



Long Nights in Didcot doing Drugs & Stuff

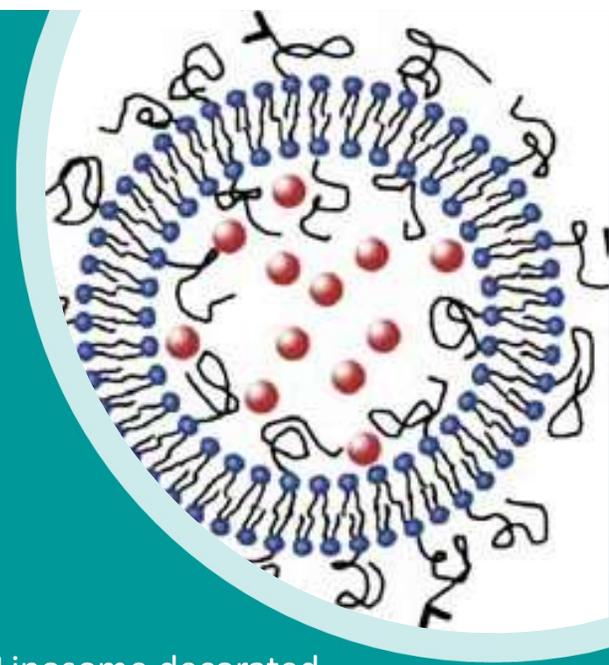
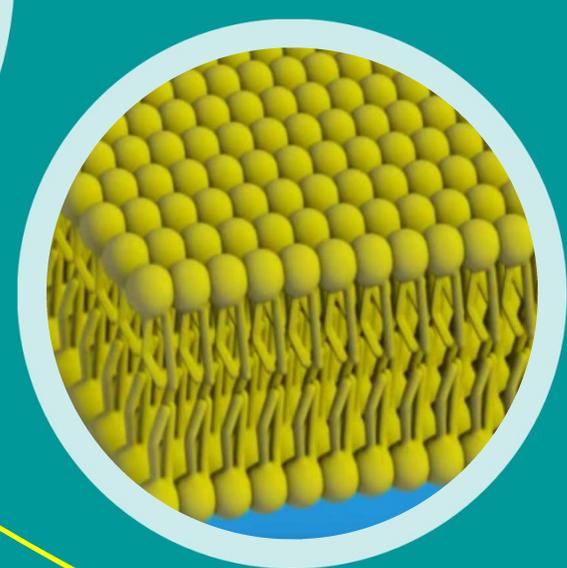
