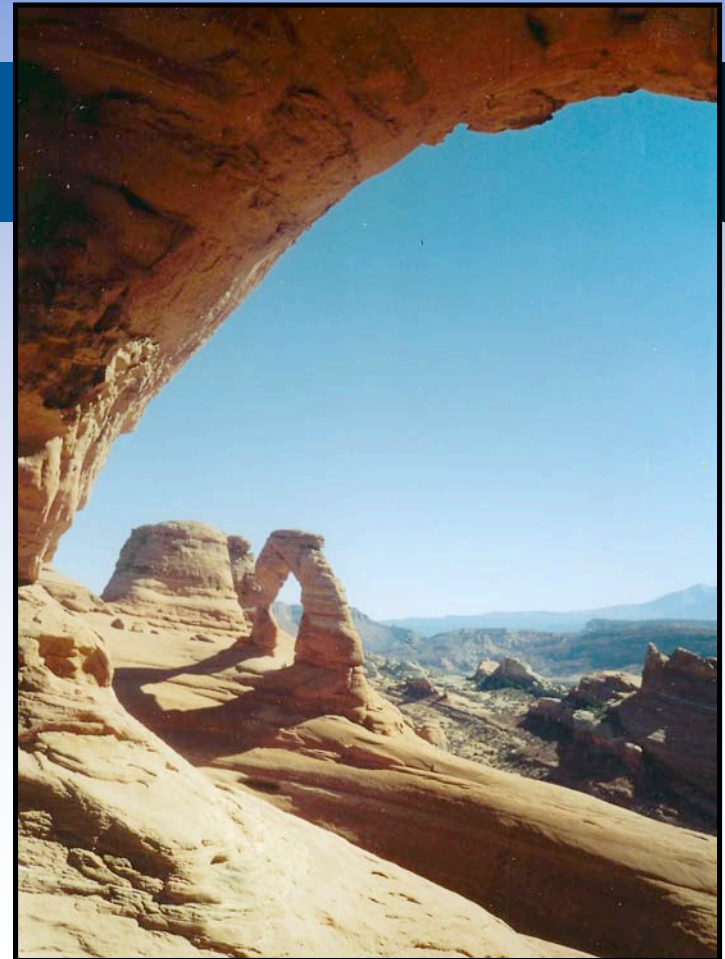


Molecular Dynamics Simulations of Excess Protons Solvation and Transport

Greg Voth
University of Utah



Acknowledgements

- **Research Funded by the National Science Foundation and the National Institutes of Health**
- **Thanks to Udo Schmitt, Tyler Day, Matt Petersen, Yujie Wu, Boaz Ilan, Jiancong Xu, Alex Smondyrev, Hanning Chen, Martin Cuma, Alexander Soudakov, Feng Wang, Sergei Izvekov, Christian Burnham**

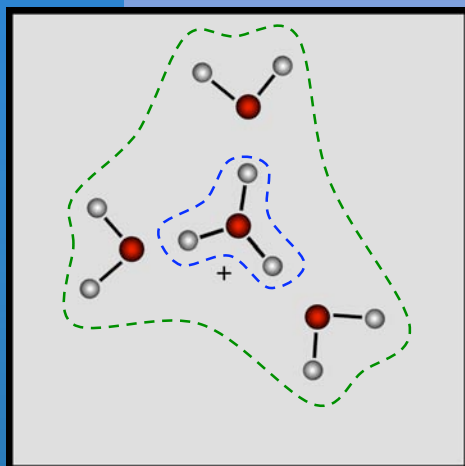
Guiding Principles

- Study **actual proton transport** (as much as 100 ns of trajectory data)
- Try to do as much of the **actual system** as possible (as many as 10's of thousands of total atoms)
- Study protons in many **diverse environments**

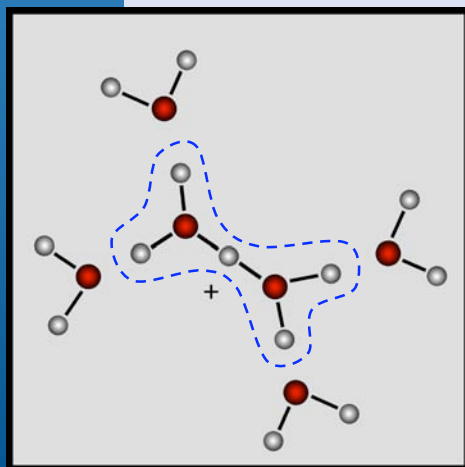
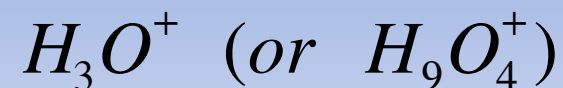
Outline

- **Computational Methodology (Briefly)**
- **Proton Solvation and Transport in Bulk Water**
- **Mechanism of Proton Transport**
- **Proton Solvation in Clusters, at Interfaces, in Hydrophobic Channels, in Mixtures**
- **Biological Proton Channels**
- **Generalizations of the Method**
- **Proton Conducting Polymer Electrolyte Membranes**

Solvation of An Excess Proton in Water



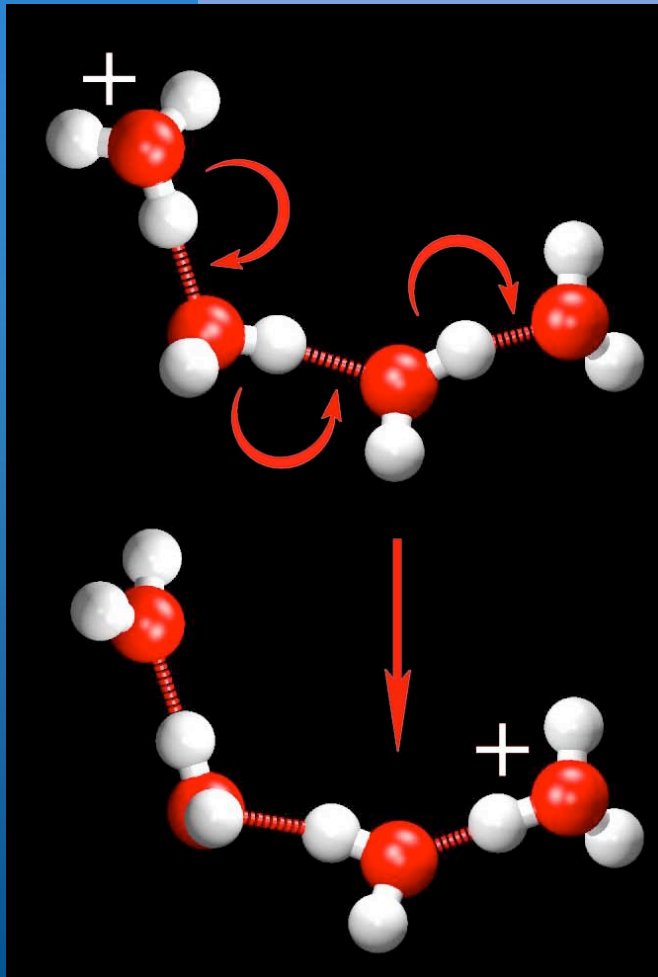
- Solvated Eigen complex



- Solvated Zundel complex



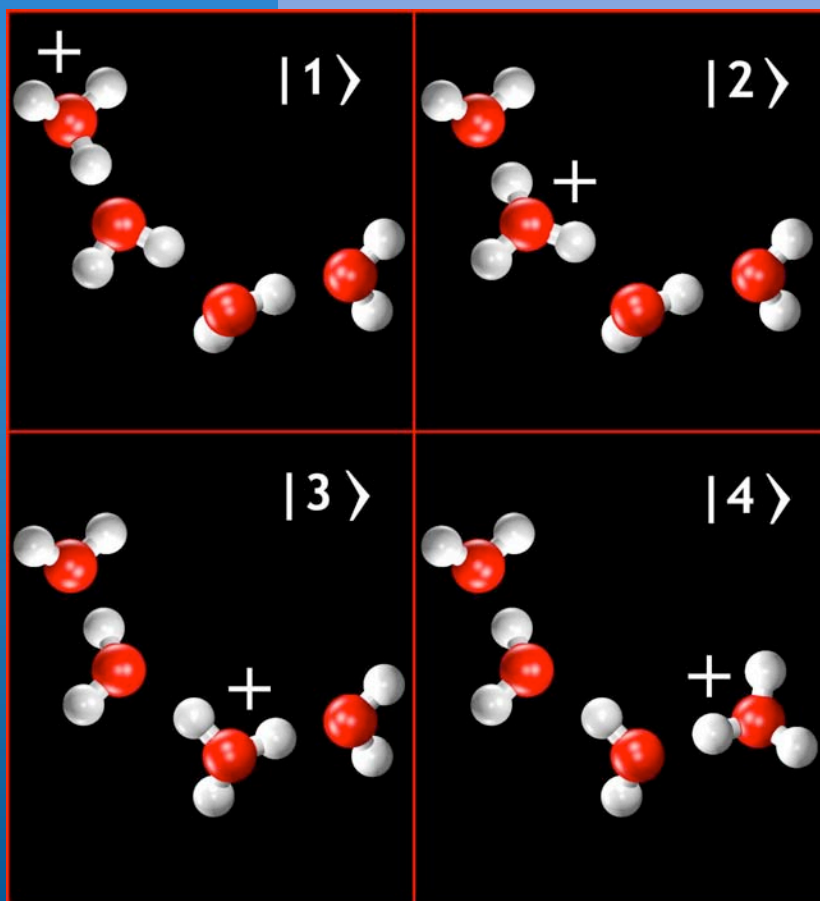
The Grotthuss Mechanism



Cation	Mobility $\text{cm}^2 \text{V}^{-1} \text{sec}^{-1}$
NH_4^+	0.763×10^{-3}
Na^+	0.519×10^{-3}
K^+	0.762×10^{-3}
H^+	3.620×10^{-3}

- The **unusually high diffusion** rate of an excess proton is attributable to the Grotthuss Mechanism (i.e. “chemical diffusion”).
- A **big challenge** for MD simulation because the **bonding topology changes with time**.

Multi-State Empirical Valence Bond Method (MS-EVB)



- Example at left for a **proton wire**
- Form the EVB matrix for all nuclear configurations:

$$H = \begin{bmatrix} H_{11} & V_{12} & V_{13} & V_{14} \\ V_{21} & H_{22} & V_{23} & V_{24} \\ V_{31} & V_{32} & H_{33} & V_{34} \\ V_{41} & V_{42} & V_{43} & H_{44} \end{bmatrix}$$

- The off-diagonal terms **allow transformations** between states
- In the bulk phase there are **many such possible states (30+)**

Schmitt and Voth, *J. Phys. Chem. B* 102, 5547 (1998).

Schmitt and Voth, *J. Chem. Phys.* 111, 9361 (1999).

Day, et al, *J. Chem. Phys.* 117, 5839 (2002). (MS-EVB2)

(MS-EVB3 soon)

(See also work of Warshel and Borgis)

MS-EVB Ground State Energy and Forces

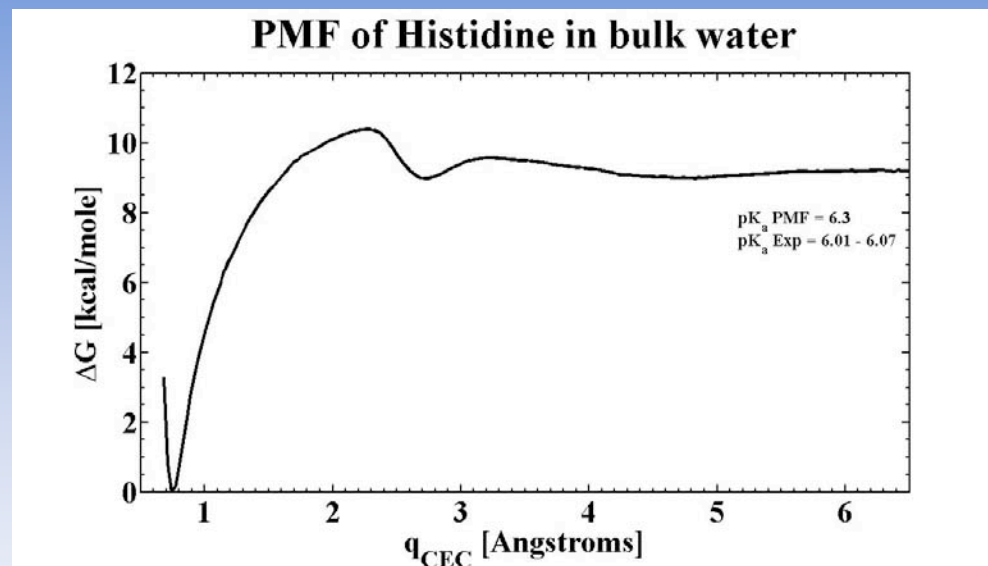
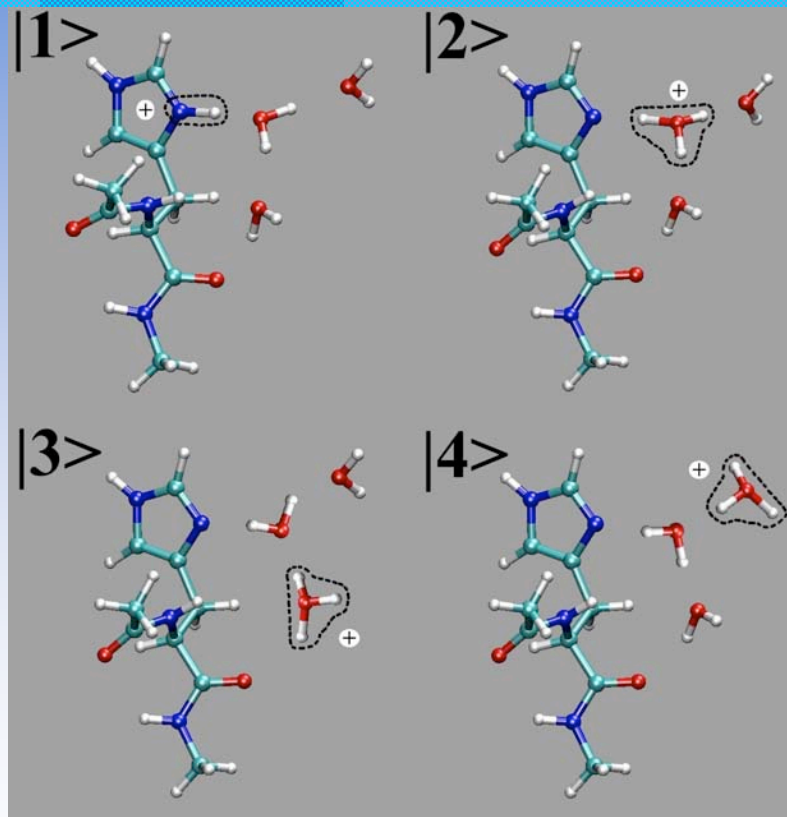
- The energy for an instantaneous configuration is given by the **lowest eigenfunction of the MS-EVB matrix**:

$$E_0(\mathbf{x}) = \sum_{m,n}^{N_{EVB}} c_m^0 c_n^0 H_{mn}(\mathbf{x})$$

- The **forces** are obtained from the Hellmann-Feynman Theorem:
- This forms the underlying basis for an MD algorithm with **explicit proton transport** (including Grotthuss hopping).

$$F_i(\mathbf{x}) = - \sum_{m,n}^{N_{EVB}} c_m^0 c_n^0 \frac{\partial}{\partial x_i} H_{mn}(\mathbf{x})$$

Extension to Ionizable Groups



- **Example: The histidine amino acid.** Such groups are responsible for the exchange of protons with the solvent (water)

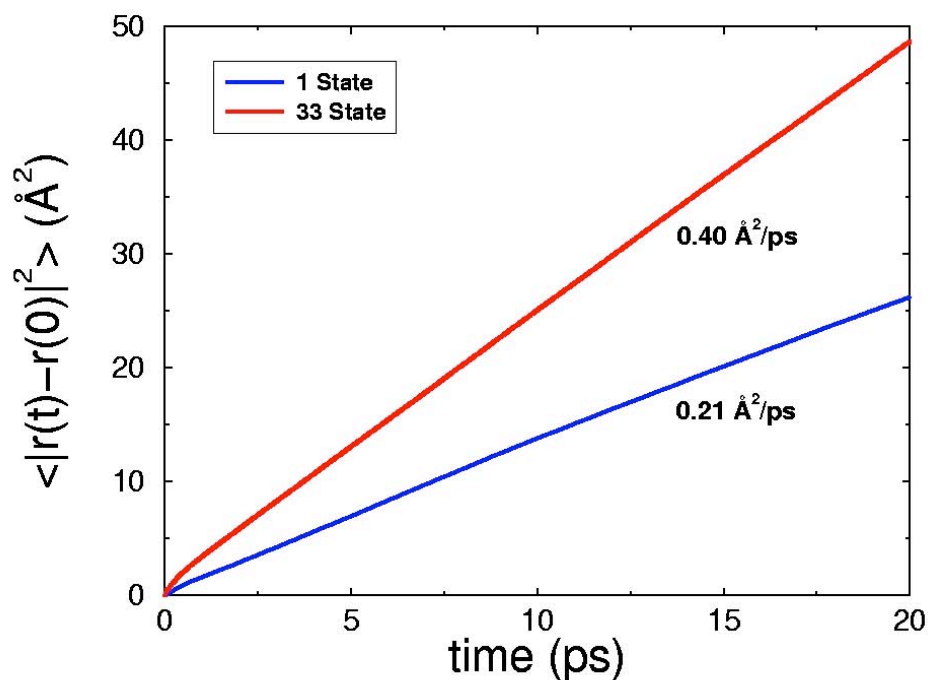
C. M. Maupin, A. Soudakov and G. A. Voth
(to be published)

