Characterization of Bicelle Membrane Mimetics

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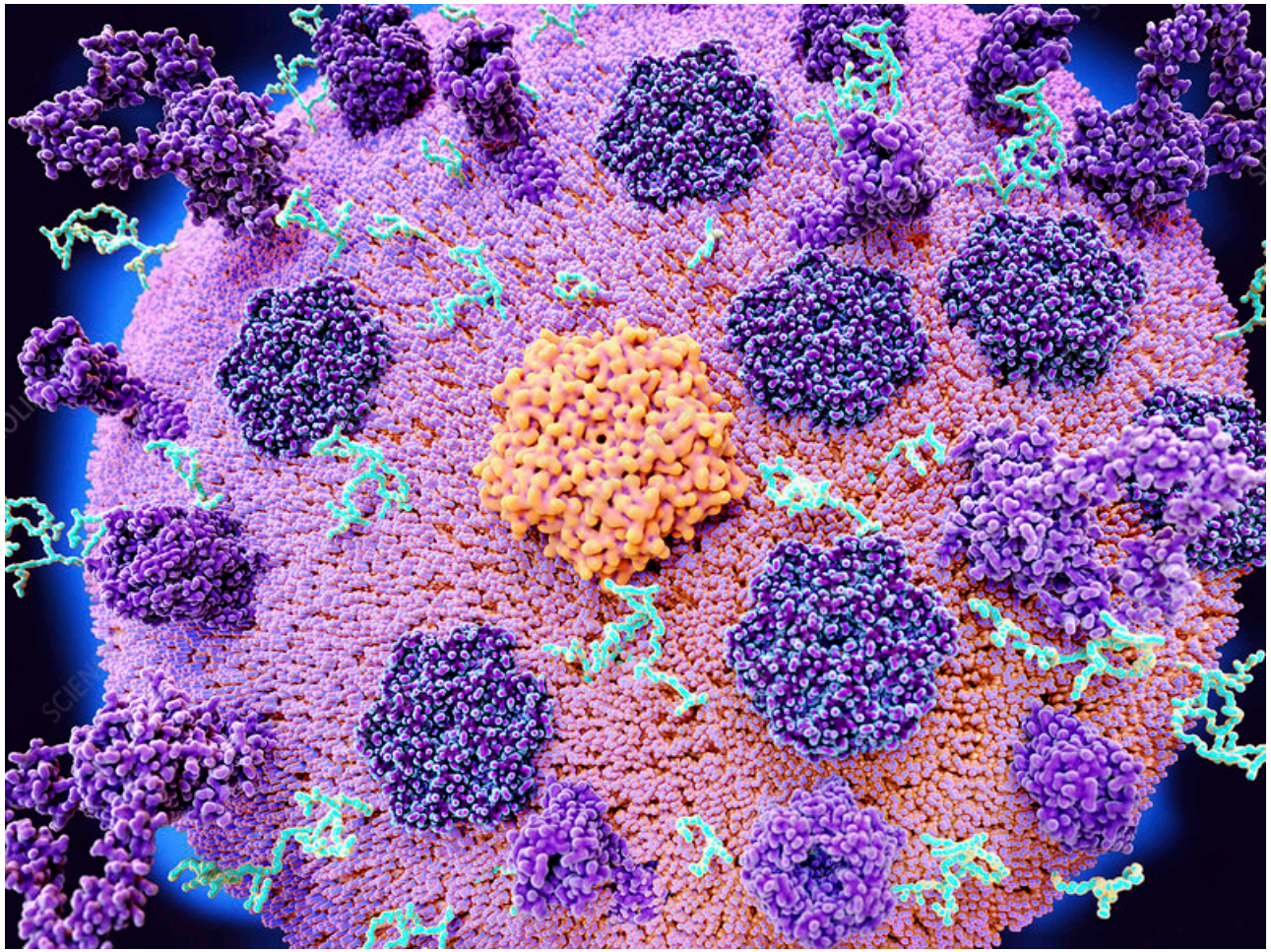
Advisor: Dr. Linda Columbus

