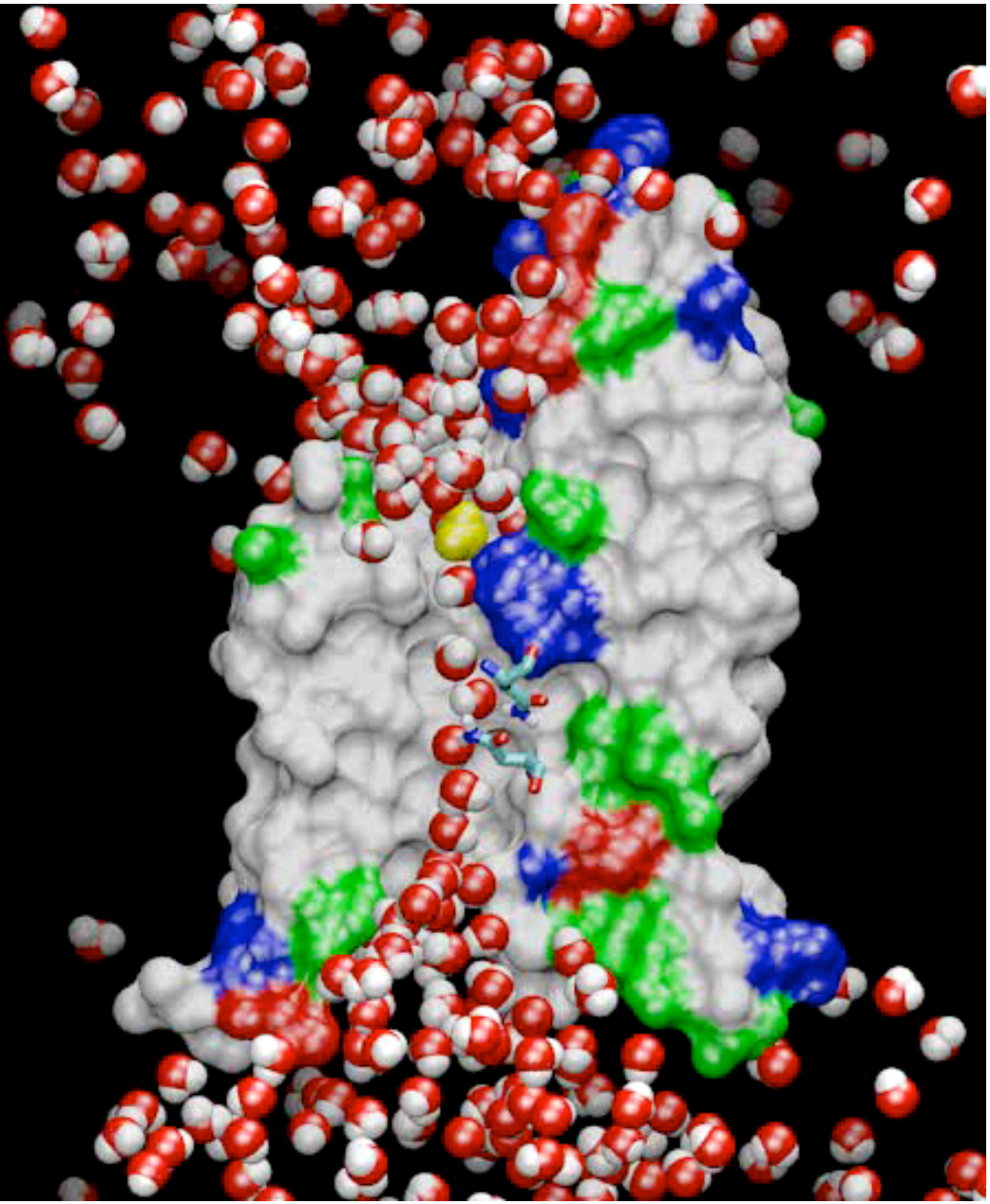
Molecular Dynamics Simulations



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

Major limitations:

- Time scale / sampling
- Force field approximations

SPEED LIMIT

1 fs

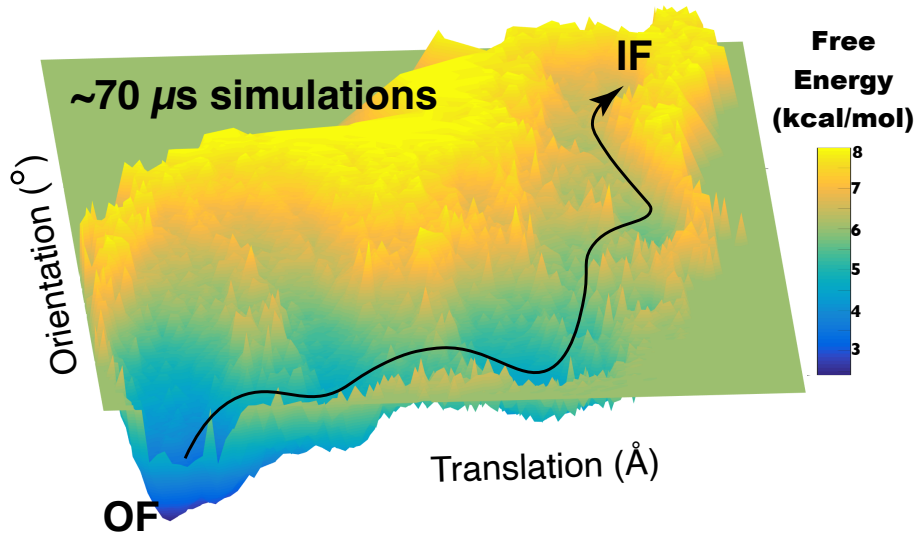
Major advantage:

- Unparalleled spatial and temporal resolutions, simultaneously

Overcoming Timescale limitation

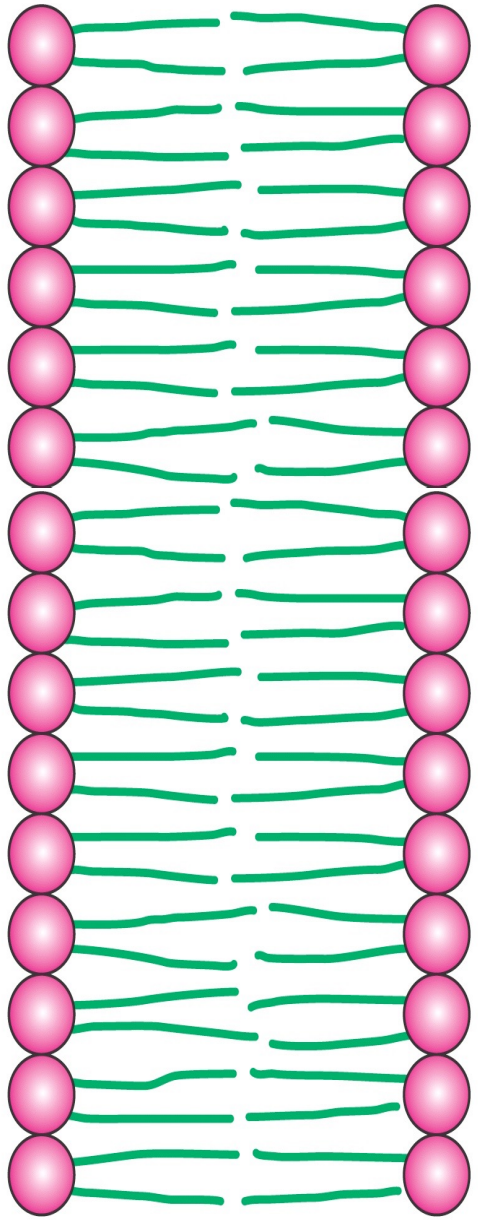
Visiting more regions in the Configuration Space

Enhanced Sampling

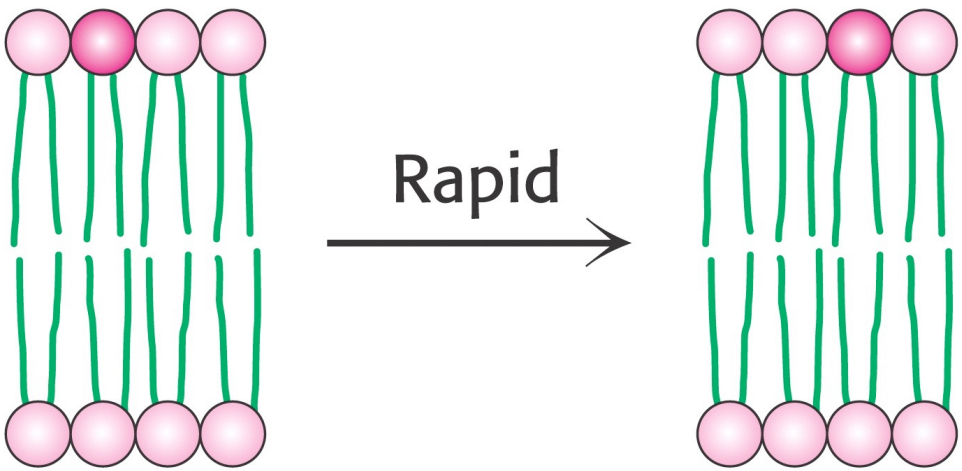


Phospholipid Bilayers Are Excellent Materials For Cell Membranes

- Hydrophobic interaction is the driving force
- Self-assembly in water
- Tendency to close on themselves
- Self-sealing (a hole is unfavorable)
- Extensive: up to millimeters



Lipid Diffusion in a Membrane



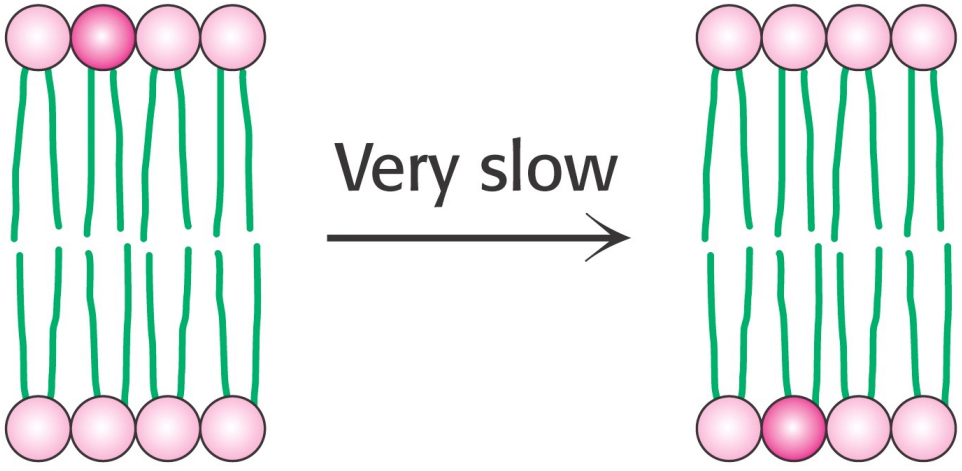
Lateral diffusion

$D_{lip} = 10^{-8}\ cm^2.s^{-1}$

(50 Å in ~ 5 x 10^{-6} s)

$D_{wat} = 2.5 \times 10^{-5}\ cm^2.s^{-1}$

Modeling mixed lipid bilayers!



Tranverse diffusion
(flip-flop)

Once in several hours!

(~ 50 Å in ~ 10^4 s)

~9 orders of magnitude slower
ensuring bilayer asymmetry

Technical difficulties in Simulations of Biological Membranes

- Time scale
- Heterogeneity of biological membranes ☹

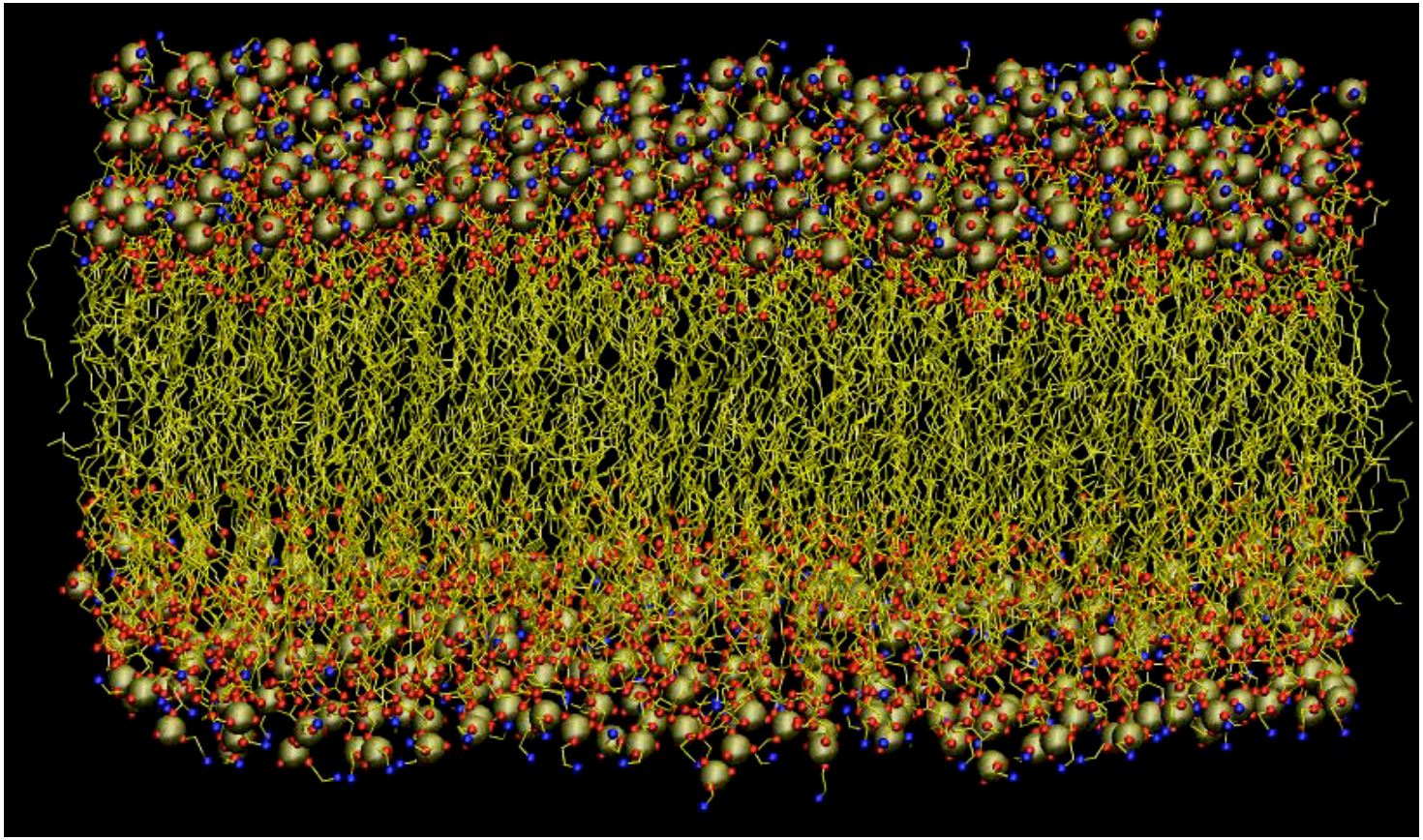
60 x 60 Å

Pure POPE

5 ns

~100,000

atoms

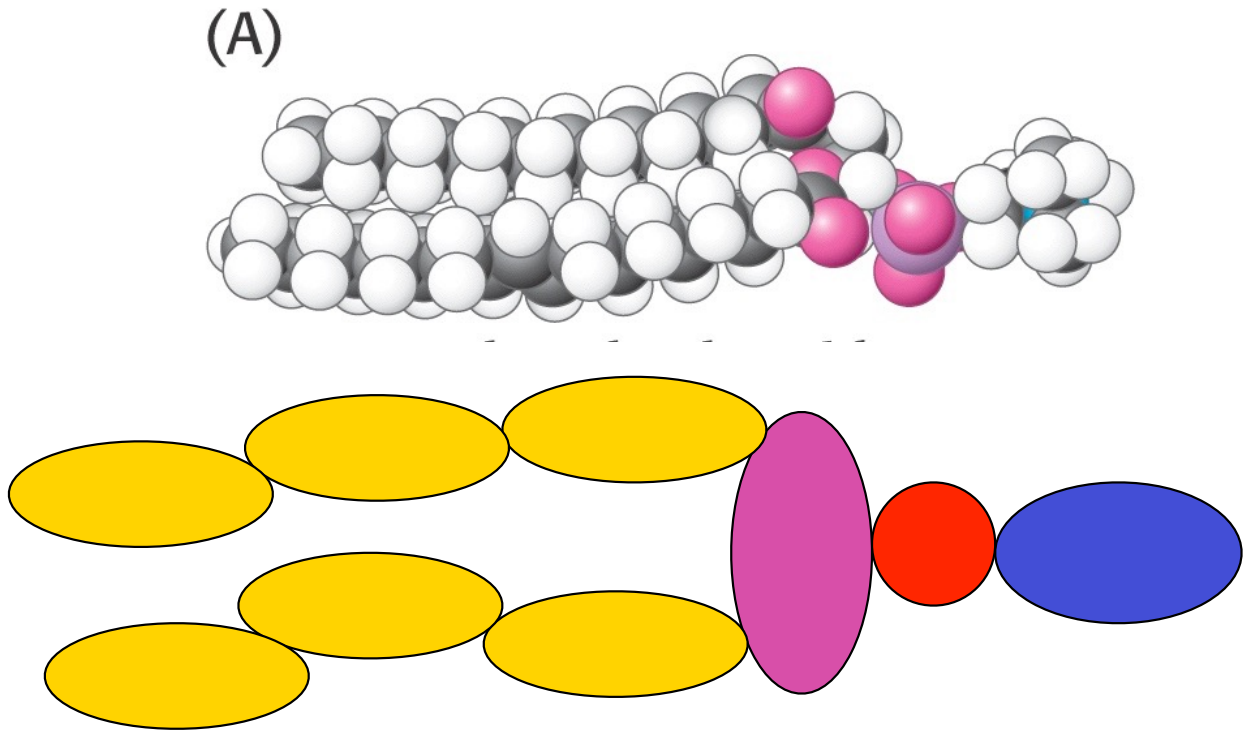


Battling the Timescale - Case I

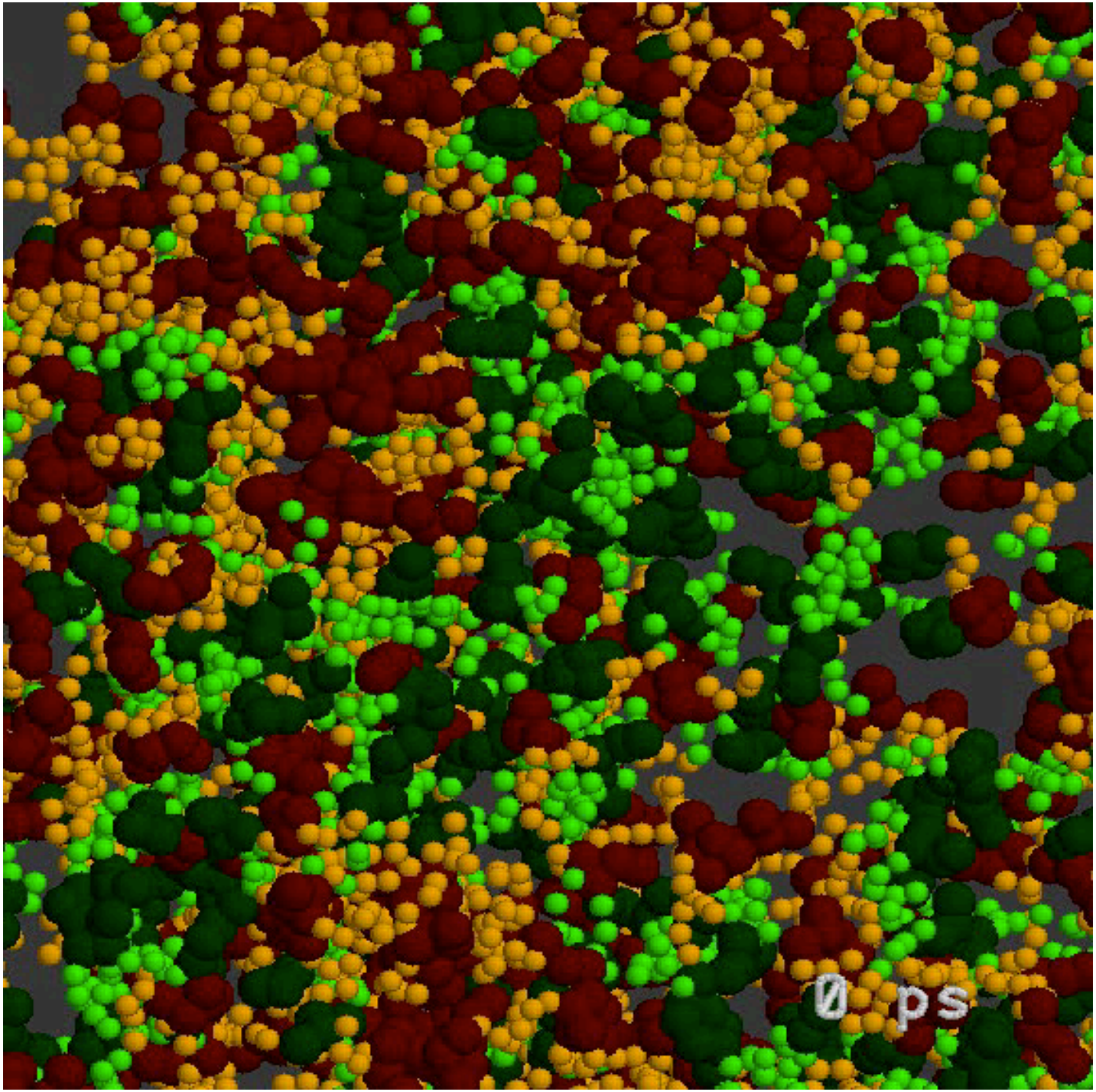
Coarse-grained modeling of lipids

150 particles

9 particles!



