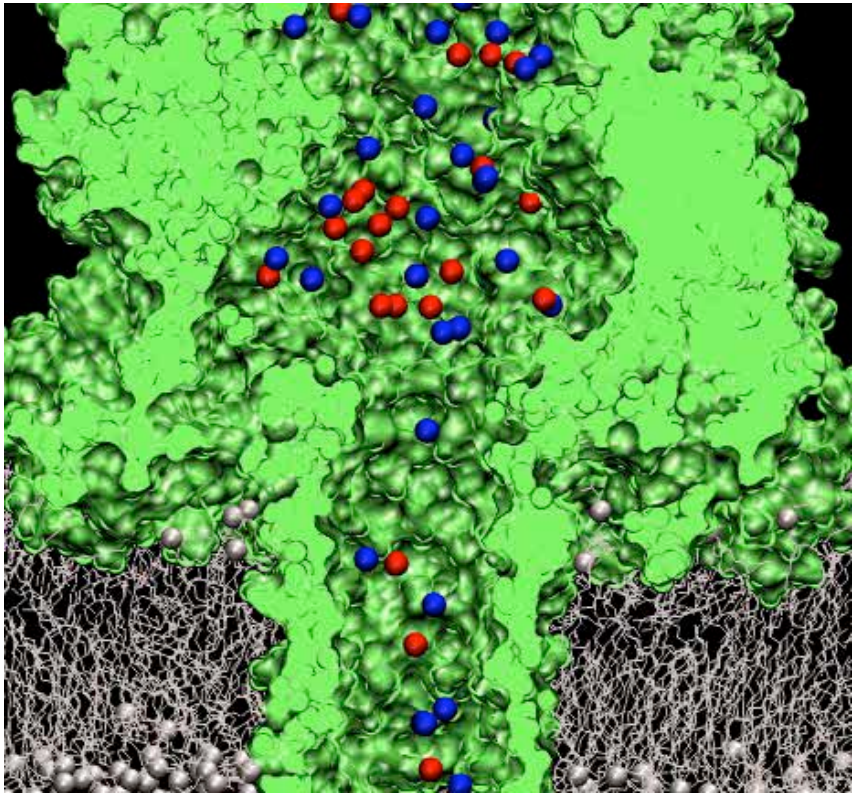


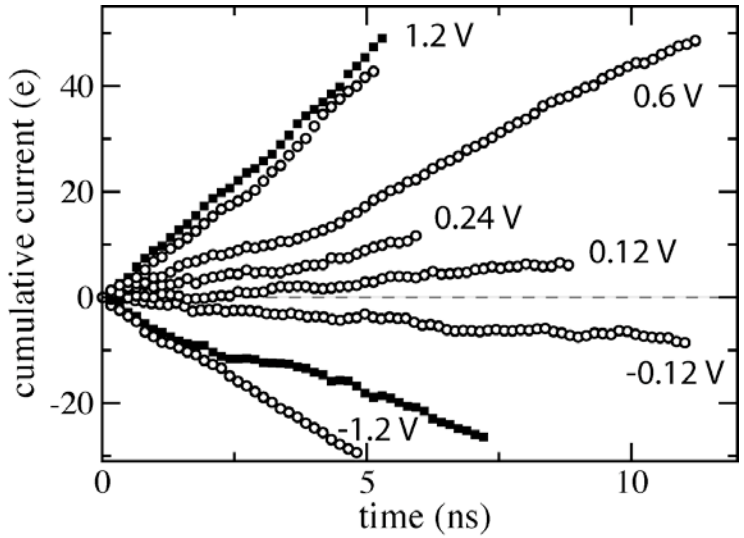


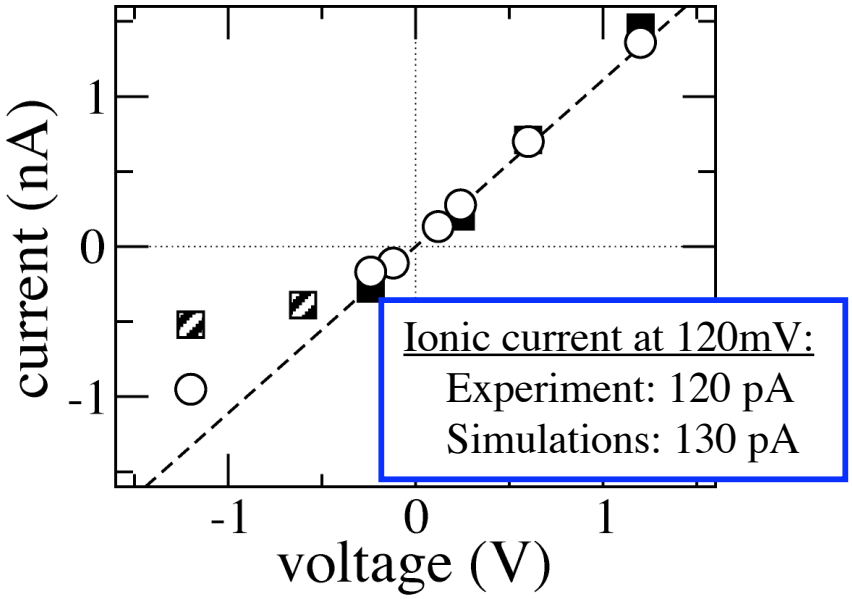
$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^{N} q_i (z_i(t + \Delta t) - z_i(t))$$

Instantaneous current

Current-Voltage curve: excellent agreement with experiment



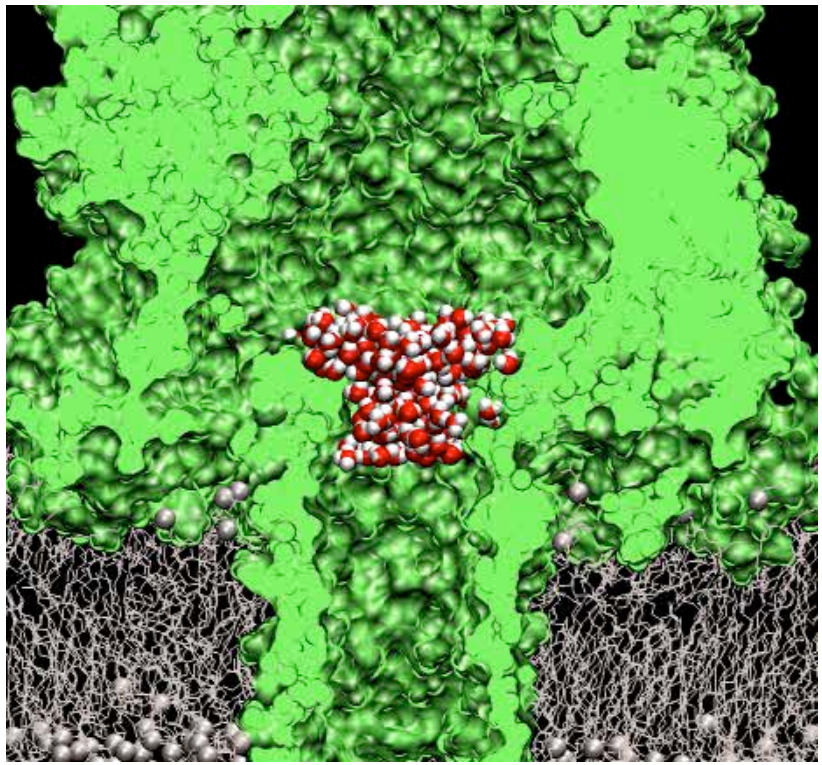


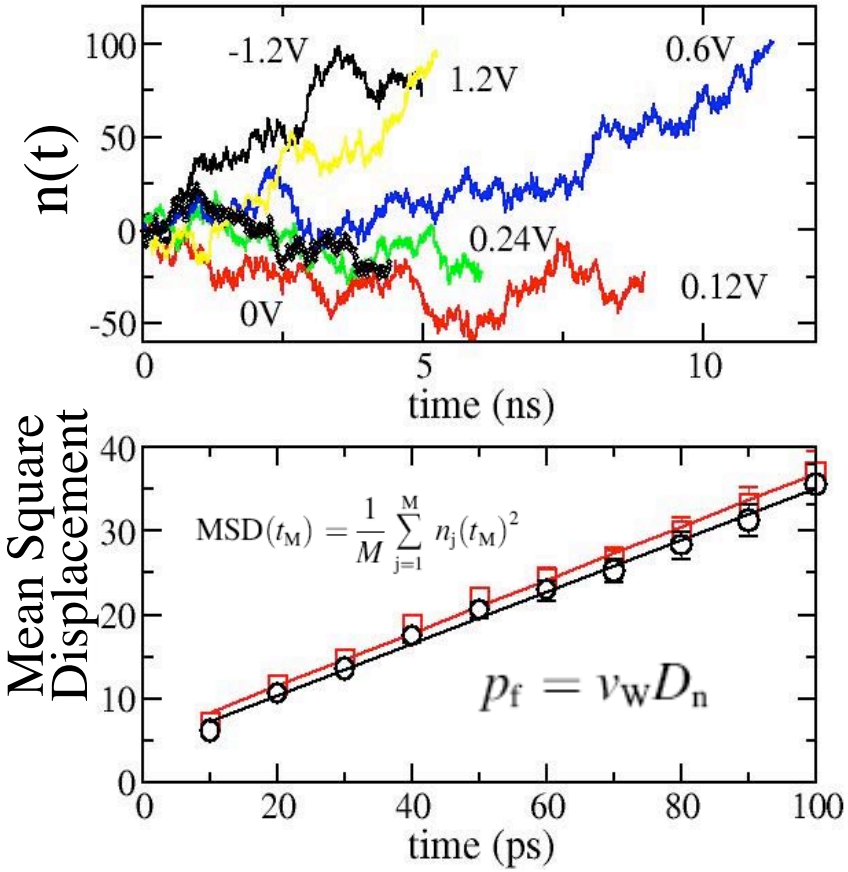


$$I(t) = \frac{1}{\Delta t L_z} \sum_{i=1}^{N} q_i (z_i(t + \Delta t) - z_i(t))$$