M. Cuma, U.W. Schmitt, and G.A. Voth, *Chem. Phys.*, 258, 187 (2000).

M. Cuma, U.W. Schmitt, and G.A. Voth, *J. Phys. Chem. J. Phys. Chem.* 105, 2814 (2001).

Excess Proton Self-Diffusion Constant (MS-EVB2)

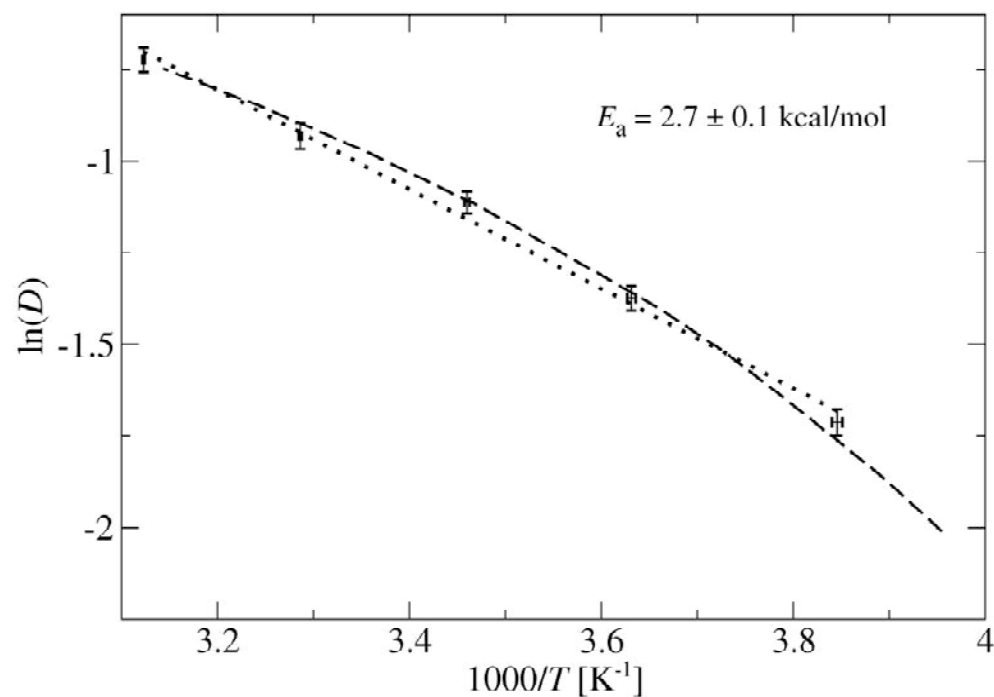
Experiment = 0.9 Å²/ps (Quantum Enhancement)



$$q_{CEC} = \bar{r}_N - \sum_i^{n_{EVB}} c_i^2 \bar{r}_i$$

\bar{r}_i = center of charge
of EVB state i

Activation Energy for Proton Transfer

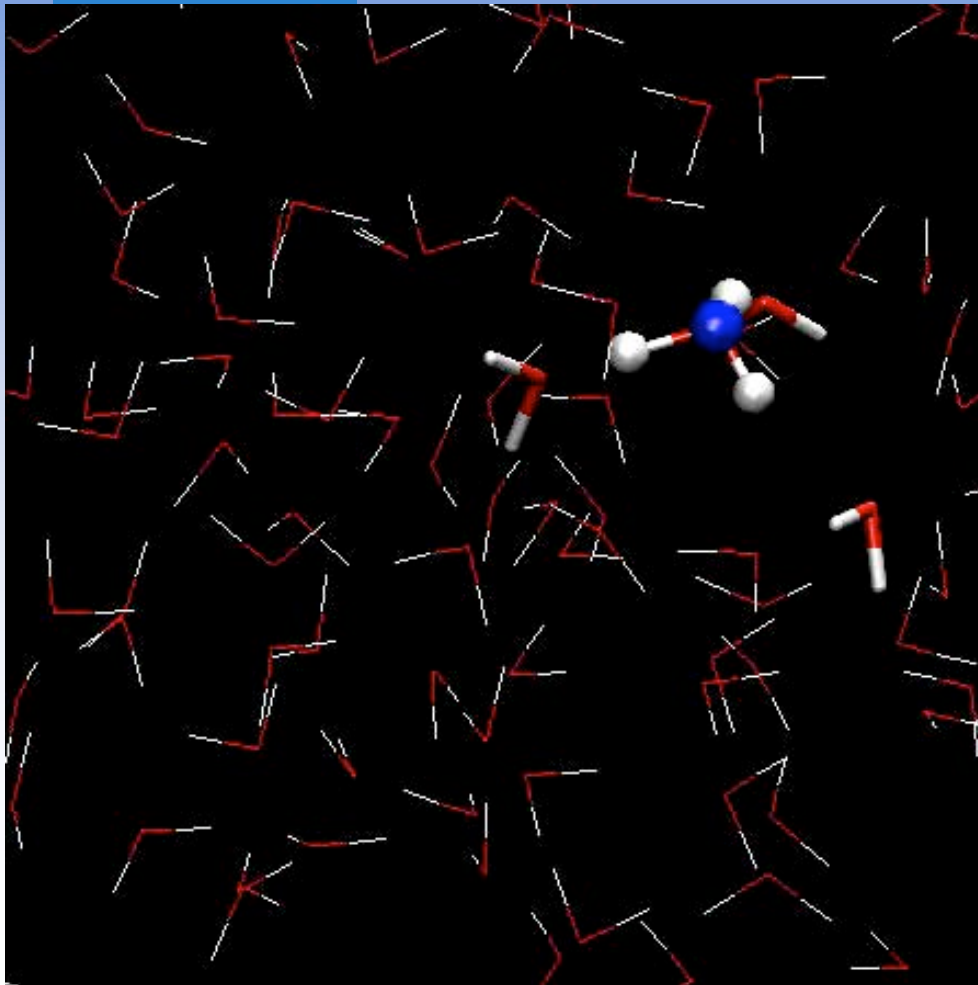


- MS-EVB2 Arrhenius curve around 300K

- Experiment:
~ 2.5 kcal/mole

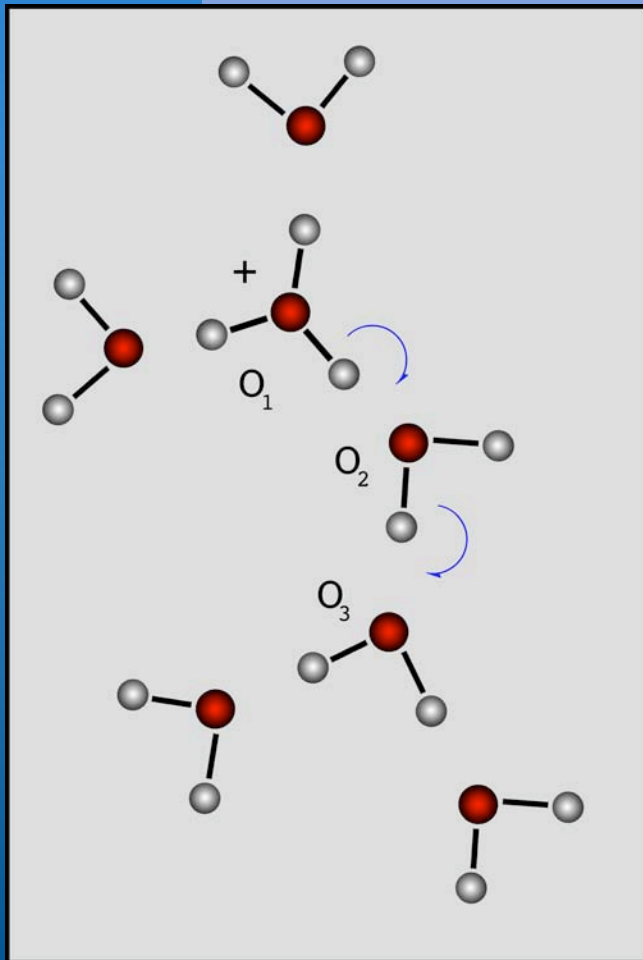
[Cornish and Speedy, *J. Phys. Chem.*
88, 1888 (1984)]

Proton in Bulk Phase Water Simulation



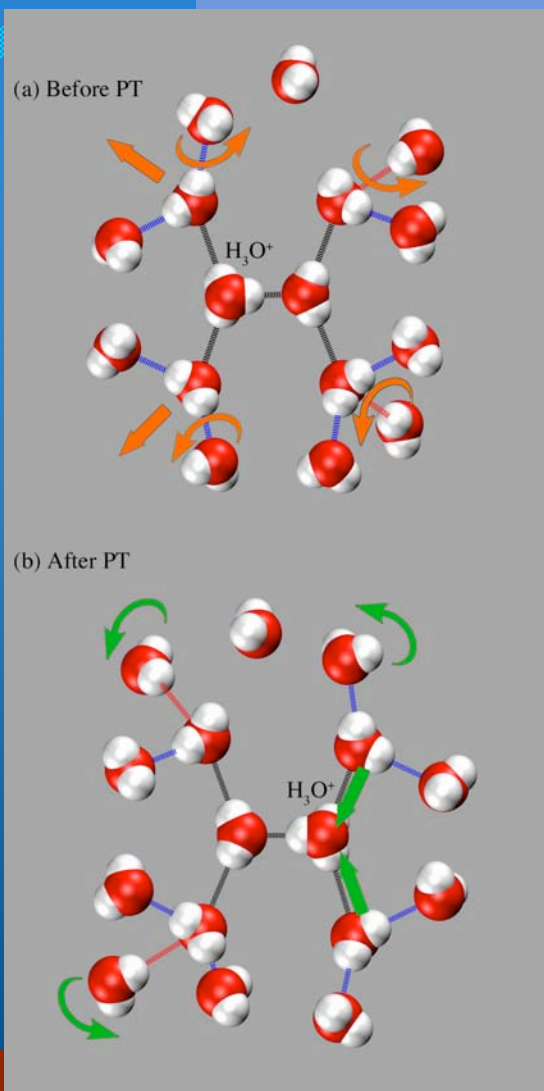
- Illustrative 7 ps trajectory of an excess proton in 125 waters at 300K.
- Four largest EVB states are explicitly shown, the largest (in blue) drawn as the hydronium
- **Completely deterministic trajectory for the underlying forces**
- **Hopping not really a “Moses Mechanism”**

What is the Proton Transport “Process”?



- **The “Moses Mechanism” (Agmon):** Involves the breaking and formation of single hydrogen bonds, owing to the different coordination number of water and hydronium. Also suggested by Parrinello and co-workers (Sprik, Tuckerman, Marx, etc).

The Proton Transport Mechanism

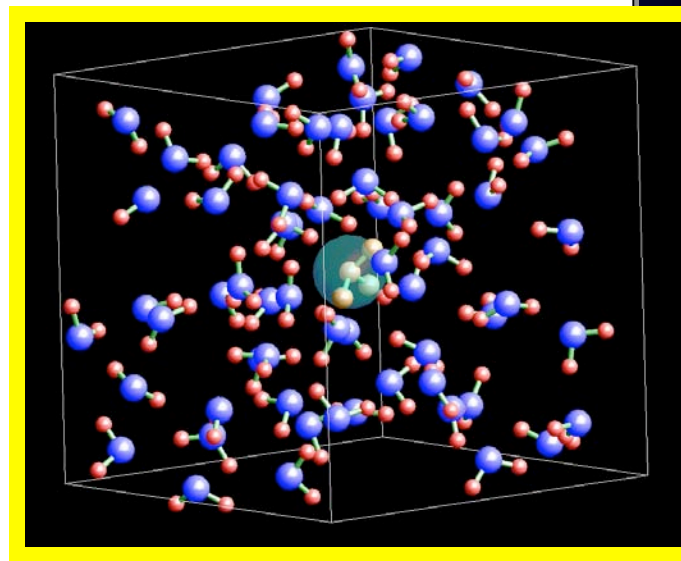


- Analysis of **many** hopping events using Pauling bond order analysis for the h-bonds.
- **NOT** a simple h-bond-breaking mechanism. Instead, a **“local-delocalized” h-bond rearrangement mechanism**.
- H. Lapid, N. Agmon, M. K. Petersen, and G. A. Voth, JCP 122, 014506(1-11) (2004).

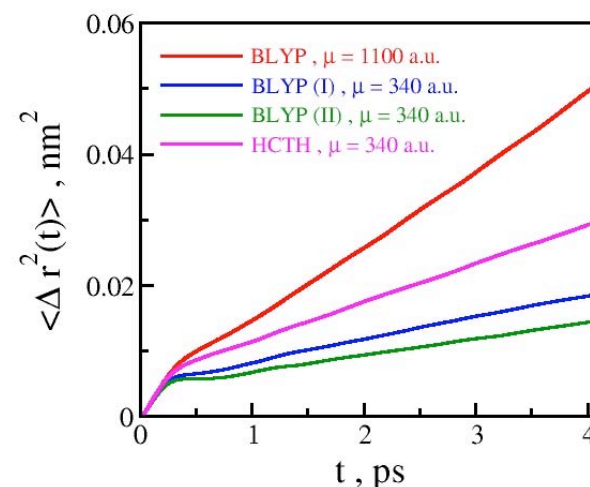
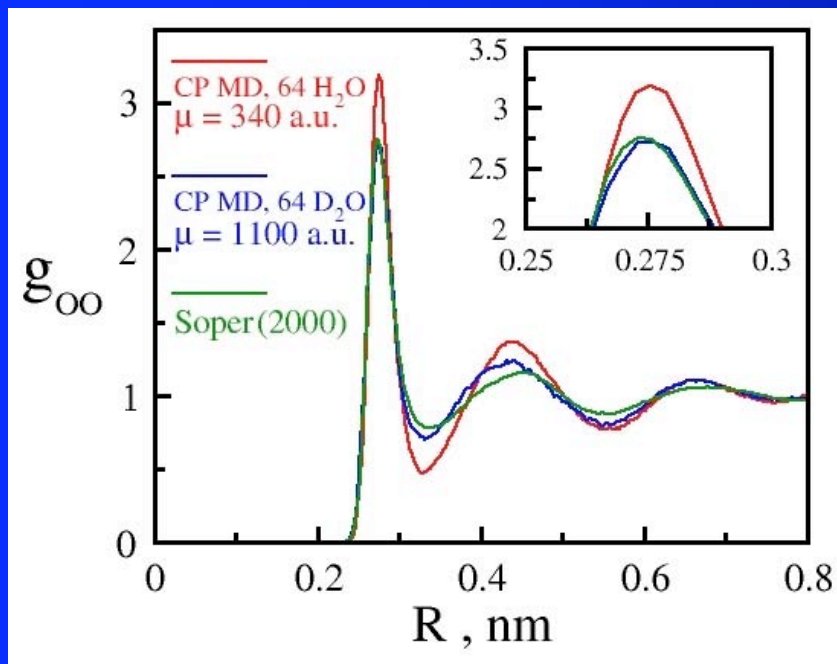
CPMD Simulations of an Excess Proton in Water

System Setup and Simulation Detail:

- **Car-Parrinello MD** simulation in plane wave basis
 - **DFT** with the **BLYP, HCTH** gradient corrected **XC** energy functionals
 - Electron-ion interaction by **Troullier-Martins PP**
 - Plane-wave cutoff of **80 Ry**
- **64 H₂O** , **H⁺** , $a = 1.2429$ nm ($\rho = 997$ kg/m³)
- Time step **3 a.u. (0.072 fs)**
- **$\mu = 340$ a.u.** (dynamics close to BO surface)
- **4 ps** equilibration run (microcanonical)
- **~ 40 ps** production runs (microcanonical)
- **No thermostat** for electronic degrees of freedom
- Ionic **$T_{\text{average}} = 297-302$ K**



A Problem: The Underlying Structural and Dynamical Properties of CPMD Water



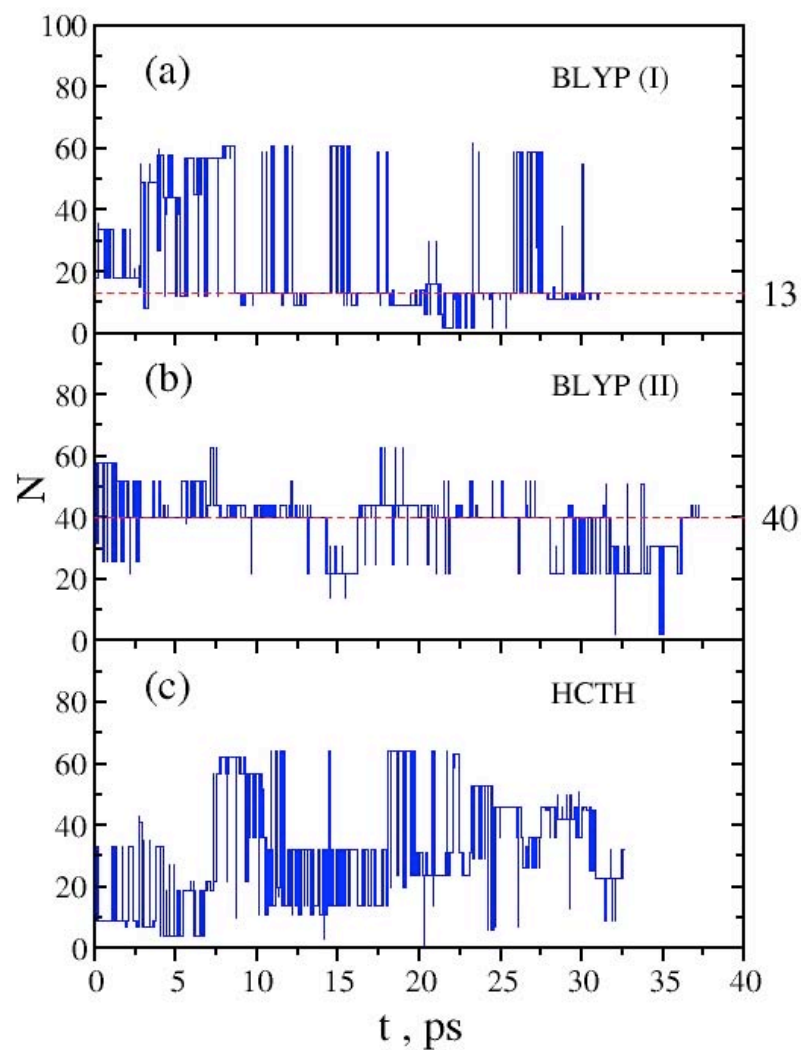
• Oxygen-Oxygen RDFs

- Our results are consistent with those of Galli, Pratt, Sprik, Parrinello, and their co-workers.

