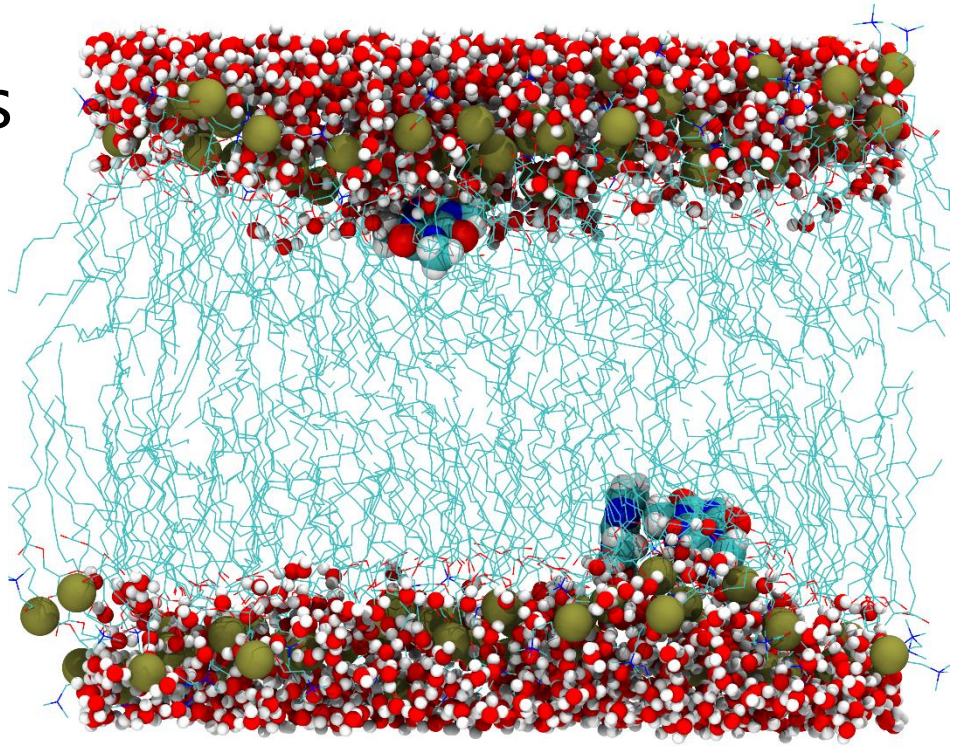
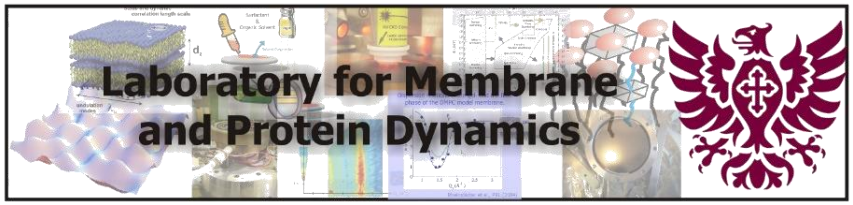
Partitioning of Caffeine in Lipid Bilayers Reduces Membrane Fluidity and Increases Membrane Thickness



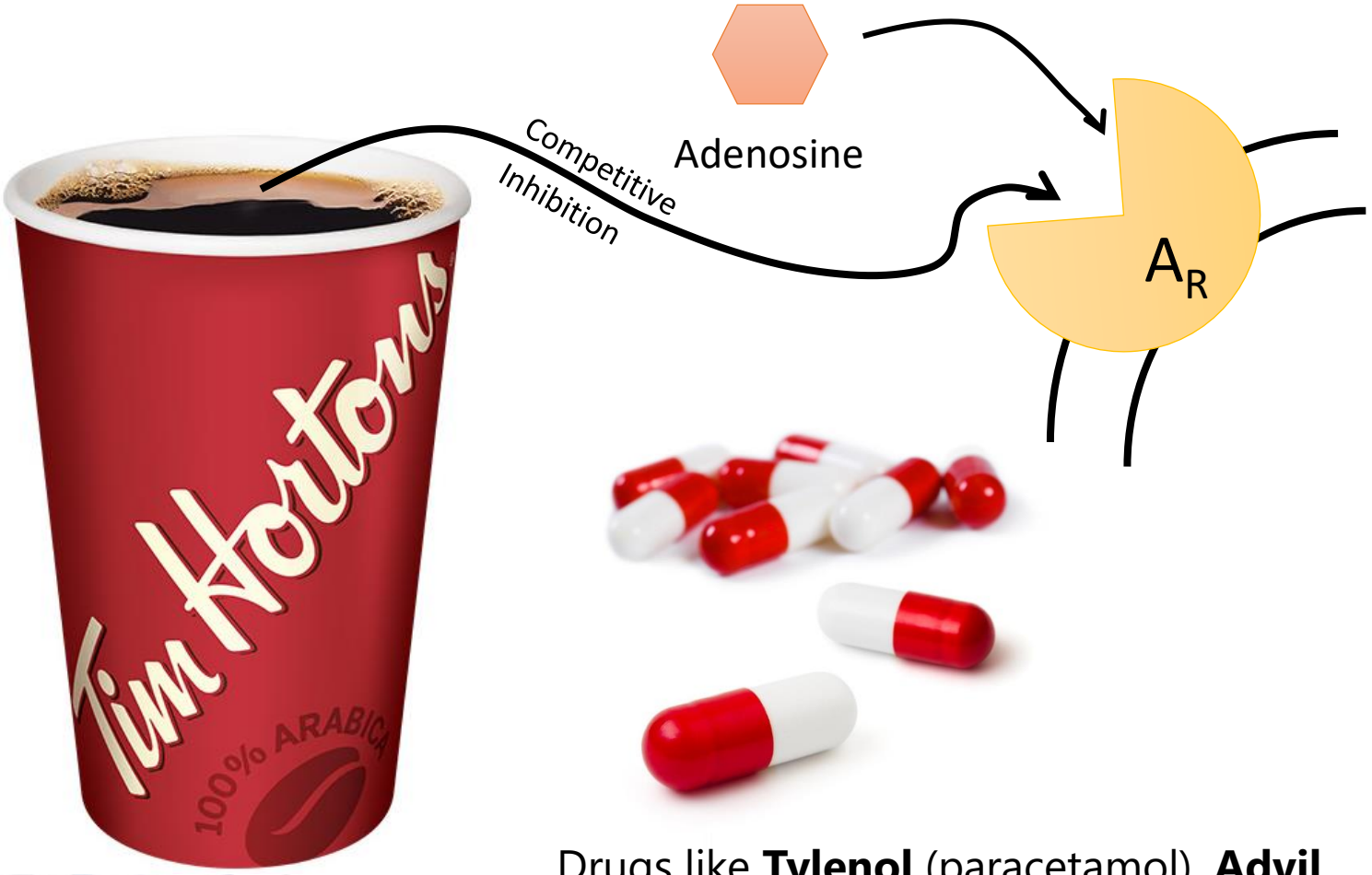
Adree Khondker[1], Alexander Dhaliwal[1], Richard J Alsop[1], Jennifer Tang[1], Matilda Backholm[2], An-Chang Shi[1], Maikel C. Rheinstädter[1].

1. Department of Physics and Astronomy, McMaster University.
2. Department of Applied Physics, Aalto University.



McMaster University

Caffeine the Drug Adjuvant



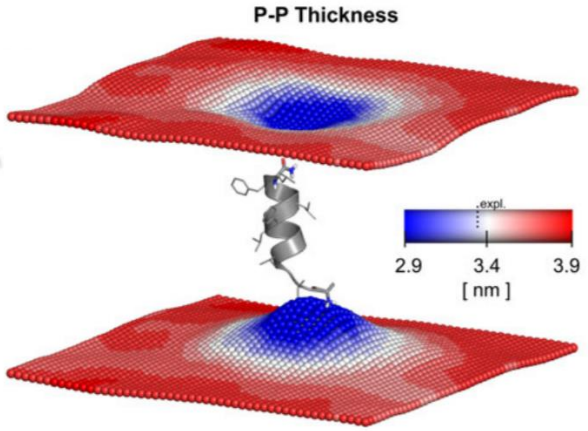
Drugs like **Tylenol** (paracetamol), **Advil** (ibuprofen), and **Aspirin** (acetylsalicylic acid) are often **complexed with caffeine**. Why?