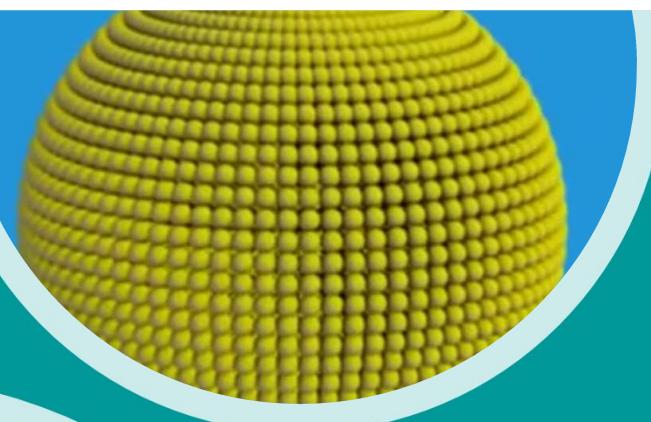
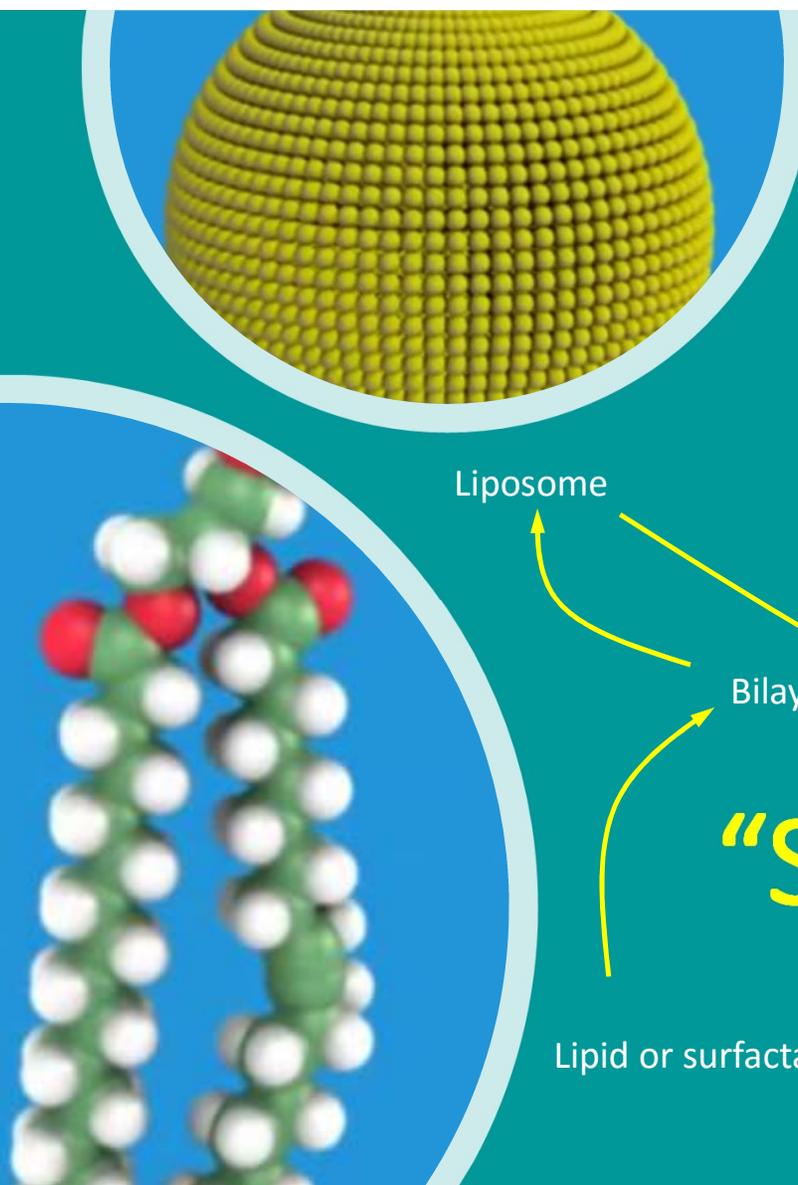
Dave Barlow, Institute of Pharmaceutical Science, King's College London