Membrane proteins serve many vital functions

~30% of genome

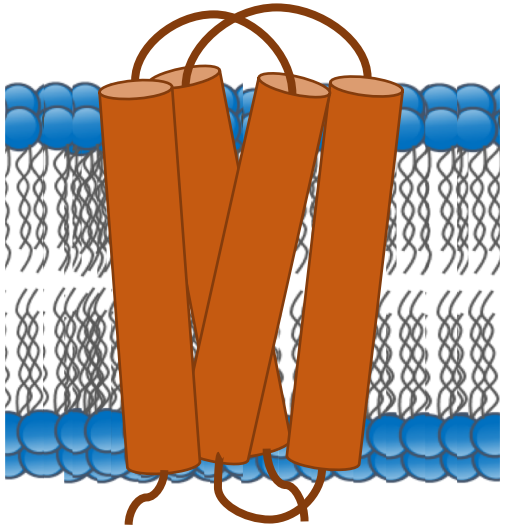
>50% of drug targets

<2% of protein structures

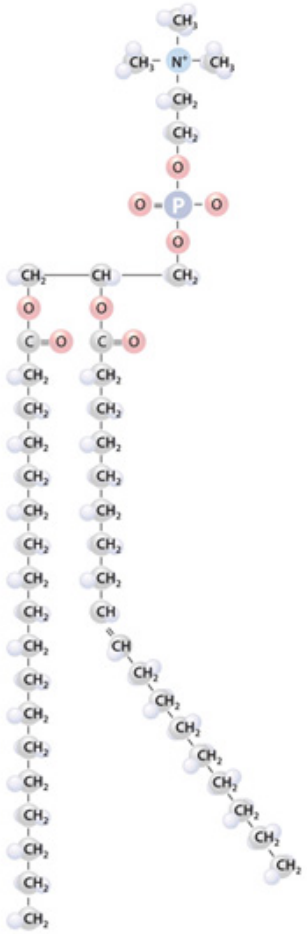


Juan Gaertner, Science photo library

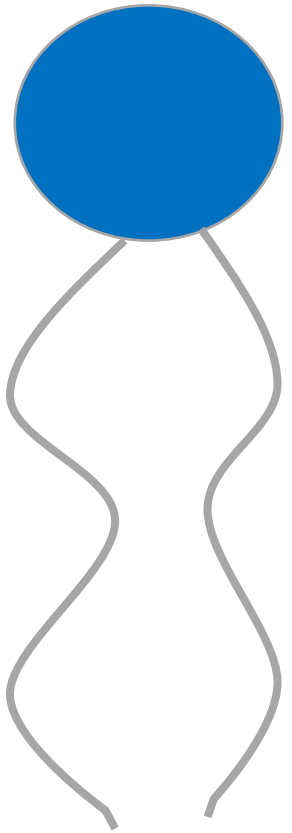
Native membrane is made of lipids



Membrane



Phospholipid

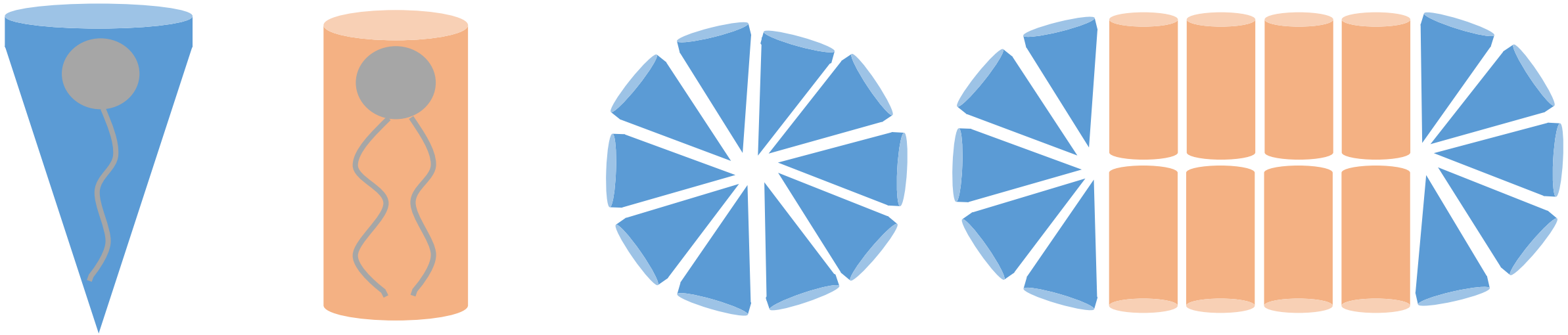


Lipid

Headgroup

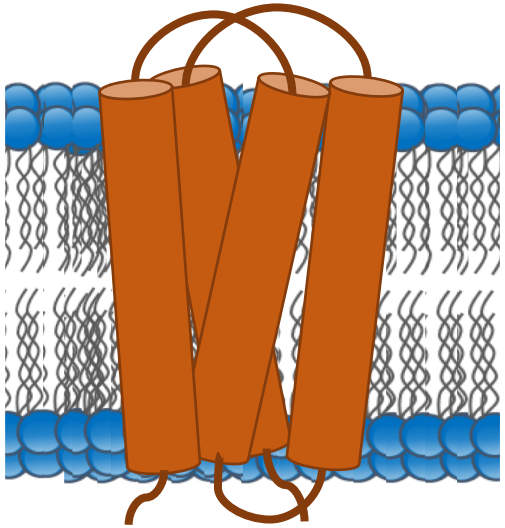
Hydrocarbon tails

Detergents and lipids are used to mimic hydrophobic membrane environment

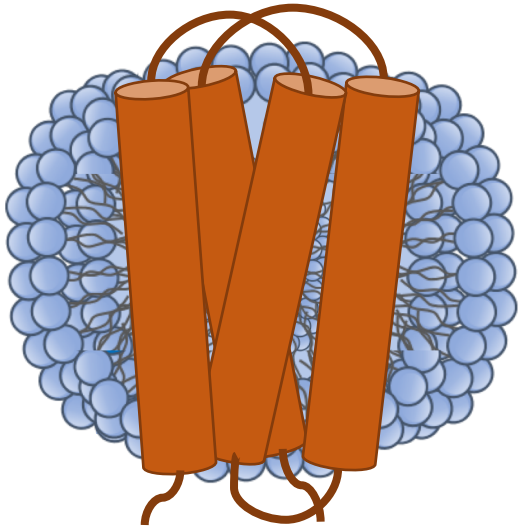


Detergent Lipid Micelle Bicelle

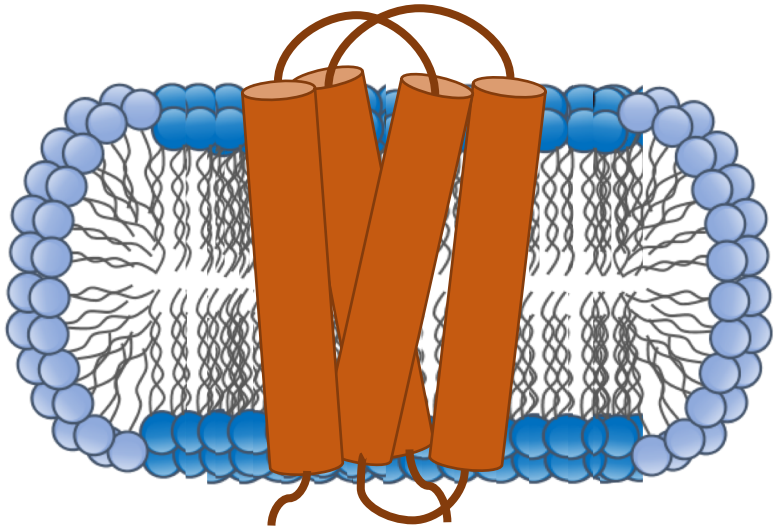
Study of membrane proteins requires membrane mimetic



Membrane

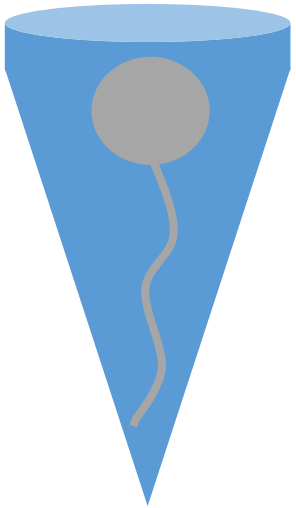


Micelle

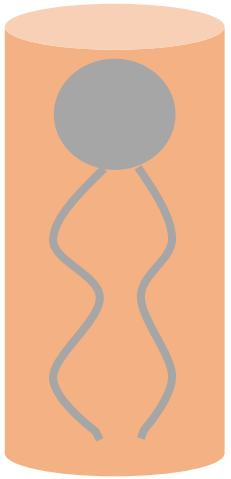


Bicelle

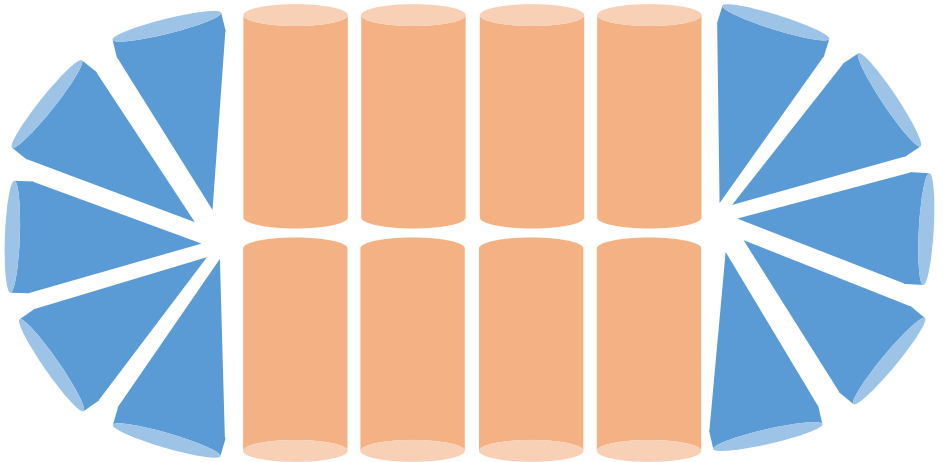
Ideal bicelle has a lipid core and detergent rim



Detergent

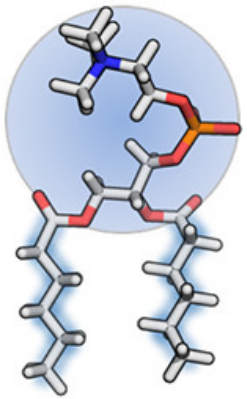


Lipid

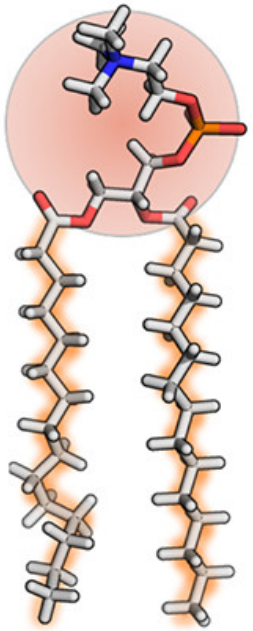


$$q = \frac{[\text{Lipid}]}{[\text{Detergent}]}$$

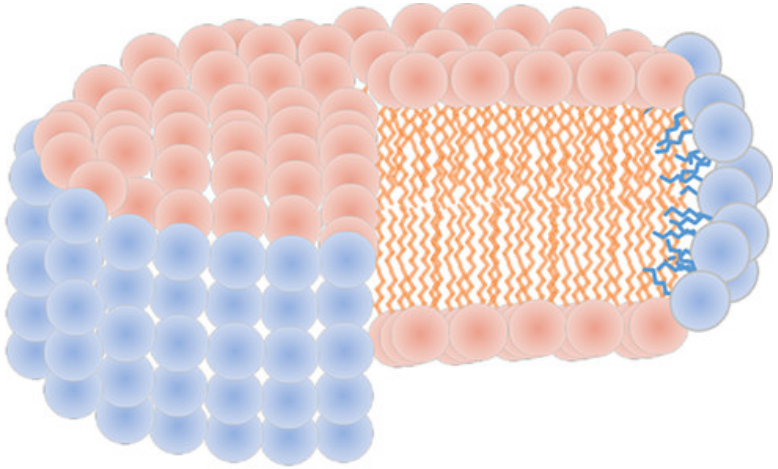
Are low-q bicelles really “bilayer-like”?