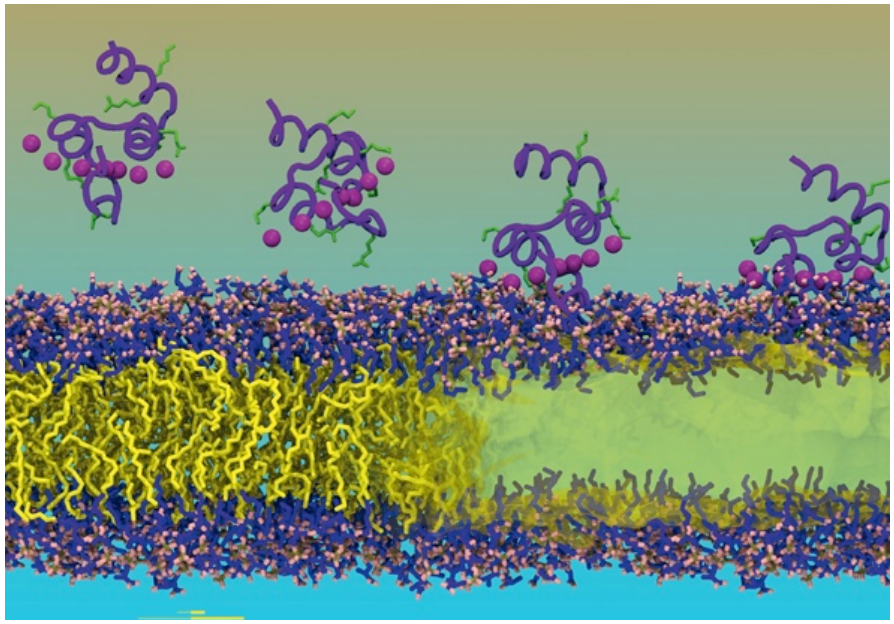
Also, increasing the time step by orders of magnitude.

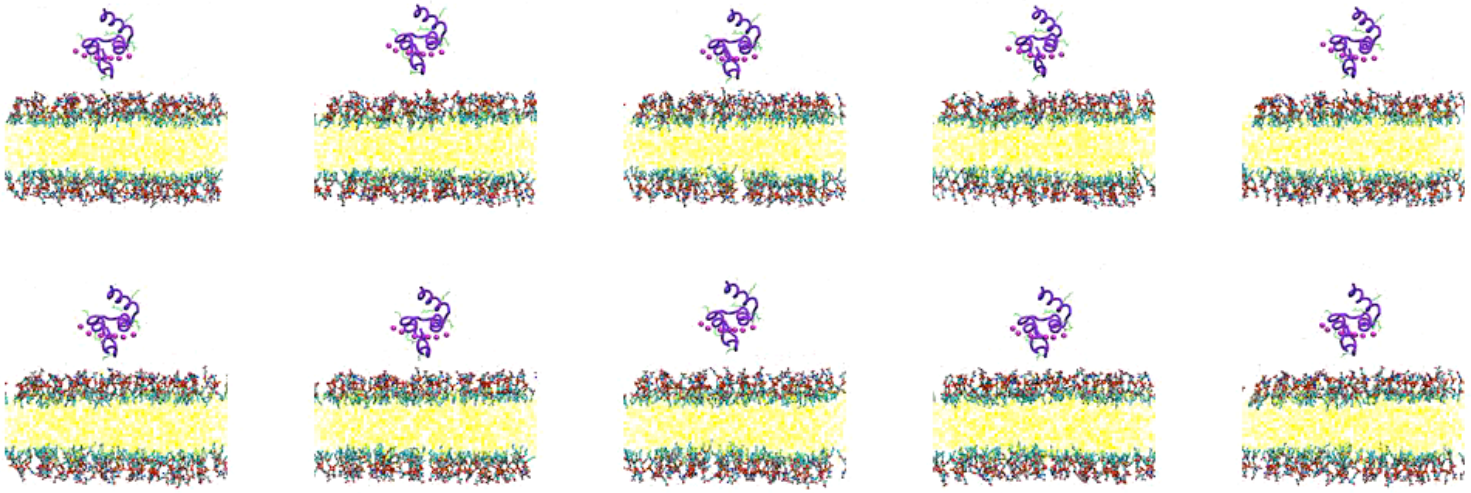


by: J. Siewert-Jan Marrink and Alan E. Mark, University of Groningen, The Netherlands

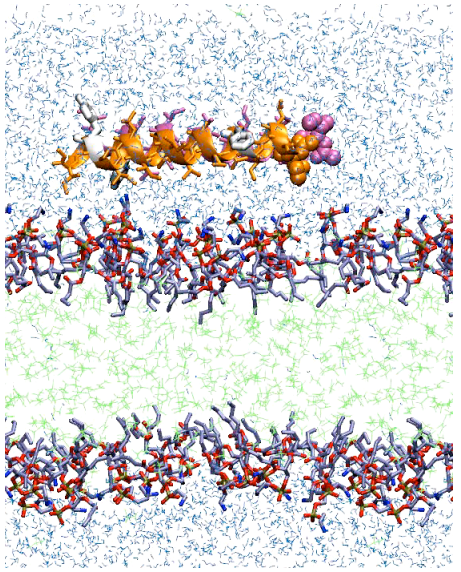
Battling the Timescale - Case II
Reduced Representations

Highly Mobile Membrane Mimetic model

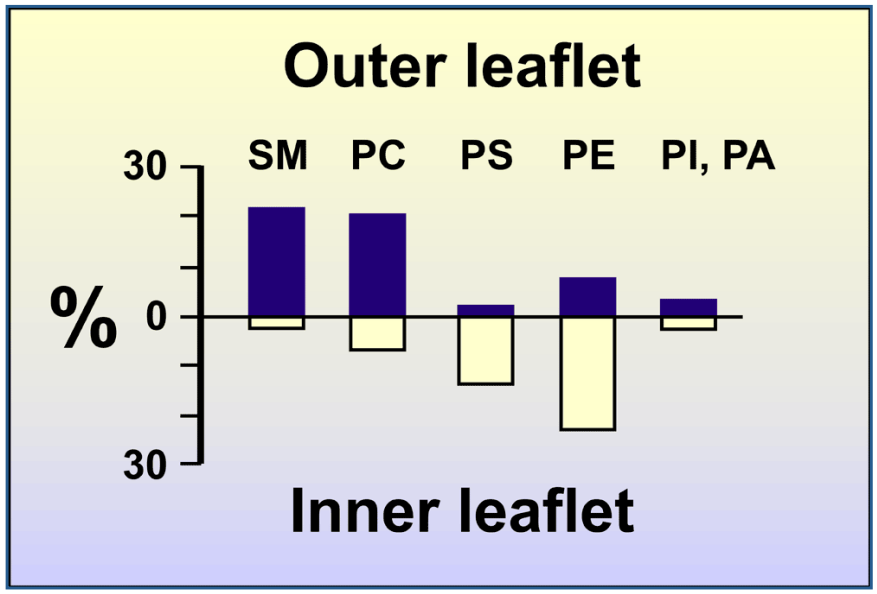


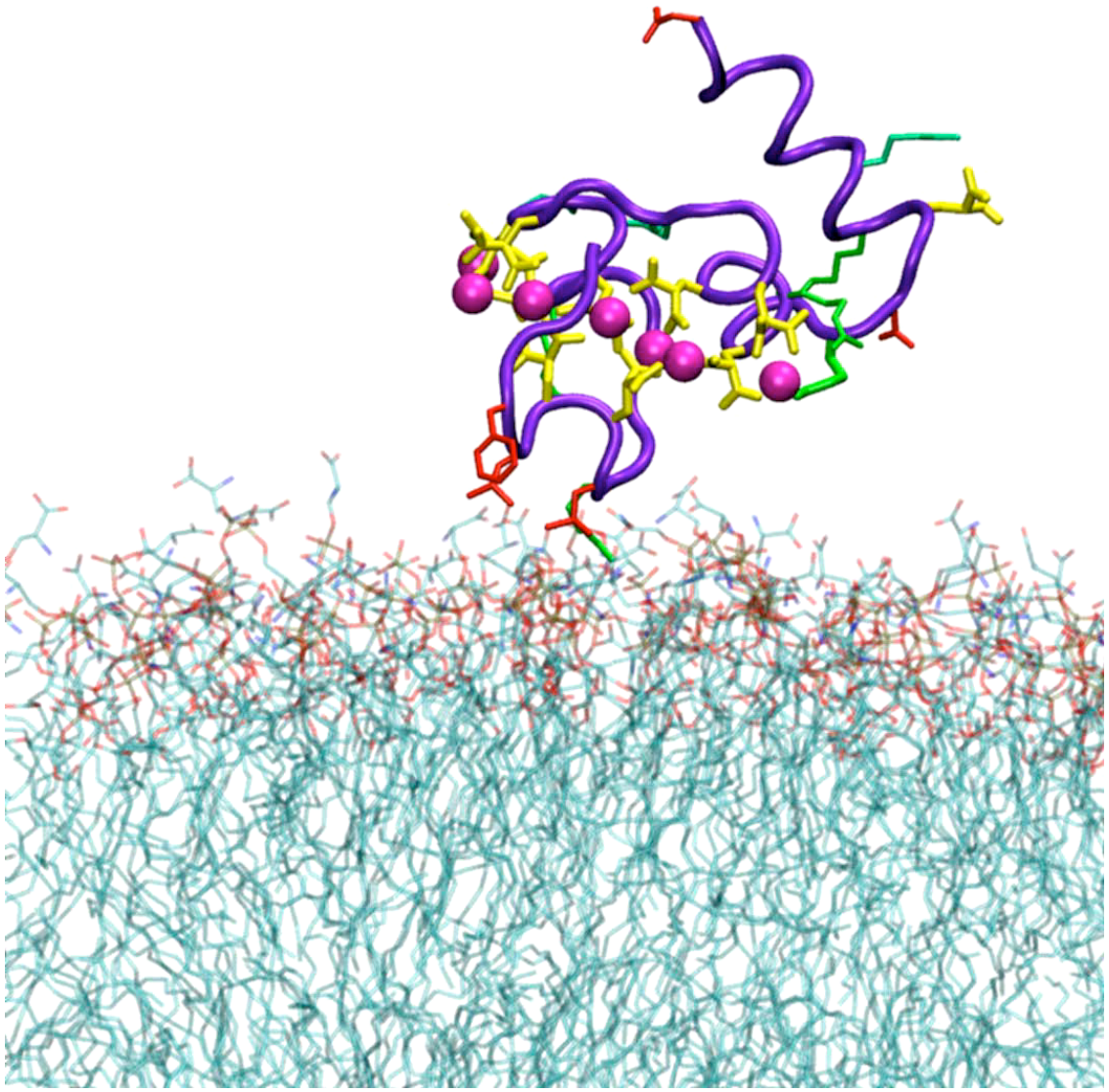


GpA insertion in 12 ns



Simulation of Binding with Full Membrane Representation





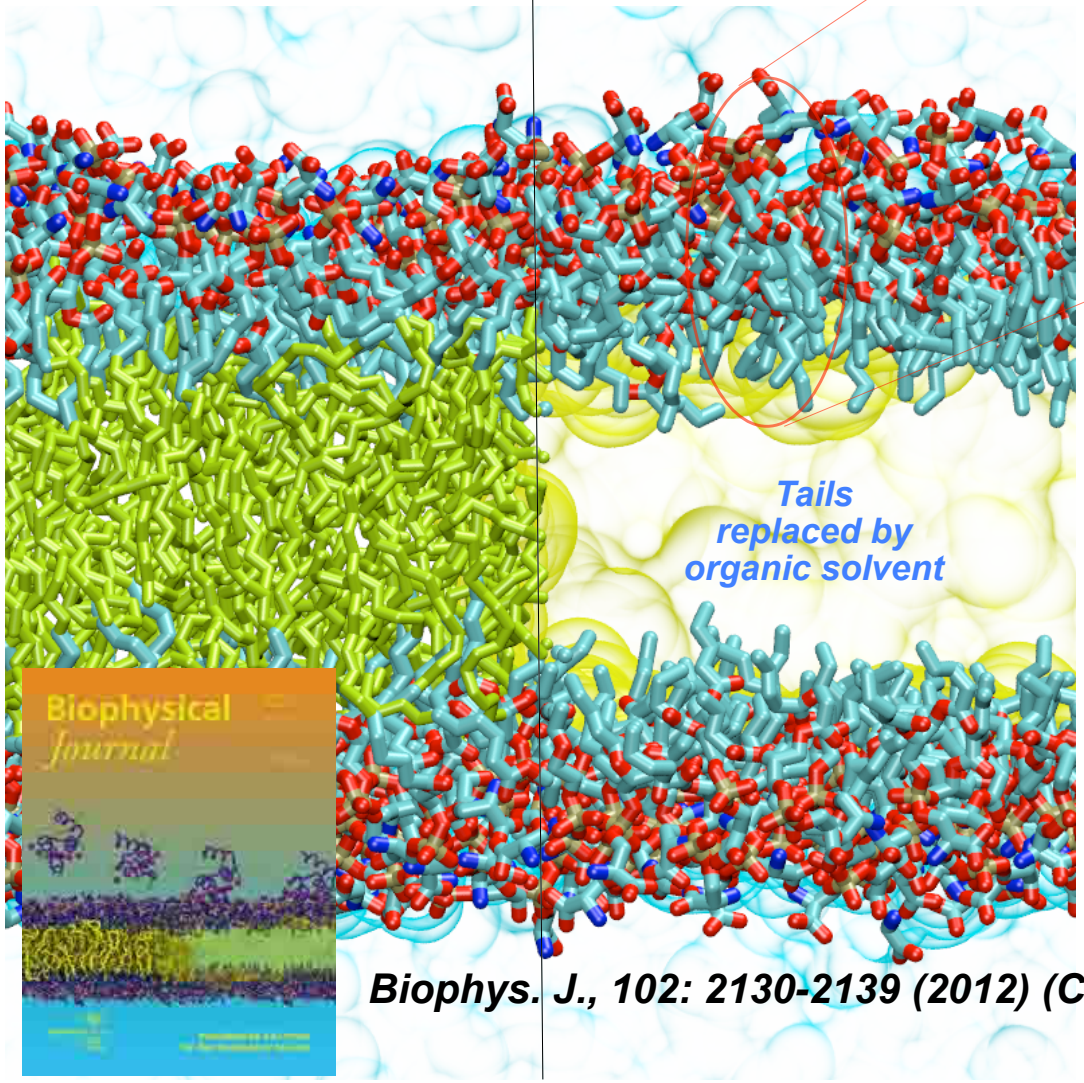
Partial list of technical problems:

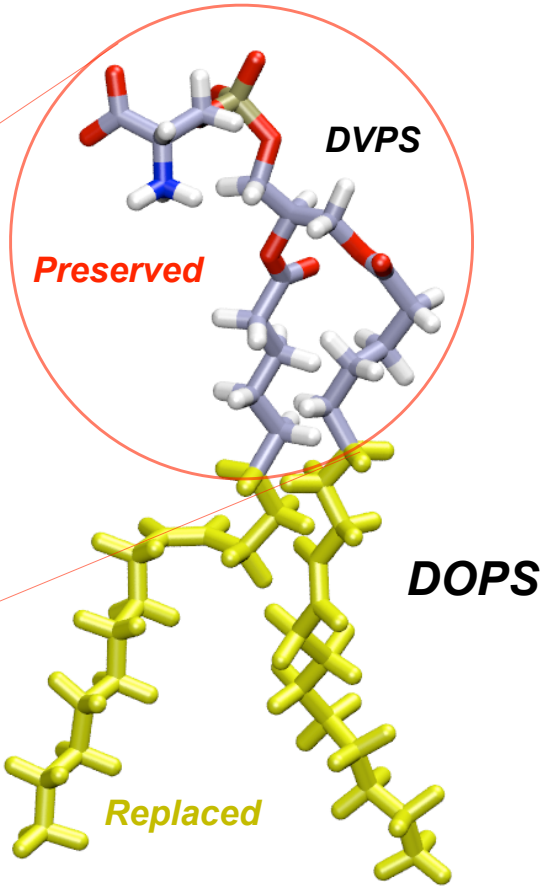
- Biased simulations
- Unknown depth of insertion
- Single binding event
- Frequently failing
- **Minimal lipid reorganization**

Z. Ohkubo and E. T., **Structure**, 16: 72-81 (2008)

HMMM model

Highly Mobile Membrane Mimetic model





Advantages

Increased mobility of lipids

Retain explicit headgroups allowing for atomic details

Biophys. J., 102: 2130-2139 (2012) (Cover Article)