Why ISIS? Why Neutrons ?

- Non-invasive
- Non-destructive
- Structural information on the nanometre length scale
- Direct means to probe structure in multicomponent systems
- Furnish valuable information on the structure of drugs, drug delivery systems, and pharmaceutical formulations





Liposome

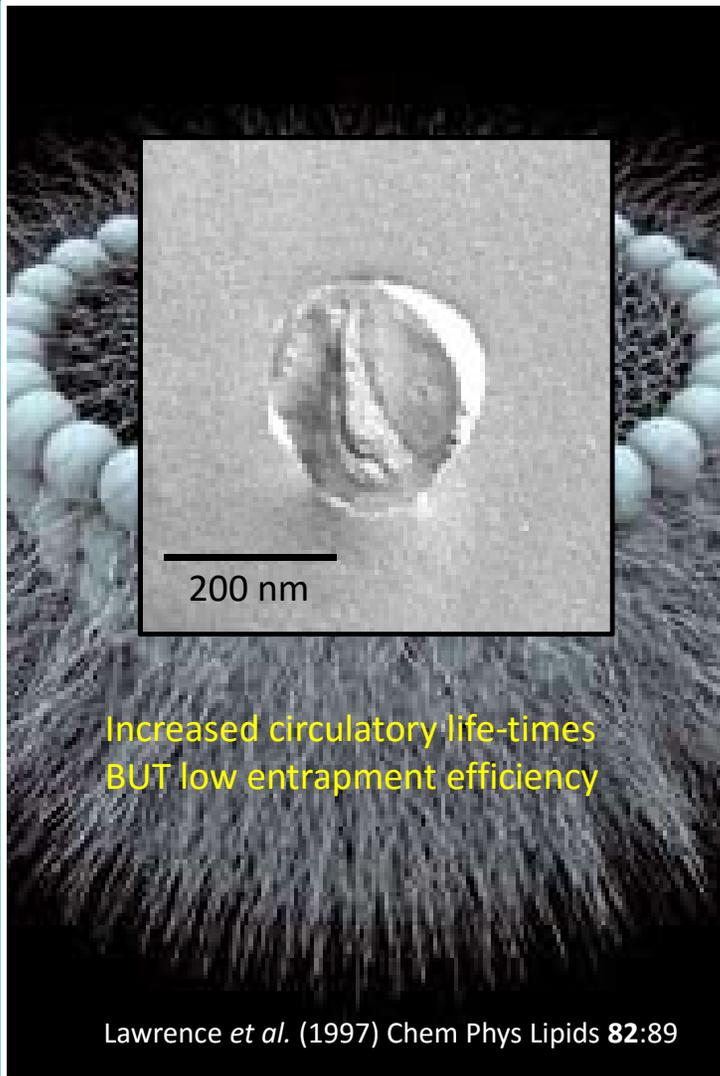
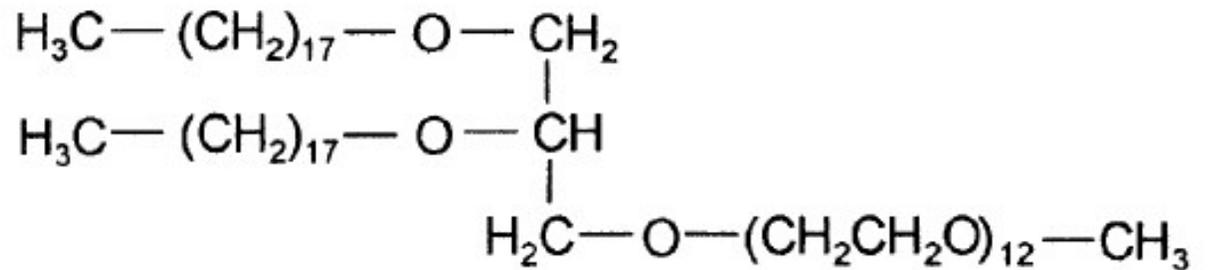
Bilayer

Liposome decorated with long PEG chains

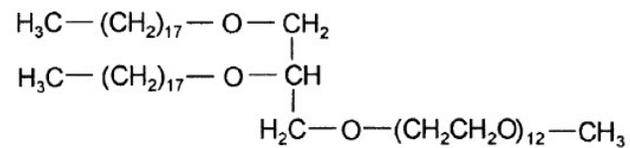
Lipid or surfactant

"Stealth" Liposomes

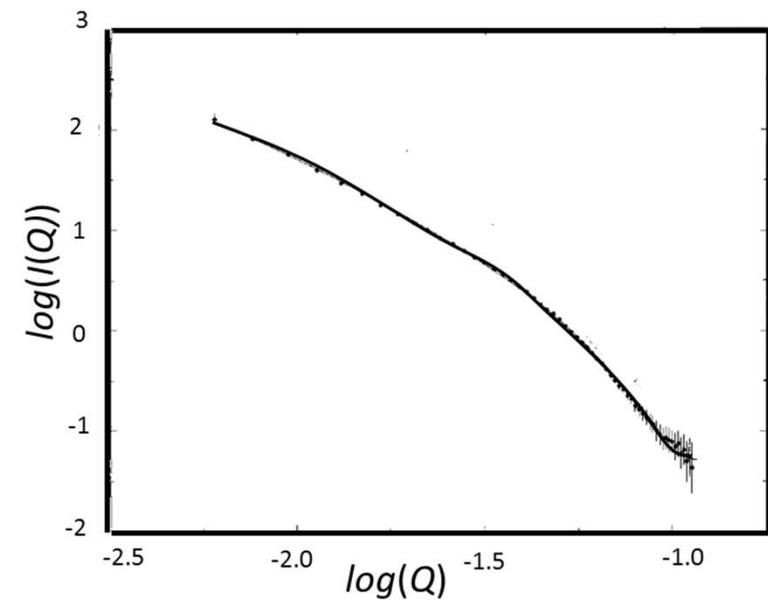
Single excipient stealth delivery vehicle / simplified formulation