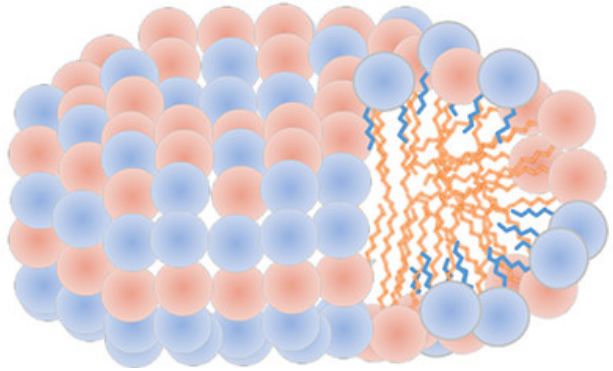
DHPC



DMPC

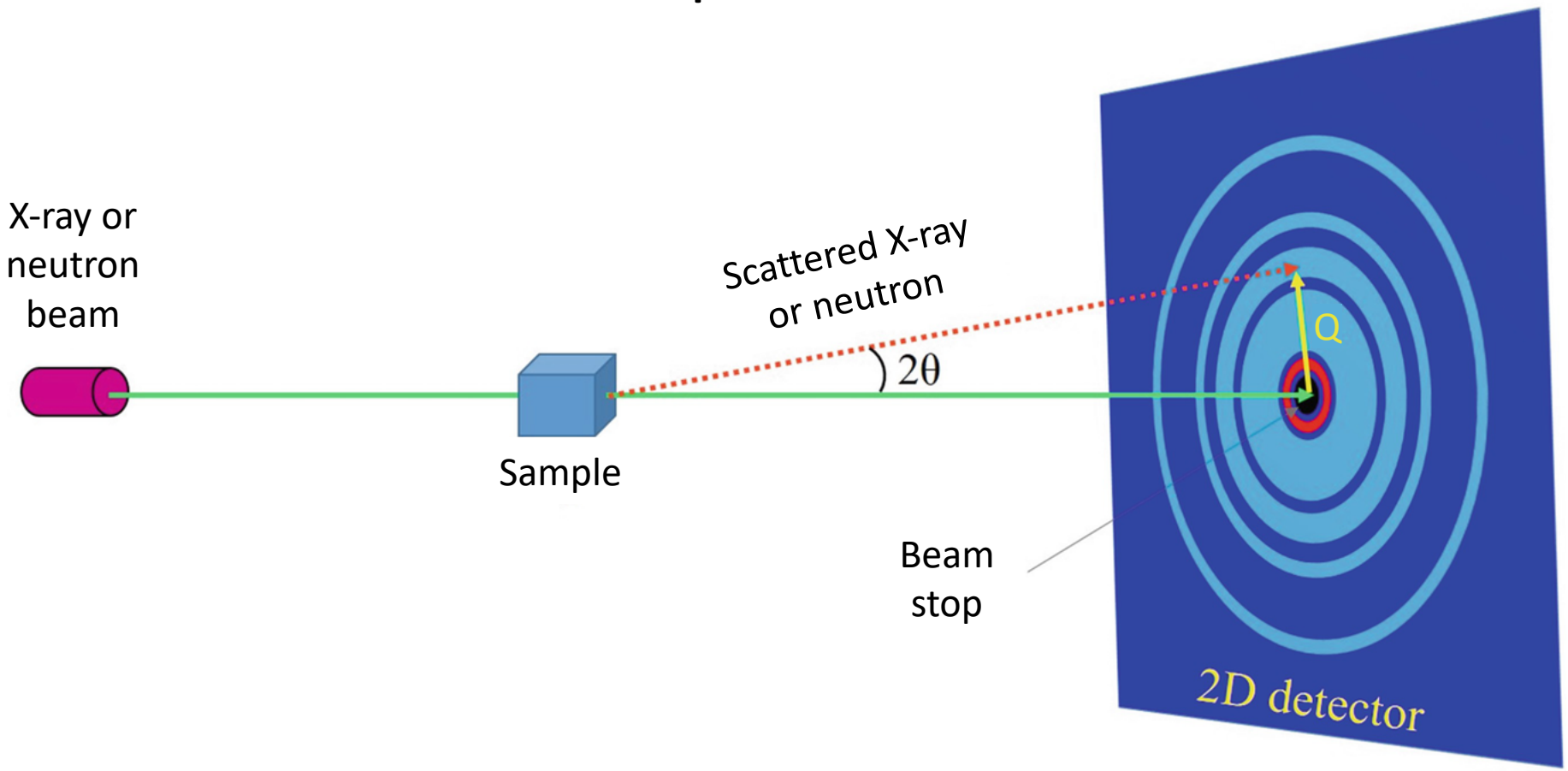


Ideal Bicelle



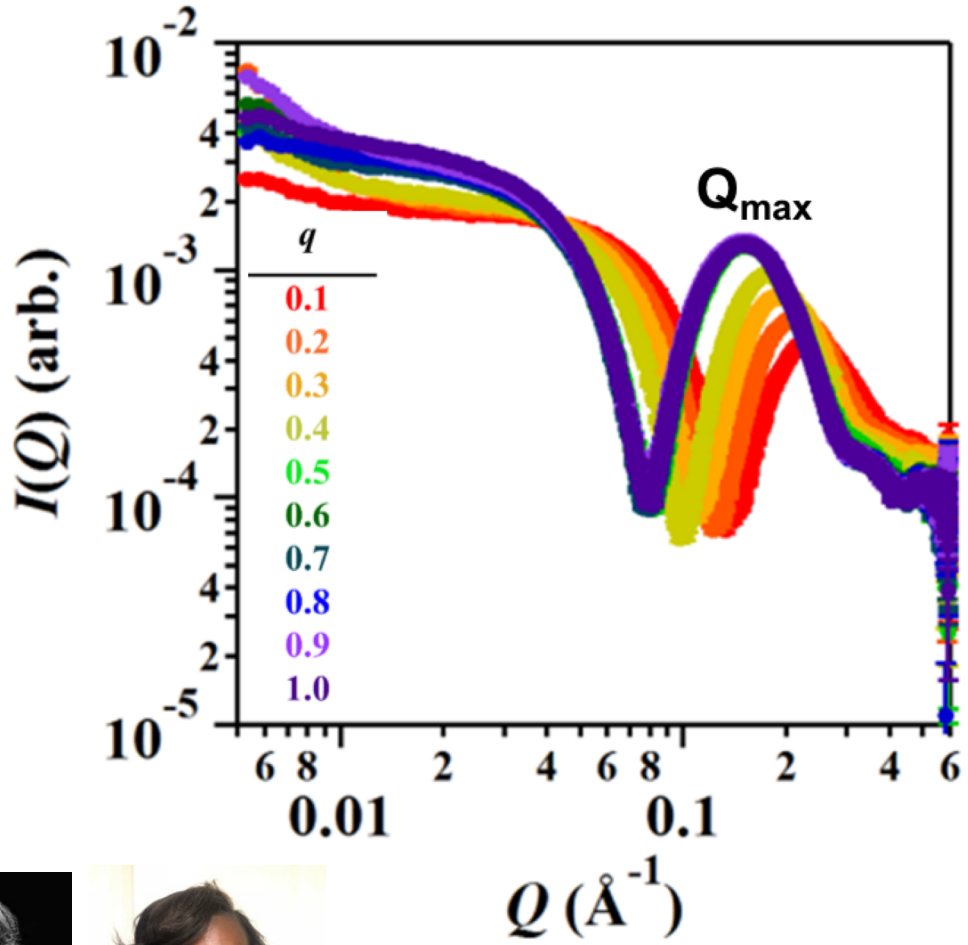
Mixed Micelle

Small angle scattering used to characterize low-q bicelles

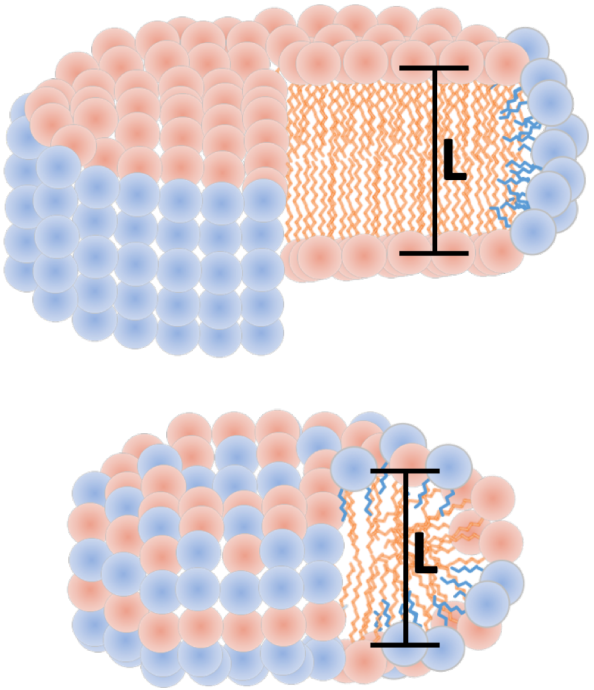


Londono *et al. (*2018) Handbook of Materials Characterization 37-75

SAXS data shows length changes up to q=0.5



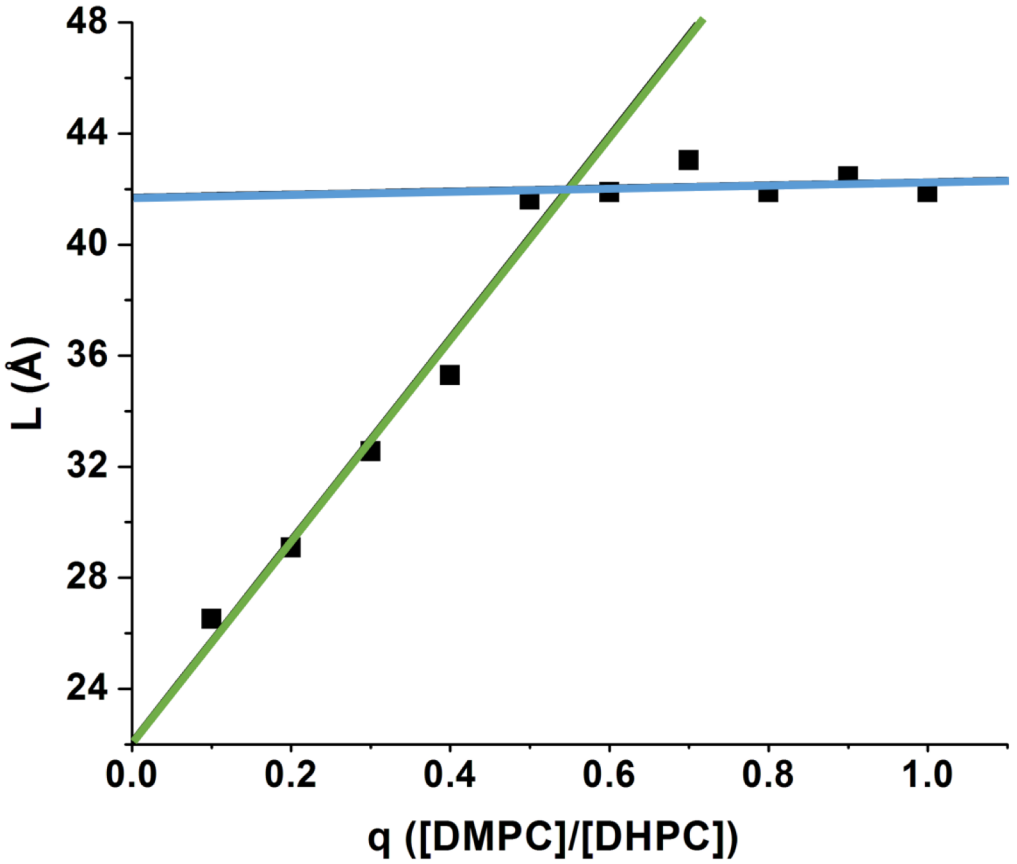
$$L = \frac{2\pi}{Q_{max}}$$