- MSD of oxygen atoms (BLYP)
Experiment : $D = 2.3 \times 10^{-9} \text{ m}^2/\text{s}$
 $\mu = 340$ a.u. : $D = 0.4 \times 10^{-9} \text{ m}^2/\text{s}$

- MSD of oxygen atoms (HCTH)
 $\mu = 340$ a.u. : $D = 1.0 \times 10^{-9} \text{ m}^2/\text{s}$

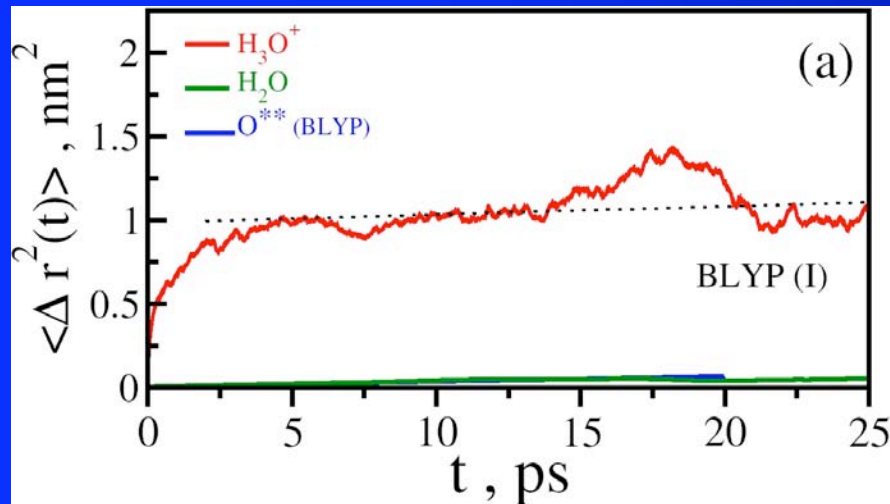
The Proton Hopping Dynamics



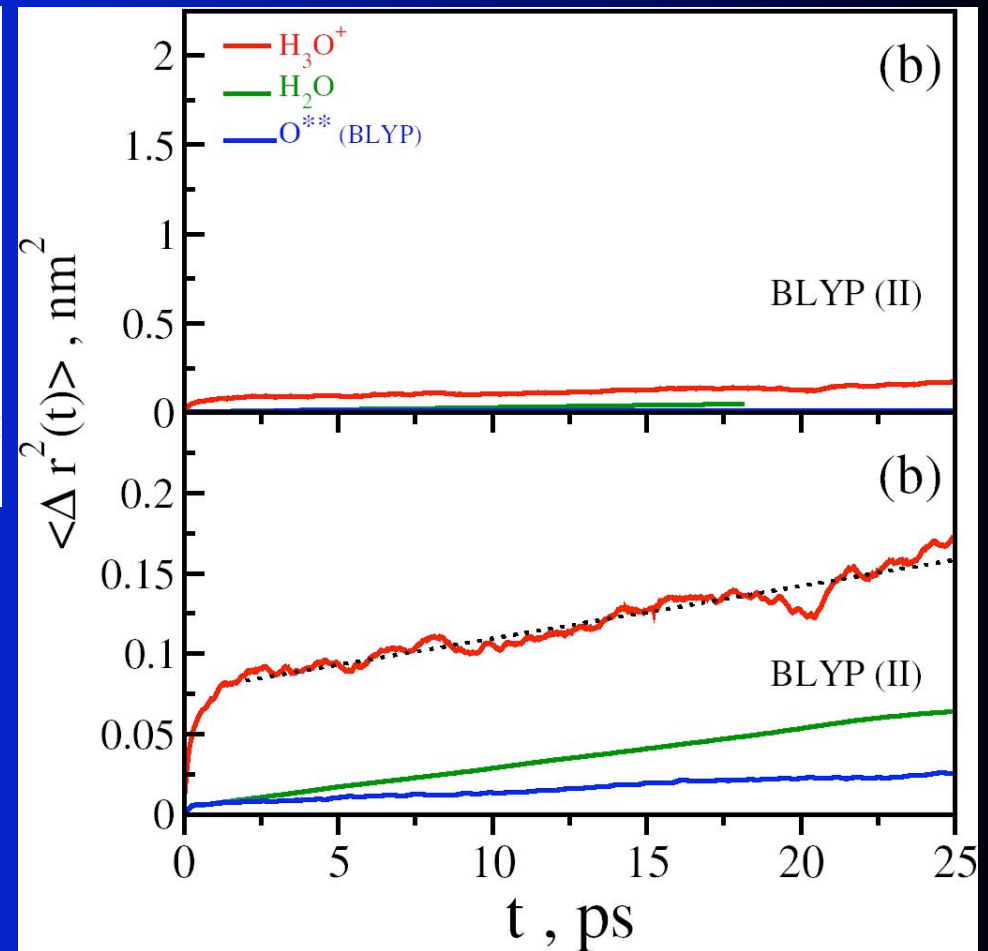
- **Index N of the oxygen atom carrying the excess proton as a function of time.**

- **In the two BLYP CPMD simulations the excess proton never really leaves one of the water molecules because of the unphysically 'sticky' h-bond network.**

Excess Proton Diffusion Rate in CPMD



The excess proton diffusion is defined by the underlying water diffusion and especially the ‘special’ water molecule O^{**} .

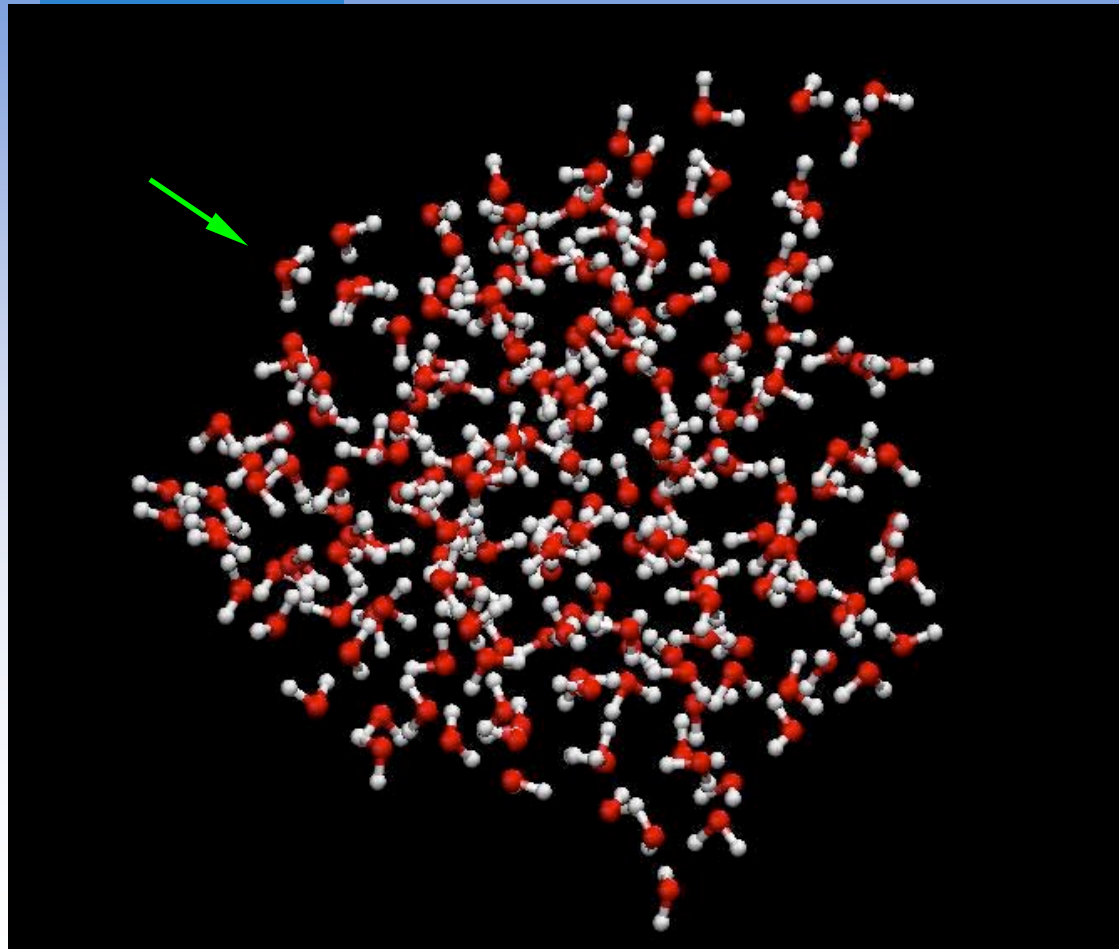


HCTH CPMD is much better than BLYP, but still not especially good.

Proton Solvation: The Hydronium Cation as an “Amphiphile”

- **Results first presented at the August 2002 ACS Meeting (Boston). Clearly not a case of “publish in haste”.**
- **Extensive tests have been performed for three different MS-EVB models, as well as *ab initio* MD simulations. (Recent apparent experimental confirmation)**
- **Water Liquid/Vapor Interface:** M. K. Petersen, S. S. Iyengar, T. J. F. Day, and G. A. Voth, “The Hydrated Proton at the Water Liquid/Vapor Interface,” *J. Phys. Chem. B* **108**, 14804 (2004).
- **Protonated Water Clusters:** S. S. Iyengar, T. J. F. Day, and G. A. Voth, “On the Amphiphilic Behavior of the Hydrated Proton: An *Ab Initio* Molecular Dynamics Study,” *Int. J. Mass. Spec.* **241**, 197-204 (2005).

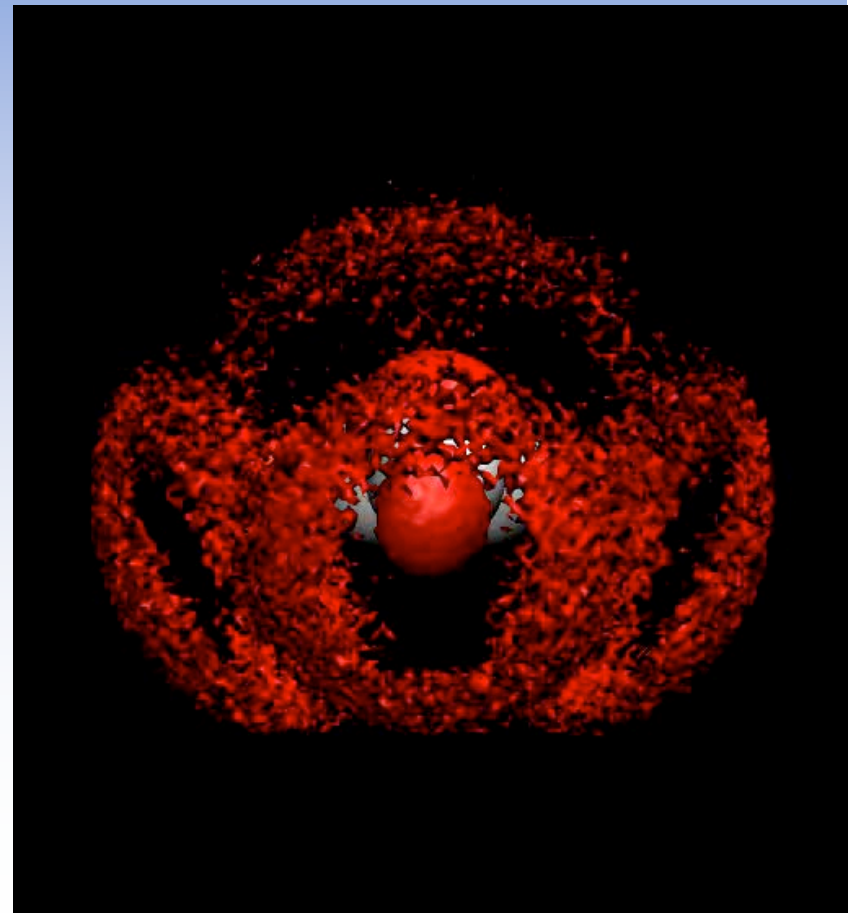
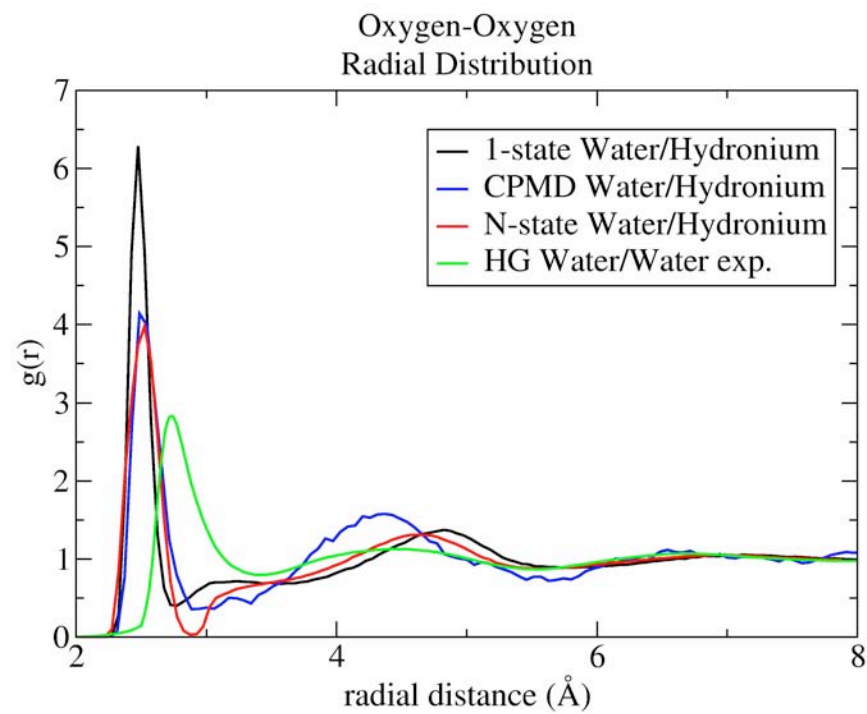
Large Protonated Water Clusters



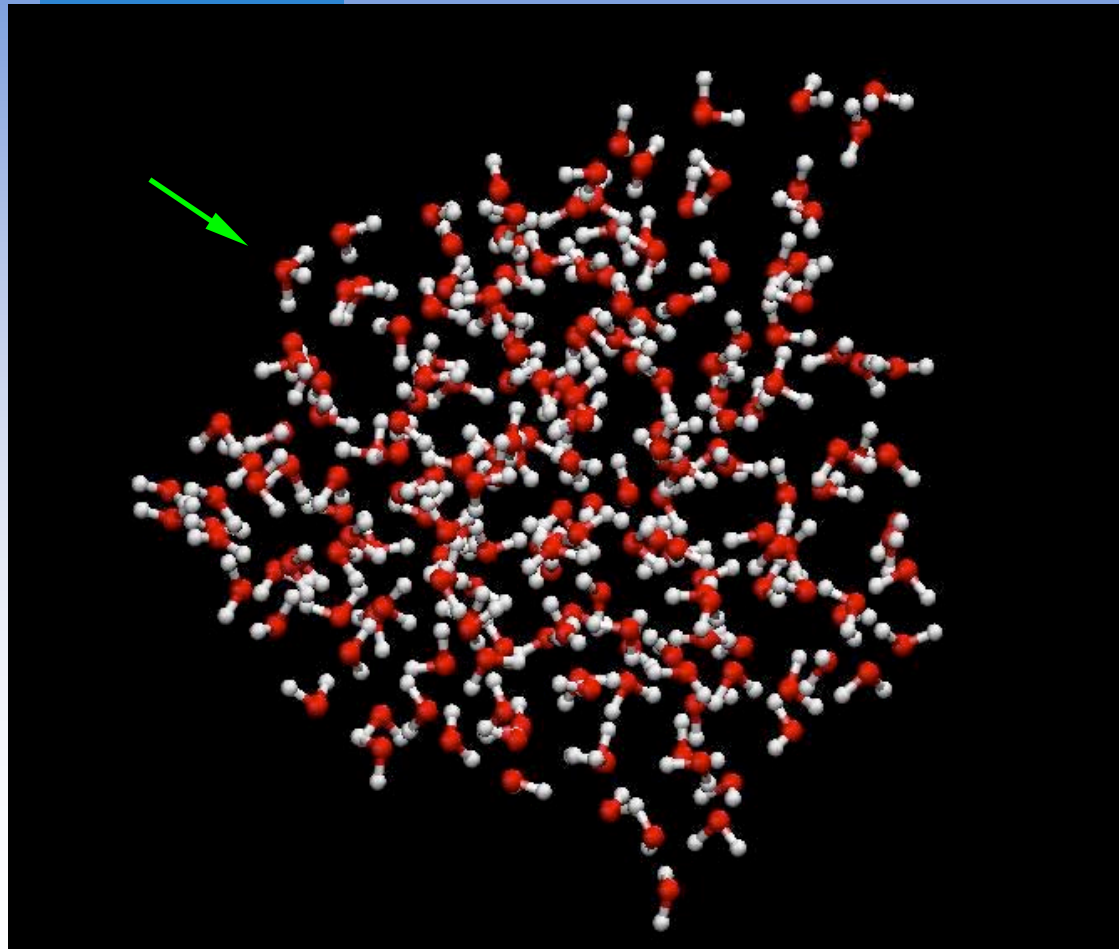
- **200 water cluster**
- **Eigen cation**
on the surface