Zenmei Ohkubo


Mark Arcario


Taras Pogorelov

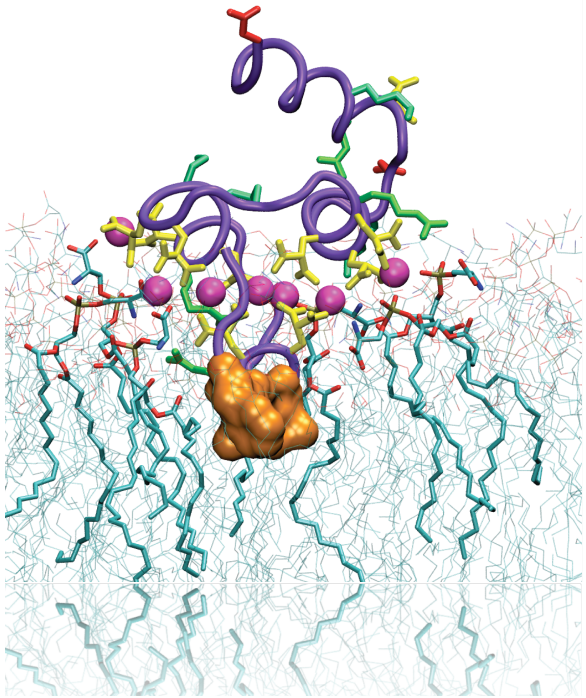

Josh Vermaas

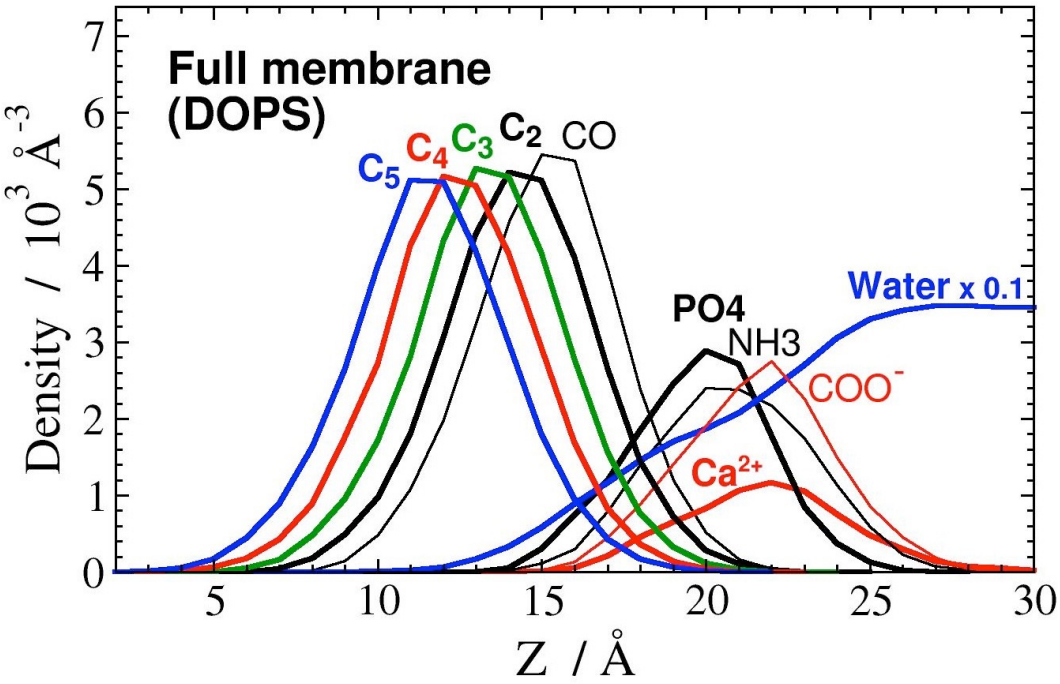

Javier Baylon

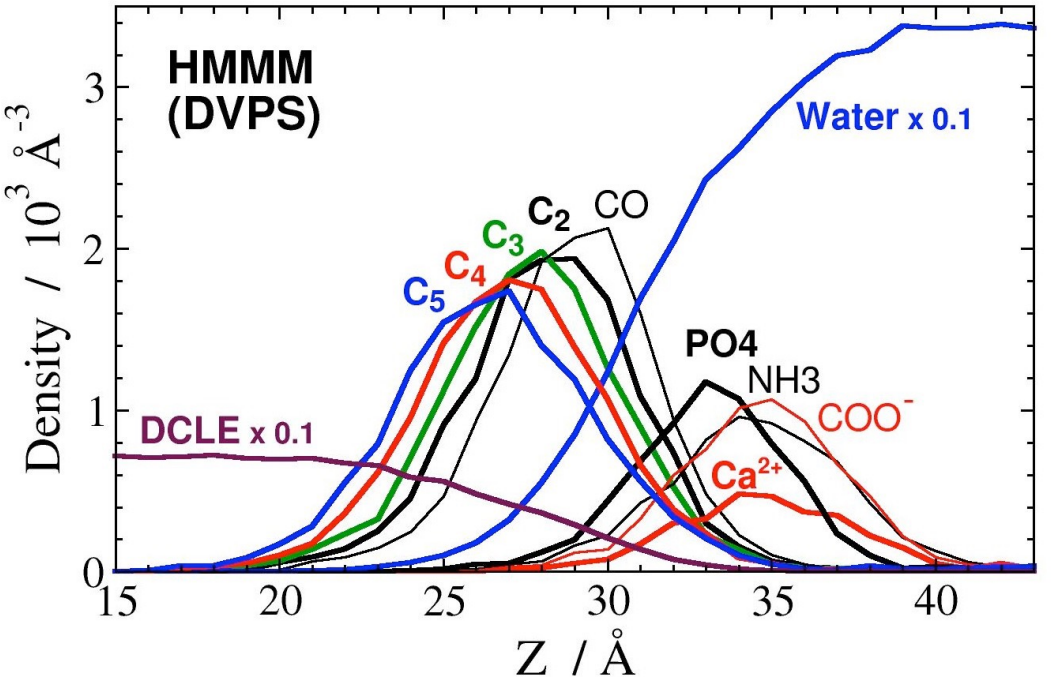
HMMM- Preserving the "Face" of the Lipid Bilayer

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

Critical for proper description of lipid protein interactions

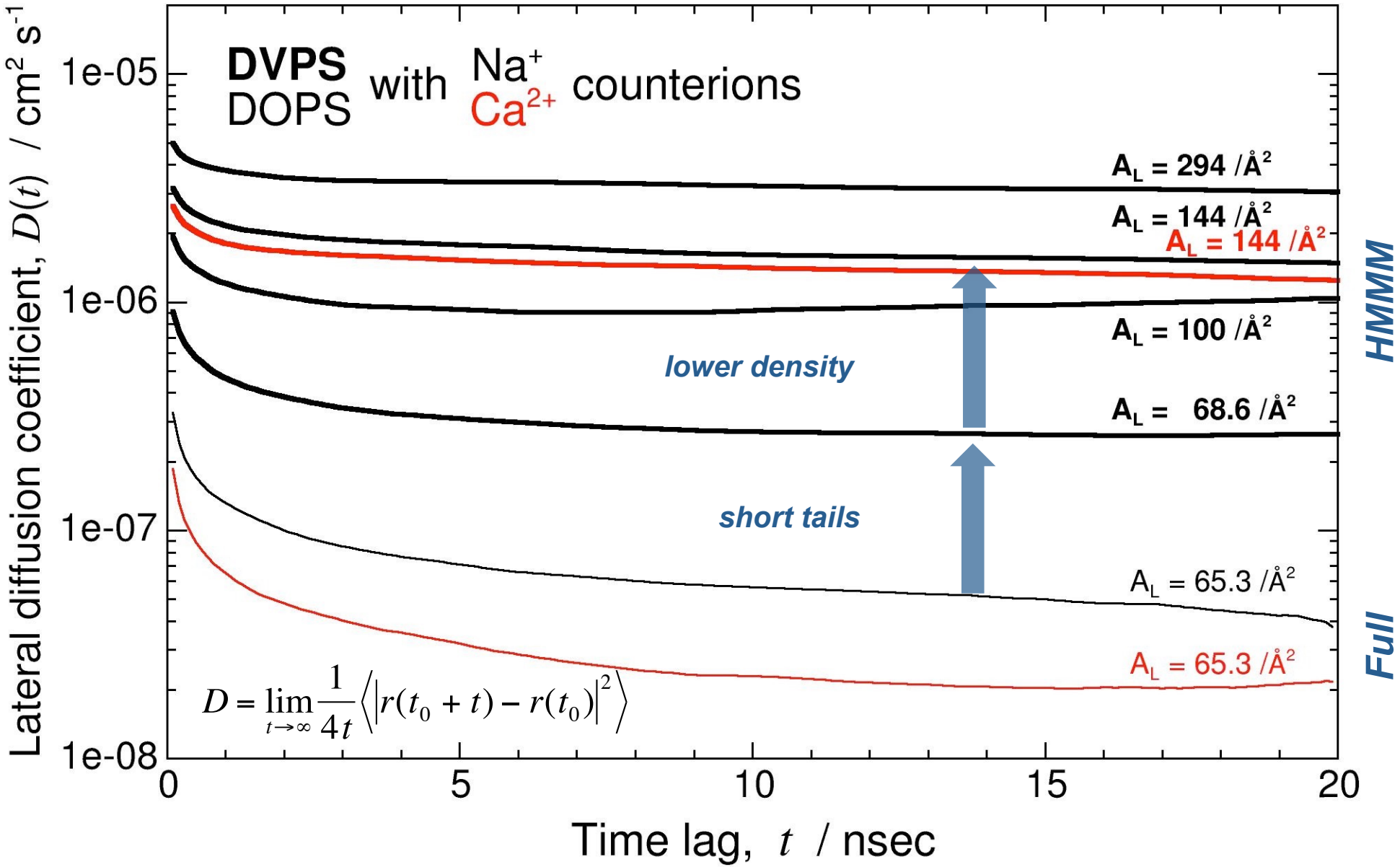






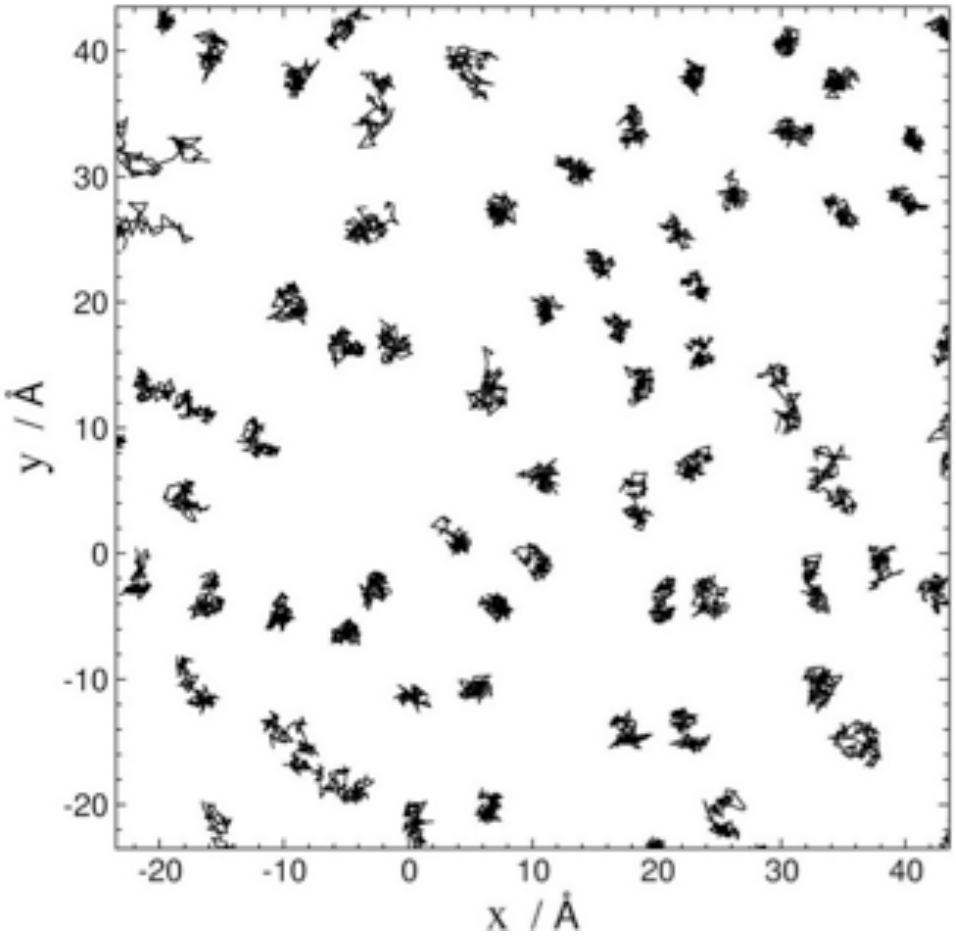
Enhanced Lipid Lateral Diffusion

Without Compromising Atomic Details of the Headgroups

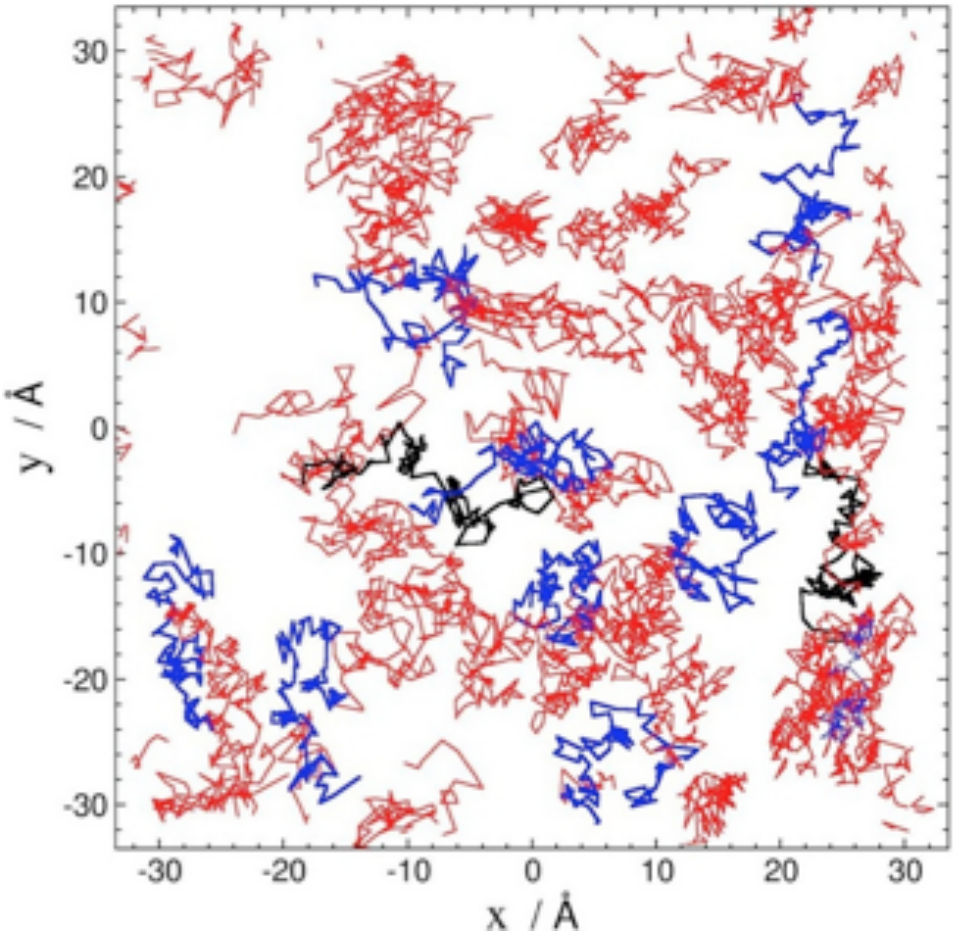


Enhanced Lipid Lateral Diffusion

Without Compromising Atomic Details of the Headgroups

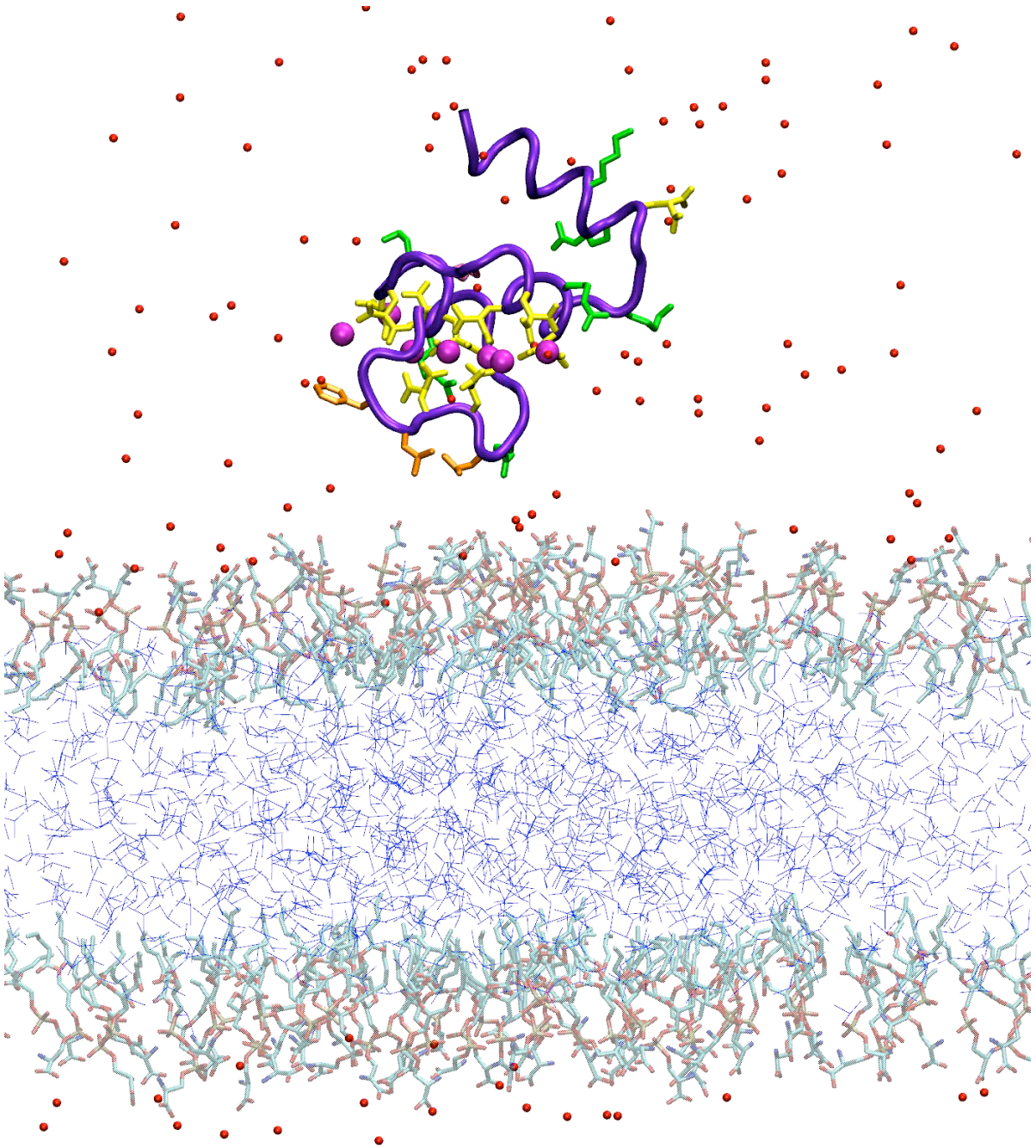


Conventional membrane (10 ns)



