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Indolicidin Binding Induces Thinning of a Lipid Bilayer

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New and Notable

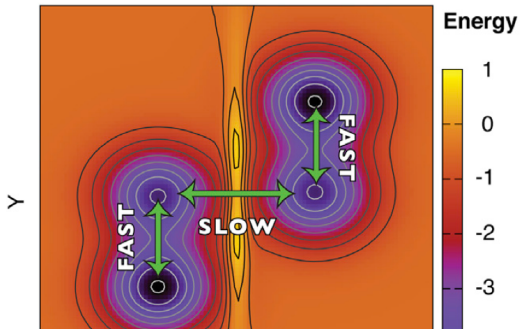
Unknown Unknowns: the Challenge of Systematic and Statistical Error in Molecular Dynamics Simulations

Tod D. Romo and Alan Grossfield*

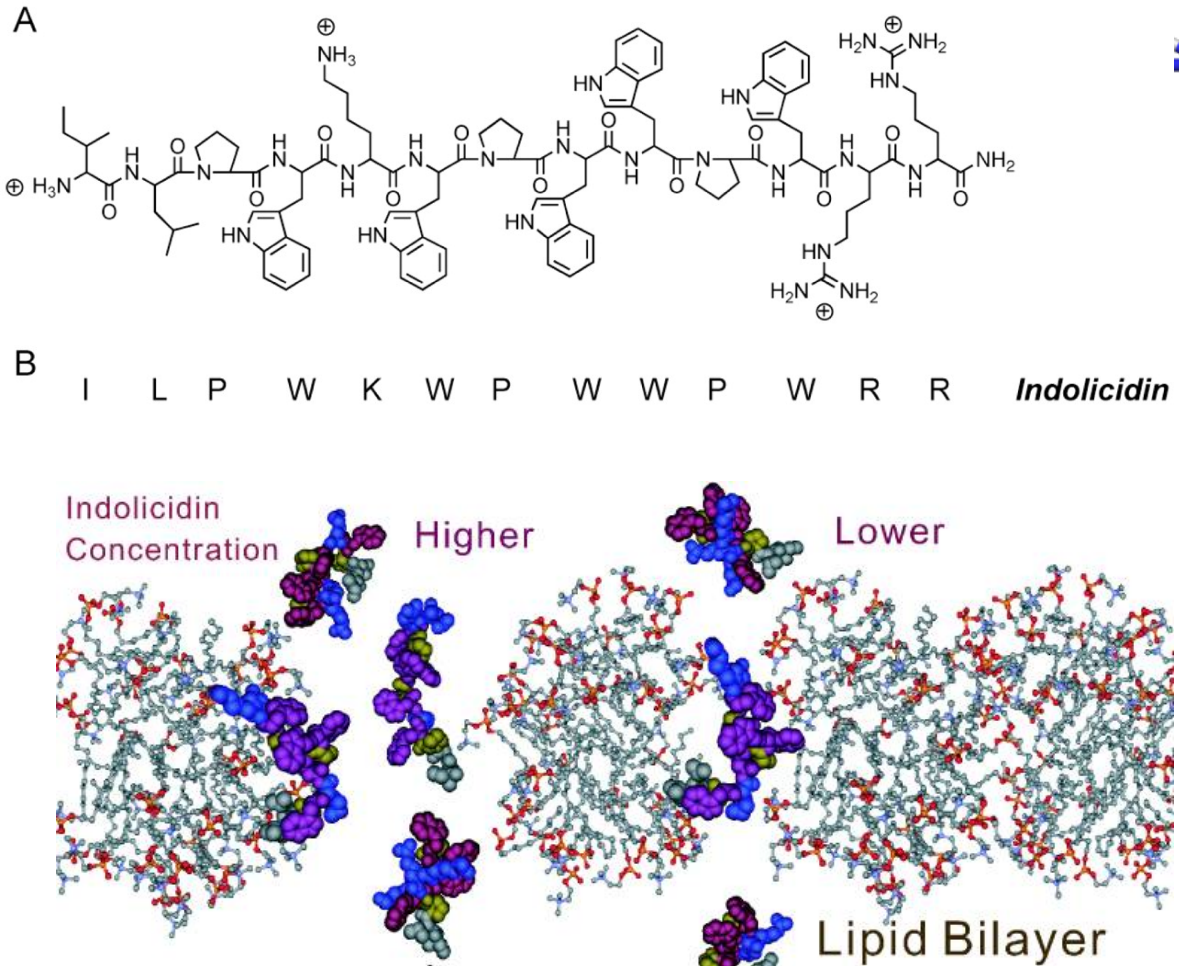
Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, New York

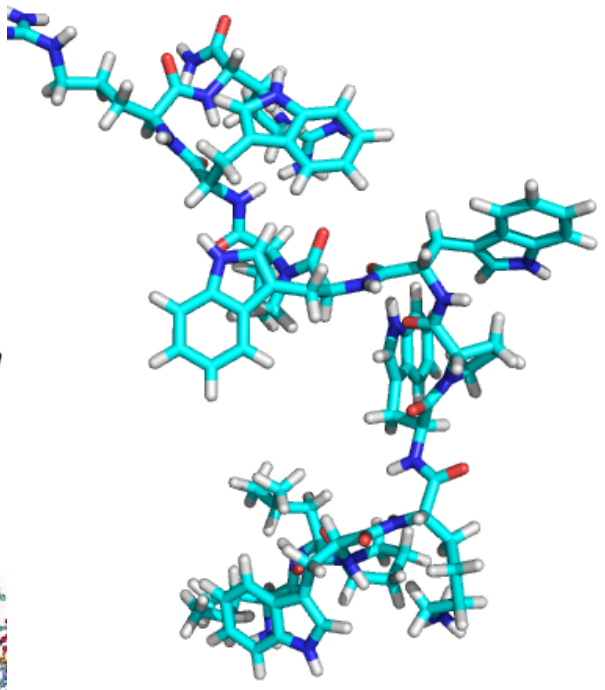
the force field and simulation conditions); and