$2\text{C}_{18}\text{E}_{12}$ Vesicles

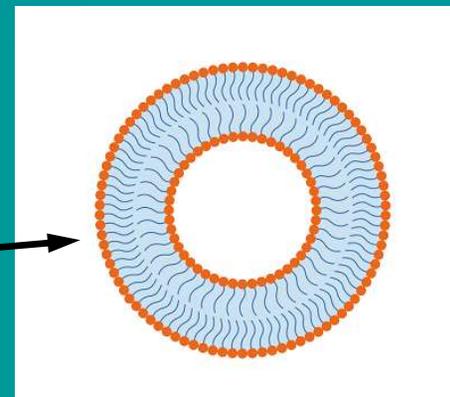


D_2O

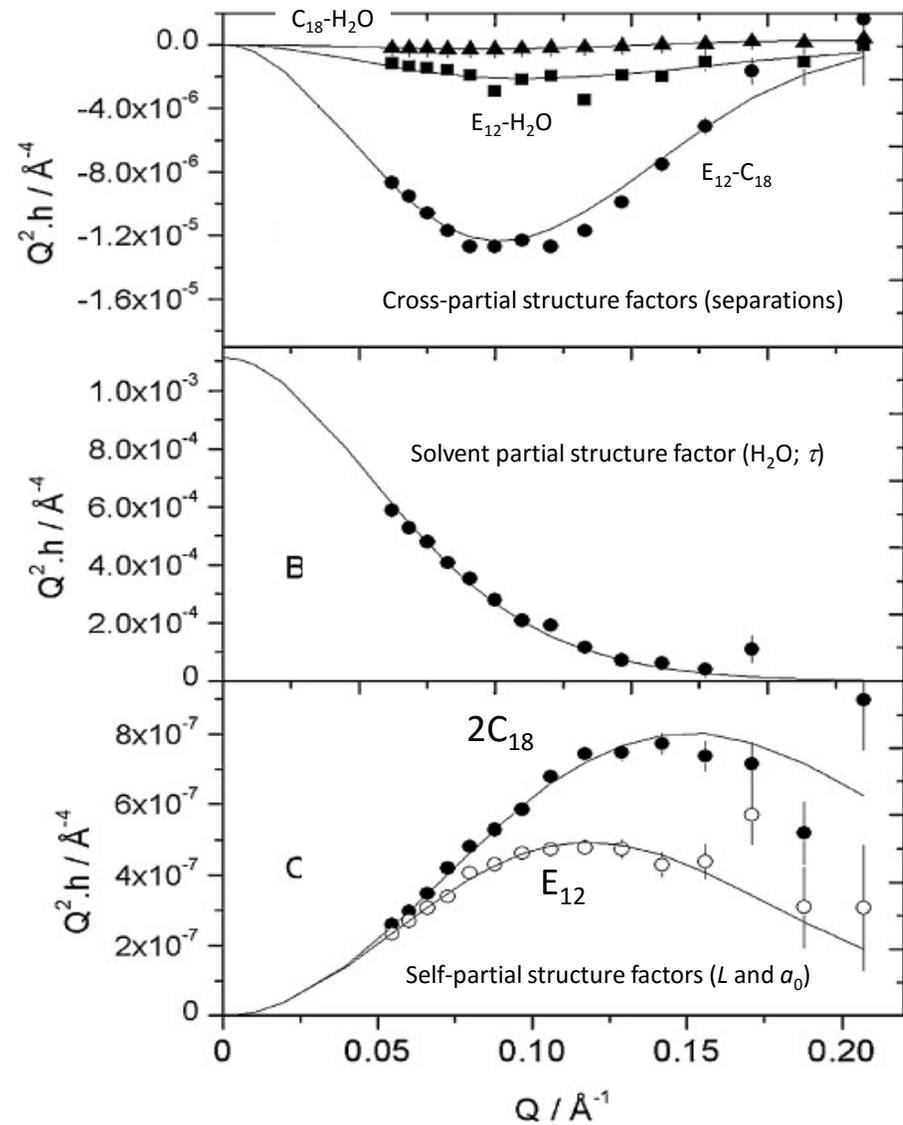


Ma *et al.* (2000) *J Phys Chem B* **104**:9081

Very thin (51 Å) bilayer
(adequately modelled just
as uniform slab)