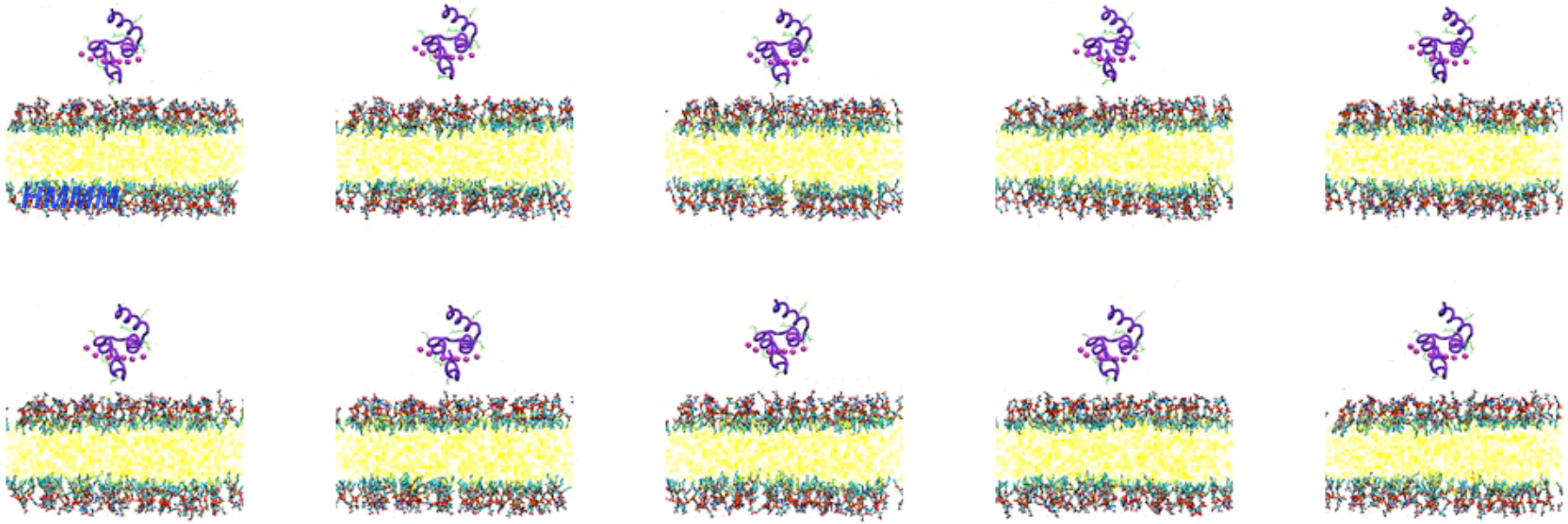
HMMM membrane (1 ns)

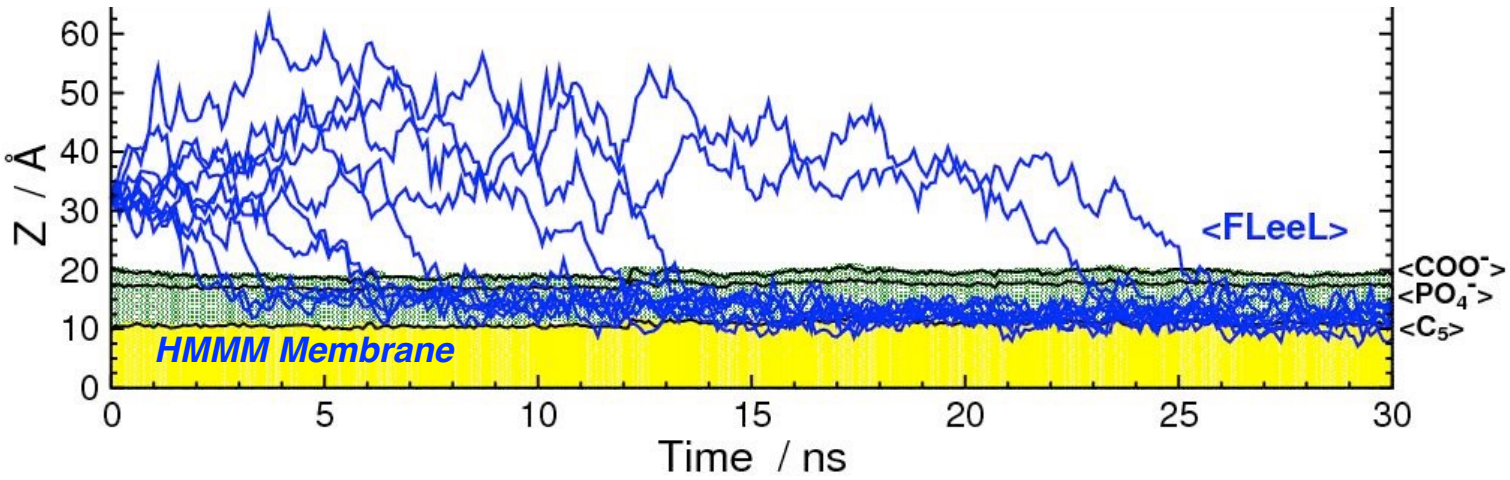
PS-Dependent Spontaneous Insertion of FVII-GLA



Zenmei Ohkubo

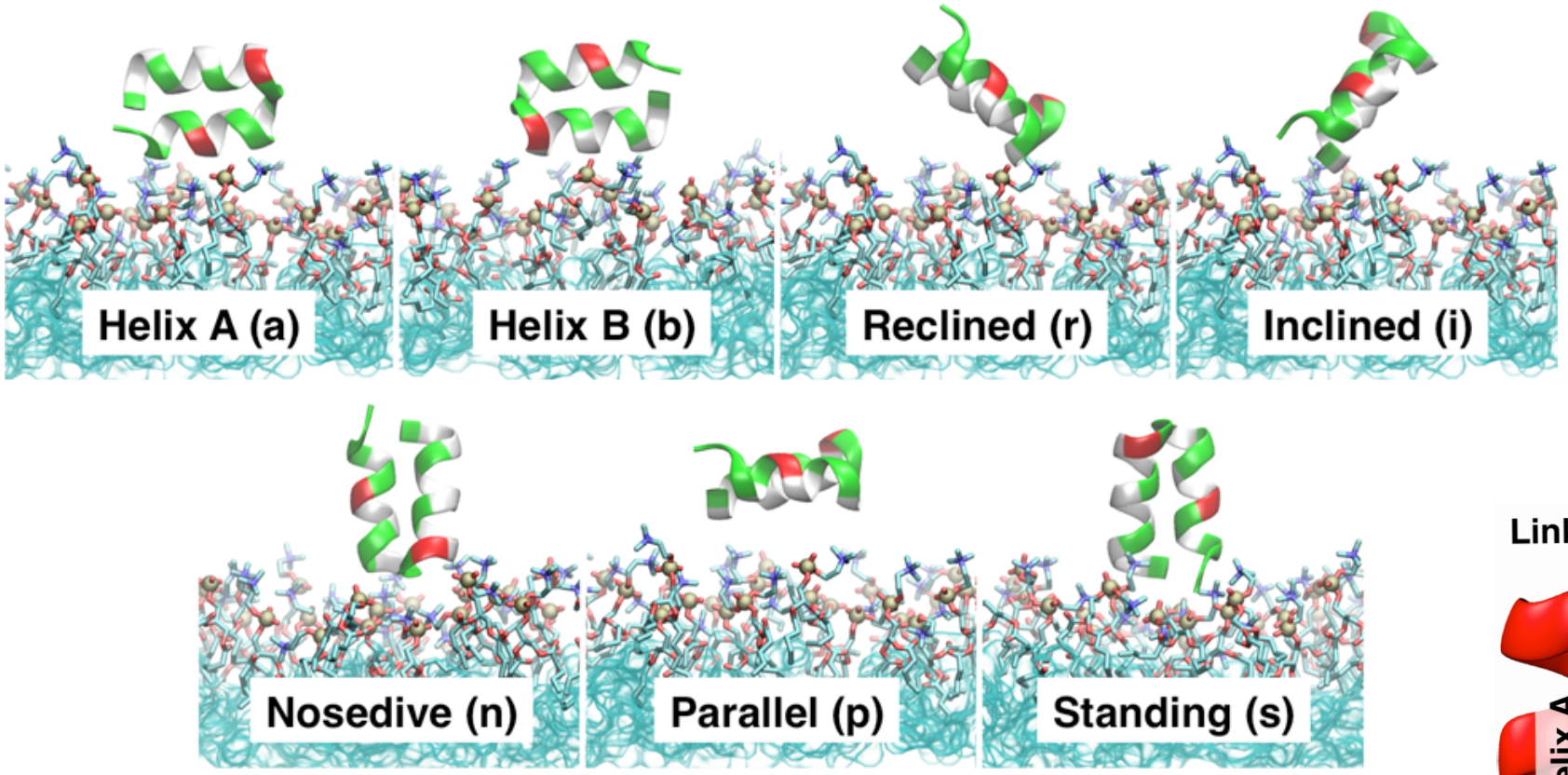
Spontaneous, Unbiased Membrane Binding
Accelerated Process Allows for better sampling (***n = 10***)

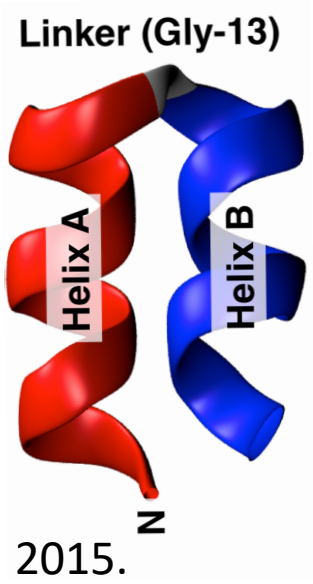




Z. Ohkubo, …, E.T., **Biophys. J.**, 102: 2130-2139 (2012) (Cover Article)

Membrane Binding of Influenza Hemagglutinin Fusion Peptide





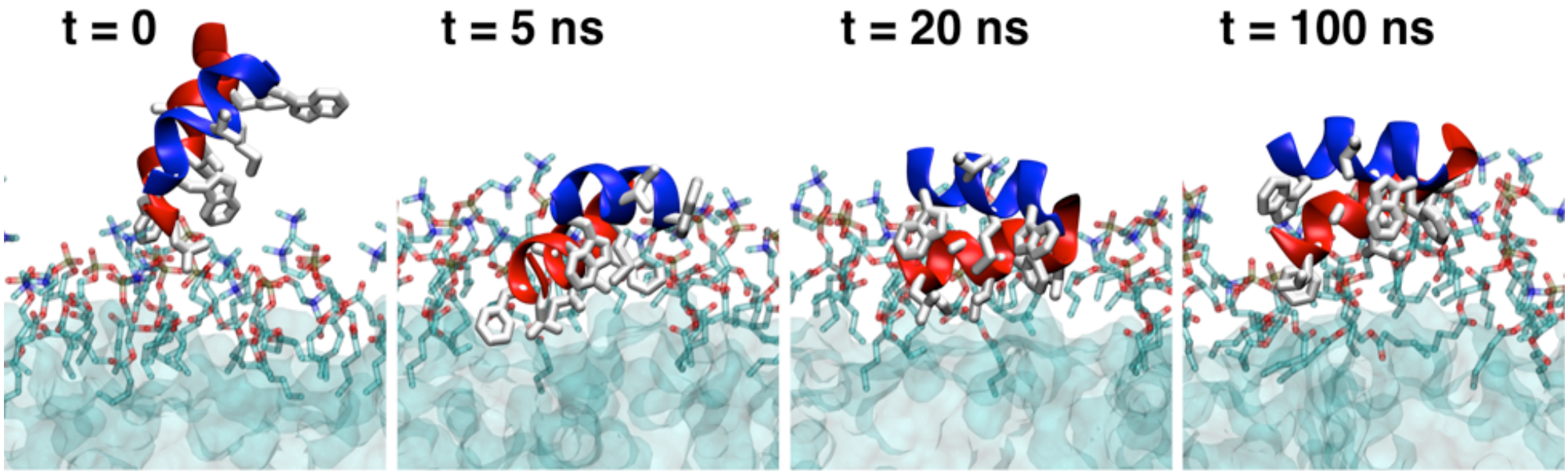
7 different initial orientation
each simulated 3 times

J. Baylon and E. T., **J. Phys. Chem.B**, 2015.

Membrane Binding of Influenza Hemagglutinin Fusion Peptide

Spontaneous binding observed in the majority of the simulations:

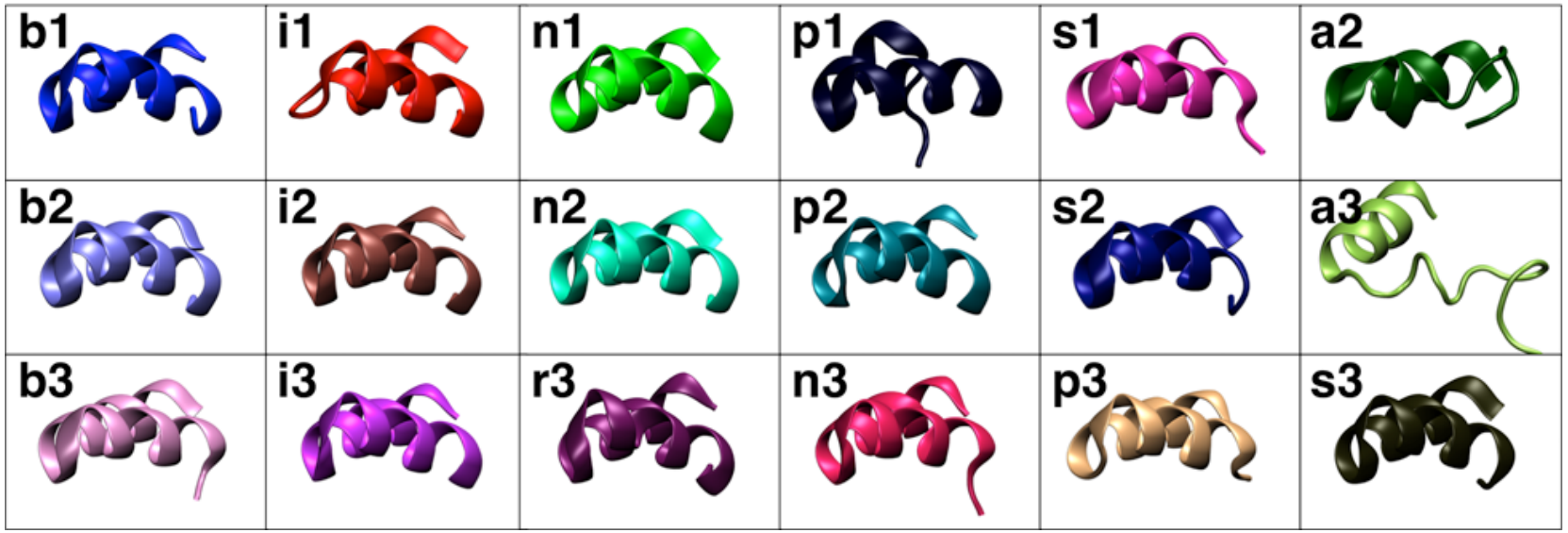
21 independent simulations starting from 7 different orientations



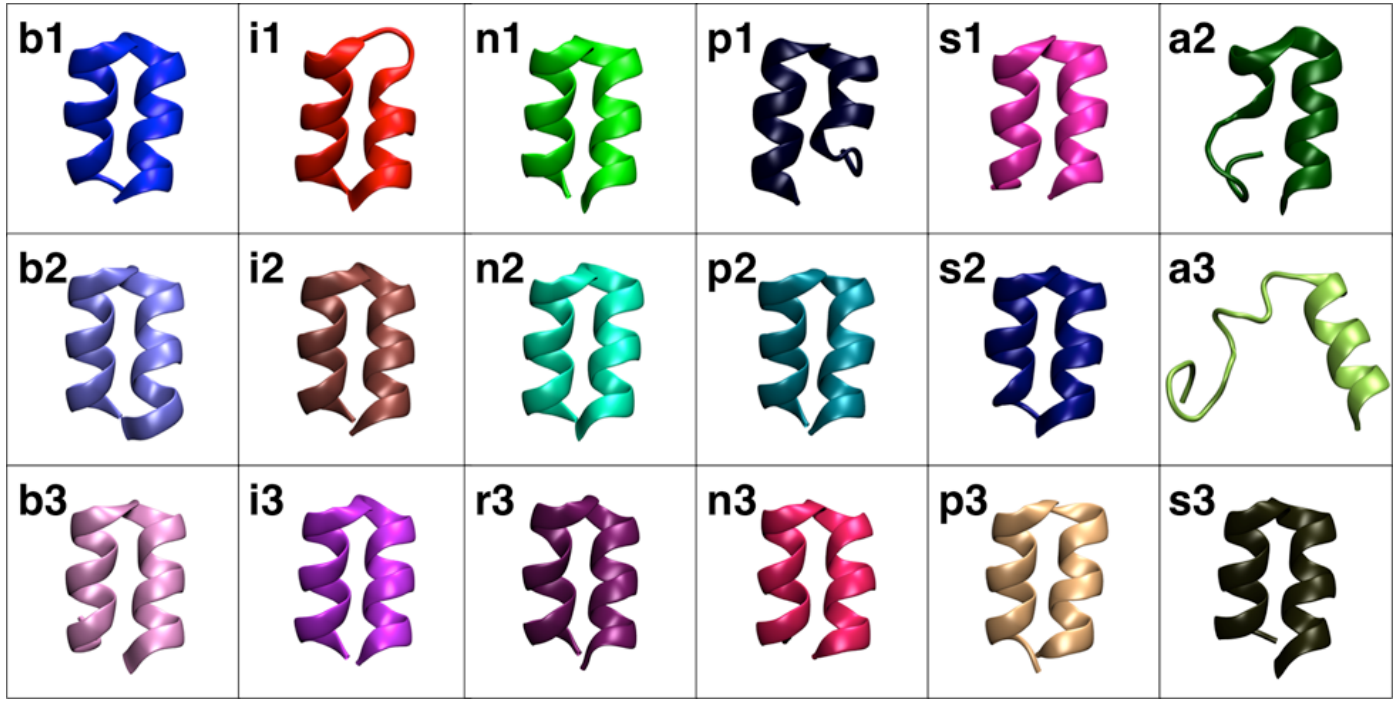
J. Baylon and E. T., **J. Phys. Chem.B**, 2015.