Oxygen Density distribution around the Hydronium in Bulk Water

- The oxygen density around the hydronium cation is highly anisotropic

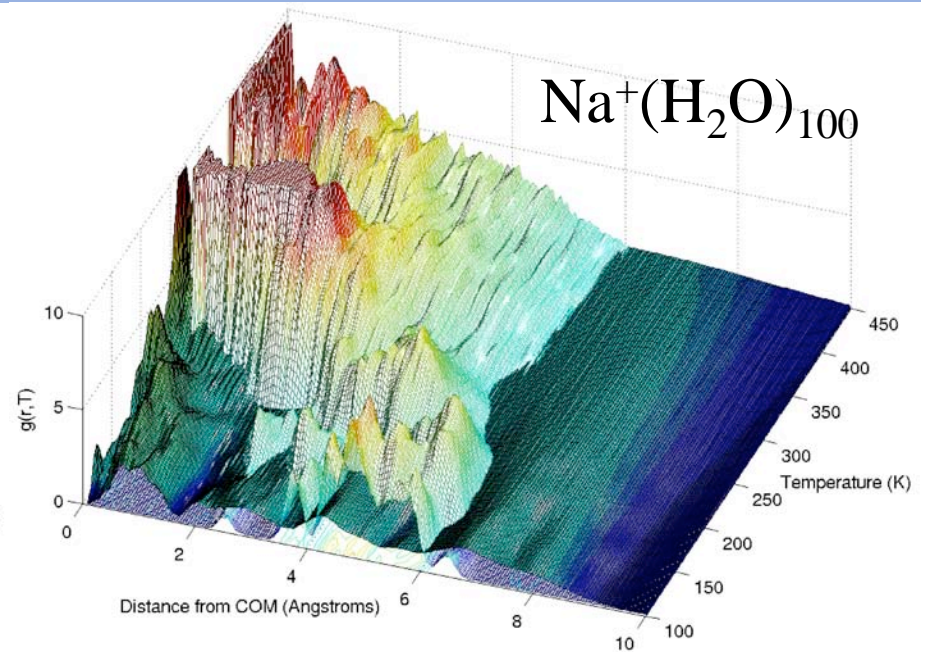
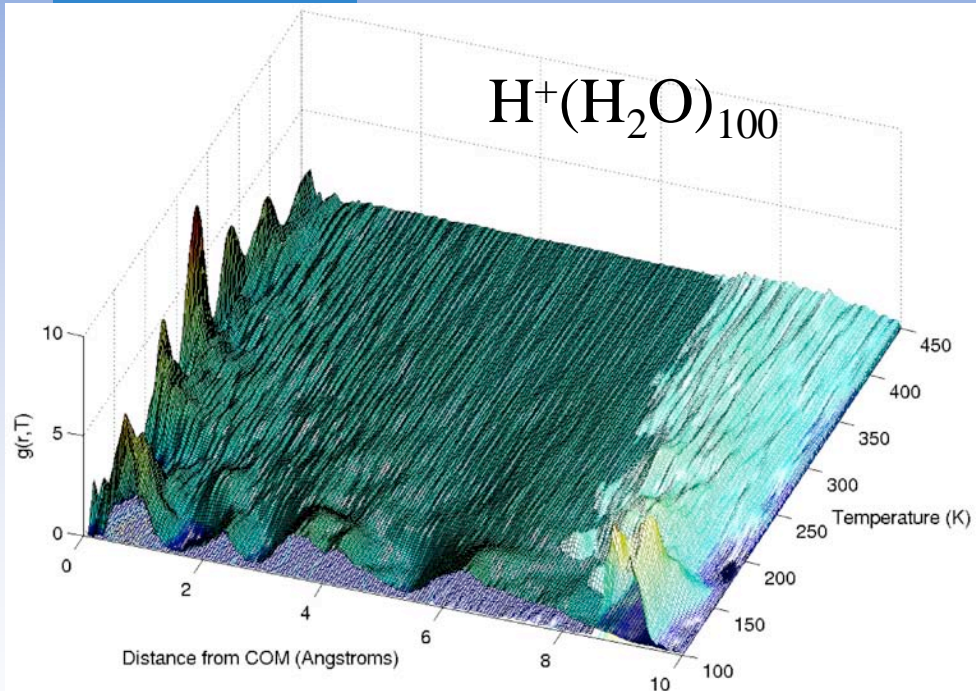


Hydronium versus Other Simple Cations

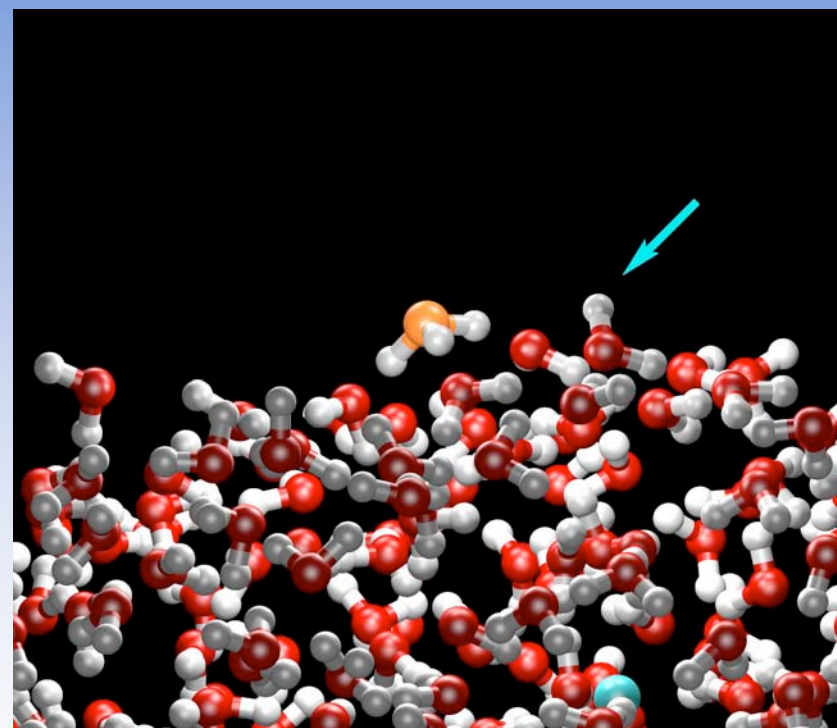
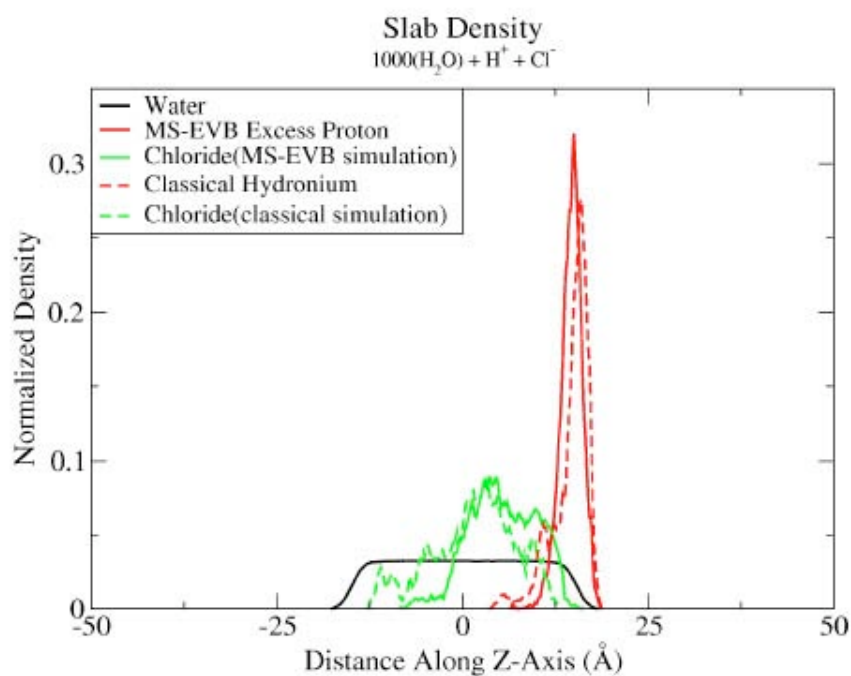


- **Na⁺ in the interior** (depending on temperature)
- **Eigen cation on the surface**

H⁺ vs. Na⁺ in 100 Water Clusters



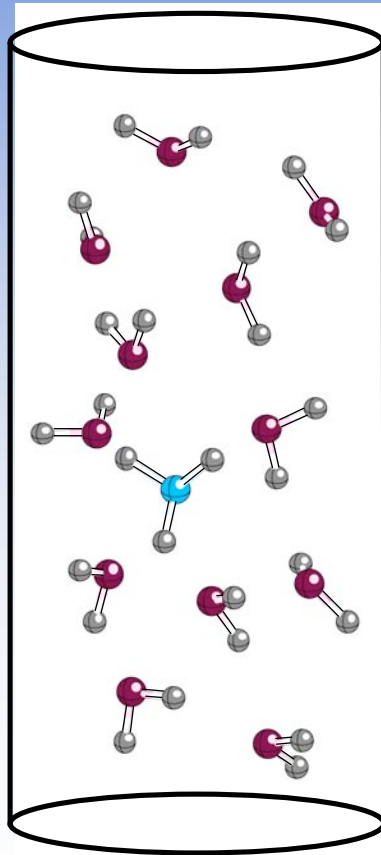
Excess Proton at the Water-Air Interface



M. K. Petersen, S. S. Iyengar, T. J. F. Day, and G. A. Voth, "The Hydrated Proton at the Water Liquid/Vapor Interface," J. Phys. Chem. B **108**, 14804 (2004).

***Recent experimental confirmation by Saykally, Allen, and their co-workers**

PT in Confined Geometries (Tubes)



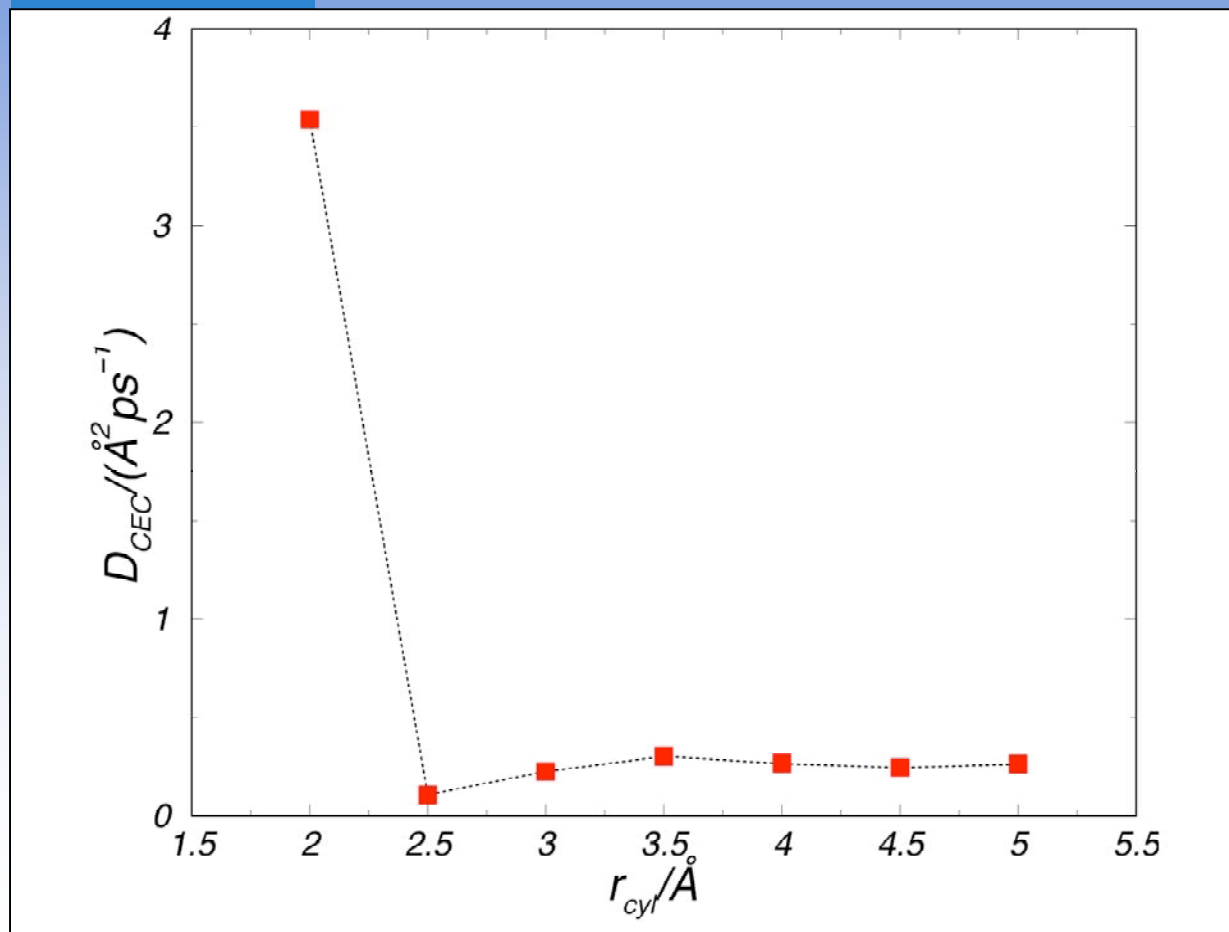
$$V_{\text{water}} = A \exp[-B(r_o - r_{\text{cyl}})]$$

r_o = oxygen-axis distance

r_{cyl} = cylinder radius

M. Brewer, U.W. Schmitt, and G.A. Voth,
Biophys. J. **80**, 1691 (2001).

Channel Axial Proton Diffusion Constants

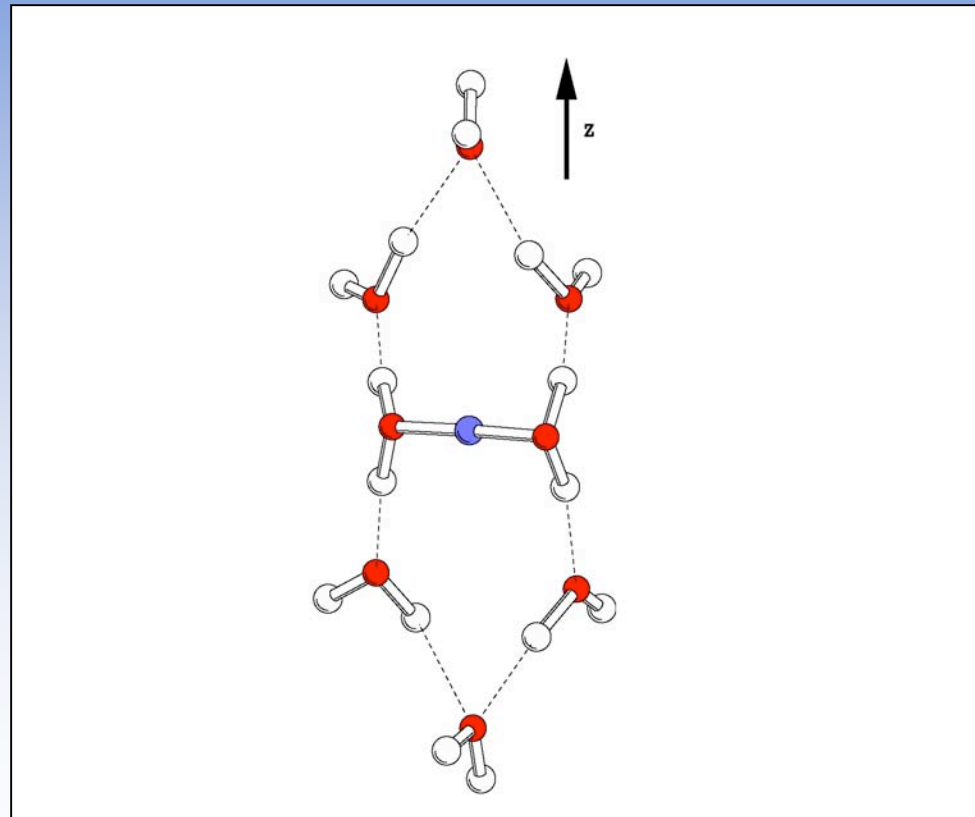


- Proton transport in the narrow channel about 20 times higher than bulk water.*

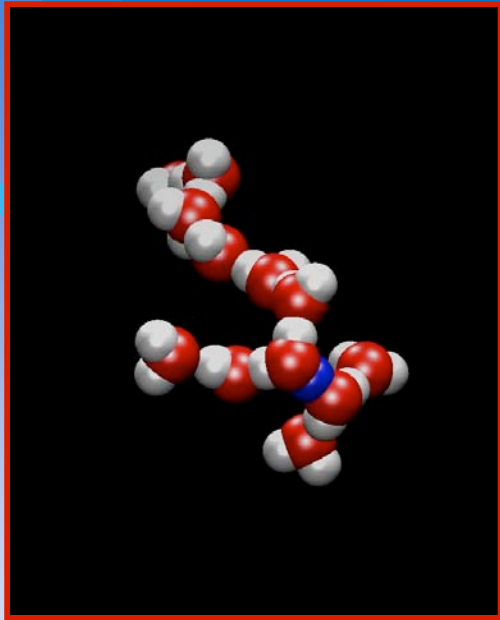
*M. Brewer, U.W. Schmitt, and G.A. Voth, *Biophys. J.* 80, 1691 (2001).