Instantaneous current

Water Conductance





$$\mathrm{d}n = \sum_{i \in S(t)} \mathrm{d}z_i / L$$

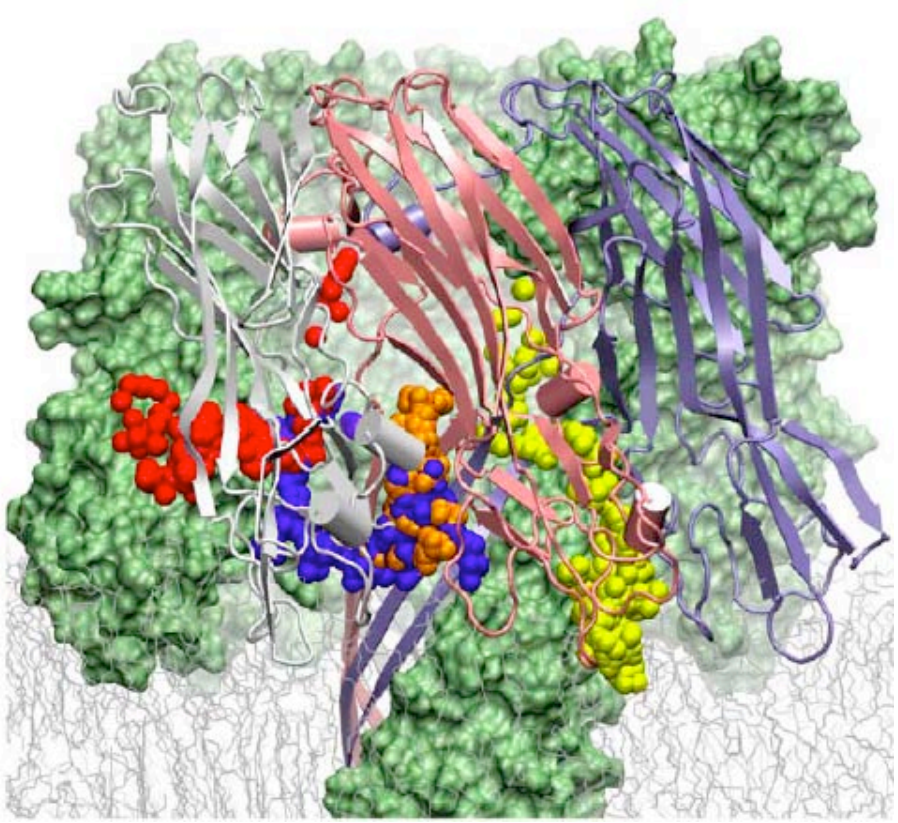
Collective coordinate of water molecules confined in the channel

<u>Osmotic permeability of αHL:</u>

Experiment: 1.5×10^{-12} cm/s

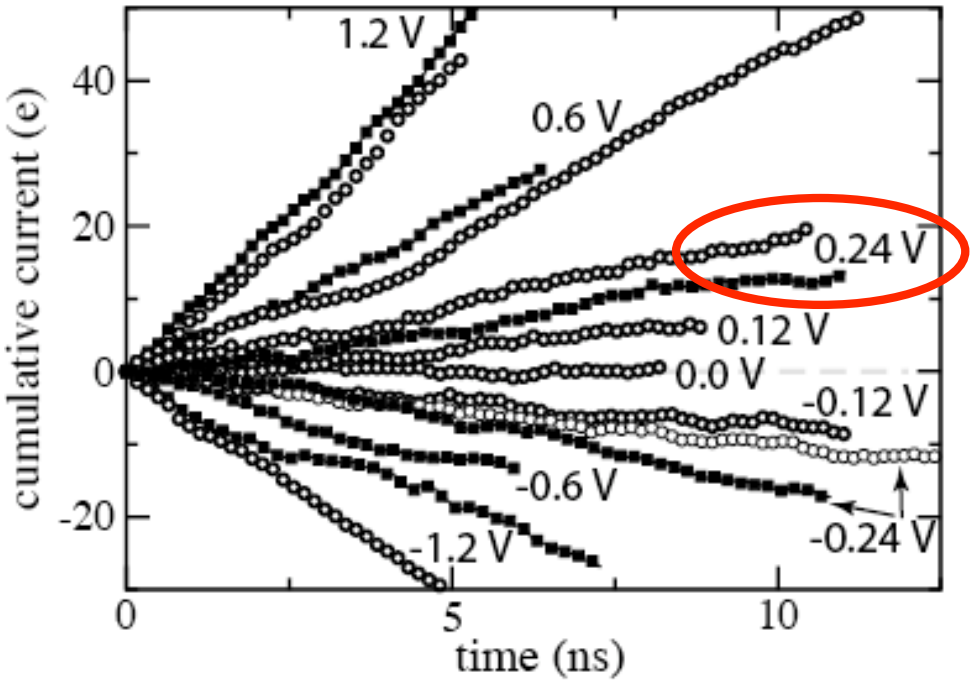
Simulations: 1.8×10^{-12} cm/s

Modulation of the current by the protonation state of His144



Water can access His 144 !

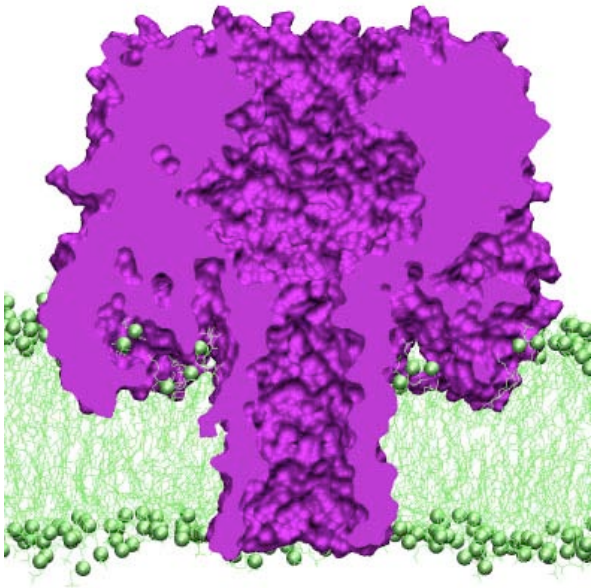
(Aksimentiev, Biophys. J. 2005)

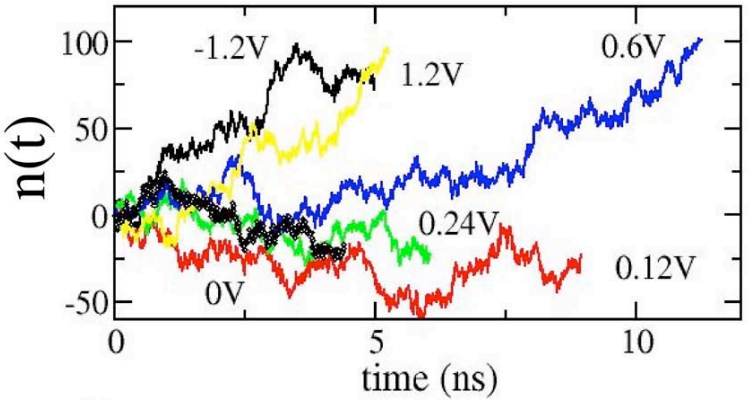


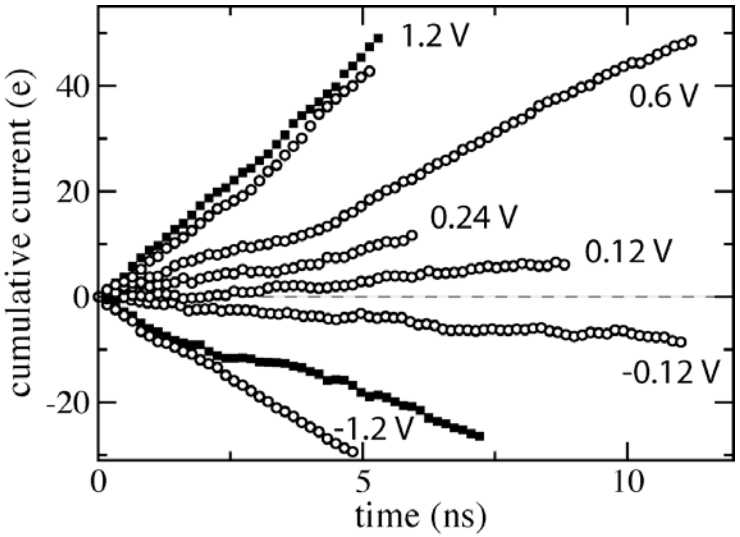
○ pH 8.0 ■ pH 4.5

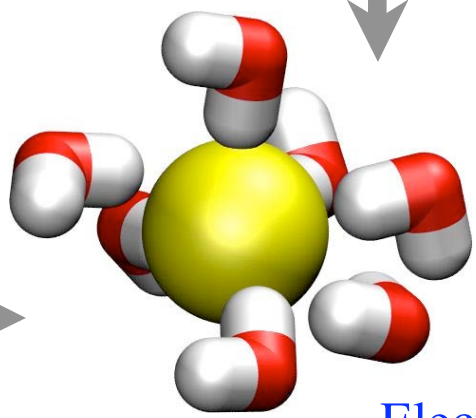
Changing the protonation states of seven His144 alters the channel conductance

Not ions alone!



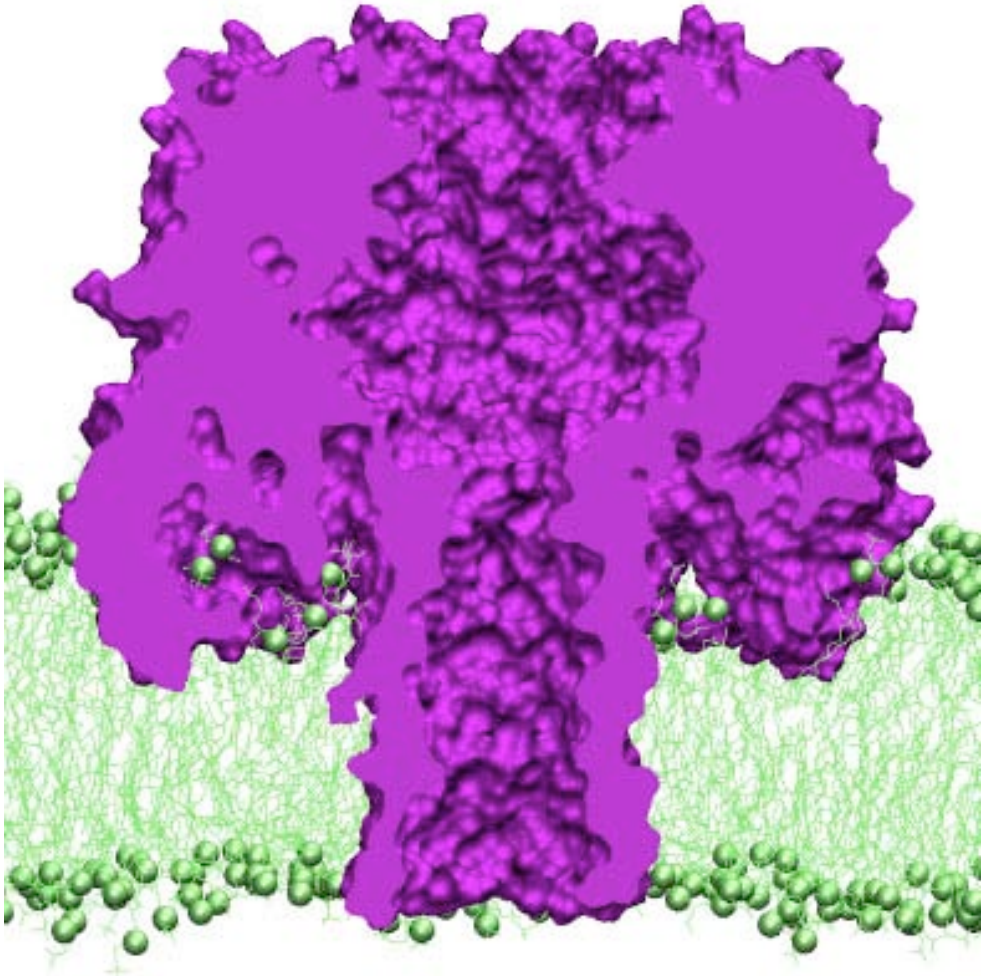




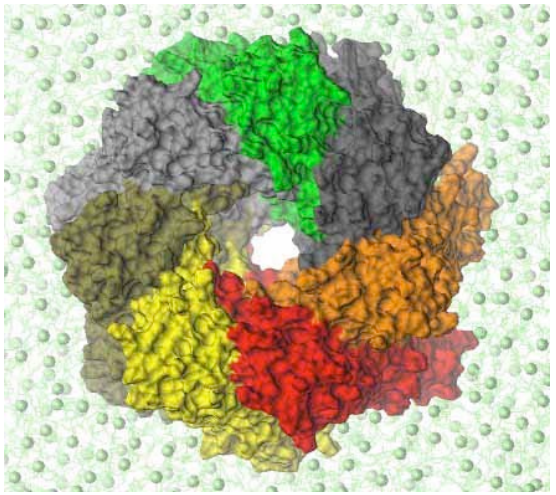


[Electroosmotic effect:](#)
9 water molecules
are transported on
average with every ion