2. We can expect that if we run multiple trajectories, the values of the $\langle A \rangle$ value computed from the trajectory will be distributed randomly about A_o, with a variance that drops roughly as $1/\sqrt{T_{sim}}$, where T_{sim} is

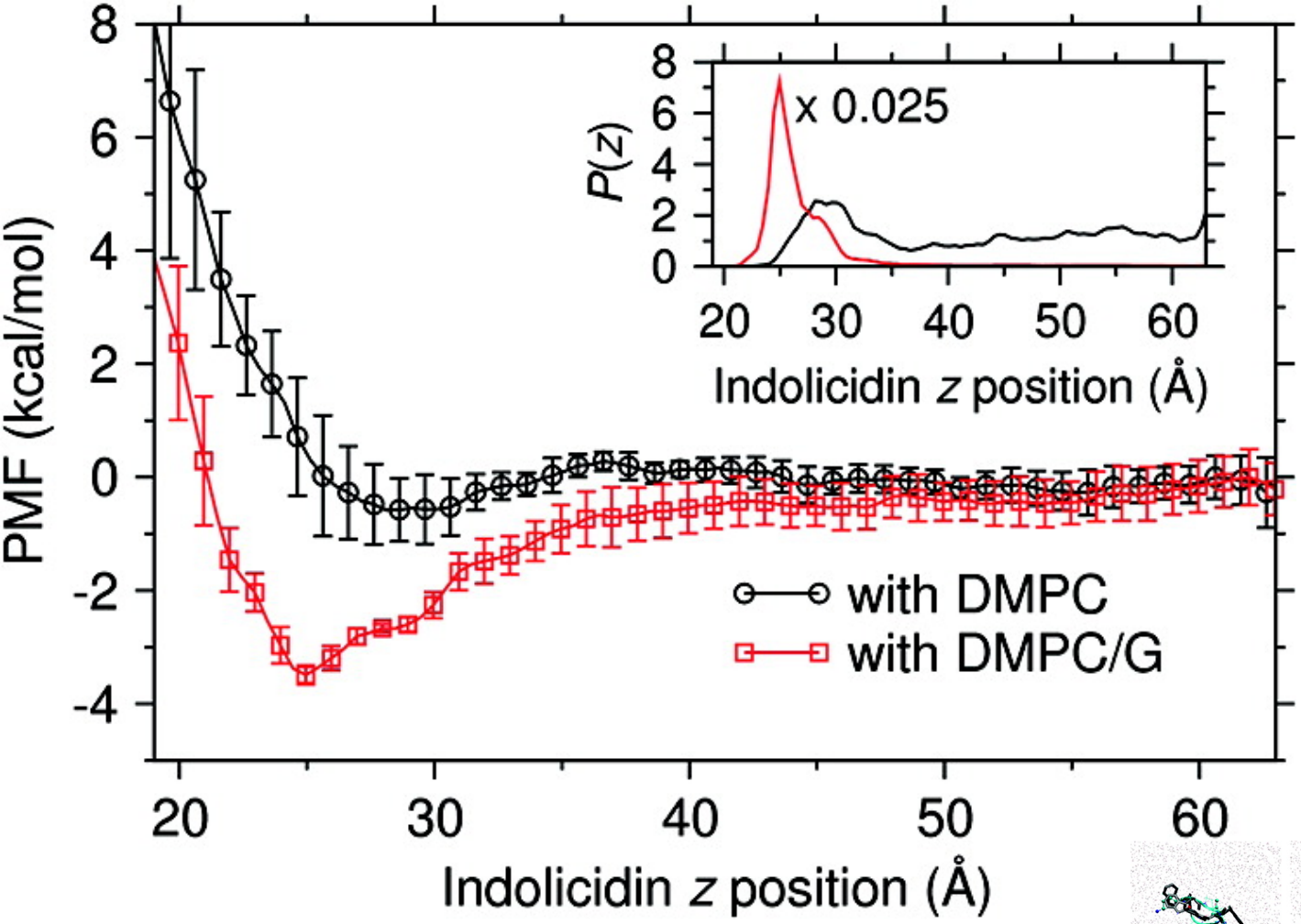


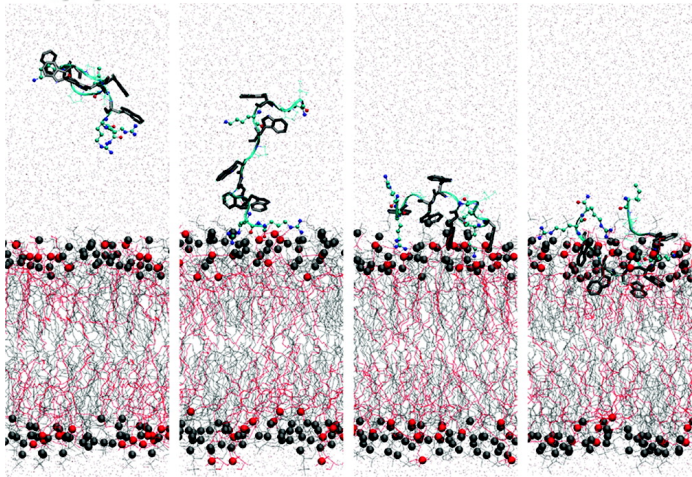
System Importance





Marchand, C., et al. 2006. *Nucl. Acids Res.* **34:** 5157-5165.
Rozek, A., et al. 2000. *Biochemistry*. **39:** 15765-15774.
Hsu, C.H., et al. 2005. *Nucl. Acids Res.* **33:** 4053-4064.





