Ion Channels as Devices

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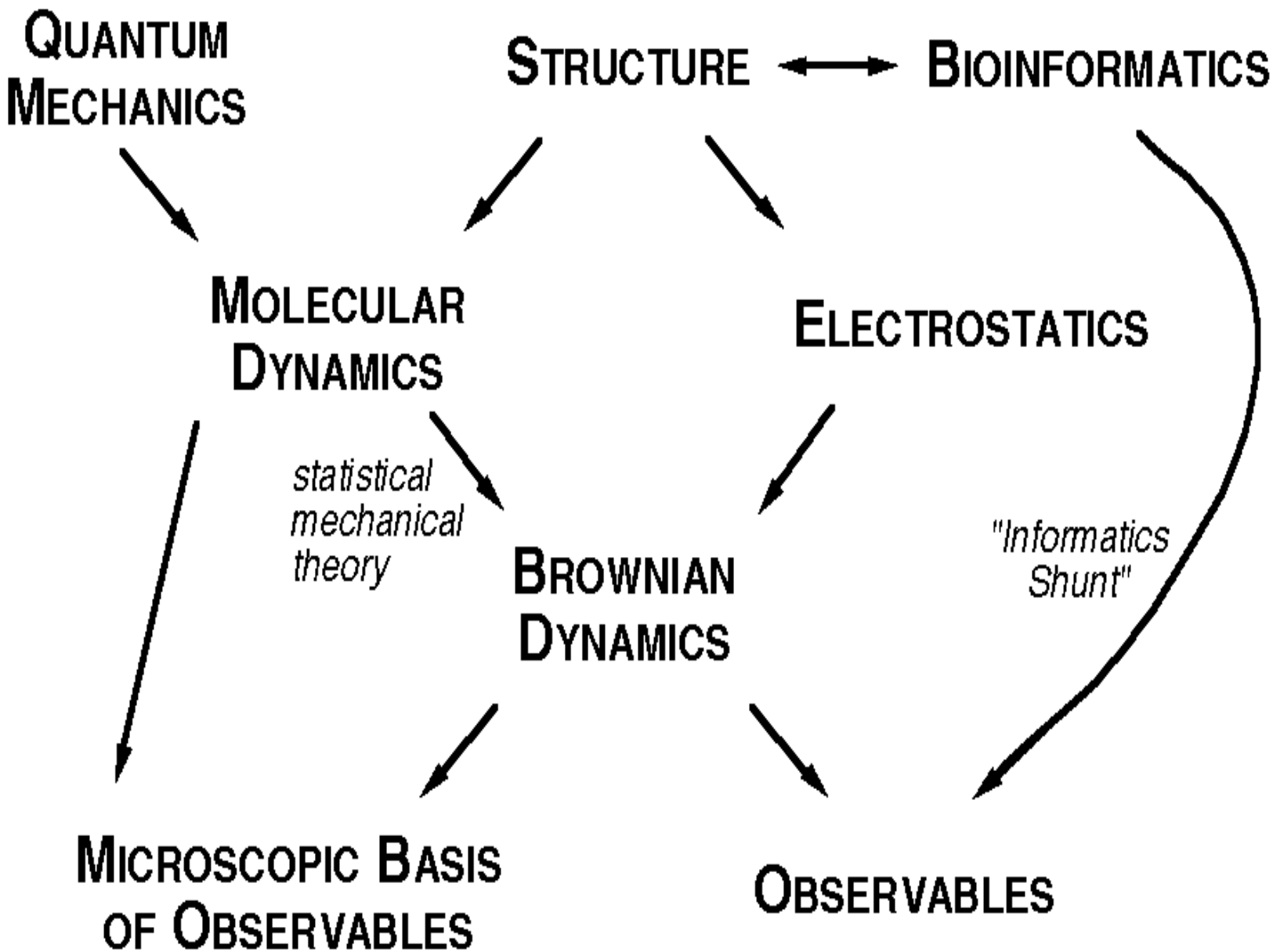
With added program perspective by Eric Jakobsson, National Institutes of Health

Work described was done by: See-Wing Chiu, Sony Joseph, Jay Mashl, Shreedhar Natarajan, Yuzhou Tang, Trudy van der Straaten, and Sameer Varma

Multiscale simulations of ion channel function.

See-Wing Chiu, Jay Mashl, Shreedhar Natarajan, Yuzhou Tang, Trudy van der Straaten, Sameer Varma

Ion Channel Computational Hierarchy



Toward an Integrated Computational Environment for Multiscale Computational Design of Nanoscale Ion Channel Semiconductors

