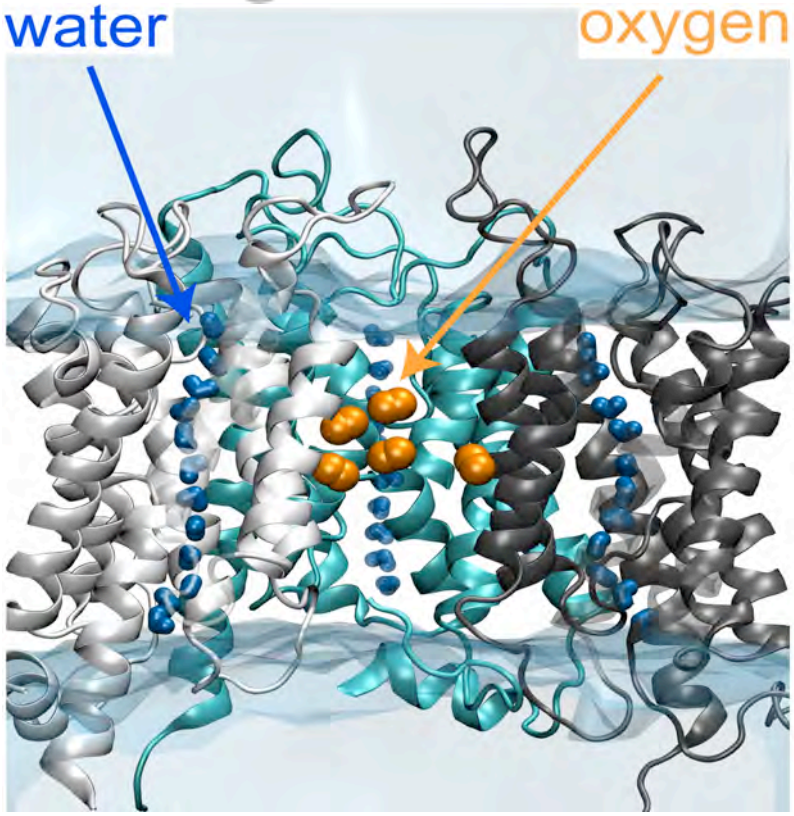
Visualizing Gas Permeation Pathways Through Proteins at Sub-Angstrom Resolution



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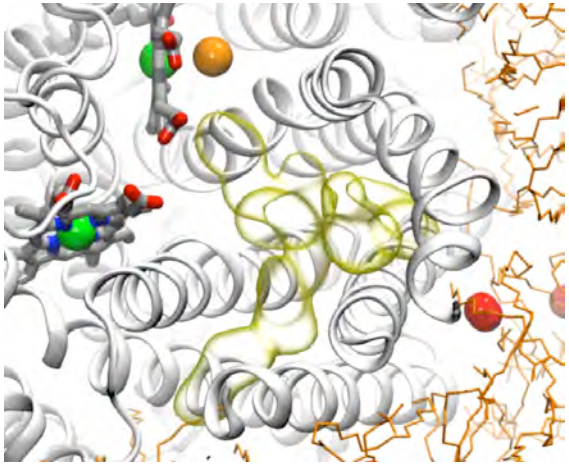
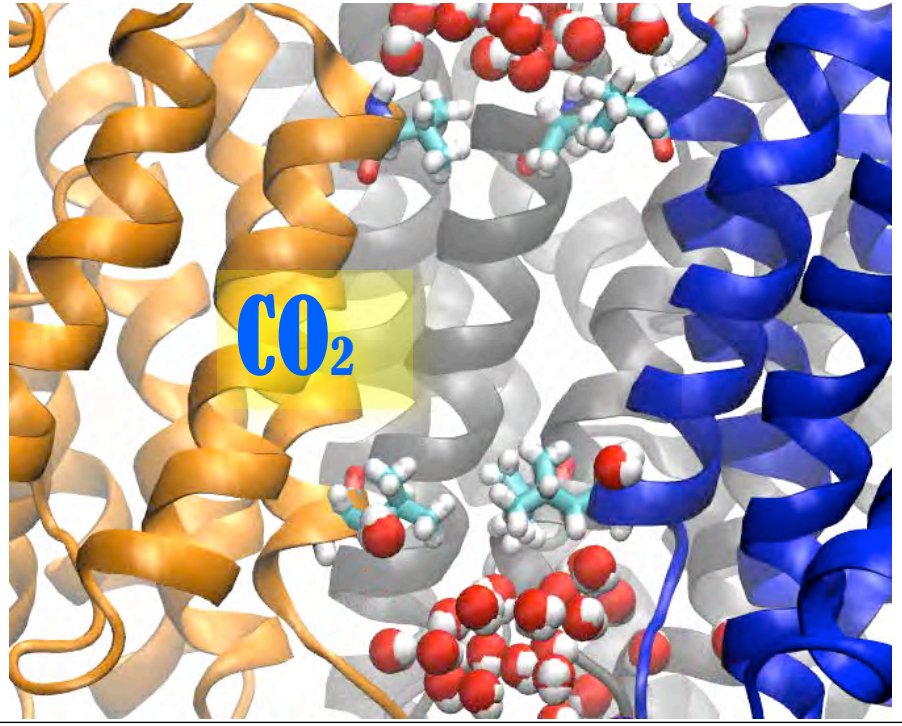
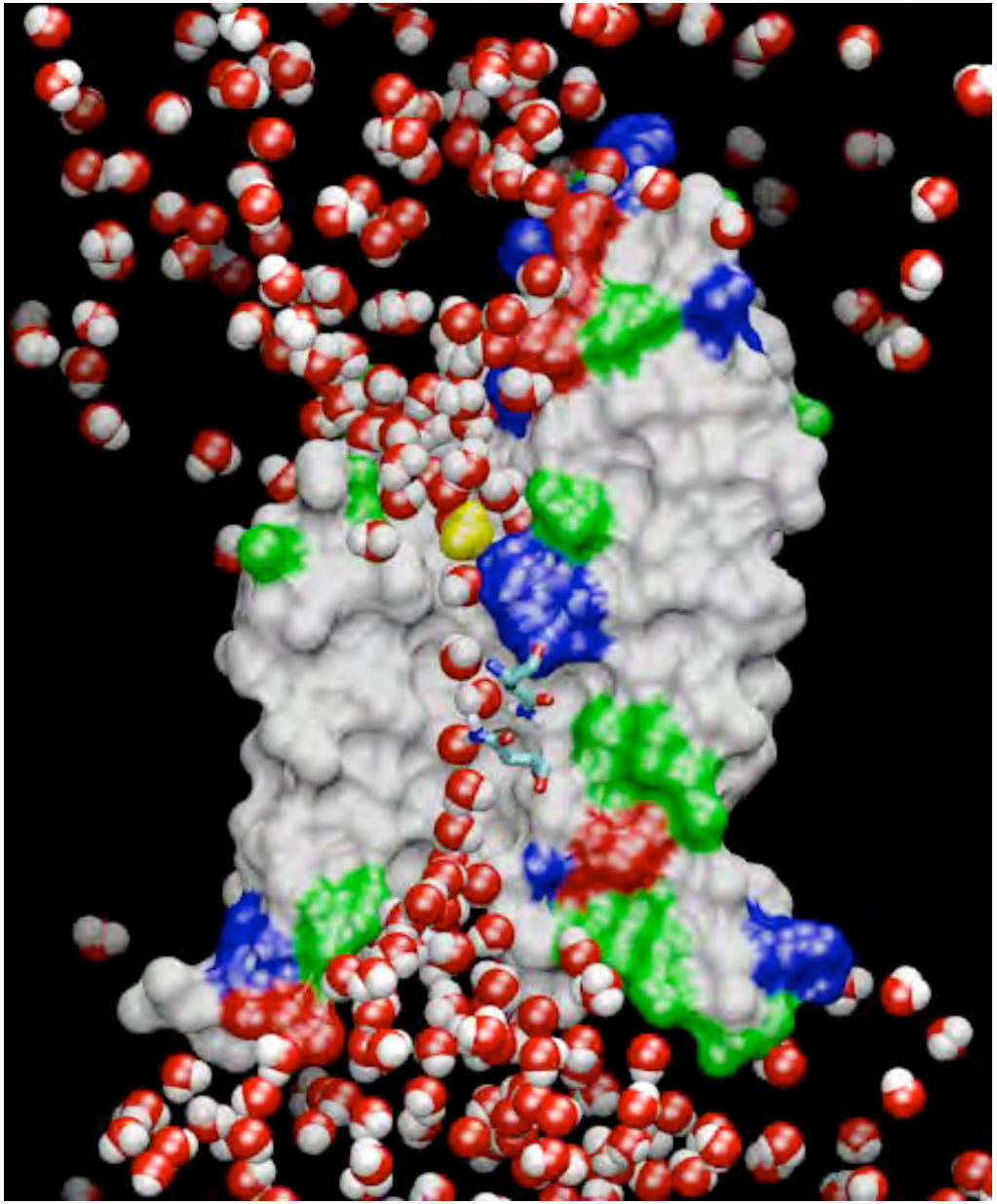
University of Illinois at Urbana-Champaign





Molecular Dynamics Simulations



nobelprize.org/nobel_prizes/chemistry/laureates/2003/animations.html

Solving the Newtonian equations of motion for all particles at every time step

SPEED LIMIT

1 fs

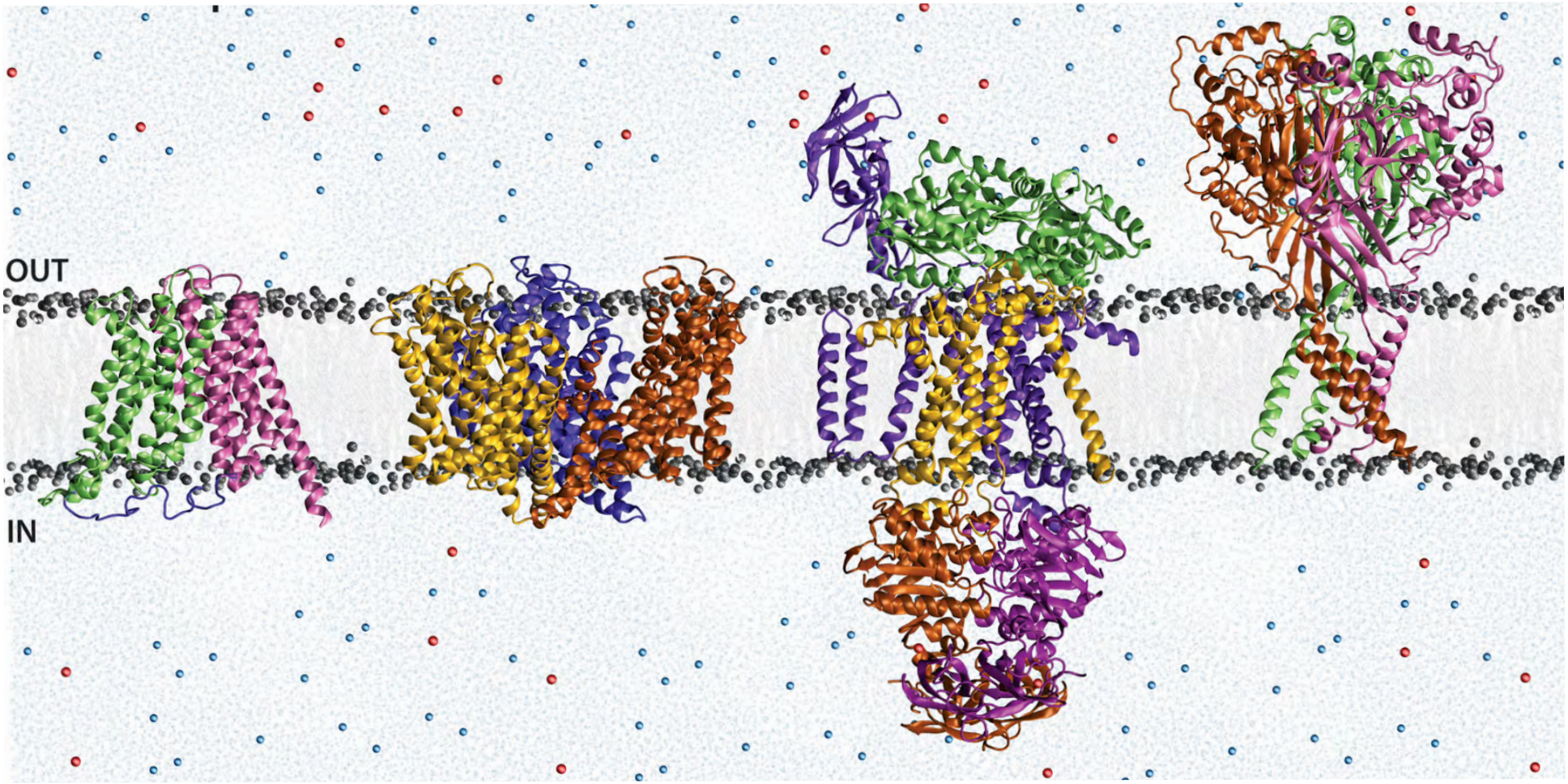
Major limitations:

- Time scale / sampling
- Force field approximations

Major advantages:

- Providing a dynamical description
- Unparalleled spatial and temporal resolutions, **simultaneously**

In situ Molecular Dynamics Simulations



Atom count: 100-500k
~10 ns/day on 128-1024 processors
100-500 ns for each system

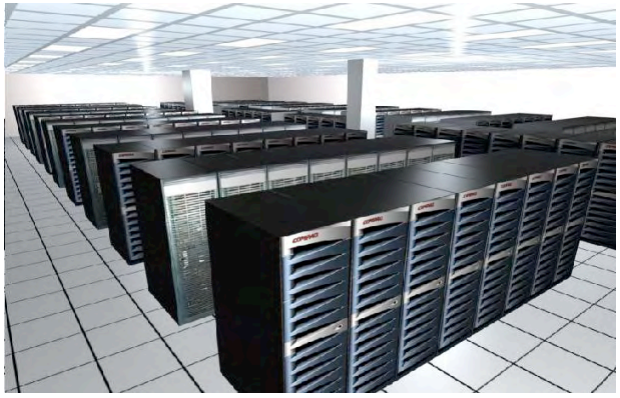
Fast Growth of Computational Power

HP 735 cluster
12 processors
(1993)

SGI Origin 2000
128 processors (1997)

Blue Waters (UIUC)
200,000+ processors (2013)

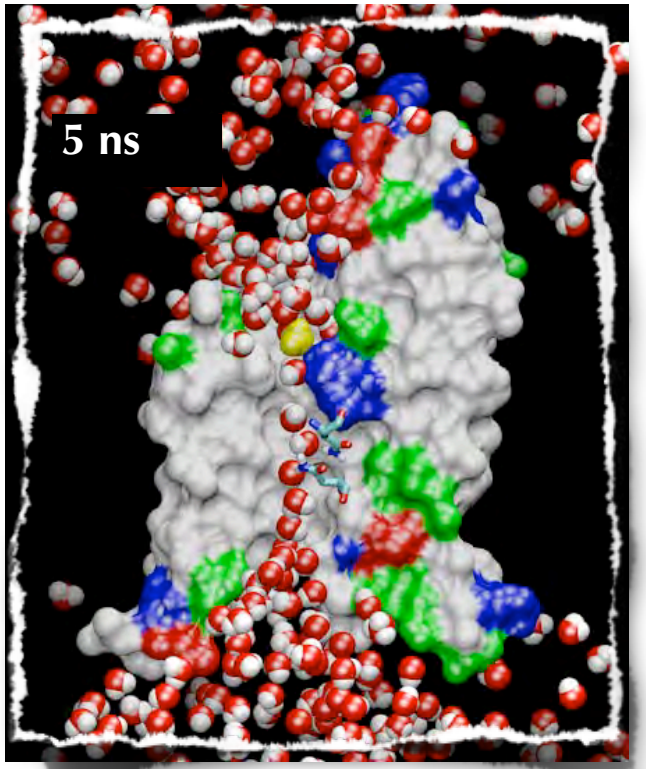
Anton/DESHAW/PSC
512 processors (2010)

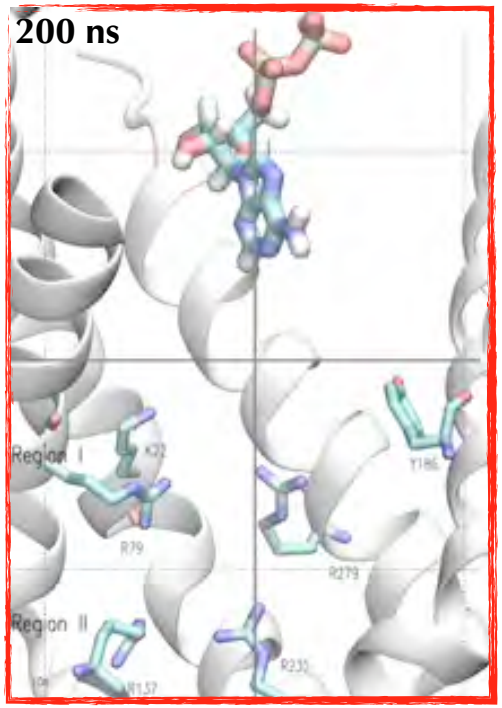


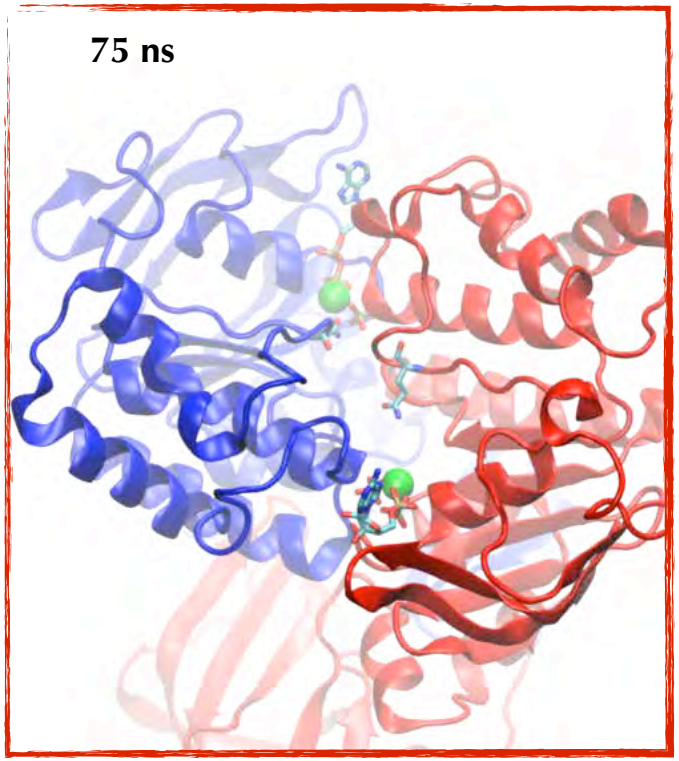
PSC LeMieux AlphaServer SC
3000 processors (2002)

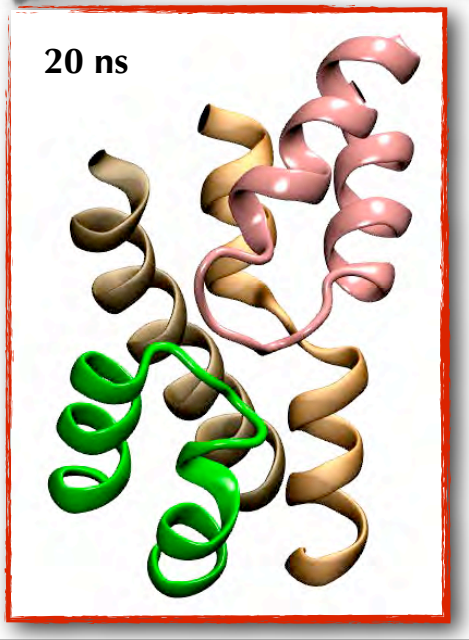
Ranger/Kraken
~60,000 processors (2007)

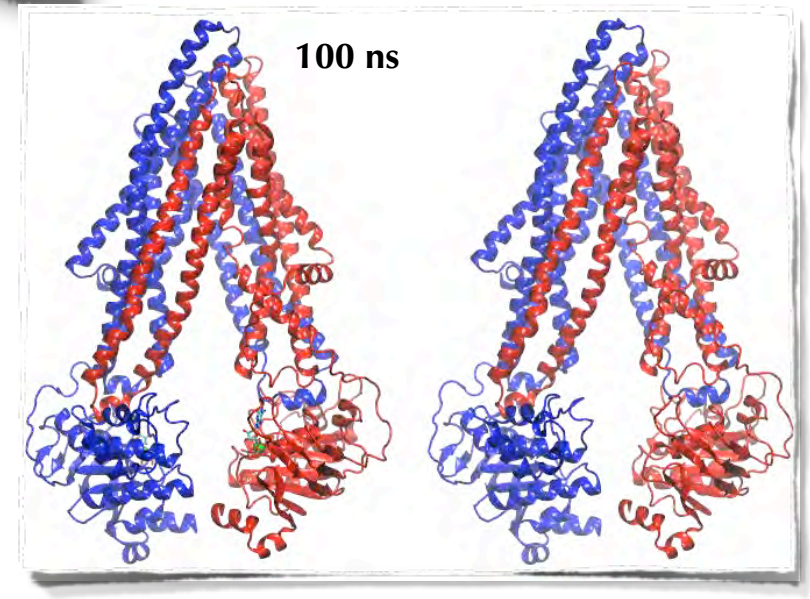
Capturing Biology at sub-Å Resolution

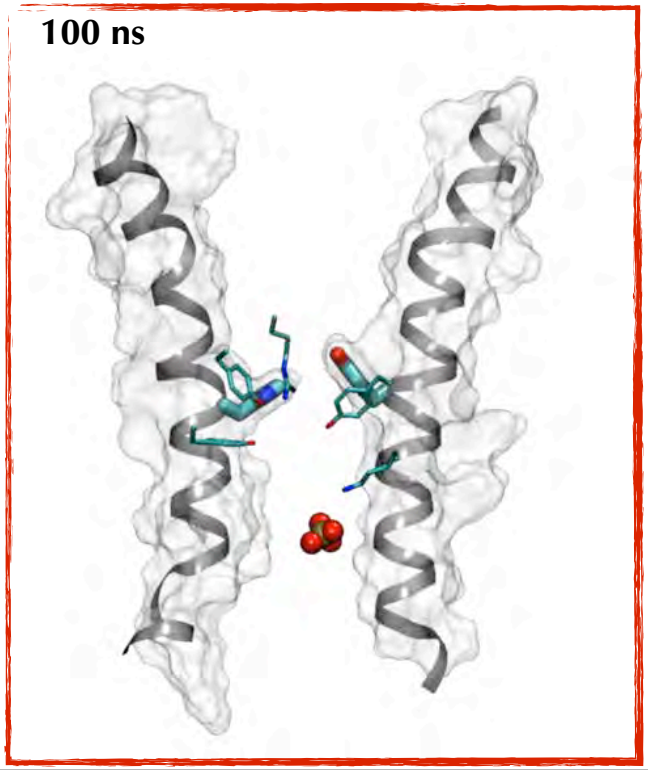




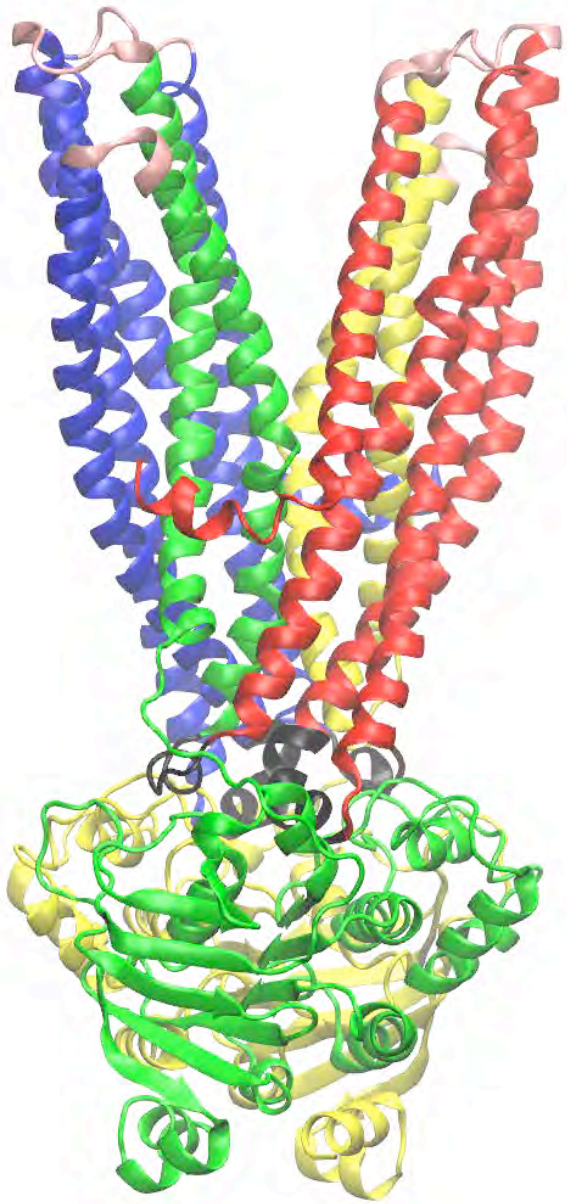


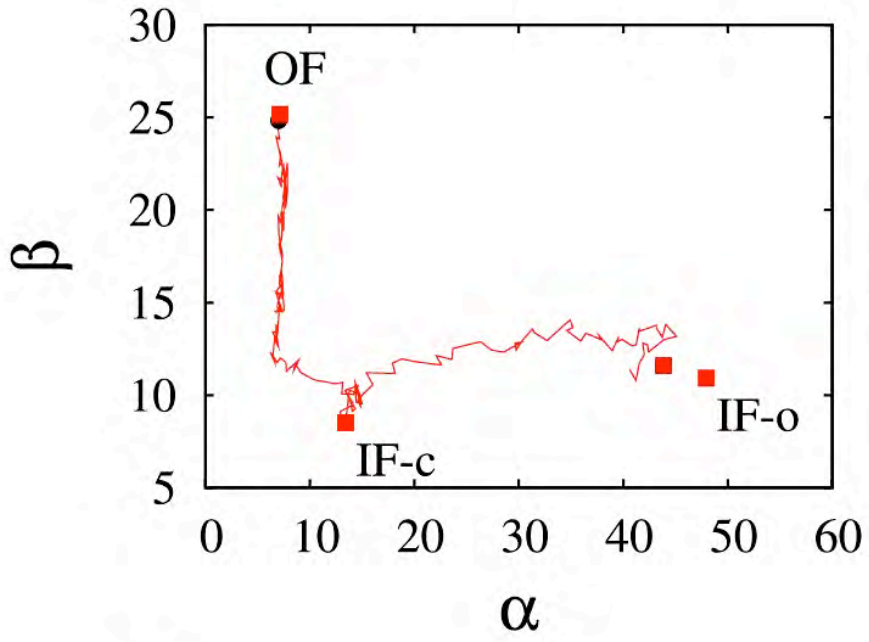


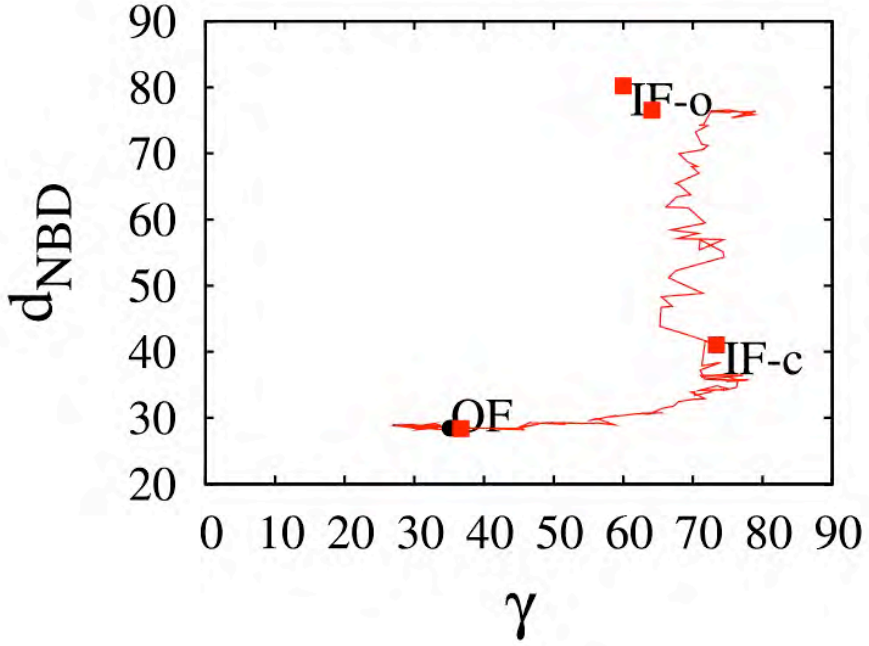




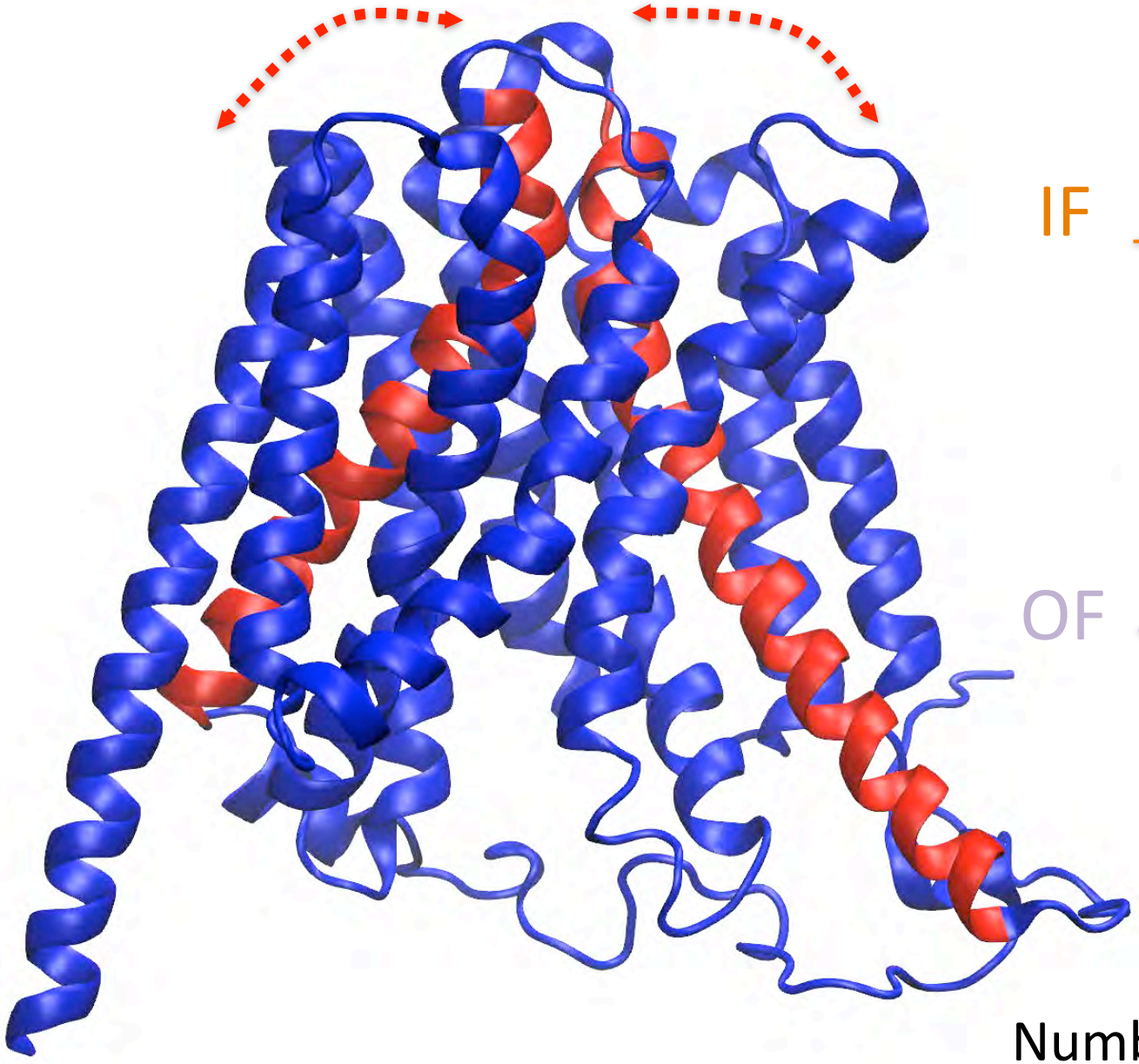
Large-Scale Transition of an ABC Transporter in the Membrane