Note: Dellago, Naor, and Hummer subsequently found a factor of 40 in carbon nanotubes (PRL, 2003).

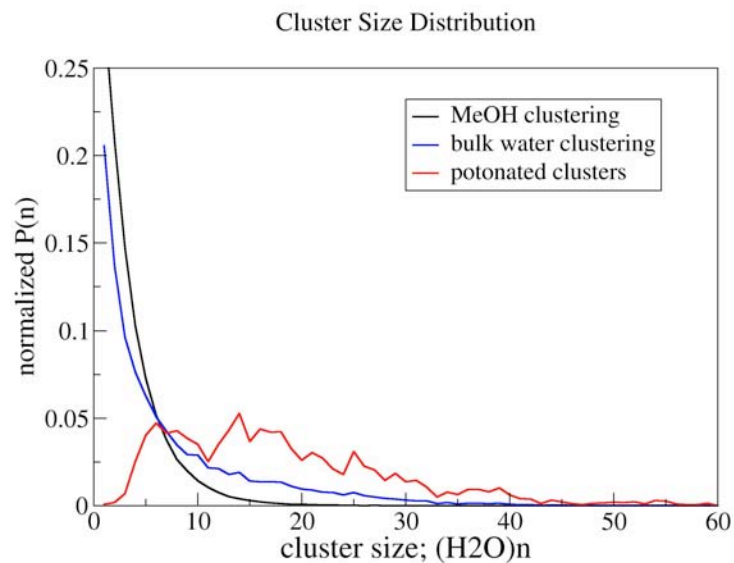
Stable Structure in 2.5 Å Radius Channel



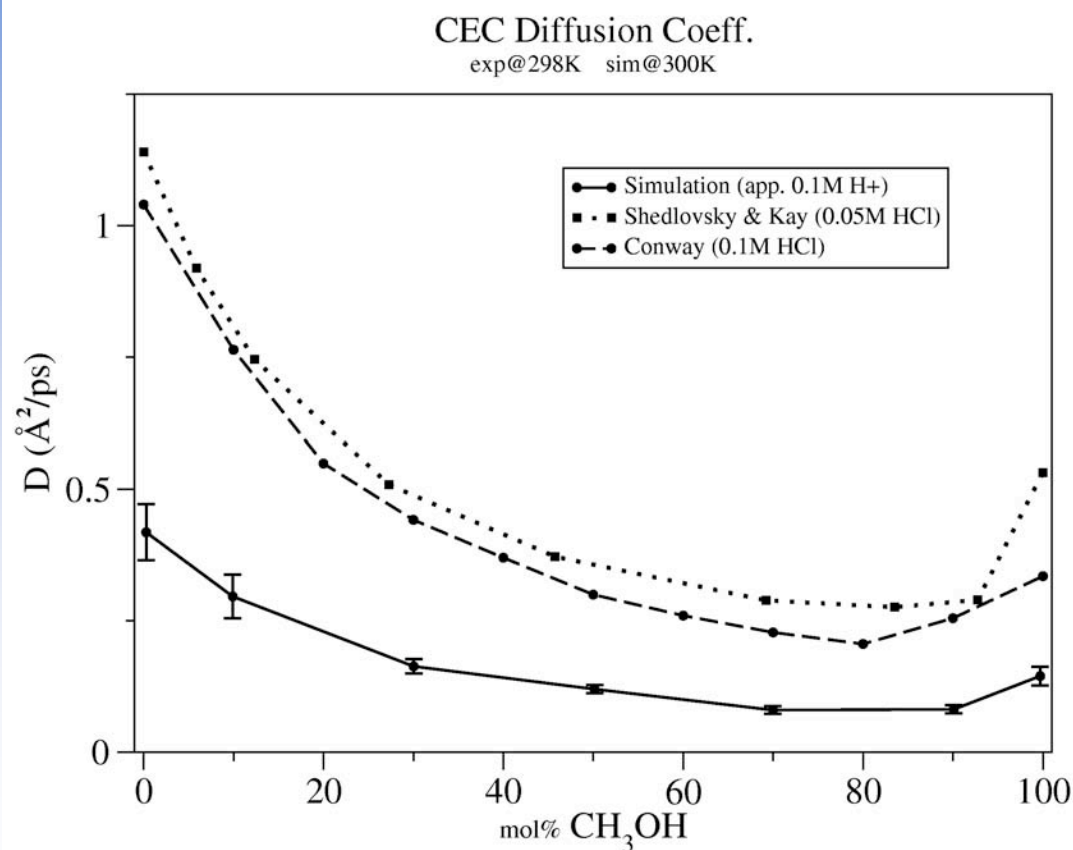
Excess Proton in Water-Methanol Solutions



- Pictured is a representative ‘cluster’ with the excess proton in blue.
- Cluster size distribution for a 70% MeOH/H₂O solution.
- Size distribution data was averaged from 10,000 instantaneous configuration collected over 2 ns.
- Probability for bulk clustering is that of a cluster with size n containing a randomly chosen molecule.
- Probability for proton clustering is that of a cluster with size n containing a proton averaged over all proton containing clusters.

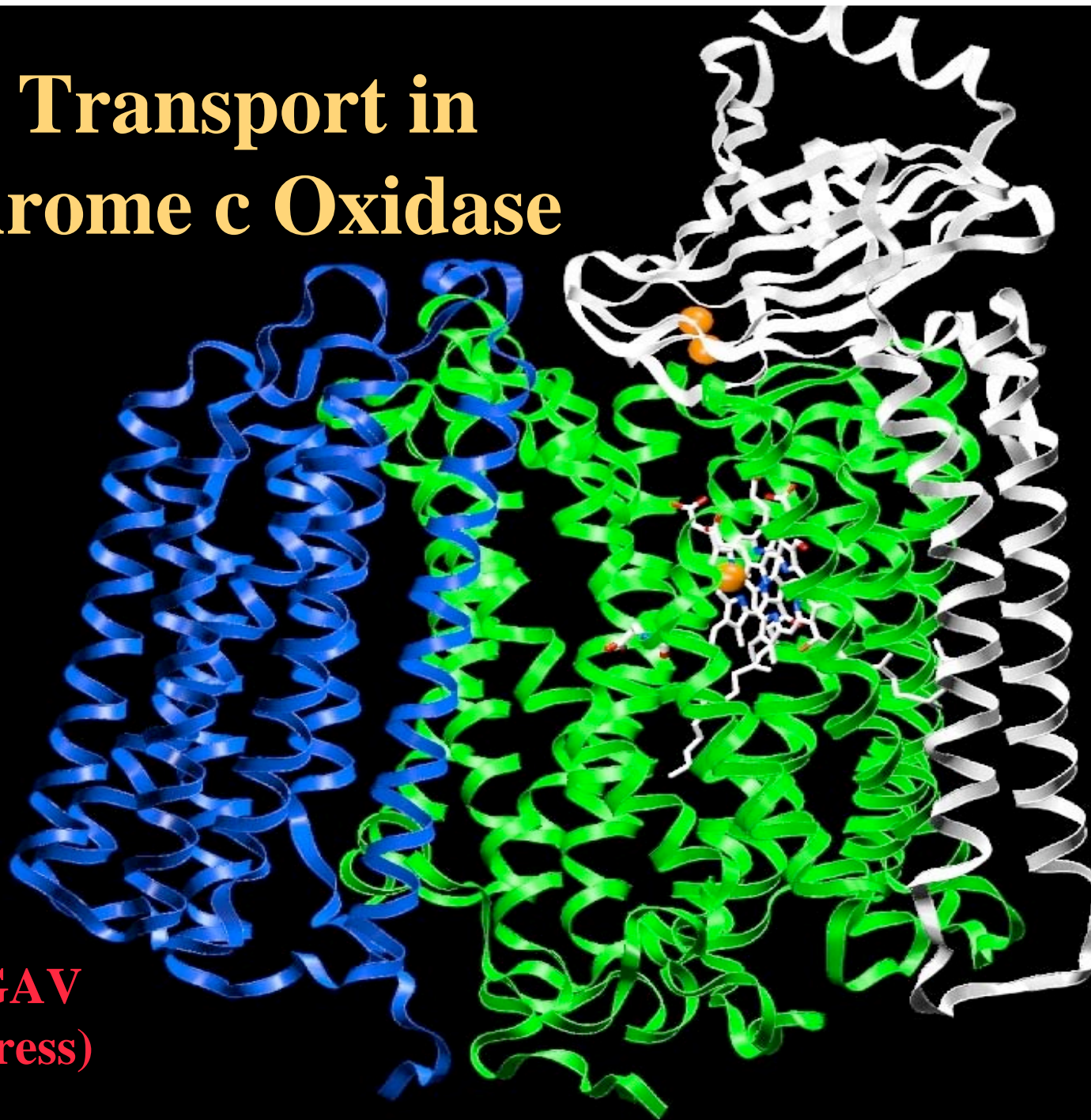


Proton Diffusion in Methanol/Water Mixtures



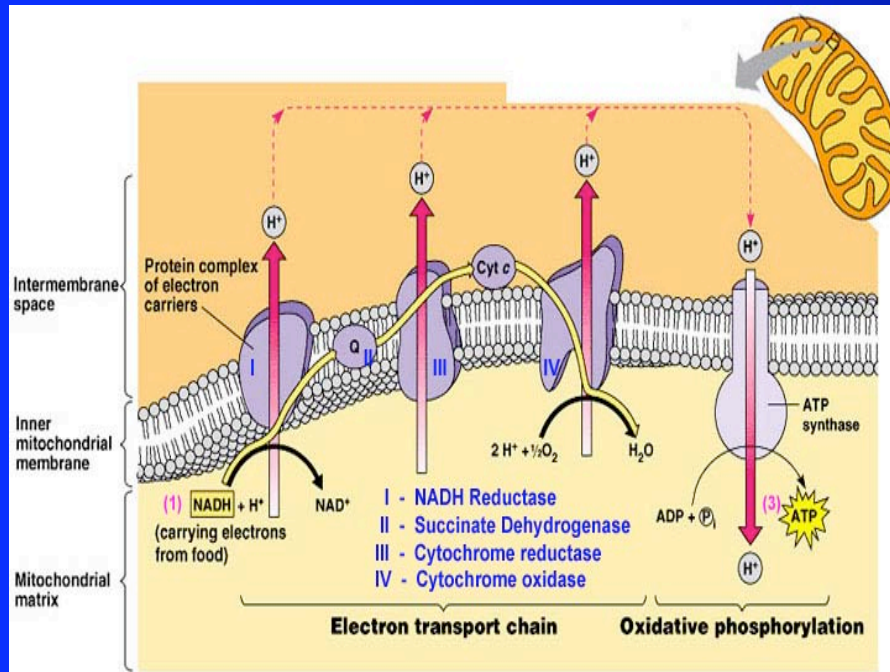
- **MS-EVB2 simulation curve should be shifted upwards by a factor of ~2 to correct for the missing quantum effect.**
- **343 total molecules at ambient densities. 5 ns of MD data for each point.**
- **In these simulations, no shuttling of the excess proton is allowed through methanol molecules, yet the curve still turns upward for low water concentrations.**

Proton Transport in Cytochrome c Oxidase

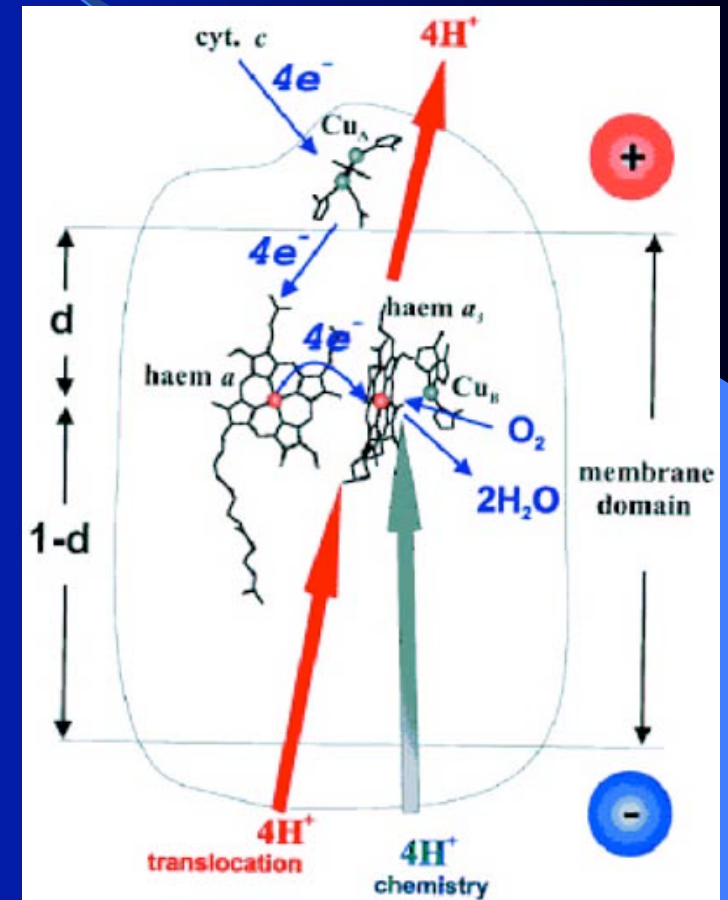


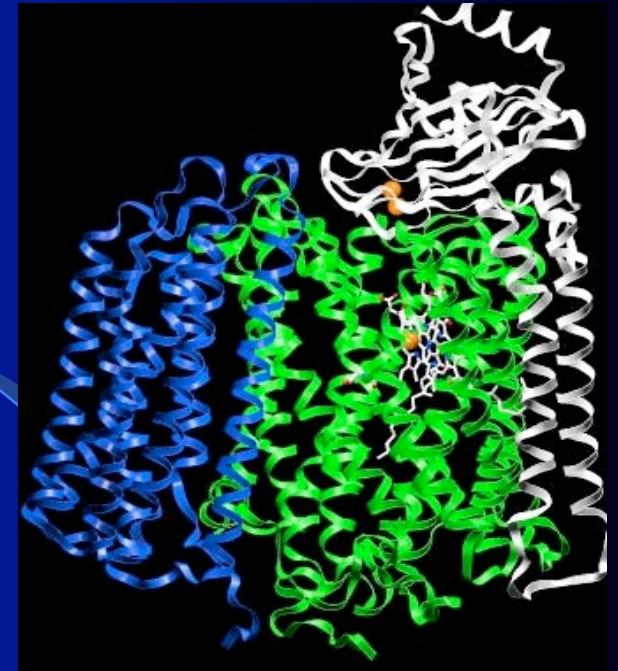
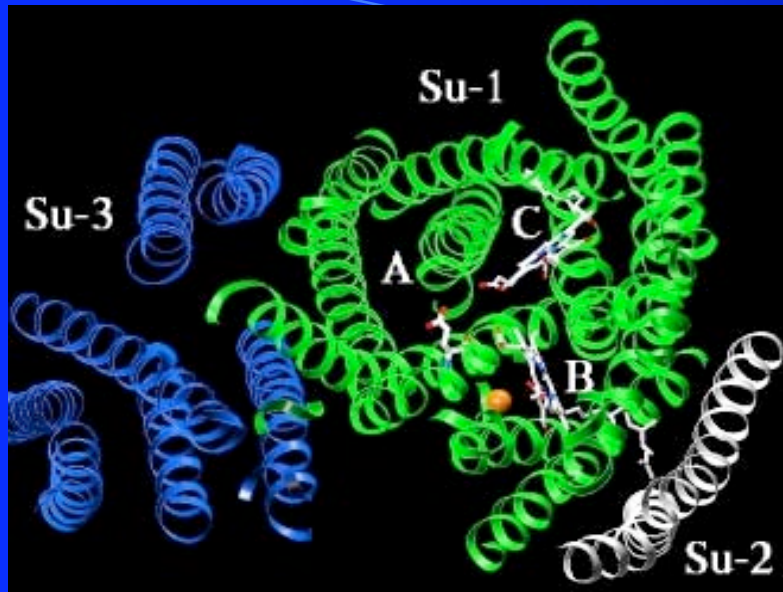
J. Xu and GAV
PNAS (in press)