Bacterial toxin α-hemolysin

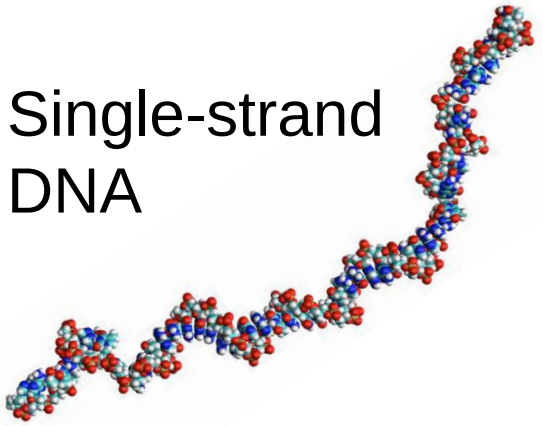


a-hemolysin in a lipid bilayer

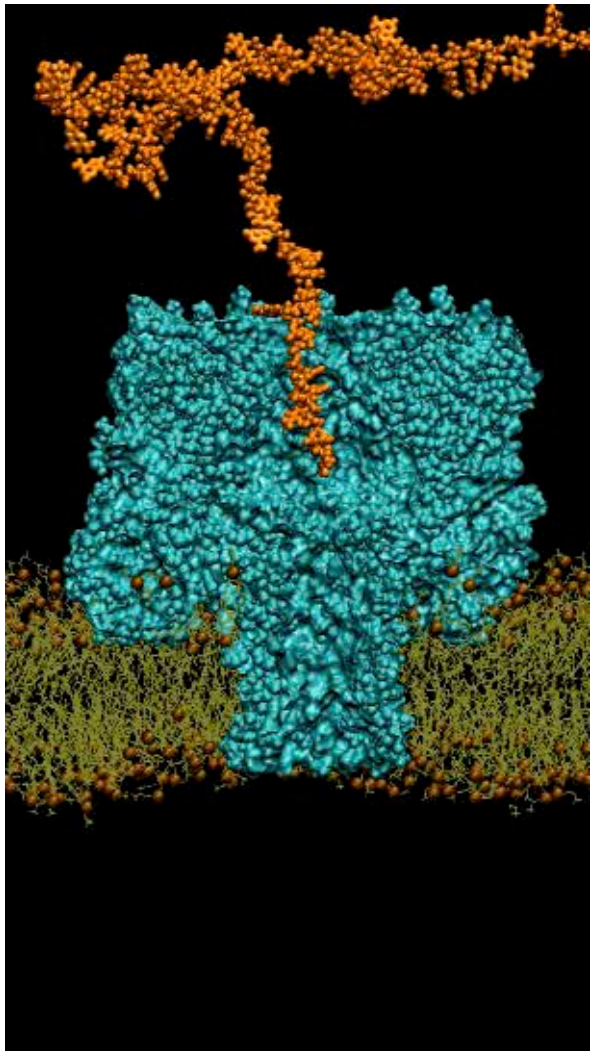


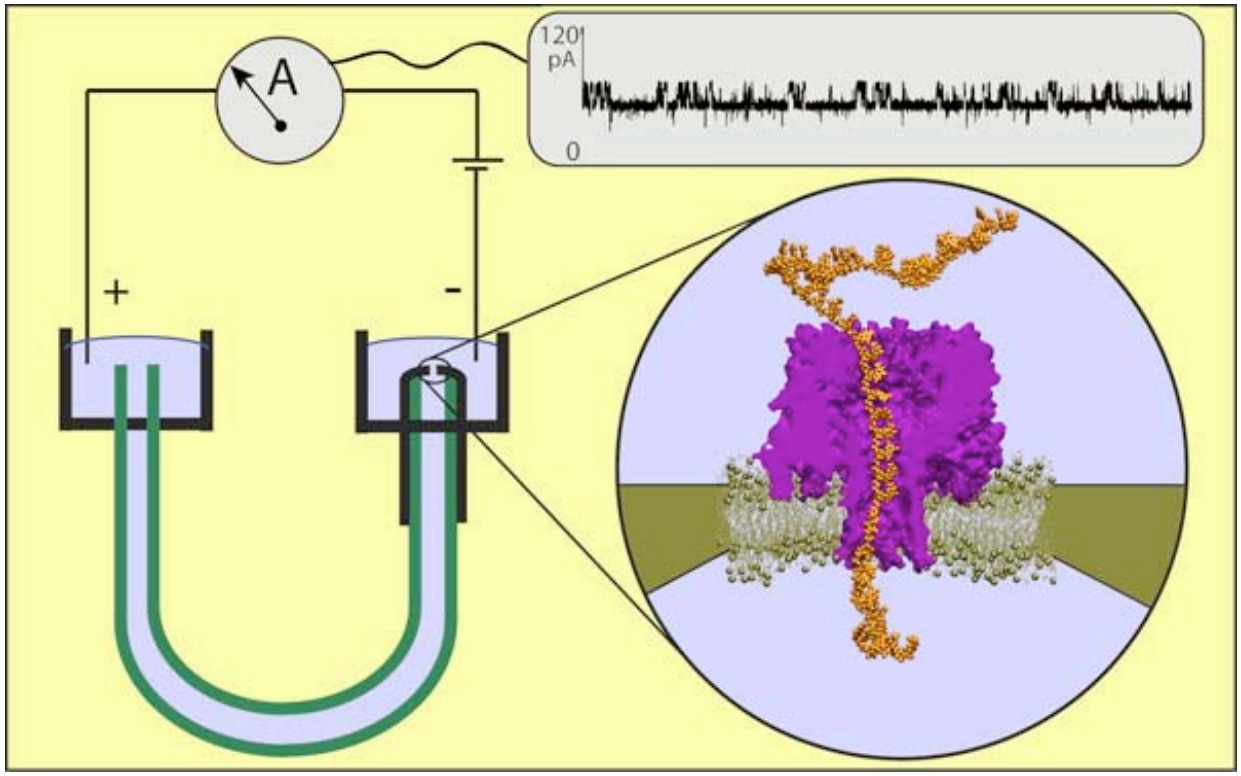
- Pore diameter: 1.3-2.6 nm

Single-strand DNA



DNA permeation through α-hemolysin

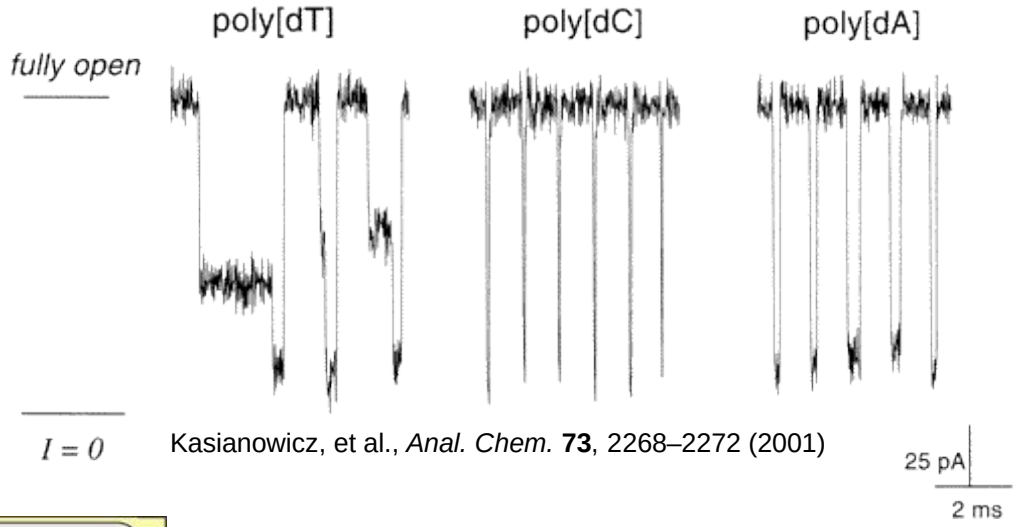




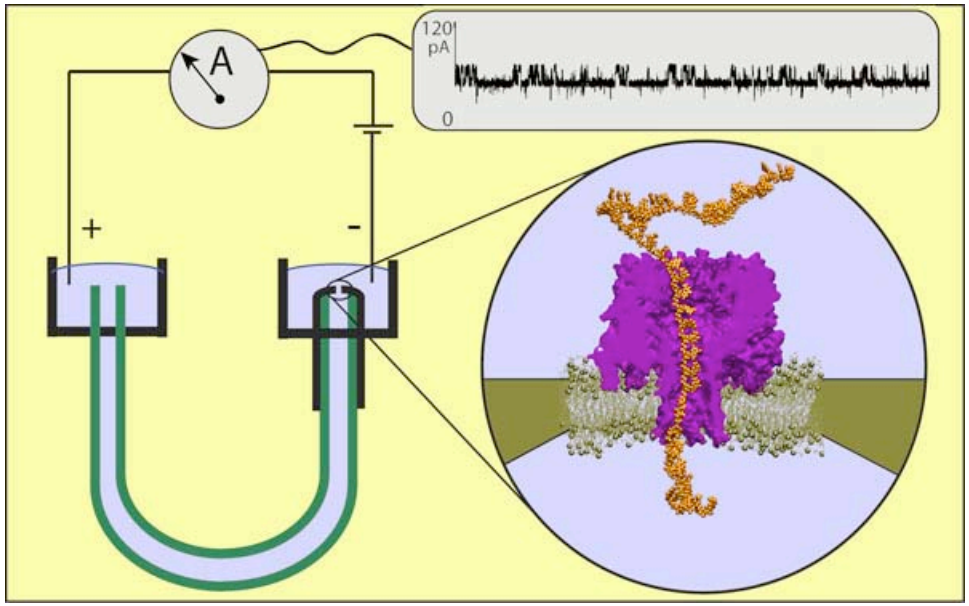
Kasianowicz *et al* (1996), Akeson *et al* (1999)
Meller *et al* (2000), Howorka *et al* (2001)