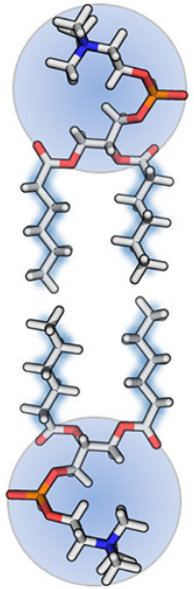


$$q = \frac{[Lipid]}{[Detergent]}$$

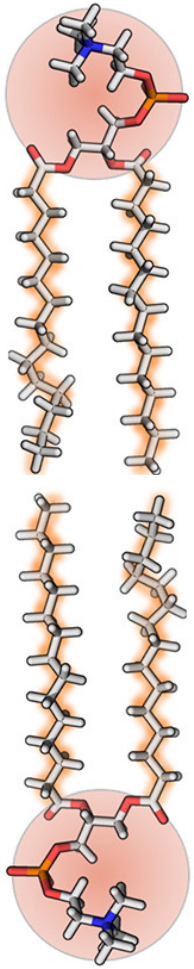
Dr. Ryan Oliver
Dr. Ashton Brock

SAXS data shows length changes up to q = 0.5





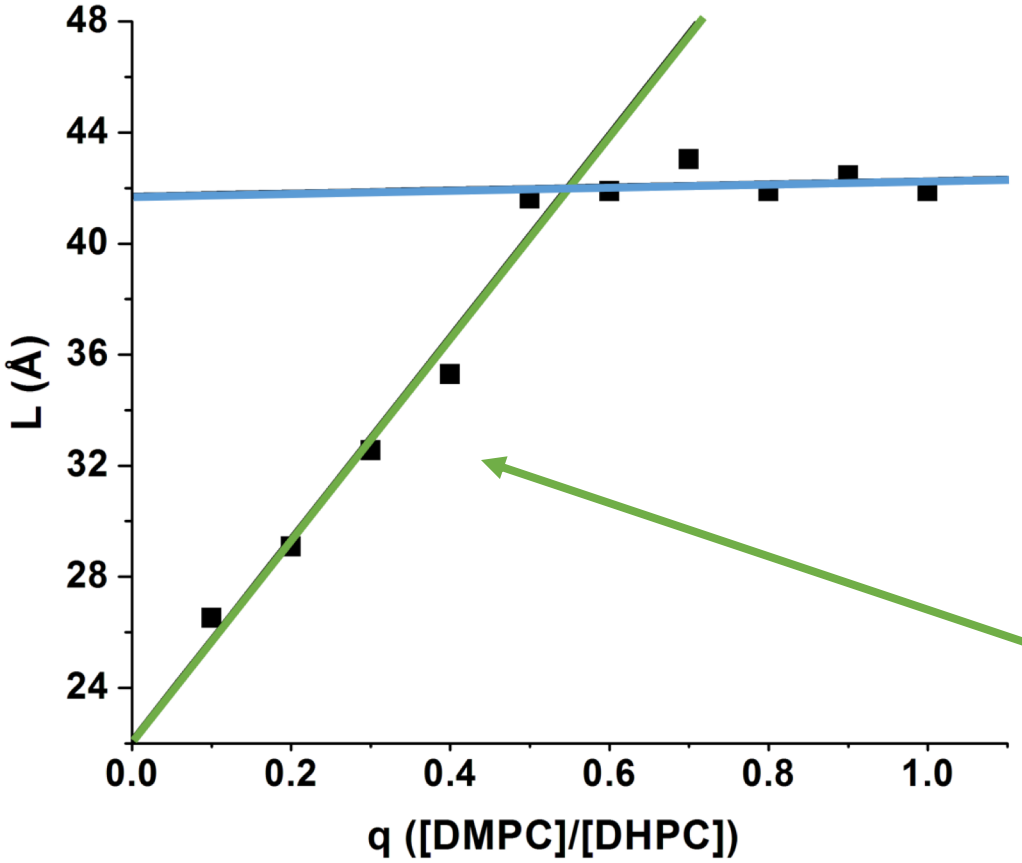
Pure DHPC
L = 22 Å

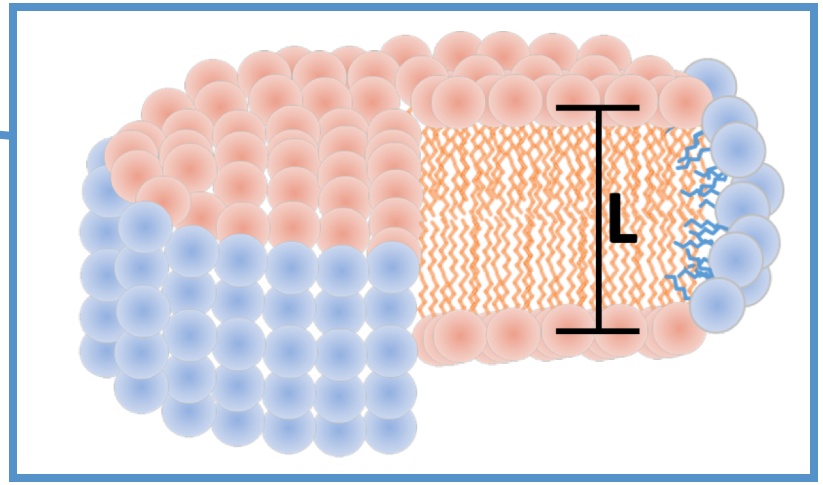


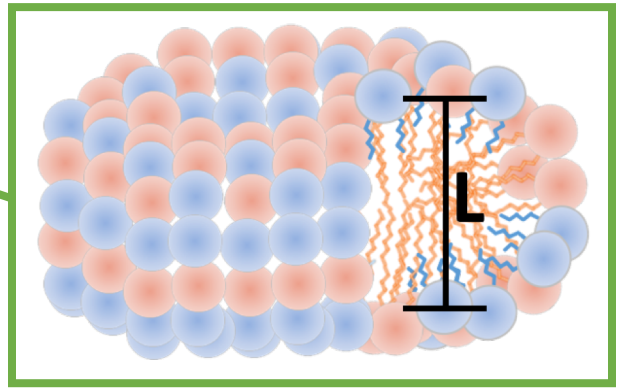
Pure DMPC
L = 42 Å

Dr. Ryan Oliver
Dr. Ashton Brock

SAXS data suggests segregation at q > 0.5

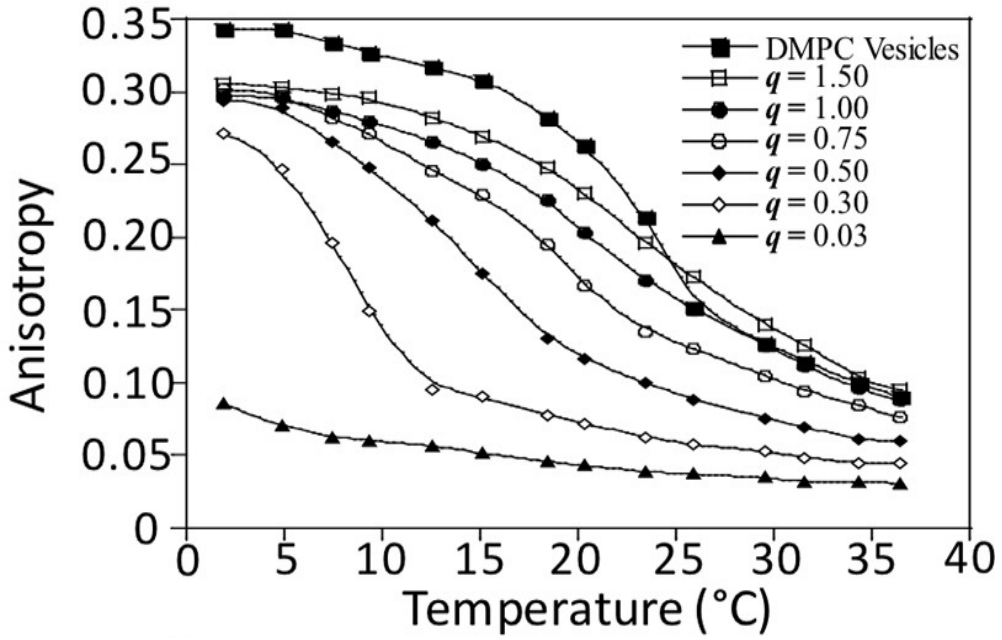