Cytochrome *c* Oxidase: the function



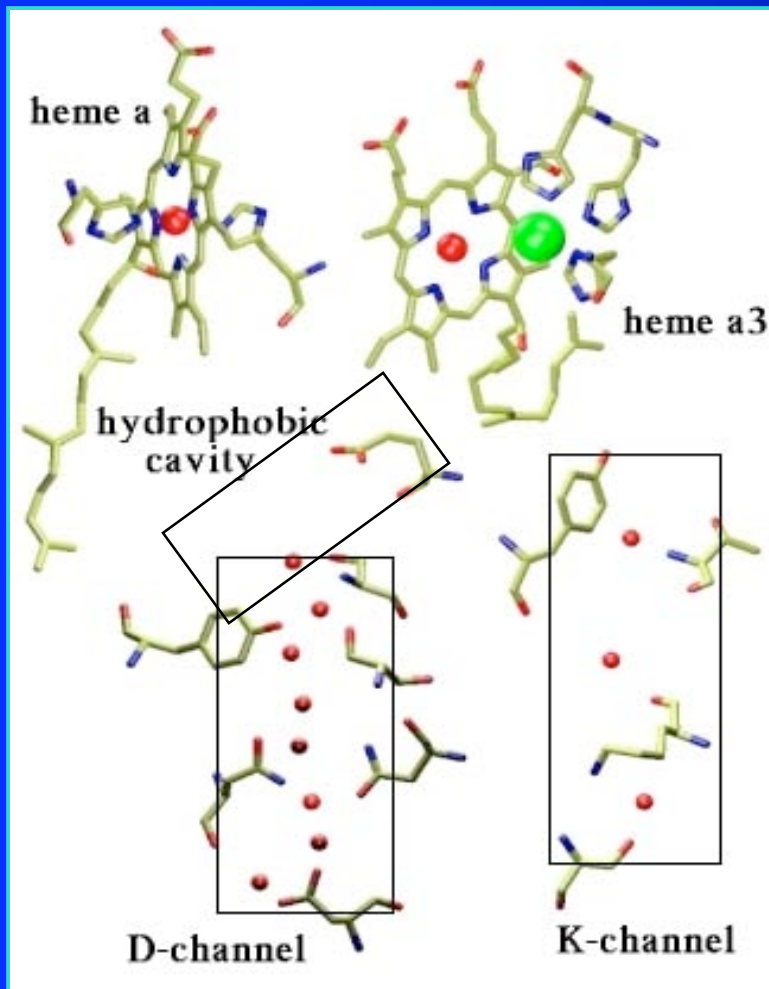
- Cytochrome *c* Oxidase (CcO) is the terminal enzyme in the respiratory chain.
- The movement of protons generates electrochemical proton gradient.
- CcO is a redox-linked proton pump.
- $\text{O}_2 + 8\text{H}^+ + 4\text{e}^- \rightarrow 2\text{H}_2\text{O} + 4\text{H}^+$





- **Subunit III**
Its function remains enigmatic. It's not necessary for either electron transfer or proton translocation.
- **Subunit II**
Electron process transfer; 2 CuA atoms
- **Subunit I**
The largest and best conserved subunit of CcO; 2 proton channels; process is electron transfer and proton translocation.

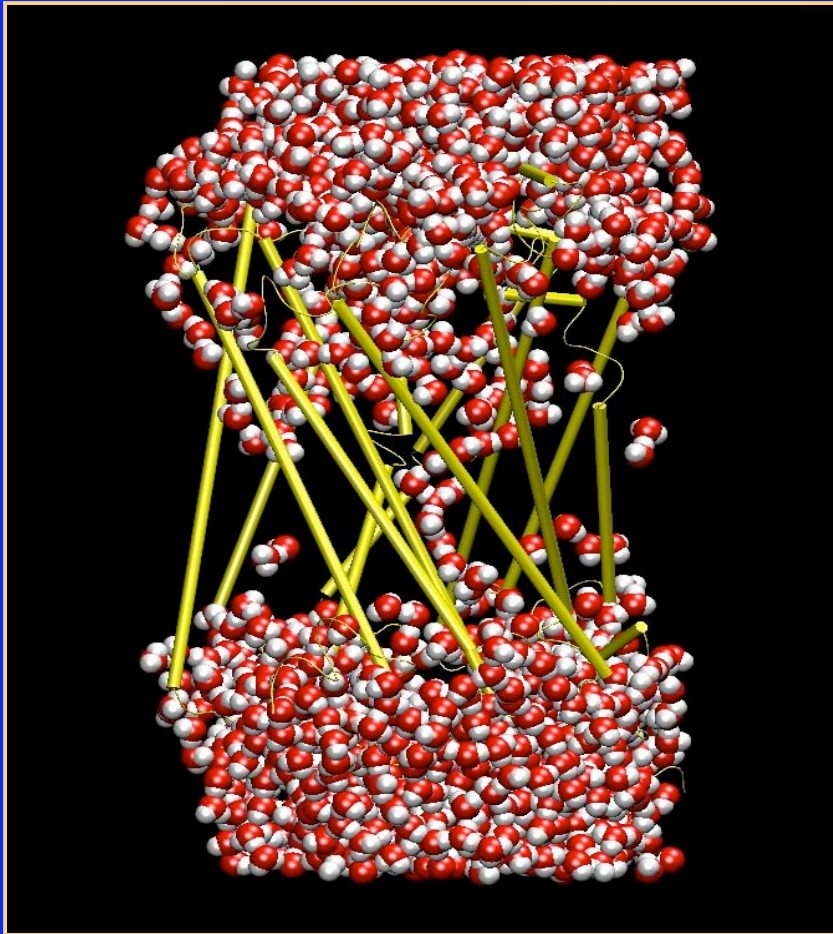
Proton Transport Pathways



- **K-channel**
Leads to the binuclear center via conserved residues Lys319, Thr316, Tyr244
- **D-channel**
conserved residues Asp91, Asn80, Asn98, Tyr19, Ser101, Ser157, waters.
- **Hydrophobic cavity**
connecting D-channel and Glu-242, no fixed crystal waters, but electron density of solvent molecules was observed.
- **Beyond Glu242**
the pathway becomes less clear.....

- Multiple proton channels
- Different functional roles for D, K channel

MD Simulation Set-up



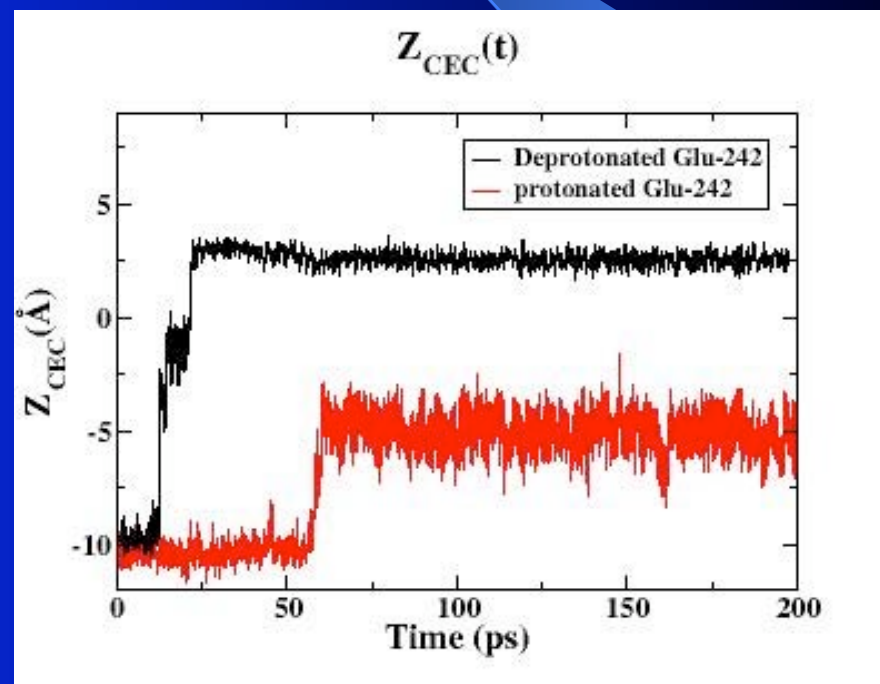
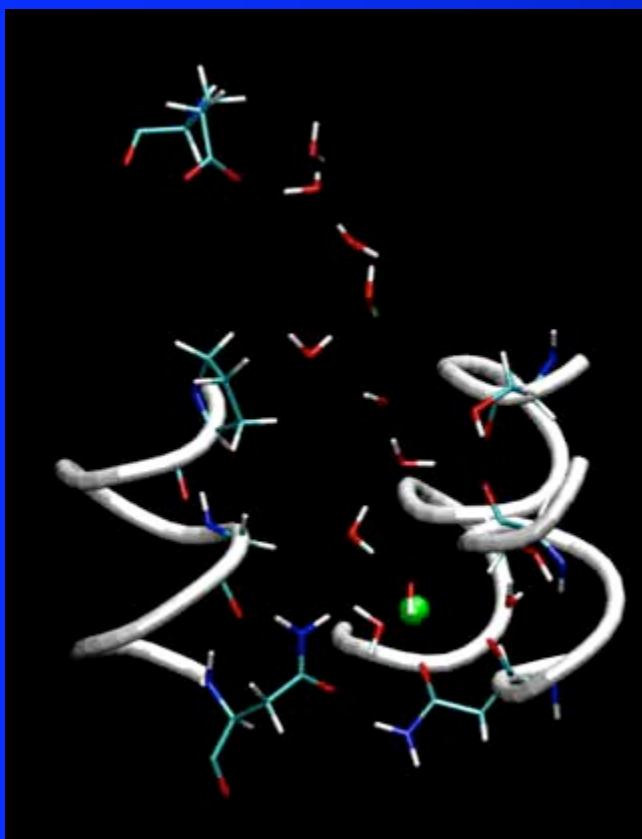
System setup:

- X-ray crystal structure: 1v54 (fully oxidized state)
resolution: 1.8Å
- Subunit I (514 a.a), 375 crystal waters, 960 added waters, total system size: ~12,000 atoms
- C-alpha atoms except those lining the channel are restrained.
- Force constant= 1 kcal/mol/Å²
- Equilibration: 300k, NVT, PBC, 1.6ns

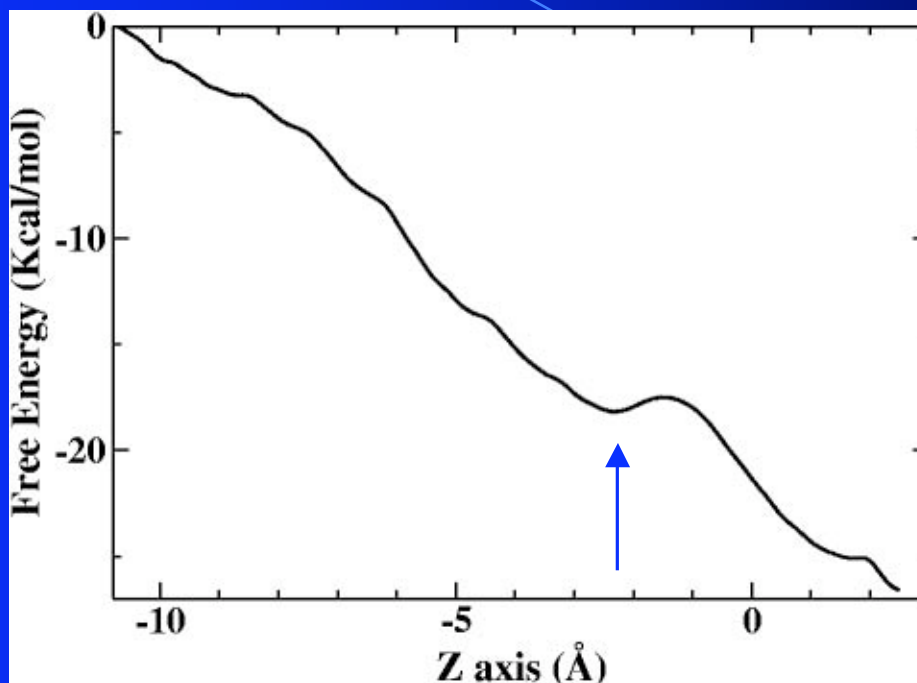
MS-EVB simulations (D-channel)

GLU-242: the branching point; the conformational isomerization of its side chain is consistent with a proton shuttling role.

- Simulation below: Unprotonated Glu-242



Potential of Mean Force (PMF) Calculation



Potential of mean force (PMF) for proton translocation along the z-axis of the CcO D-pathway with Glu-242 in its deprotonated state.

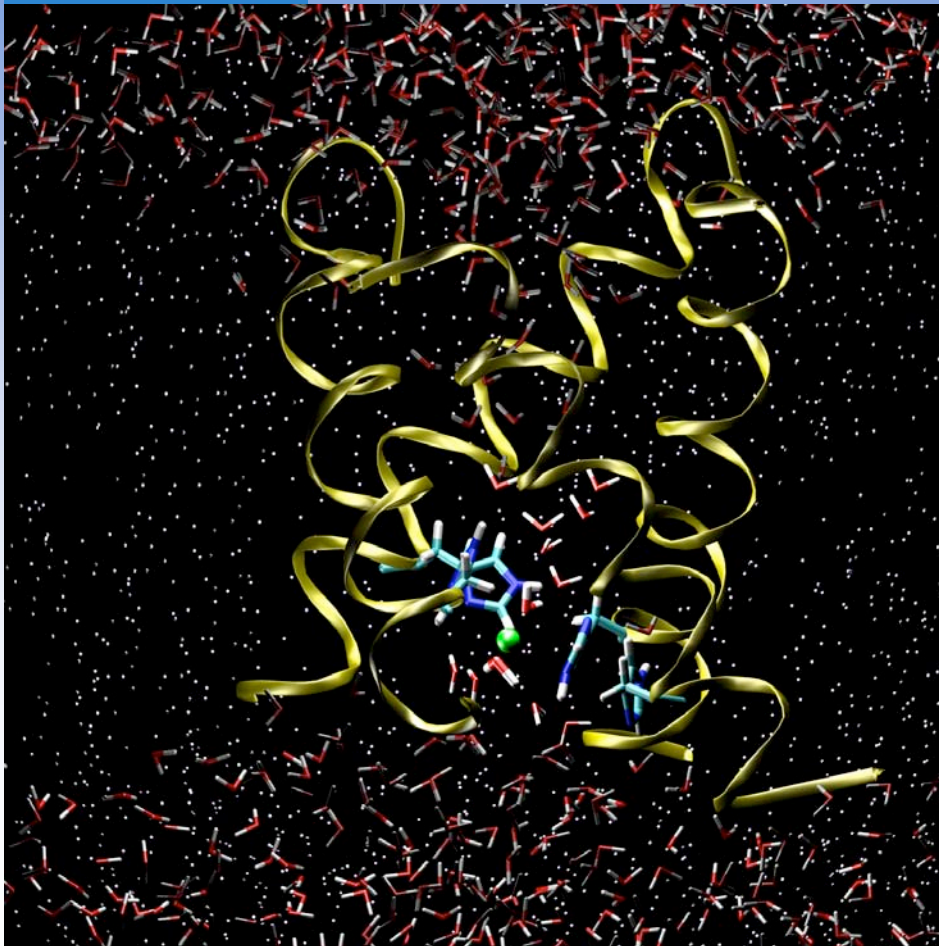
Umbrella sampling: 700ps/window, 52 windows, window size 0.25 Å

“Two-step” PT Mechanism



The “proton trap”, primarily ascribed to the wide pore, may divide the D-pathway into two short hydrogen-bonded proton wires. The proton first transfers from Asp-91 at the beginning of the D-pathway to the “proton trap” region at the top of the first proton wire through a continuous hydrogen-bonded water chain. The second proton wire facilitates another fast transfer of the excess proton between the proton trap and Glu-242. The driving force for the second step PT is attributed to the protonation state of Glu242.