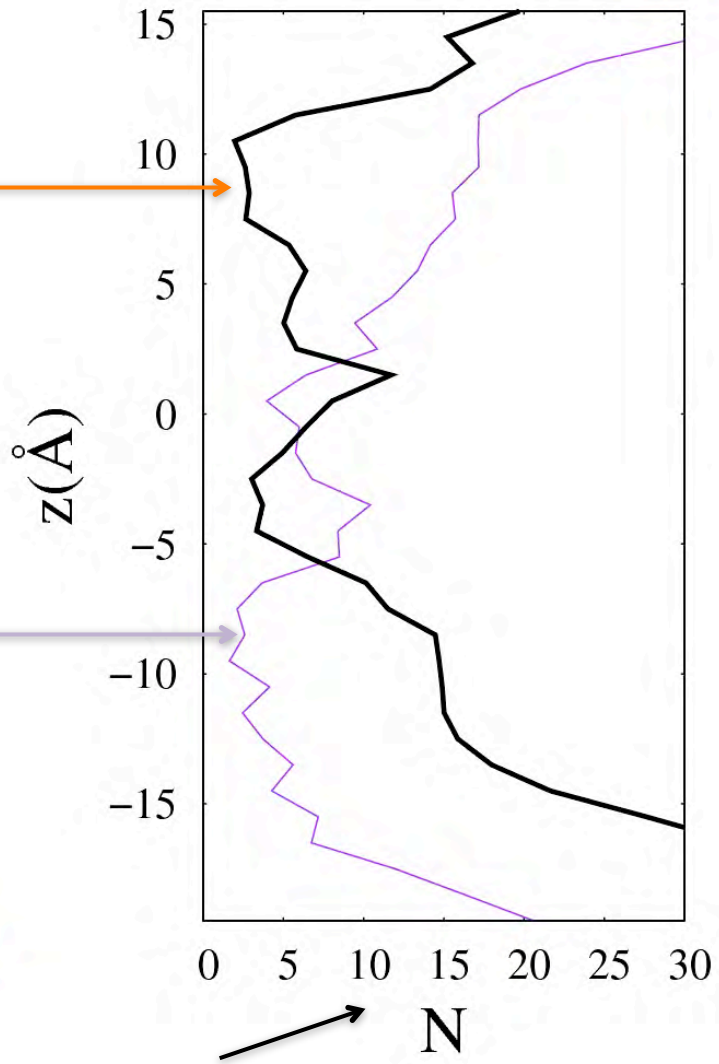






IF↔OF transition in an MFS Transporter in Membrane

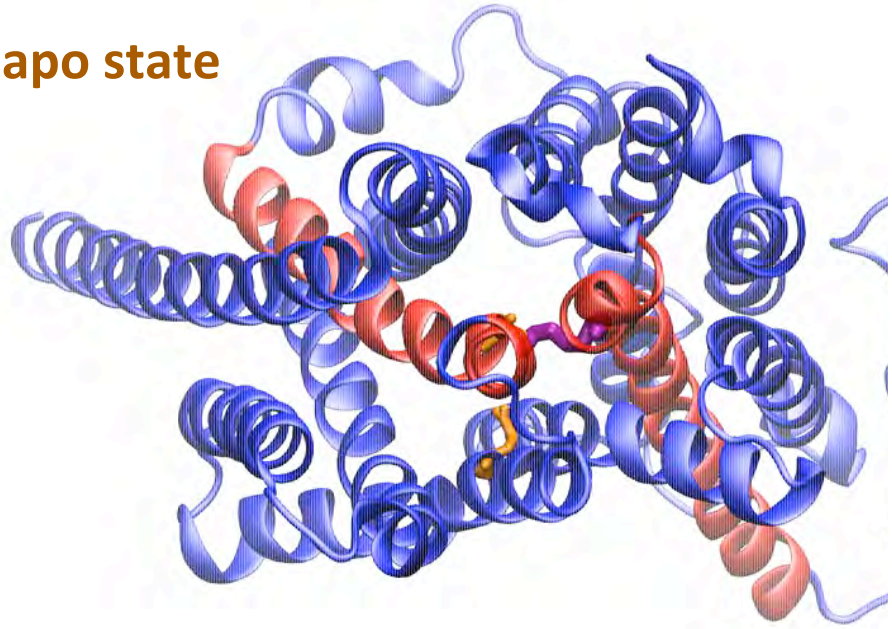




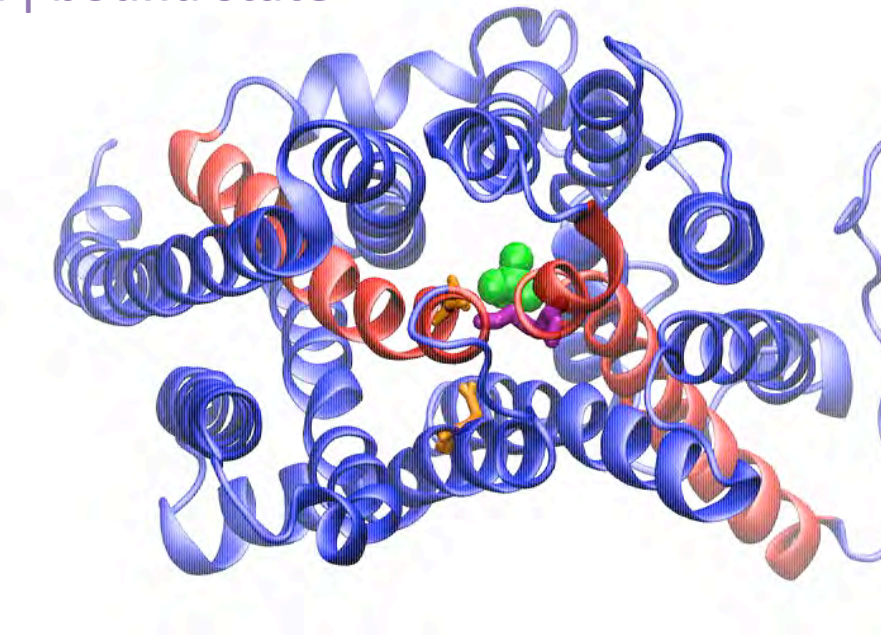
Number of water molecules
(averaged over a 1 ns window)

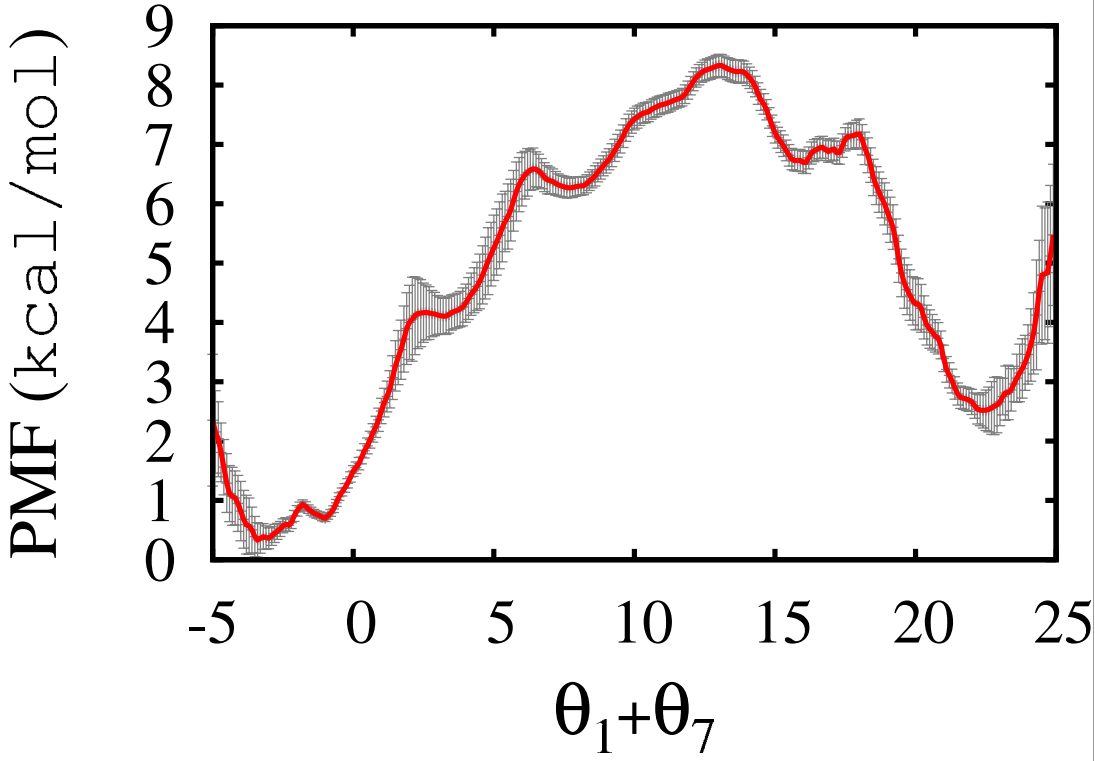
Chemomechanical Coupling in GlpT

apo state

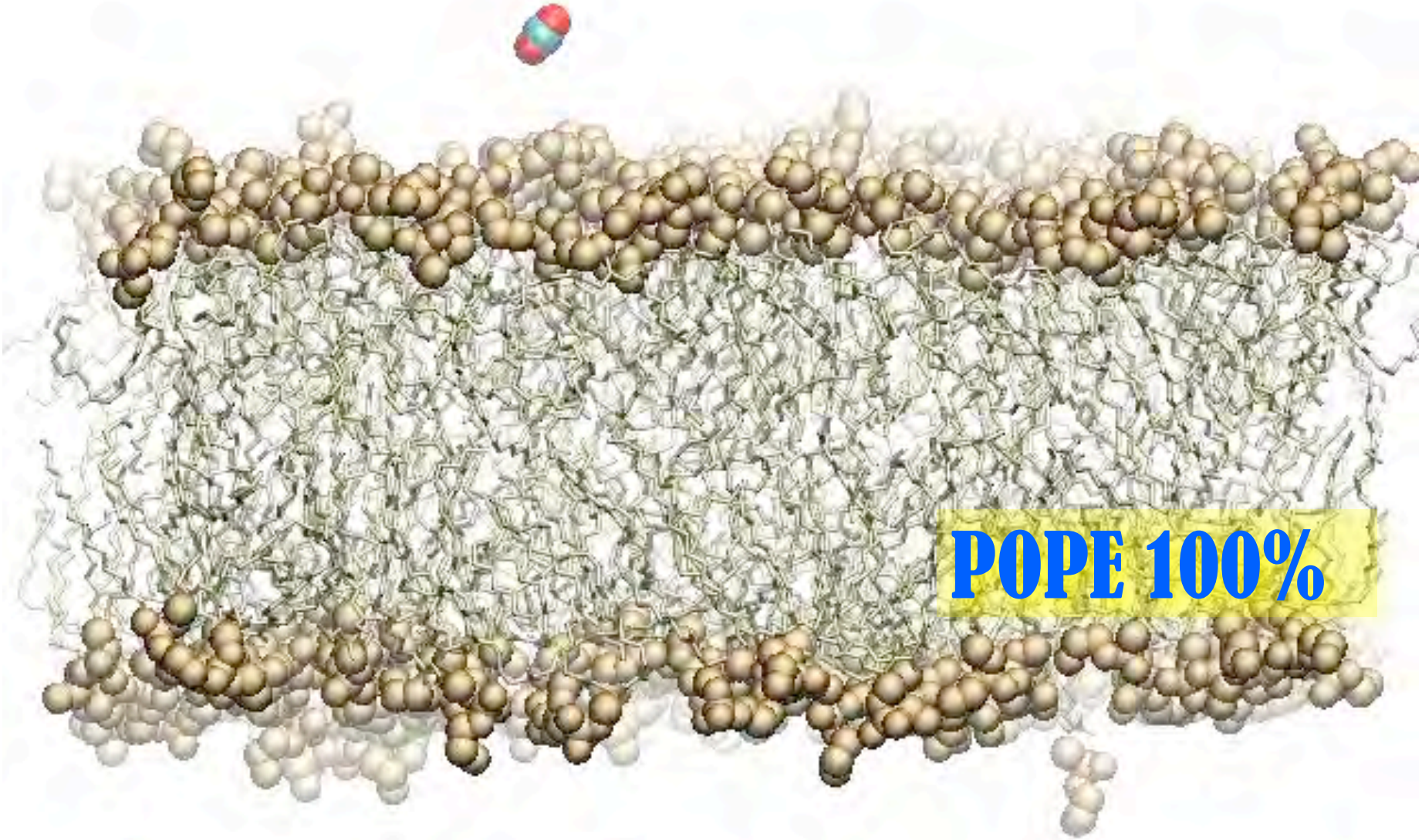


P_i-bound state



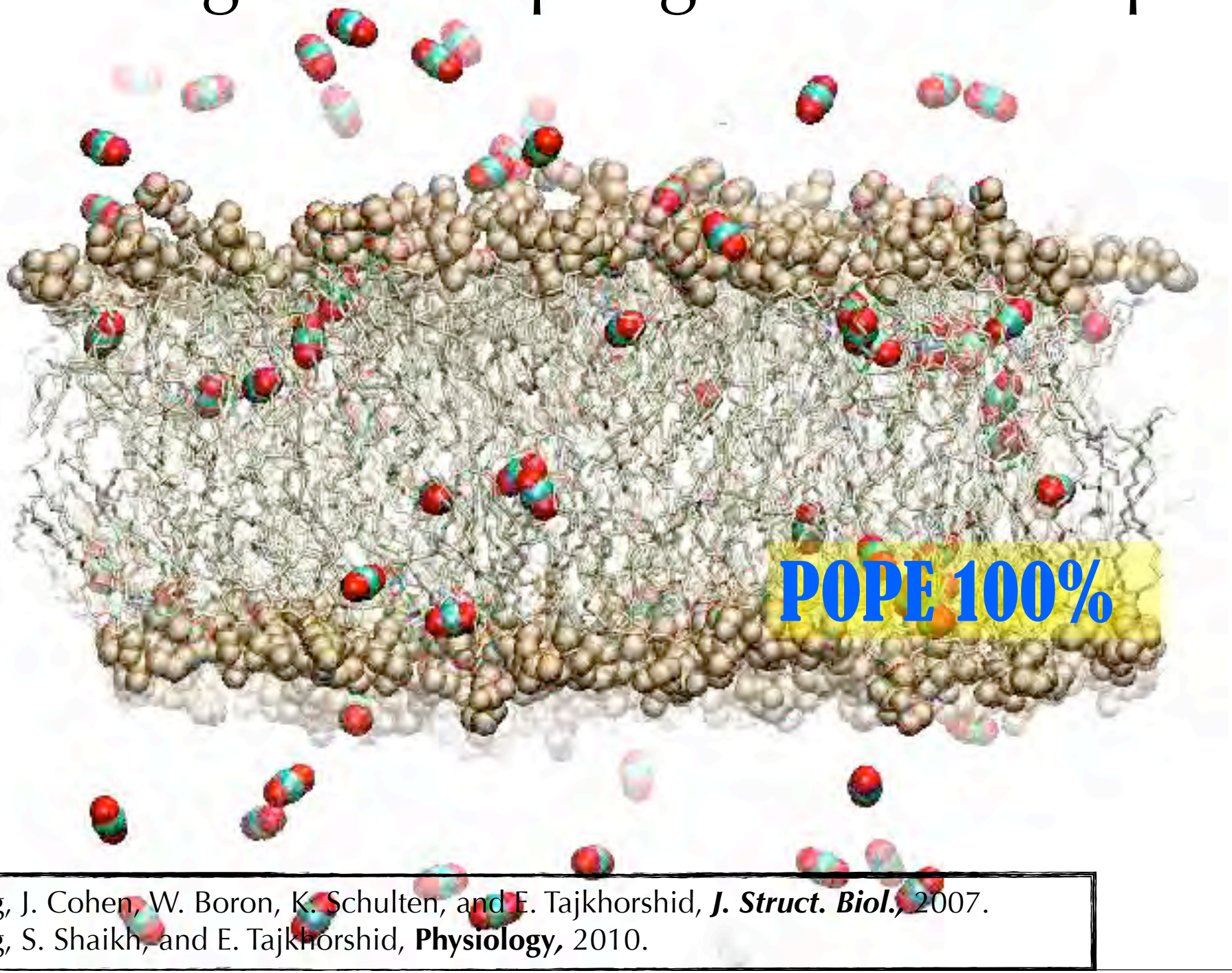


Explicit Ligand Sampling of Gas Transport



Y. Wang, J. Cohen, W. Boron, K. Schulten, and E. Tajkhorshid, ***J. Struct. Biol.,*** 2007.
Y. Wang, S. Shaikh, and E. Tajkhorshid, **Physiology,** 2010.

Explicit Ligand Sampling of Gas Transport



Y. Wang, J. Cohen, W. Boron, K. Schulten, and E. Tajkhorshid, ***J. Struct. Biol.,*** 2007.
Y. Wang, S. Shaikh, and E. Tajkhorshid, **Physiology,** 2010.

Lipid/Water Partition Coefficients

Simulation	
CO_2 in POPE	3.50
CO_2 in POPC	2.74
$O_{2(P)}$ in POPC	4.04
$O_{2(N)}$ in POPC	3.46
$O_{2(P)}$ in POPE	4.73
$O_{2(N)}$ in POPE	5.79