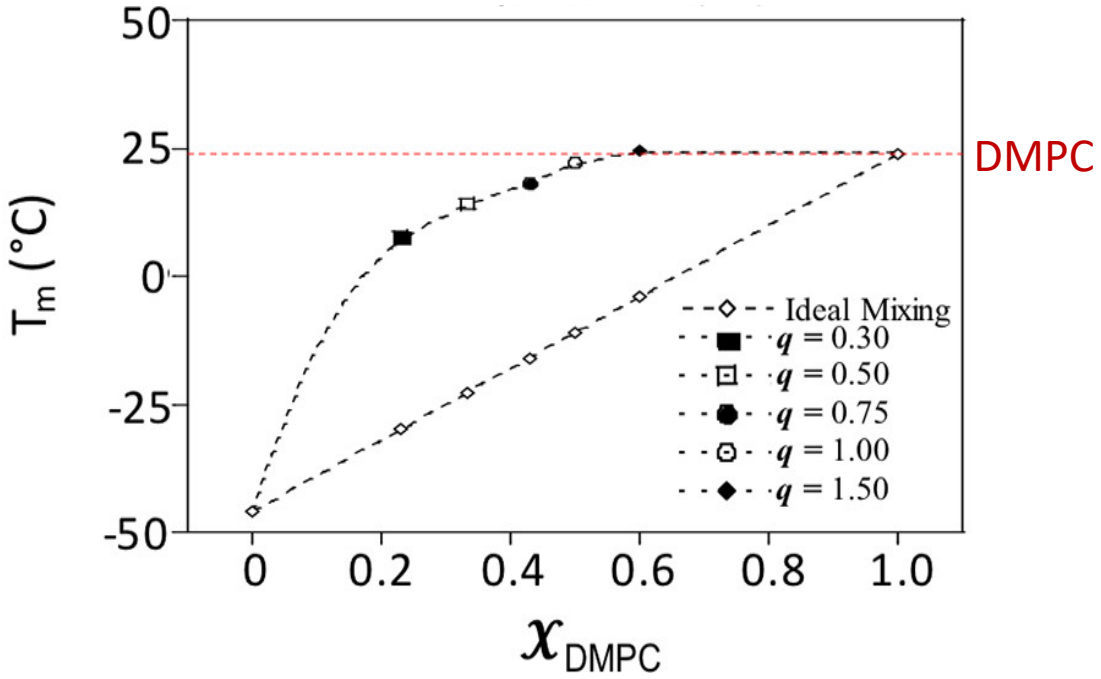




Dr. Ryan Oliver
Dr. Ashton Brock

Fluorescence anisotropy shows mixing <q=1





Dr. Kerney Jebrell Glover
Lehigh University

SANS can distinguish multiple components

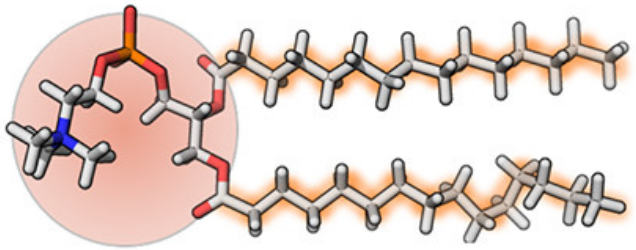
$$I(q) \propto \Delta\rho$$

$$\text{Scattering length density (SLD)} = \rho = \frac{\sum b_i}{V}$$

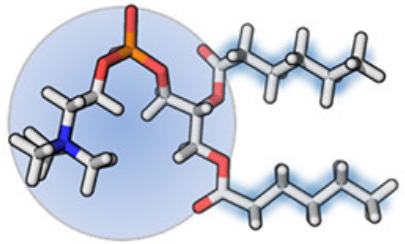
b_i: coherent neutron scattering length of atom i