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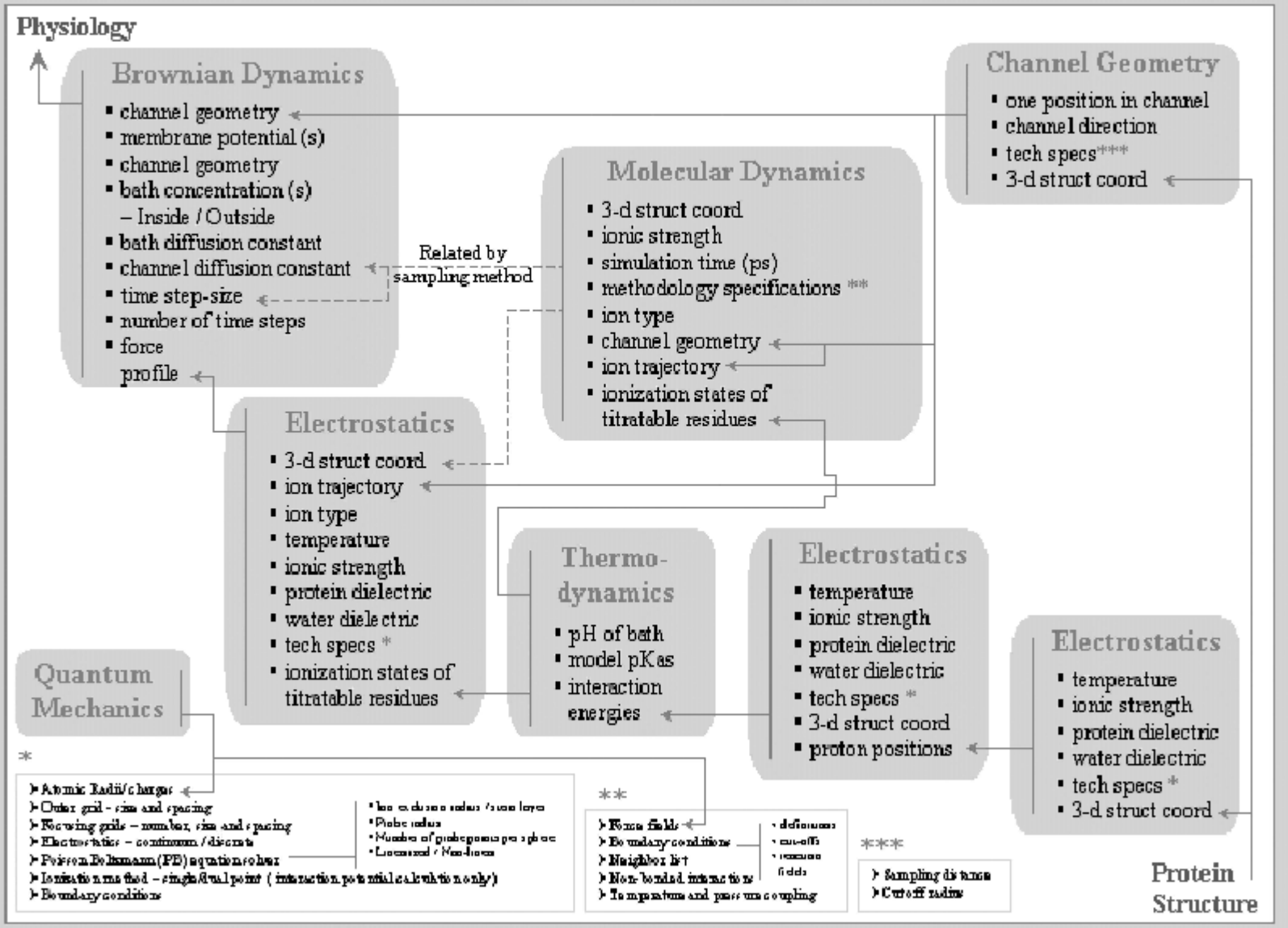
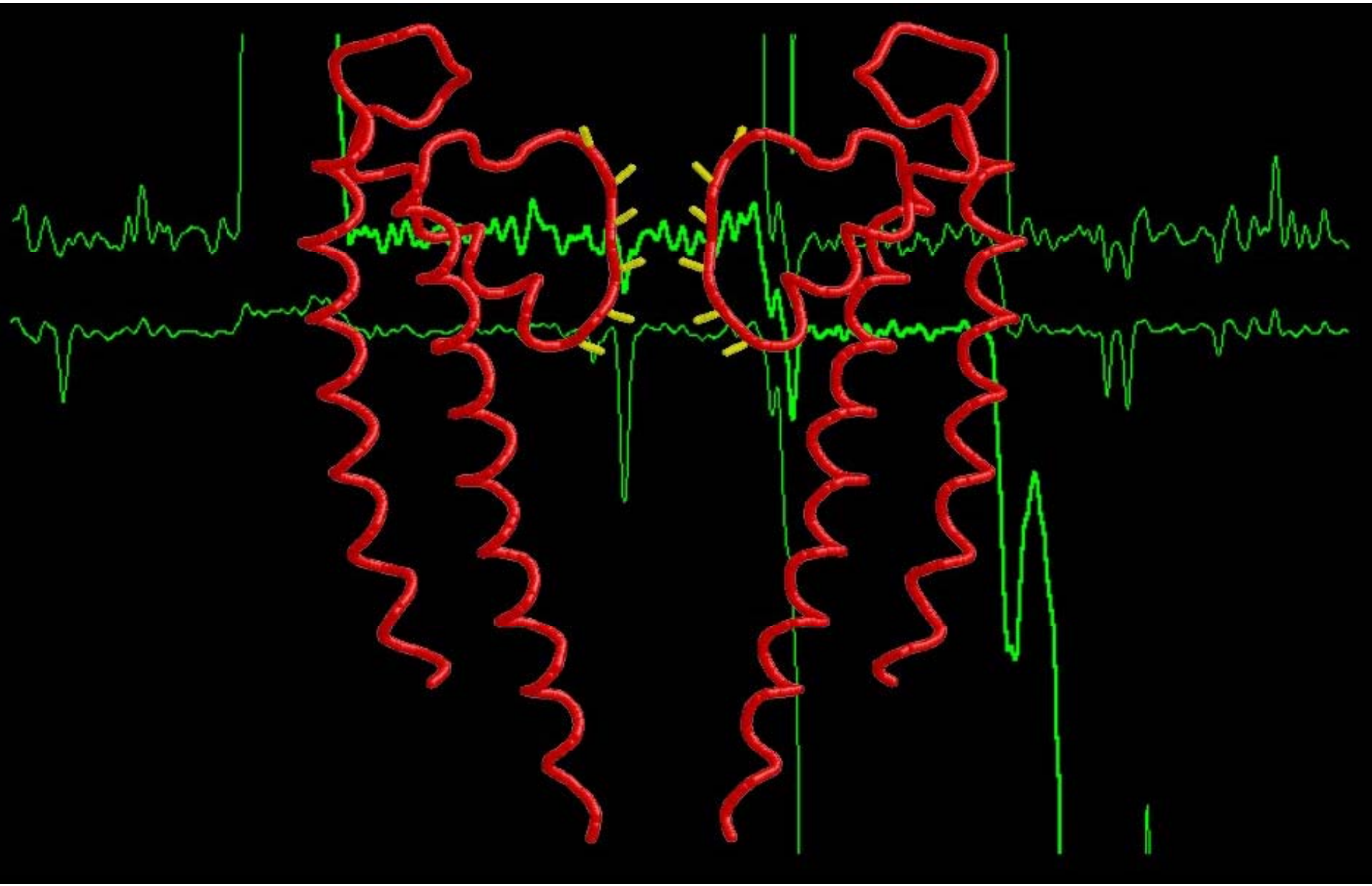
ABSTRACT

This paper describes the design and operation of an integrated multiscale computational environment for design of nanoscale ion channel semiconductors, the Ion Channel Workbench. The present work builds on an earlier multiscale calculation from our lab [1] in which we showed that this approach could provide a close correspondence to experimental electrophysiological data on potassium channels. The current paper advances the previous work by incorporation of multiscale into a single integrated computation, in which the results of calculation at one stage automatically feed as input to calculations at other stages. It also employs more advanced electrostatics and Brownian Dynamics techniques than the previous calculations. In

A multi-scale strategy is well suited for device simulation purposes. One of the requirements of a CAD system is to enable rapid prototyping. This drives the need to decompose the processes within a nanotransistor CAD system so that they can be computed efficiently. However, as we scale down in both size and time, the uncertainty inherent in the models increases and it is therefore necessary to have robust connections between these processes that capture the uncertainties effectively within a probabilistic framework. Our multi-scale approach to ion channel simulation uses well-studied statistical mechanical theory to connect across scales. This makes it a good candidate for a nanotransistor CAD system. Arguably, any biomimetic semiconductor CAD system could be modeled using this paradigm - process

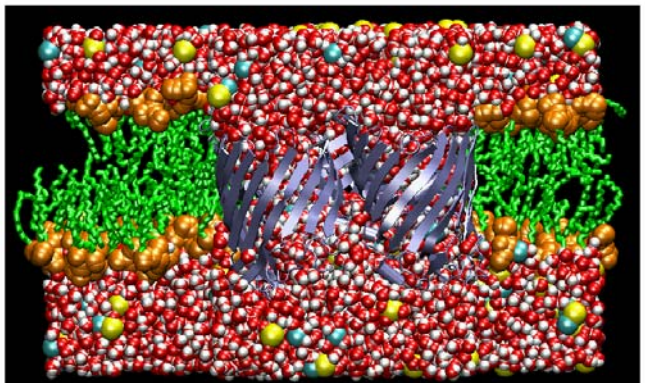
Data Flow for Hierarchical Molecular Simulations