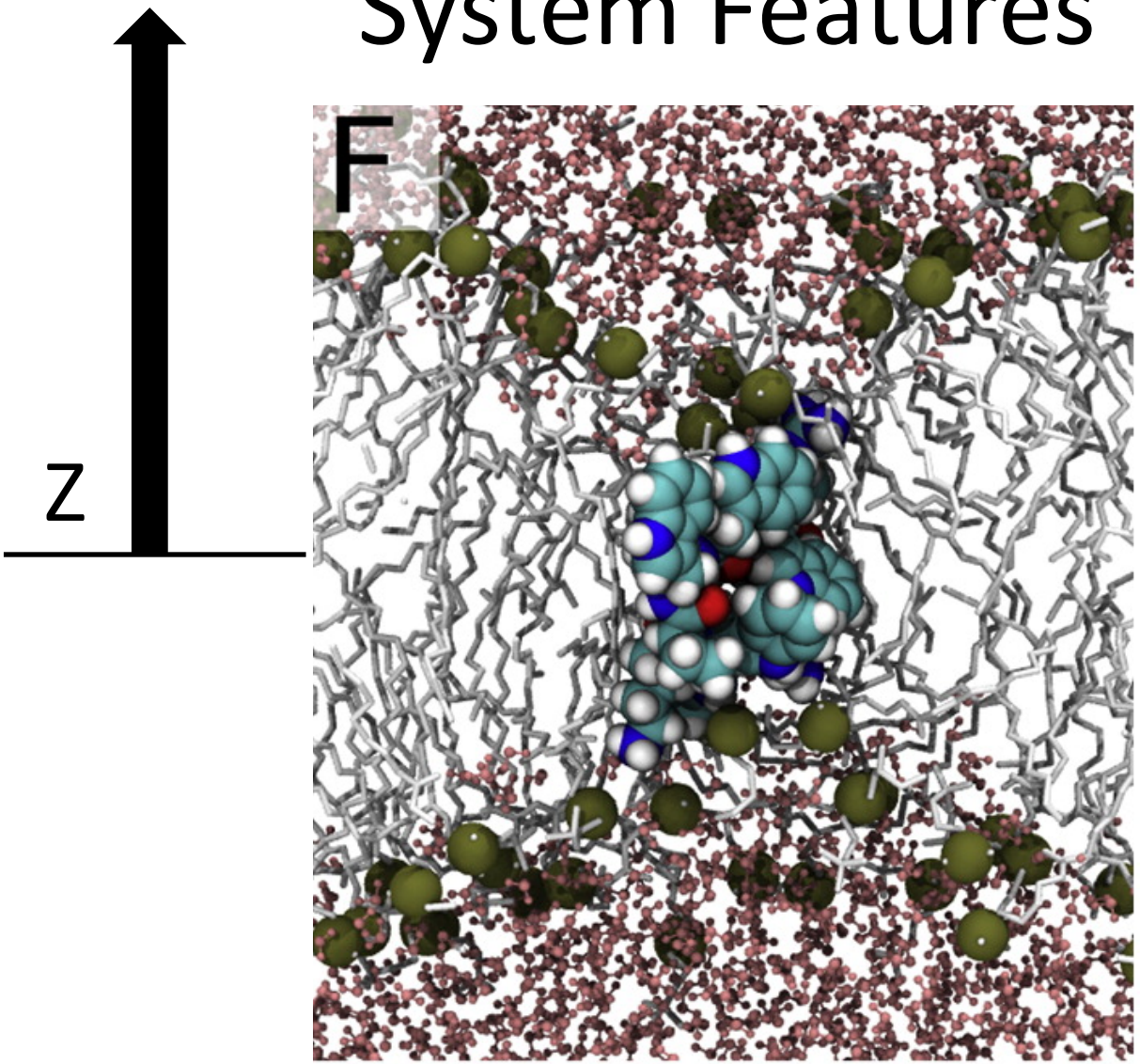
Yeh, I.C, et al. 2012. *J. Phys Chem B.* **116:** 3387-3396.

Simulation Features

- Gromacs 4.0.7 w/ TIP4P water model
- 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphatidylcholine (POPC) lipid modeled by Berger parameters
- Indolicidin modeled by OPLS-AA/L
- US/Replica Exchange framework

Berger, O., et al. 1997. *Biophys. J.* **72:** 2002-2013.