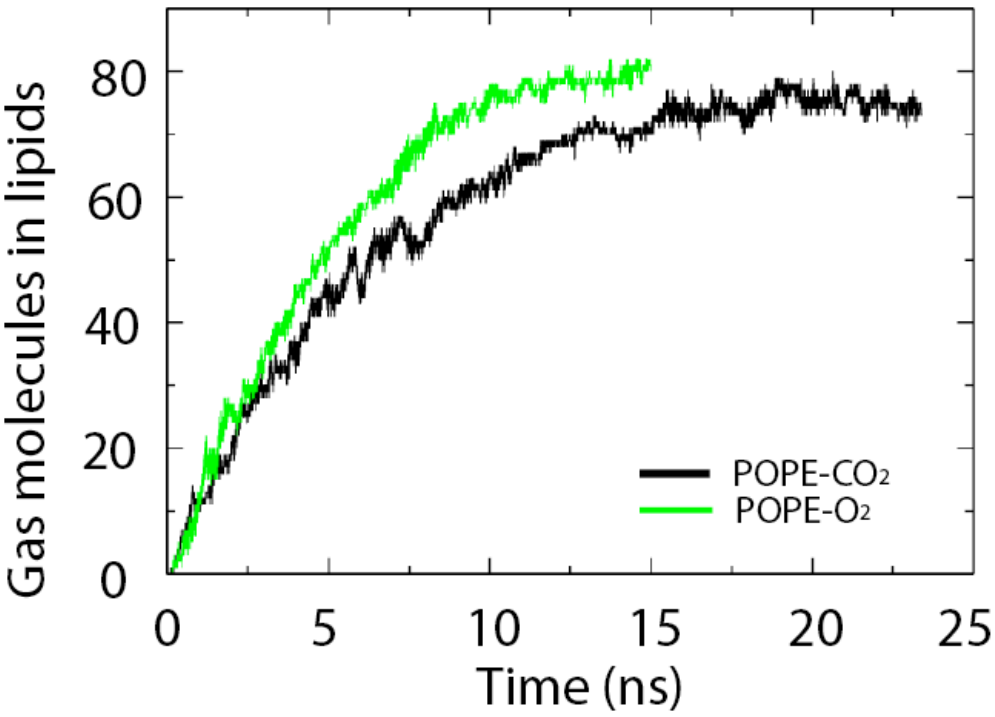
Experiment

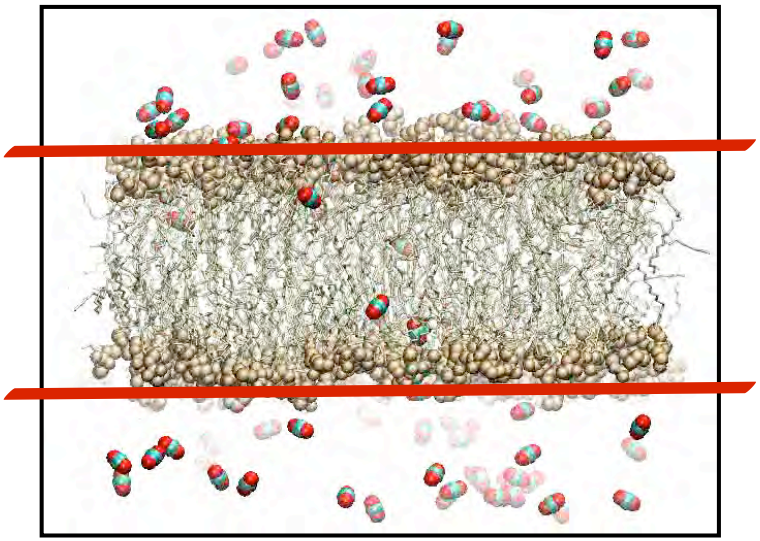
CO2

- Octanol: 1.3
- Hexadecane: 1.5
- Olive oil: 1.7

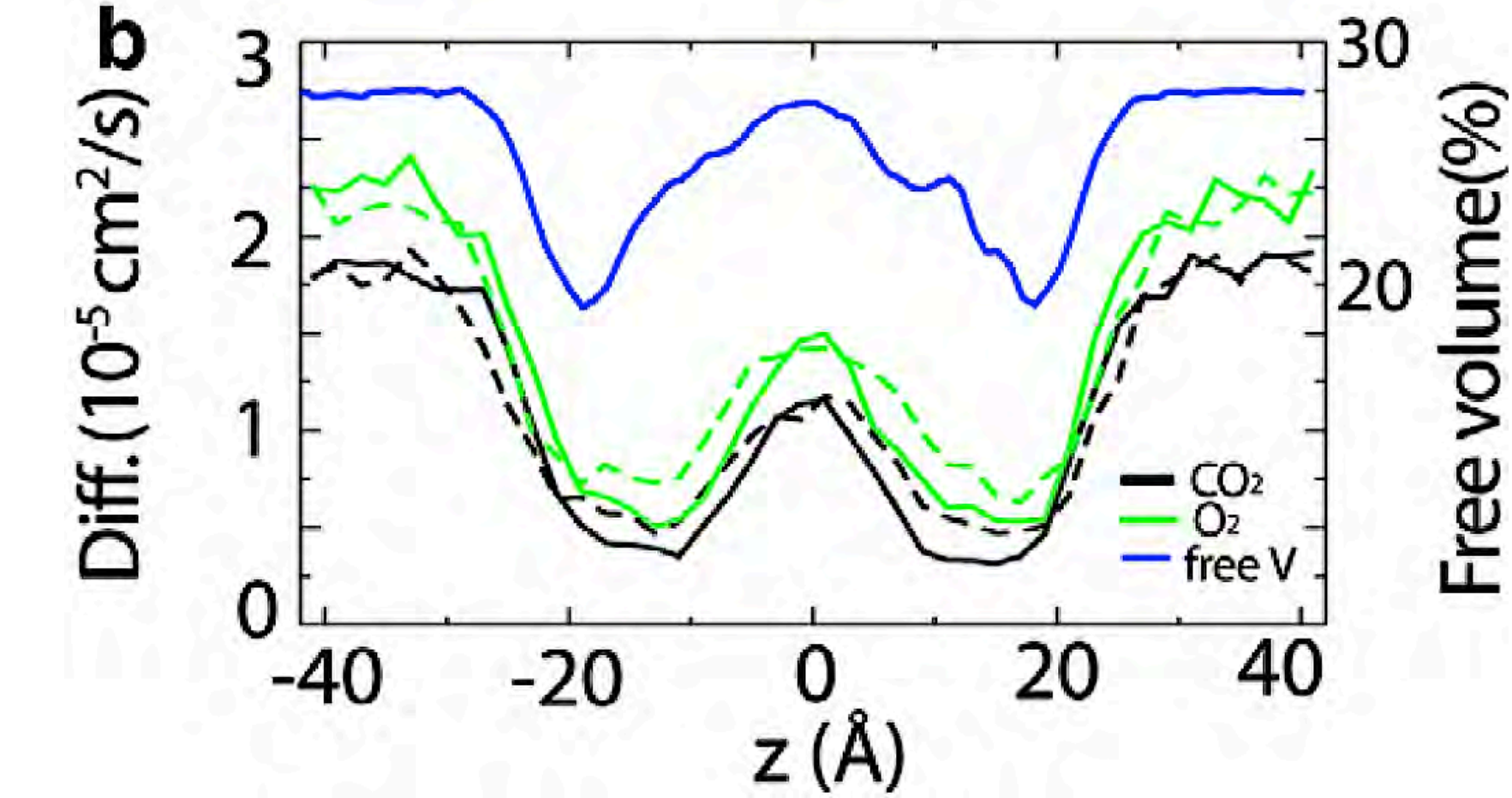
O2

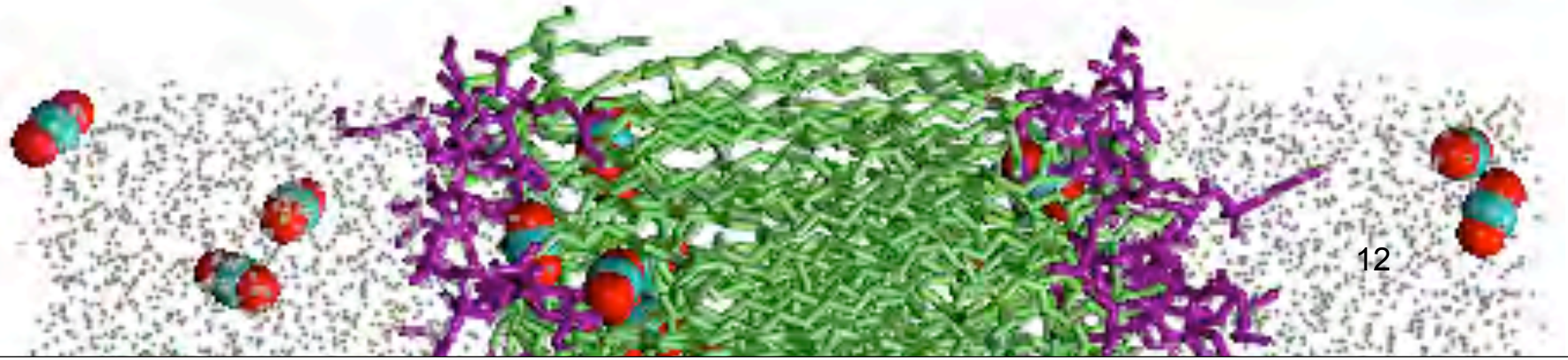
- Liposome: 3.9



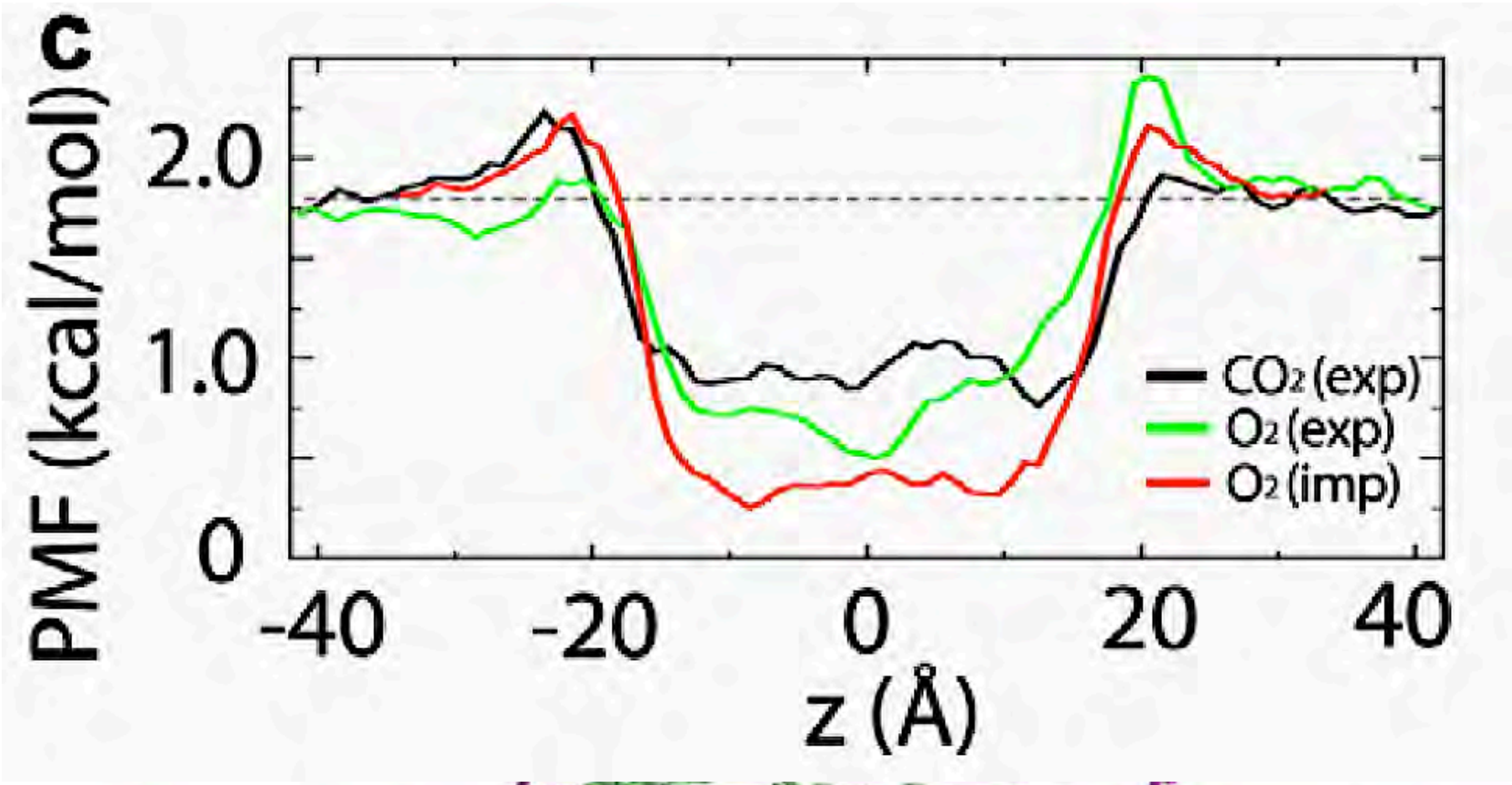


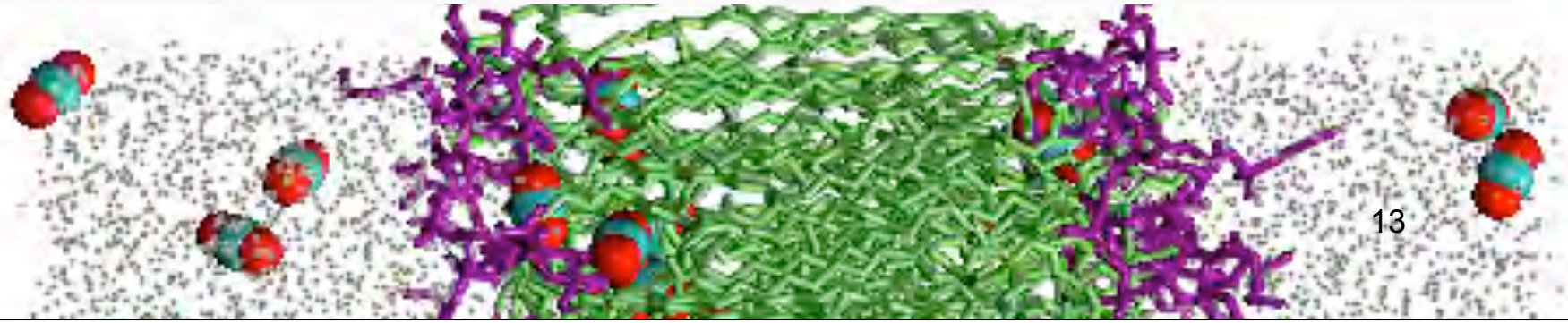
Gas Diffusion Inside the Lipid Bilayer



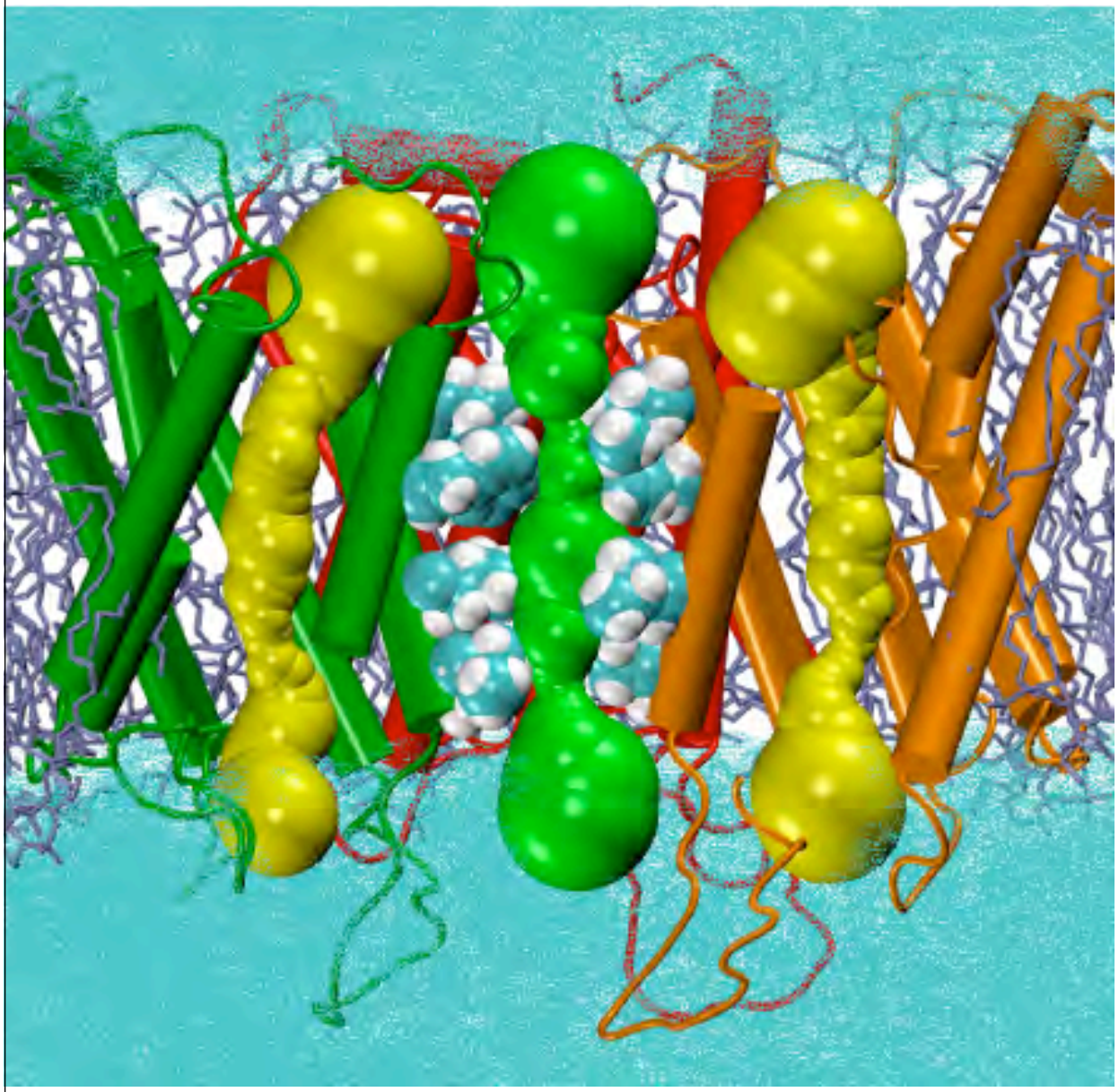


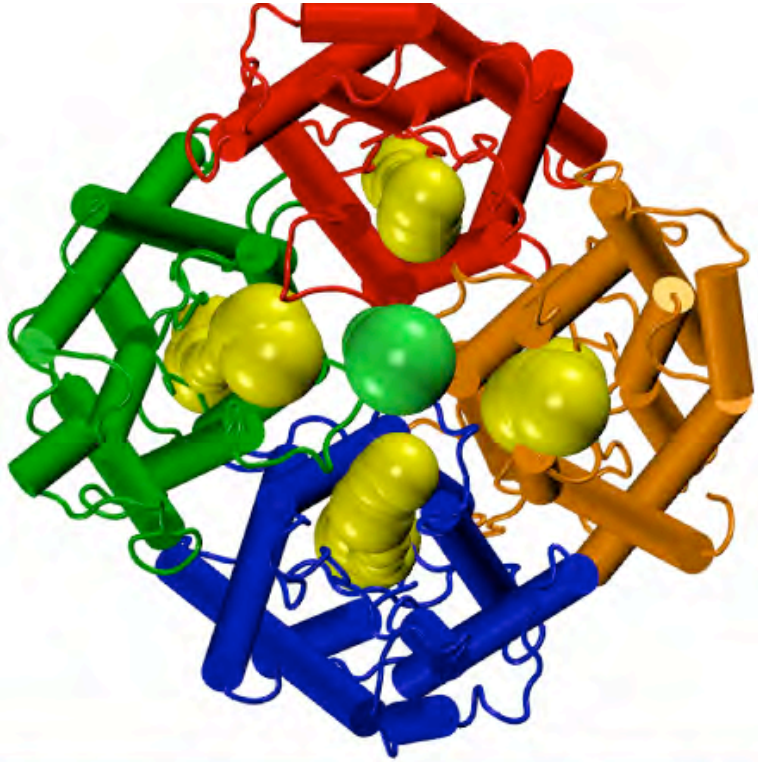
Gas Diffusion Inside the Lipid Bilayer





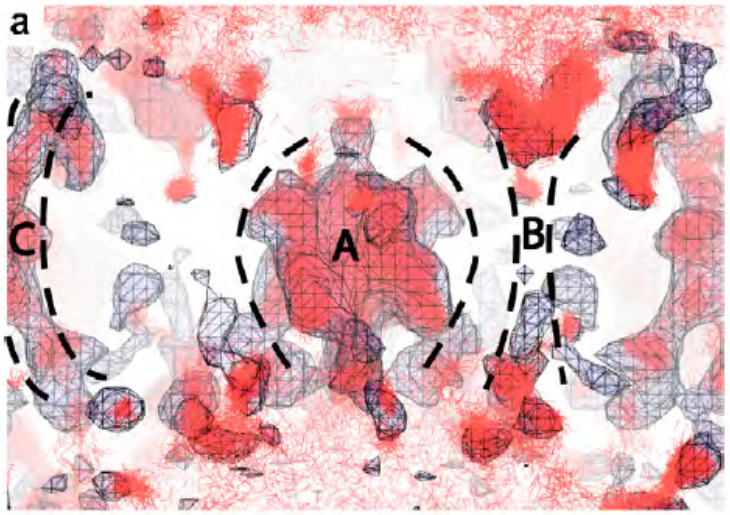
Aquporin **Water**/**Gas** Channels



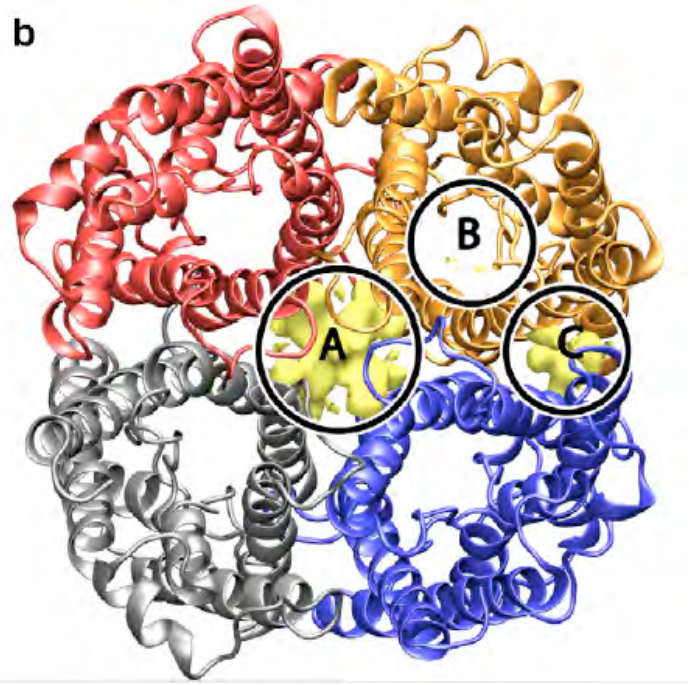


Why Tetramers?

Implicit Ligand Sampling



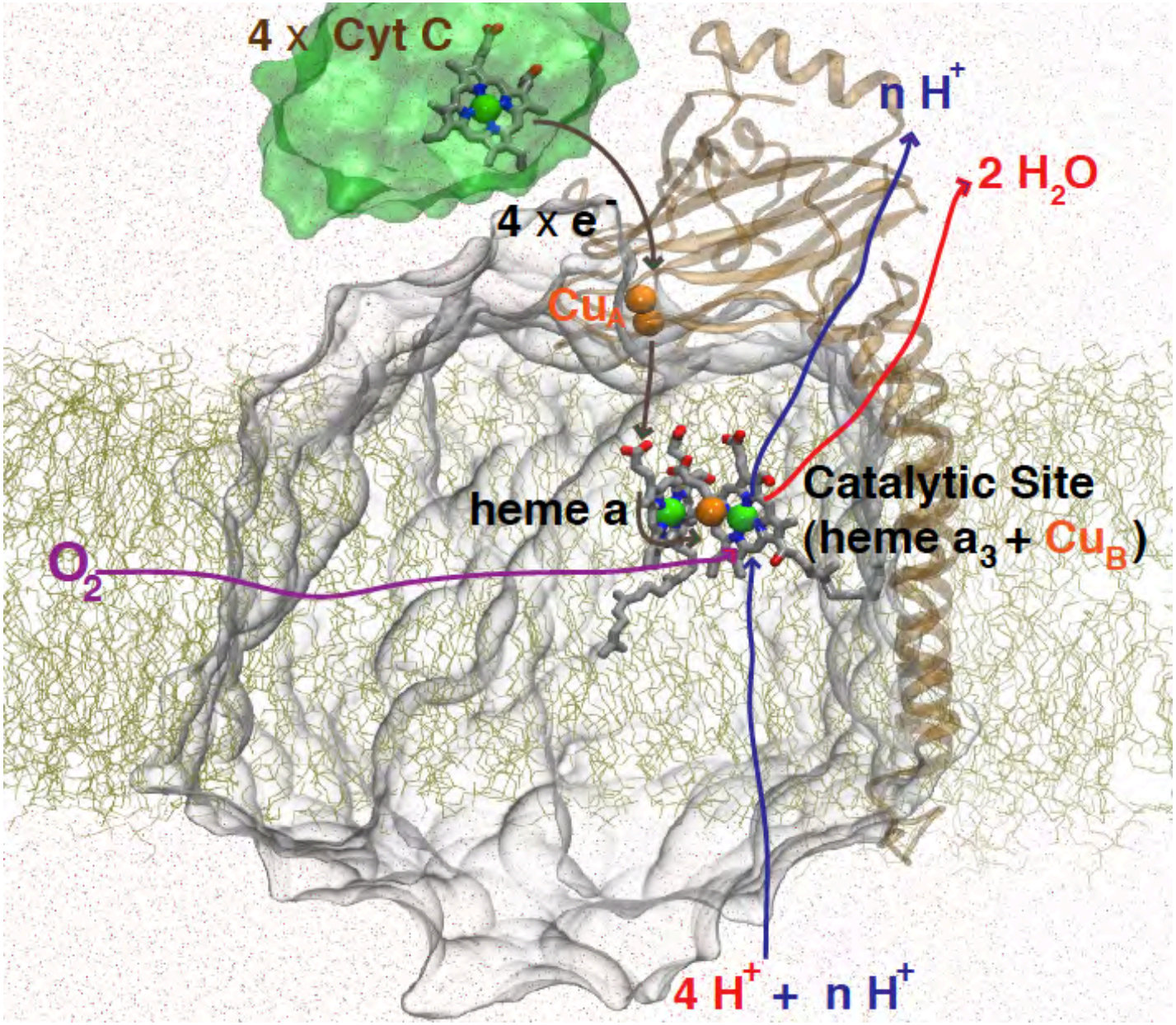
$$\mathcal{W}(\mathbf{r}) = -k_{\mathrm{B}}T\ln\left[\frac{\rho(\mathbf{r})}{\rho_{\mathrm{o}}}\right]$$



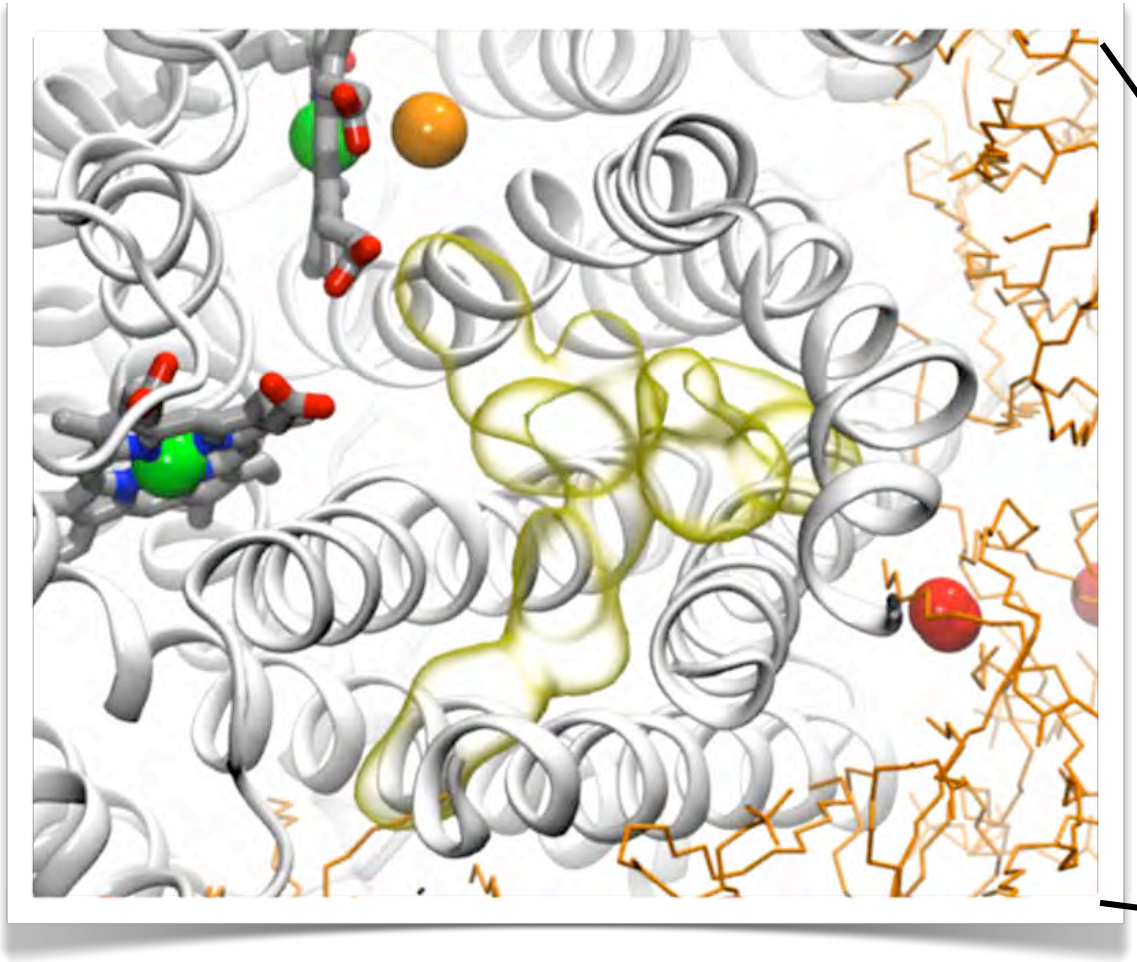
$$F(z) = -RT\ln\sum_{x,y=0}^{L_x,L_y}\frac{\mathrm{e}^{-F(x,y,z)/RT}}{L_xL_y}$$

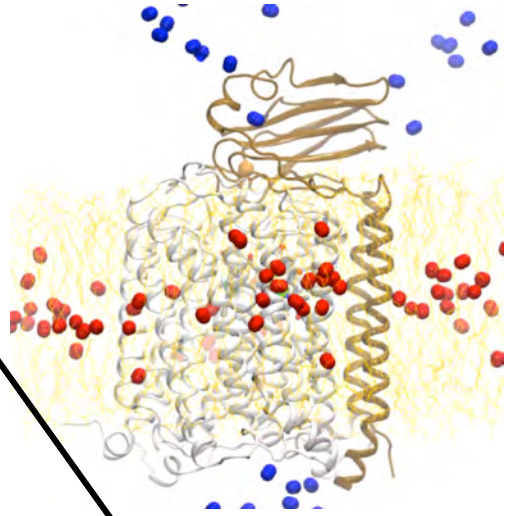
Cohen, et al., 2006; Wang, et al., 2007

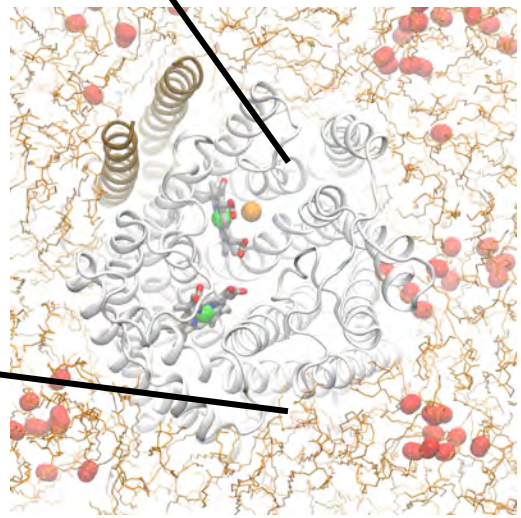
Oxido-reductase and Proton Pump



Rapid O_2 Permeation via the Hydrophobic Channel in Cytochrome C Oxidase

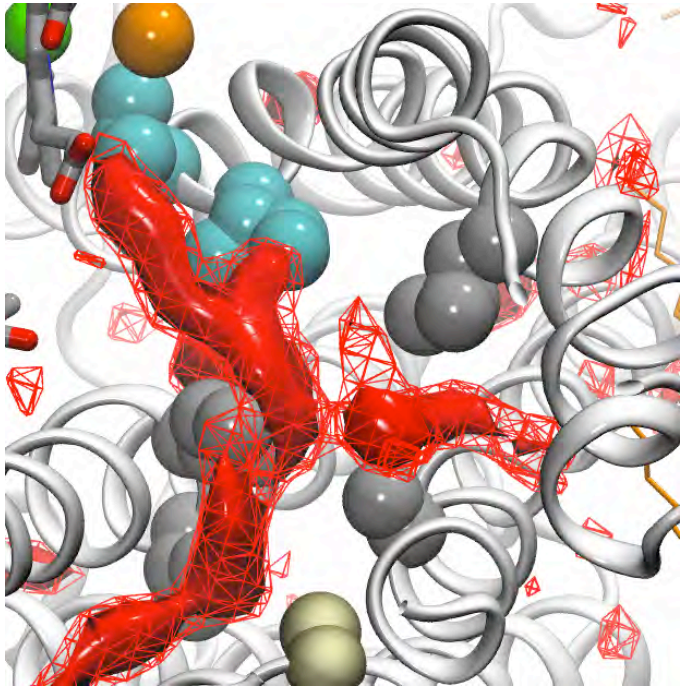




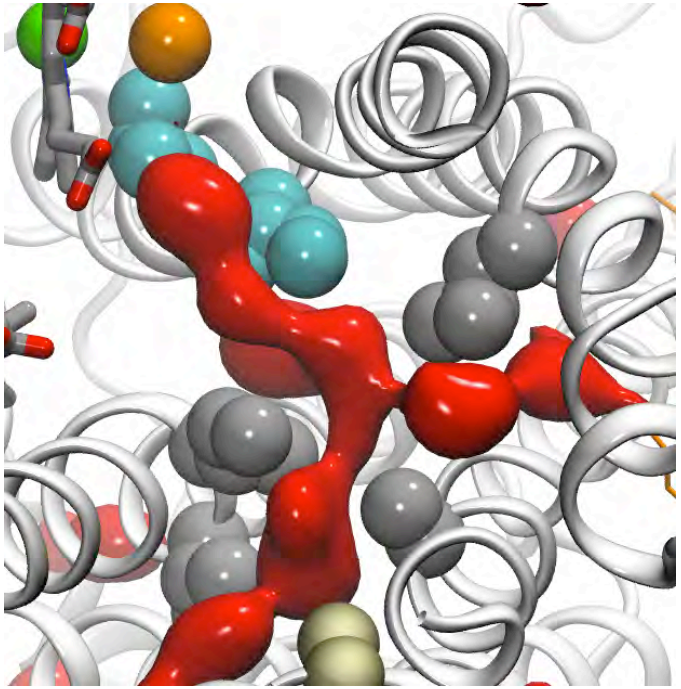


O_2 Pathway in Cytochrome C Oxidase

Implicit ligand sampling

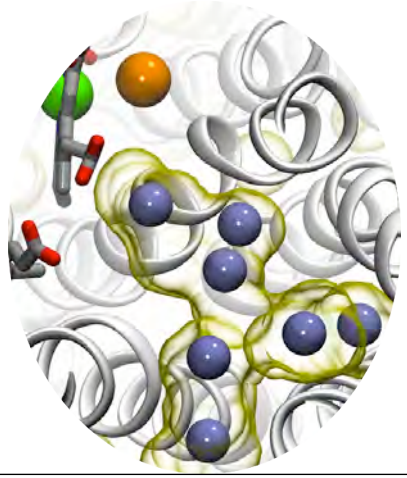


Explicit O_2 simulation



Reddish solid: ΔΔG map of ~ -3.5 kcal/mol ; Reddish wireframe: ΔΔG map of ~ -3.0 kcal/mol