Caffeine the Drug Adjuvant

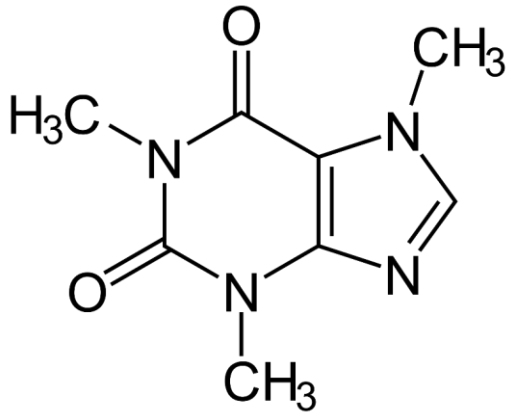
1. Commonly used **drug adjuvant**

2. Membrane-Mediated **Drug Interactions** May Affect Bioaccumulation, Partitioning, and Metabolism

3. **Lack of Mechanistic Understanding** of Adjuvant Properties

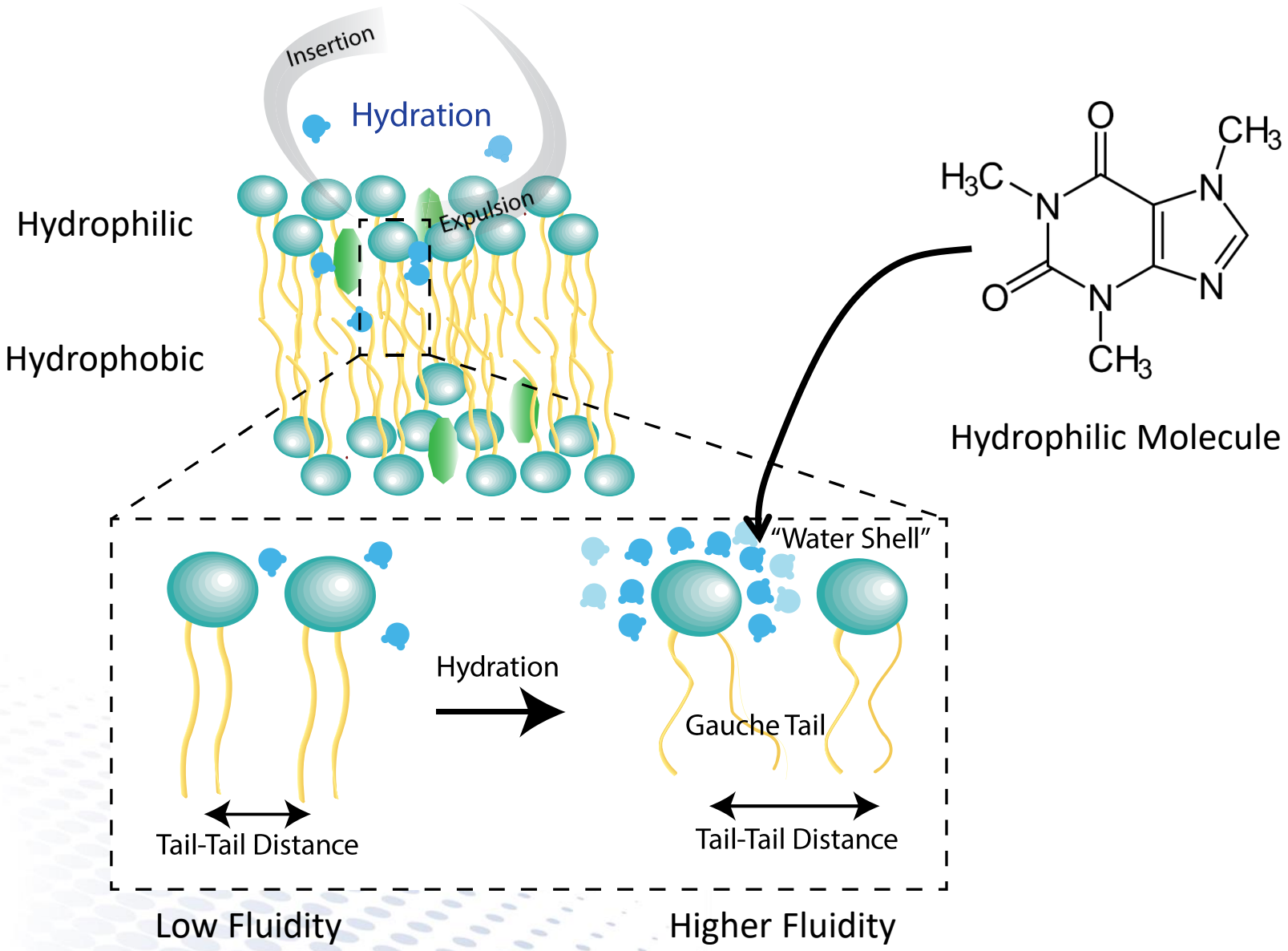


De Groot et al. 2012



Caffeine
(1,3,7- trimethylxanthine)

Caffeine and the Membrane

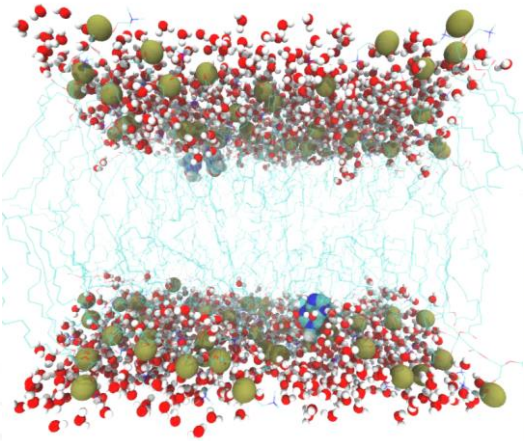


Materials and Methods

Laboratory for Membrane and Protein Dynamics

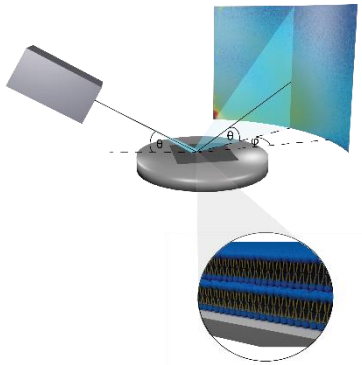
Molecular Dynamics

- GROMACS MD package
- ~15000 atom simulations
- 200ns for 6 systems



X-Ray Diffraction

- Biological Large Angle Diffraction Experiment (BLADE)
- Multi-lamellar model membranes on silicon wafers



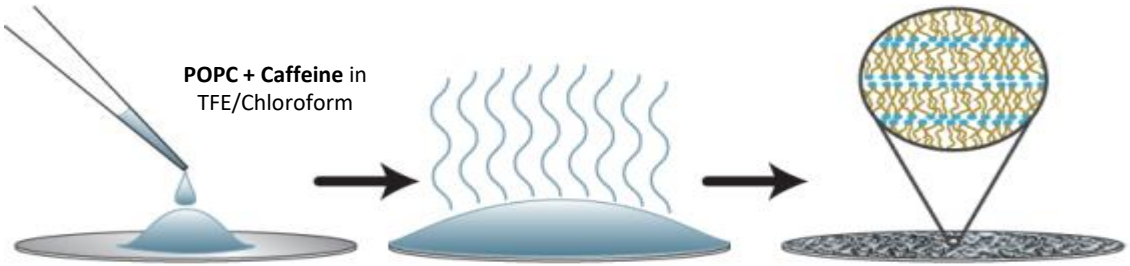
Timescale

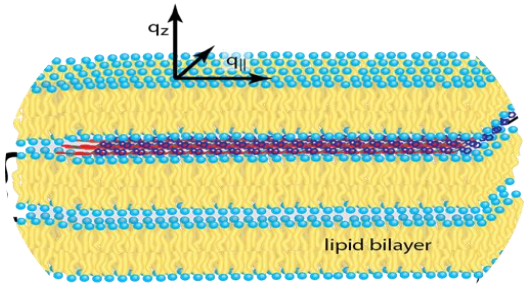
ns → days

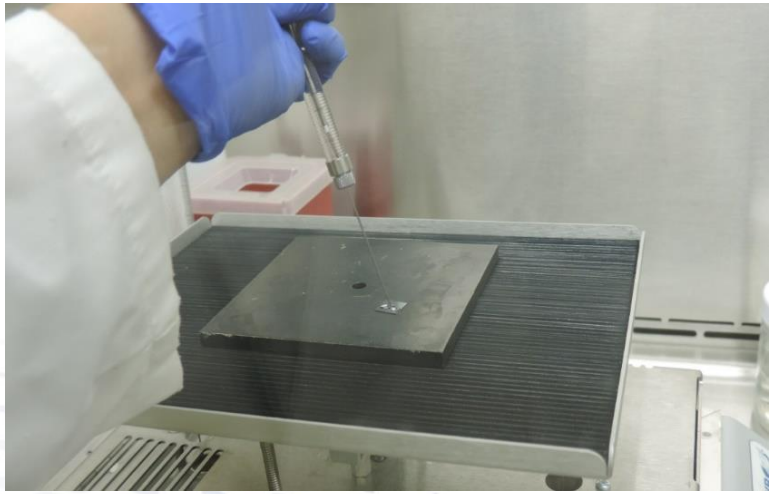
Sample Preparation

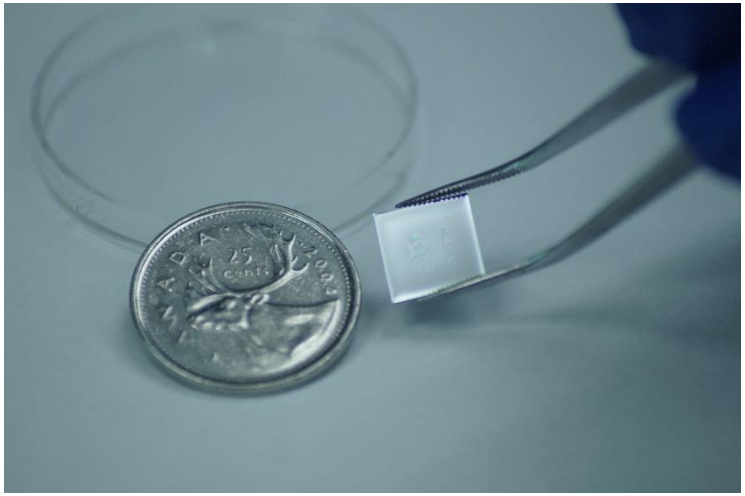
Laboratory for Membrane and Protein Dynamics