Remarkable convergence of membrane binding simulations

Side View

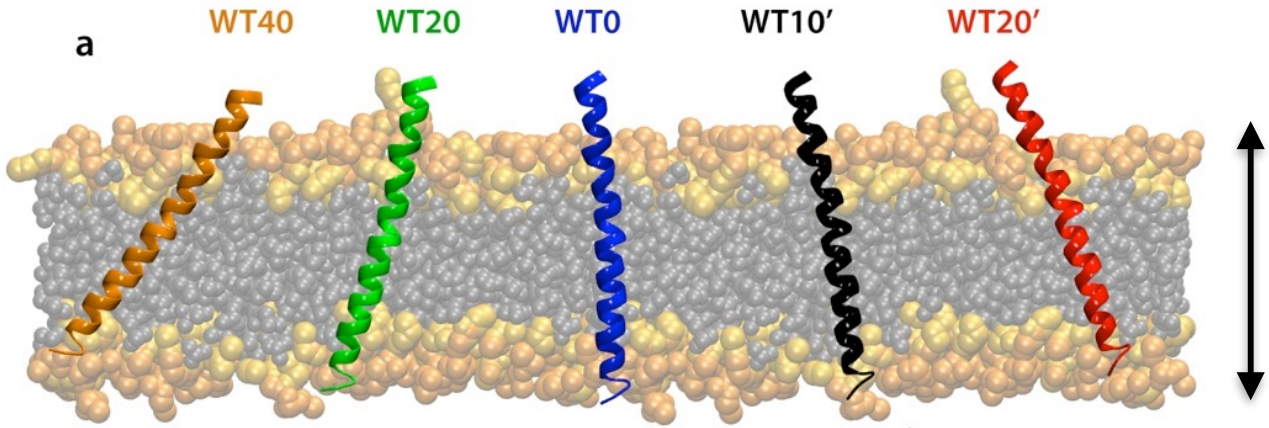


Top View

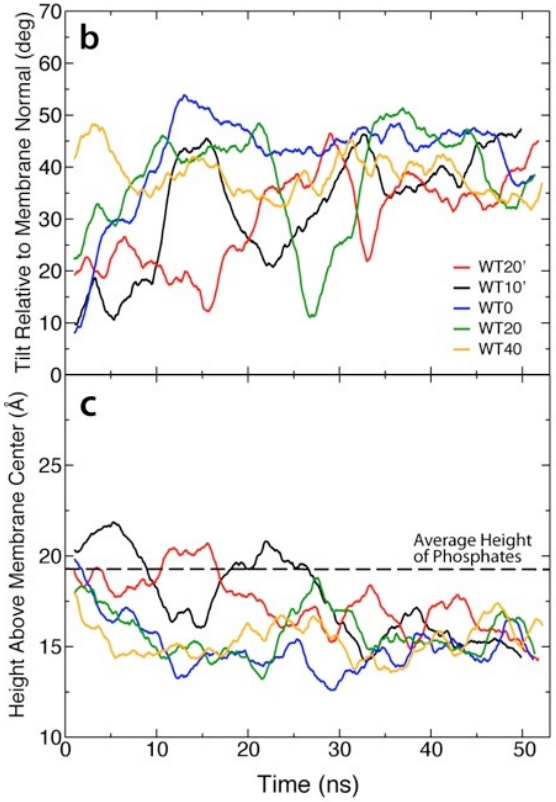


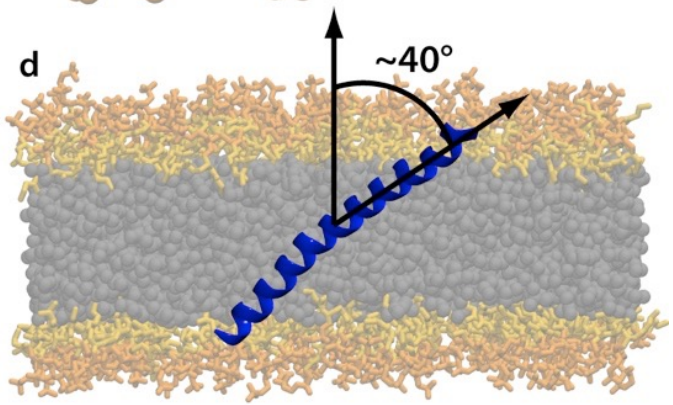
J. Baylon and E. T., **J. Phys. Chem.B**, 2015.

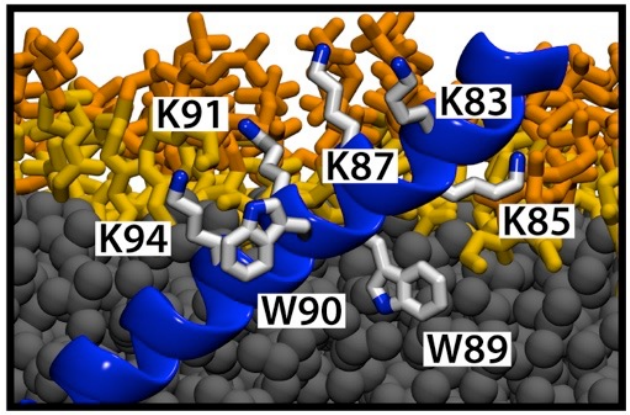
Robust Tilt Observed in Synaptobrevin



Membrane thickness mildly restrained:
one carbon/tail
k = 0.05 kcal/mole/A2



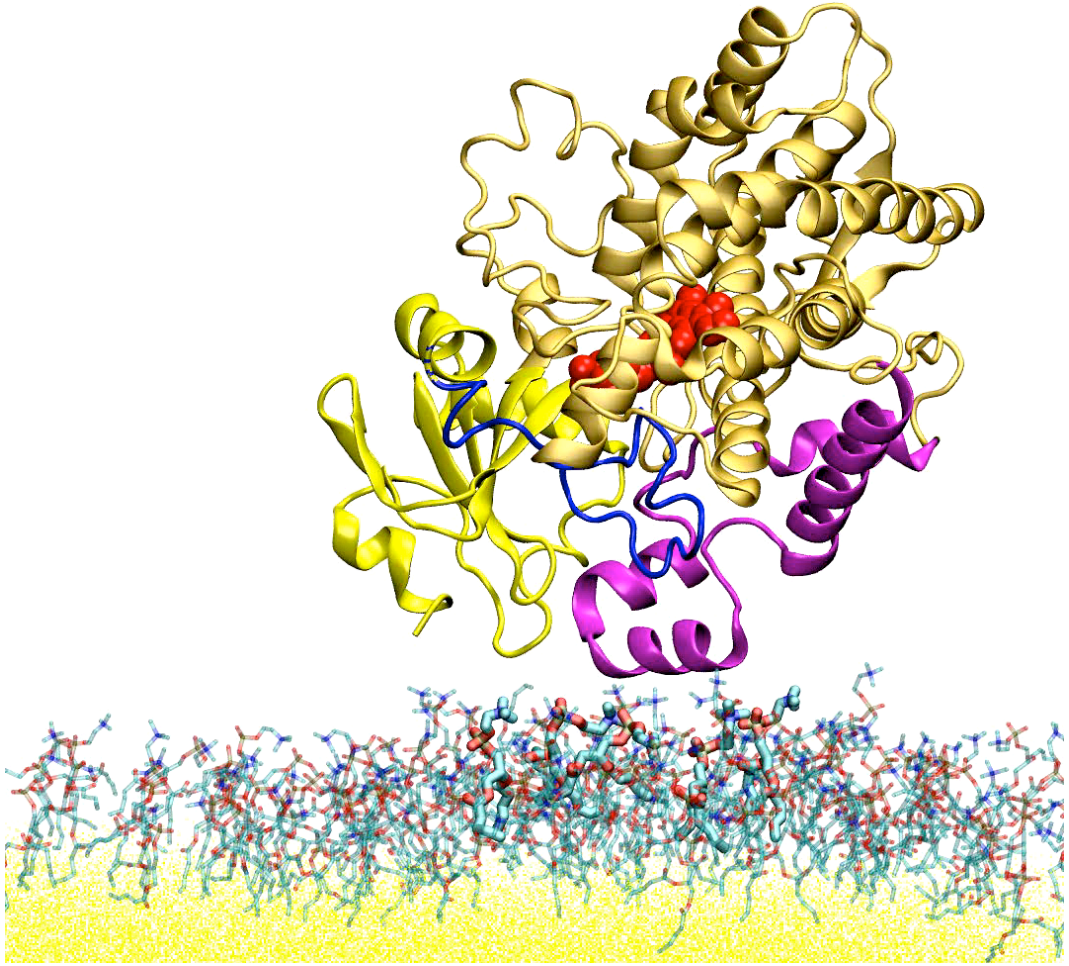


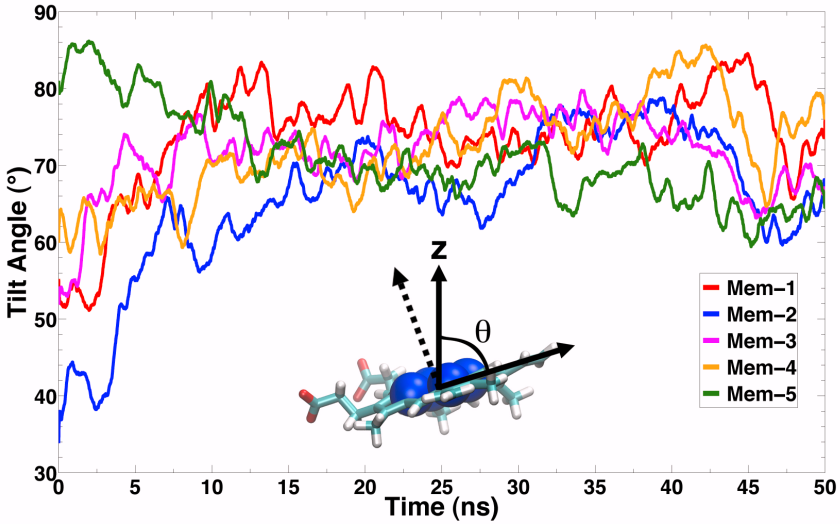


A. Blanchard*, M. Arcario*, K. Schulten, and ET, **Biophys. J.**, 107: 2112–21 (2014)

Insertion and Membrane-Induced Conformational Change of Cytochrome P450

Javier Baylon



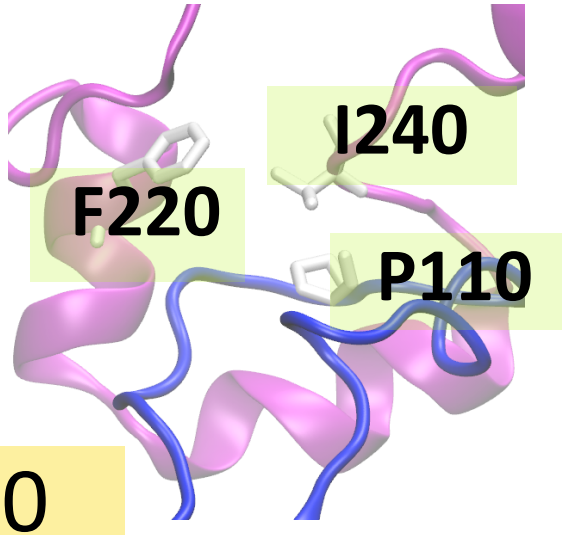


Within 10 degrees of experimental measurement of the tilt angle (S. Sligar)

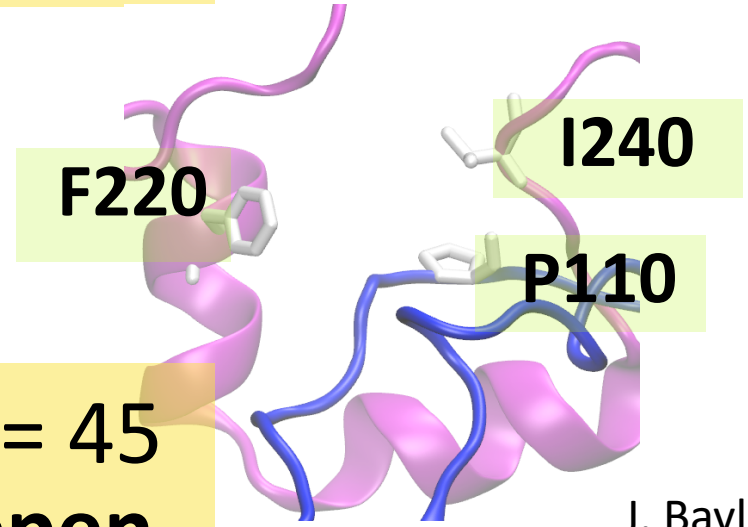
J. Baylon, I. Lenov, S. Sligar and ET, JACS, 135: 8542–8551 (2013)

Insertion and Membrane-Induced Conformational Change of Cytochrome P450

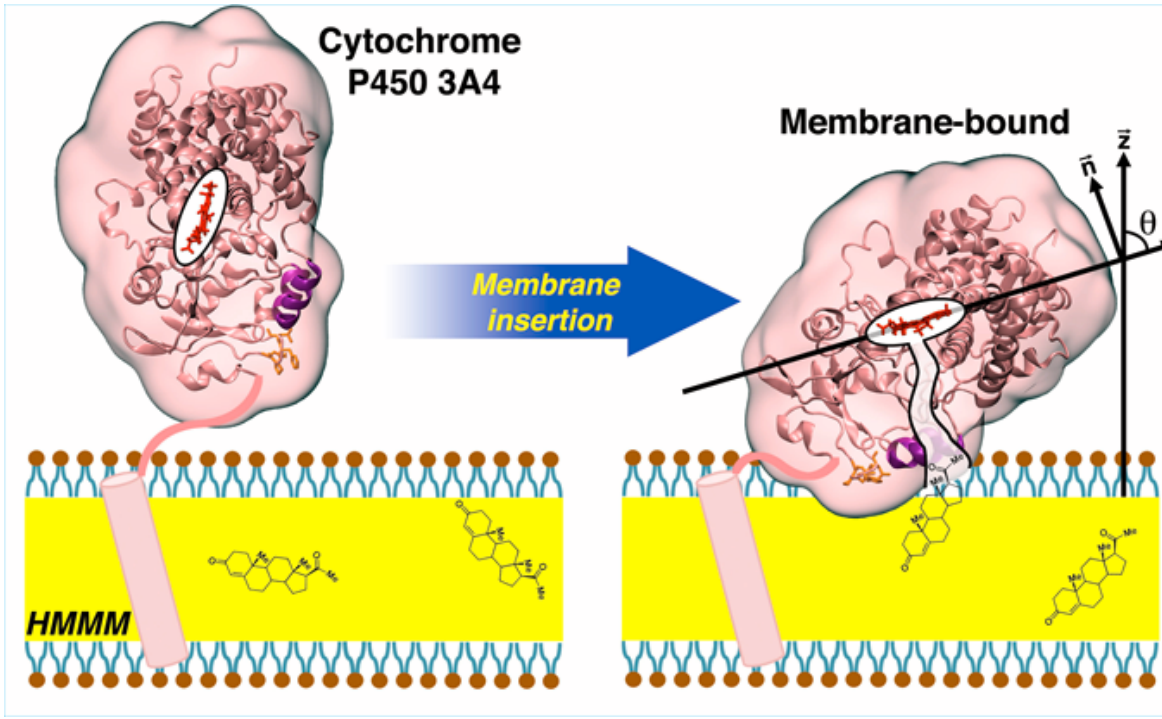
Javier Baylon



$t = 0$
closed



$t = 45$
open



J. Baylon, I. Lenov, S. Sligar and ET, *JACS*, 135: 8542–8551 (2013)

Battling the Timescale - Case III

Steered Molecular Dynamics is a non-equilibrium method by nature

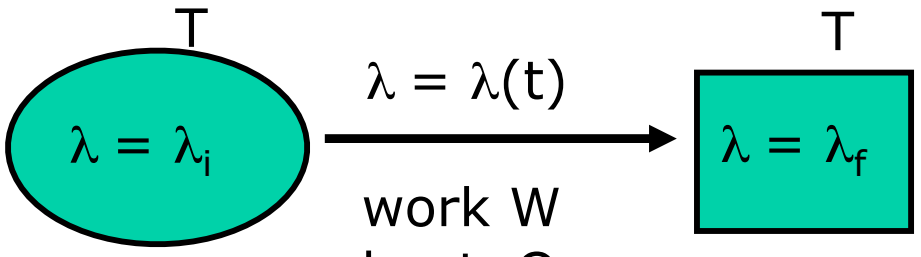
- A wide variety of events that are inaccessible to conventional molecular dynamics simulations can be probed.

- The system will be driven, however, away from equilibrium, resulting in problems in describing the energy landscape associated with the event of interest.

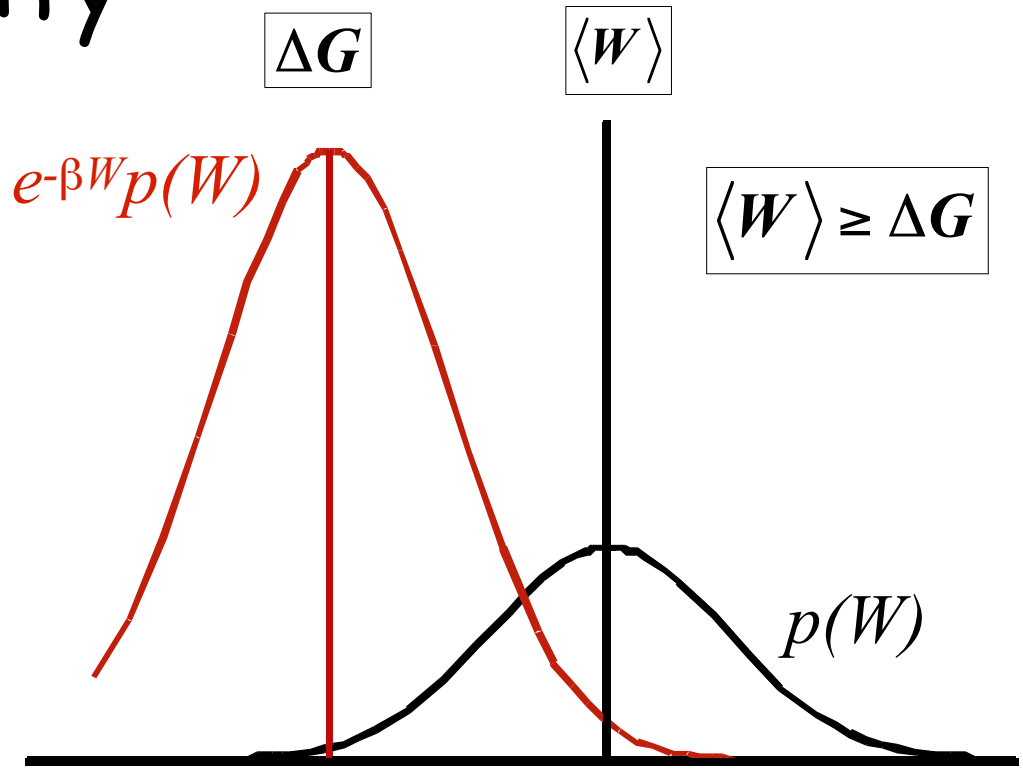
Second law of thermodynamics $\longrightarrow W \geq \Delta G$