Observed Xenon binding in CcO ba_3 crystal structures

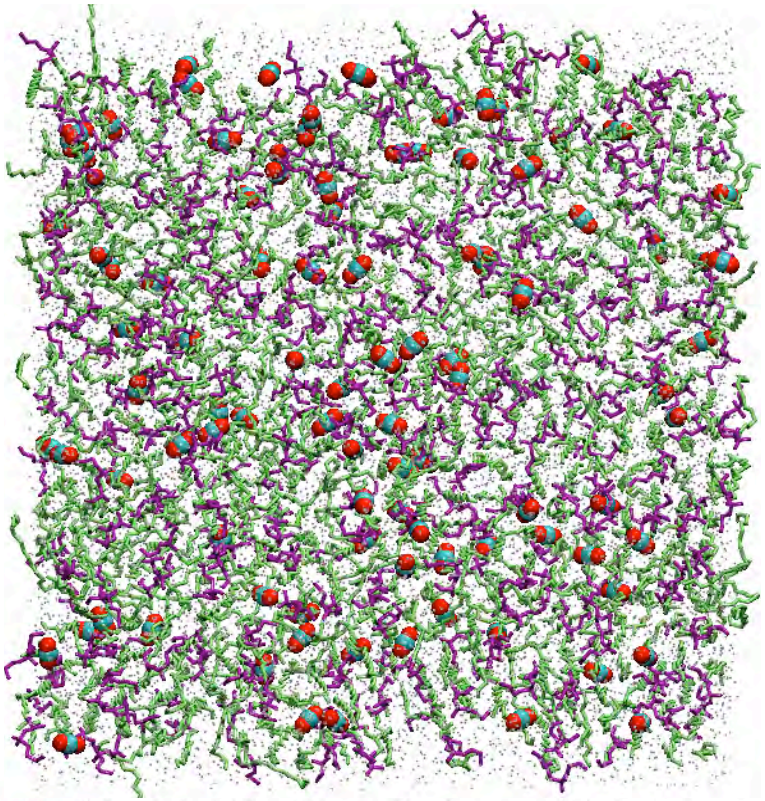


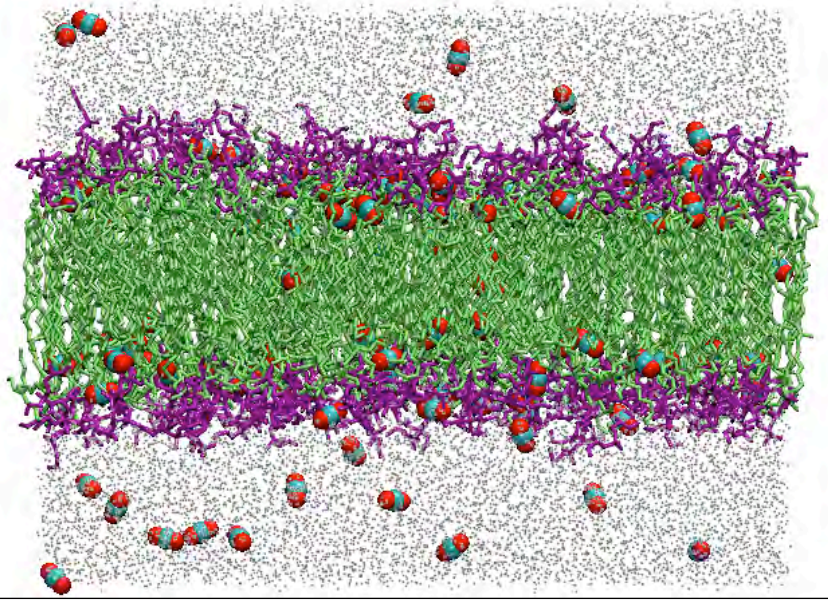
All located along the hydrophobic channel

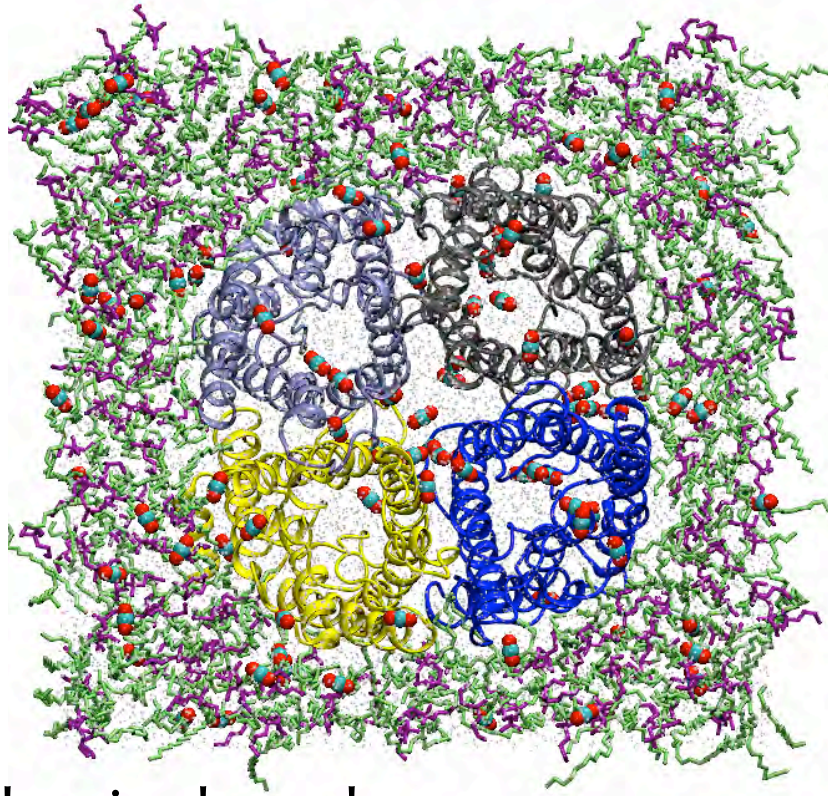
Luna VM, Chen Y., Fee JA and Stout CD (2008)
Biochemistry, 47, 4657-4665 (PDB entry 3BVD)

Luna VM, Fee JA, Deniz AA and Stout CD (2012)
Biochemistry, 51, 4669-4676

Simulating Membrane Gas Transport







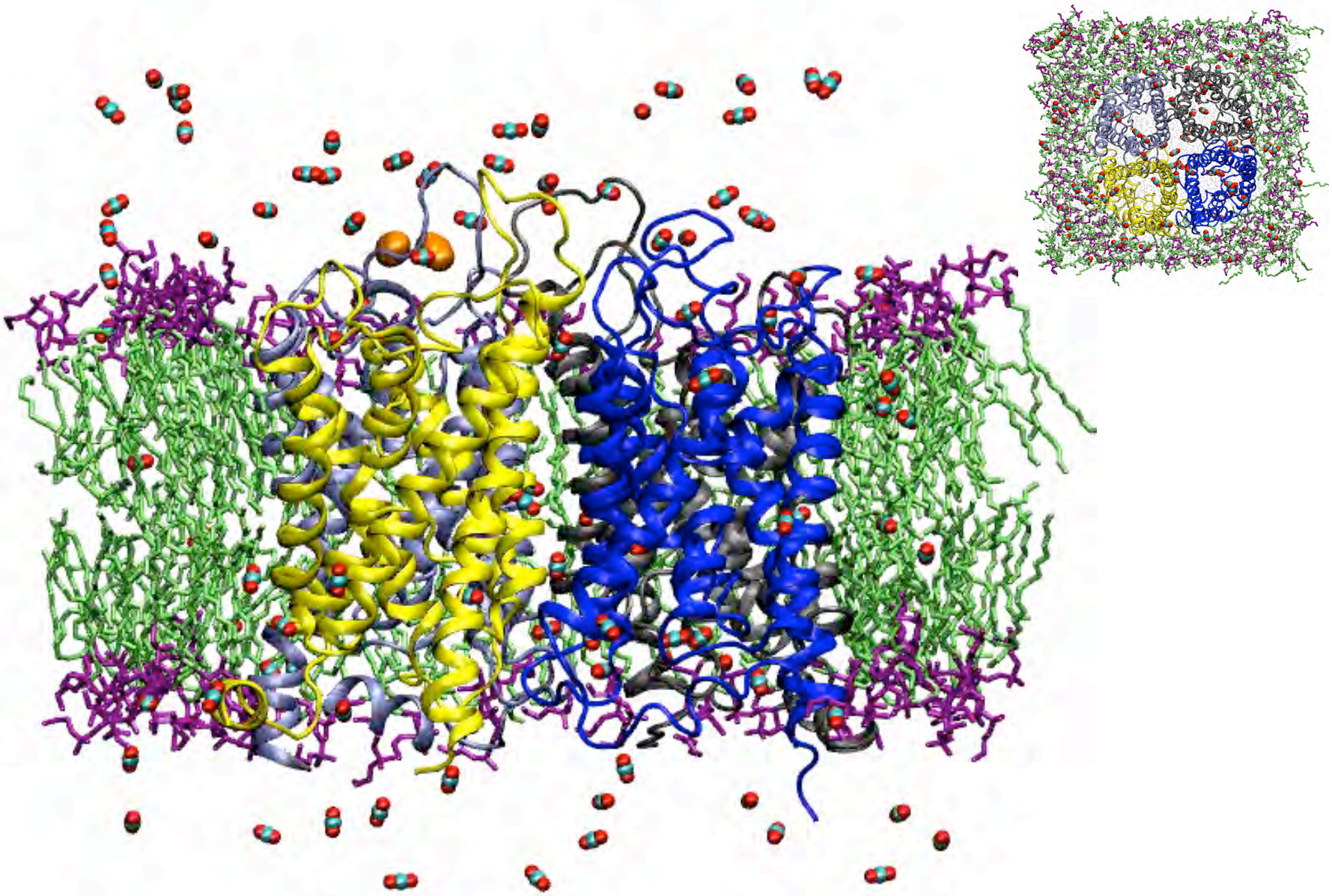
Identical total areas

Calculating permeation rate in MD simulations

AQP1 AQP4

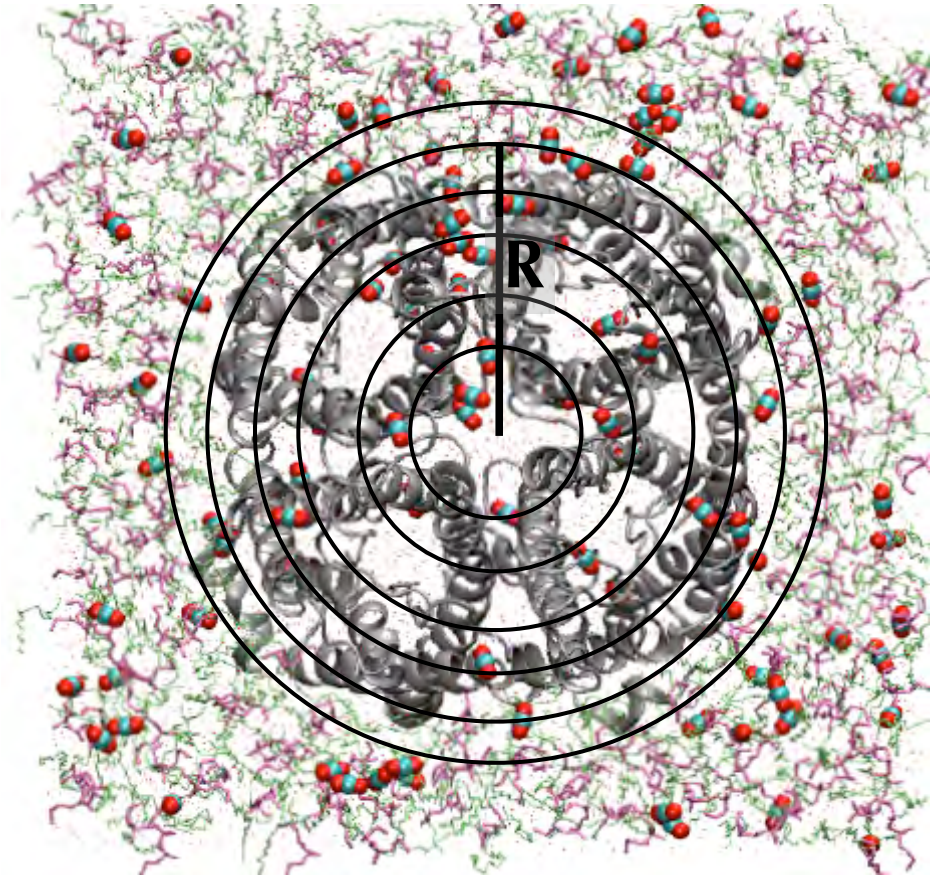
CO_2 O_2 NO

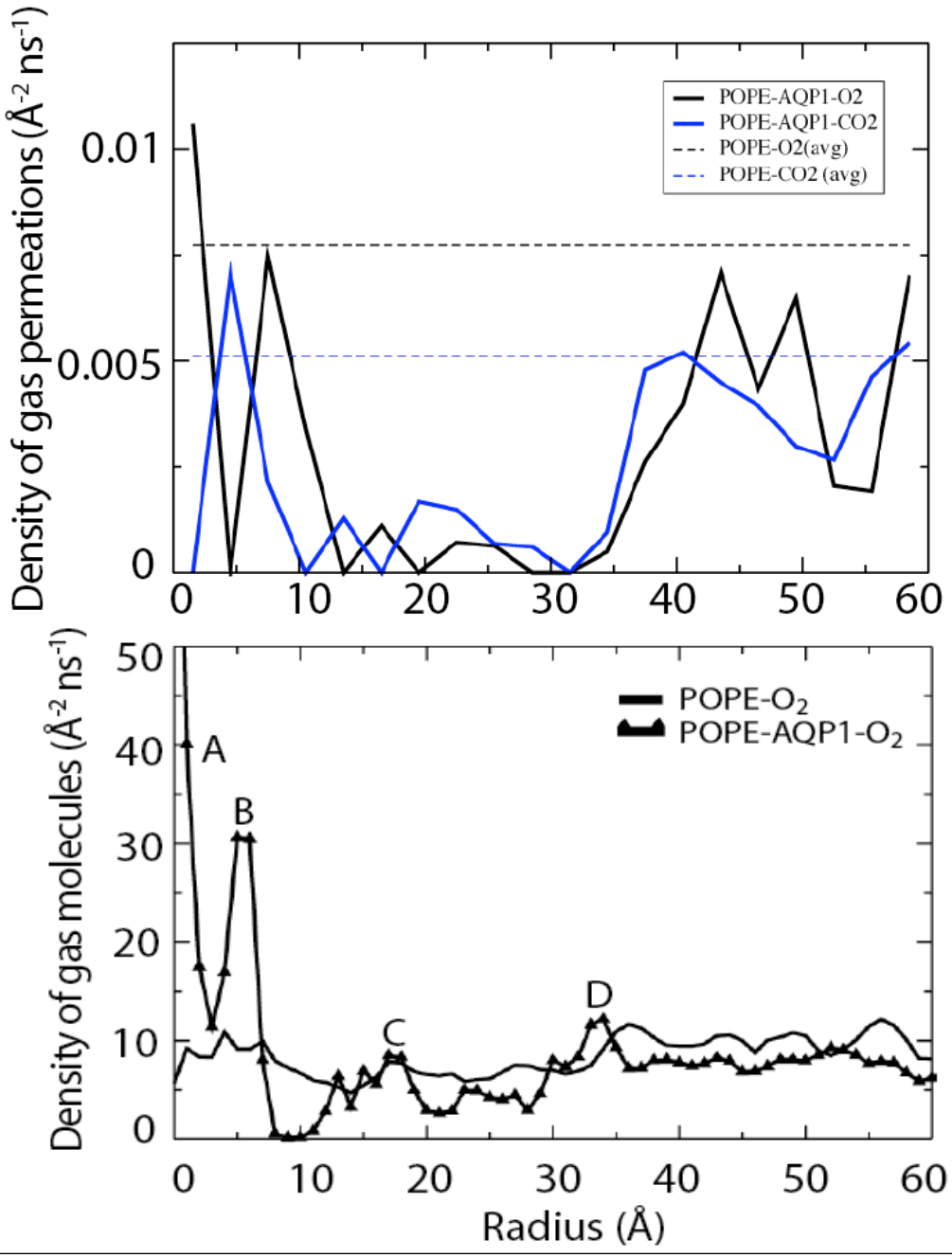
Gas Transport through Aquaporins



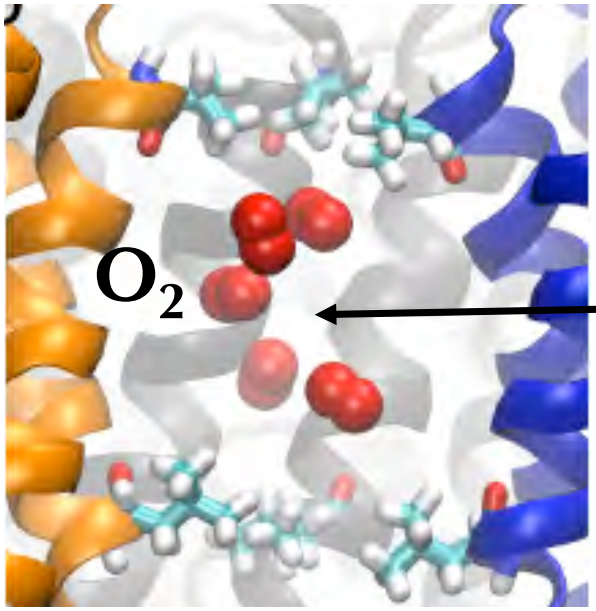
Typical permeation events (300-400 ps)

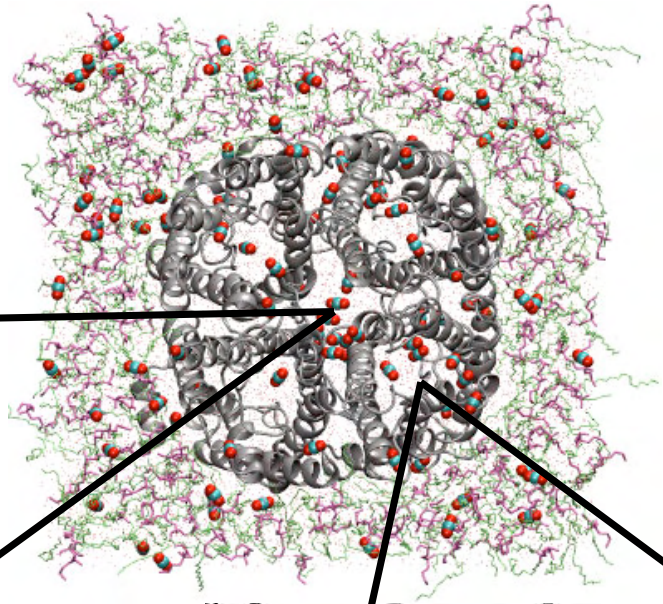
Gas Occupancy/Permeation Radial Distribution



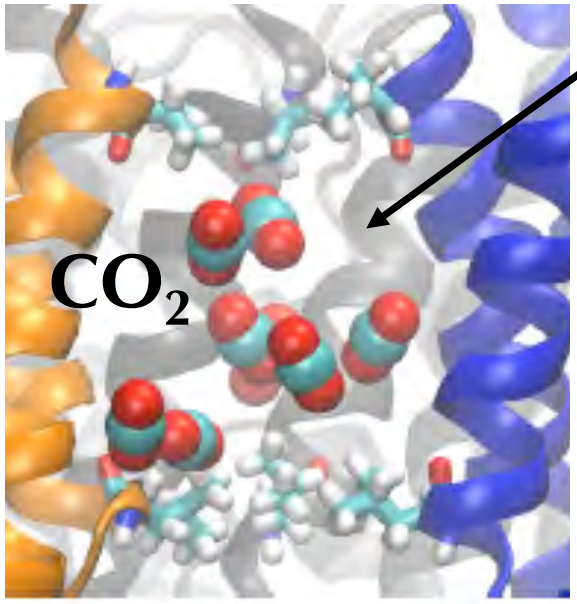


A Role for the Central Pore!

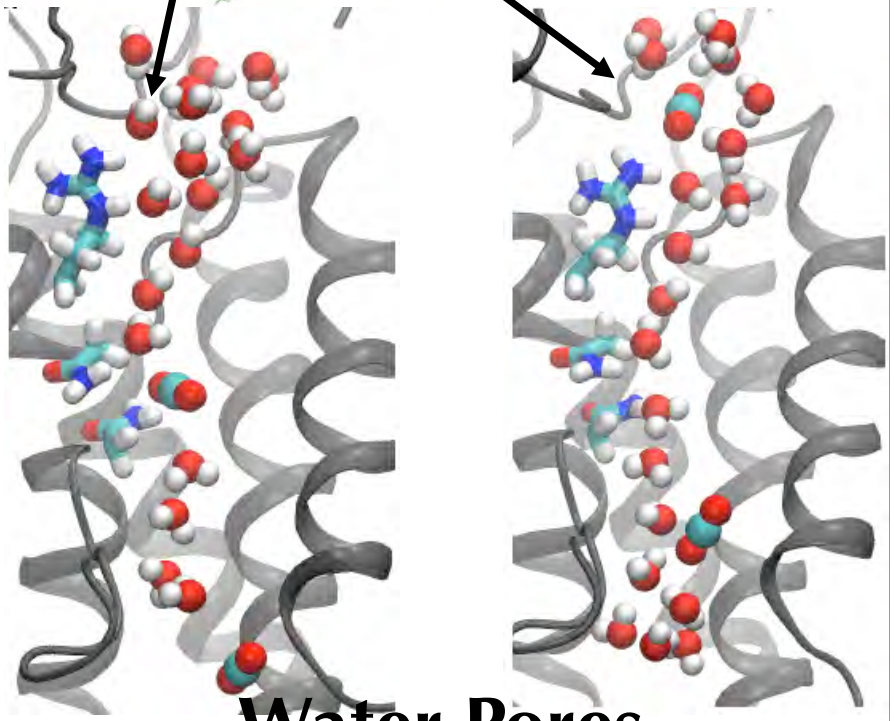




Central Pore



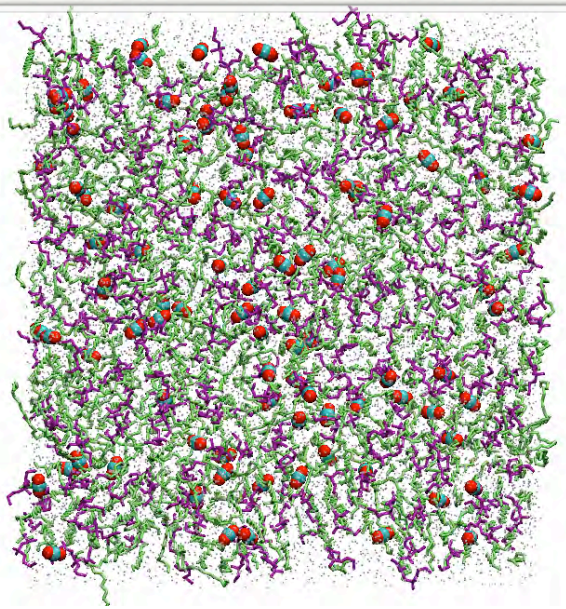
CO_2

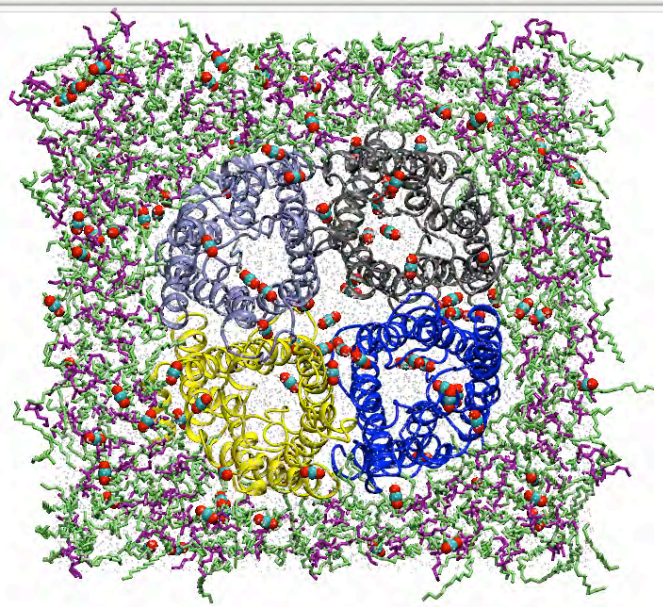


Water Pores

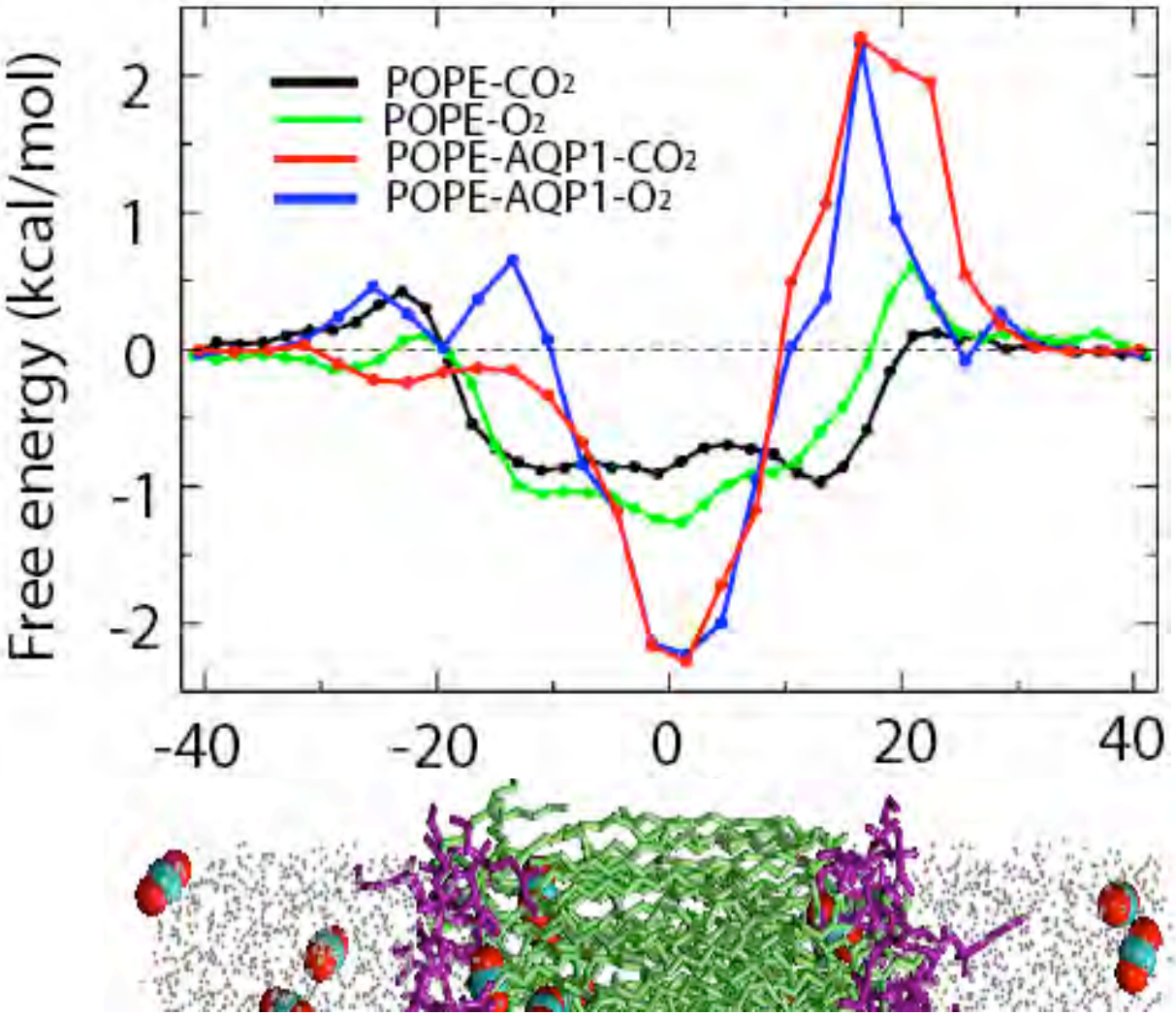
Gas Transport through Aquaporins

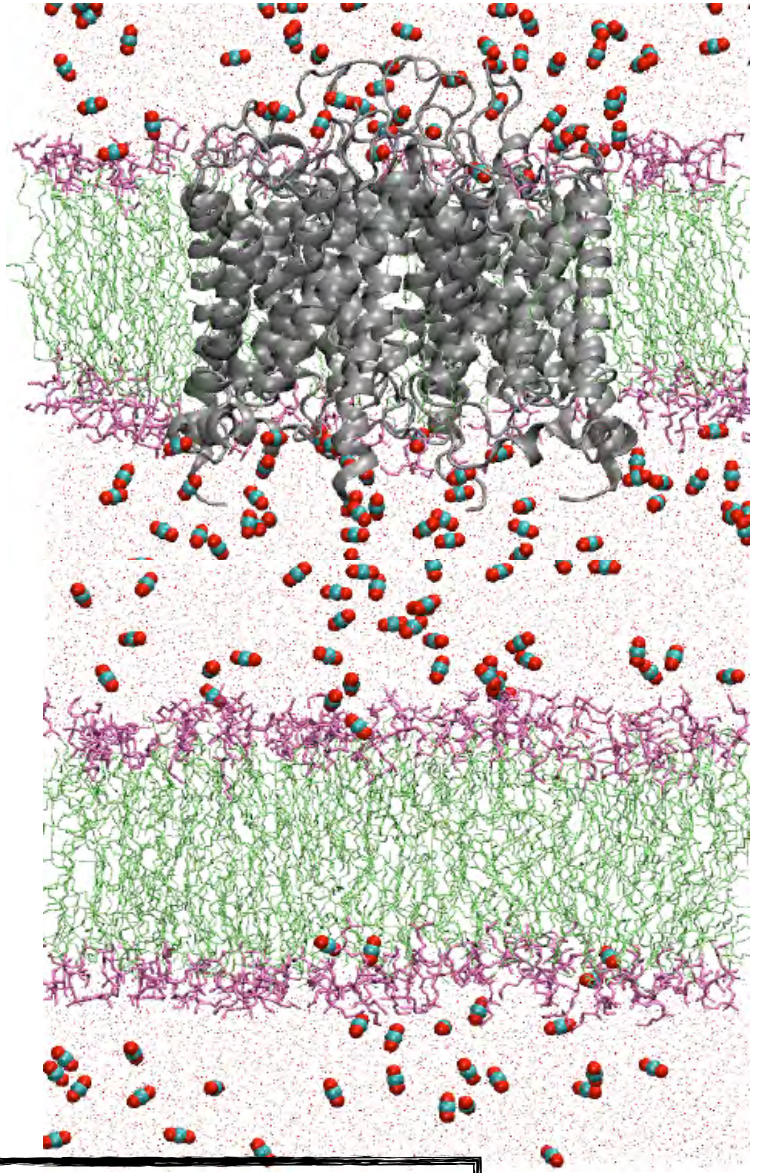
SYSTEM	TOTAL (100x100 A^2)	WATER PORES (4)	CENTRAL PORE (1)
Equi POPE-CO_2	*3*	*N/A*	*N/A*
Equi POPC-CO_2	*5*	*N/A*	*N/A*
Equi POPC-$O_{2(P)}$	*16*	*N/A*	*N/A*
Equi POPE-$O_{2(P)}$	*11*	*N/A*	*N/A*
Press POPE-CO_2	168	N/A	N/A
Press POPC-CO_2	160	N/A	N/A
Press POPE-$O_{2(P)}$	310	N/A	N/A
Press POPC-$O_{2(P)}$	208	N/A	N/A
Press POPE-AQP1-CO_2	**76**	**6**	**4**
Press POPE-AQP1-$O_{2(P)}$	**79**	**1**	**6**