Multi-lamellar, solid supported synthetic membranes

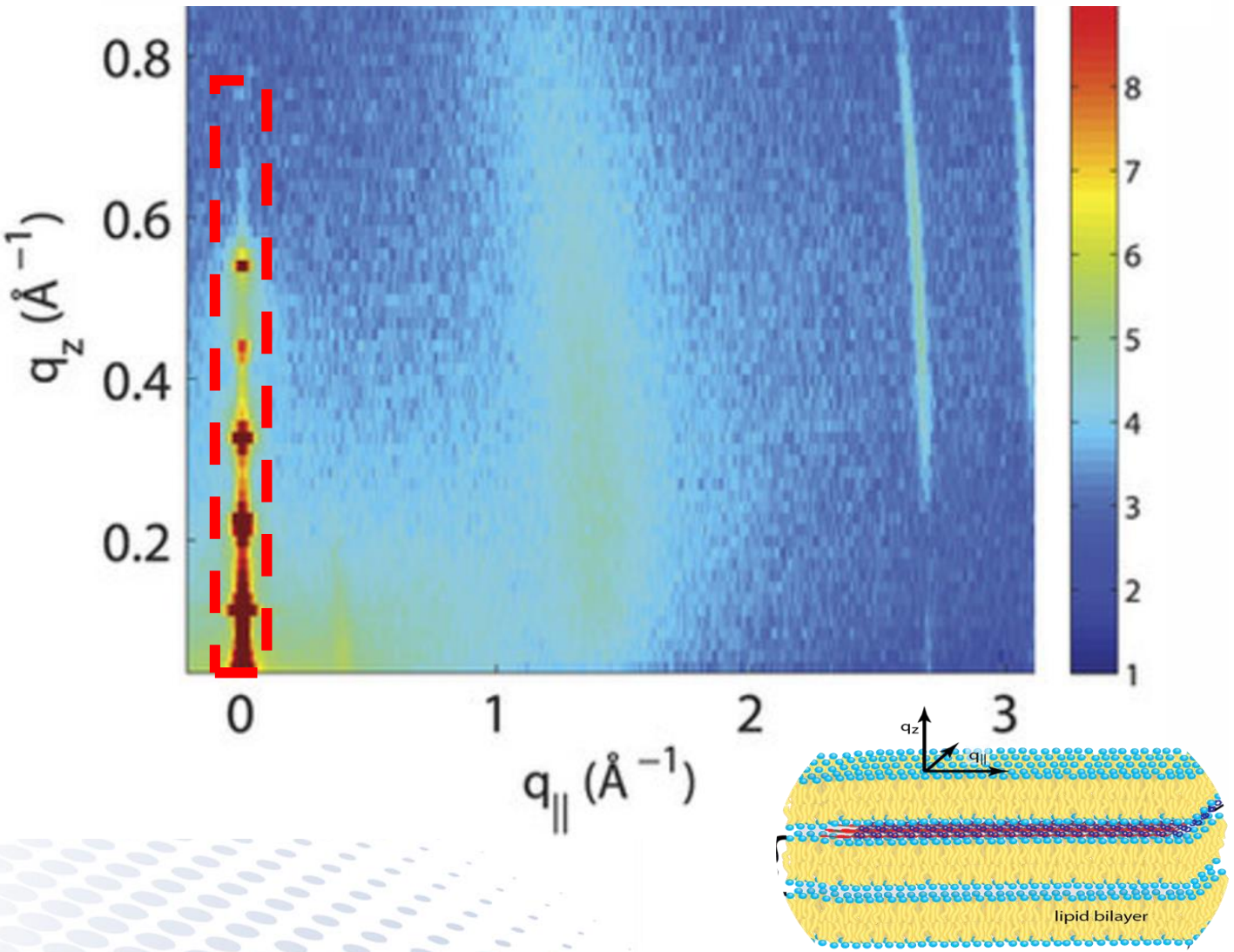




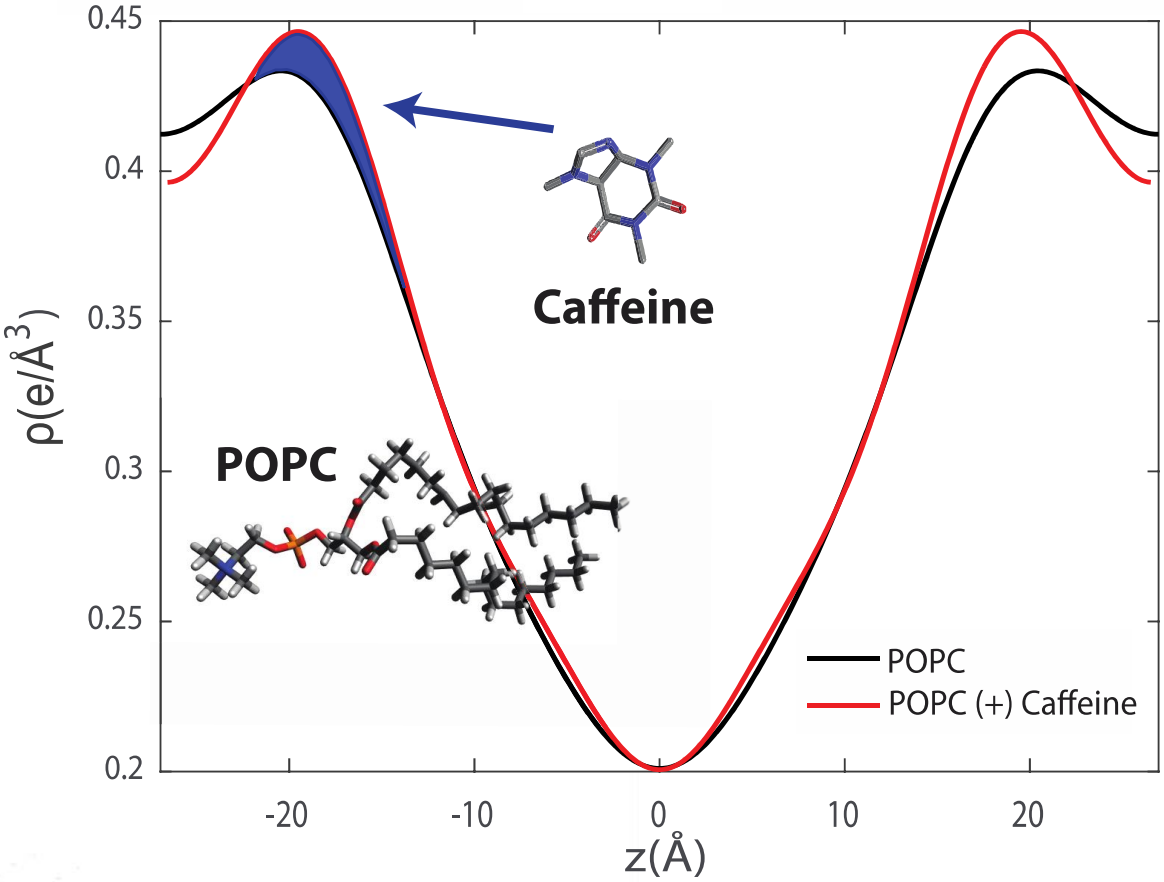




Caffeine Localization

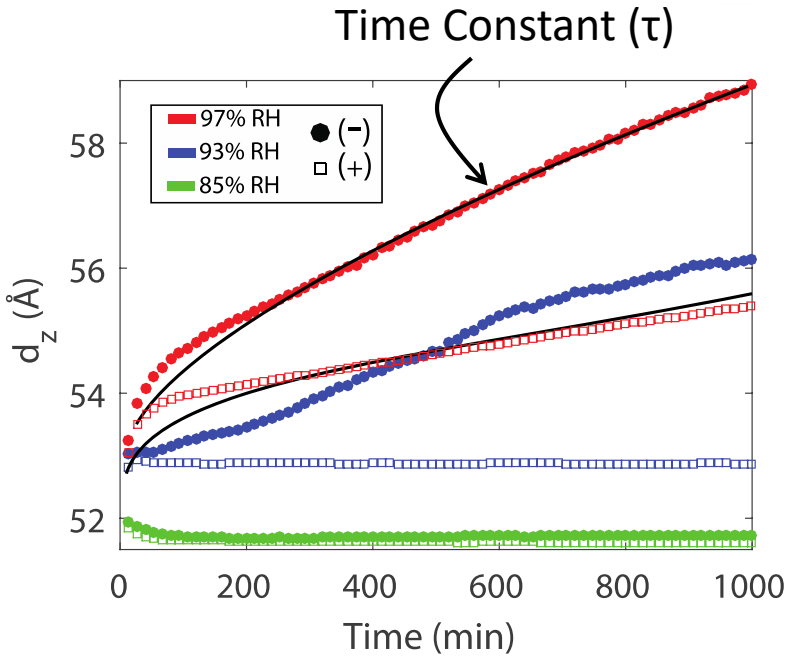


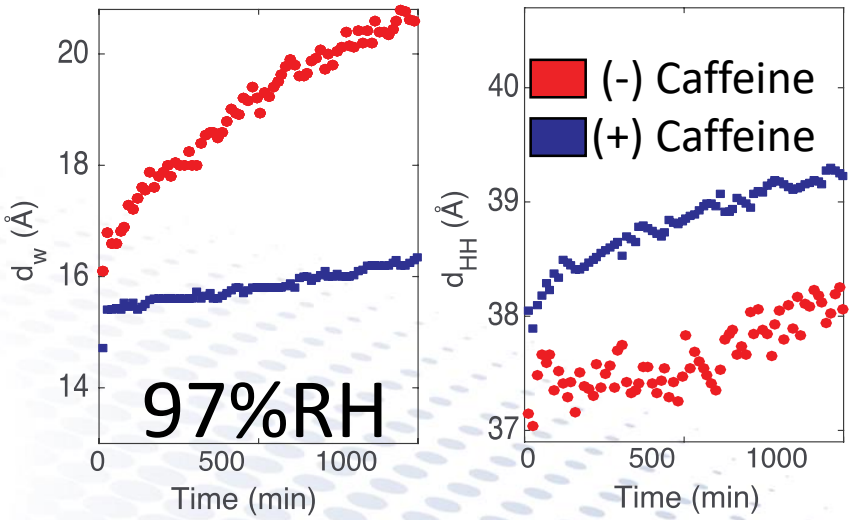
Caffeine Localization



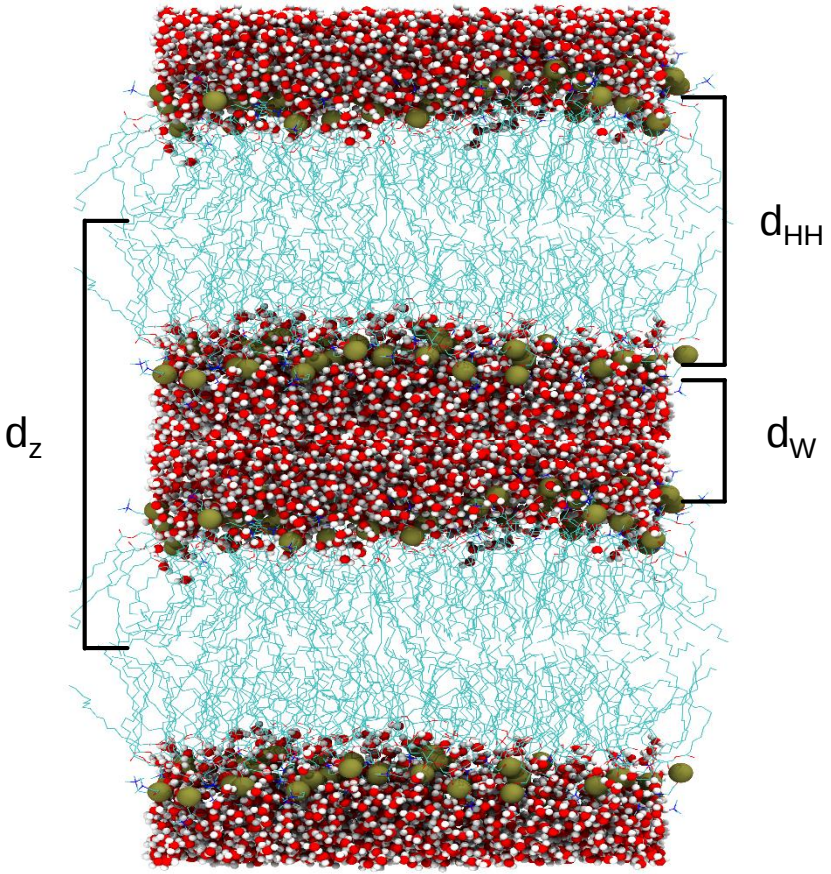
Result: Caffeine Localizes in the Head-Tail Interface