Jarzynski's Equality

Transition between two equilibrium states



$$\Delta G = G_f - G_i$$



C. Jarzynski, *Phys. Rev. Lett.*, **78**, 2690 (1997)
C. Jarzynski, *Phys. Rev. E,* **56**, 5018 (1997)

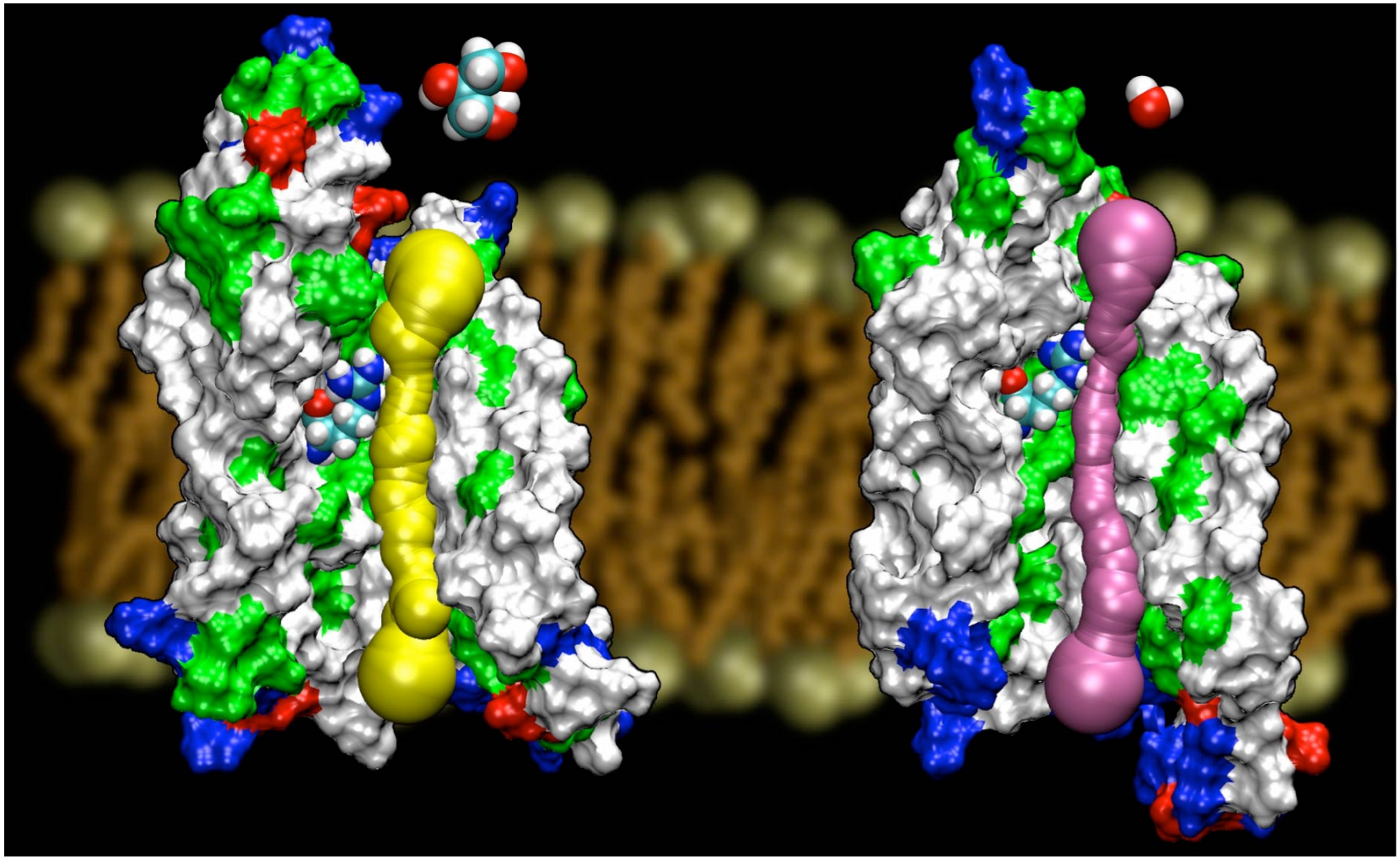
$$\left\langle e^{-\beta W} \right\rangle = e^{-\beta \Delta G}$$

$$\beta = 1/k_B T$$

In principle, it is possible to obtain free energy surfaces from repeated non-equilibrium experiments.

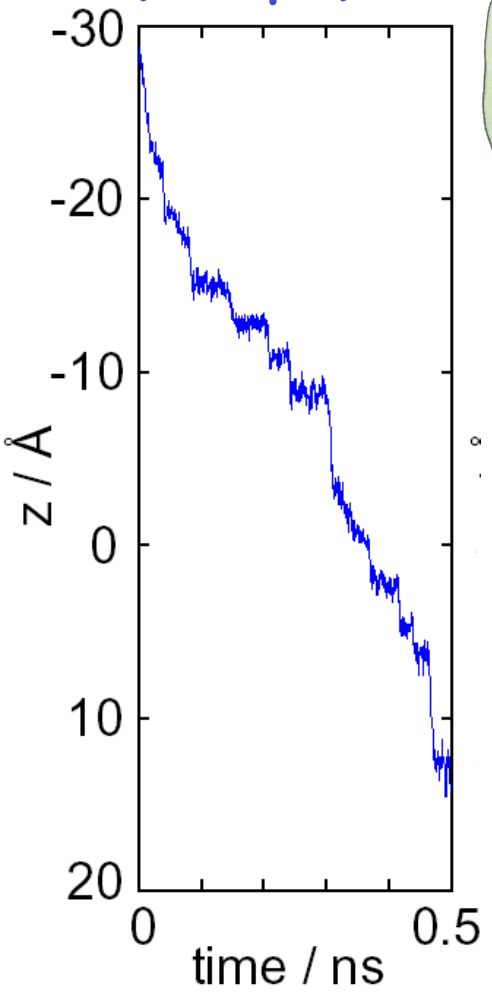
AqpZ *vs*. GlpF

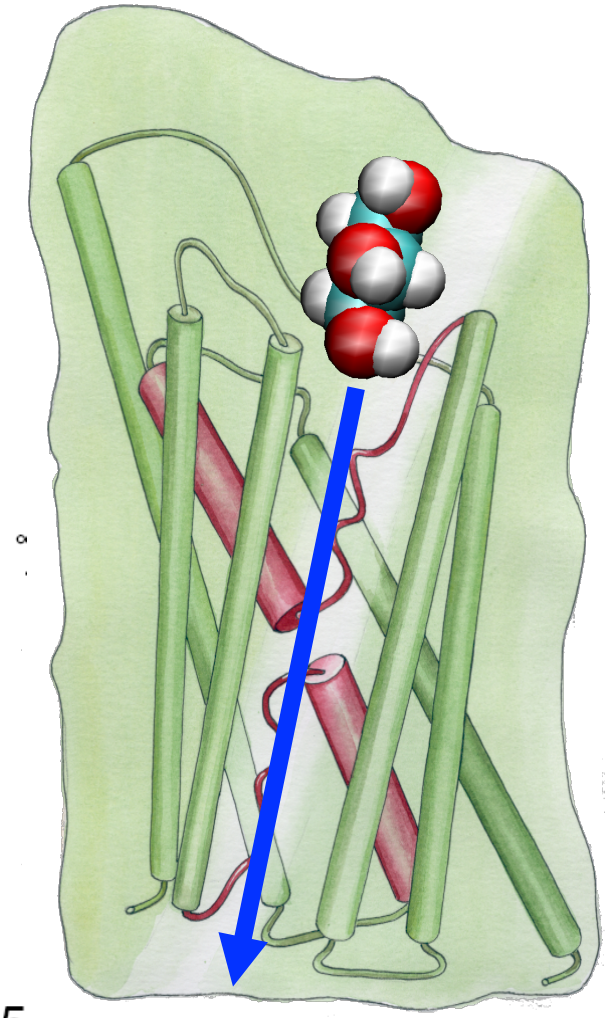
- Both from *E. coli*
- AqpZ is a pure water channel
- GlpF is a glycerol channel
- We have high resolution structures for both channels



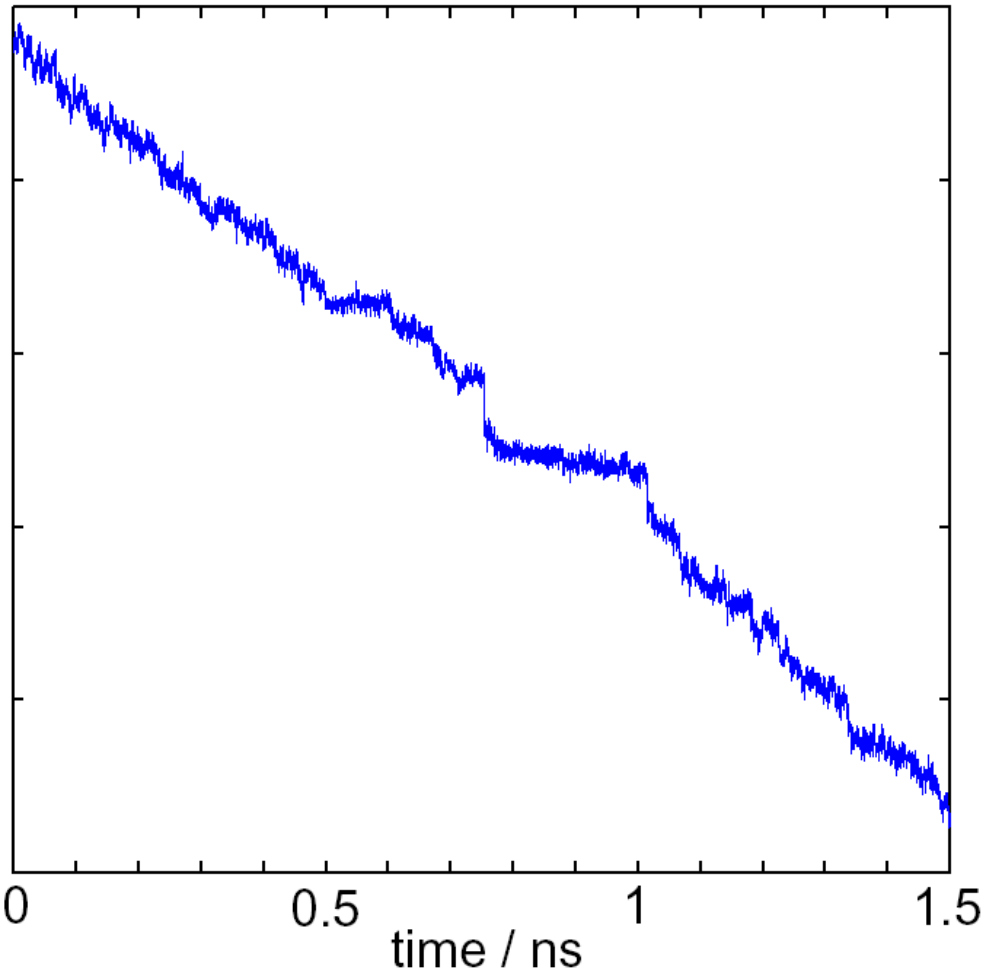
Steered Molecular Dynamics

constant force
(250 pN)

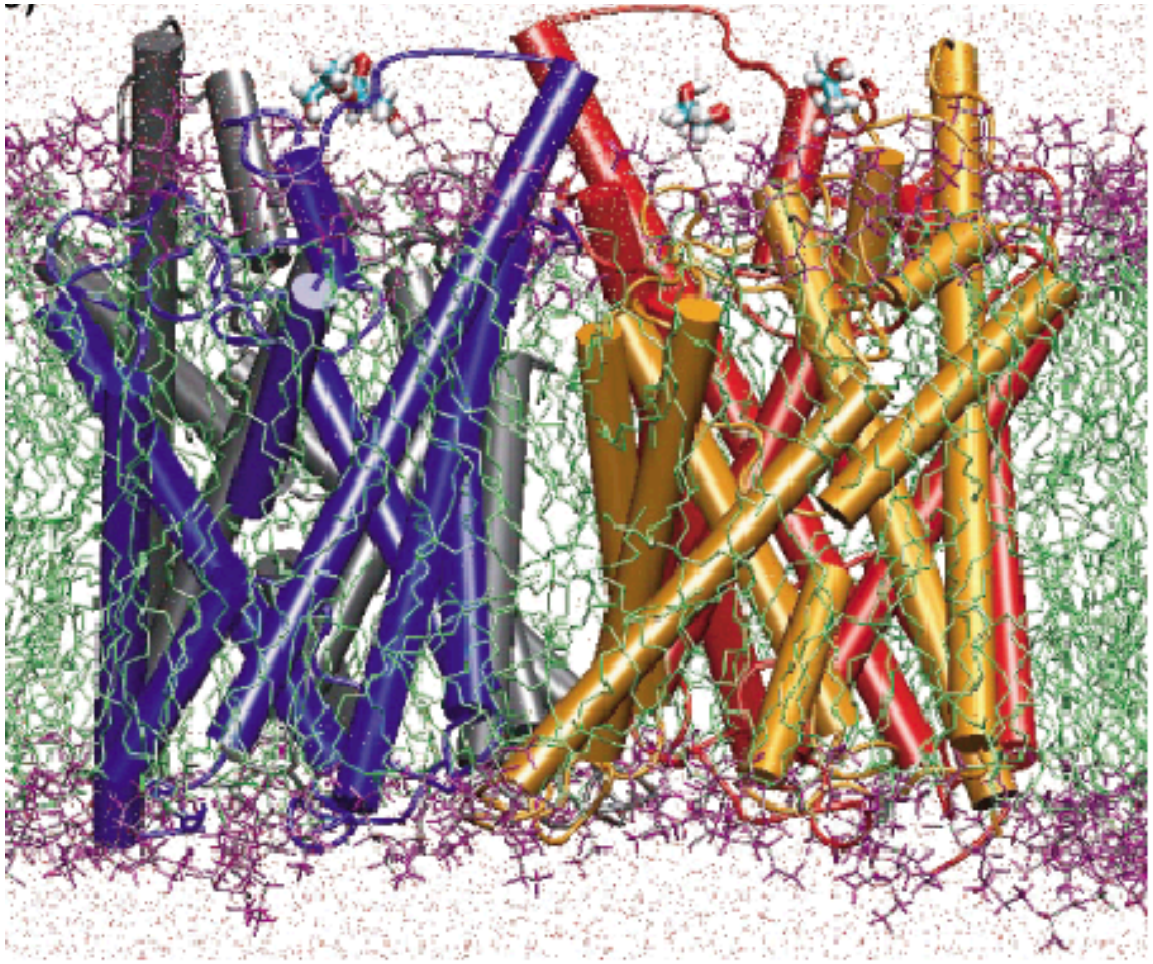


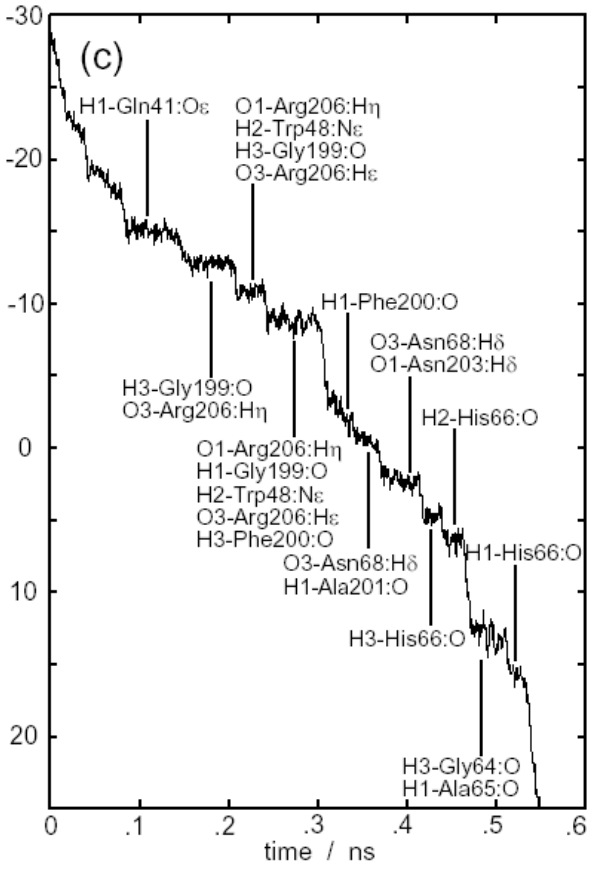


constant velocity
(30 Å/ns)