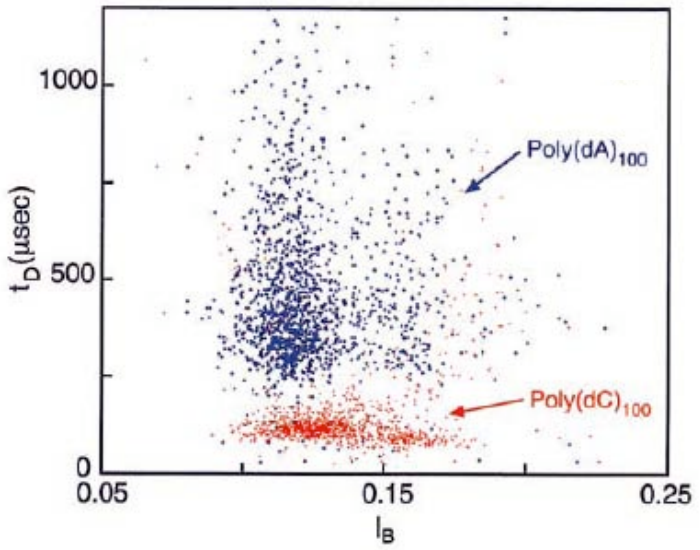
360,000-atom MD simulation

Current blockades can identify the sequence of DNA



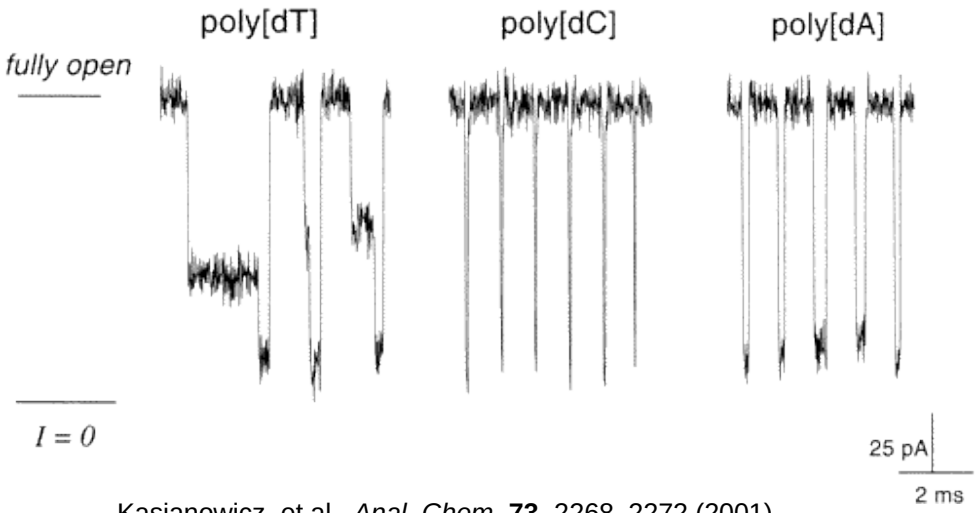
Kasianowicz, et al., *Anal. Chem.* **73**, 2268–2272 (2001)





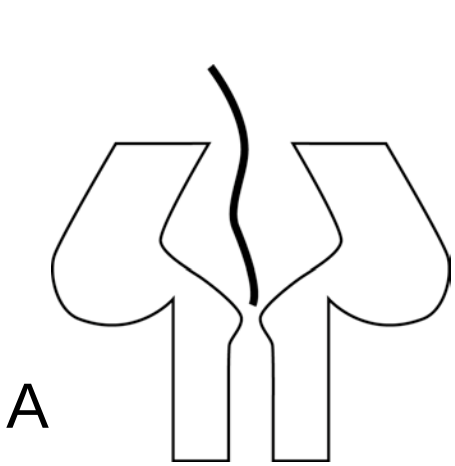
A. Meller, et al., *PNAS,* **97,** 1079 (2000)

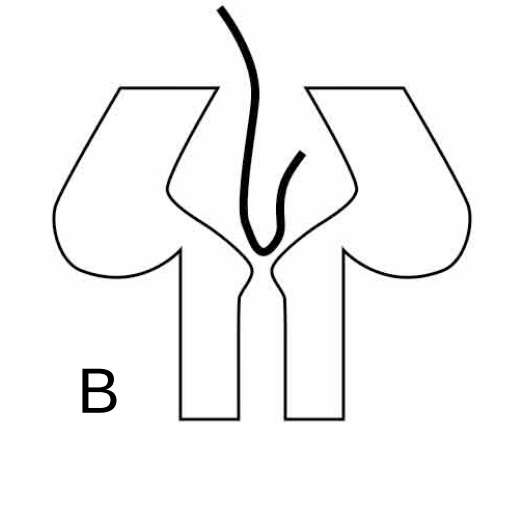
Current blockades of poly[dT]

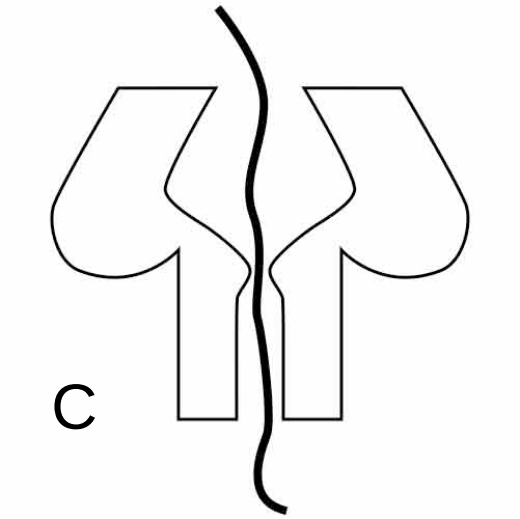


Ionic current graph showing characteristic stair-step pattern of poly(dT)

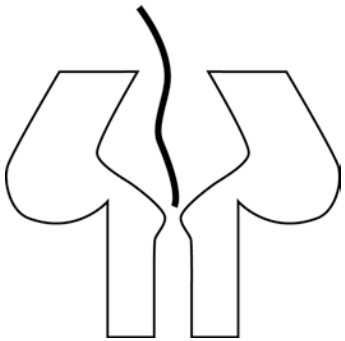
Kasianowicz, et al., *Anal. Chem.* **73**, 2268–2272 (2001)

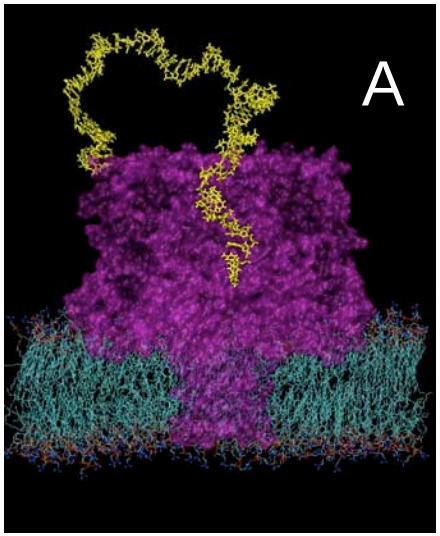




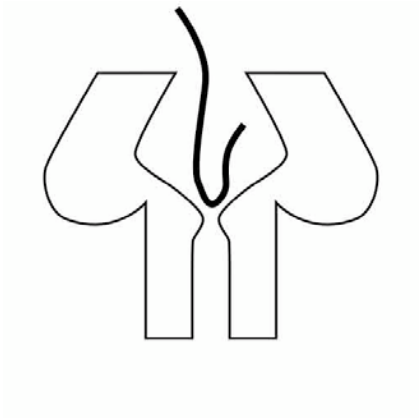


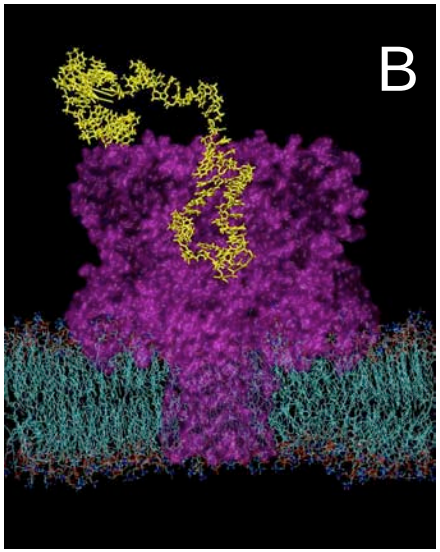
Initial DNA conformations for MD simulations