System Features

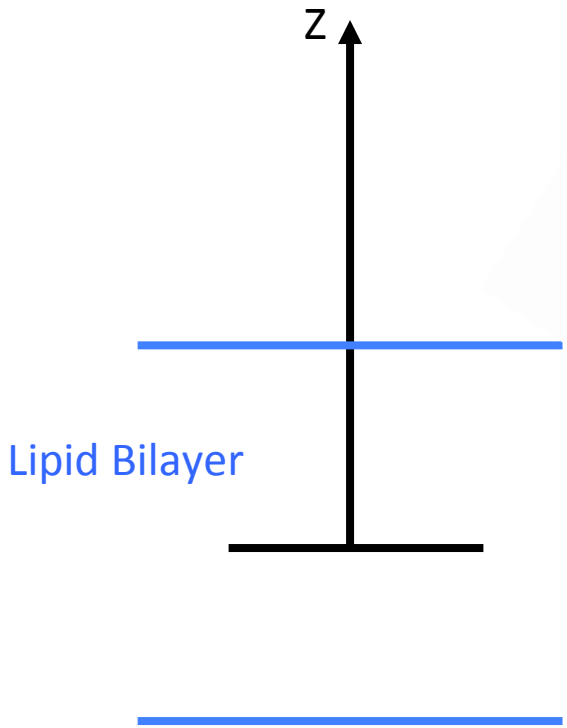


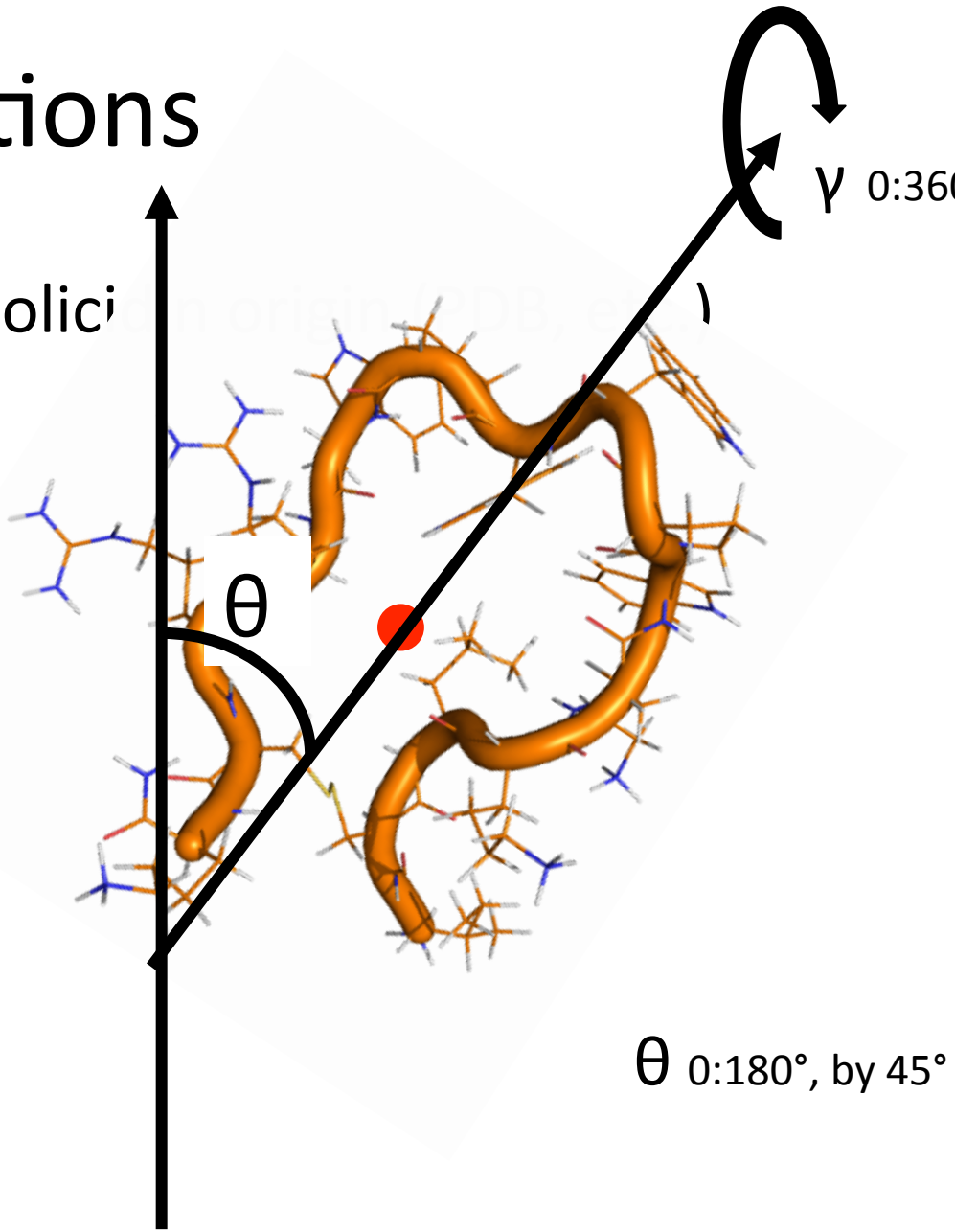
Tieleman, D.P., et al. 1999. *Biophys. J.* **76:**40-49.