SANS studies of $2\text{C}_{18}\text{E}_{12}$
vesicles

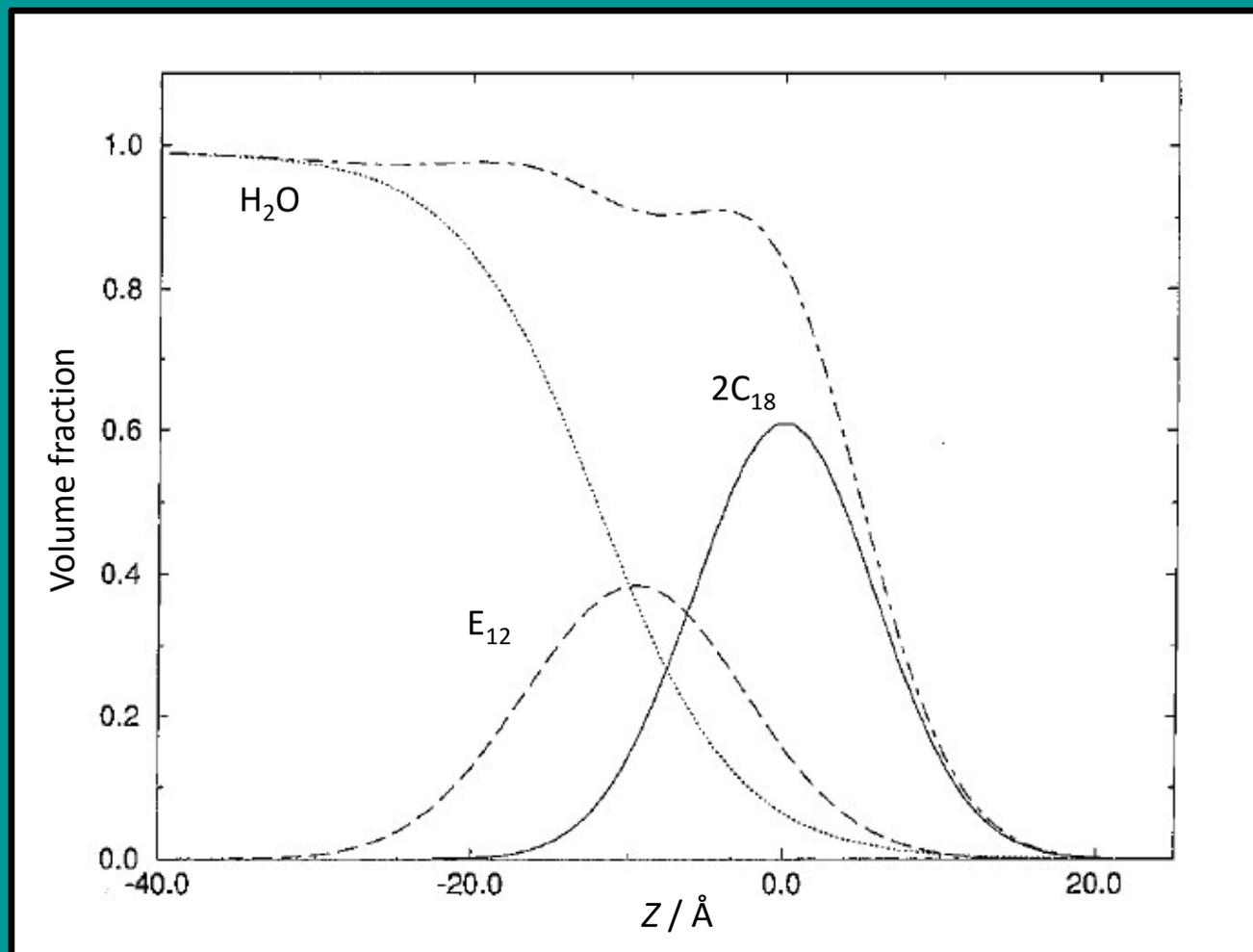


7 isotopic contrasts

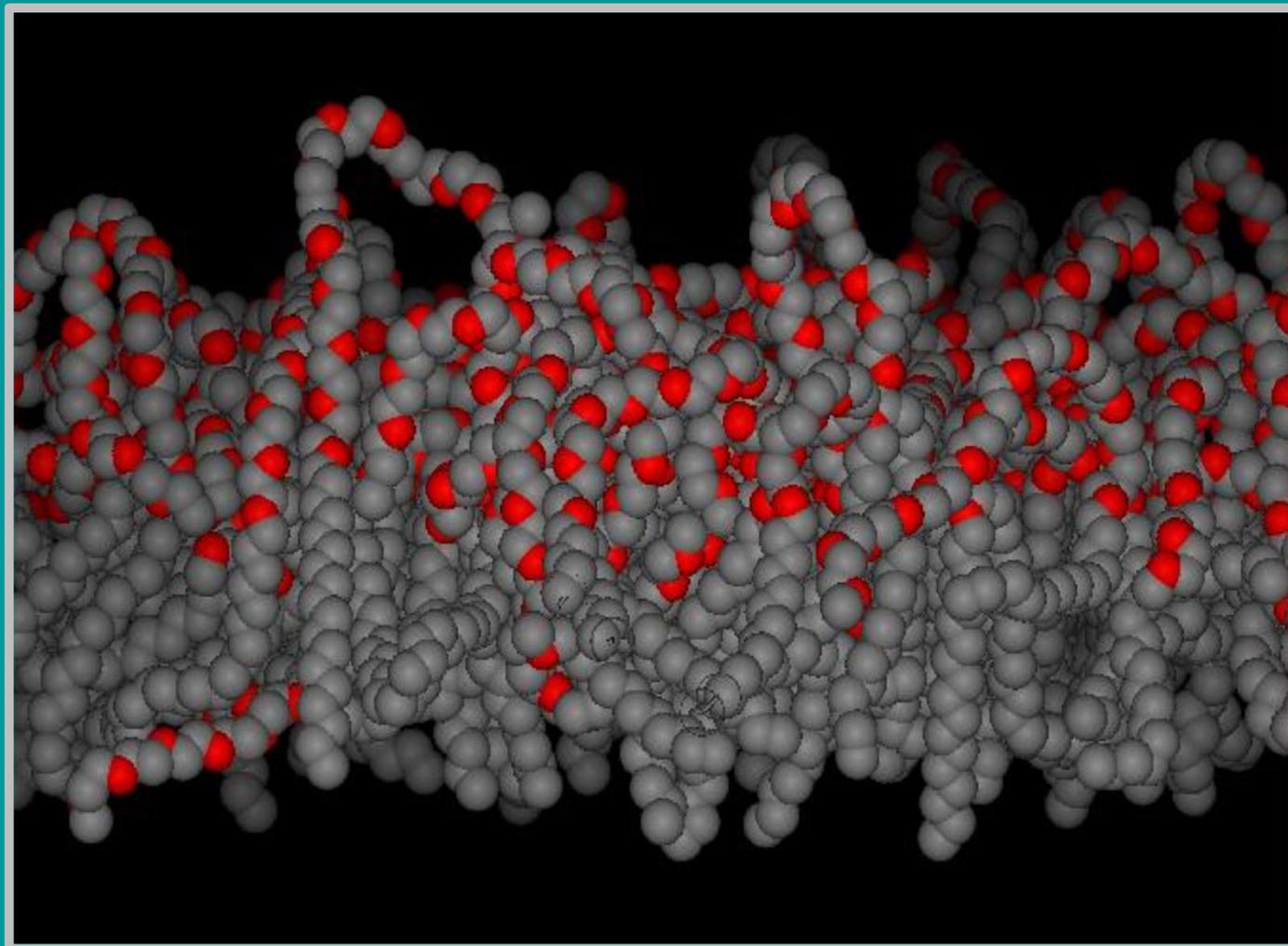
- $d\text{-}2C_{18}\text{-}h\text{-}E_{12}$ on acmw / D_2O
- $h\text{-}2C_{18}\text{-}d\text{-}E_{12}$ on acmw / D_2O
- $d\text{-}2C_{18}\text{-}d\text{-}E_{12}$ on acmw / D_2O
- $h\text{-}2C_{18}\text{-}h\text{-}E_{12}$ on D_2O