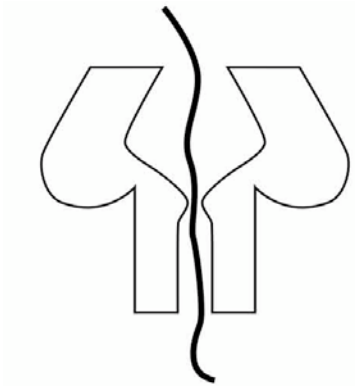


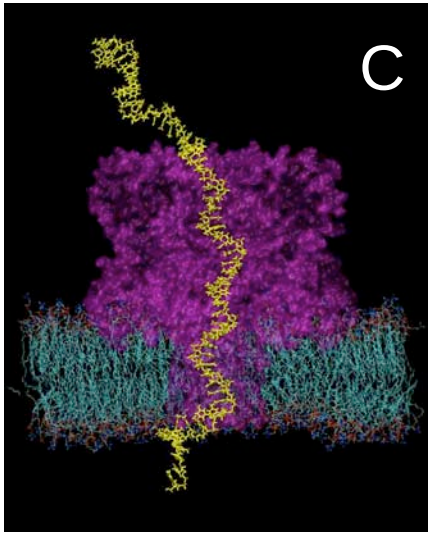


~360,000 atoms
295K
58-nucleotide poly[dT]
CHARMM97

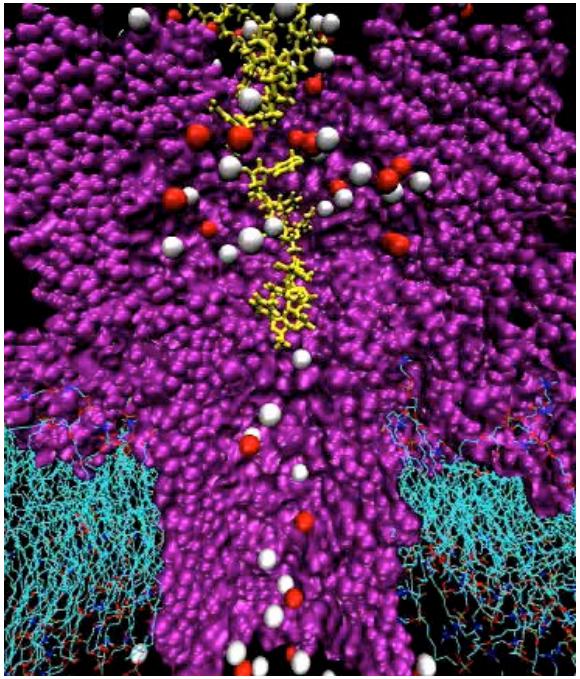


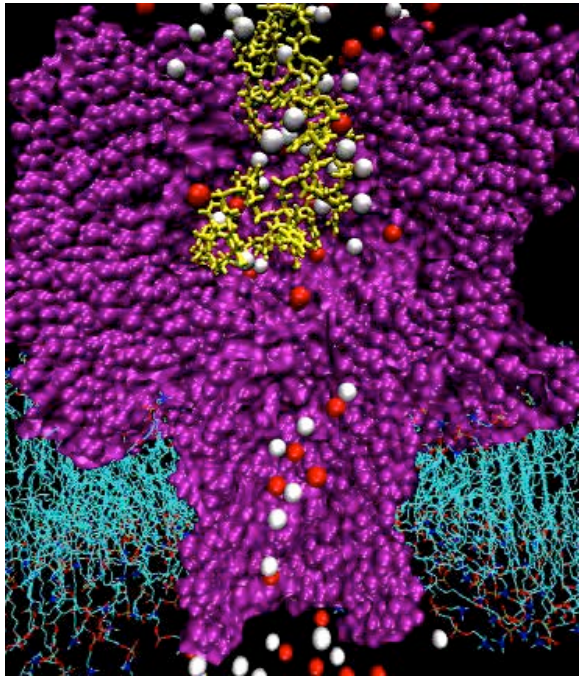


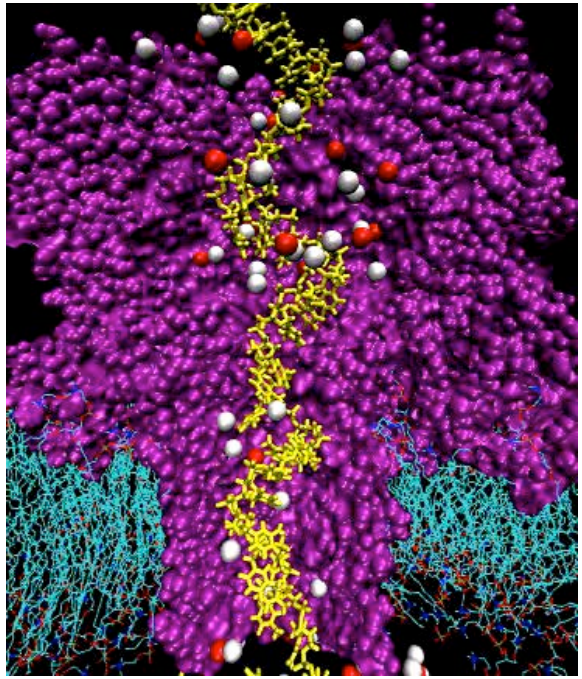




MD simulations of blocked current







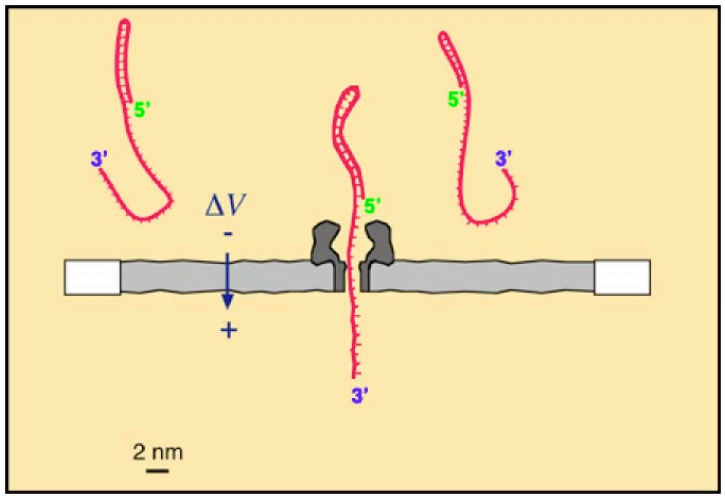
$I_{blocked}/I_{open}$ = 47%

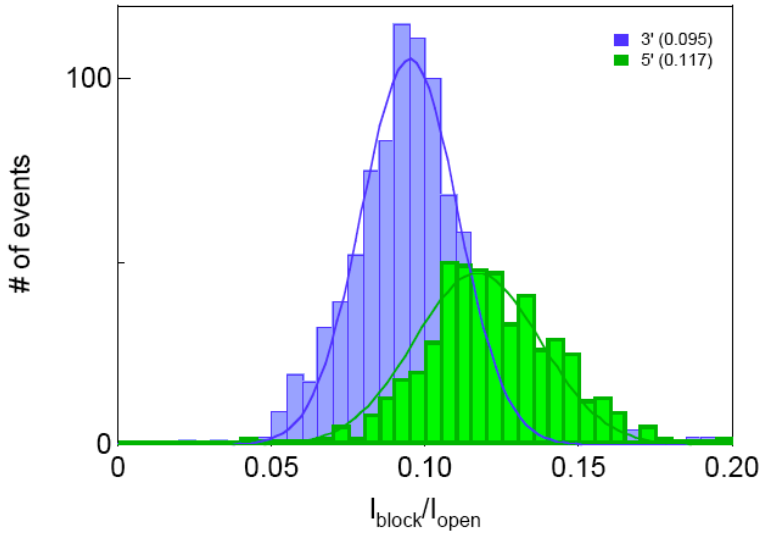
$I_{blocked}/I_{open}$ = 40%

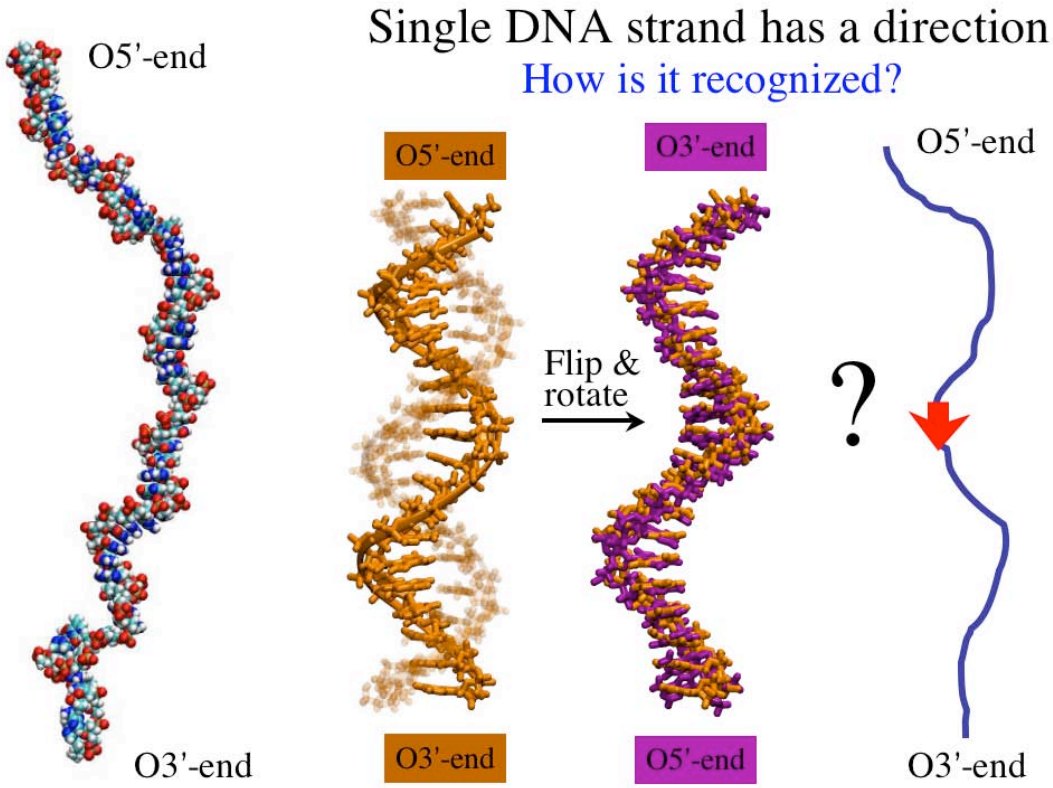
$I_{blocked}/I_{open}$ = 15%

All simulations were carried at a 1.2 V bias, 295K

Translocation of DNA through alpha-hemolysin

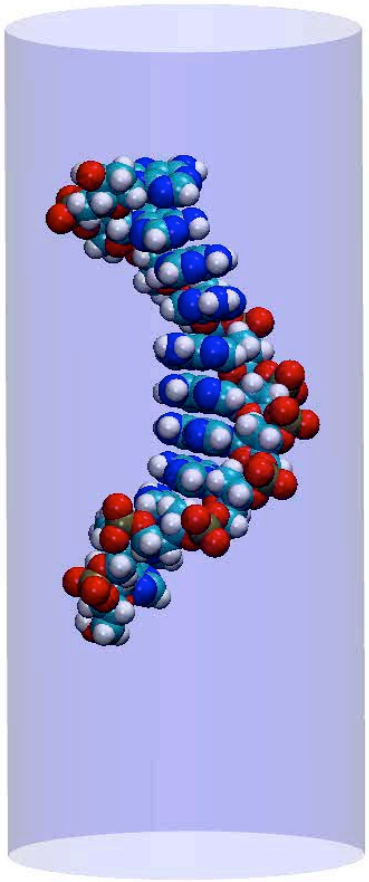




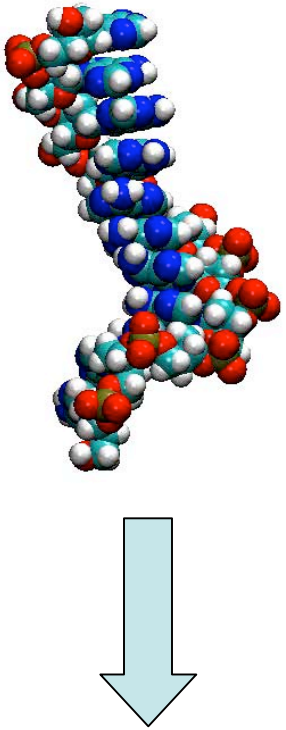


Experiment: Jerome Mathe and Amit Meller

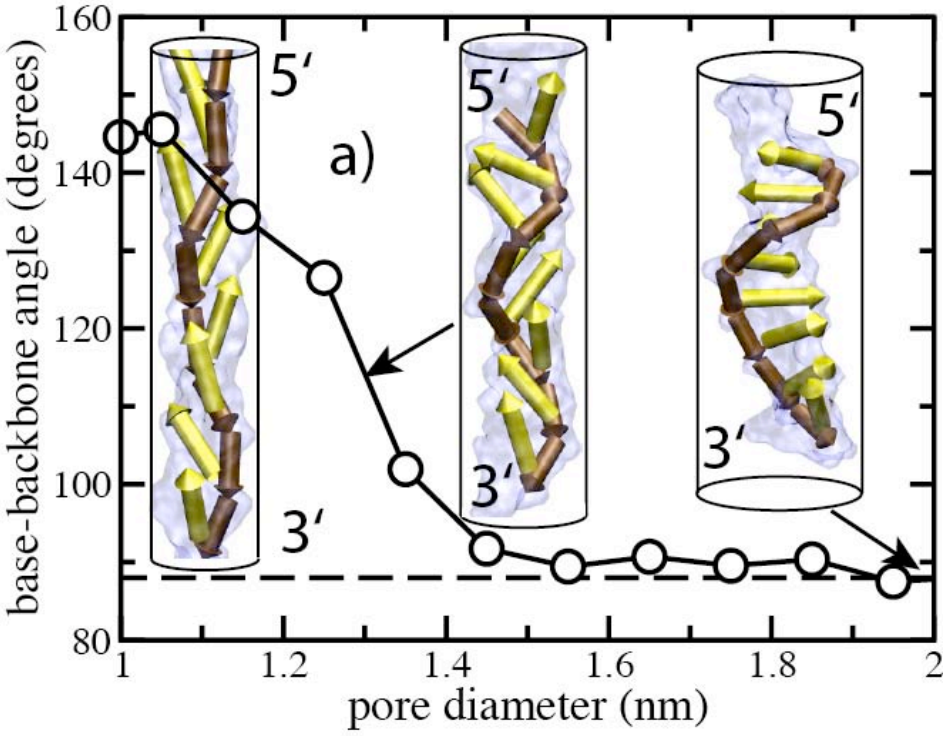
When ssDNA is stretched, its bases align toward its 5' end