Neale, C., et al. 2014. *Biophys. J.* **106:** L29-L31

Initial Conditions

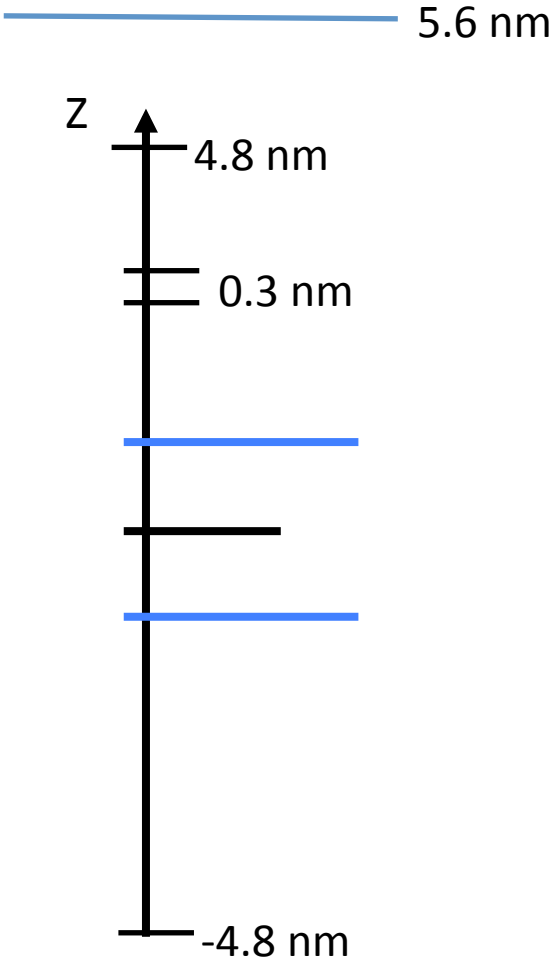
- Do not state Indolici





PDB ID: 1QX9 Rozek, A., et al. Biochem. **42:** 14130-14138.