M2 Proton Channel in Influenza A



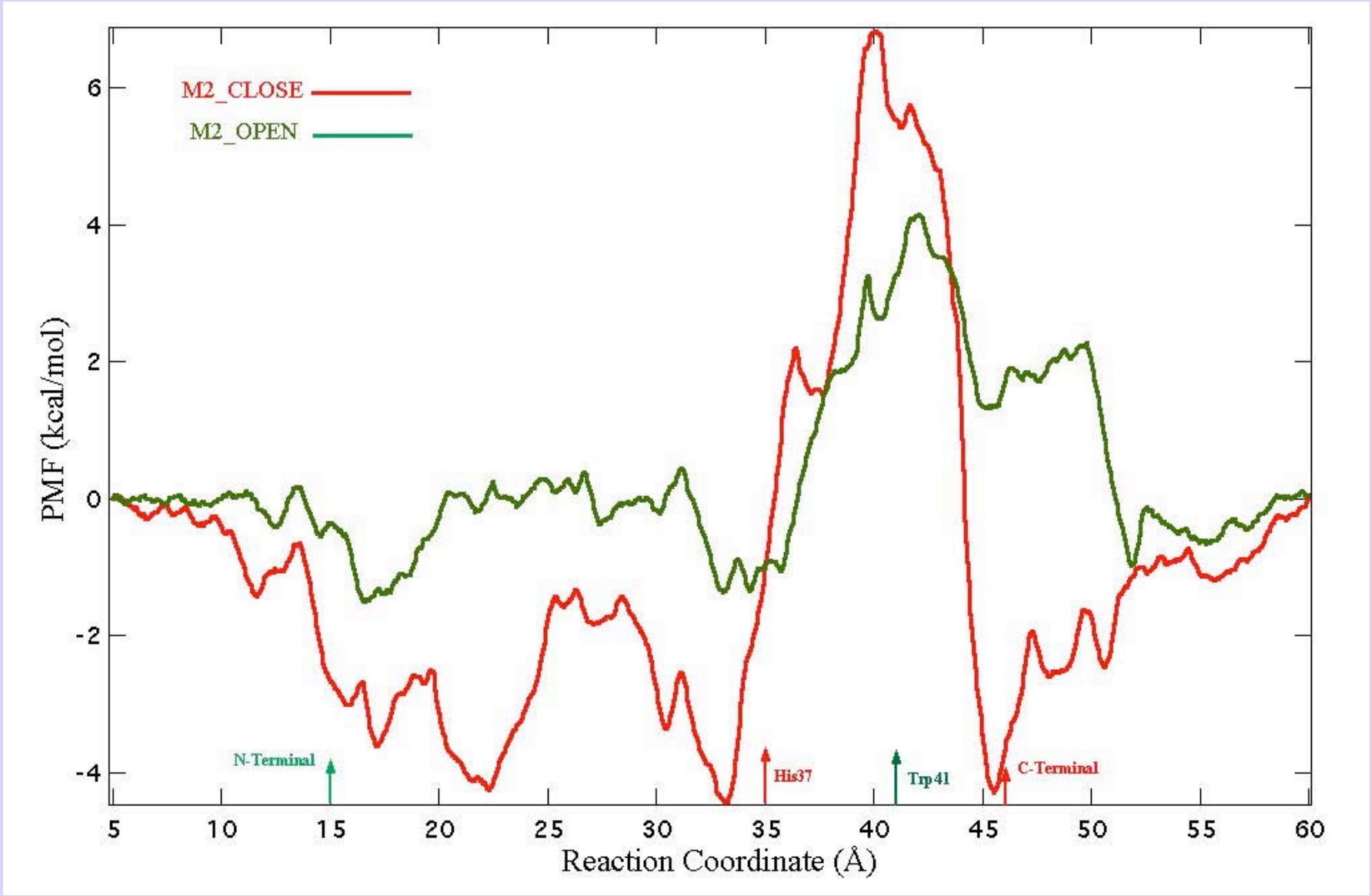
- Protons may transport via a “proton shuttle” or a “gating mechanism”
- **Protonation of histidine** residues is believed to lead to the opening of the channel in the latter

A. M. Smondyrev and G. A. Voth,
Biophys. J. 83, 1987 (2002)

Possible Open and Closed States of the M2 Channel

- All proposed PT mechanisms suggest that the protonation of His37 is responsible for opening the M2 channel. But we do not exactly know the protonation states of the four His37 residues in either open and close state.
- The (t60,t90) conformation with **four mono-protonated** His37 residues is proposed to be the most possible closed state structure. [(Y. Wu and GAV, *Biophys. J.* (submitted)].
- With only **one doubly-protonated** His37, PT takes place by hopping between two water molecules located at the opposite sides of the histidine gate. [Smondrev et al., *Biophysical J.* (2002)]

Proton Permeation Free Energy Profile for the M2 channel



Calculation of Proton Channel Conductivity

- 1-D Nernst-Planck Equation:

$$J = -D(Q) \frac{dP(Q)}{dQ} - P(Q) \frac{D(Q)}{k_b T} \frac{dW(Q)}{dQ}$$

where $D(Q)$ is the position-dependent diffusion constant as a function of reaction coordinate, $P(Q)$ is the probability density and $W(Q)$ is the equilibrium PMF. [Levitt, *Annu. Rev. Biophys. Chem.* (1986)]

- Maximum Conductivity:

$$g_{\max} = \frac{e^2}{k_B T L^2} \left\langle D(Q)^{-1} e^{+w(Q)/k_B T} \right\rangle^{-1} \left\langle e^{-w(Q)/k_B T} \right\rangle^{-1}$$

[Roux et.al, *J. Phys. Chem.* (1991)]

Proton Conductivity (PNP Analysis)

	Implicit-His37	Explicit-His37
Open	34.7 pS	$1.7 \times 10^{-3} \text{ pS}$
Closed	$3.20 \times 10^{-3} \text{ pS}$	$9.5 \times 10^{-11} \text{ pS}$
Open/Closed	1.08×10^4	1.8×10^7

$$1 \text{ pS} = 1 \text{ piconSiemens} = 1.0 \times 10^{-12} \text{ Ampere/Volt}$$

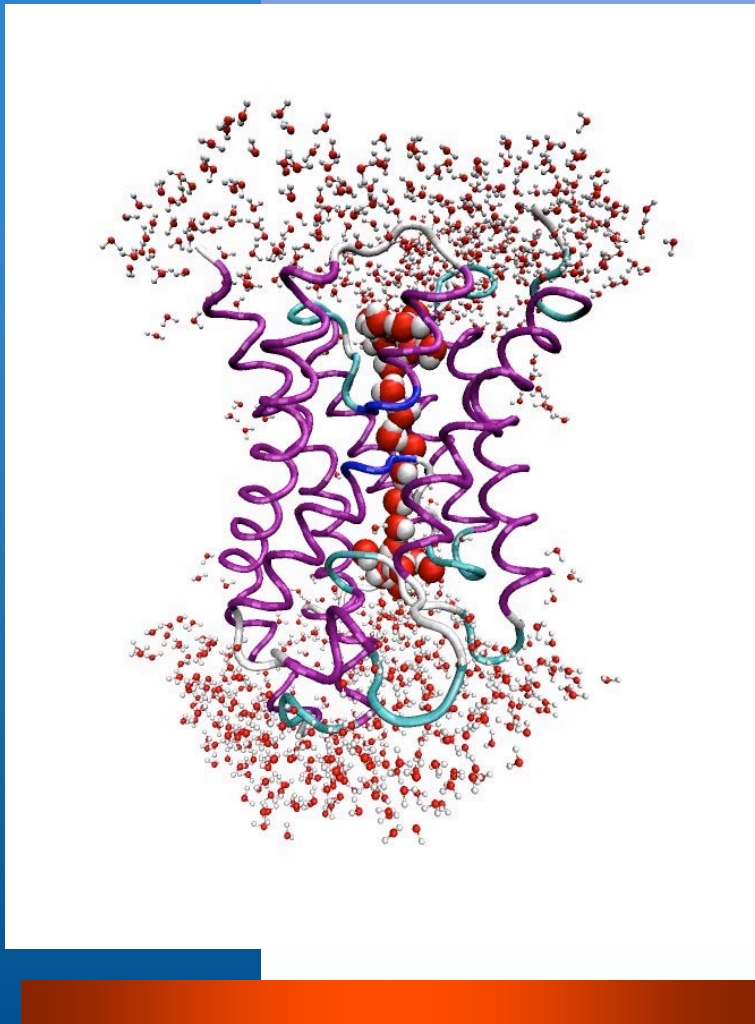
Experimental Conductivity for Open Single-M2 Channel
in DMPC lipid at PH=3:

6.0 pS

[Vijayvergiya et.al, *Biophys. J.* (2004)]

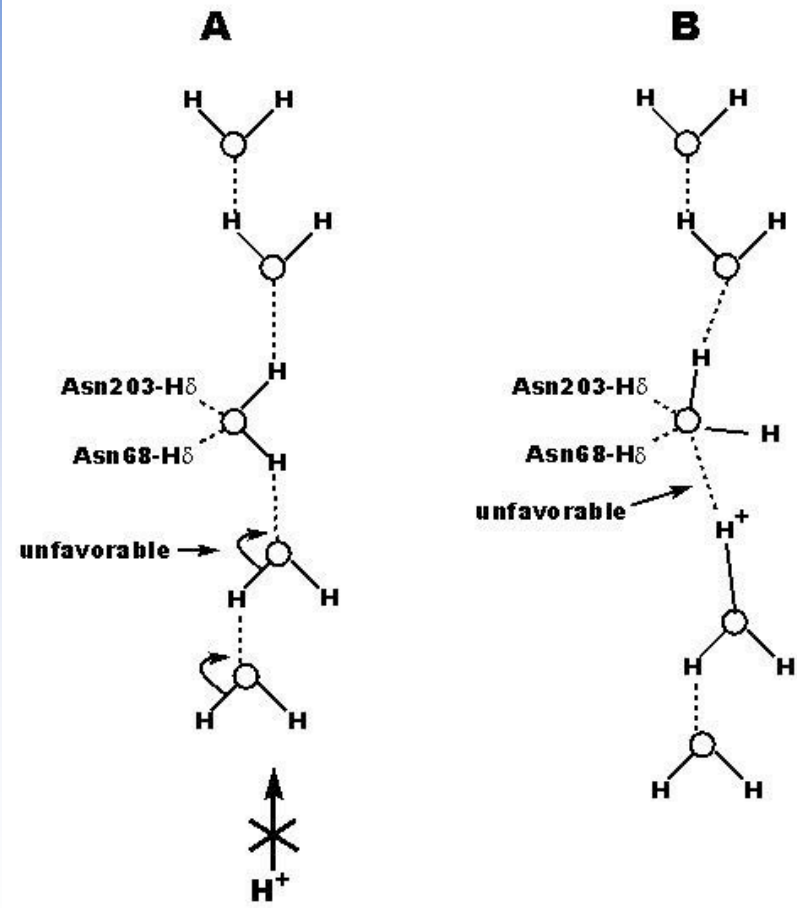
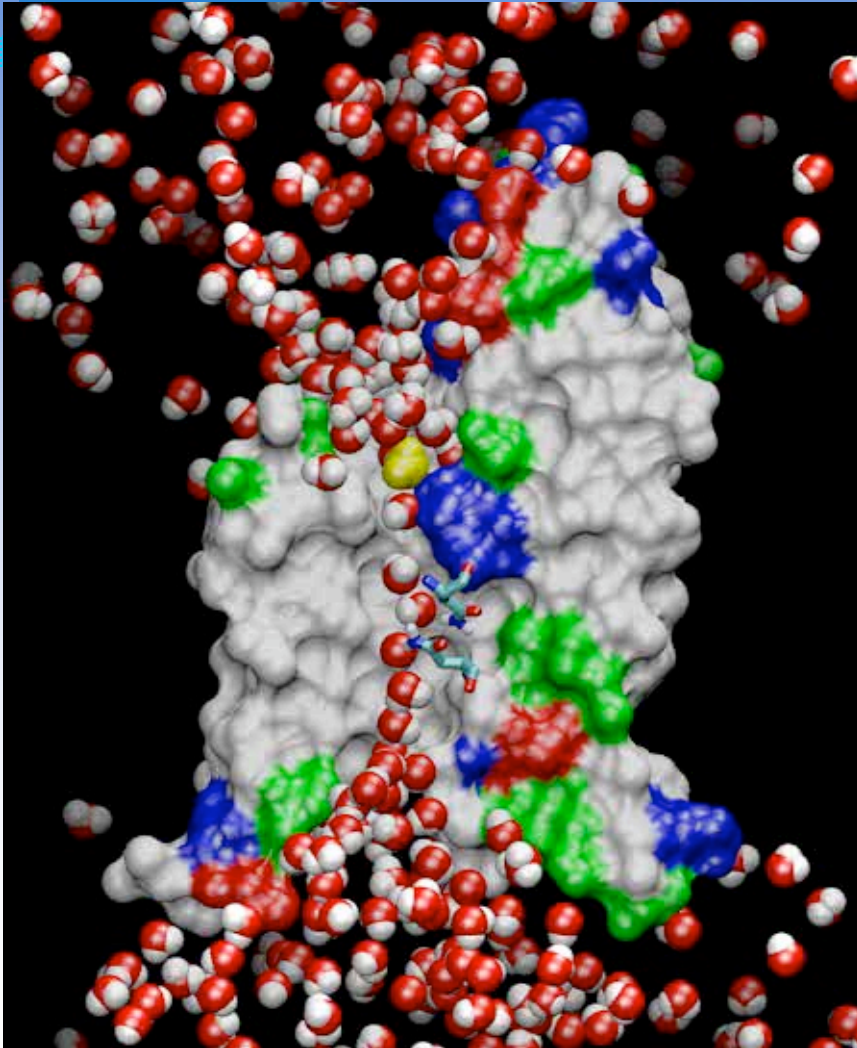
No experimental conductivity values for closed M2 available yet.

Aquaporin Channels (GlpF)

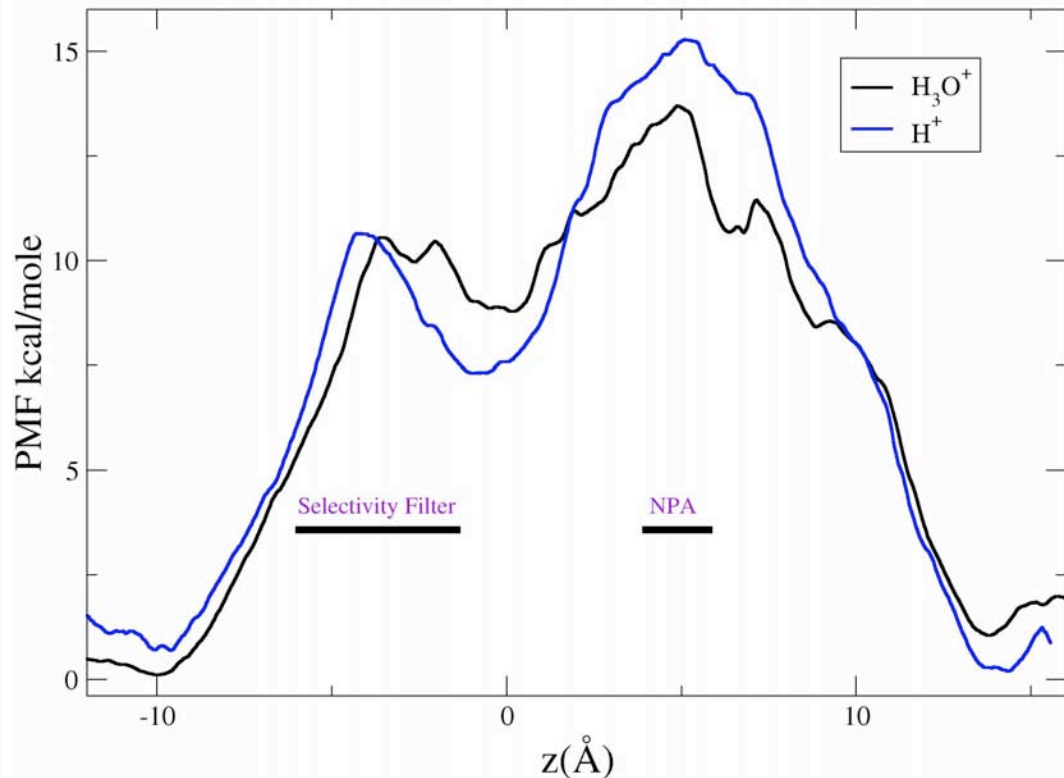


- **1/2 of 2003 Nobel Prize in Chemistry (Peter Agre)**
- **These critical channels transport water and other small molecules through cell membranes, but not ions or protons**

Water Transport (Schulten Group: UIUC)

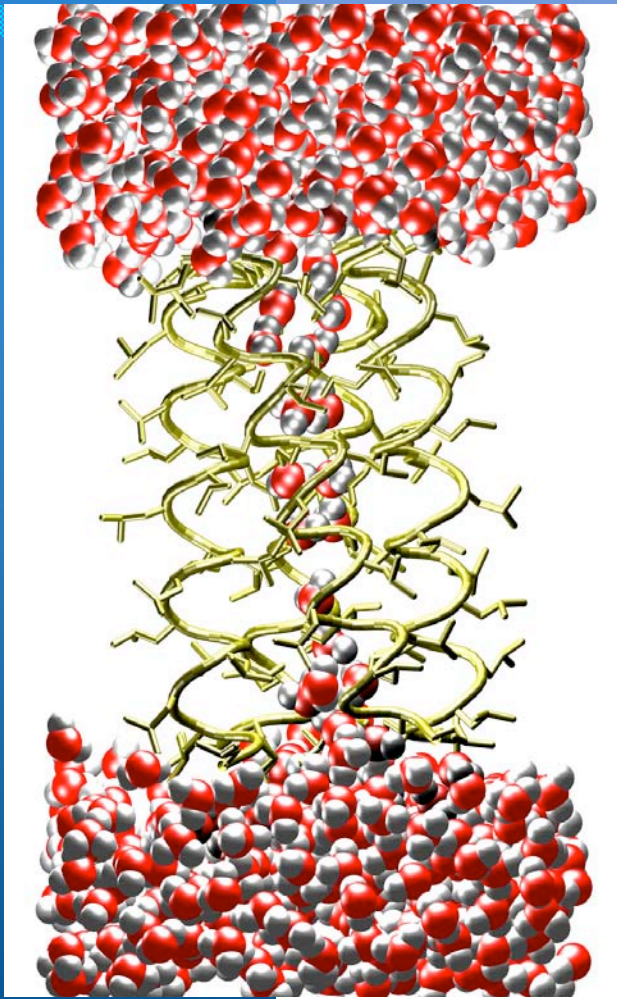


Free Energy Barrier to Proton Transport in an Aquaporin Channel (GlpF)