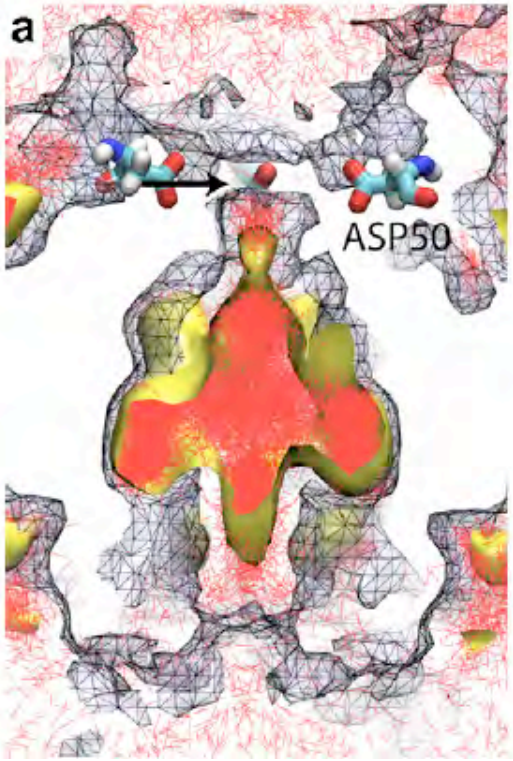
Free Energy Profiles for O_2 and CO_2

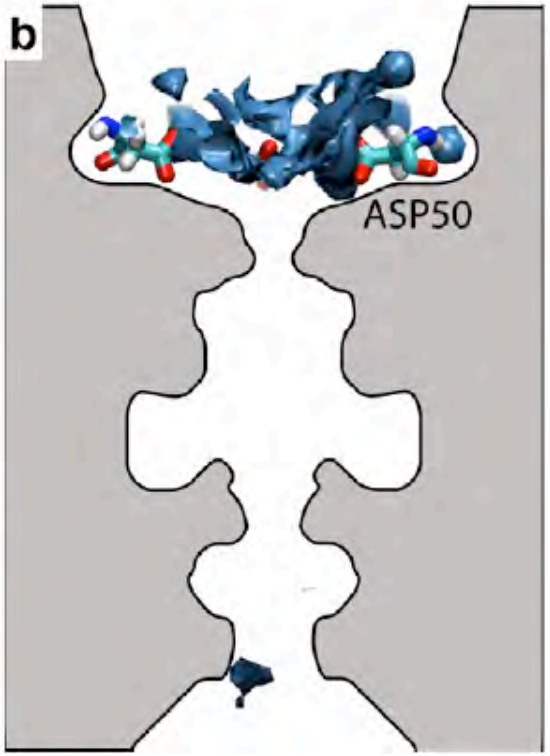


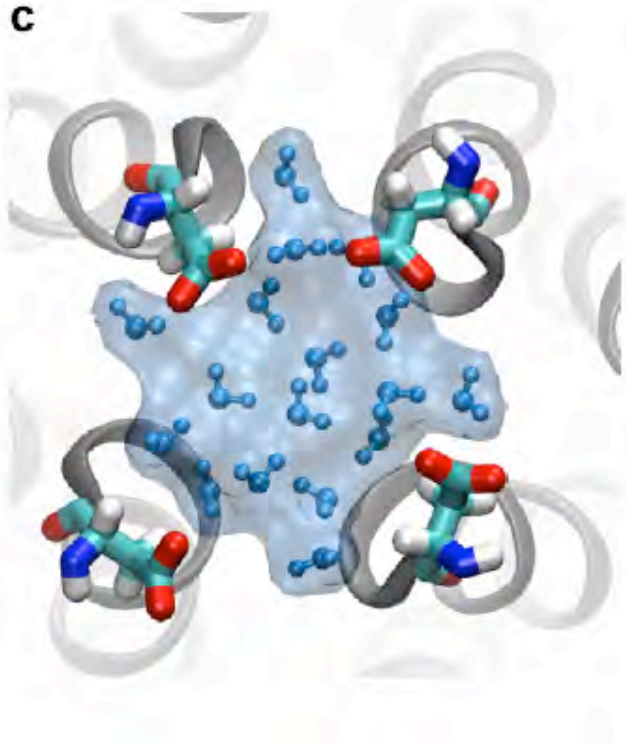


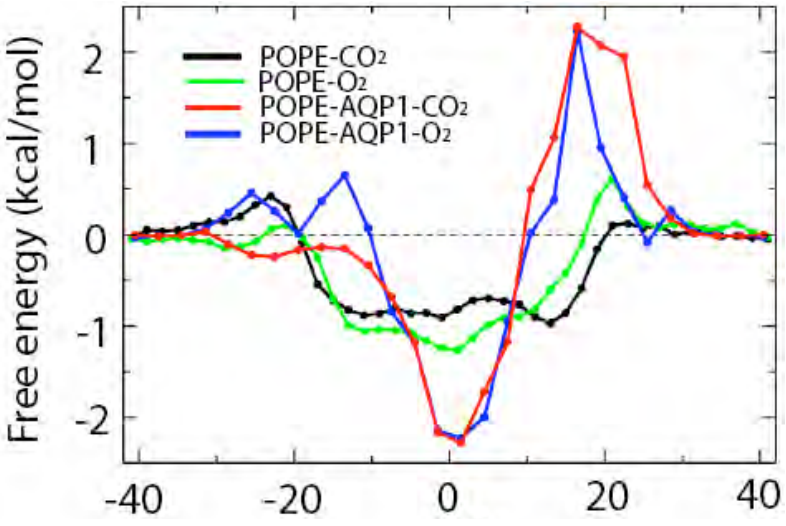
Y. Wang, J. Cohen, W. Boron, K. Schulten, and E. Tajkhorshid, ***J. Struct. Biol.,*** 2007.
Y. Wang, S. Shaikh, and E. Tajkhorshid, **Physiology,** 2010.

Major Barrier Generated by Structured Water





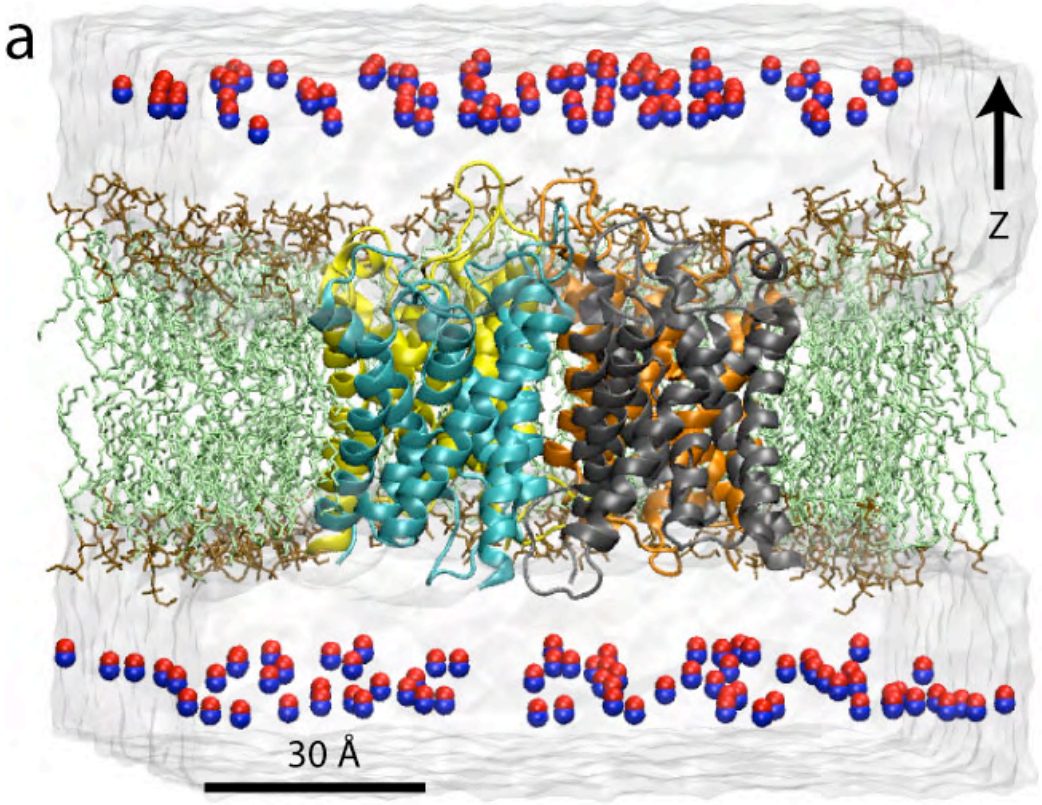


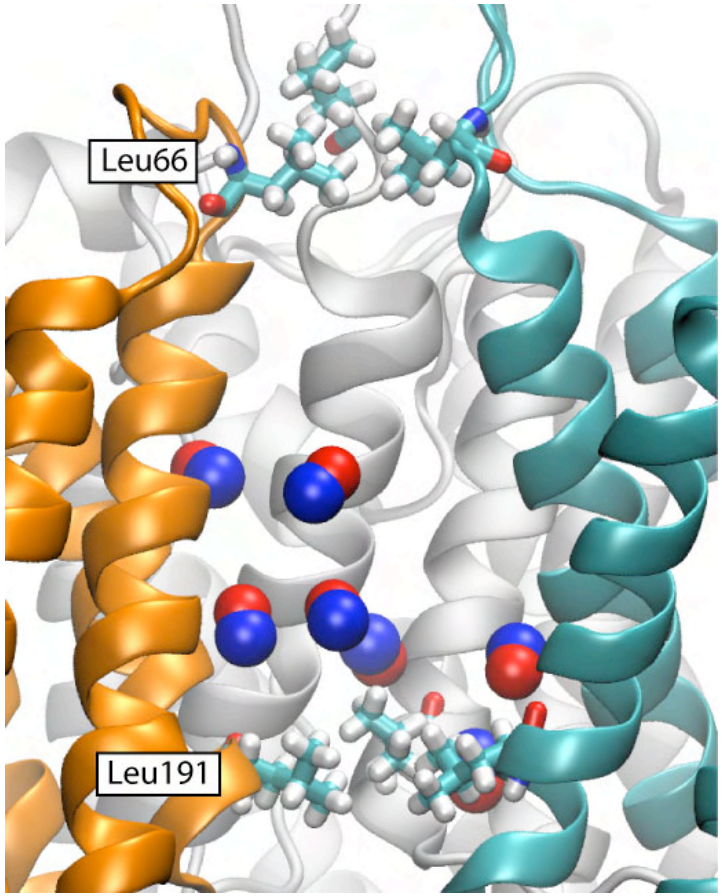


Barrier identified and characterized through combining the implicit and explicit approaches

Y. Wang, J. Cohen, W. Boron, K. Schulten, and E. Tajkhorshid, ***J. Struct. Biol.,*** 2007.
Y. Wang, S. Shaikh, and E. Tajkhorshid, **Physiology,** 2010.

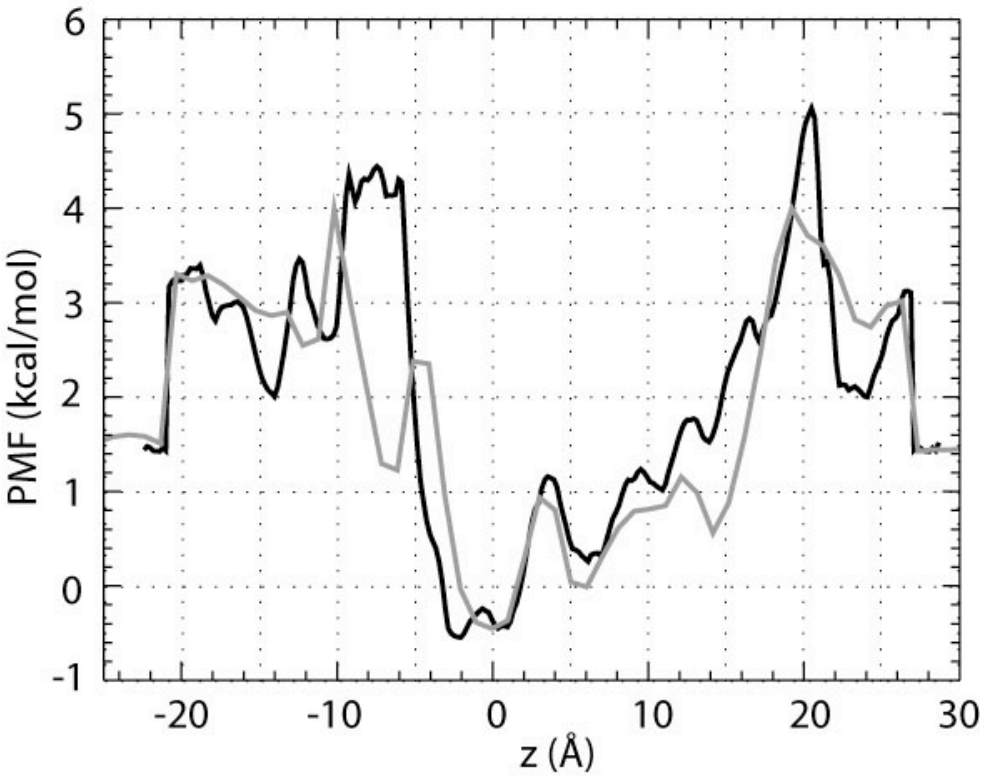
$NO^{\bullet}$ Permeation Through AQP4





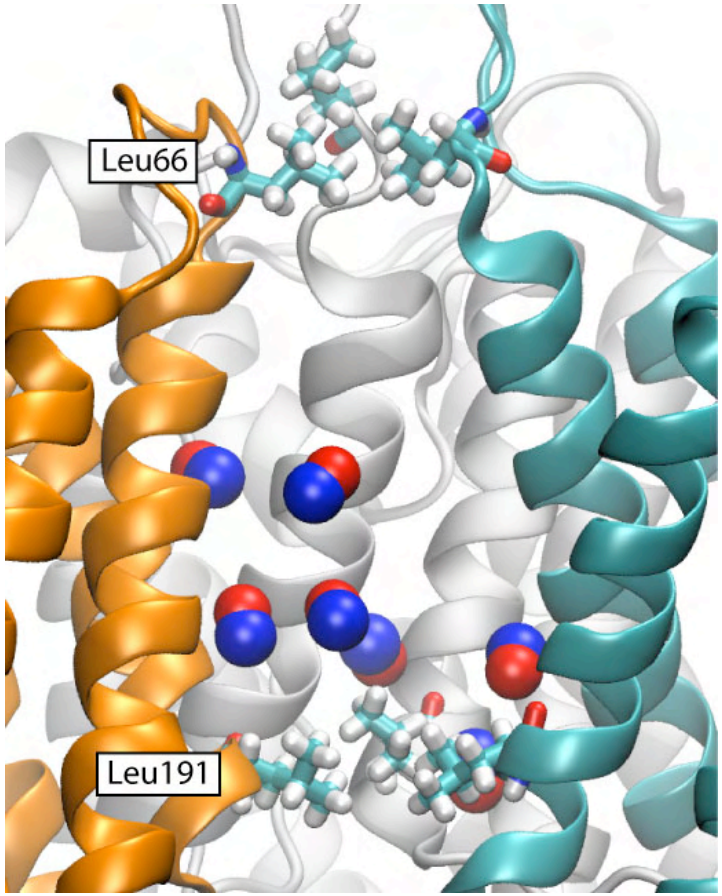
Y. Wang, and E. Tajkhorshid, ***Proteins,*** 2010.

$NO^{\bullet}$ Permeation Through AQP4



--- Umbrella sampling

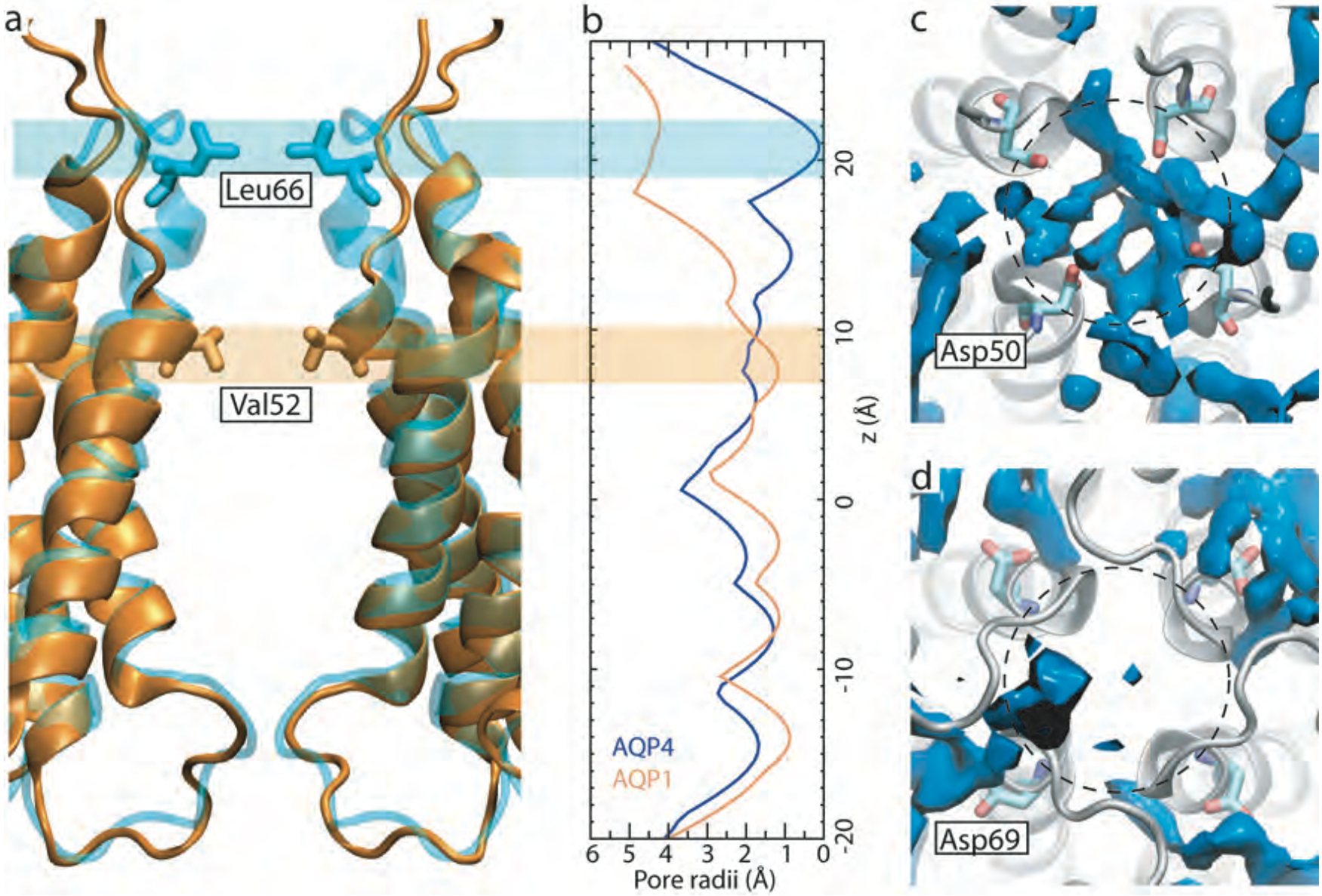
--- Implicit sampling



50 ns equilibrium simulation

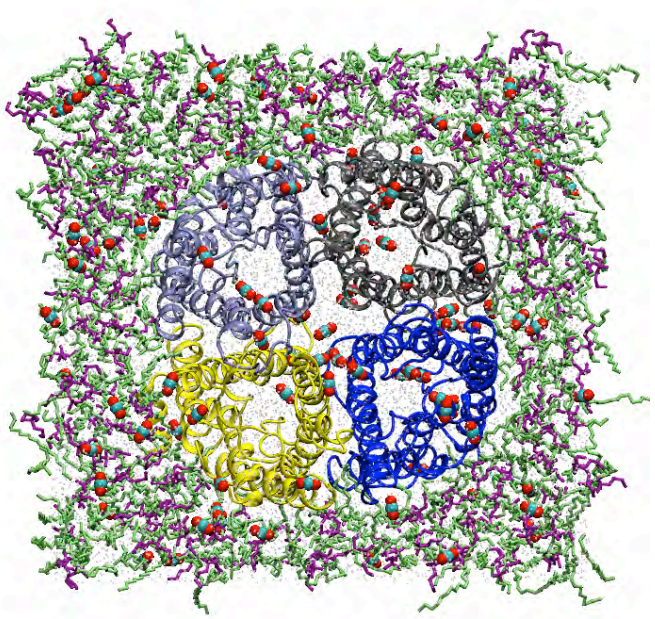
Y. Wang, and E. Tajkhorshid, ***Proteins,*** 2010.

Comparison of the Central Pore in AQP1 and AQP4



Gas Transport through Aquaporins

✦ Computational evidence for gas transport through a membrane channel



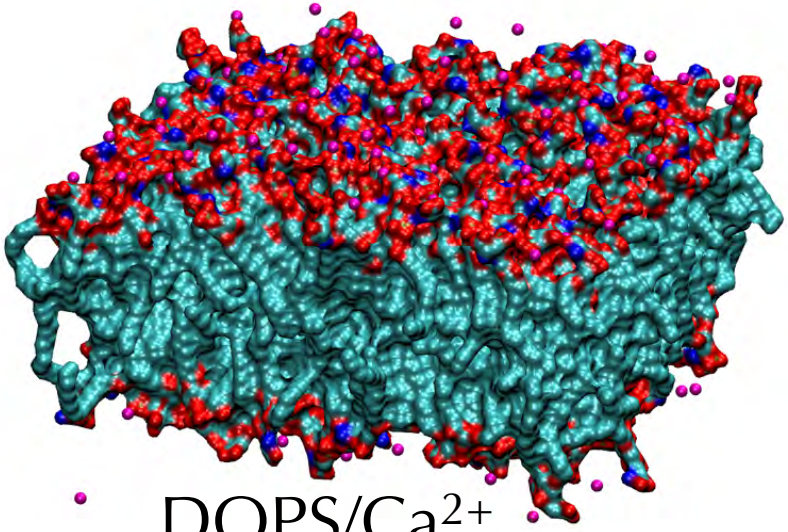
✦ Central Pore in AQPs is an optimal pathway for gas diffusion

Shared by other oligomeric membrane proteins?