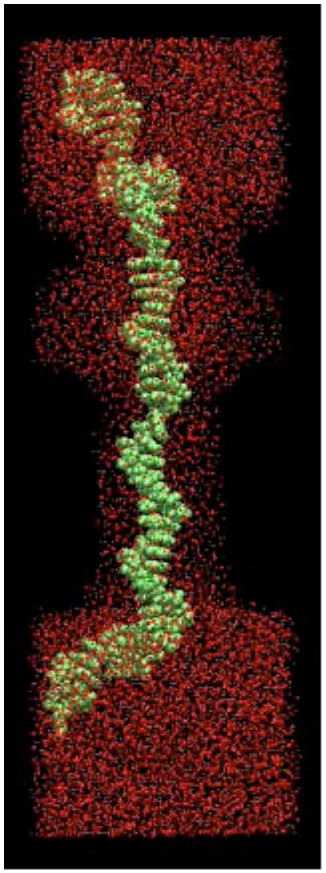
DNA is confined inside
a shrinking pore



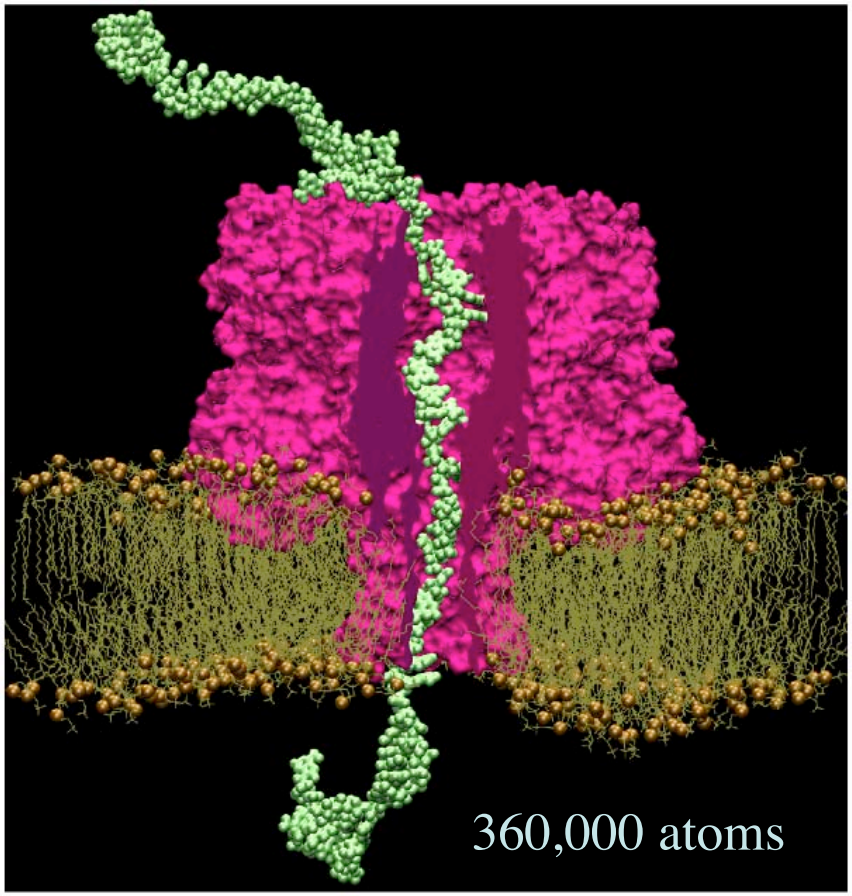
DNA is stretched
by pulling the O5' end



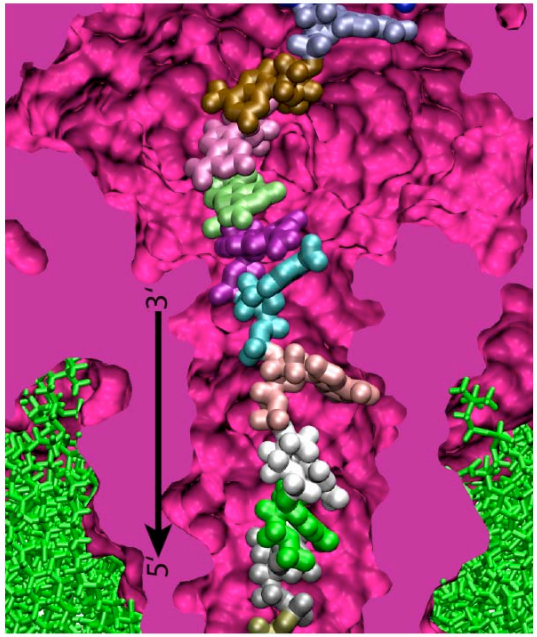
Pushing a DNA strand through a pore is …
like bringing a X-mass three through a door