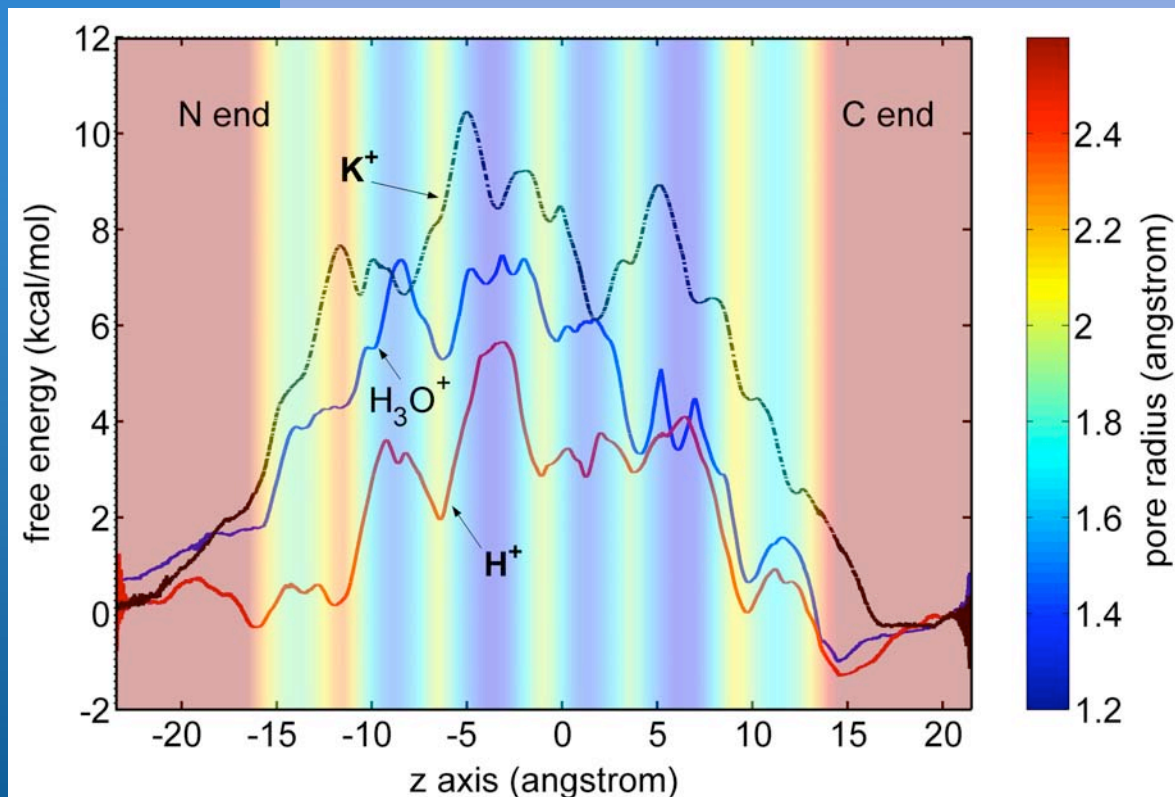
- From MS-EVB simulation **with explicit proton transport** (w/ Boaz Ilan)
- A collaboration with the Schulten group
- B. Ilan, E. Tajkhorshid, K. Schulten, and G. A. Voth, *Proteins: Structure, Function, and Bioinformatics* **55**, 223-228 (2004) (and also second paper in preparation).
- **Here the role of electrostatics is dominant, but there is an interesting twist.**

LS2 Channel (Counter-example?)



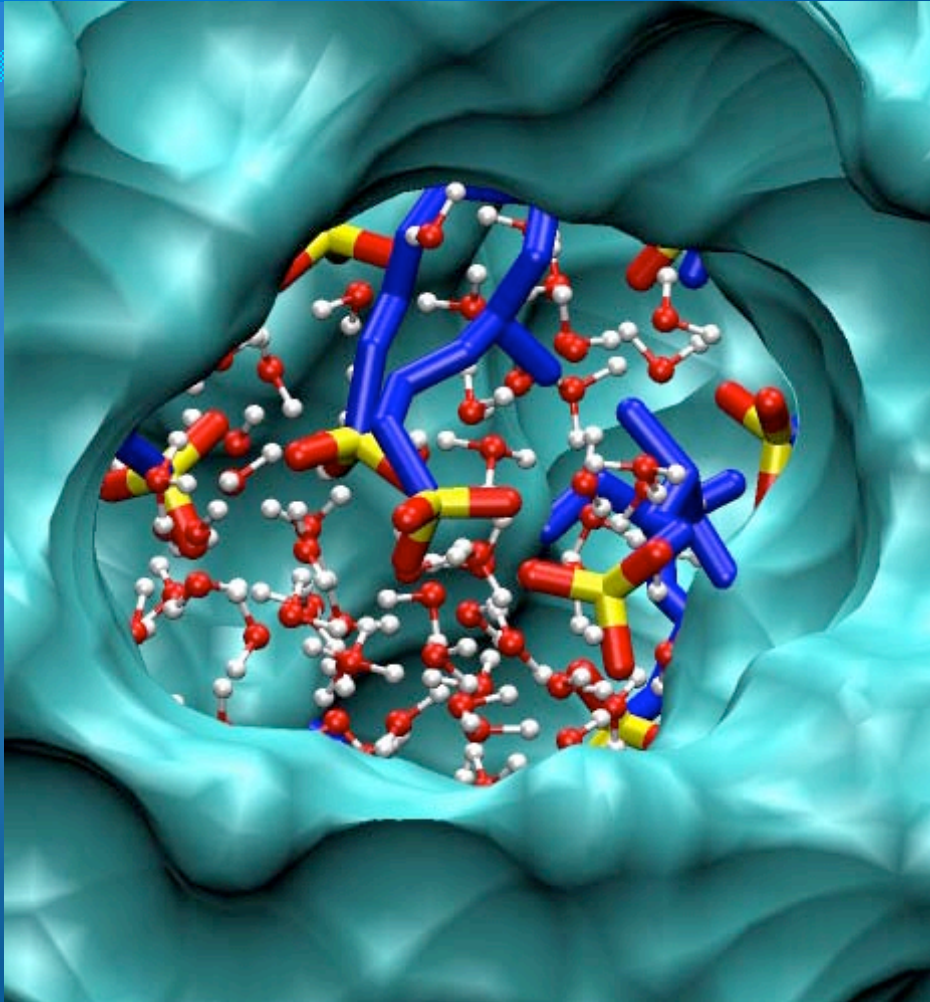
- Lear, J. D., Z. R. Wasserman, and W. F. DeGrado. 1988. *Synthetic amphiphilic peptide models for protein ion channels*. *Science*. 240:1177-1181
- Transports protons (120 pS in 0.5 M HCl solution) but **not other cations** (e.g. < 5 pS in 2.5 M KCl solution)

Free Energy Barriers (PMFs) for H^+ and K^+ Transport through the LS2 Channel



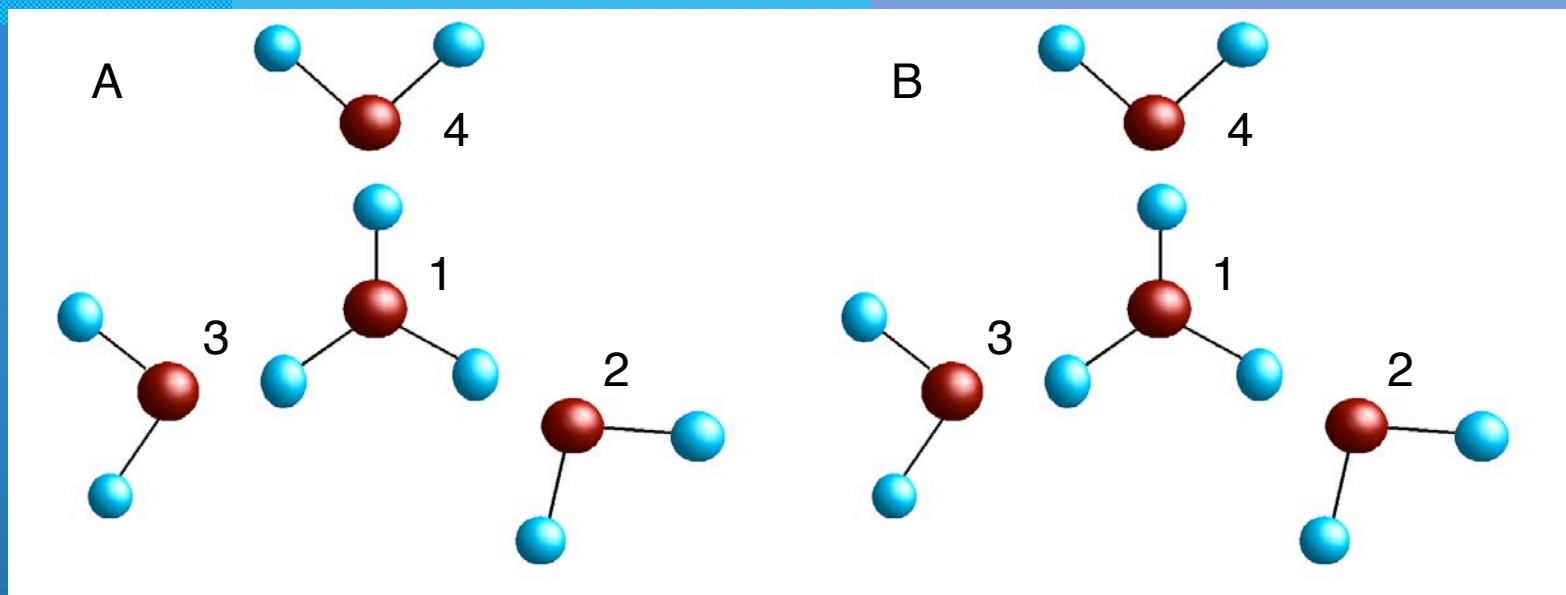
- From MS-EVB simulation with explicit proton transport: (In preparation w/ Yujie Wu, Boaz Ilan)
- Black is K^+ , blue is classical hydronium (H_3O^+), and red is proton (H^+) PMFs.

PT in Polymer Electrolyte Membranes



- Nafion™: **High concentration of hydronium ions** and sulfonate head groups.
- Water forms extended hydrogen bonded networks throughout the polymer backbone.
- Non-vehicular proton transport (shuttling) might occur (or not?) within this h-bond network.

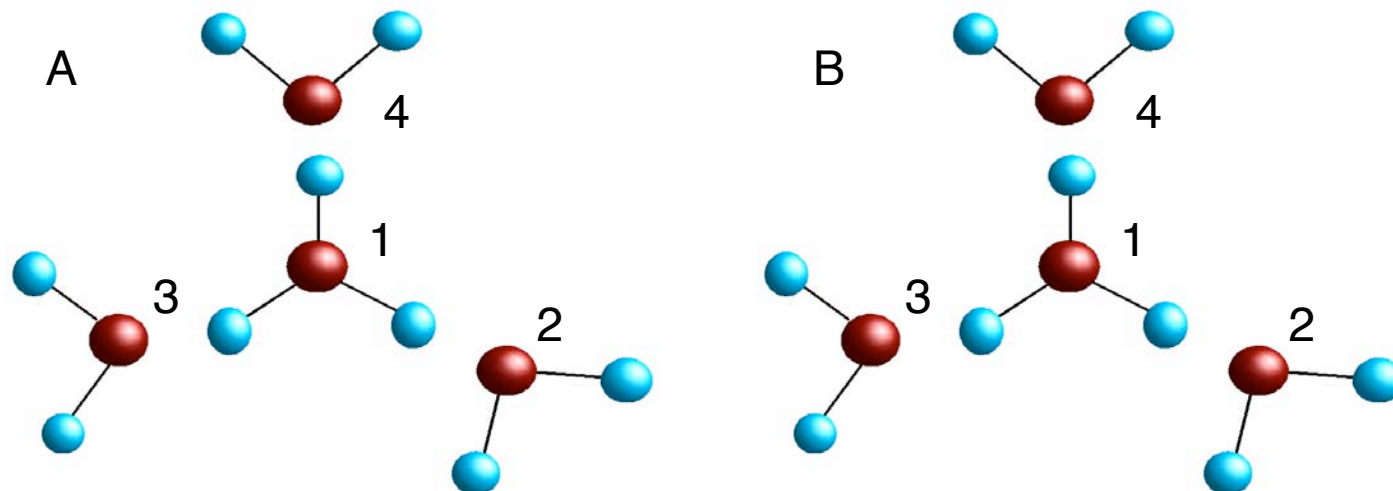
Many Protons: The Big Matrix Approach to Solve Multi-Proton MS-EVB Problem (THE DUMB WAY)



A1B1, A1B2, A1B3, A1B4, A2B1

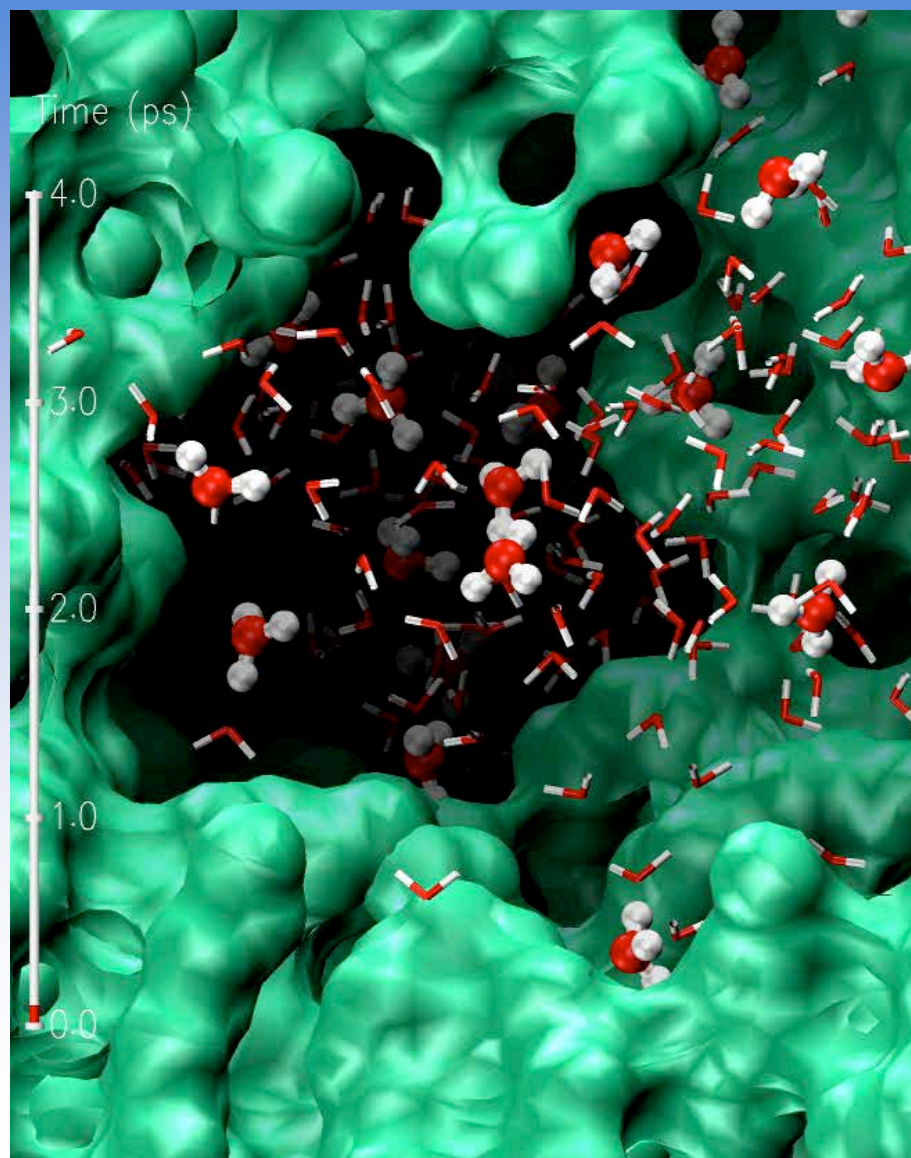
16 states required to describe
only two independent $(\text{H}_9\text{O}_4)^+$

Linear Scaling Approach (THE GOOD WAY) Feng (Seymour) Wang



- Each EVB center sees all other EVB centers as arrays of effective particles.
- Each effective particle has interaction parameters a linear combination of that of a pure hydronium or a pure water according to its local EVB vector.
- The coefficients of each EVB state are iterated until convergence. **Sparse matrix methods.**
- **This method scales linearly in the number of excess protons and over computational nodes** [F. Wang and GAV, JCP (in press)]

Our First Multiple Proton Simulations for Nafion™



- The capability of MS-EVB has now been extended to multiple protons in a scalable fashion for such systems.
- All 40 excess protons (10 M concentration) have been treated with the MS-EVB method in this simulation.
- **See poster here by Matt Petersen**

Conclusions

- **Structural and dynamical effects** correlate with the observed proton solvation transport properties. **These are not as simple as they were once thought to be.**
- An interesting picture has emerged for **protons at interfaces and other complex environments.**
- Proton transport of the **proper qualitative time scale** has been observed in water and in the M2, GlpF, LS2, CcO **biological proton channels.**
- The methodology **can be generalized** to treat complex materials such as **proton conducting polymer electrolyte membranes.**