Umbrella Sampling



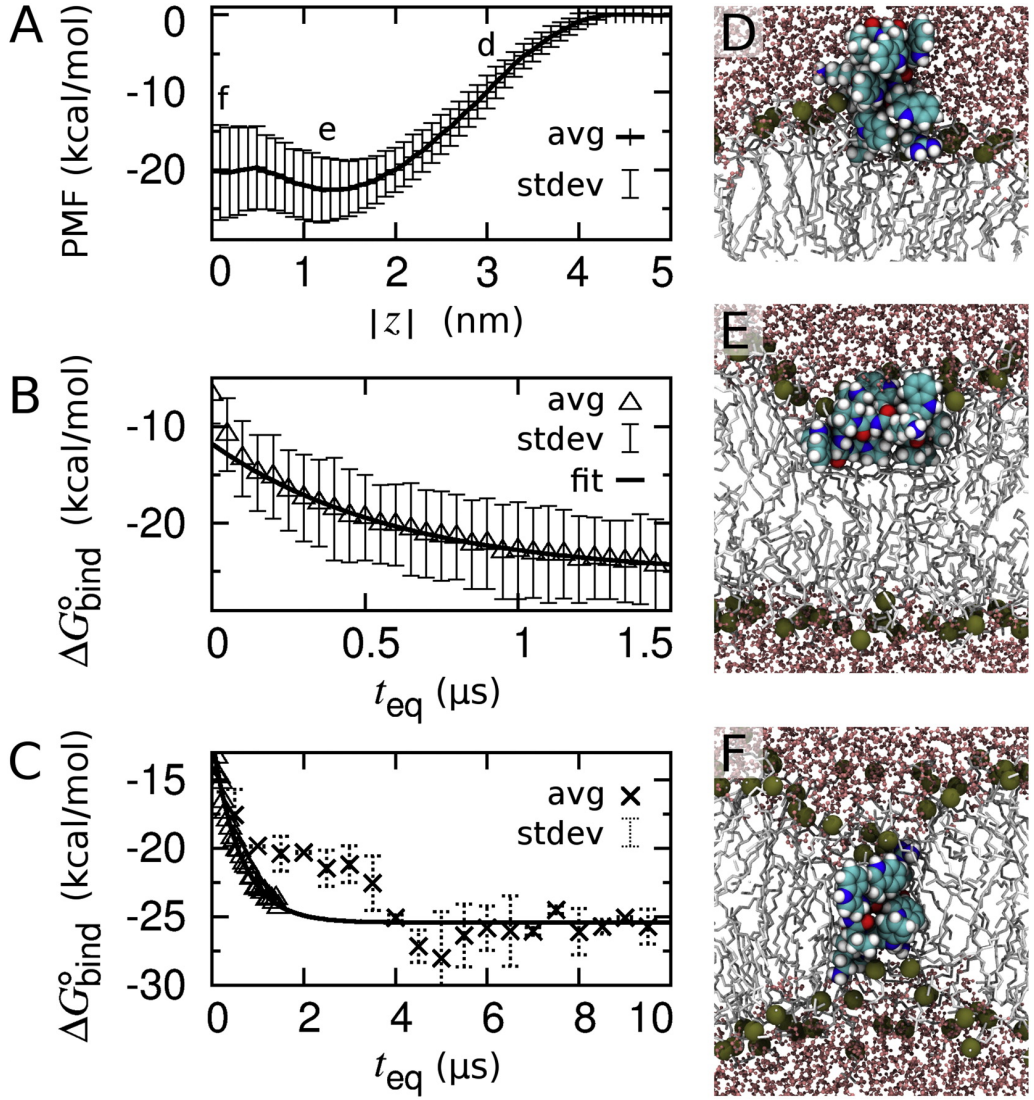
Z-axis is order parameter



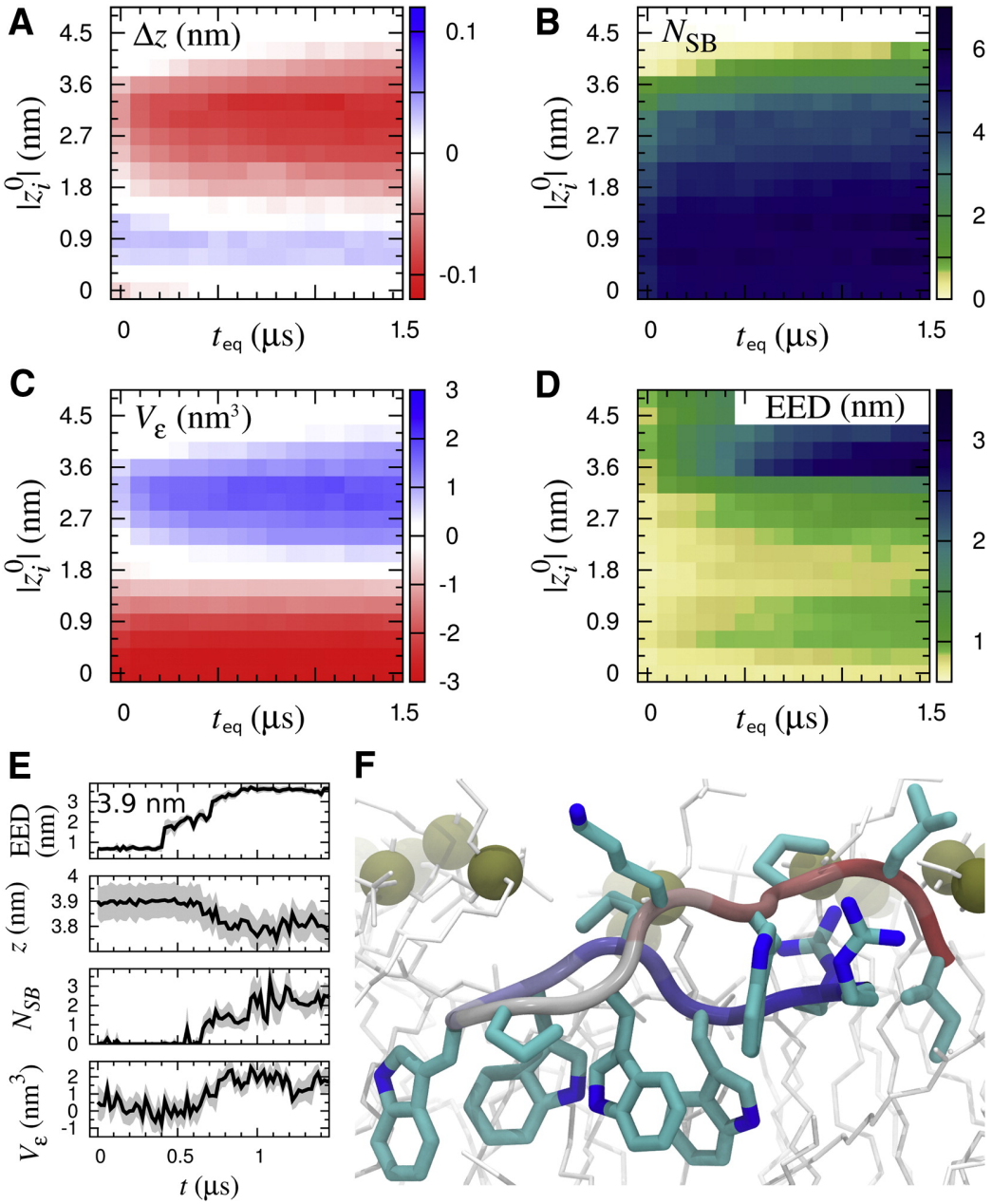
$F = -k(z-z_o)$, $k = 500$ kJ/mol/nm^2

Indolicidin COM

- 33 umbrella points along z-axis
- 30 peptide conformations
- 990 simulations*
  - 1.5μs (except 4.5, 4.8nm: 0.5μs)
- 2 simulations chosen from each umbrella point -4.2nm:4.2nm
  - 10μs
  - Replica exchange formalism