H: -3.74×10^{-5}, D: 6.67×10^{-5}

Deuterated DMPC



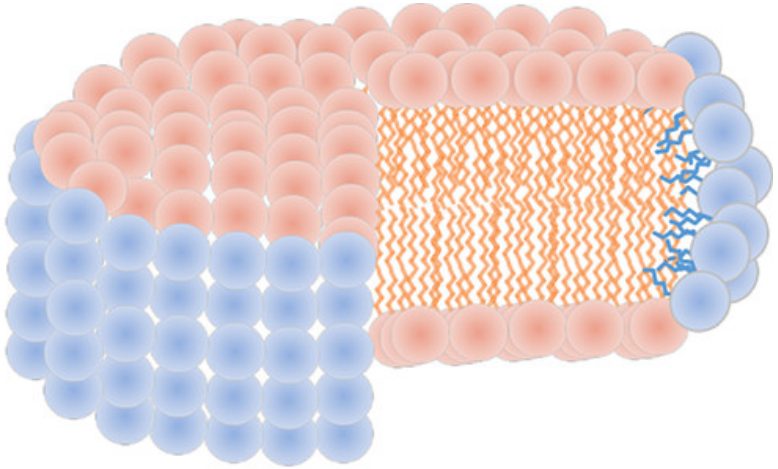
Non-deuterated DHPC



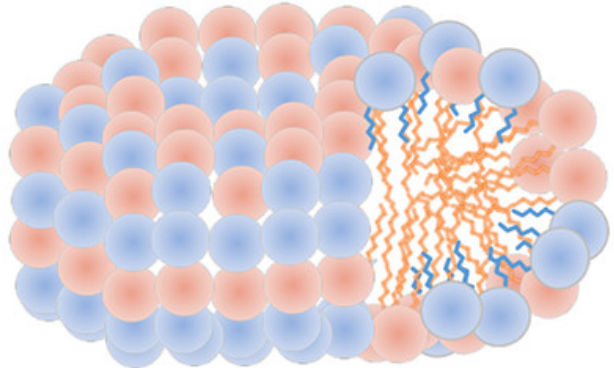
DMPC SLD > DHPC SLD

SANS can distinguish multiple components

$$I(q) \propto \Delta\rho$$



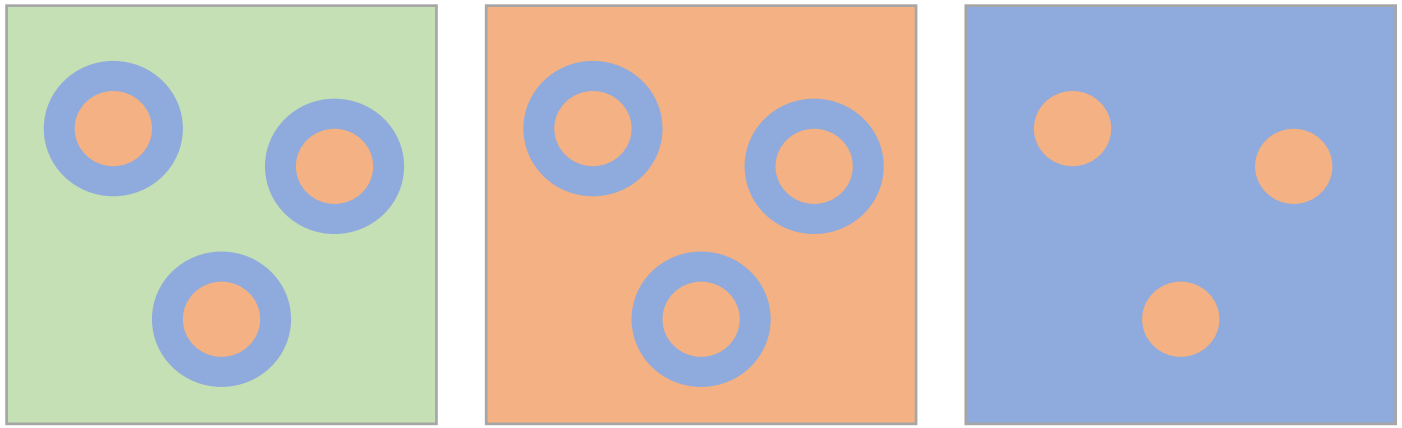
Core SLD > Rim SLD



Core SLD ≈ Rim SLD

SANS can distinguish multiple components

$$I(q) \propto \Delta\rho$$



Neutral Contrast

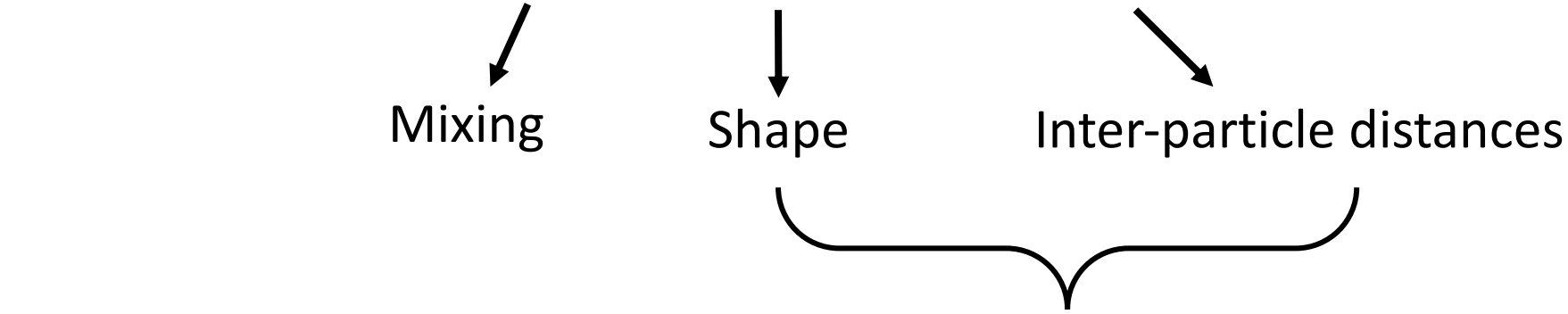
SLD solvent = SLD core
Rim Visible

SLD solvent = SLD rim
Core Visible

SANS can distinguish multiple components

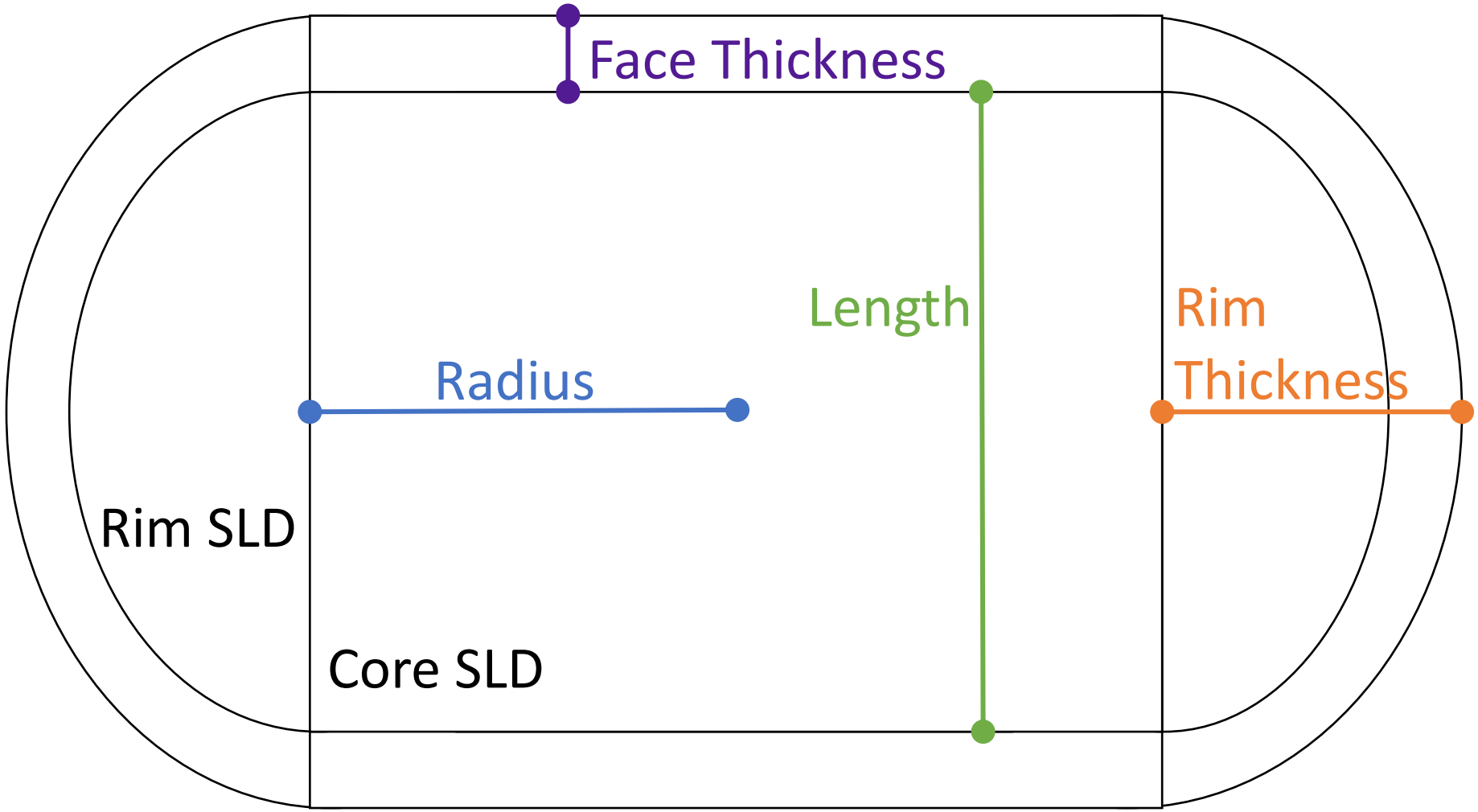
$$I(q) = V_p \Delta\rho^2 P(q) S(q)$$

Intensity = (Volume) (SLD) (Form factor) (Structure factor)