Bilayer Swelling





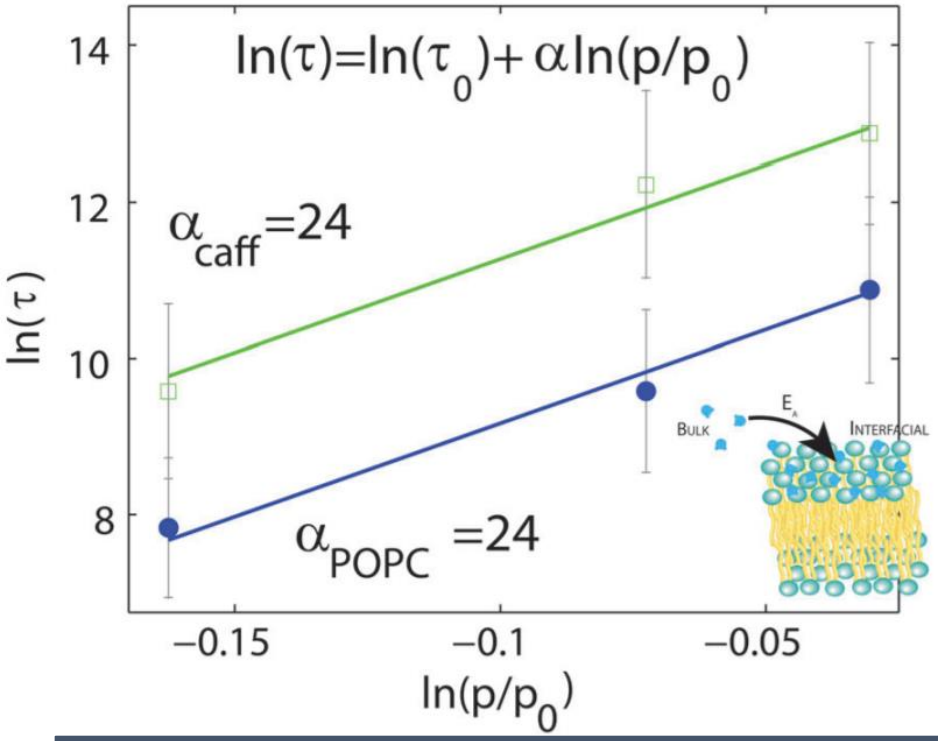
First-Order Kinetics

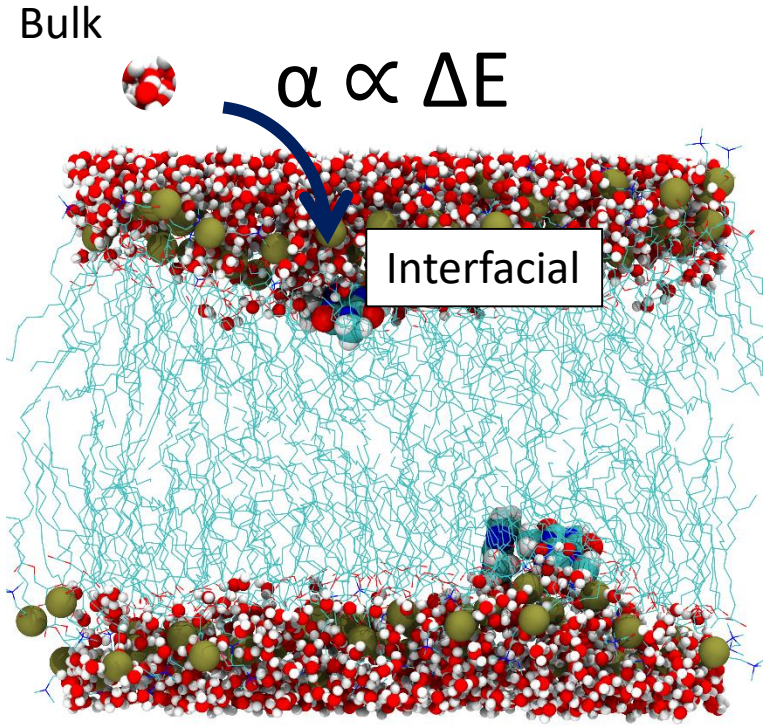


Membrane Bioenergetics

$RH = p/p_o$

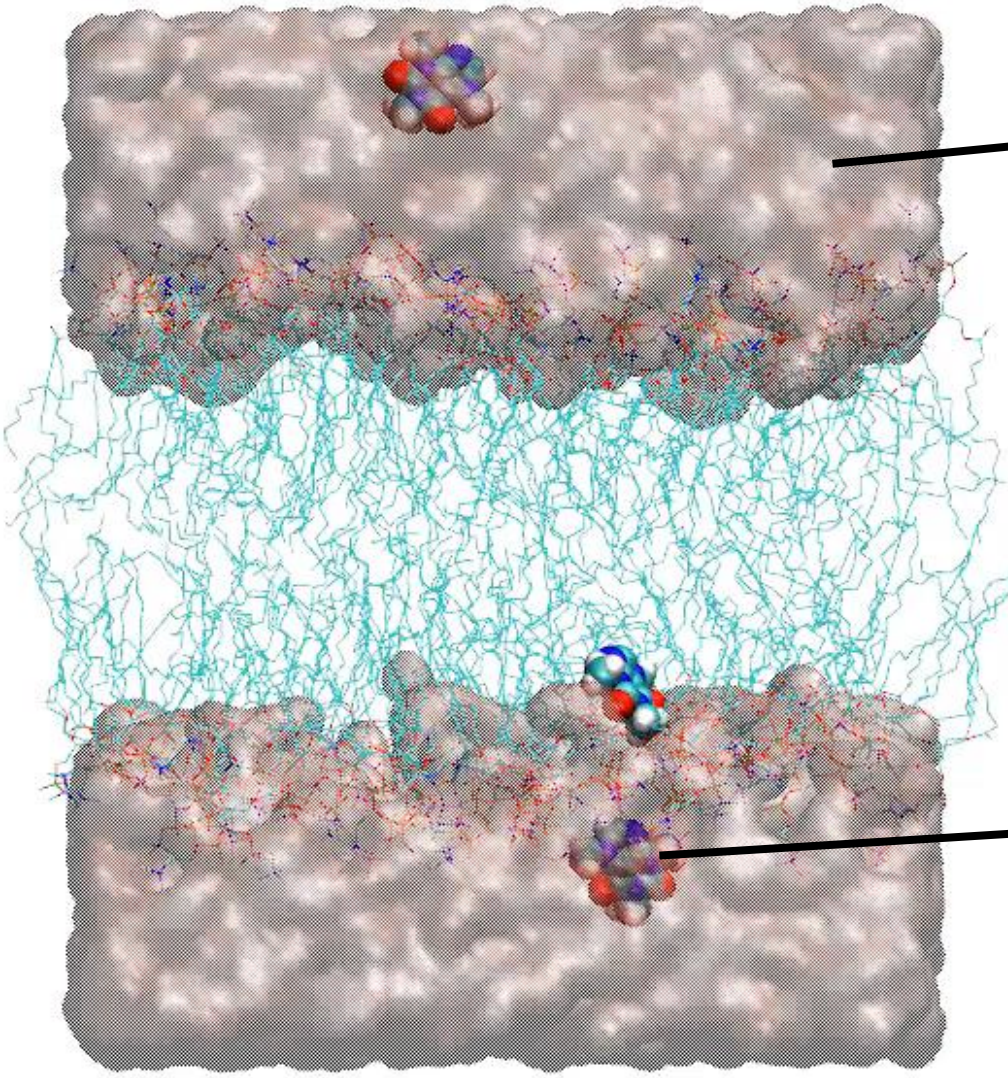
$\tau = \tau_0 e^{\alpha \ln(RH)} = \tau_0 e^{(\Delta E/k_B T)}$



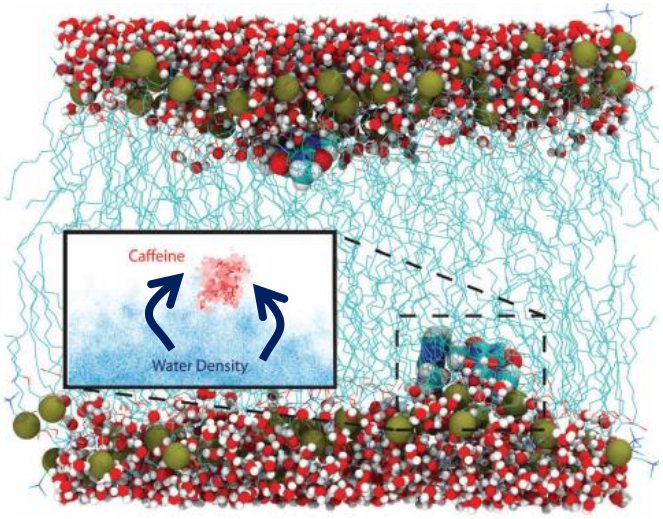


Result: Caffeine does not affect the chemical energy barrier between bulk and interfacial water