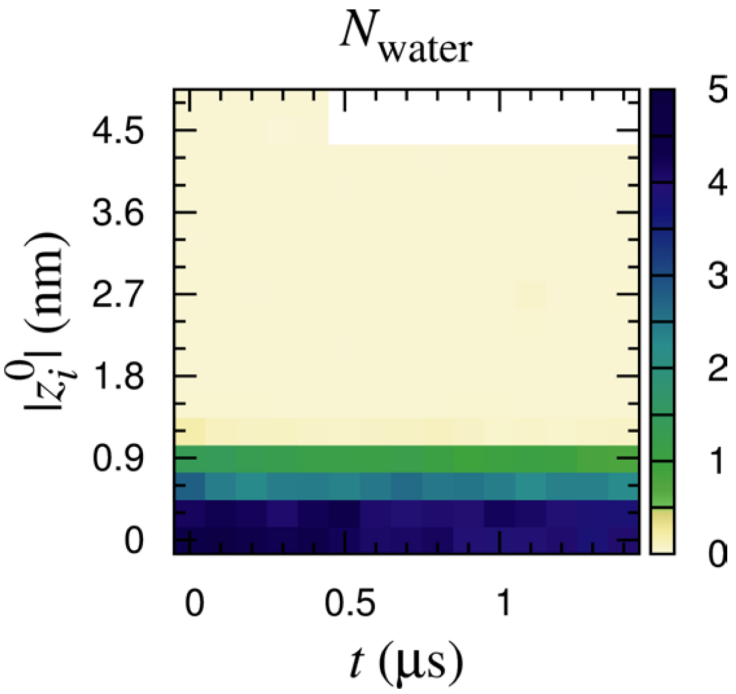


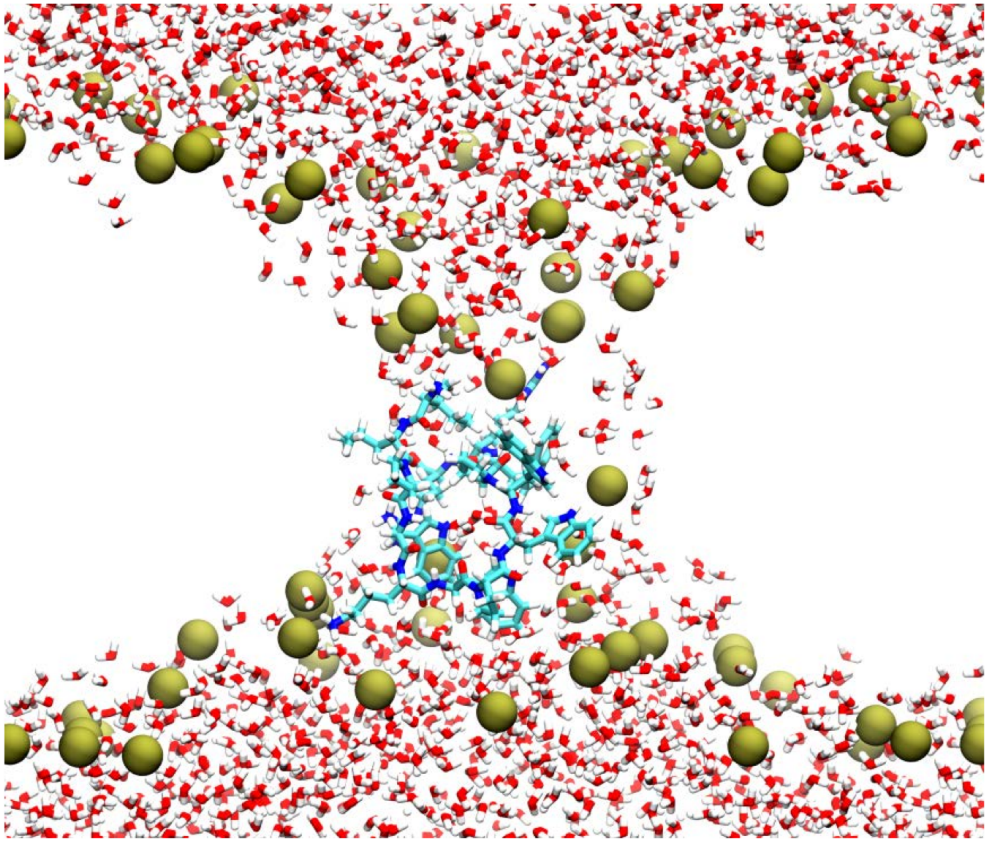
Neale, C., et al. 2014. *Biophys. J.* **106:** L29-L31



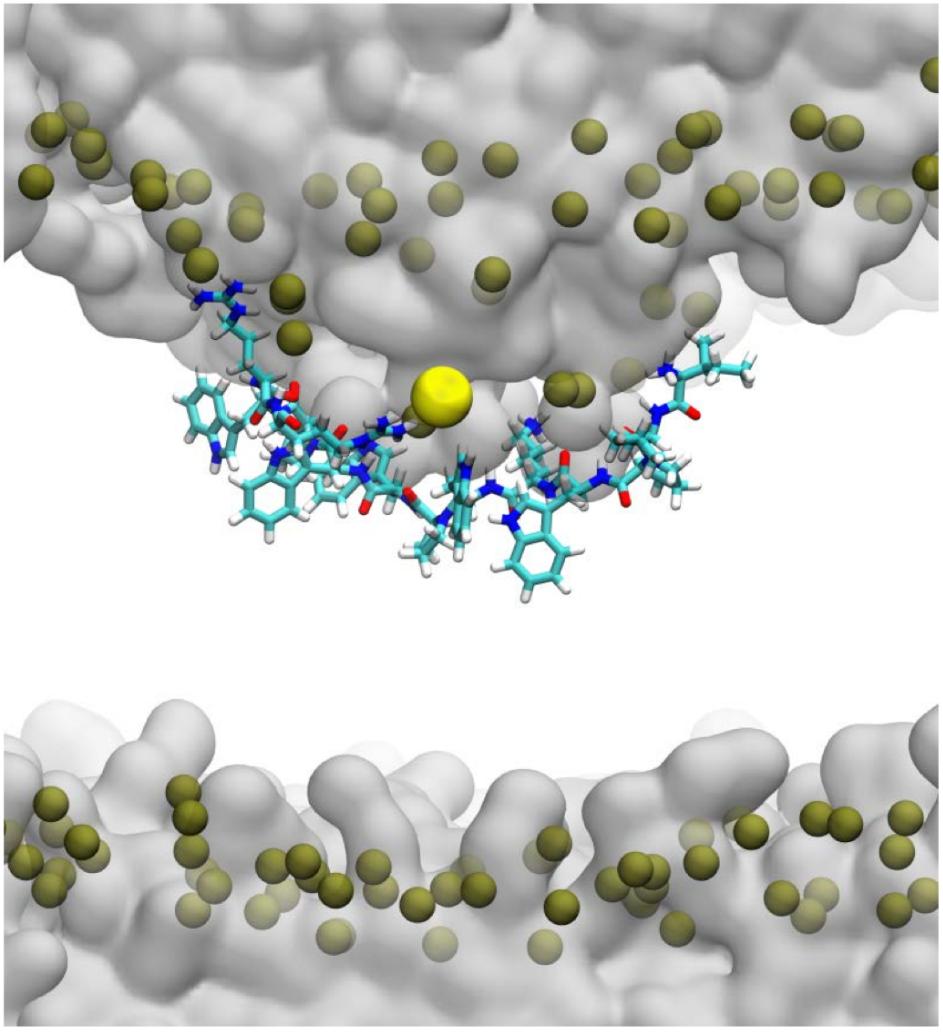
Neale, C., et al. 2014. *Biophys. J.* **106:** L29-L31

Water Pore Formation





Chloride Transport



Yeh et al. (equilibration- sampling)

Neale et al.