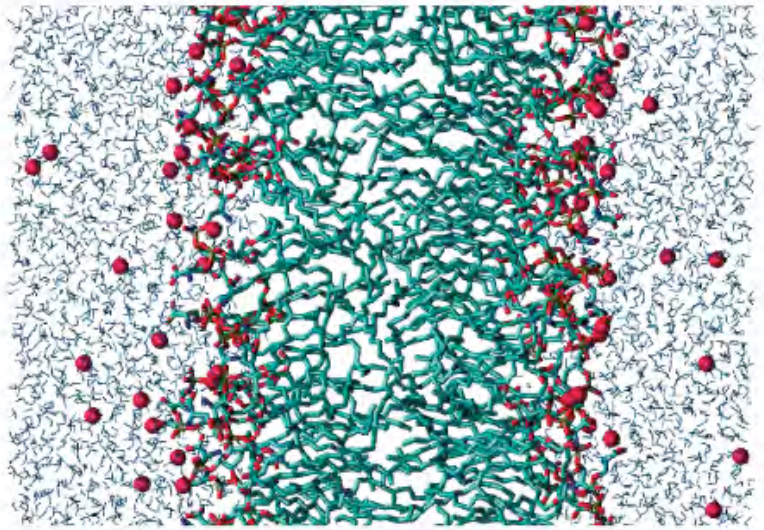
✦ AQPs can be physiologically relevant gas channels in lipid bilayer with low gas permeability

✦ We can simulate very efficiently the process of gas diffusion, but we rely heavily on reliable initial configurations of lipids/ protein

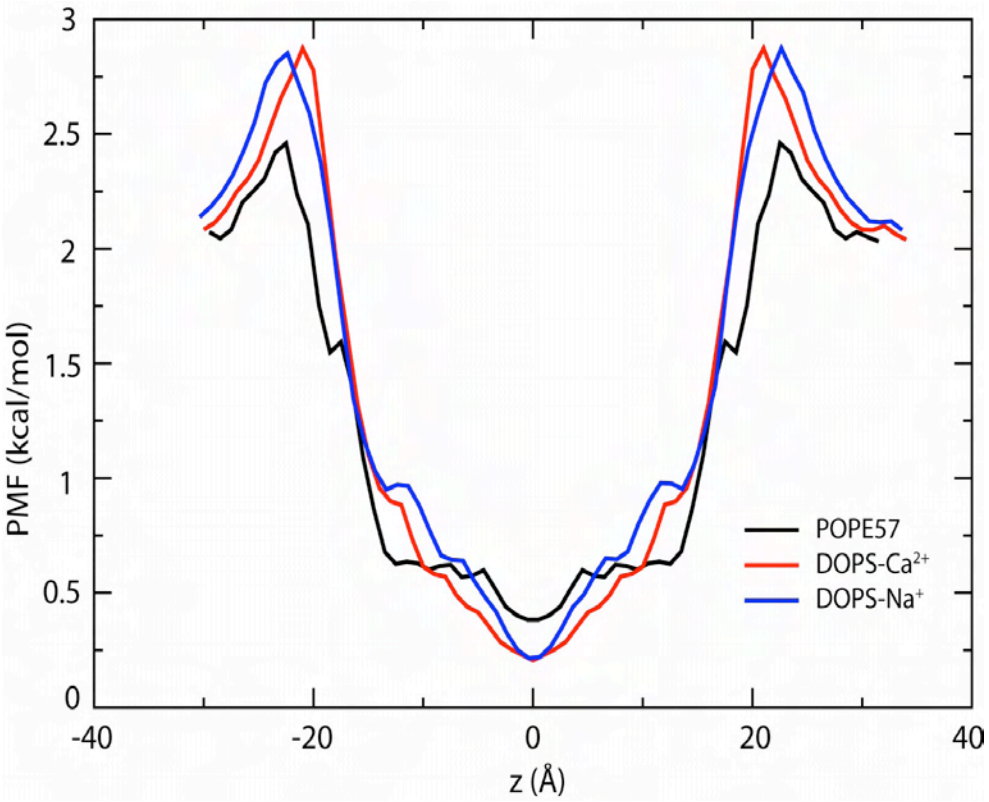
Free Energy of O_2 Permeation Across Charged Lipid Bilayers



DOPS/Ca^{2+}



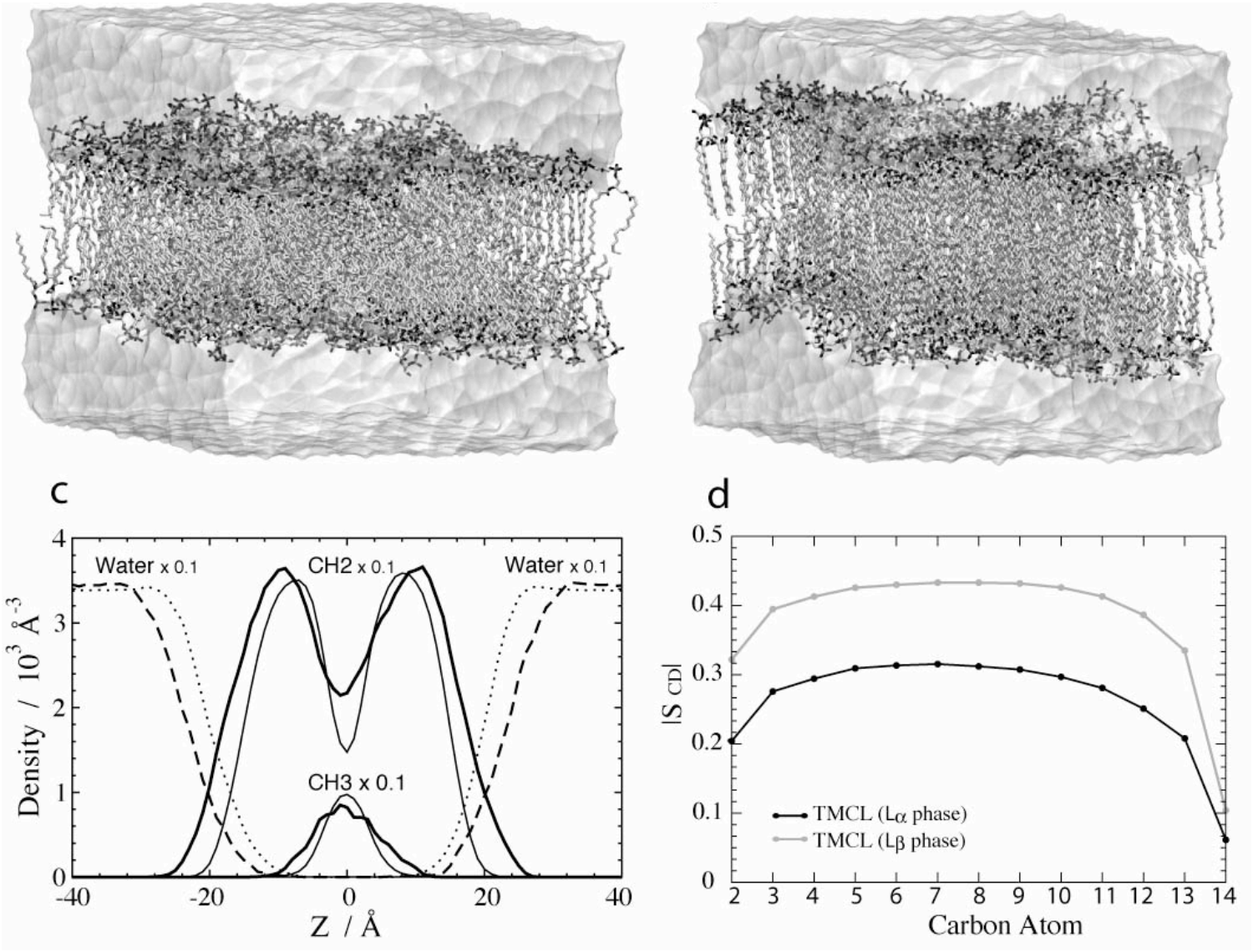
DOPS / Na^+



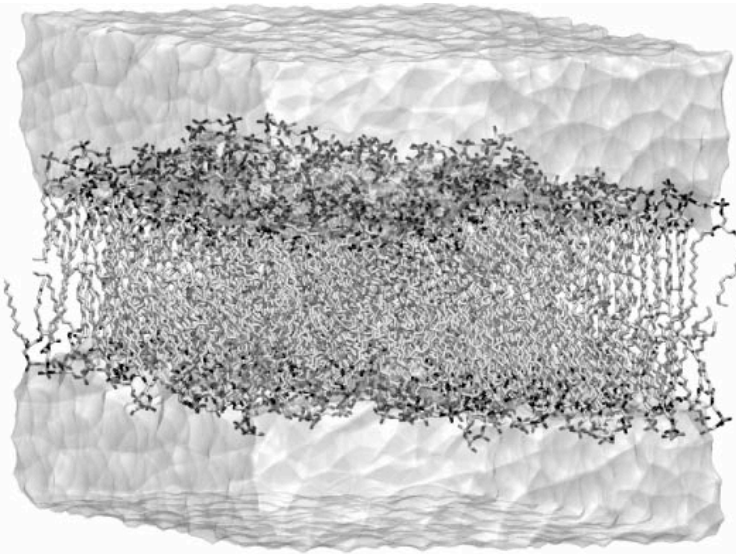
Lipid Phase and Gas Permeation

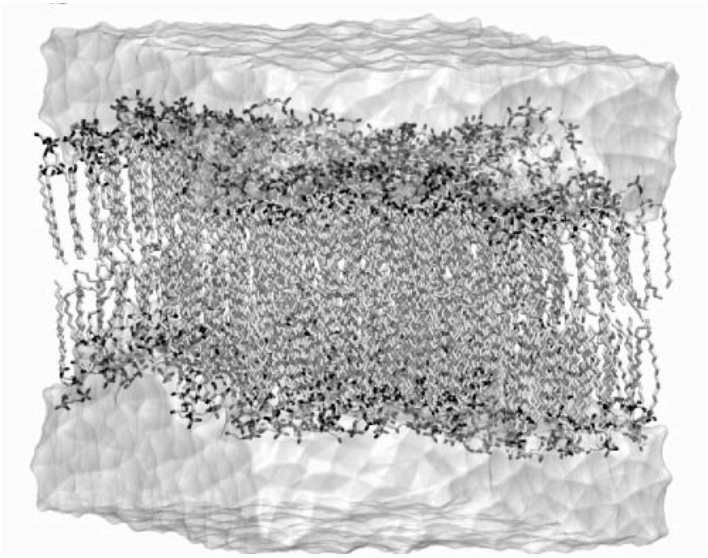
Liquid phase (30 ns)

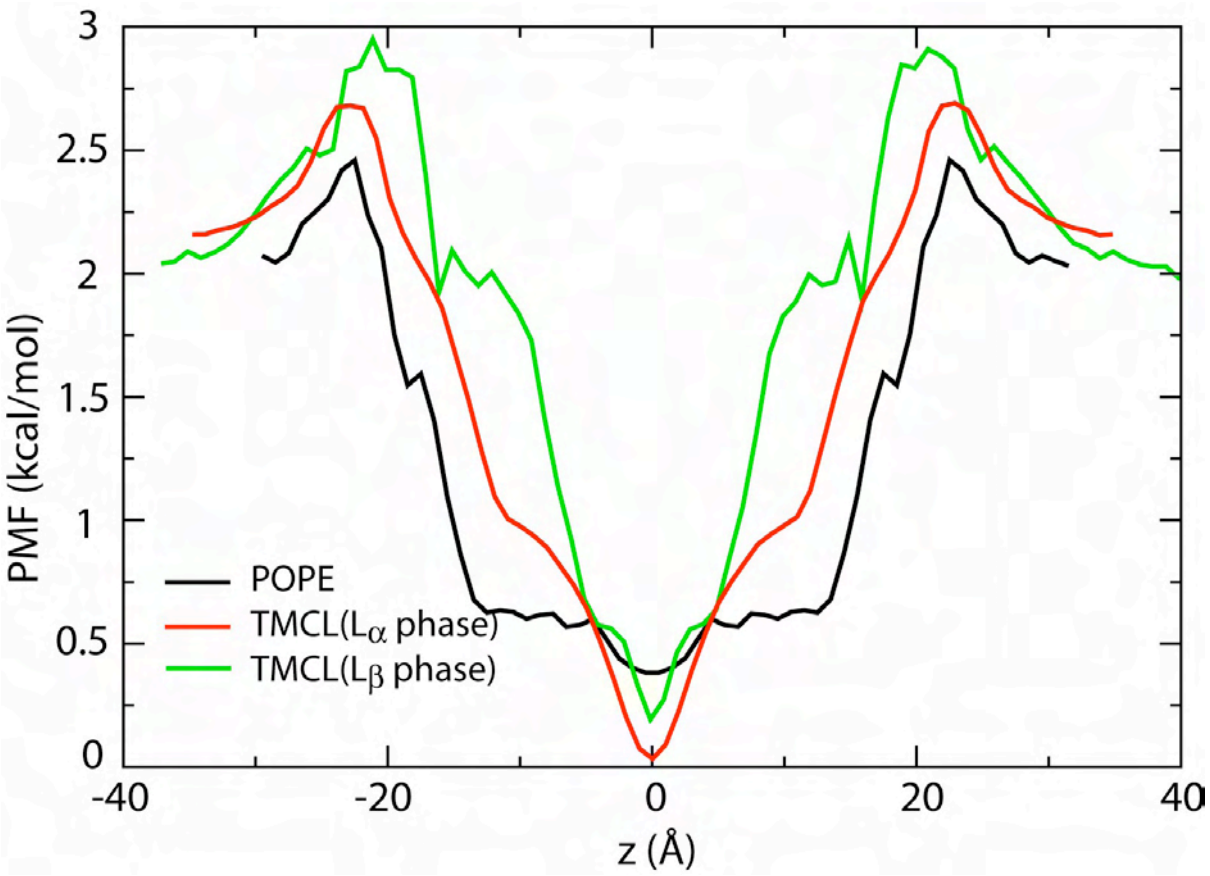
Gel phase (30 ns)



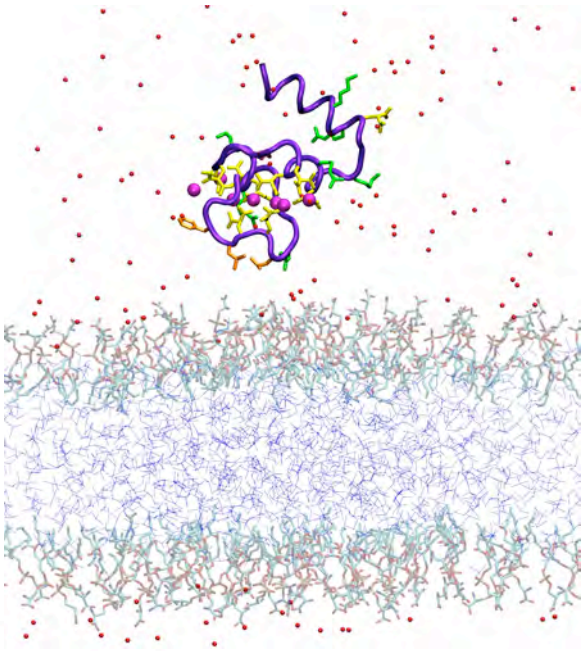
Lipid Phase and Gas Permeation

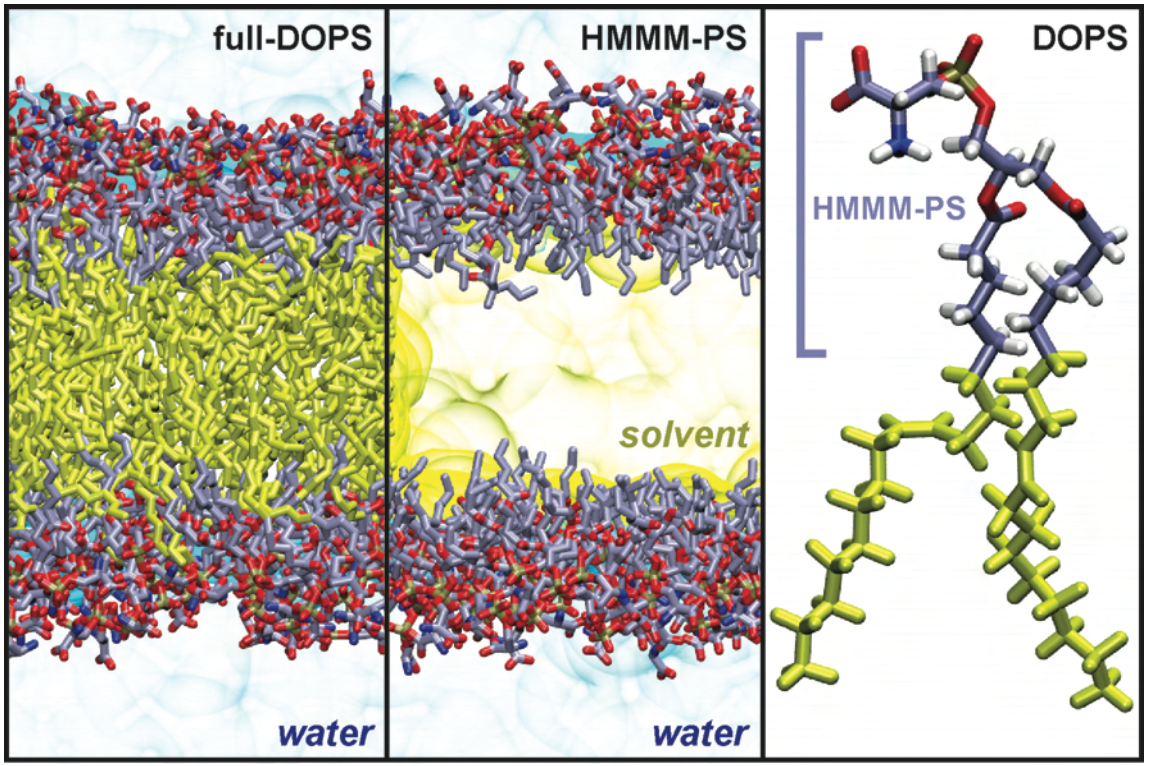


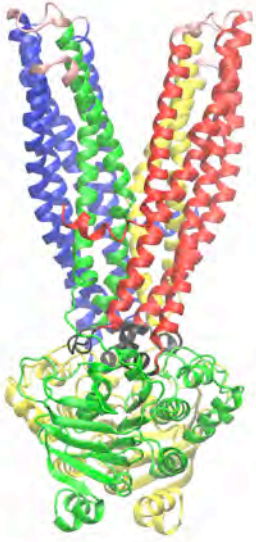


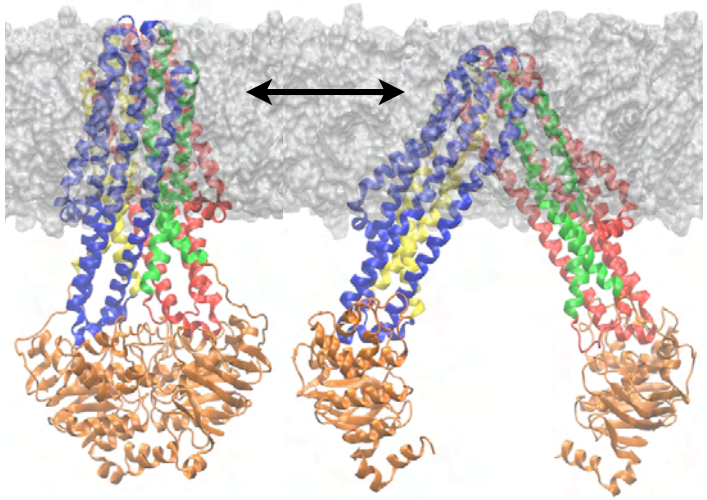


Highly **M**obile **M**embrane **M**imetic (**HMMM**) Model for Membrane Proteins and Phenomena



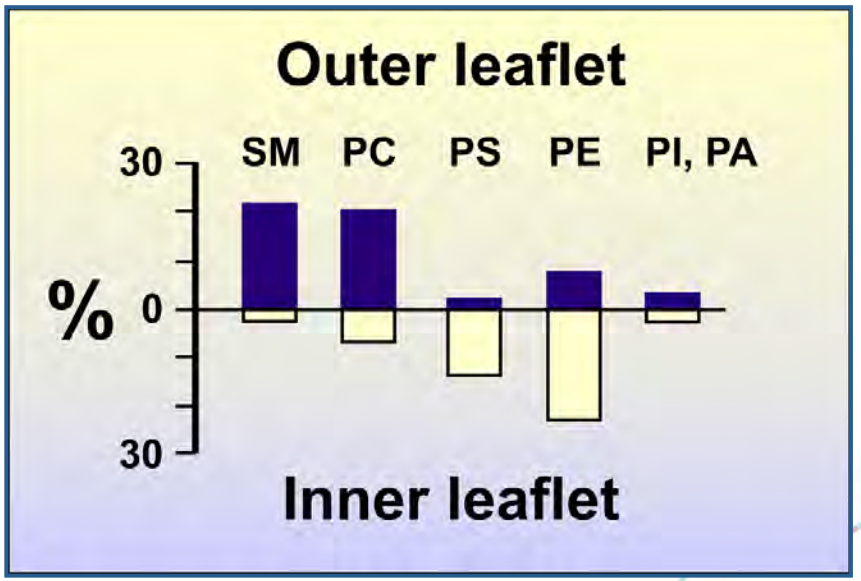


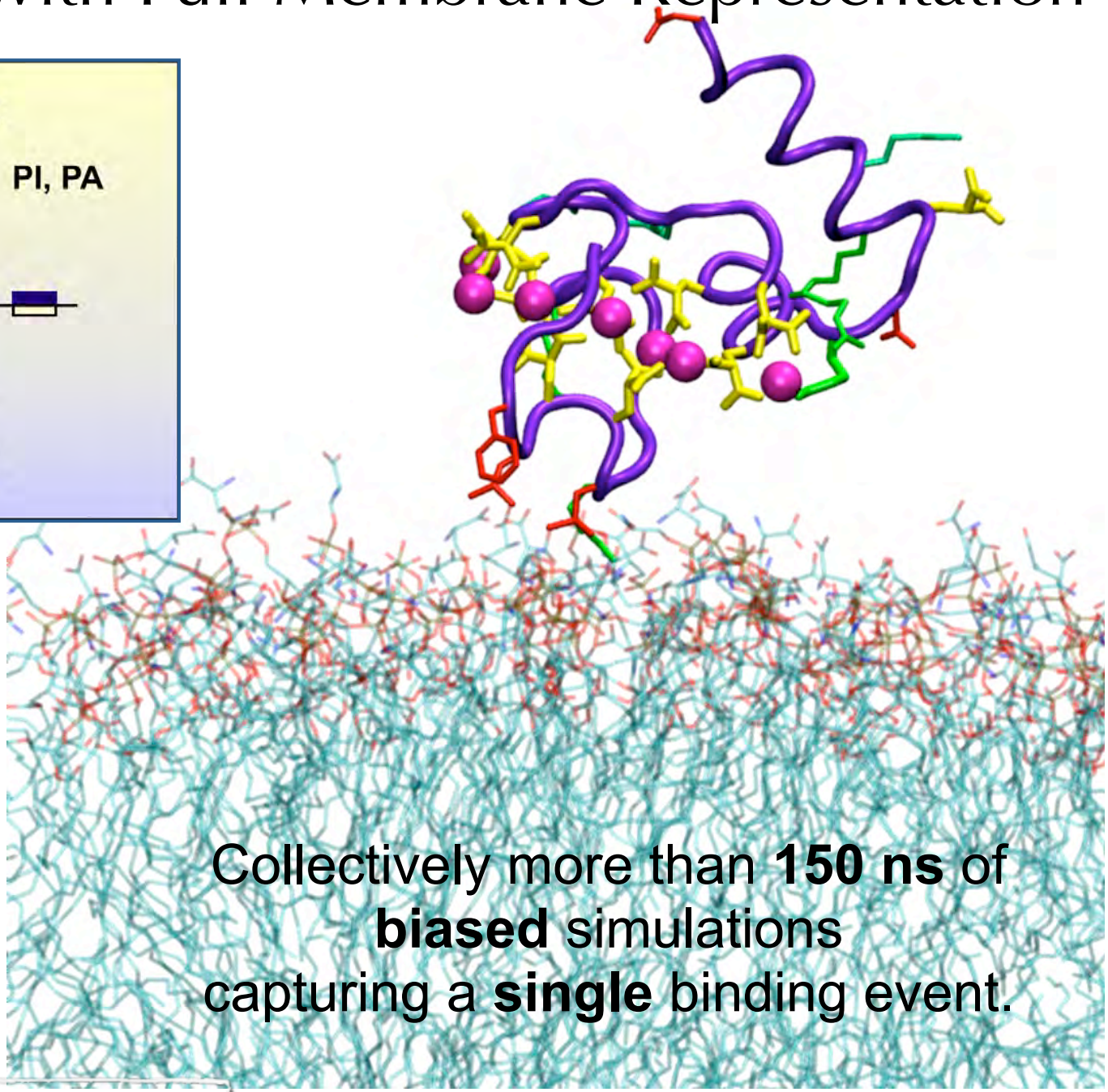




Ohkubo, Pogorelov, Arcario, Christensen, Tajkhorshid, *Biophysical J. May 2012.*

MD Simulation with Full Membrane Representation



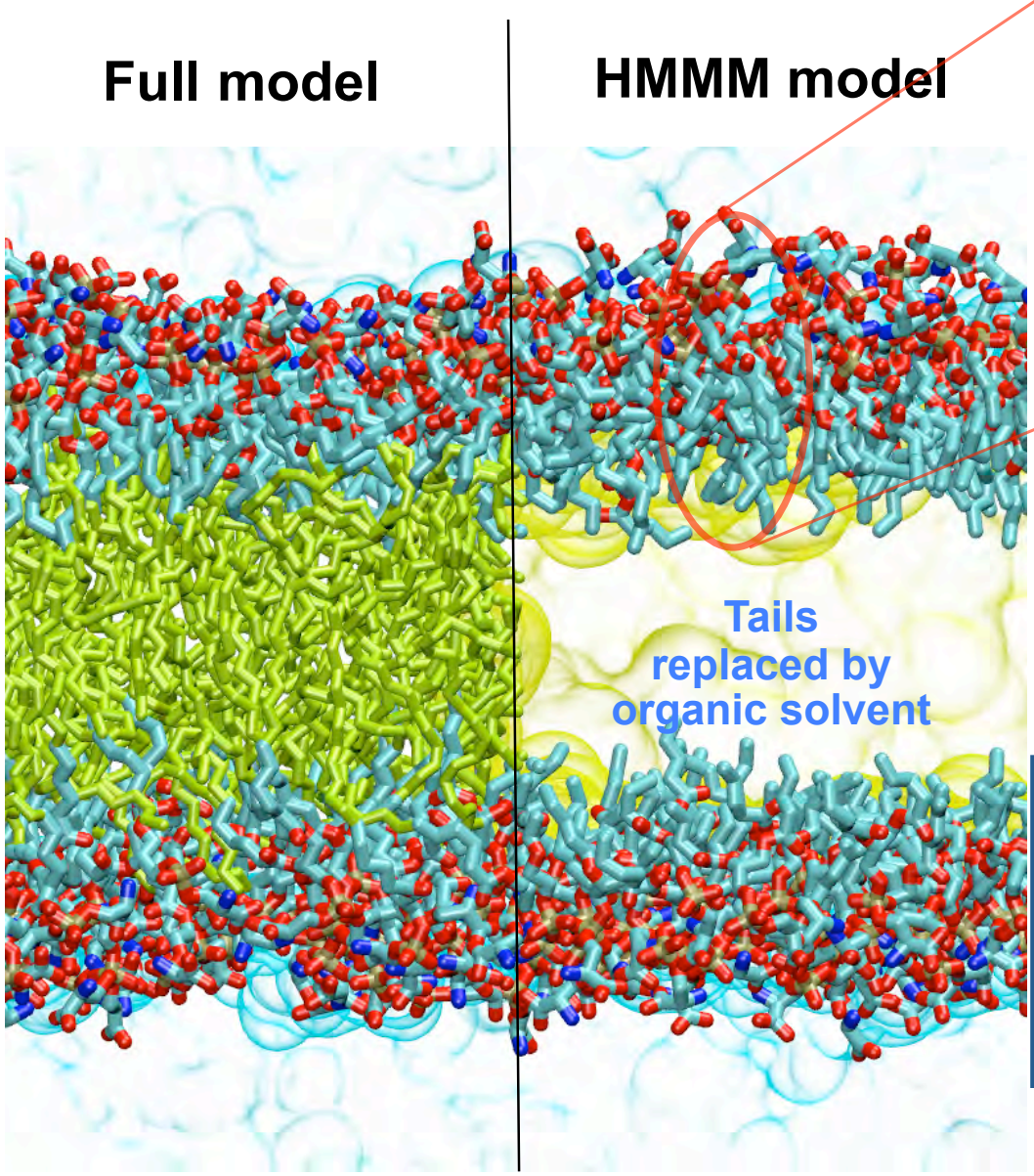


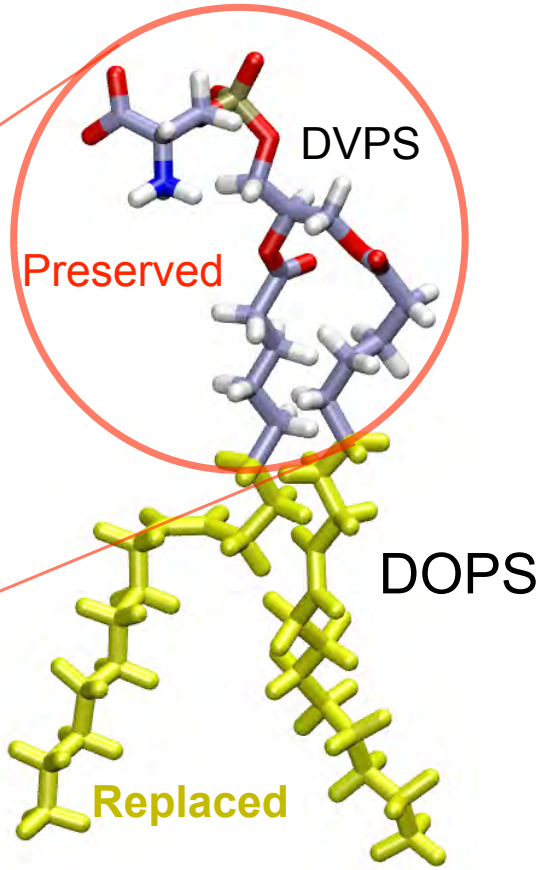
Collectively more than **150 ns** of **biased** simulations capturing a **single** binding event.