Hygroscopic Water Pockets

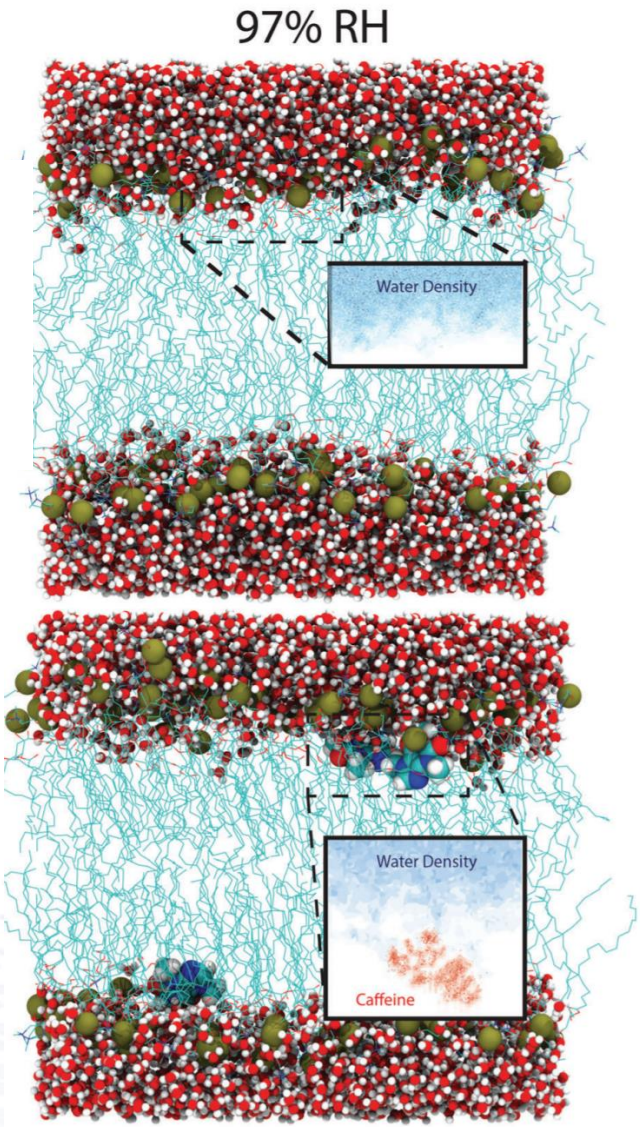


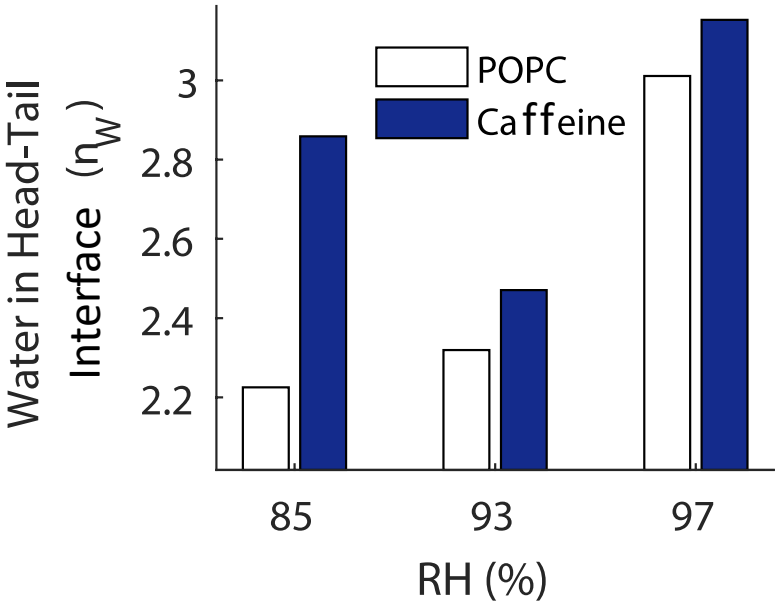
Water Density



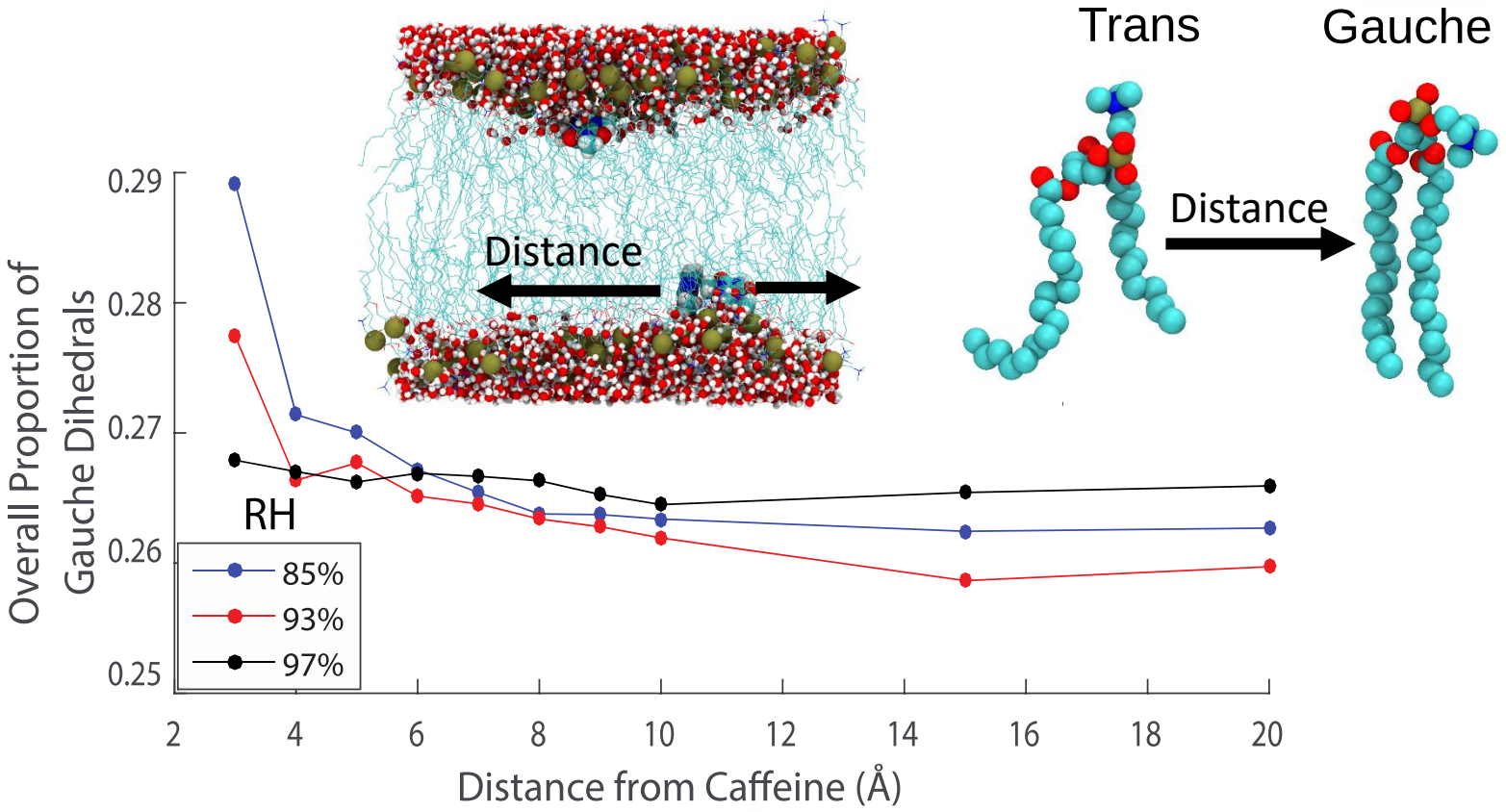
Caffeine

Hygroscopic Water Pockets





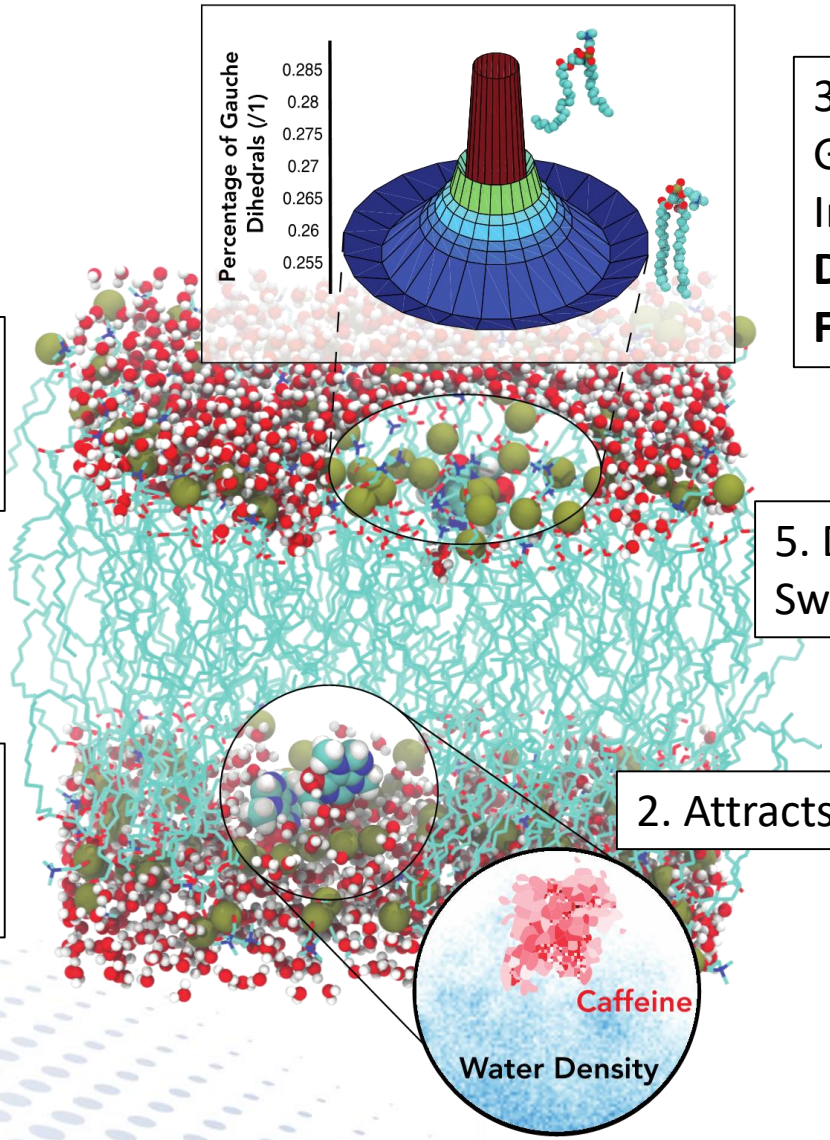
Gauche Defects and Fluidity



Result: Caffeine decreases fluidity within the membrane, functionally dehydrating the bilayer

Conclusion

1. Localization in the **Head-Tail Interface**



3. Increases Local Gauche Defects, i.e. Increased Local Fluidity, **Decreased Overall Fluidity**

5. Decreases Bilayer Swelling

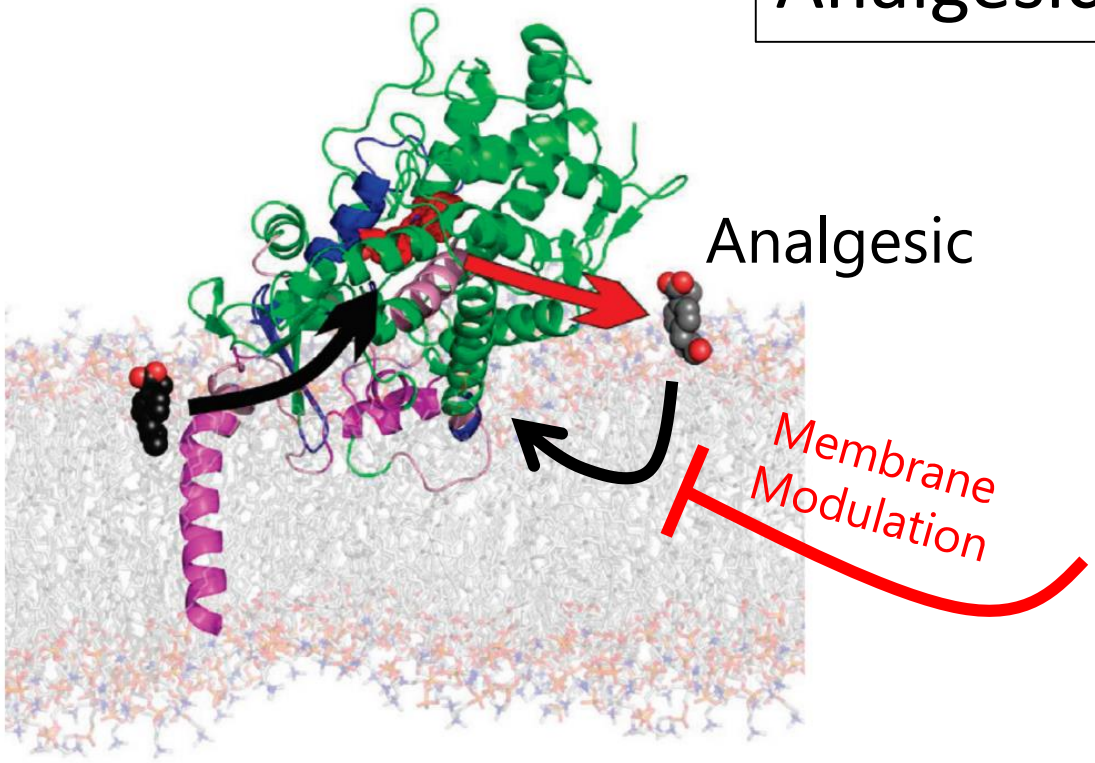
2. Attracts Local Water Density

4. Increases Membrane Thickness

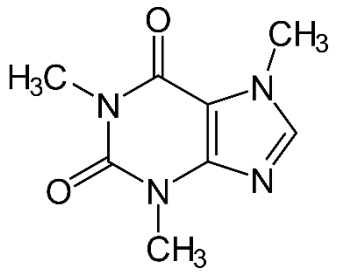
Suggested Implications

Cytochrome P450 2C9

Increased Time of Analgesic Activity

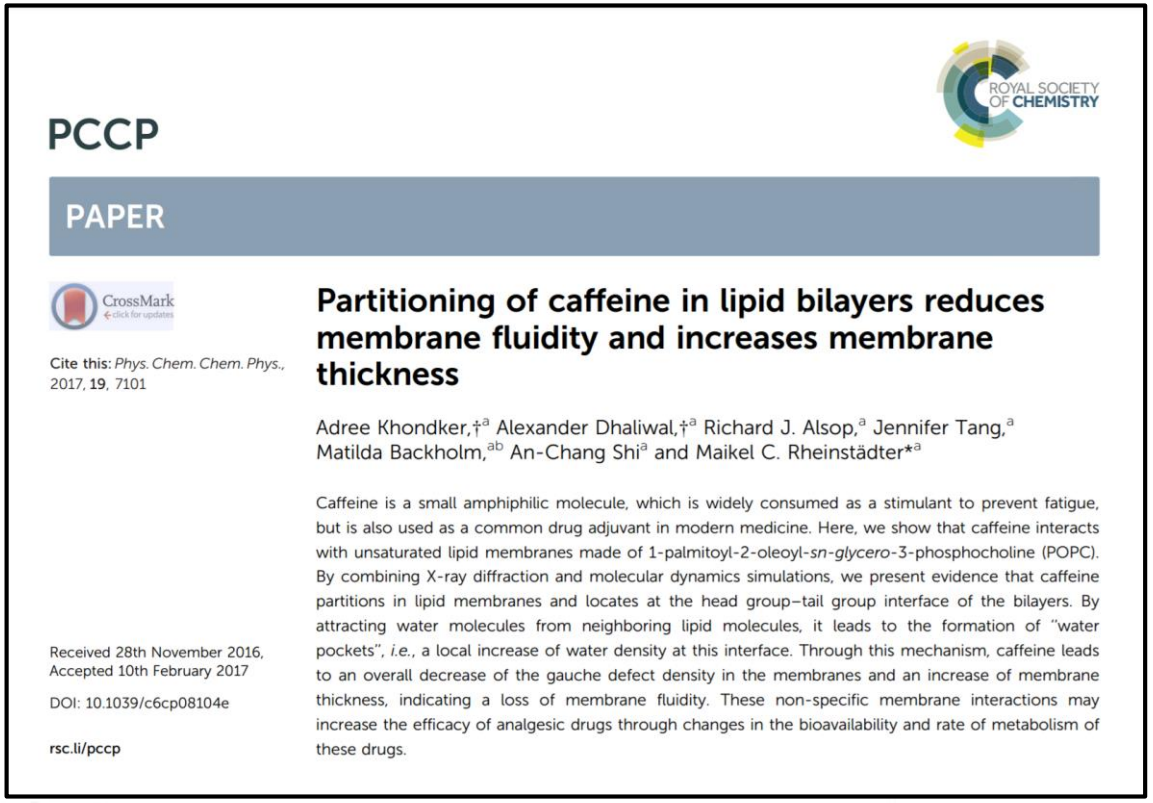


Caffeine



Picture from: Berka et al. 2011. J. Phys. Chem. A.