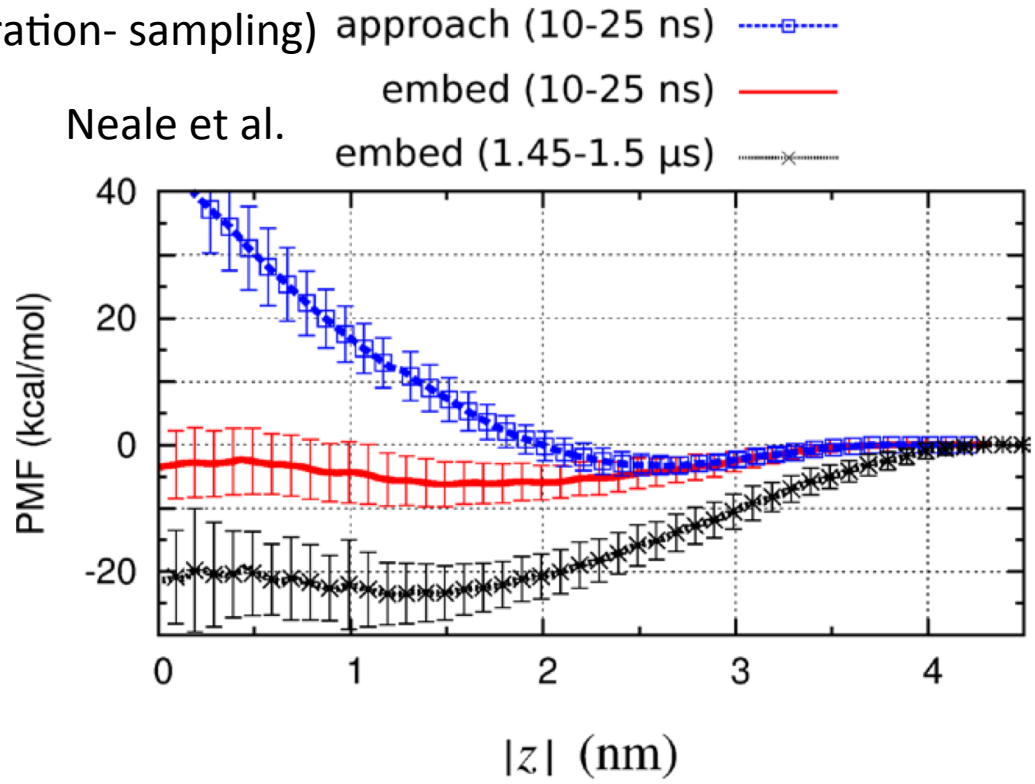


Table S2: Free energy values computed from the individual PMFs used to construct Fig. S8.

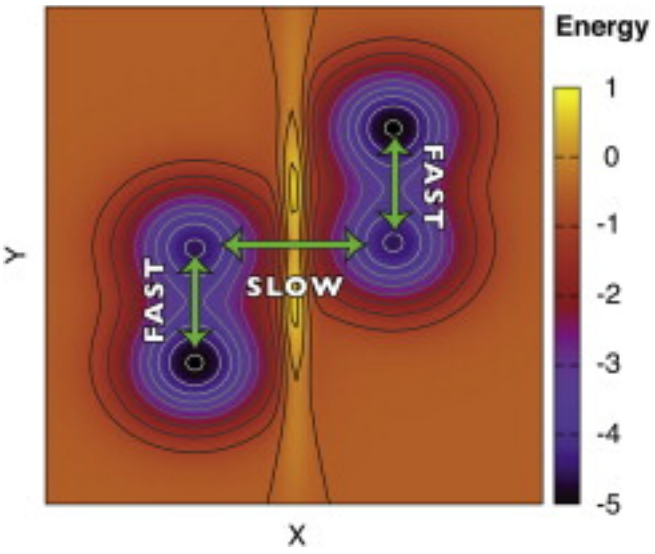
Dataset	ΔG°_{bind} (kcal/mol)	min(PMF) (kcal/mol)[a]	z of min(PMF) (nm)[b]
Approach (10—25 ns)	-2.4 ± 1.5	-3.8 ± 1.6	2.7 ± 0.2
Embed (10—25 ns)	-6.6 ± 3.4	-8.0 ± 3.5	1.4 ± 0.9
Embed (1.45—1.5 μs)	-24.4 ± 4.8	-26.0 ± 4.9	1.0 ± 0.6

[a]The minimum value of the PMF after adjusting the PMF to zero in bulk water.
[b]The location of the minimum value of the PMF.

Dr. Grossfield's Highlights

- Incredibly slow relaxation times for the system studied
- Applauded Neale et al.

Statistical Sampling	Slow Relaxation
$t \rightarrow \infty$, $A_{avg} \rightarrow A_{exp}$	Autocorrelation and block averaging do not detect.
Multiple trajectories, A randomly distributed about A_o Variance = $1/(t^{0.5})$	Variance between trajectories not randomly distributed
Variance monotonically decreases over time	Variance may decrease, but later increase



Romo, T, and A. Grossfield. 2014. *Biophys J*. **106:** 1553-1554.

Pertinence

- Membrane – Protein interactions require long simulation times to capture dynamics
- Partial remediation by running multiple simulations

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Bayesian Energy Landscape Tilting: Towards Concordant Models of Molecular Ensembles

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Probing the U-Shaped Conformation of Caveolin-1 in a Bilayer

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