Z. Ohkubo and E. Tajkhorshid, *Structure* **2008**

HMMM model

Highly Mobile Membrane Mimetic model





Advantages

Increased mobility of lipids

Retain explicit headgroups allowing for atomic details


Zenmei Ohkubo

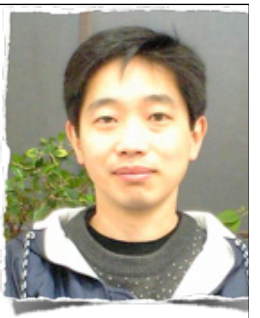

Mark Arcario


Taras Pogorelov

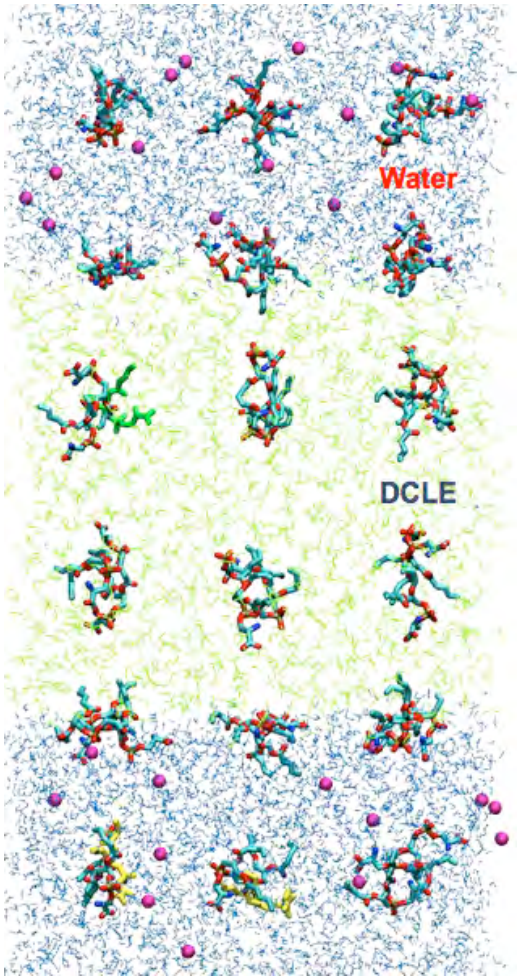

Josh Vermaas

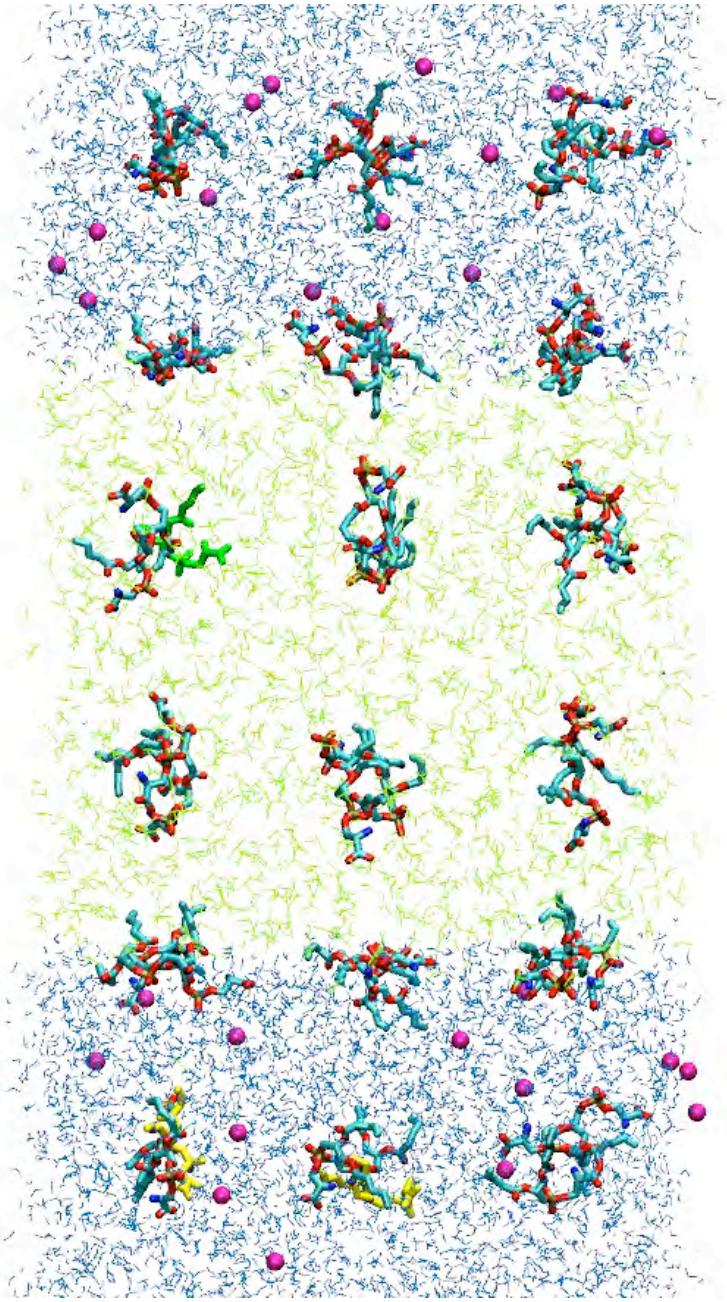

Javier Baylon

Spontaneous and Rapid Formation of a Bilayer



Zenmei Ohkubo



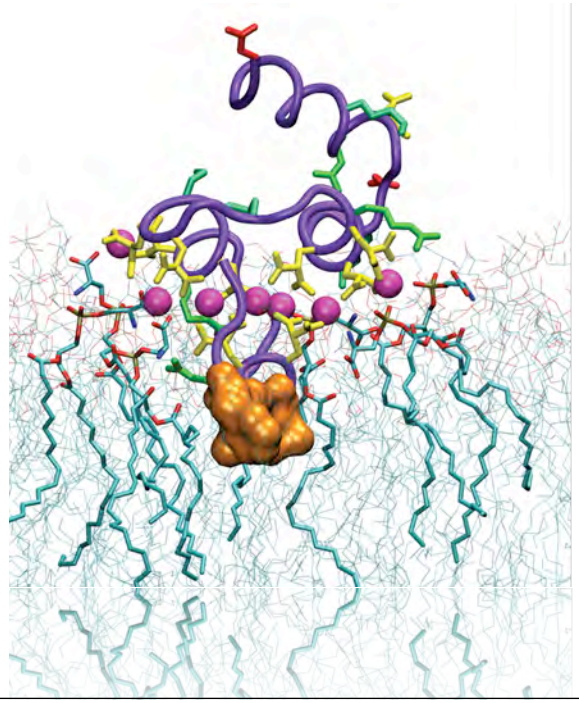


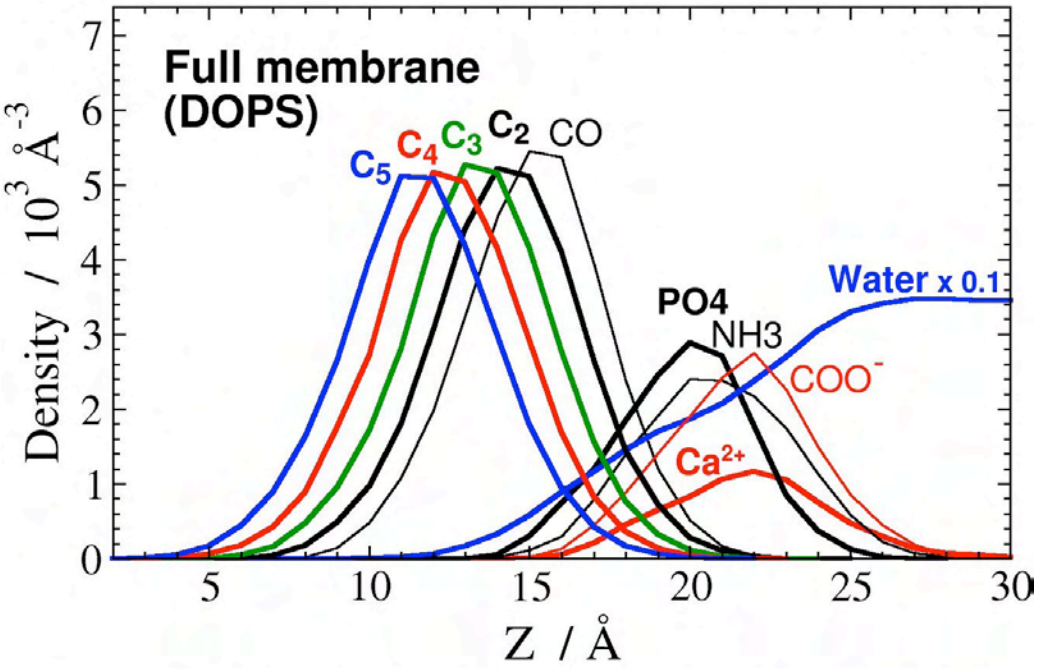
60 x 60 x 120 Å
DVPSs at 3 x 3 x 6 grid points
(22 ns)

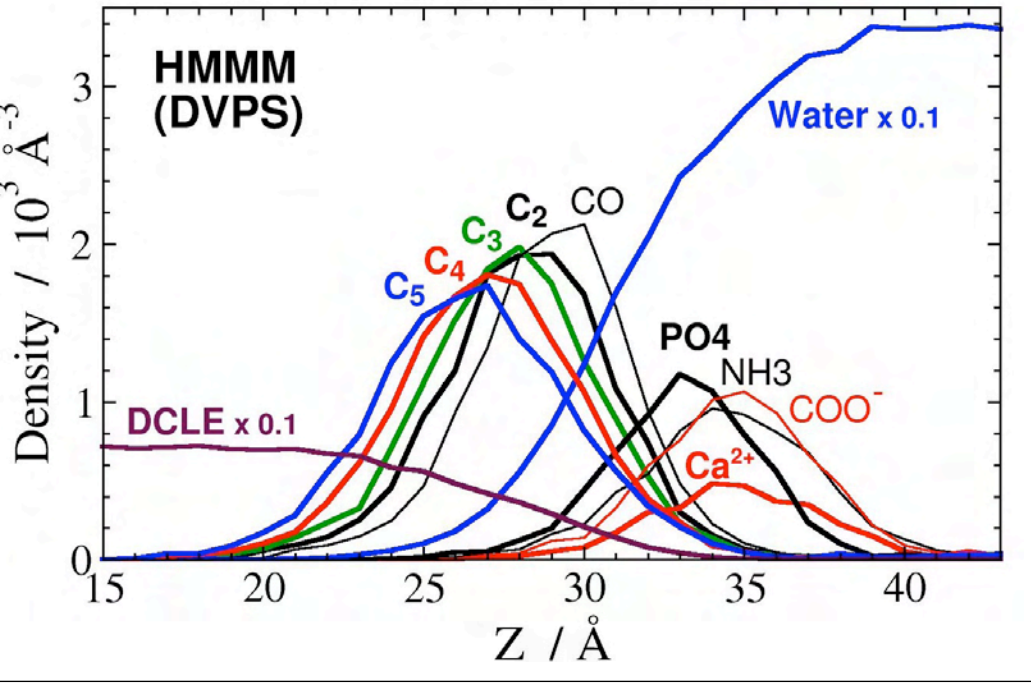
HMMM- Preserving the "Face" of the Lipid Bilayer

Perfect match in the membrane profile particularly in the head group region

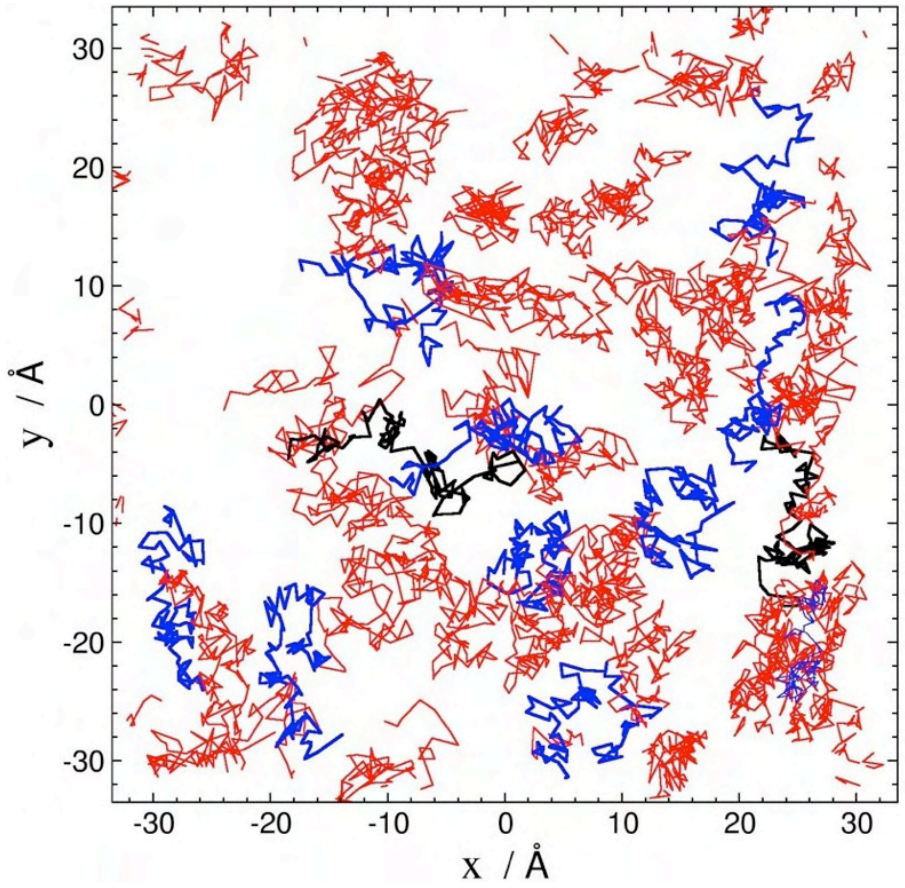
Critical for proper description of lipid protein interactions

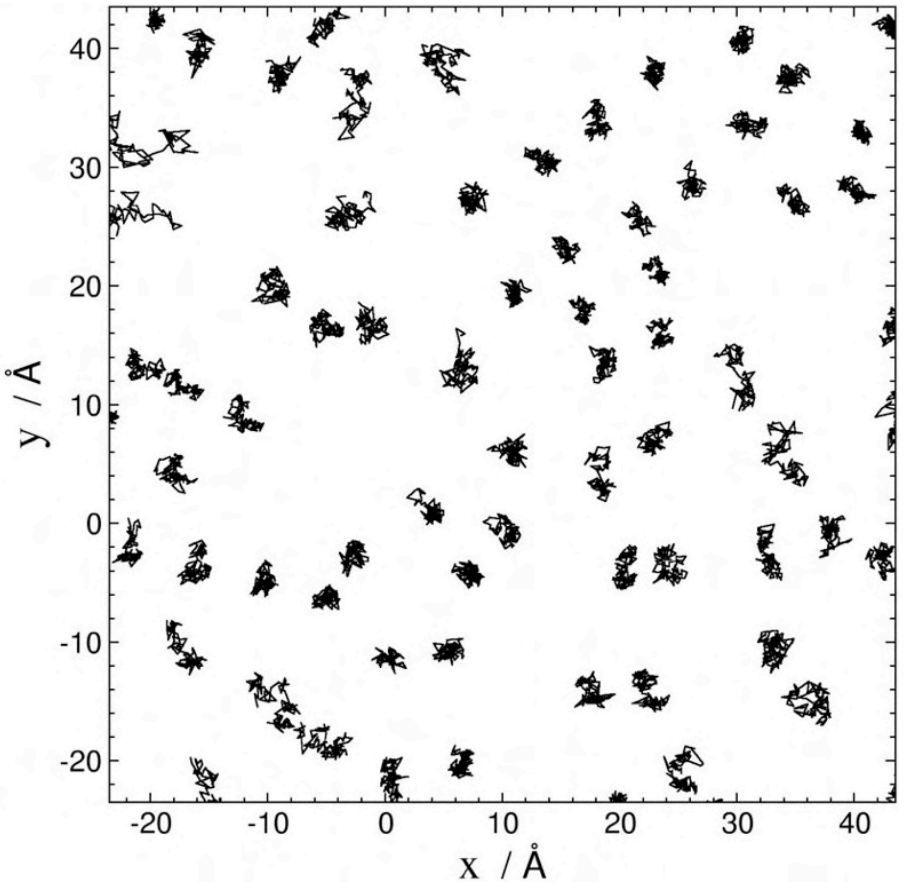




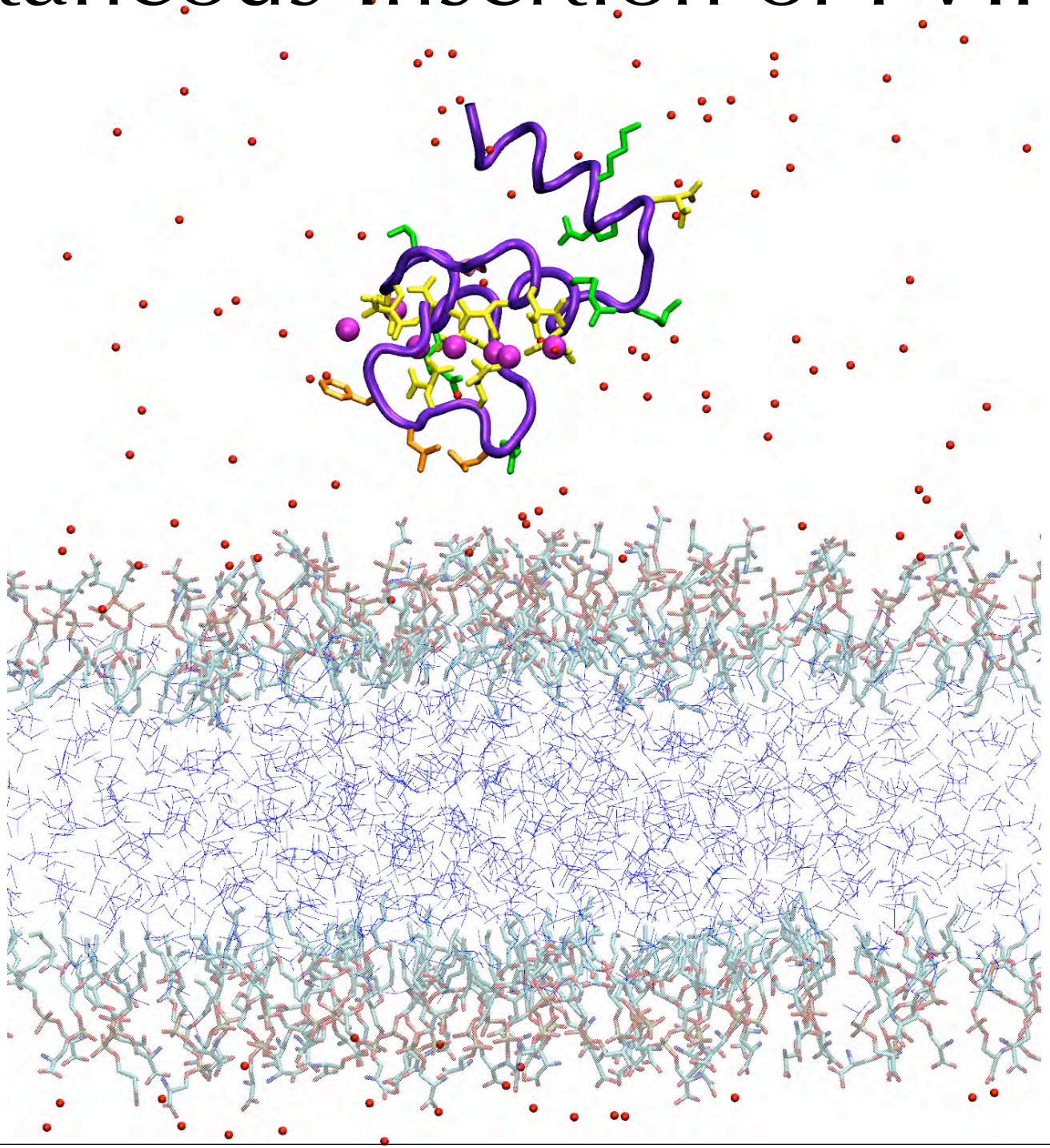


HMMM – lipids are more mobile than full-lipids

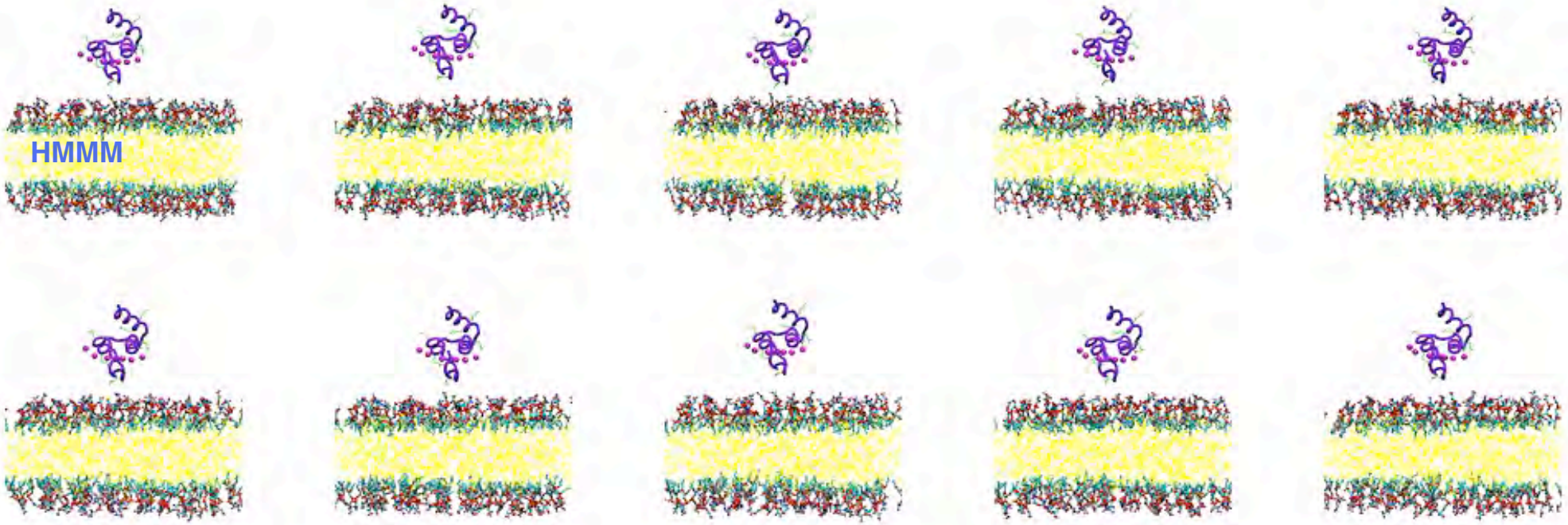


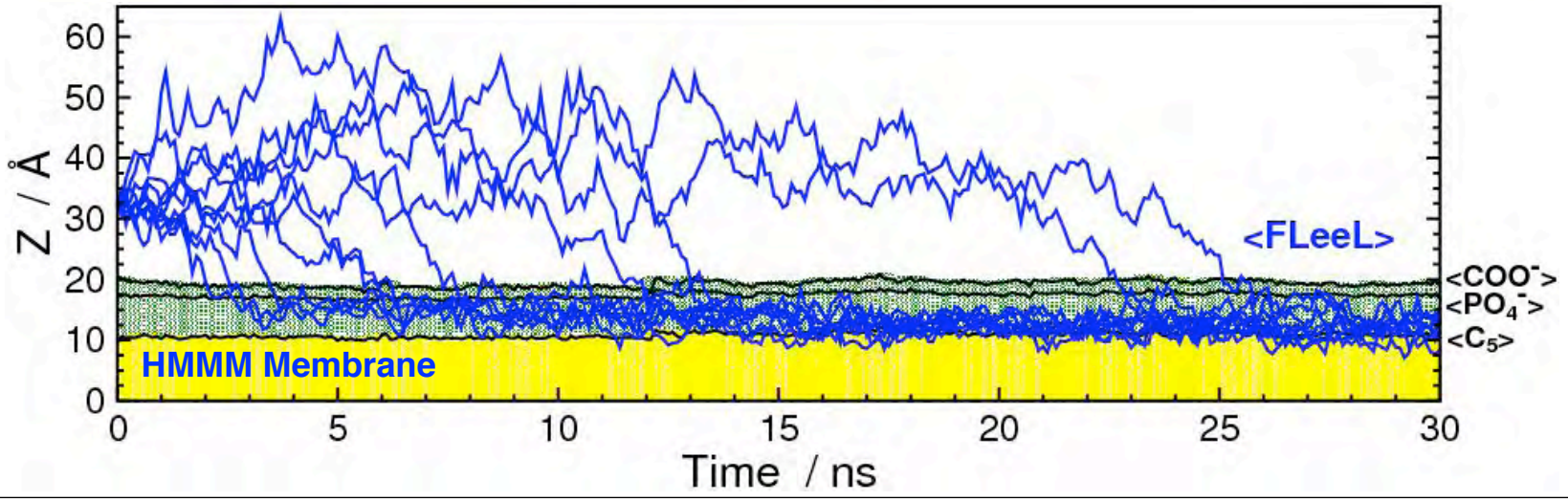


Spontaneous Insertion of FVII-GLA



Spontaneous Membrane Binding (*n = 10*)