Reference



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Cite this: *Phys. Chem. Chem. Phys.*, 2017, **19**, 7101

Partitioning of caffeine in lipid bilayers reduces membrane fluidity and increases membrane thickness

Adree Khondker,†[a] Alexander Dhaliwal,†[a] Richard J. Alsop,[a] Jennifer Tang,[a] Matilda Backholm,[ab] An-Chang Shi[a] and Maikel C. Rheinstädter*[a]

Caffeine is a small amphiphilic molecule, which is widely consumed as a stimulant to prevent fatigue, but is also used as a common drug adjuvant in modern medicine. Here, we show that caffeine interacts with unsaturated lipid membranes made of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC). By combining X-ray diffraction and molecular dynamics simulations, we present evidence that caffeine partitions in lipid membranes and locates at the head group–tail group interface of the bilayers. By attracting water molecules from neighboring lipid molecules, it leads to the formation of "water pockets", *i.e.*, a local increase of water density at this interface. Through this mechanism, caffeine leads to an overall decrease of the gauche defect density in the membranes and an increase of membrane thickness, indicating a loss of membrane fluidity. These non-specific membrane interactions may increase the efficacy of analgesic drugs through changes in the bioavailability and rate of metabolism of these drugs.

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Physical Chemistry Chemical Physics, 2017, 19, 7101 - 7111

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Jennifer Tang

Matilda Backholm

Maikel C. Rheinstädter

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NSERC CRSNG

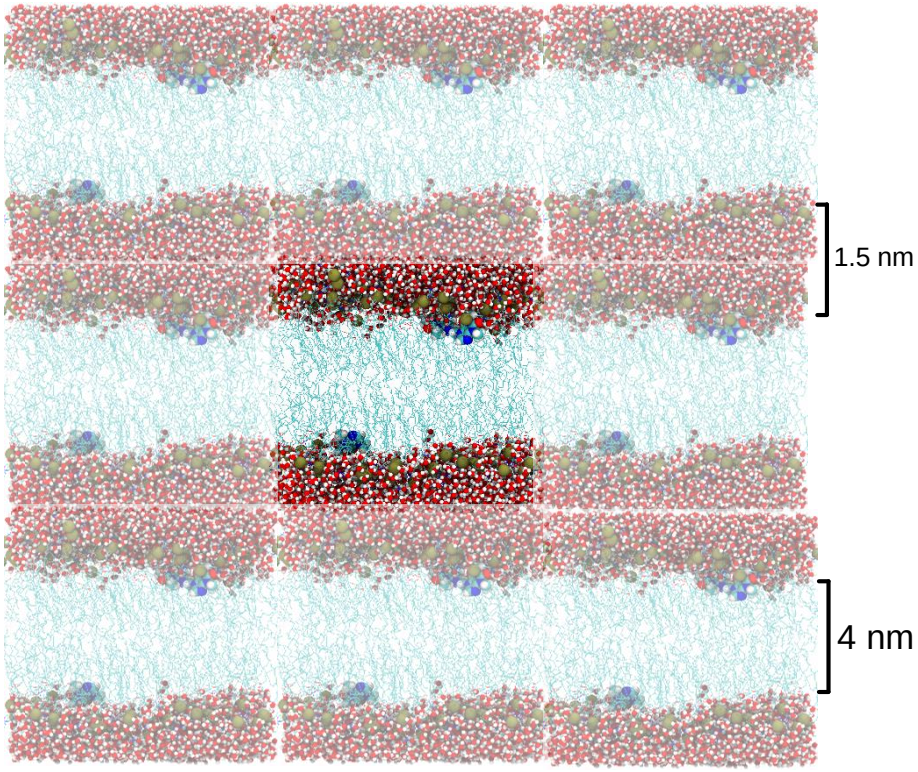
CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Method Comparison