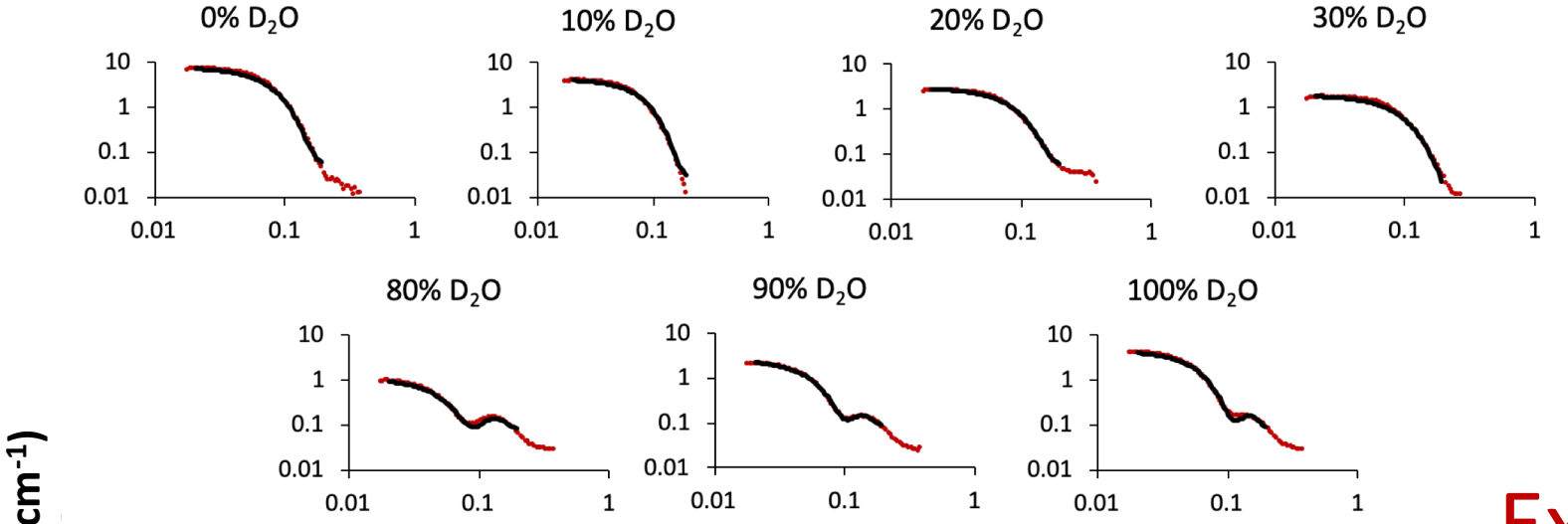


Core-shell bicelle model

Core-shell bicelle model



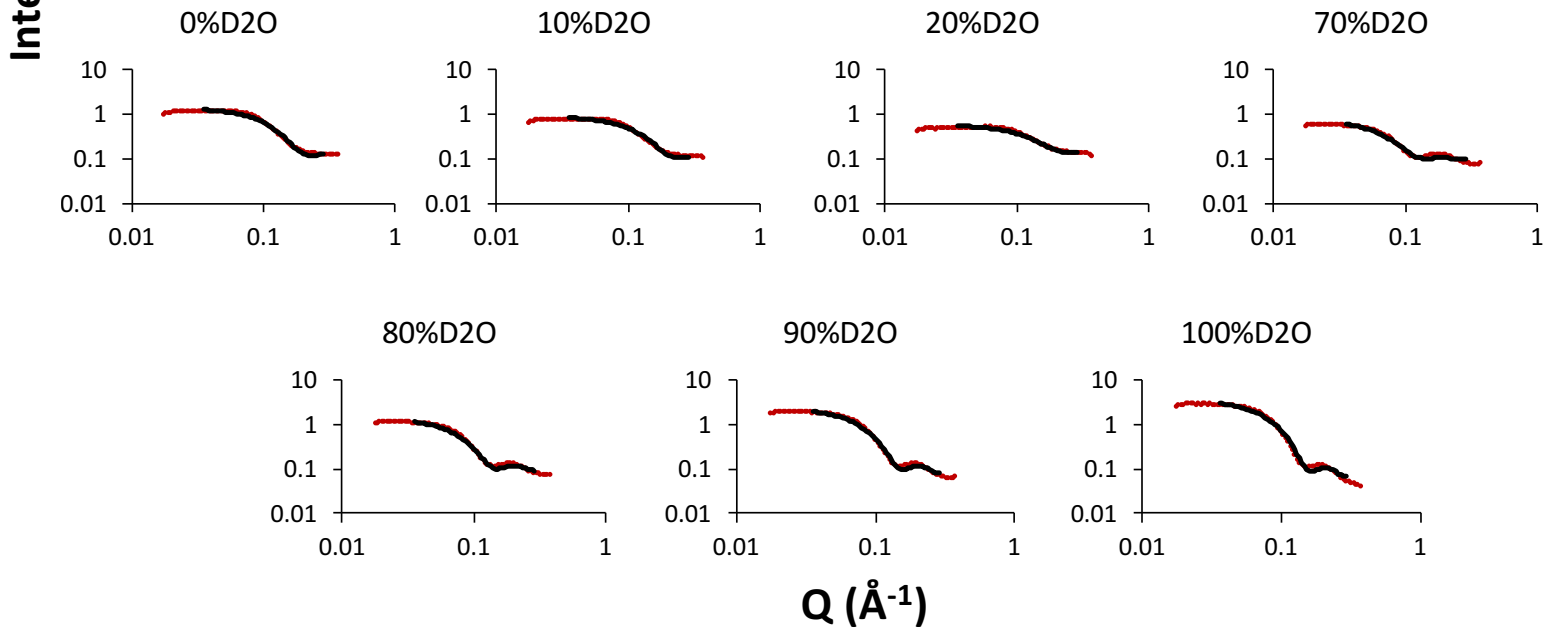
q=0.7



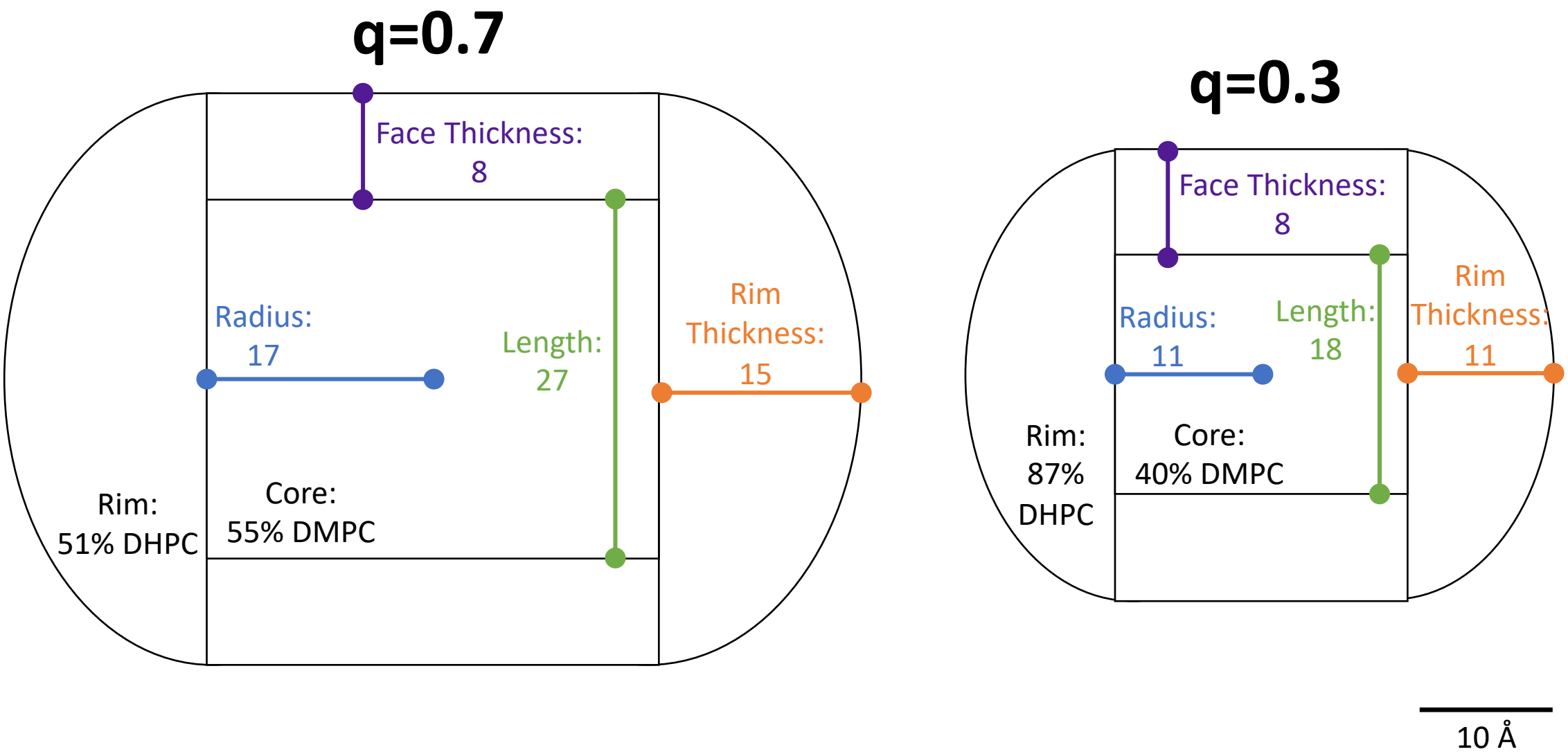
Experimental

Fit

q=0.3



q=0.7 bicelles are larger, q=0.3 more spherical



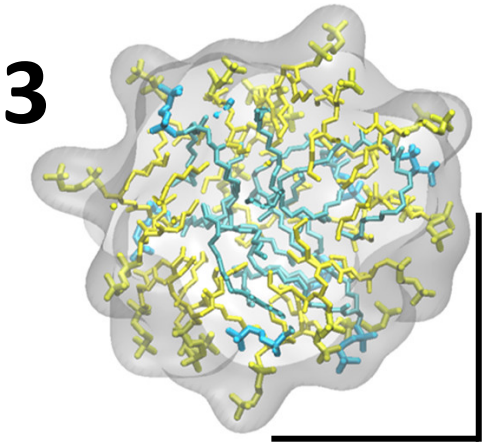
q=0.3 bicelles are more mixed than q=0.7

SANS Bicelle Results				
	q=0.7		q=0.3	
	Average	Range	Average	Range
Radius	17	10-27	11	4-21
Rim Thickness	15	11-23	11	10-13
Face Thickness	8	7 - 12	8	7 - 12
Length	27	18-36	18	15-23
Core % DMPC	55	51-63	40	23-62
Rim % DHPC	51	49-59	87	76-100

If fully mixed:		
	q=0.7	q=0.3
% DMPC	44	24
% DHPC	56	76