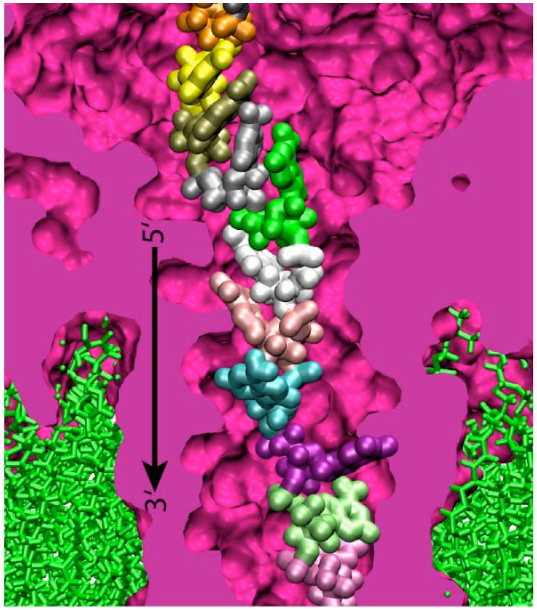


ssDNA in a
phantom pore

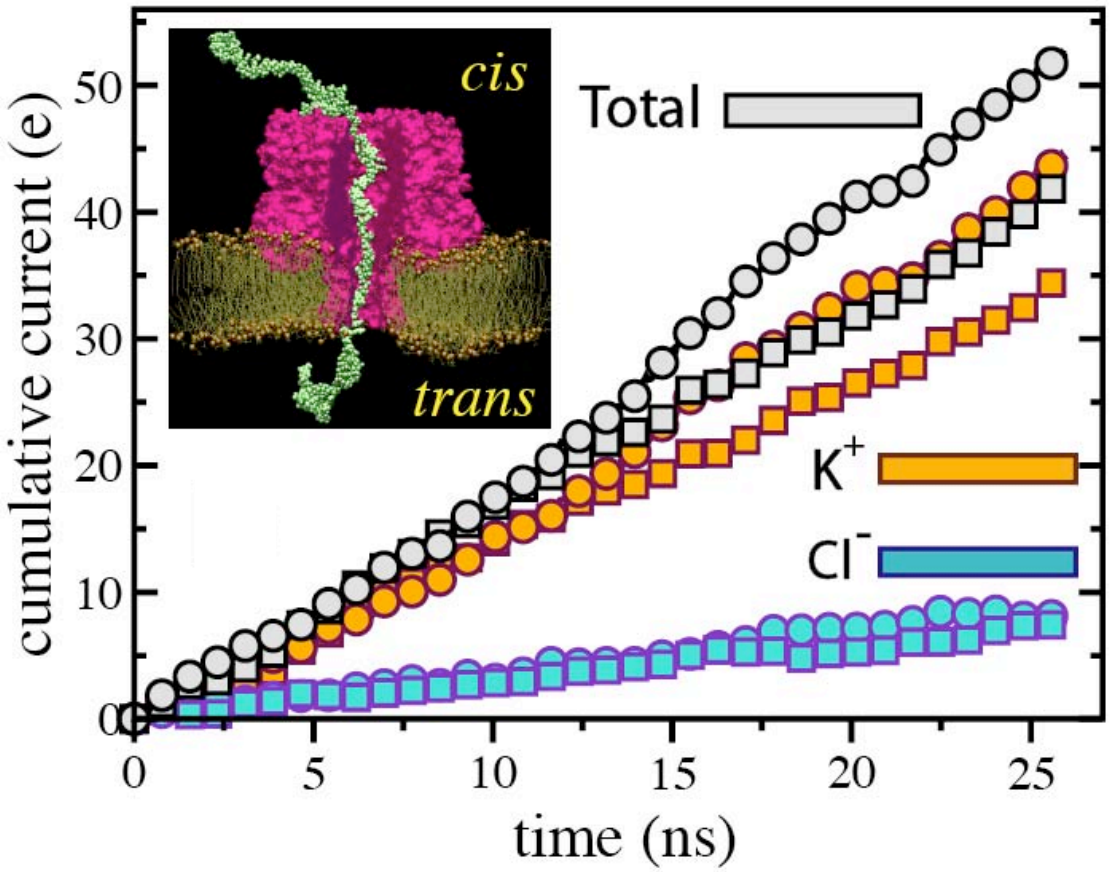


All-atom MD simulation
of DNA translocation

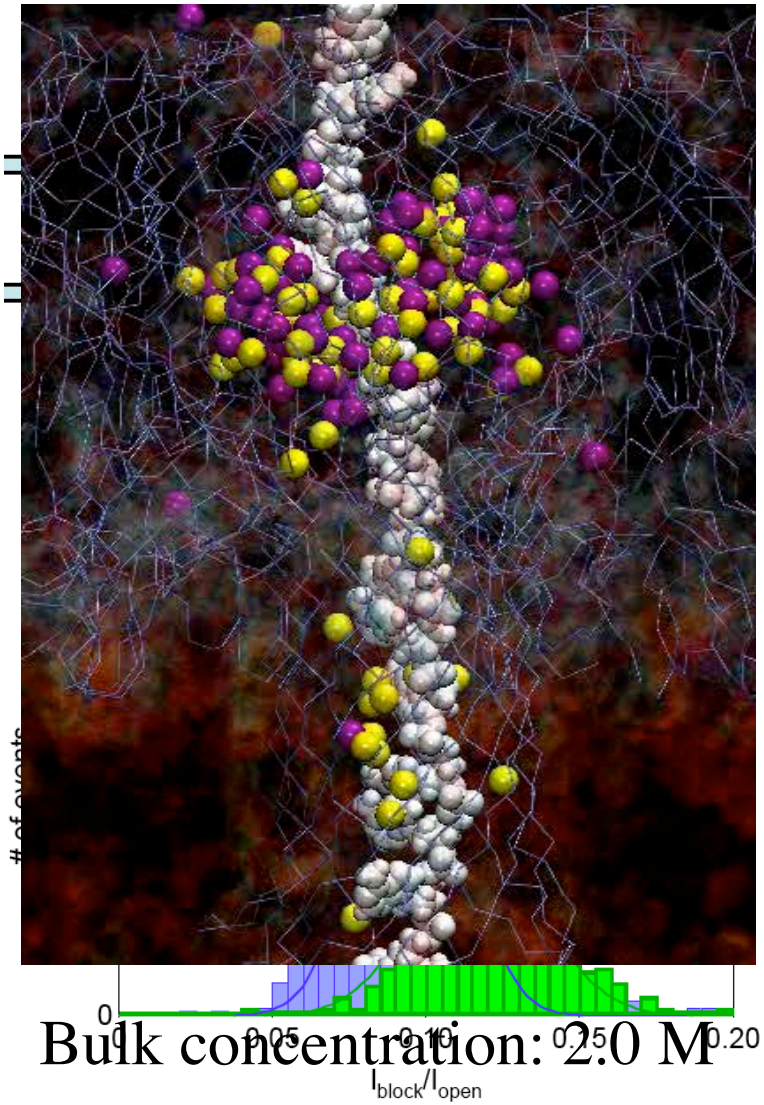




MD correctly predicts the ratio of blocked currents

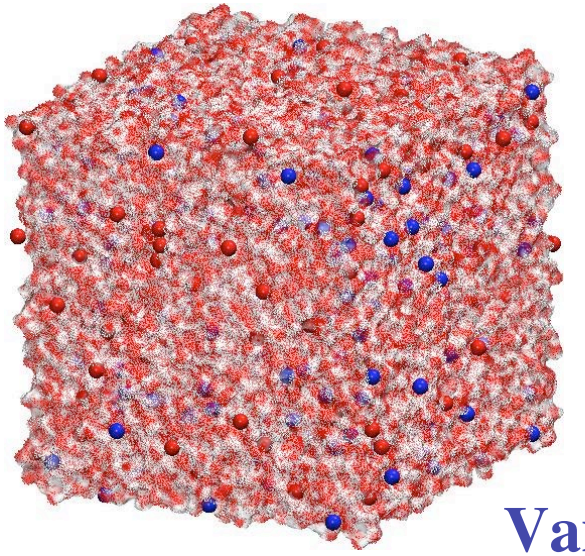


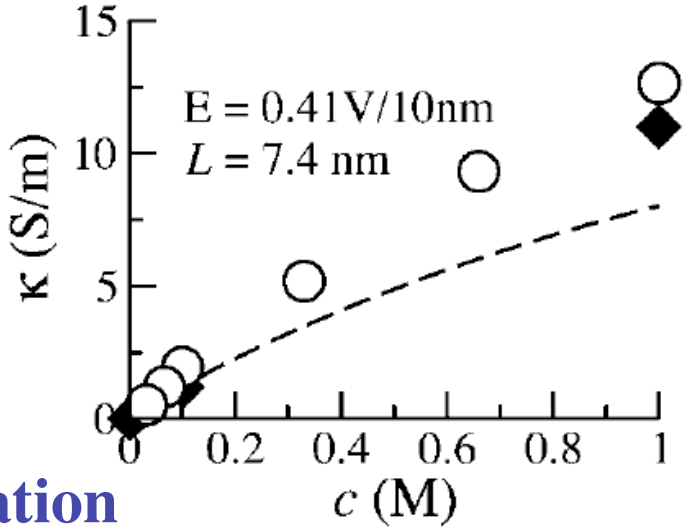
(Mathe et al, PNAS 2005)