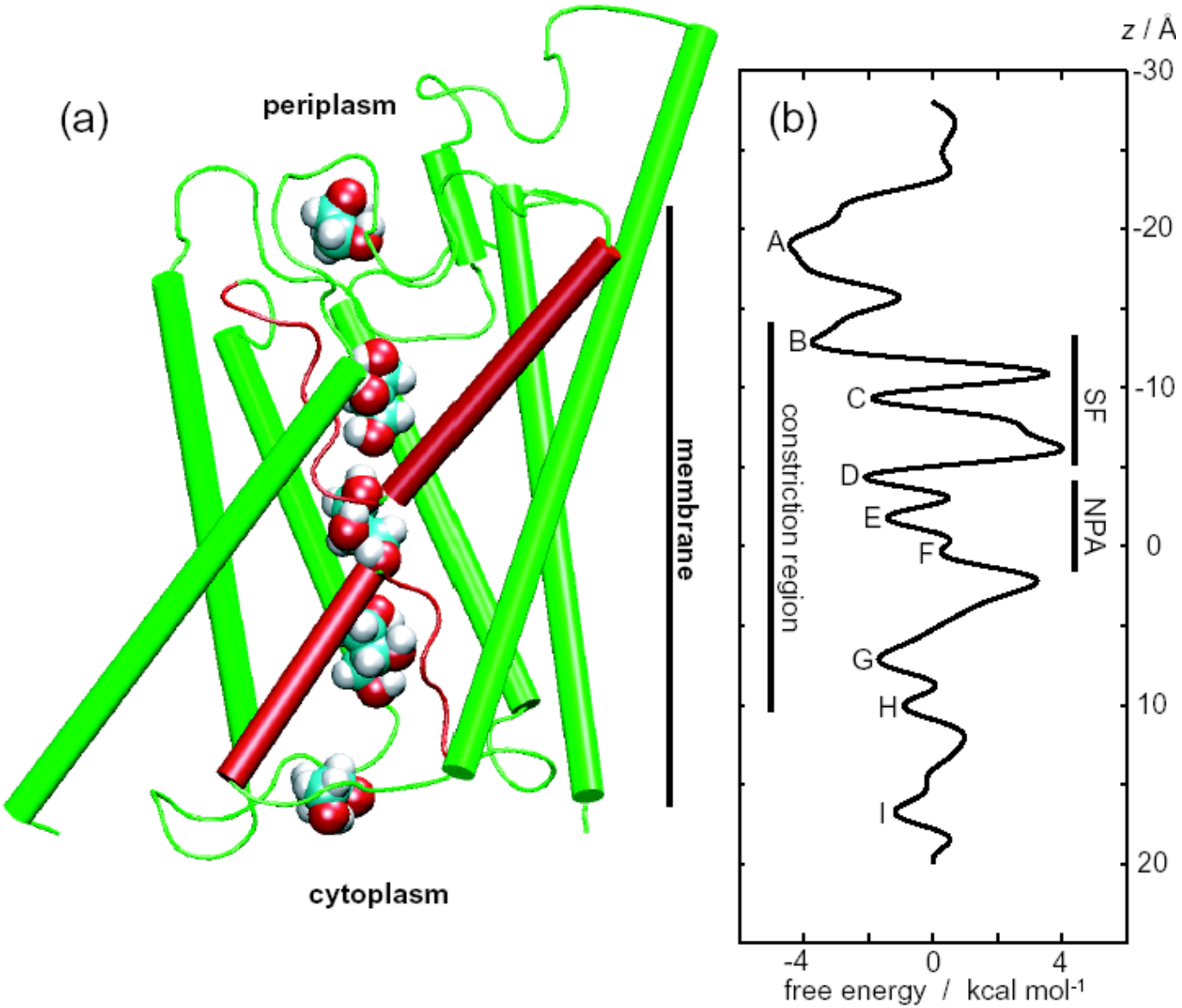
SMD Simulation of Glycerol Passage





Trajectory of glycerol pulled by **constant force**

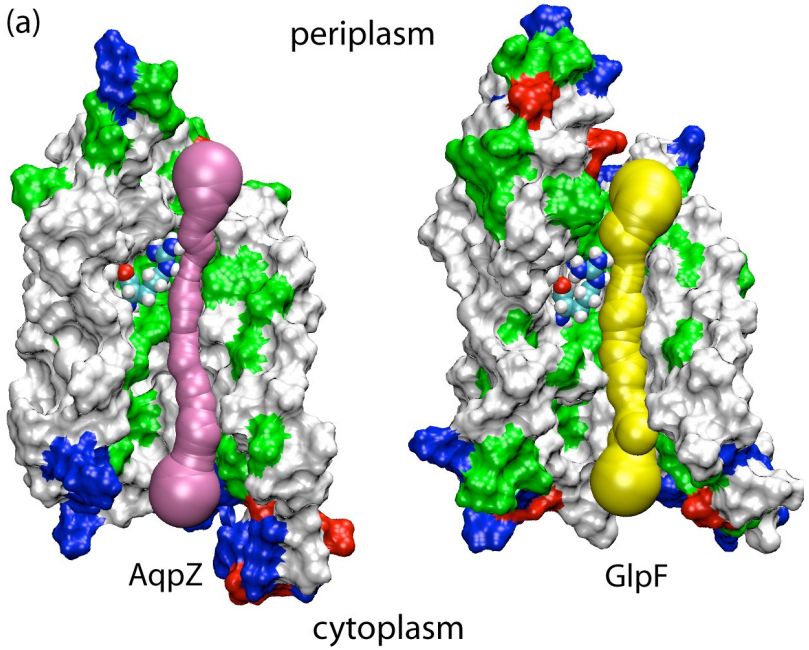
Features of the Potential of Mean Force

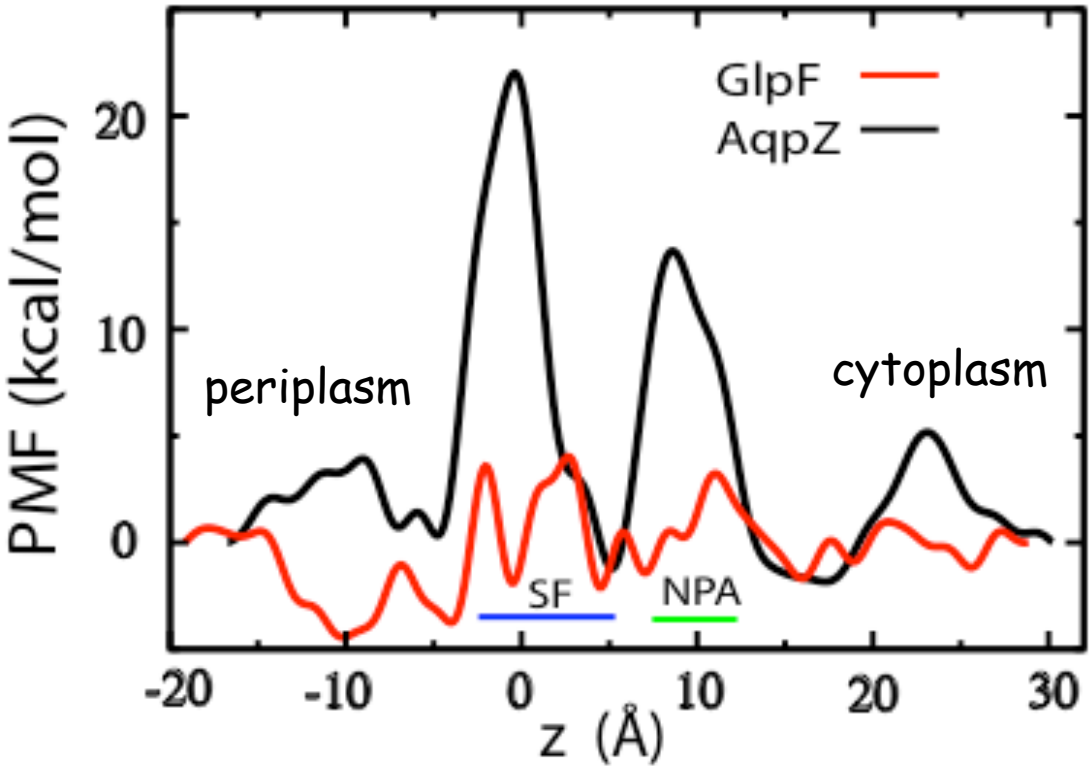


- Captures major features of the channel
- The largest barrier ≈ **7.3 kcal/mol; exp.: 9.6±1.5 kcal/mol**

Jensen et al., *PNAS*, 99:6731-6736, 2002.

Three fold higher barriers

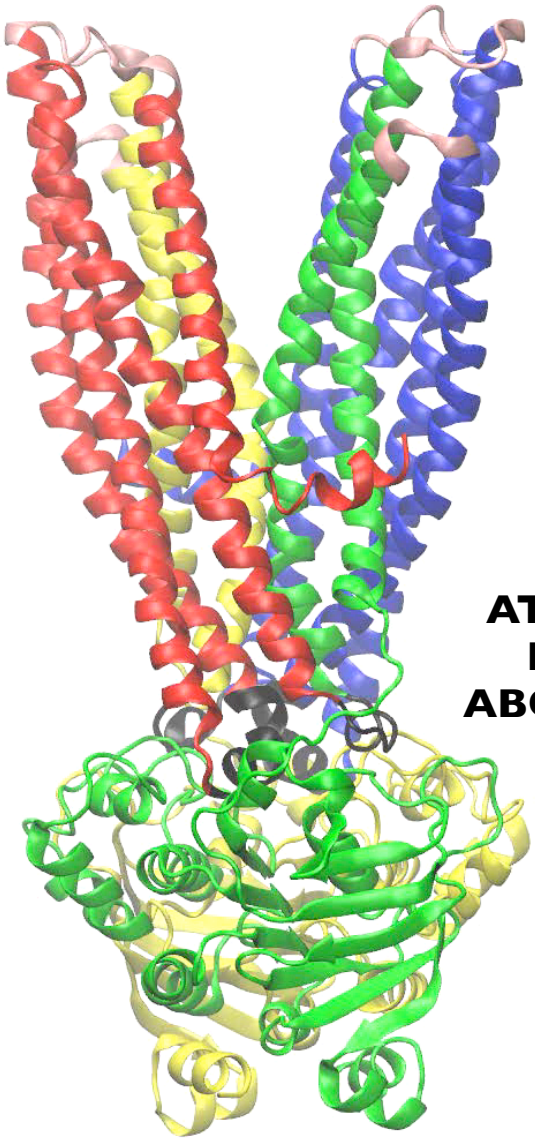




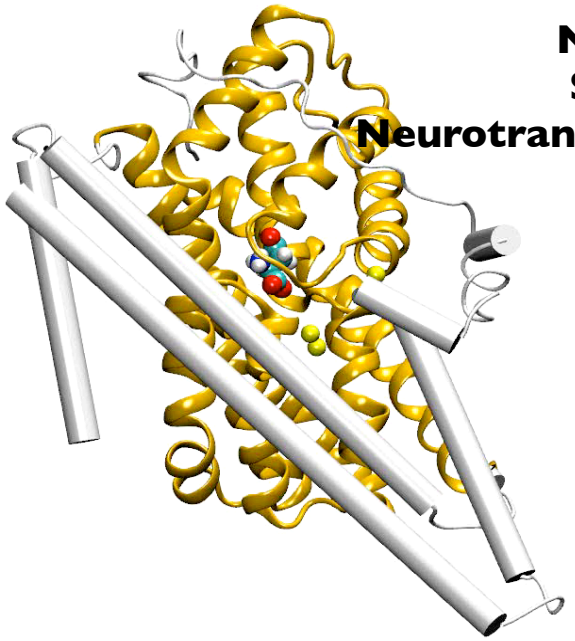
AqpZ 22.8 kcal/mol
GlpF 7.3 kcal/mol

Y. Wang, K. Schulten, and E. Tajkhorshid ***Structure*** 13, 1107 ***(***2005)

Battling the Timescale - Case IV
Biased (nonequilibrium) simulations along more complex reaction coordinates (COLVARS)

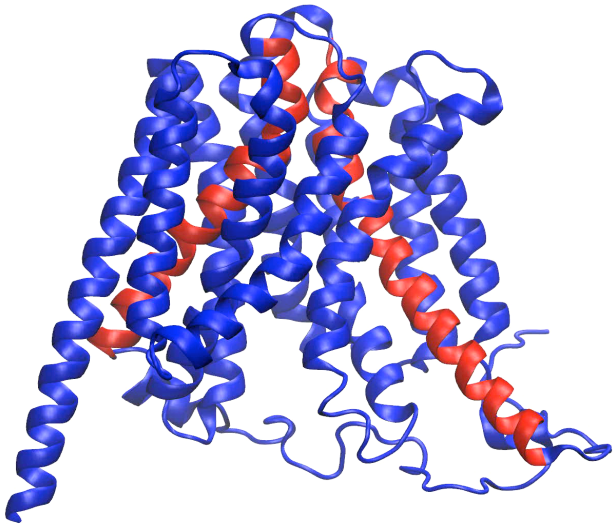


ATP-Driven Primary ABC Exporter



Na-coupled Secondary Neurotransmitter Transporter

Secondary Phosphate Antiporter



Complex Processes Require Complex Treatments

I.1 Defining Practical Collective Variables
Empirical search for practical collective variables for inducing the conformational changes involved in the transition.

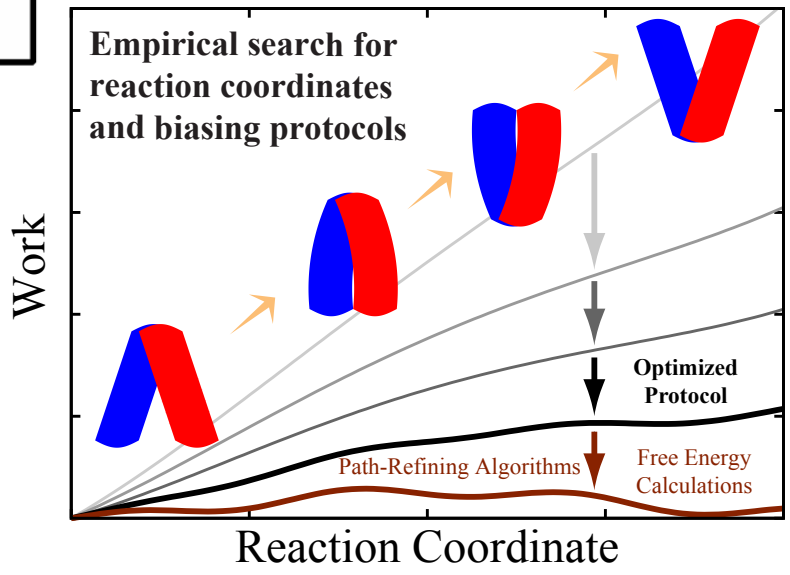
I.2 Optimizing the Biasing Protocols
Systematic search for a practical biasing protocol by using different combinations of collective variables.

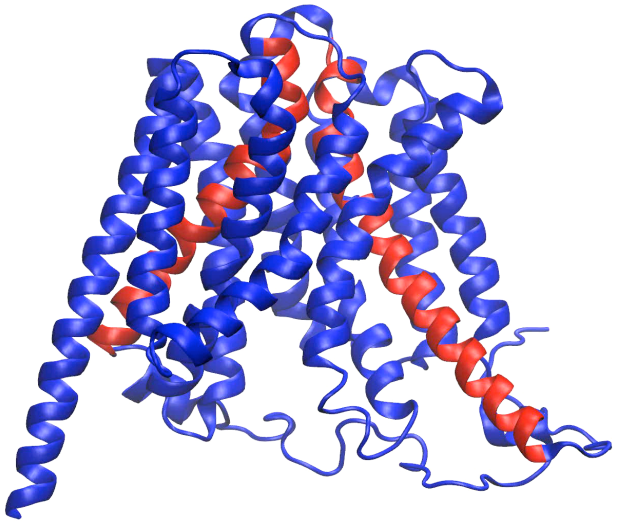
II. Optimizing the Transition Pathway
Use all of the conformations available to generate the most reliable transition pathway:
1. Bayesian approach for combining the data
2. Post-hoc string method (analysis tool)
3. String method with swarms of trajectories

III.1 Free Energy Calculations
Using the most relevant collective variables (from I.1), biasing protocol (from I.2), and initial conformations (from I.2).

III.2 Assessing the Sampling Efficiency
Detecting the poorly sampled, but potentially important regions, e.g., by using PCA.

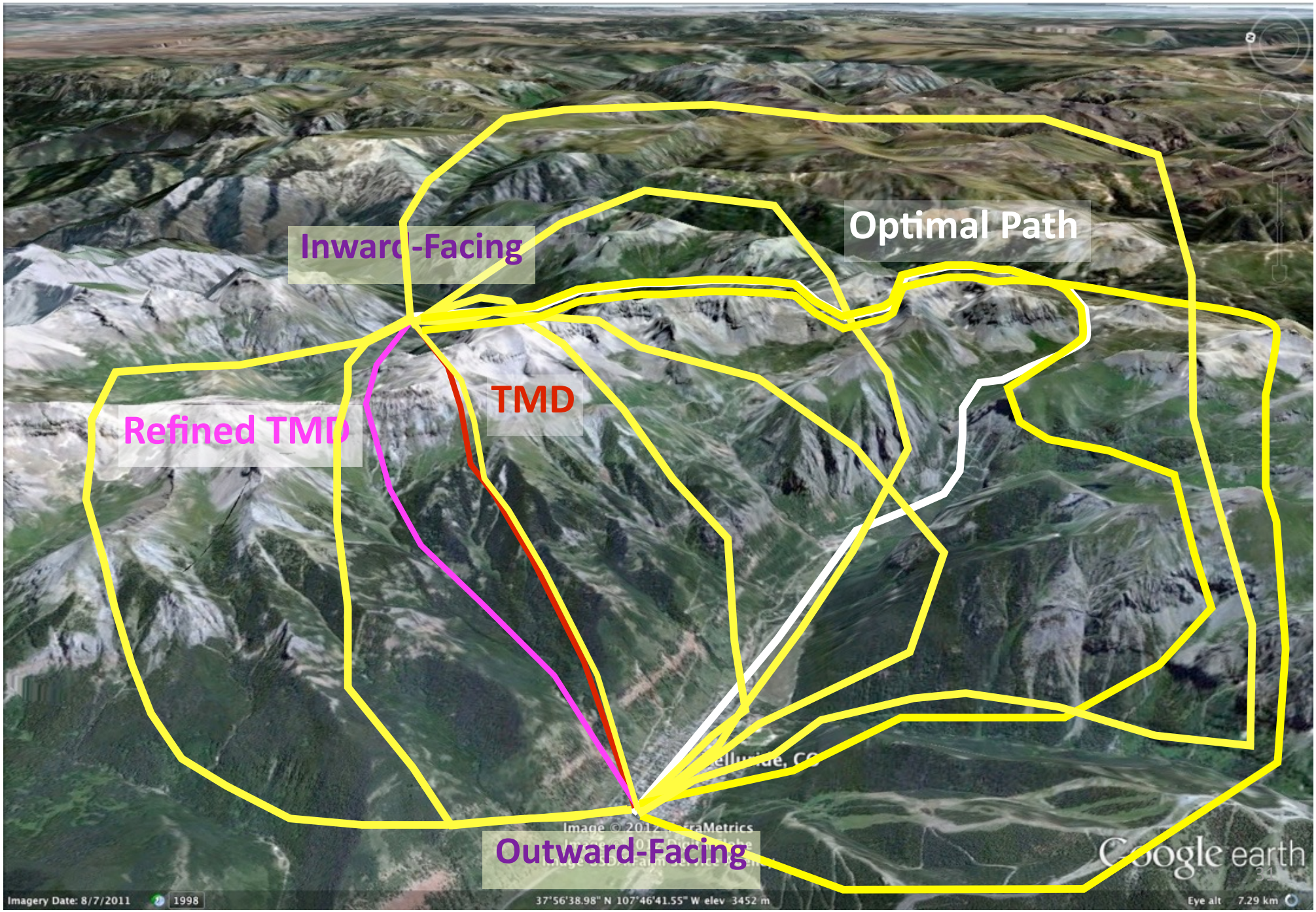
Mahmoud Moradi





M. Moradi and ET (2013) **PNAS**, 110:18916–18921.
M. Moradi and ET (2014) **JCTC**, 10: 2866–2880.
M. Moradi, G. Enkavi, and ET (2015) **Nature Comm.**, 6:8393.