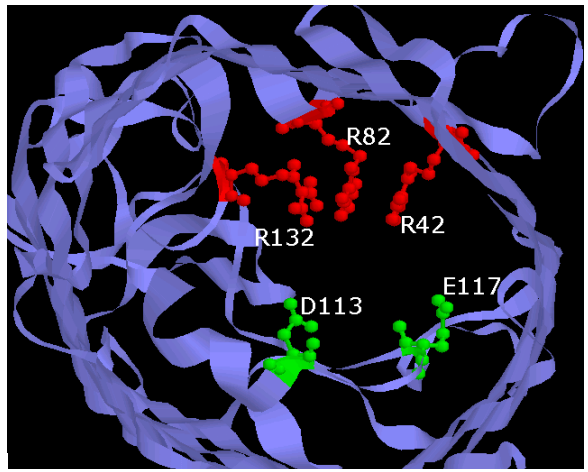


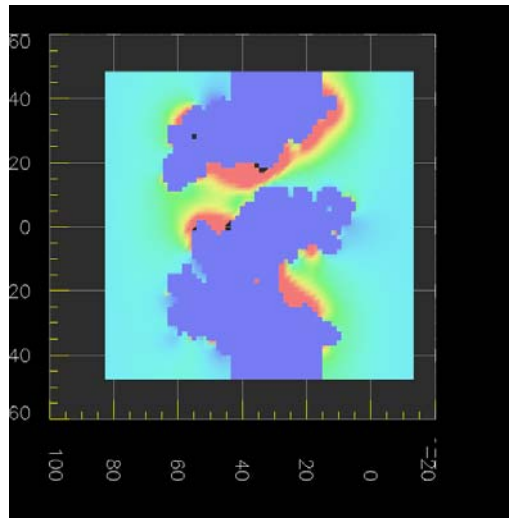


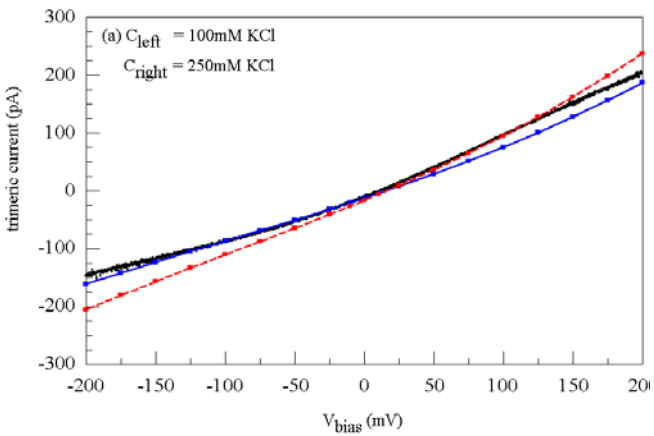
A hybrid calculation combining techniques of computational chemistry and computational electronics to understanding permeation in a protein ion channel—A joint project of the Computational Biology Group, UIUC/NCSA and the Computational Electronics Group, UIUC/Beckman Institute

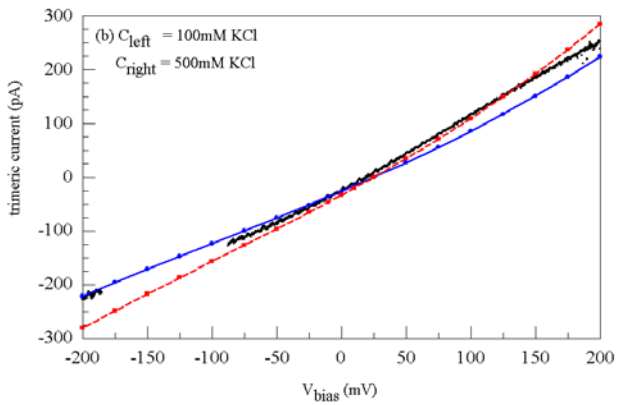
Visualizations below illustrate molecular dynamics to calculate ion mobilities, electrostatics to calculate ionization state of titratable groups, drift-diffusion to calculate permeant ion distributions, and resultant current-voltage curves.

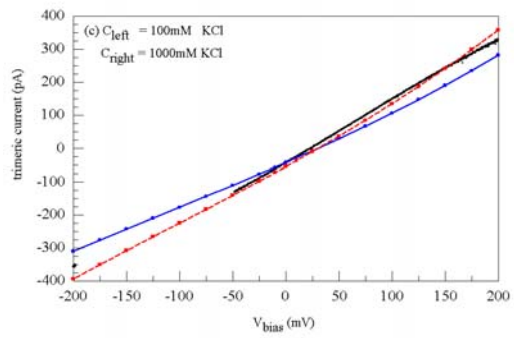










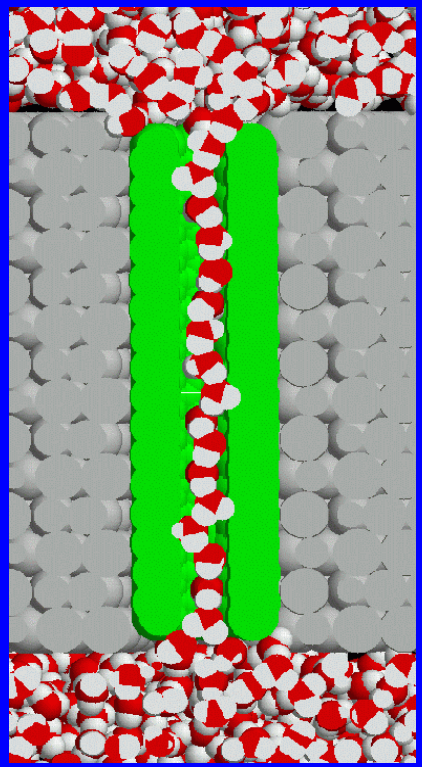


Science mini-story

Water structure in Carbon nanotubes

Jay Mashl and Sony Joseph

System Setup



- Carbon nanotube (fixed)

  8 sizes of nanotubes ranging 5.4 – 16.3 Å dia., armchair (5,5) - (12,12). Length ~40 Å.

- Bilayer mimetic (hcp CH_2's, fixed)
- SPC/E water (T = 300 K)

  $2q_H = -q_O = 0.8476\ e$

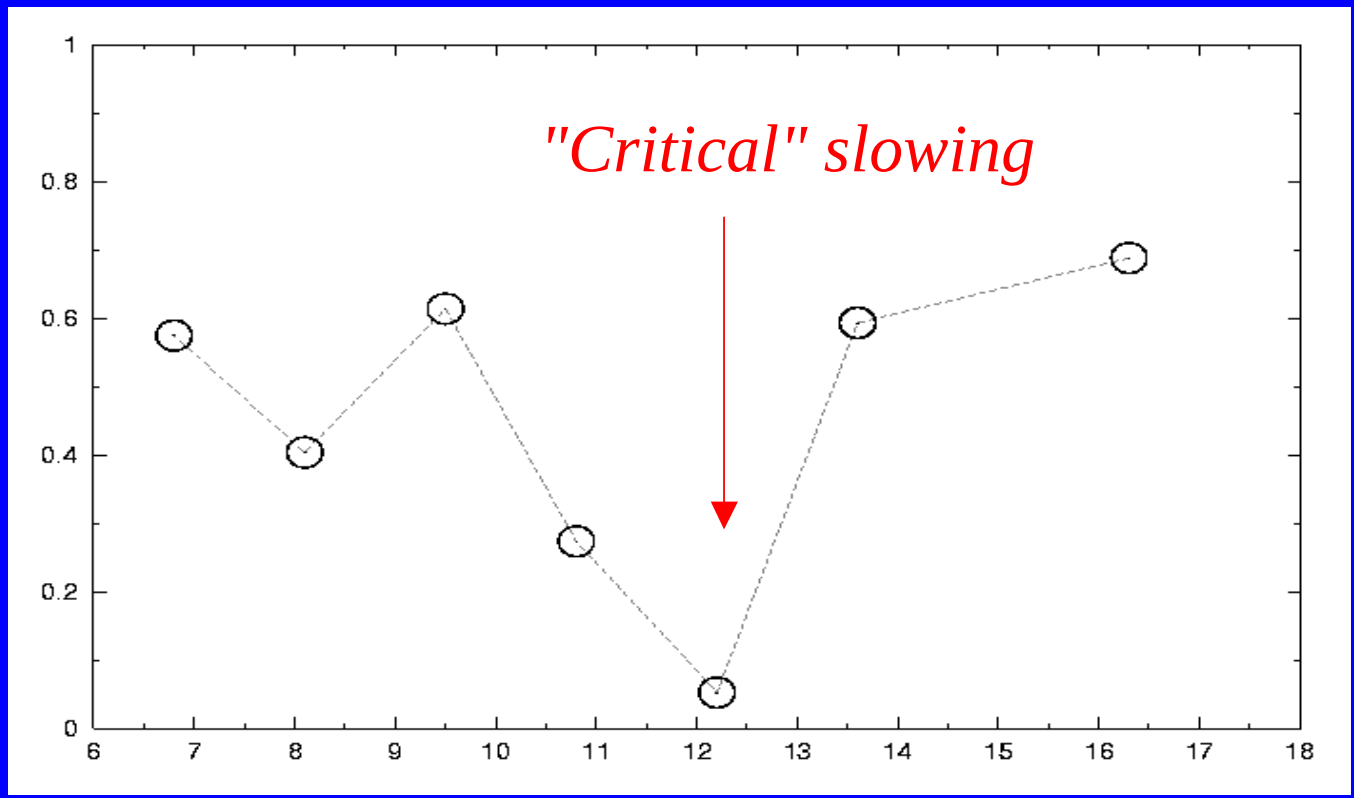
  - Electrostatics: PME
  - Nose-Hoover coupling
  - Pressure piston (P_z = 1 bar)
  - Runs of ~2 ns each using GROMACS