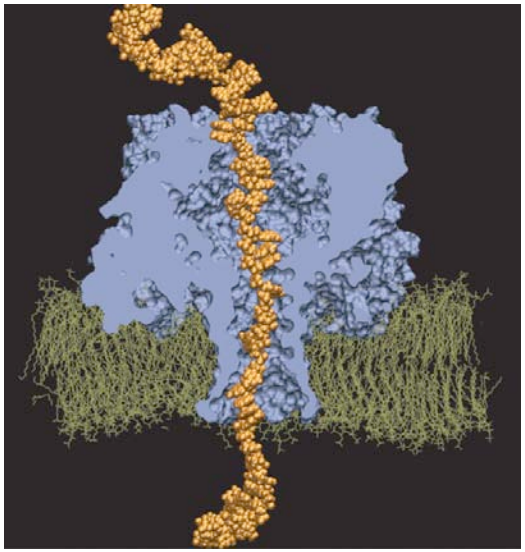
Bulk concentration: 2.0 M

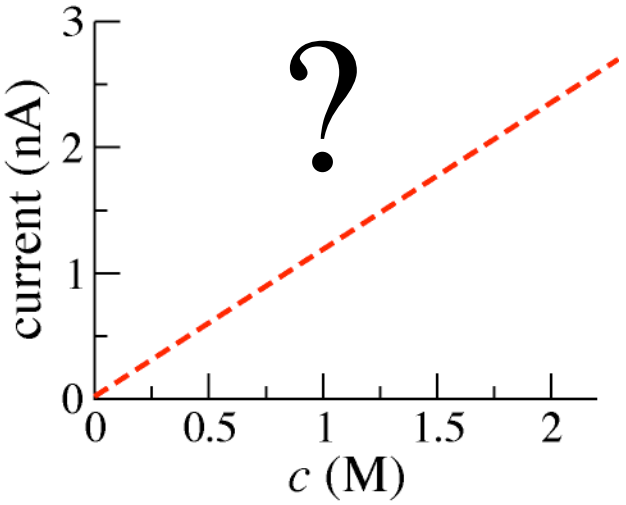
Current versus electrolyte strength



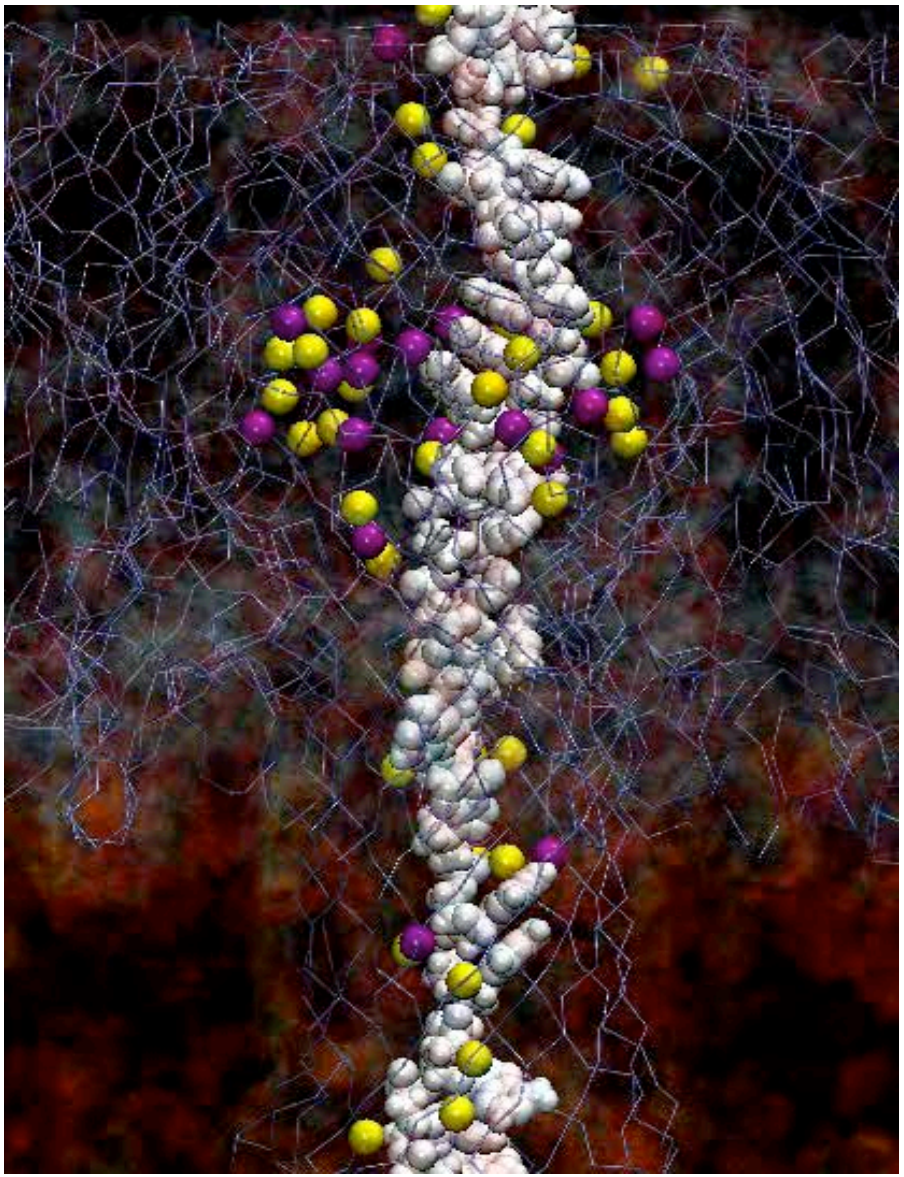


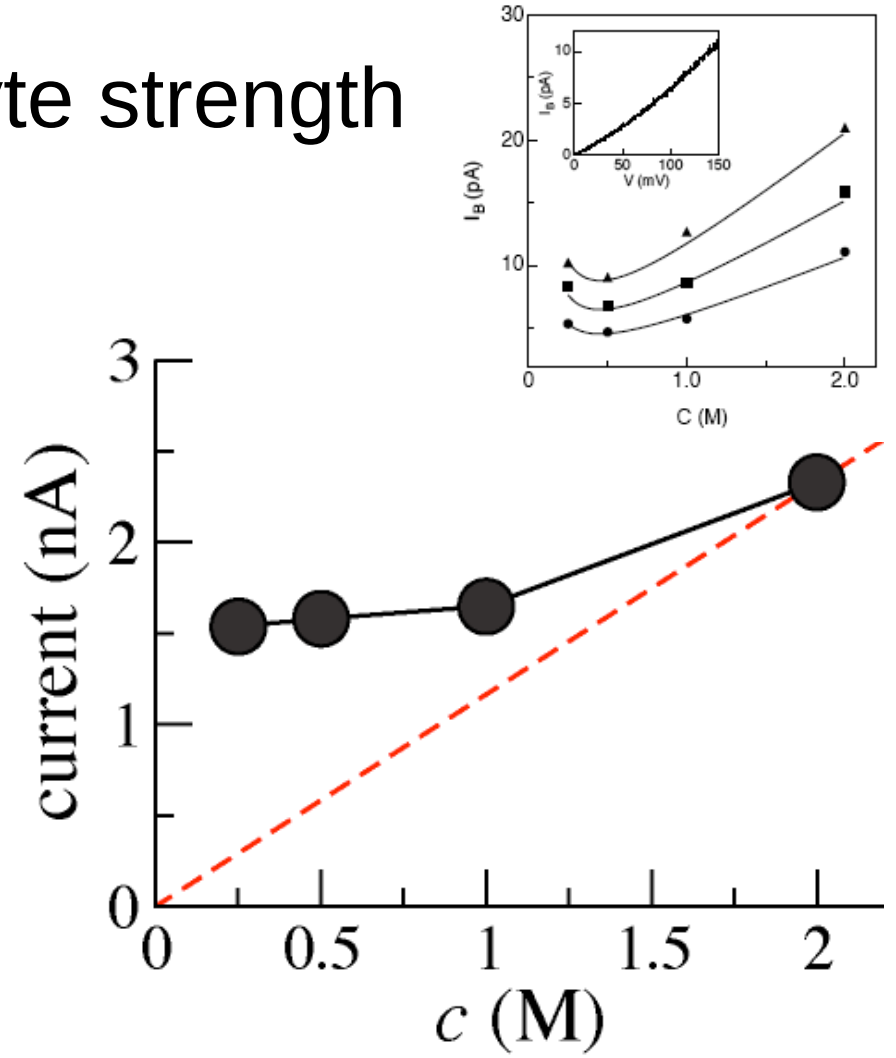
Vary concentration from 2 to 0.1 M





Current versus electrolyte strength

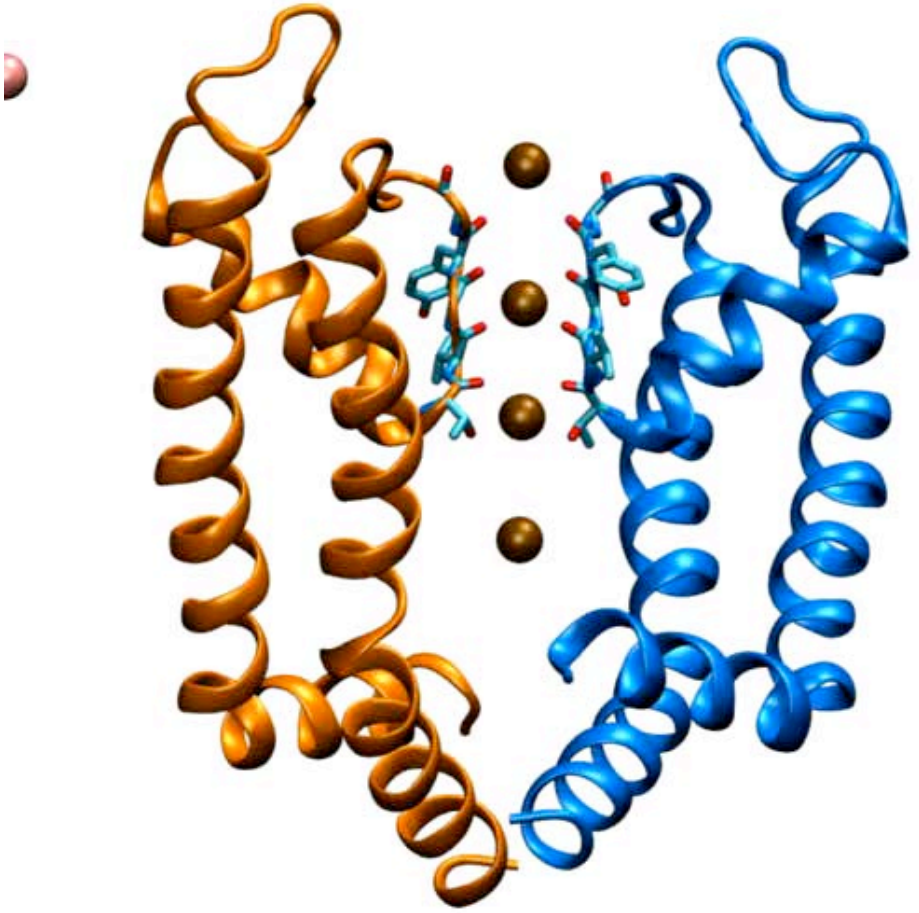




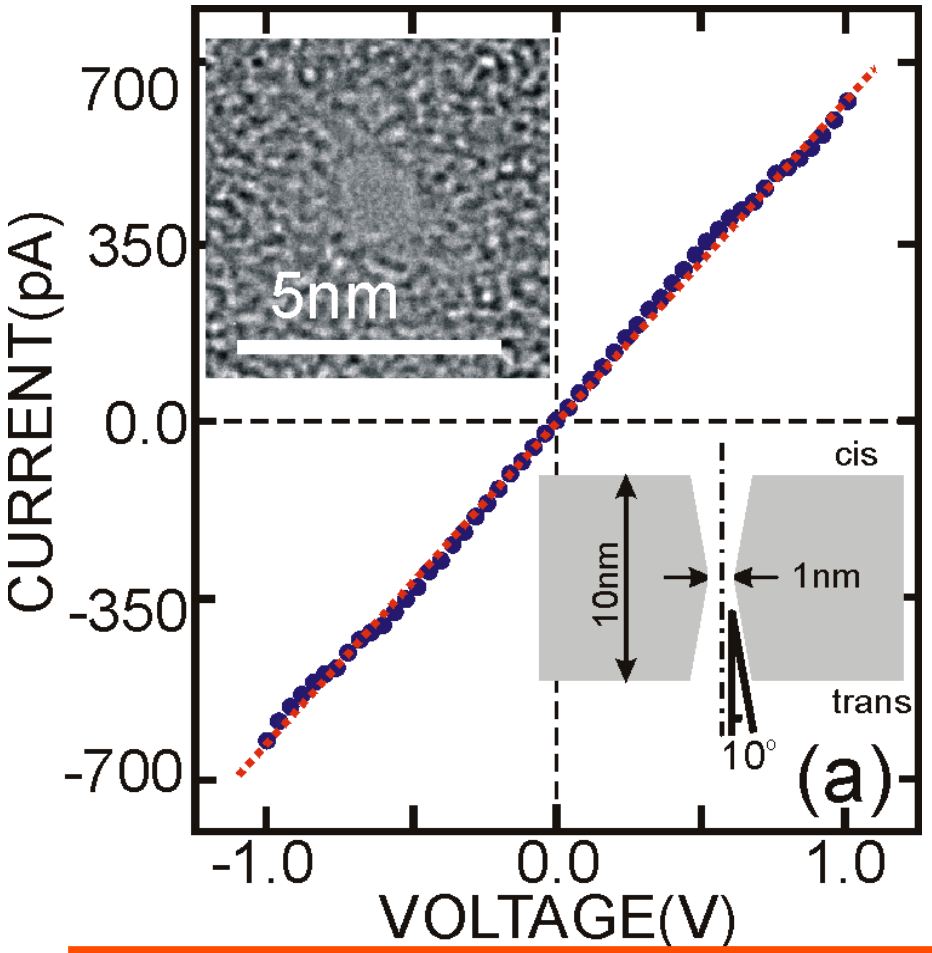
Below 0.5 M, the conductance no longer depends on bulk concentration of KCL

Simulation of Ion Conduction (here for Kv1.2)

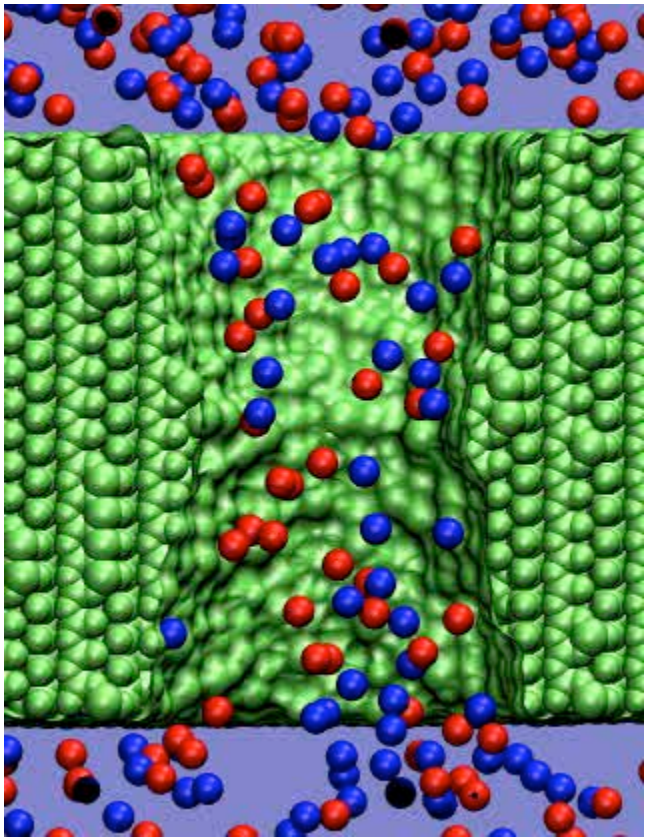
Fatemeh Khalili Araghi
Emad Tajkhorshid
Klaus Schulten (2006)



Ionic current through single nanopore

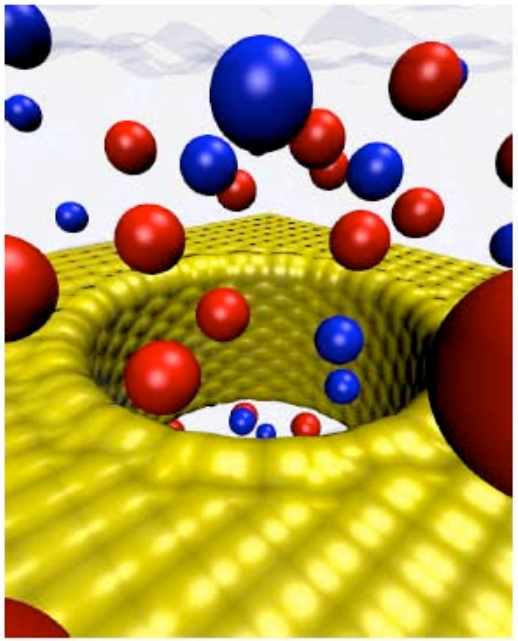


- linear conductance
- wetting kinetics extremely slow
- ionic conductivity through a nanopore less than bulk for high concentrations.



MD simulation of nanopore conductivity at 1M KCl.
Simulation time: 0.3 ns, V=1.4V

Ion Conduction and Electrostatic Maps



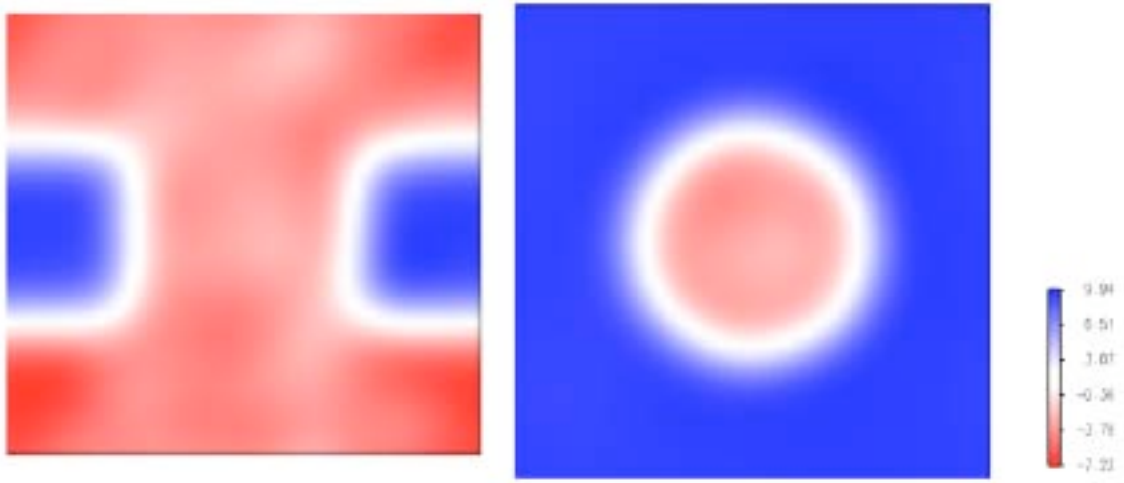
Alek Aksimentiev

Marcos Sotomayor

David Wells

Highlights: Volumetric data

Water density distribution computed using the volmap plugin



Distribution of the electrostatic potential computed with the PMEpot plugin