Laboratory for Membrane and Protein Dynamics

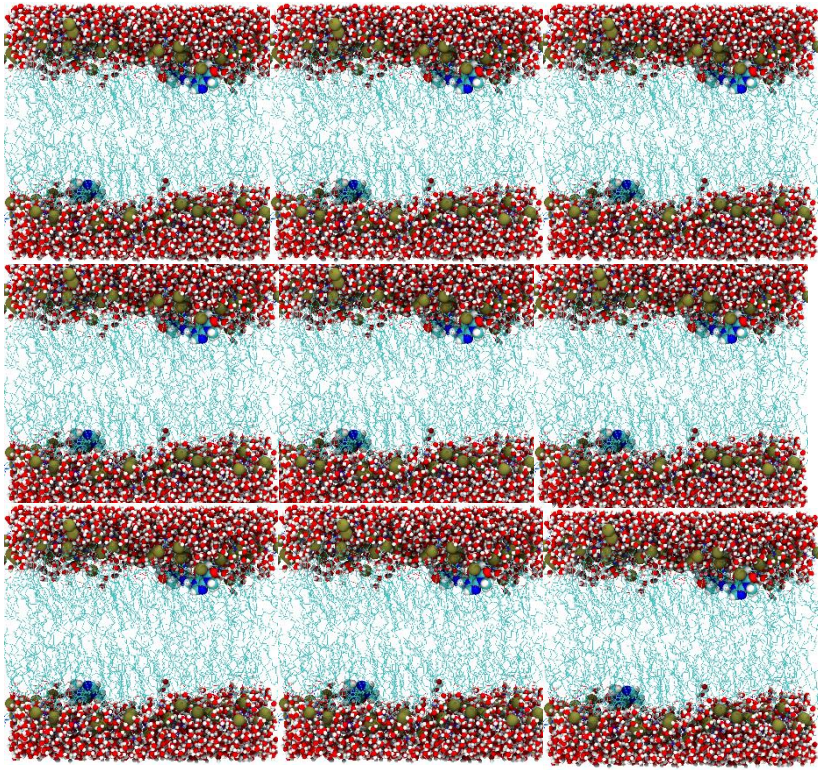
Molecular Dynamics

With periodic boundary conditions

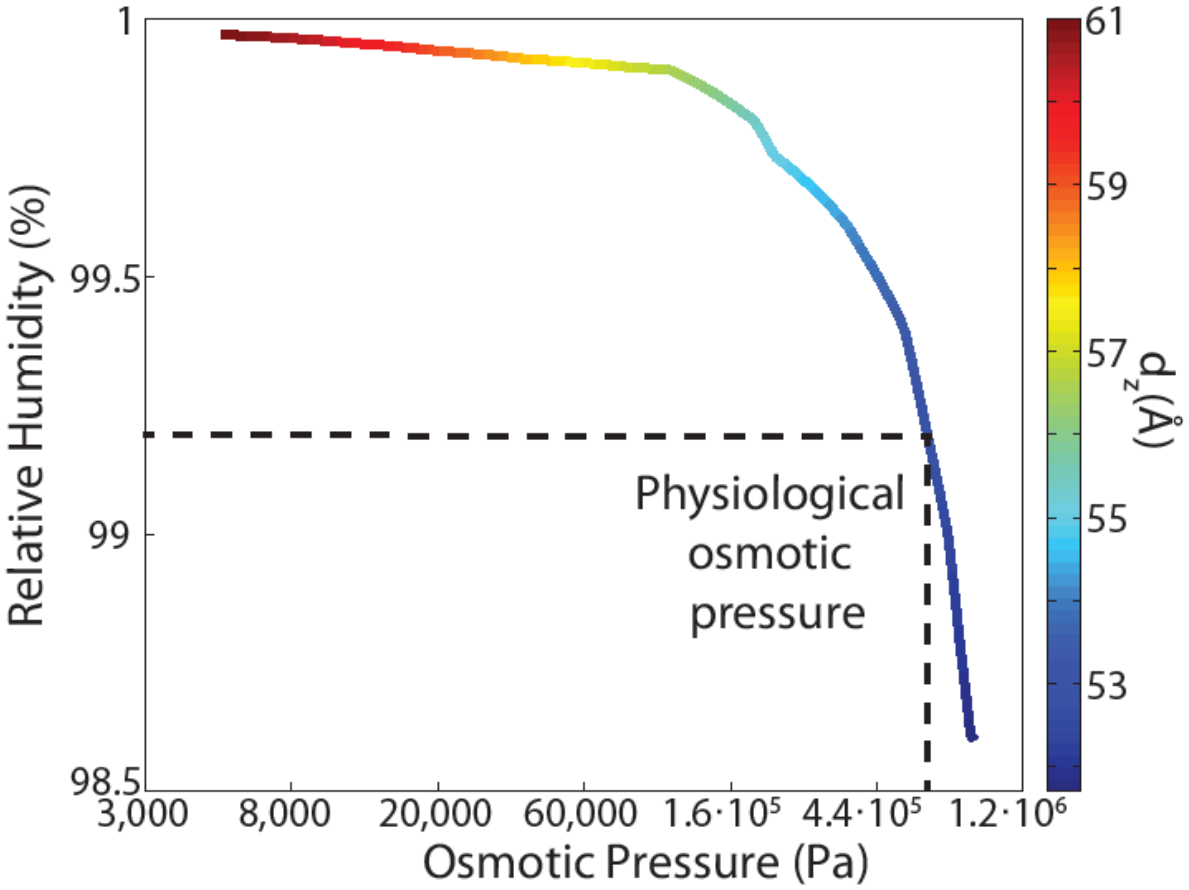


X-Ray Diffraction

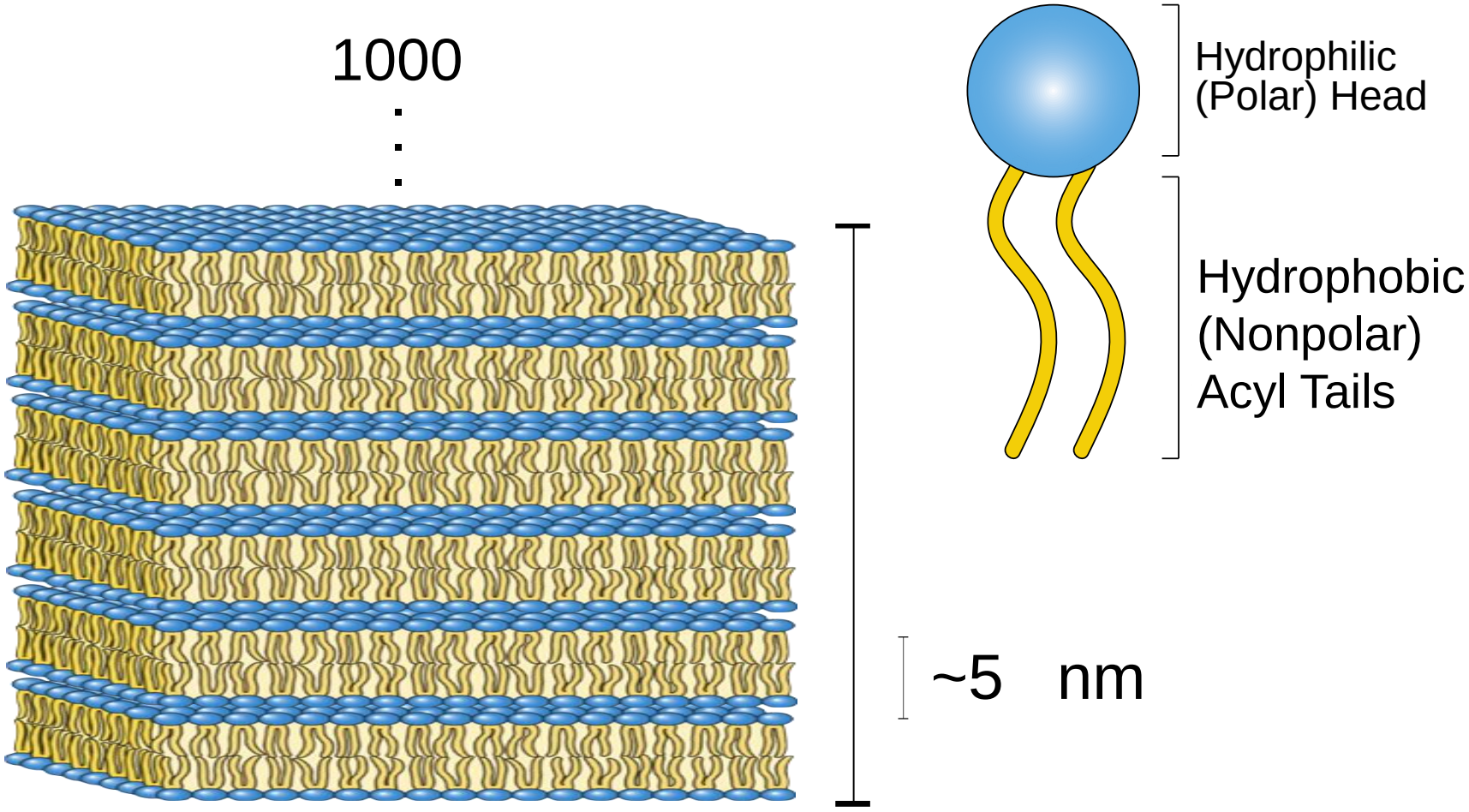
Multi-lamellar stacks



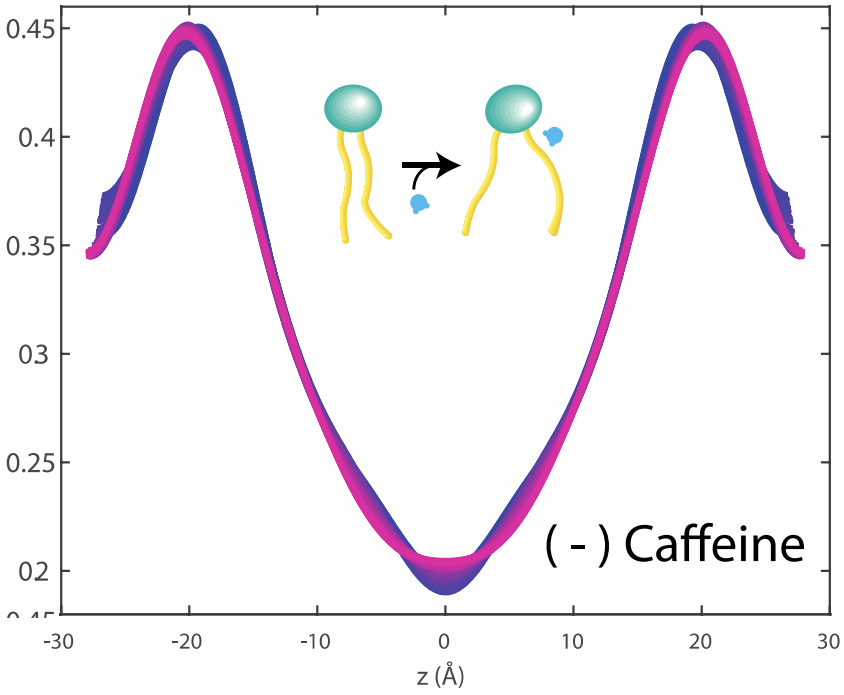
Physiological Relevance

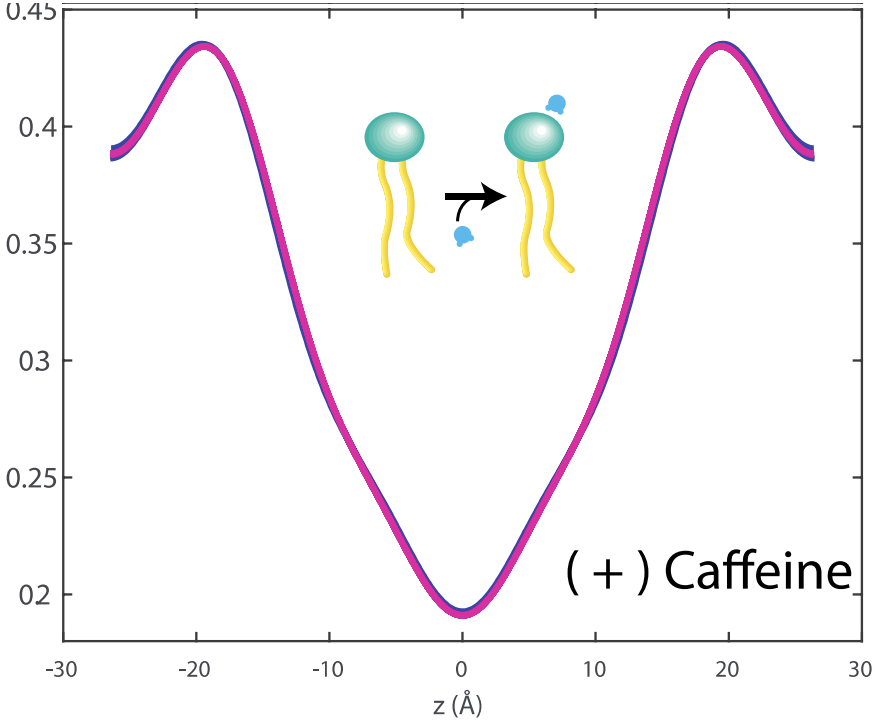


Membrane Stacks



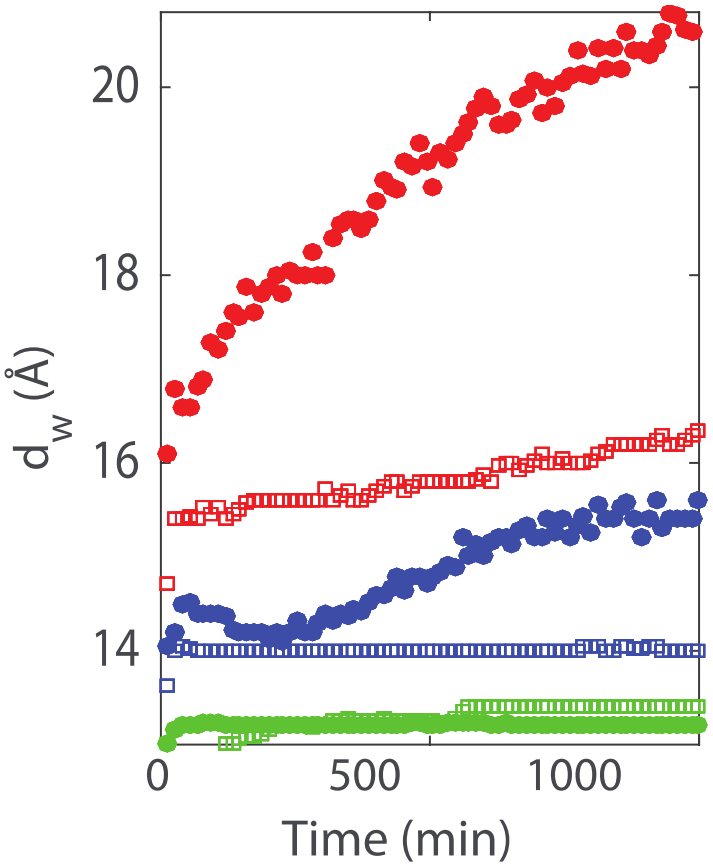
Low Resolution Structure