    (See www. gromacs.org)

• Simulations done on NCSA IA32 and IA64 Linux superclusters

Relative Diffusion coefficients

Water in Nanotube vs. bulk(=1)



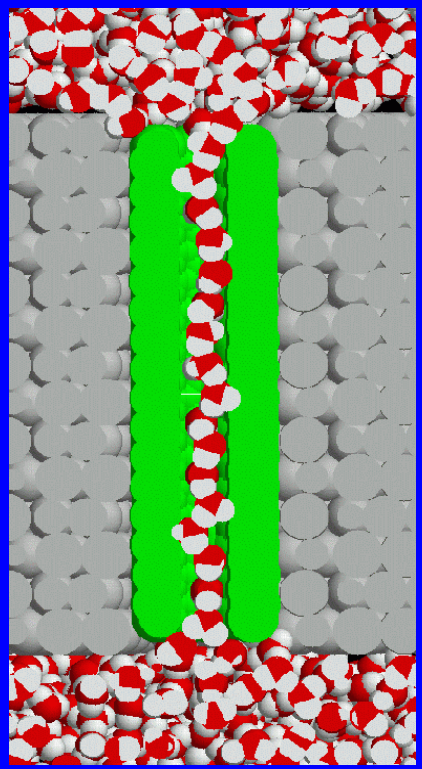
D_z(tube) / D_z(bulk)

Nanotube diameter (Å)

Snapshots of Water Configurations

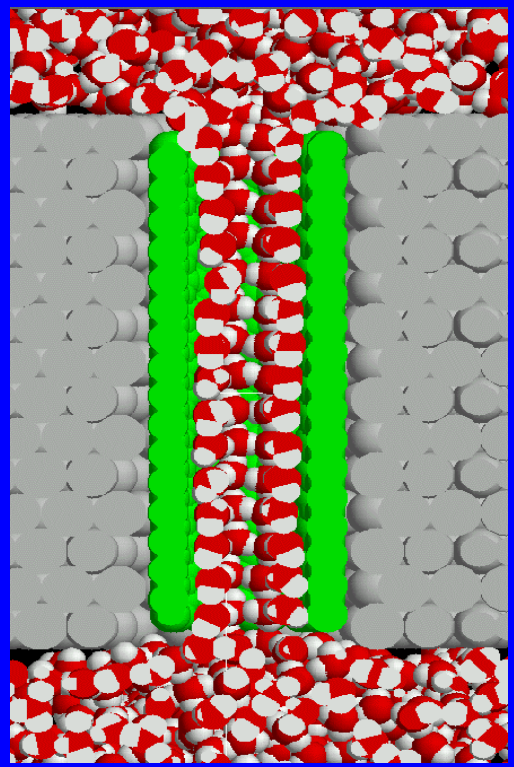
T = 300 K (water), fixed tube & slab

(6,6)



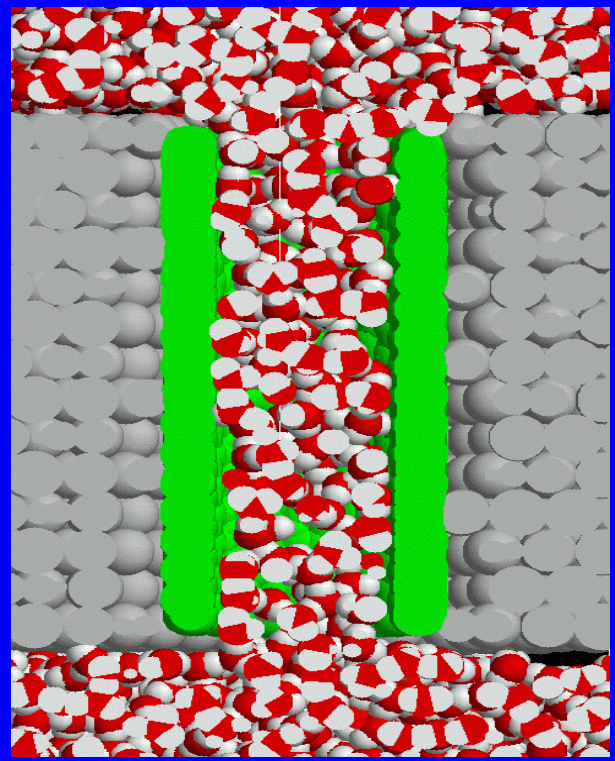
- Single file
- 1-D hydrogen bonding

(9,9)



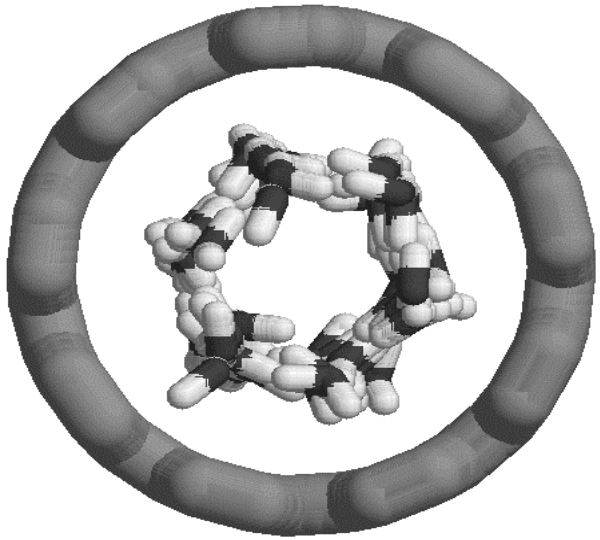
- Critical size for order
- 2-D hydrogen bonding