Aggressive Search of the Space



Non-equilibrium Driven Molecular Dynamics:

Applying a time-dependent external force to induce the transition

Along various pathways/mechanisms (collective variables)

Harmonic constant

Initial state

$$U_{dr}(\boldsymbol{x}, t) = \frac{1}{2}k\left(\xi(\boldsymbol{x}) - \xi_A + (\xi_B - \xi_A)\frac{t}{\mathrm{T}}\right)^2$$

Biasing potential

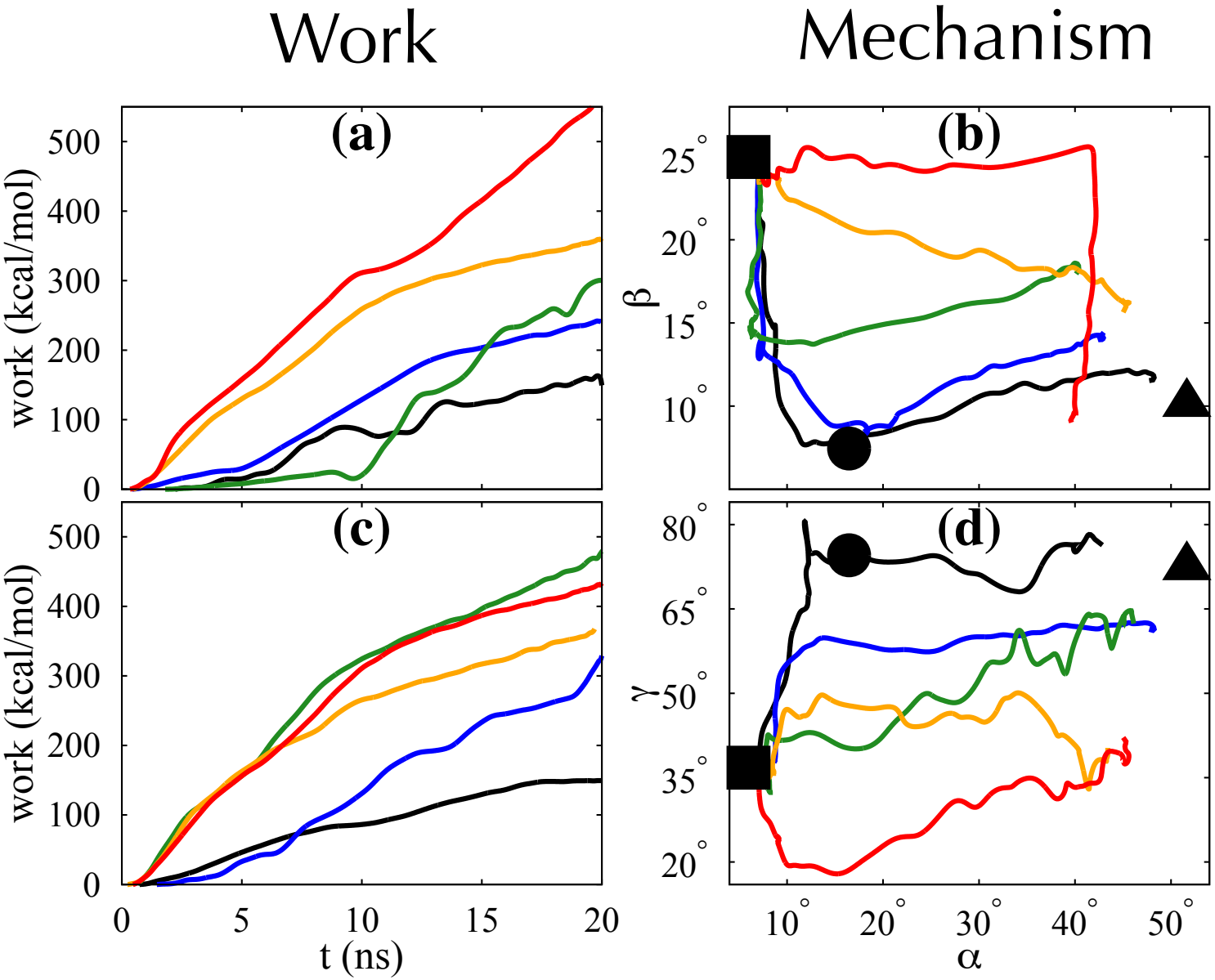
Collective variables:
RMSD, distance,
R_g, angle, …
orientation quaternion

Final state

Total simulation time

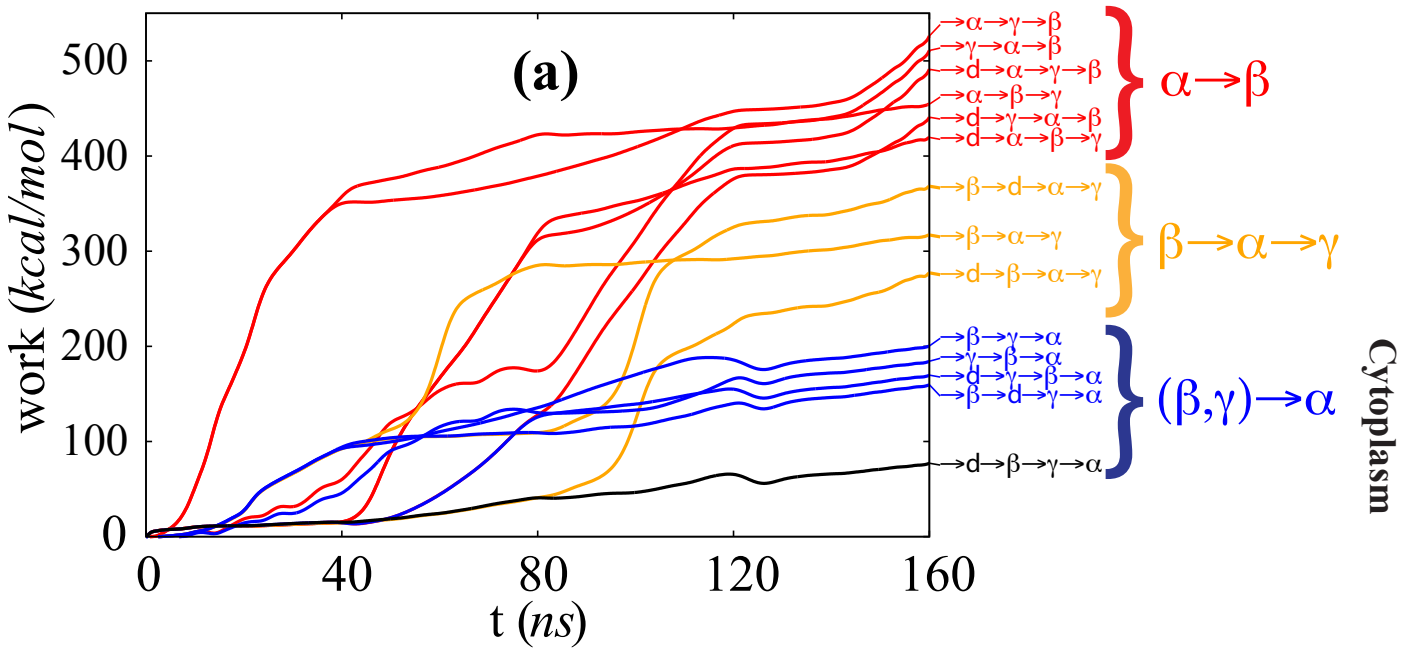
M. Moradi and ET (2013) **PNAS**, 110:18916–18921.
M. Moradi and ET (2014) **JCTC**, 10: 2866–2880.
M. Moradi, G. Enkavi, and ET (2015) **Nature Comm.**, 6:8393.

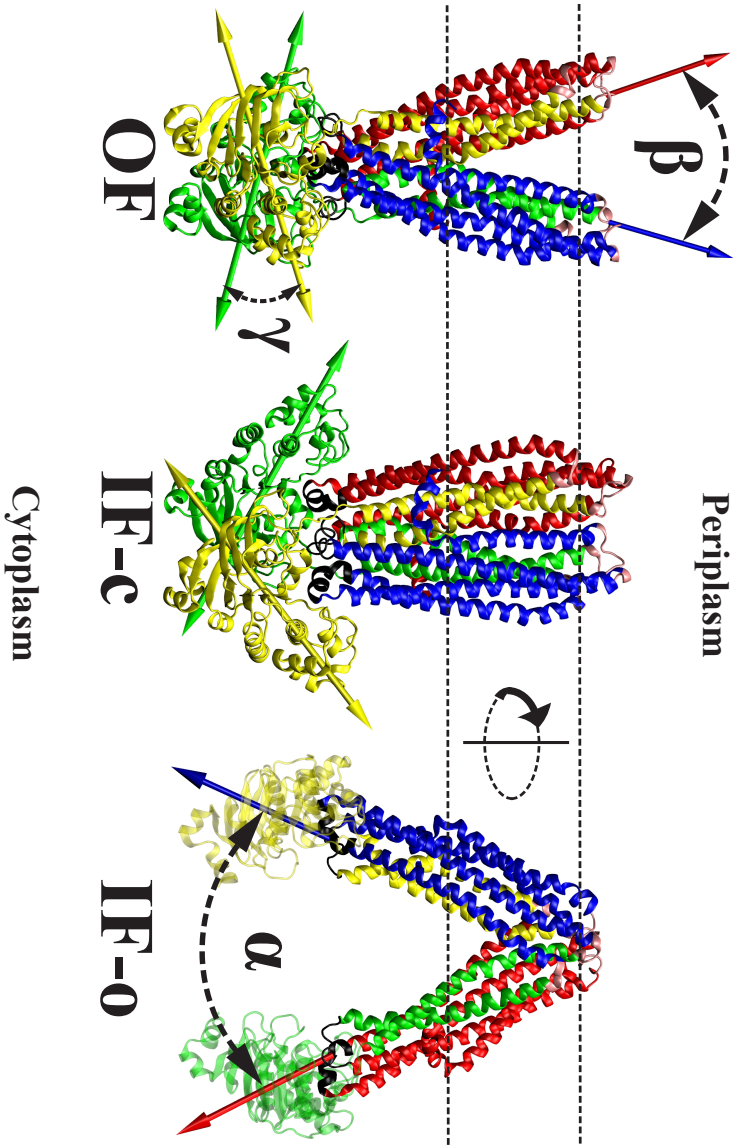
Progressively Optimizing the Biasing Protocol/Collective Variable using non-Equilibrium Work as a Measure of the Path Quality



Example set taken from a subset of 20 ns biased simulations

Mechanistic Insight From Transition Pathways in ABC exporters from Non-Equilibrium Simulations





M. Moradi and ET (2013) **PNAS**, 110:18916–18921.

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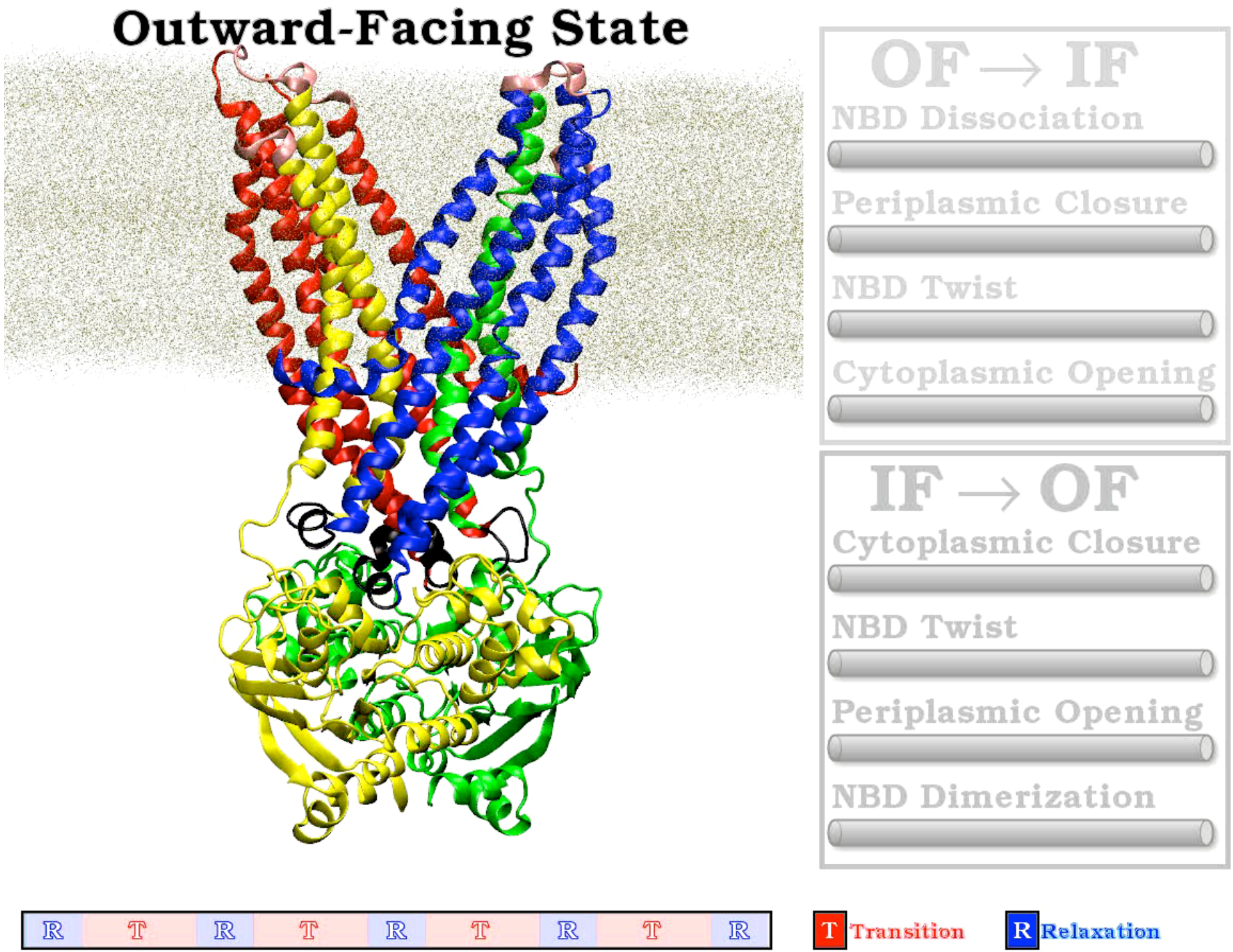
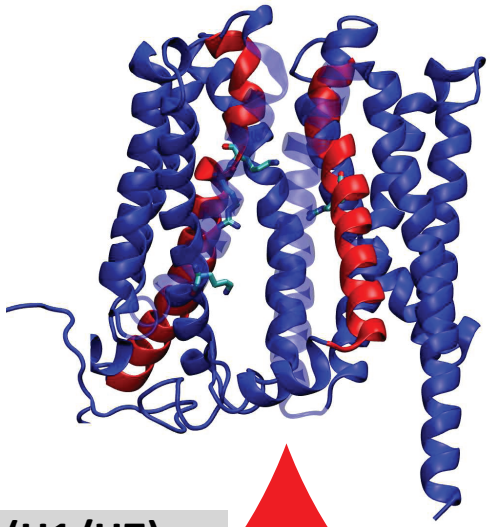


NBD Doorknob Mechanism

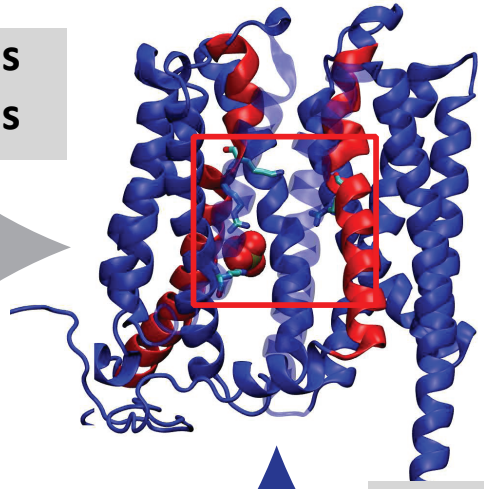
M. Moradi and ET (2013) **PNAS**, 110:18916–18921.

Describing a Complete Cycle (Adding Substrate) Requiring a Combination of Multiple Collective Variables



IF_{apo}

30 r x 20 ns
30 r x 20 ns

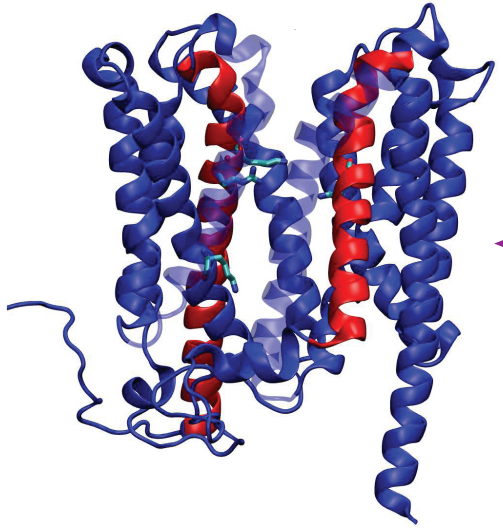


IF_{bound}

12 replicas x 40 ns (H1/H7)
50 replicas x 20 ns (10 Hs)

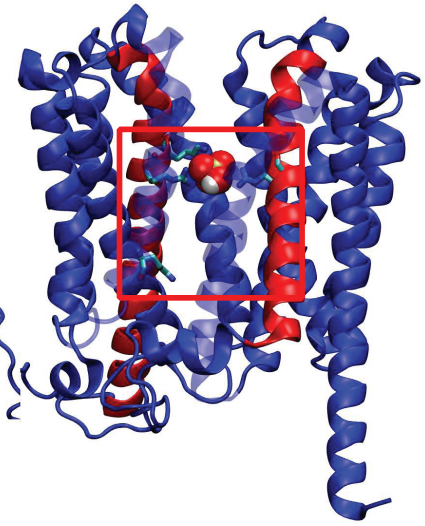
150 replicas

12 replicas x 40 ns (H1/H7)
24 replicas x 20 ns (H1/H7)
200 replicas (2D) x 5 ns
50 replicas x 20 ns

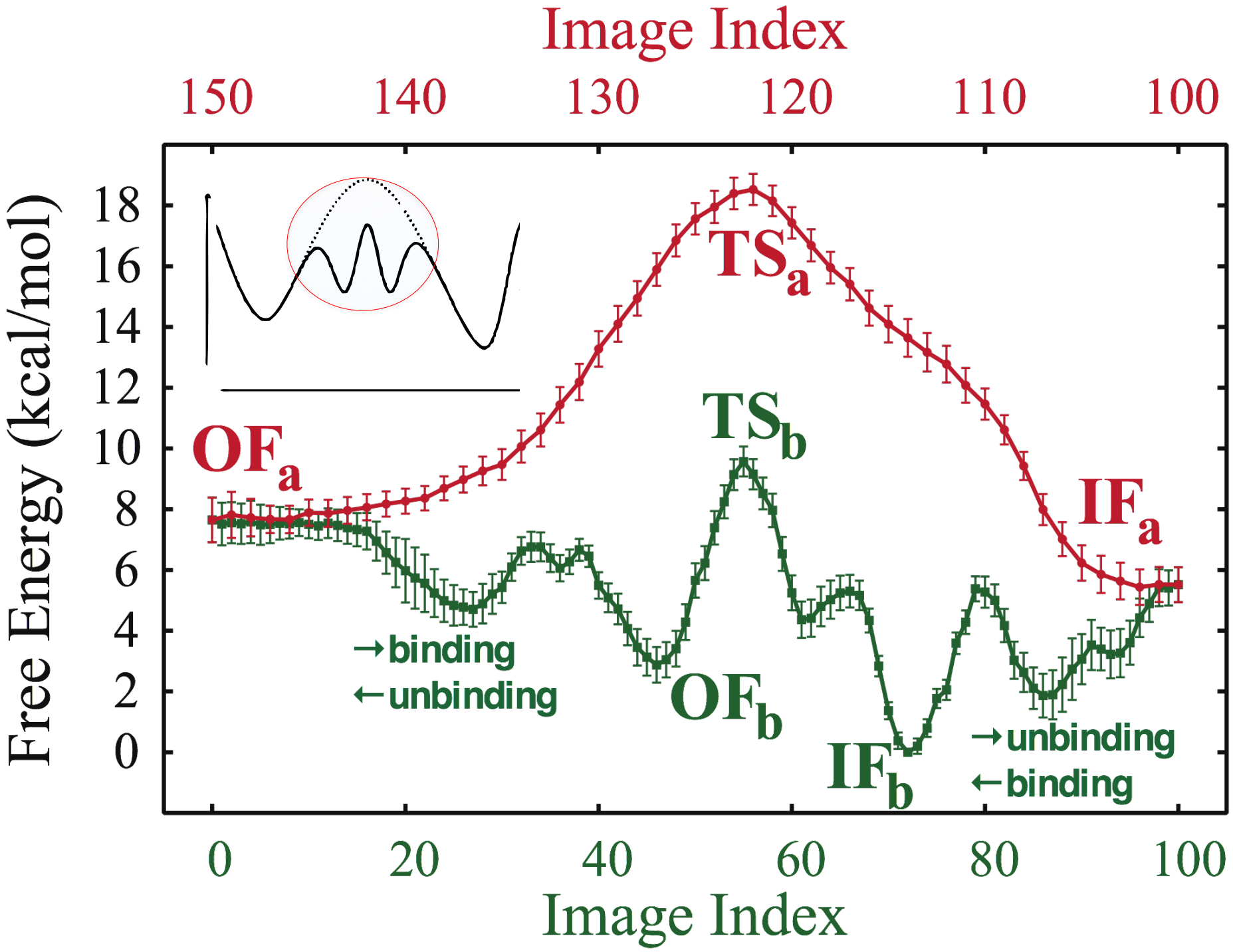


OF_{apo}

30 r x 20 ns
30 r x 20 ns
30 r x 20 ns



OF_{bound}



M. Moradi, G. Enkavi, and ET (2015) **Nature Communication**, 6: 8393.