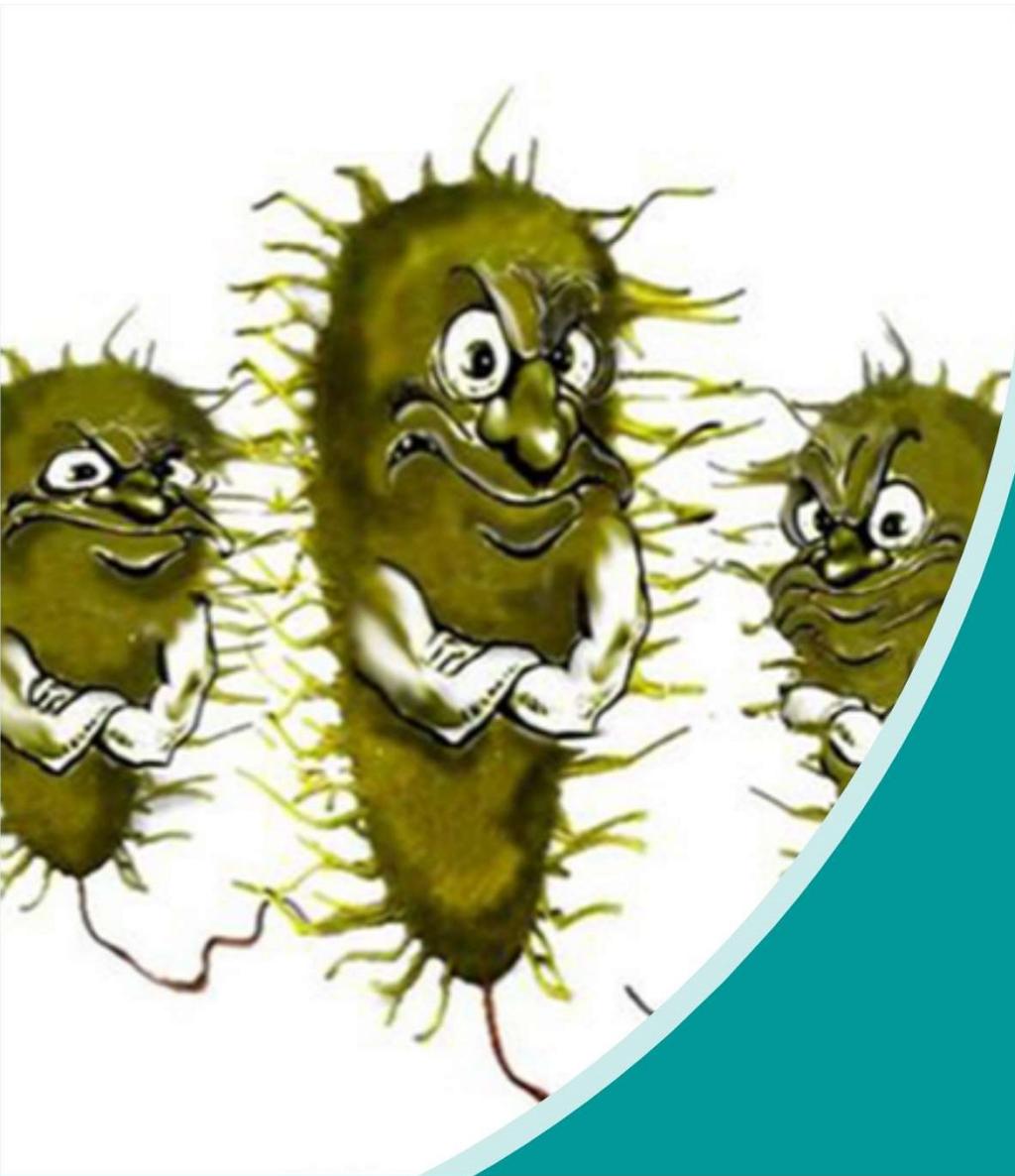
Neutron Reflectivity of $2C_{18}E_{12}$ monolayers

$2C_{18}E_{12}$
monolayer



$2C_{18}E_{12}$
monolayer





Anti-microbial resistance



Common operations including caesarean sections and hip replacements could become **LETHAL** due to growing resistance to antibiotics, health officials warn

- Public Health England said cases of antibiotic-resistant blood infections on rise
- Crisis is getting worse amid growing concerns that drugs are losing their power
- Figures revealed there were 16,504 cases where antibiotics didn't work last year

By **DAILY MAIL REPORTER**

PUBLISHED: 02:08, 23 October 2018 | **UPDATED:** 10:40, 23 October 2018



More than 3 million operations and cancer treatments a year in England may become life-threatening without antibiotics.

Public Health England warned that cases of antibiotic-resistant blood infections have risen by more than a third in just four years.

Experts say the crisis is getting worse amid growing concerns that the drugs are losing their power and can no longer treat many infections. Without antibiotics, infections related to surgery could double, putting people at risk of dangerous complications, health officials say.