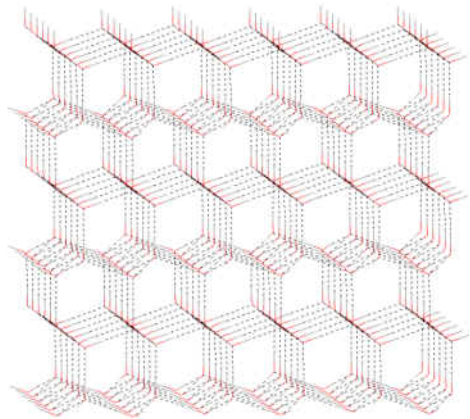
(12,12)

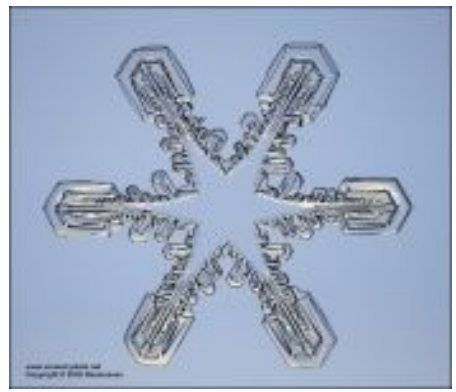


- Bulk water properties not yet achieved

Snapshot from end of "critical-diameter" nanotube of water structure, showing configuration similar to hex ice at 300K, (basis of snowflake symmetry) (Snowflake pictures by Susan Rasmussen)







Take home lessons and questions

- Confinement can change fluid structure dramatically
- Near phase boundaries, subtle changes in simulation parameters can have dramatic effects.
- Could confinement-induced phase change be used as a switching mechanism in nano-scale semiconductors?

Take home lessons

- Understanding ion channel (and all macromolecular) function is a multi-scale problem.
- Physical chemists, **nanoscientists**, molecular biophysicists, and materials scientists are all working on the same problem.

The Computational Nanoscience Challenge

Develop a computer-aided design system for nanodevices; be able to design molecules to functional specifications.

(An eminent protein simulation expert, when presented with this challenge at a recent meeting, said, “That’s not science, that’s engineering!”)

Take Home Lessons and Questions

- It is computationally feasible to do a self-consistent solution for the protonation states of electrostatically interacting titratable residues.
- For accurate calculations, it is NECESSARY to do a self-consistent solution for the protonation states of electrostatically interacting titratable residues.
- How much of the oft-remarked-on deficiencies in atom-scale force fields is due to a failure to assign the correct protonation states to titratable sites?

Now wearing the NIH hat (but speaking only for myself) and asking: What are the high-performance computing challenges in molecular physical science that could have big payoff for the NIH mission?

- Immediately: Being able to do accurate in silico screening of lead compounds for drugs.
- Immediately: Being able to do high quality homology modeling of proteins.
- Intermediate term: Being able to do accurate computer-aided design of nanodevices.
- Intermediate term: Being able to do reliable computer-aided design of biomaterials.
- Longer term (At least 5 years or so): Accurate dynamical modeling of cells. (The limitation is having the data to put in to the models, but that is being resolved by high-throughput experiments and getting enough complete genomes sequenced that comparative genomics analysis will be effective in characterizing reaction networks.)

Science Story #2

Protonation states of electrostatically interacting titratable residues

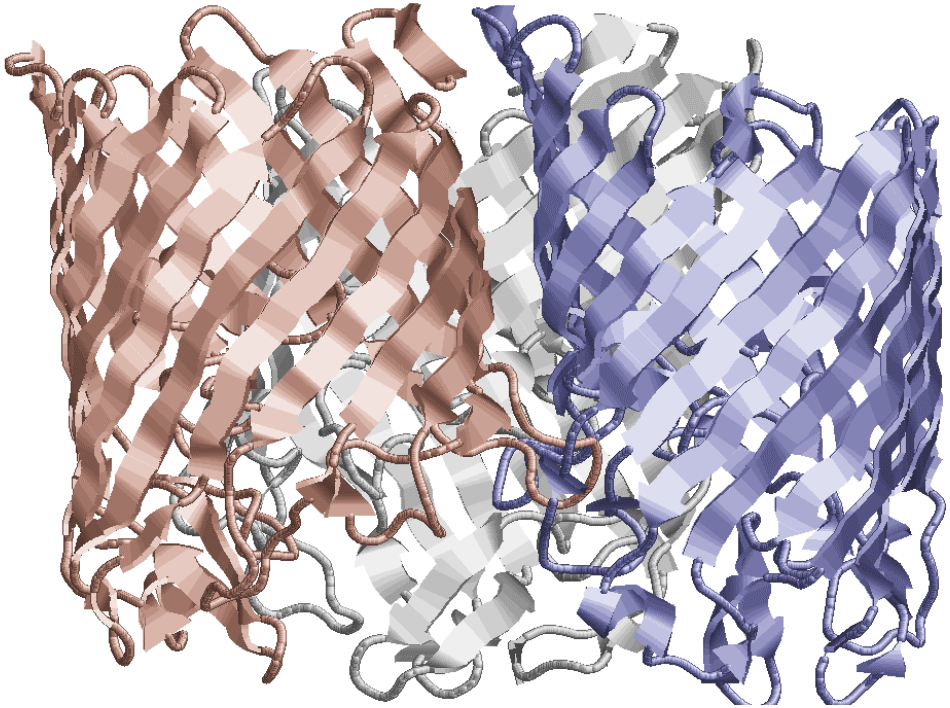
Sameer Varma and See-Wing Chiu

Protonation states

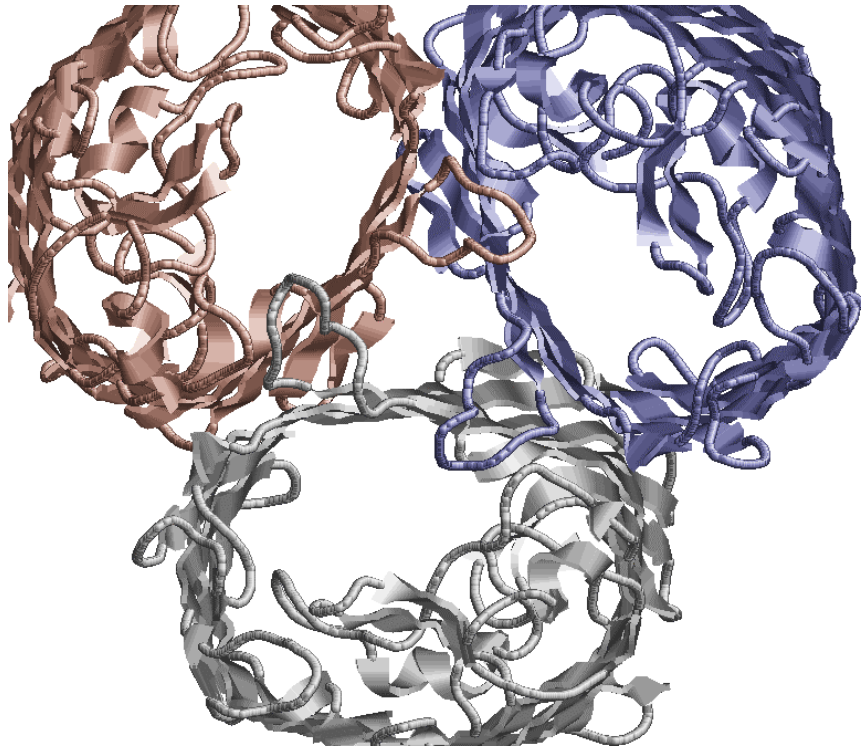
- Problem: Titratable states interact with each other, thus need a self-consistent solution of Poisson-Boltzmann equation.
- Solution: Link iterated solutions together until convergence is achieved.
- Test Case: OmpF
- Result: Protonation states computed in this fashion retain crystal structure, other choices do not.
- Publication: Varma and Jakobsson, Biophysical Journal 2004 (for electrostatics) and in preparation (for molecular dynamics.)