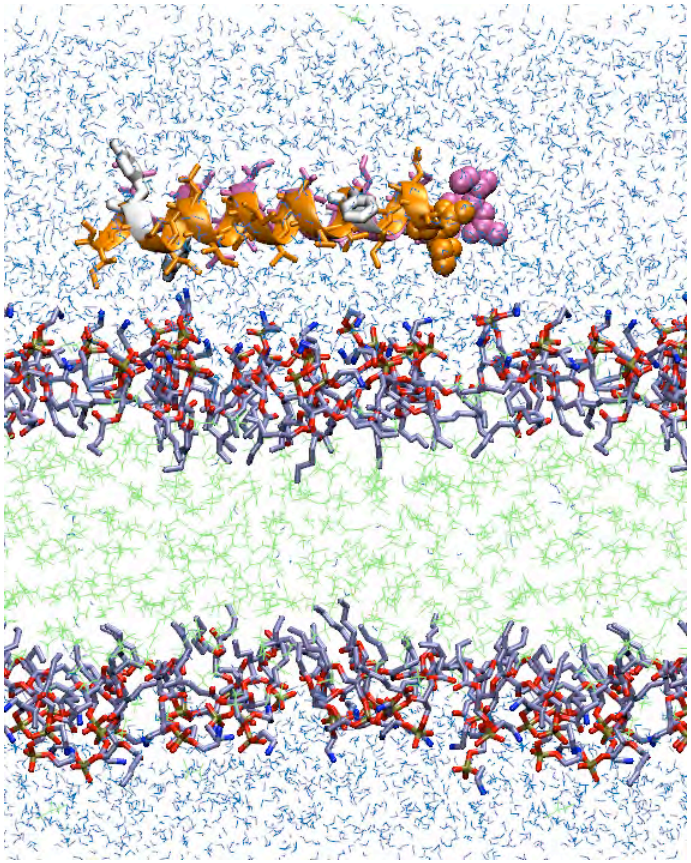




Spontaneous Insertion of Transmembrane Helices

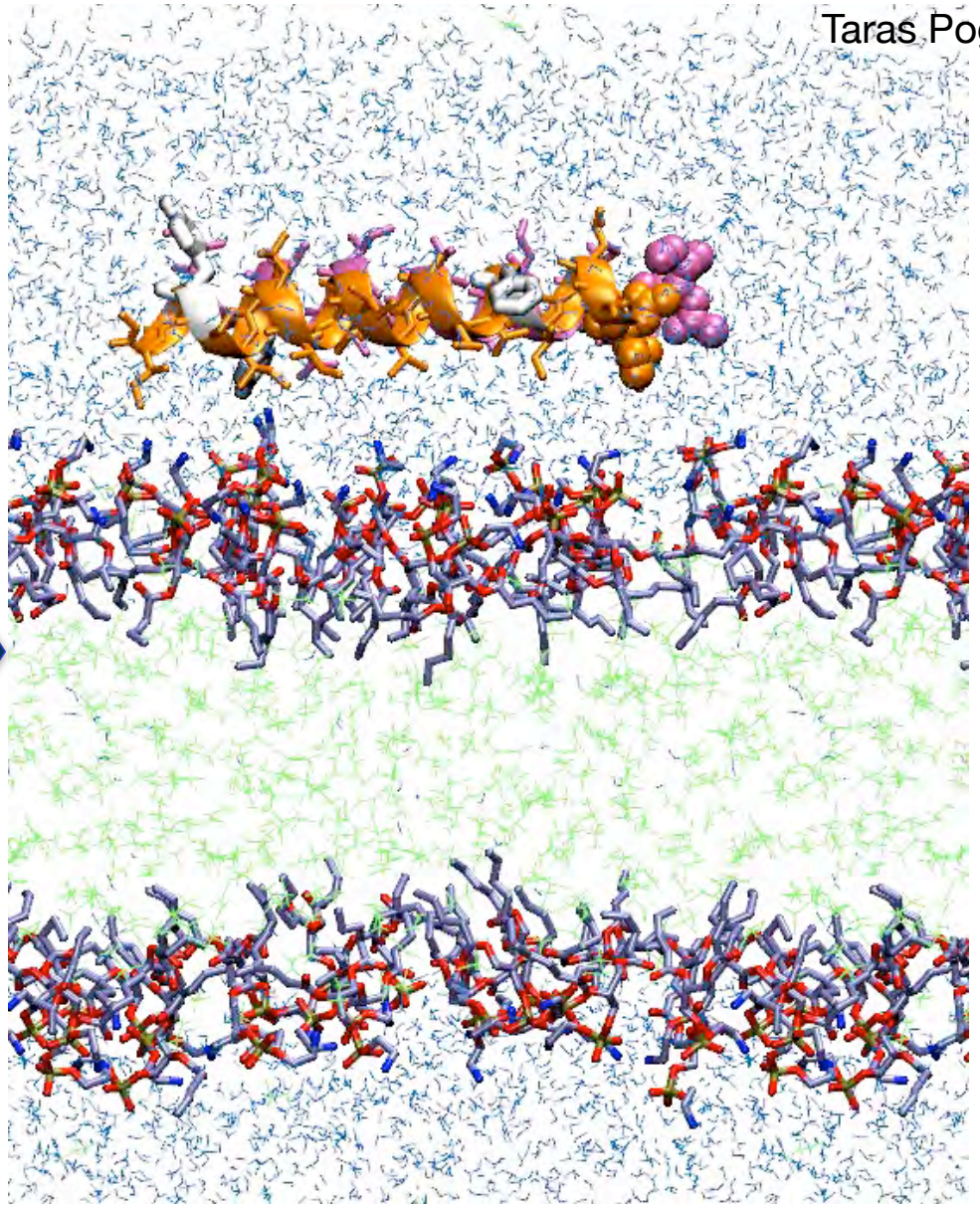
Taras Pogorelov

t = 0

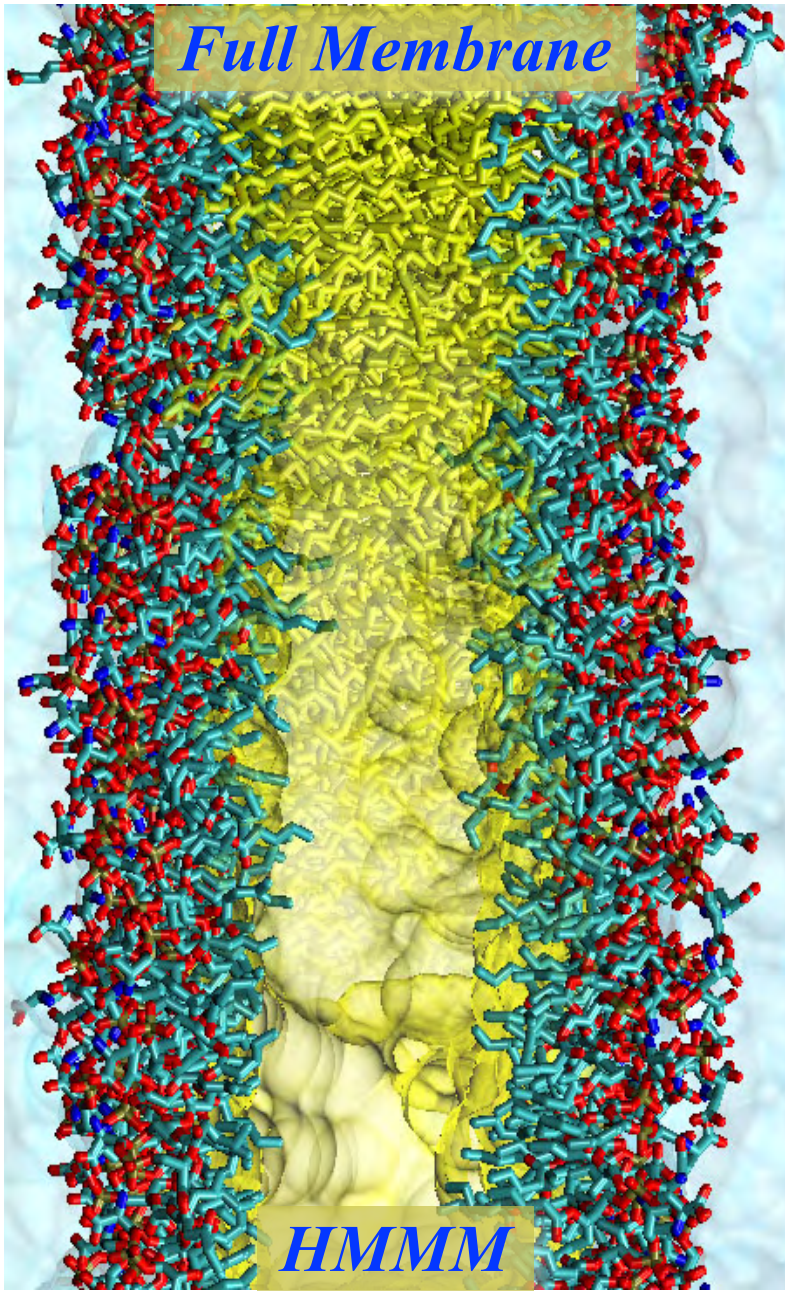


50 x 50 x 75 Å
Glycophorin A monomers: 2
z-constraint on 2 carbonyl carbons

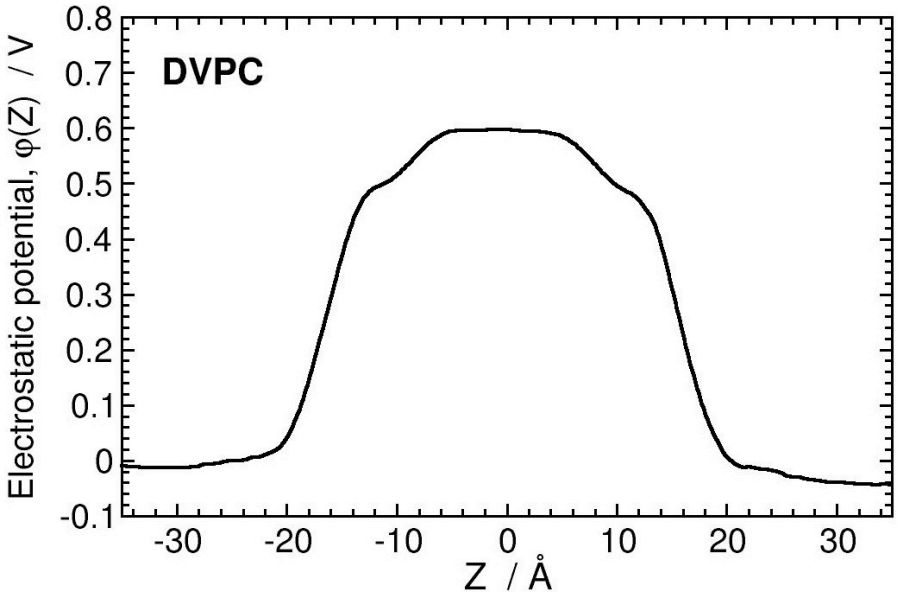
12 ns

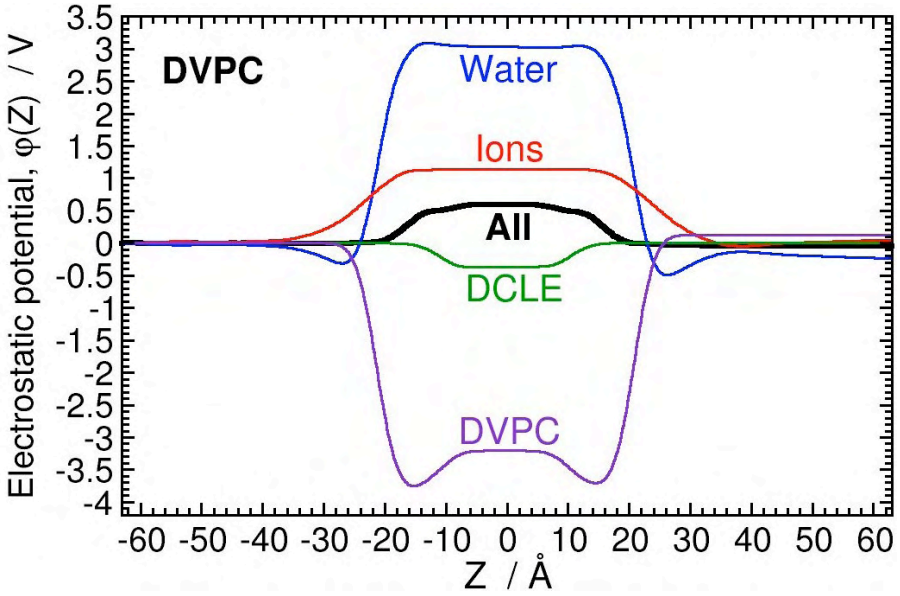


Quantitative Characterization and Optimization of HMMM



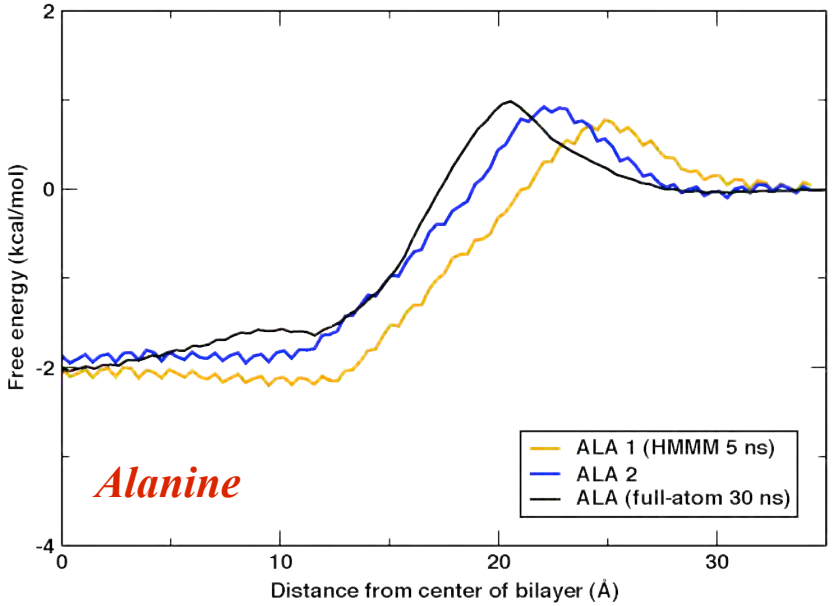
Membrane Dipolar Potential

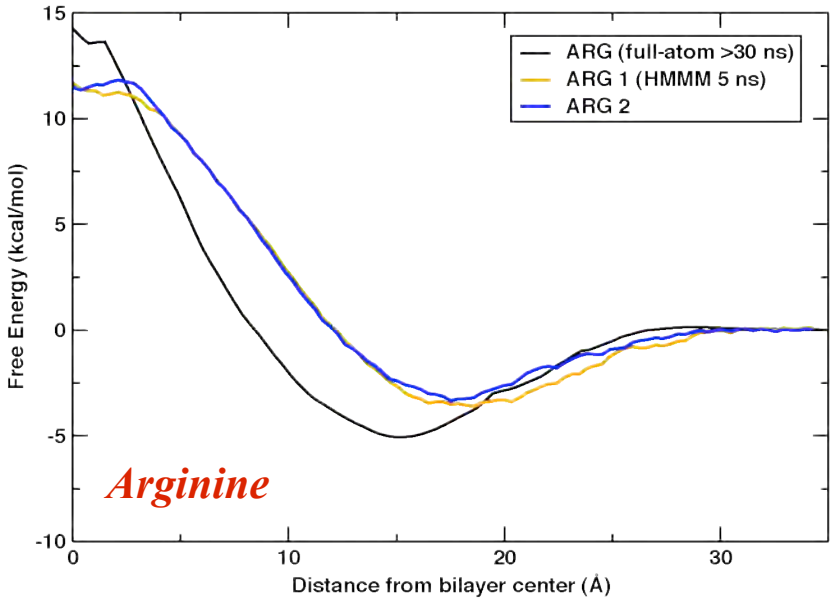


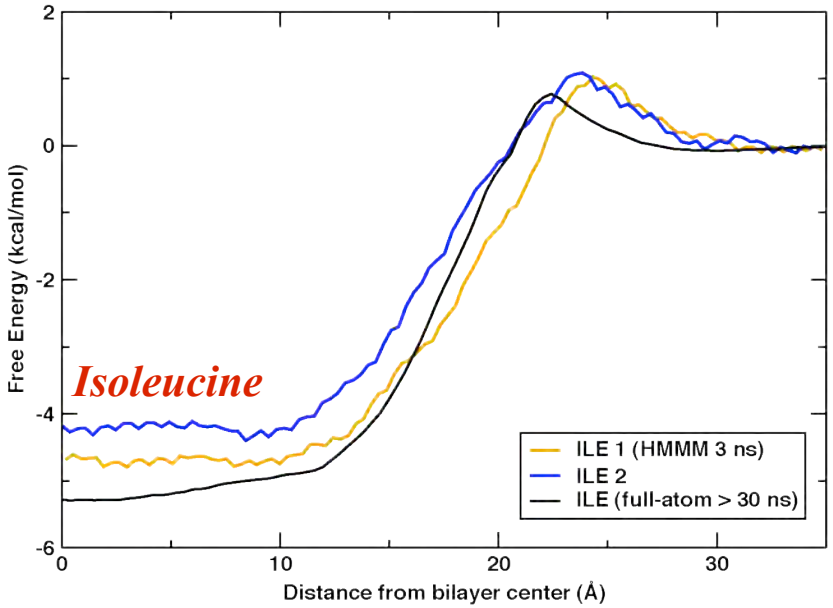


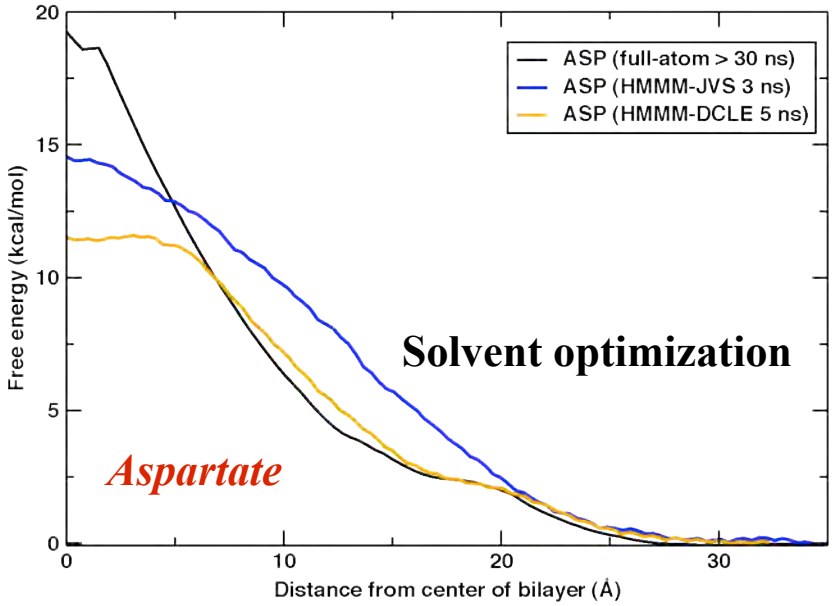
Quantitative Characterization and Optimization of HMMM

PMF of Amino Acid Insertion





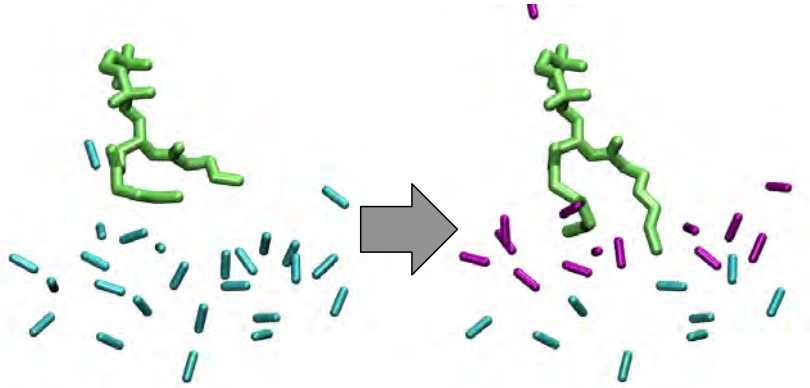


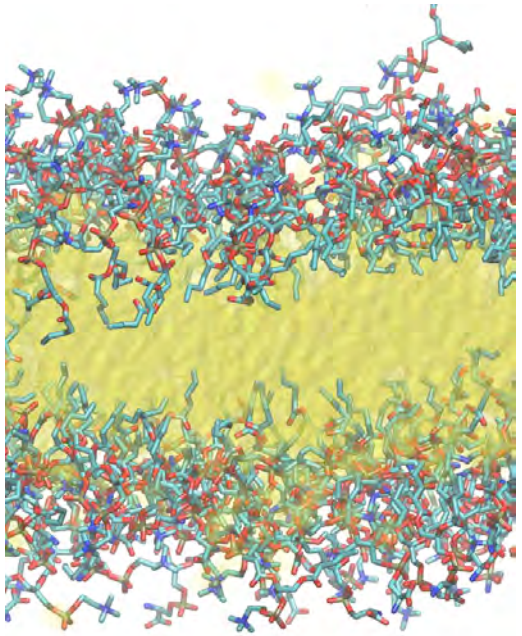


* Black lines: Full membrane data from Biophys. J. 94, 3393, 2008.

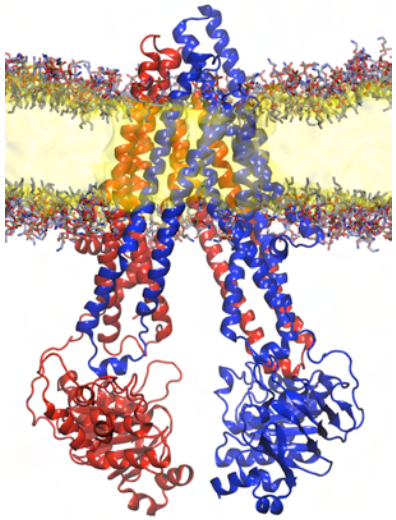
Tail-Gro - Stepwise transformation of HMMM to full membrane representation

Josh Vermaas



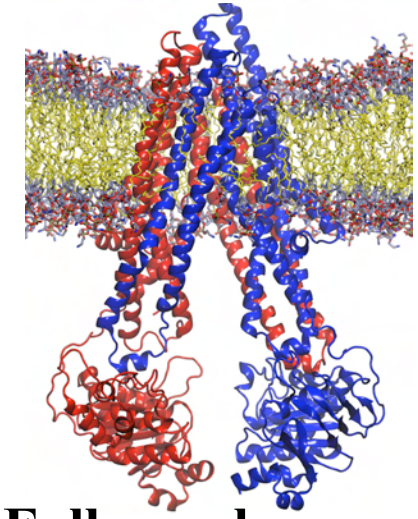


Step-wise insertion of P-glycoprotein



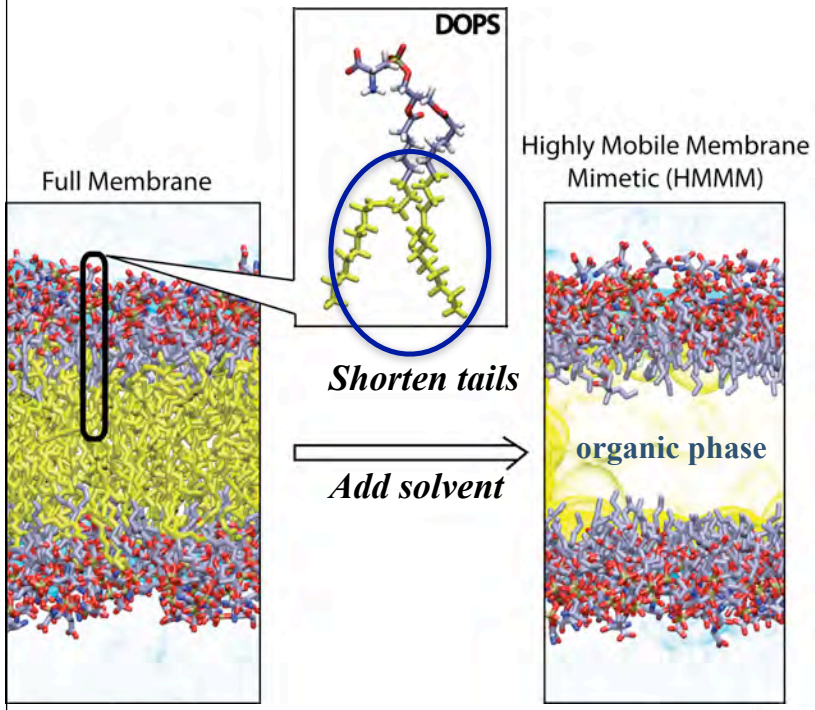
HMMM

Grow tails

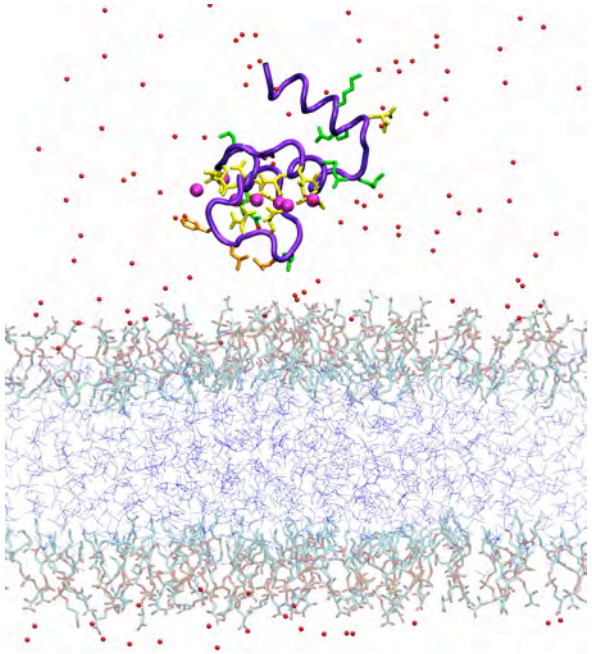


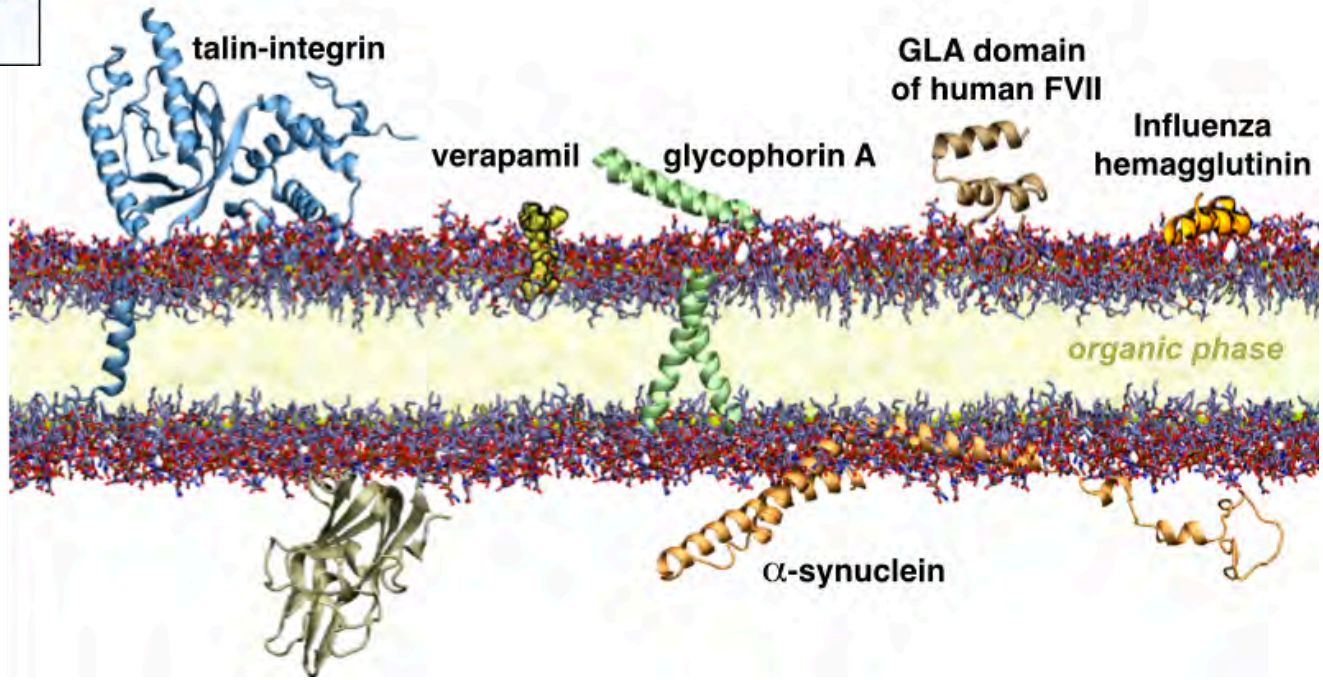
Full membrane

Highly Mobile Membrane Mimetic Model (HMMM)

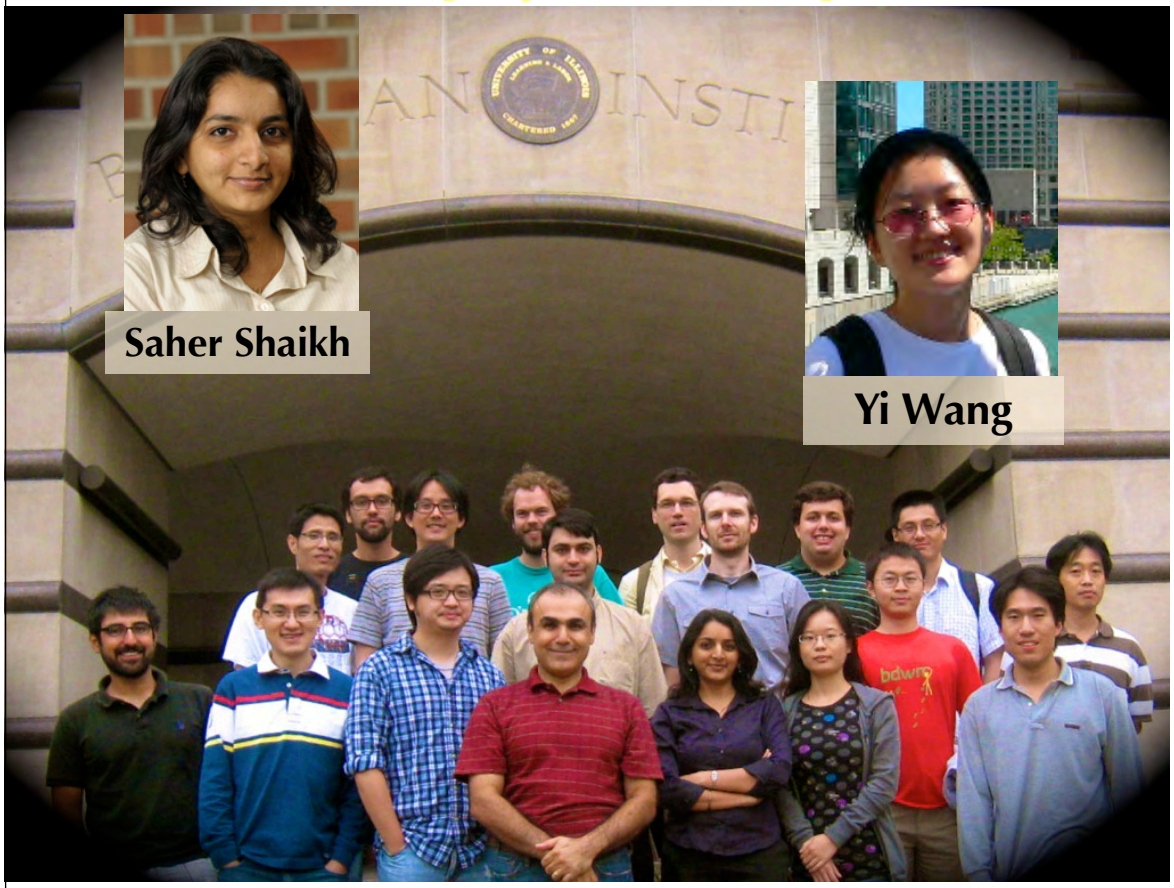


Facilitating dynamical studies of membrane-associated phenomena





Computational Structural Biology and Molecular Biophysics Group (CSBMB)



csbmb.beckman.illinois.edu

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- Raif Musa-Aziz
- Xue Qin

- Robert Gennis

Transporter Team

Zhijian Huang
Jing Li
Giray Enkavi
Mahmoud Moradi
Wei Han
Saher Shaikh
Paween Mahin
Po-Chao Wen
Wenxun Gan

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