Molecular dynamics show mixed micelles at q=0.3 and ellipsoidal bicelles at q=0.7

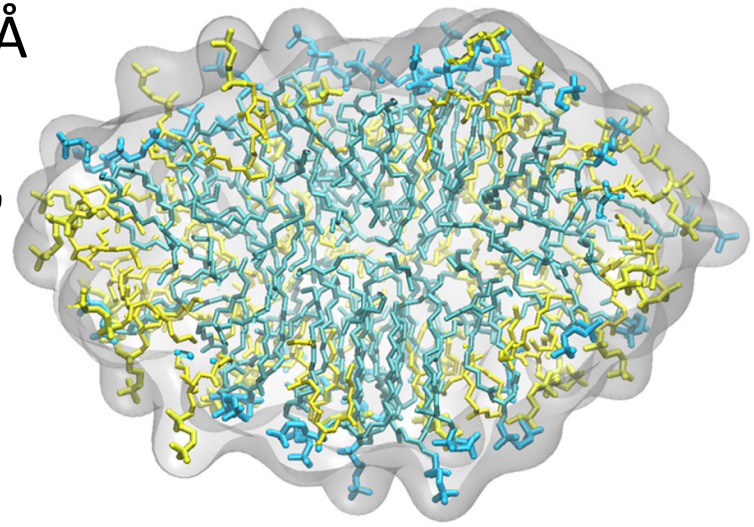
q=0.3



24 Å

29 Å

q=0.7



27 Å

40 Å

DMPC

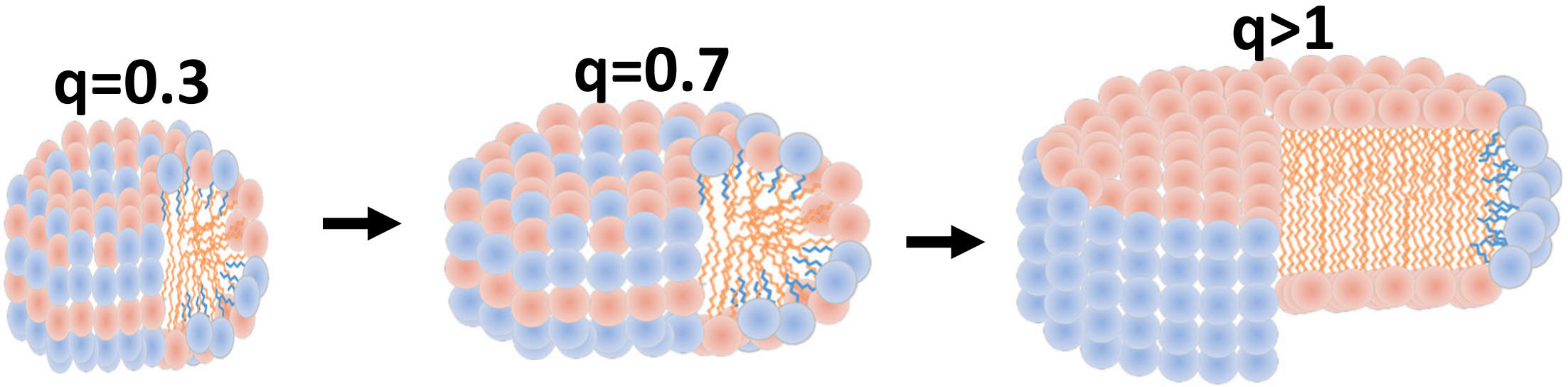
DHPC

	DHPC	
q	Expected if fully mixed (%)	Observed (%)
0.7	56	49
0.3	76	76

Dr. Peter Tieleman
Dr. Svetlana Baoukina
University of Calgory

Conclusions

- At q-values less than 1, lipid and detergent molecules mix and deviate from the ideal bicelle model
- As q increases, transitions from spherical mixed micelle to ellipsoidal micelle to disc-like bicelle
- Care should be taken when interpreting results using bicelles



Caldwell *et al. (*2018) J. Phys. Chem. Letters, 9