OmpF trimer – Outer Membrane Porin F

Cytoplasmic Side

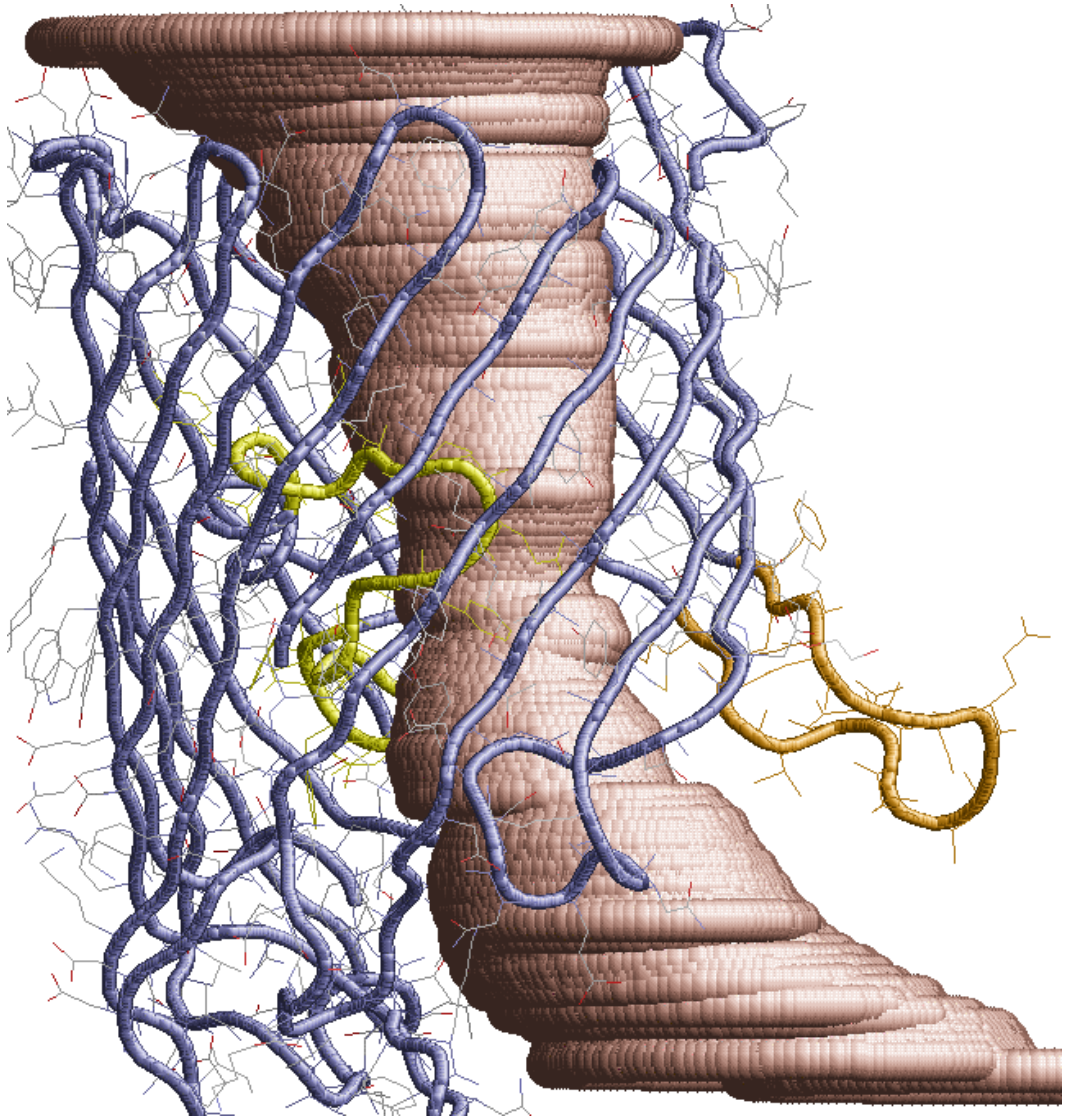


Periplasmic Side

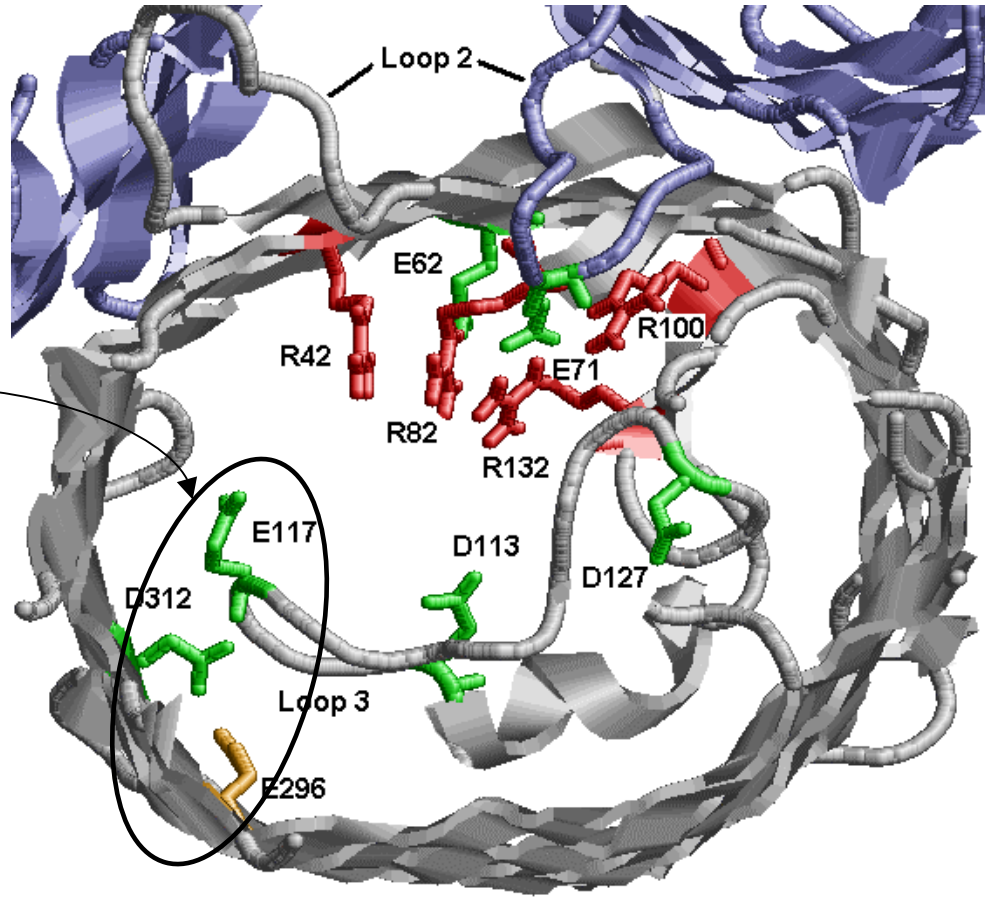


View from the
Periplasmic side

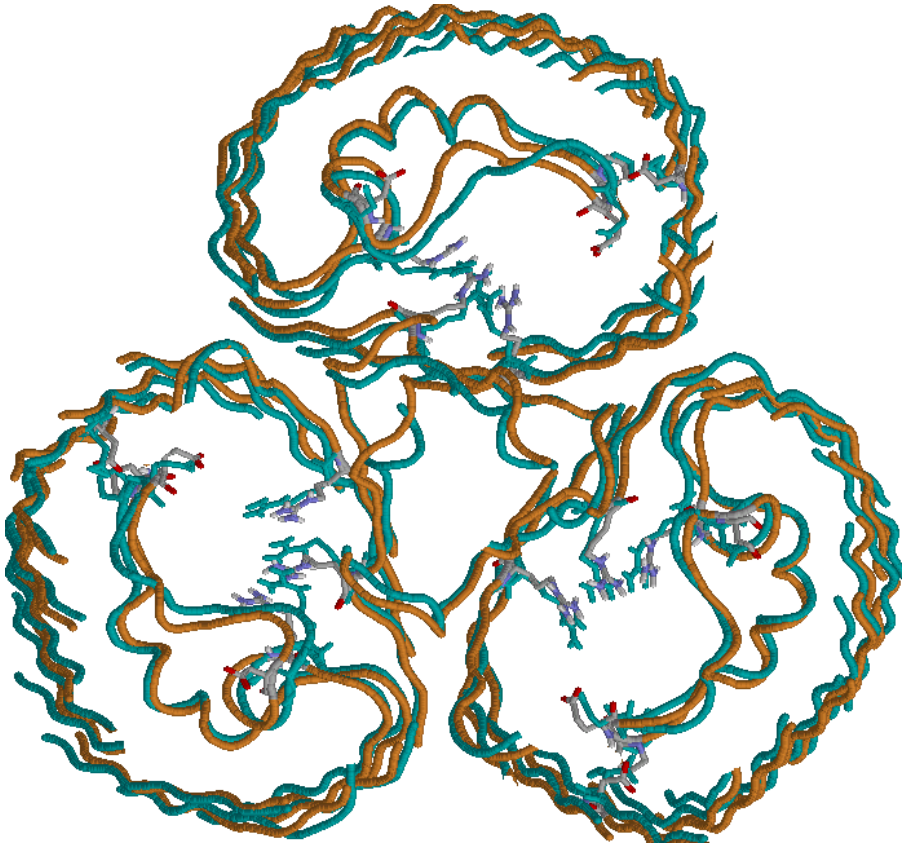
- Monomer - 340 residues long
- Loop 3 (shown in **yellow**) folds inside the barrel and narrows the pore giving it an ***hourglass-like*** appearance
- Loop 2 (shown in **orange**) connect one monomer to its neighbor