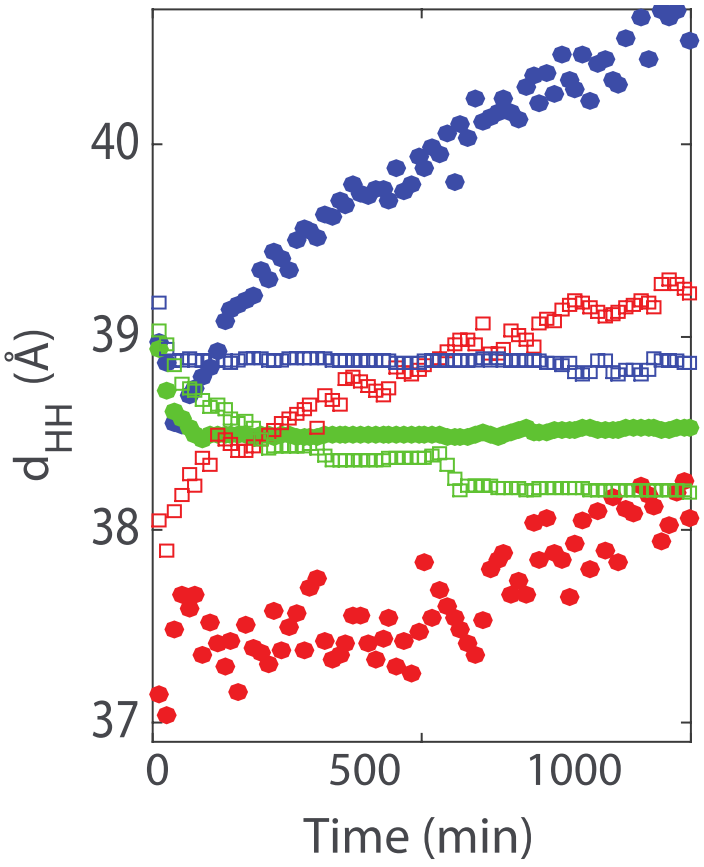




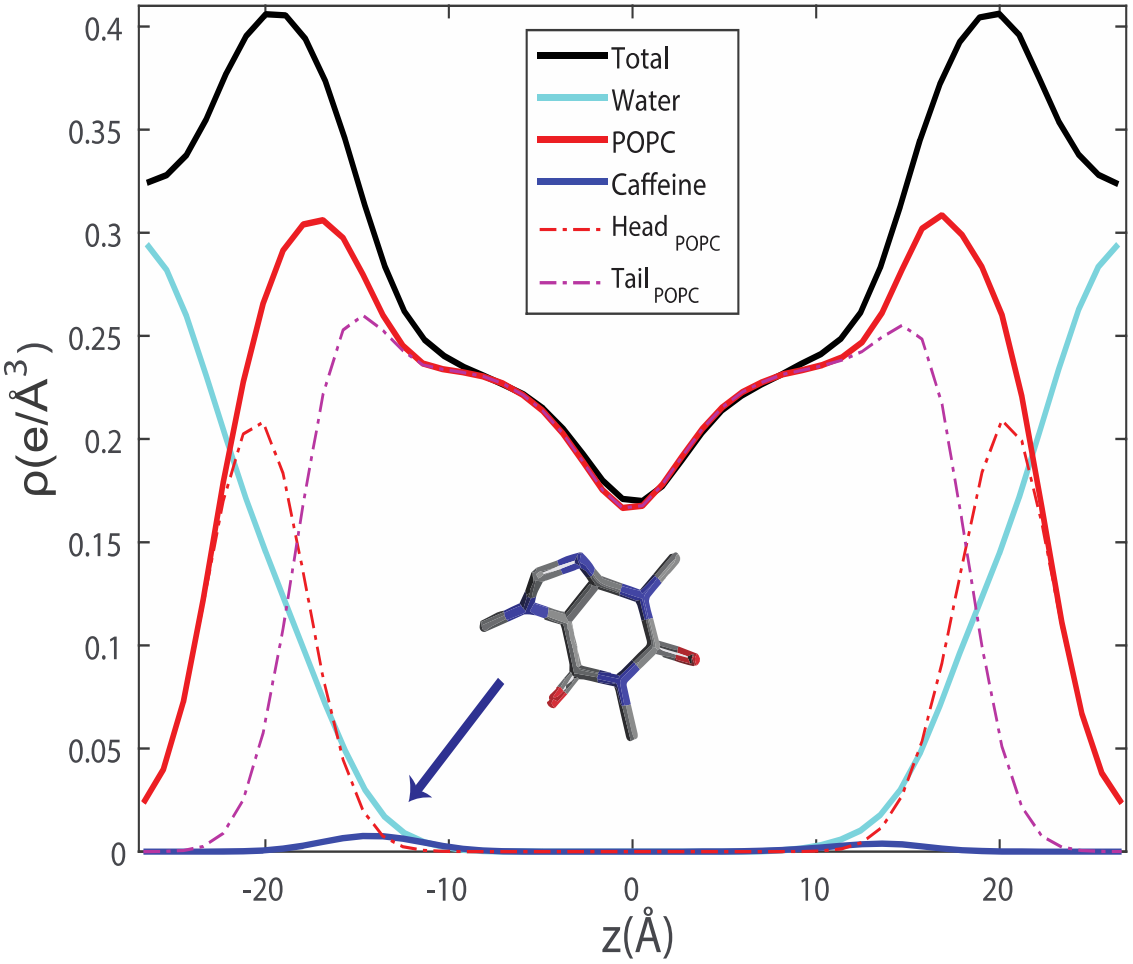
0 min Time 1000 min

Bilayer Swelling

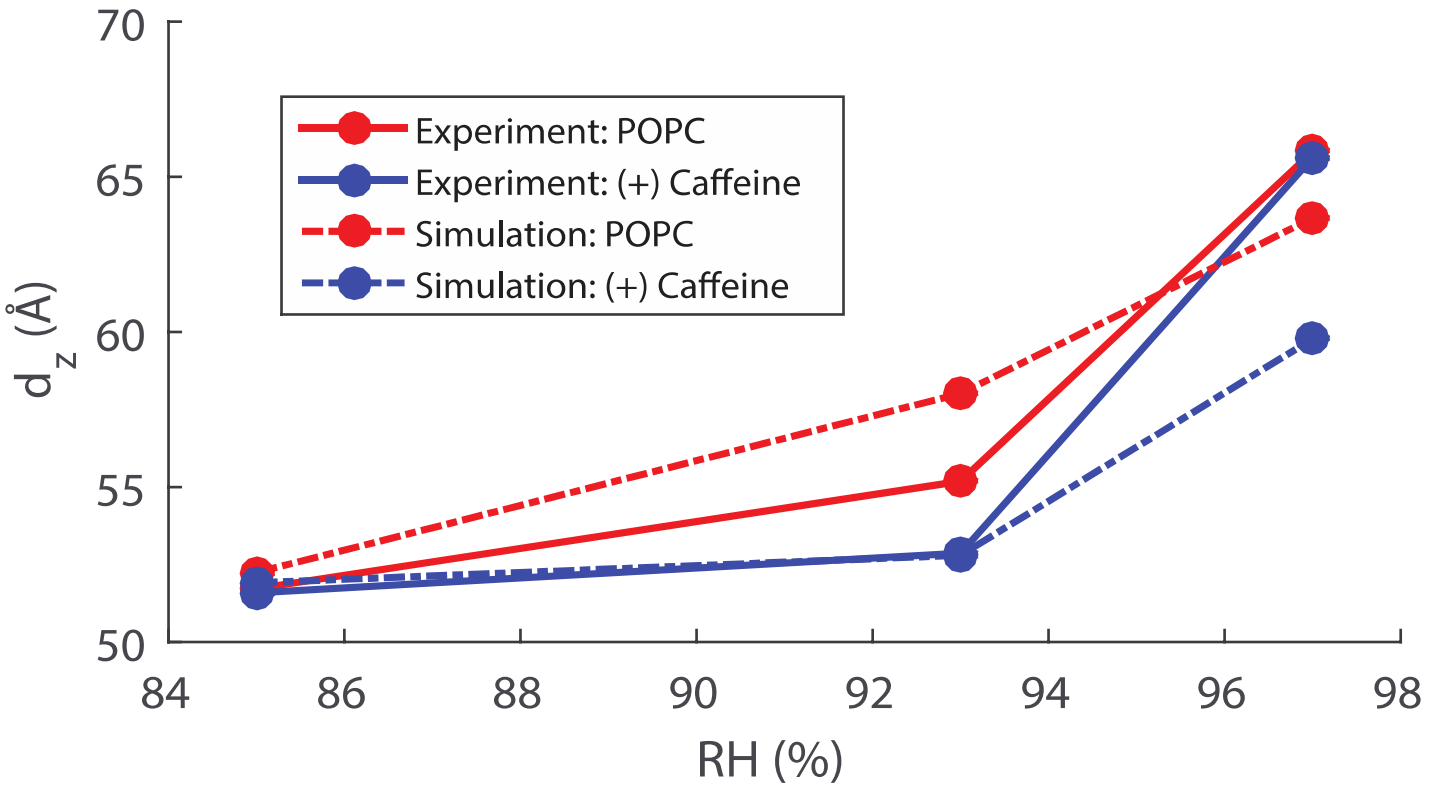




MD Electron Density

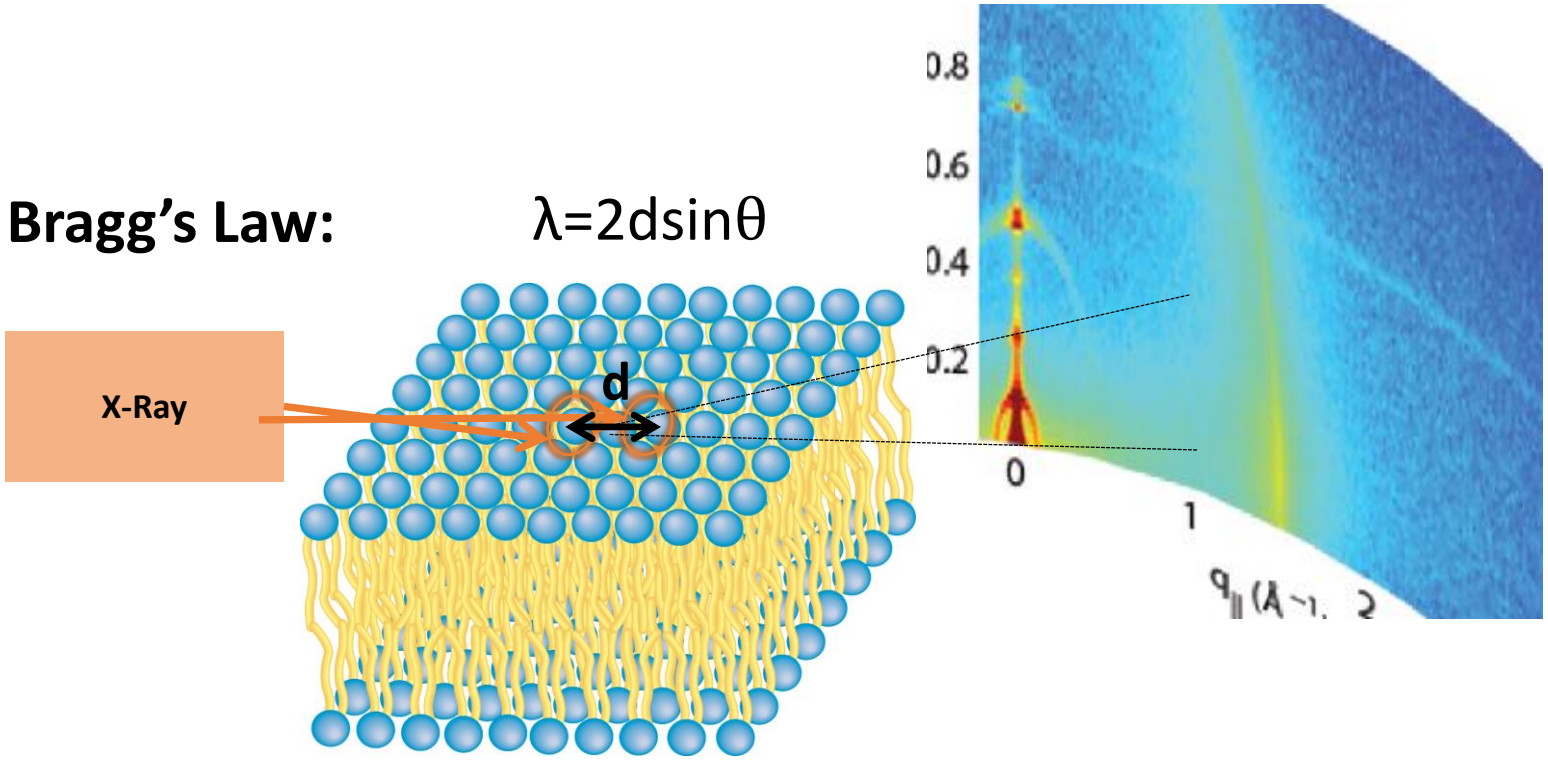


Comparison of Width



Bragg's Law

Bragg's Law: $\lambda = 2d\sin\theta$



d ≈ 1Å – 10nm

1. **Highly oriented stacks of lipid bilayer**
2. **Prepared with different doses of cortisone**
3. **Scanned along in-plane and out-of-plane axes**