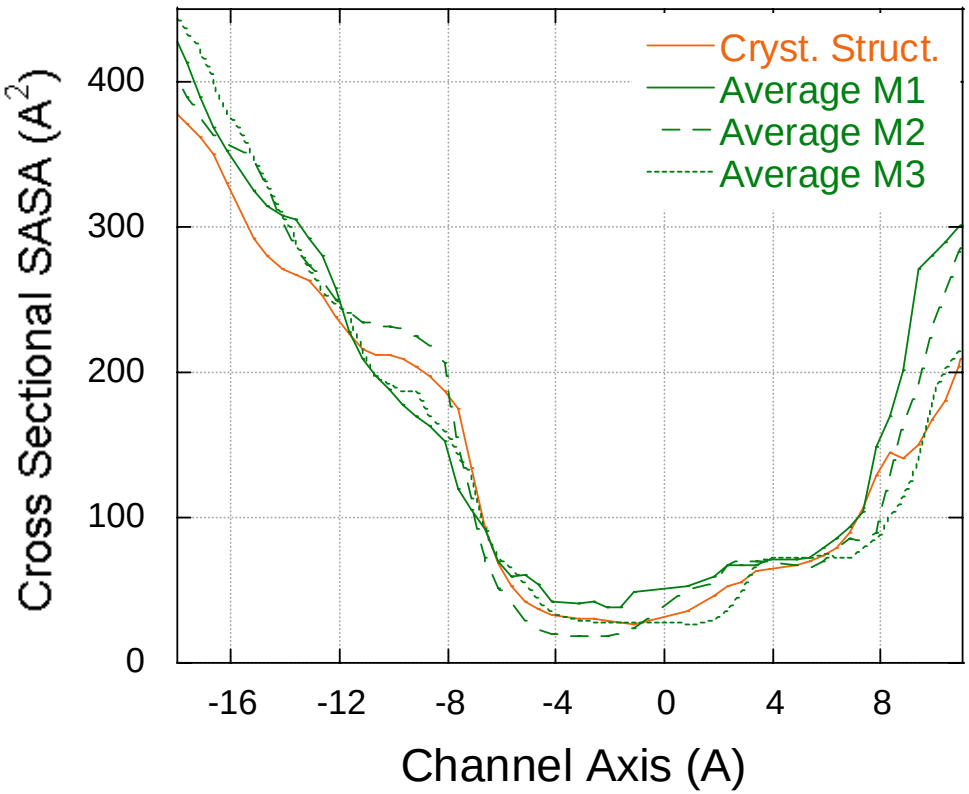


Like the ones shown, there are over 50 titratable residues facing the permeation pathway of the channel



Residues involved in a H-bond network that tethers the loop to the β-barrel

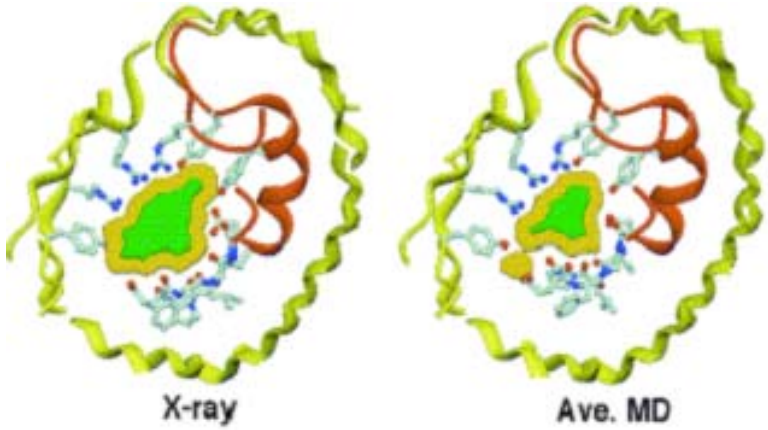




The x-ray structure is drawn in orange and the average structure of the last 2ns trajectory is drawn in green. The structures were aligned using a PSV algorithm.

A large reduction in the Cross-Sectional SASA

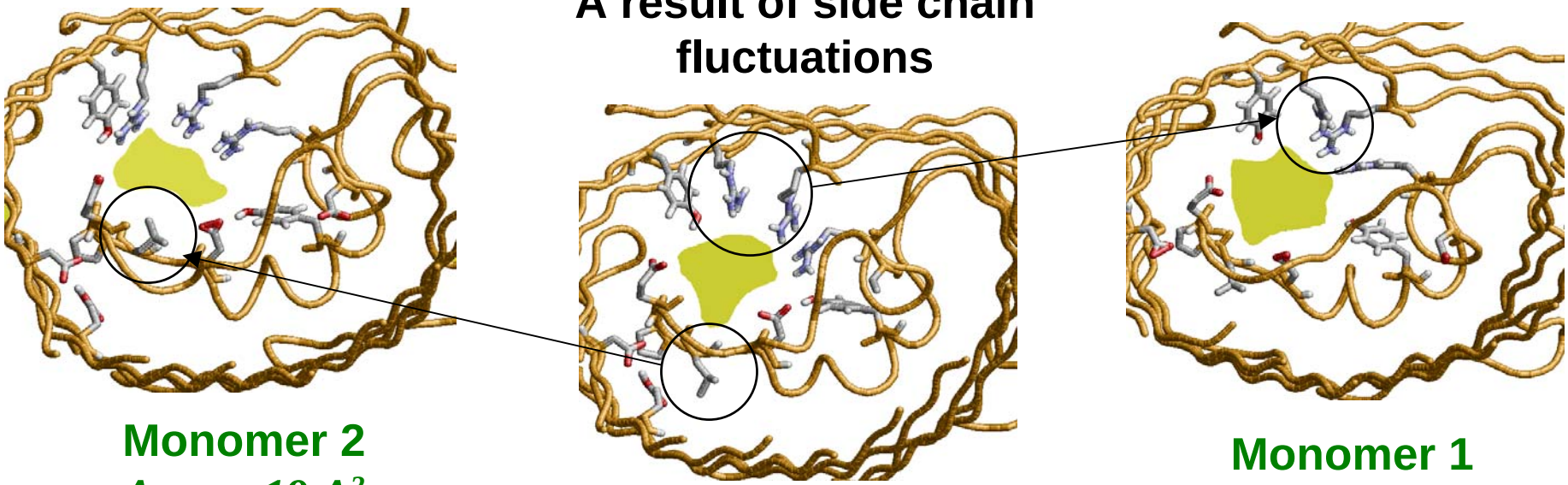
A result of movement of Loop 3 into the permeation pathway



Taken From: Im & Roux, *JMB 2002*

Variations in Cross-Sectional SASA

A result of side chain fluctuations

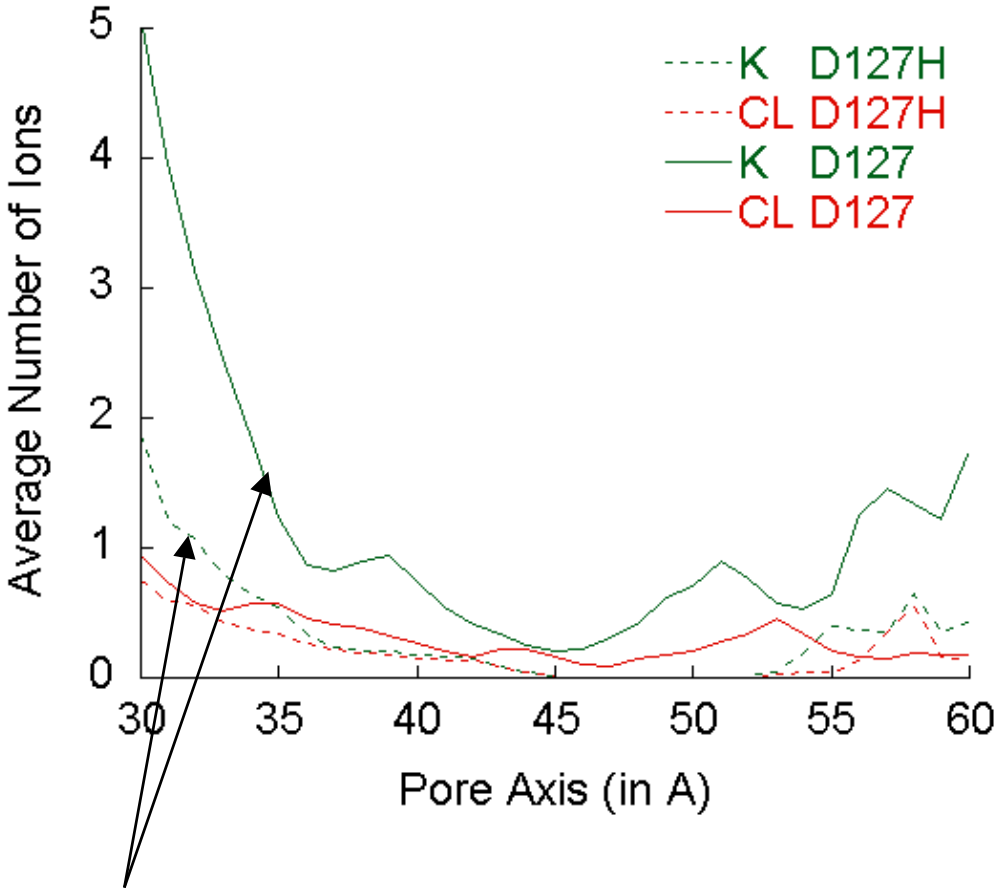


Monomer 2
Area = 19 A²

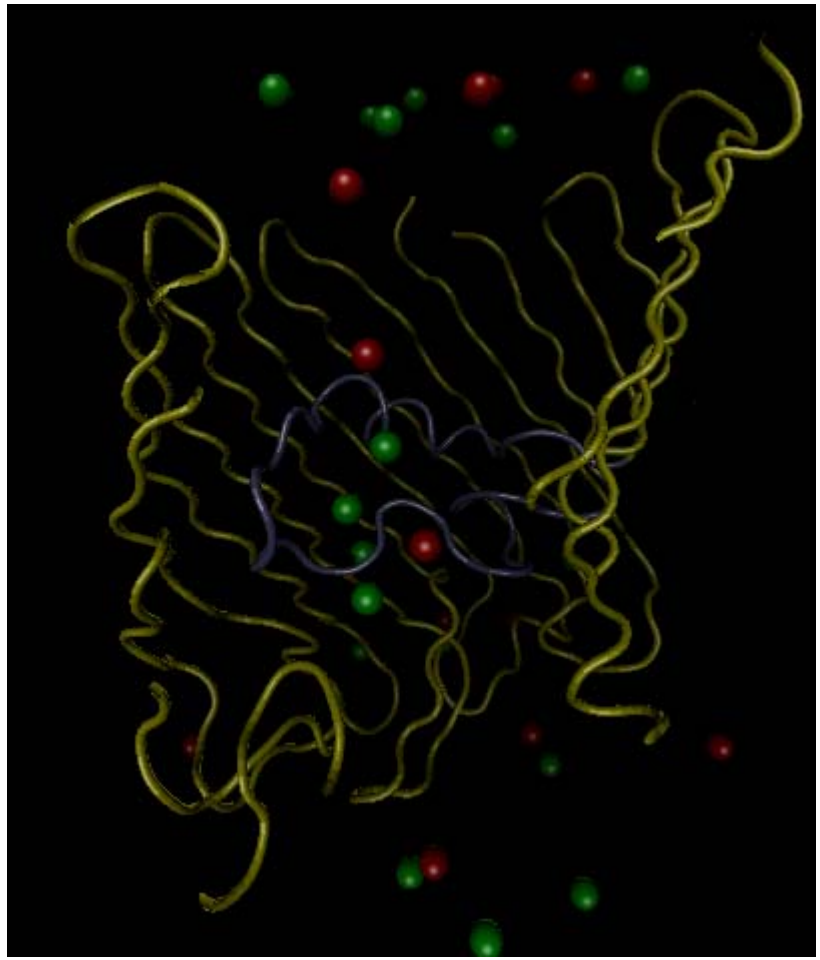
X-ray structure
Area = 27 A²

Monomer 1
Area = 32 A²

Effect of assigning a protonation state to D127 on the distribution of Ions



Deprotonating D127 increases the density of K^+ ions in the channel



A 5ns snapshot of monomer M1 of OmpF simulated with with deprotonated D127.

Final take-home question: Should all of these be attacked under the aegis of an Integrated Molecular Science Initiative, that would embrace nanoscience, biomolecular physics, biomaterials, and computational stat. mech?