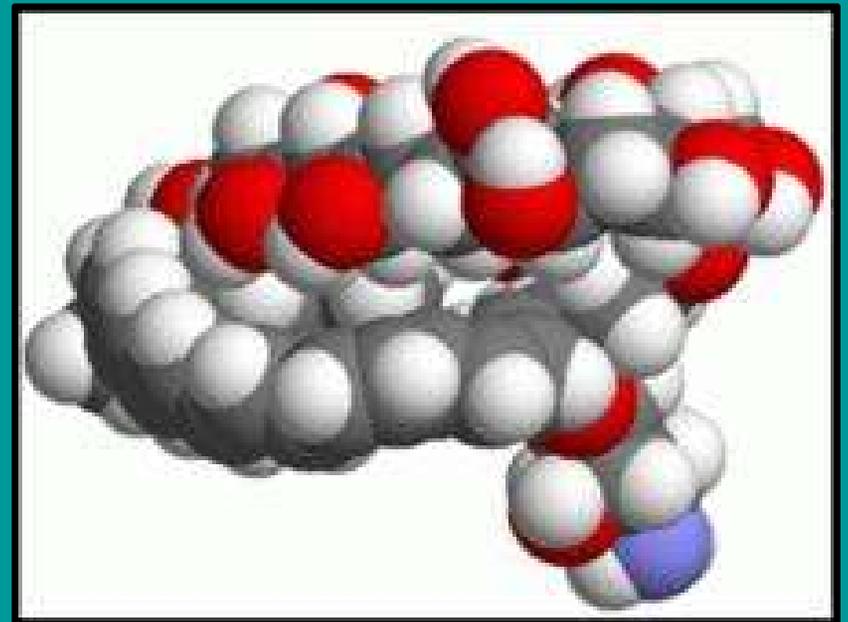
If the Daily Mail says it's a problem, then ...

Amphotericin

First-line treatment for deep-seated systemic fungal infections (eg, infections of the lungs in AIDS and chemotherapy patients)

Increasing incidence of amphotericin-resistant fungal strains

Amphotericin-induced kidney failure



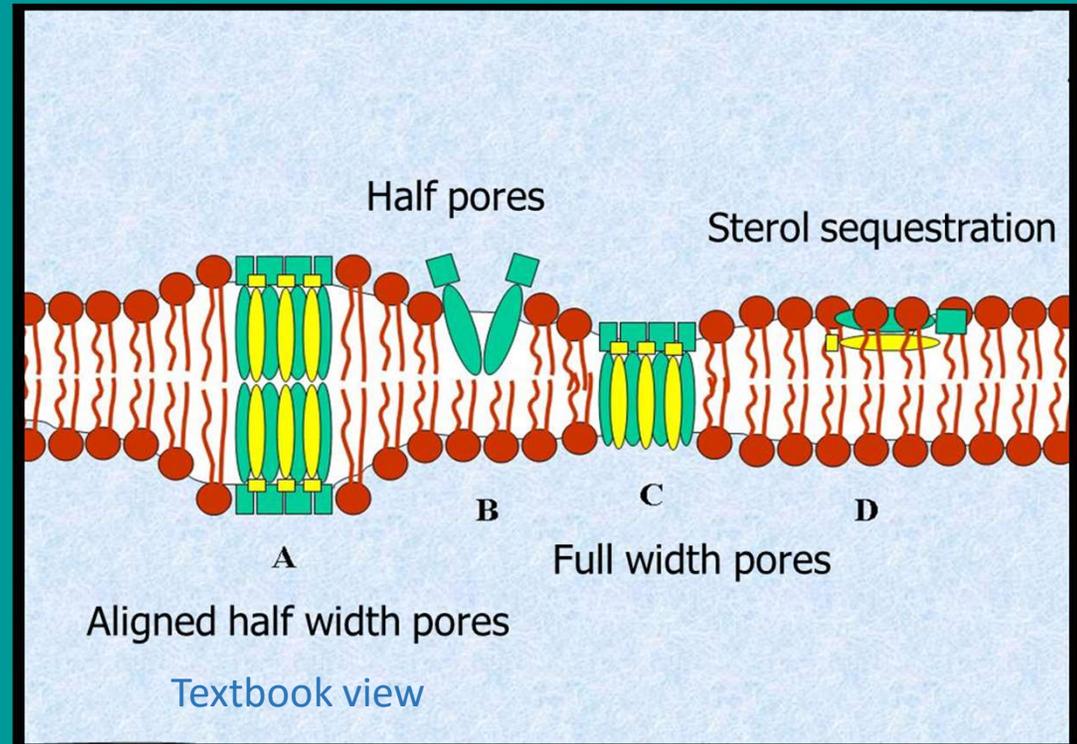
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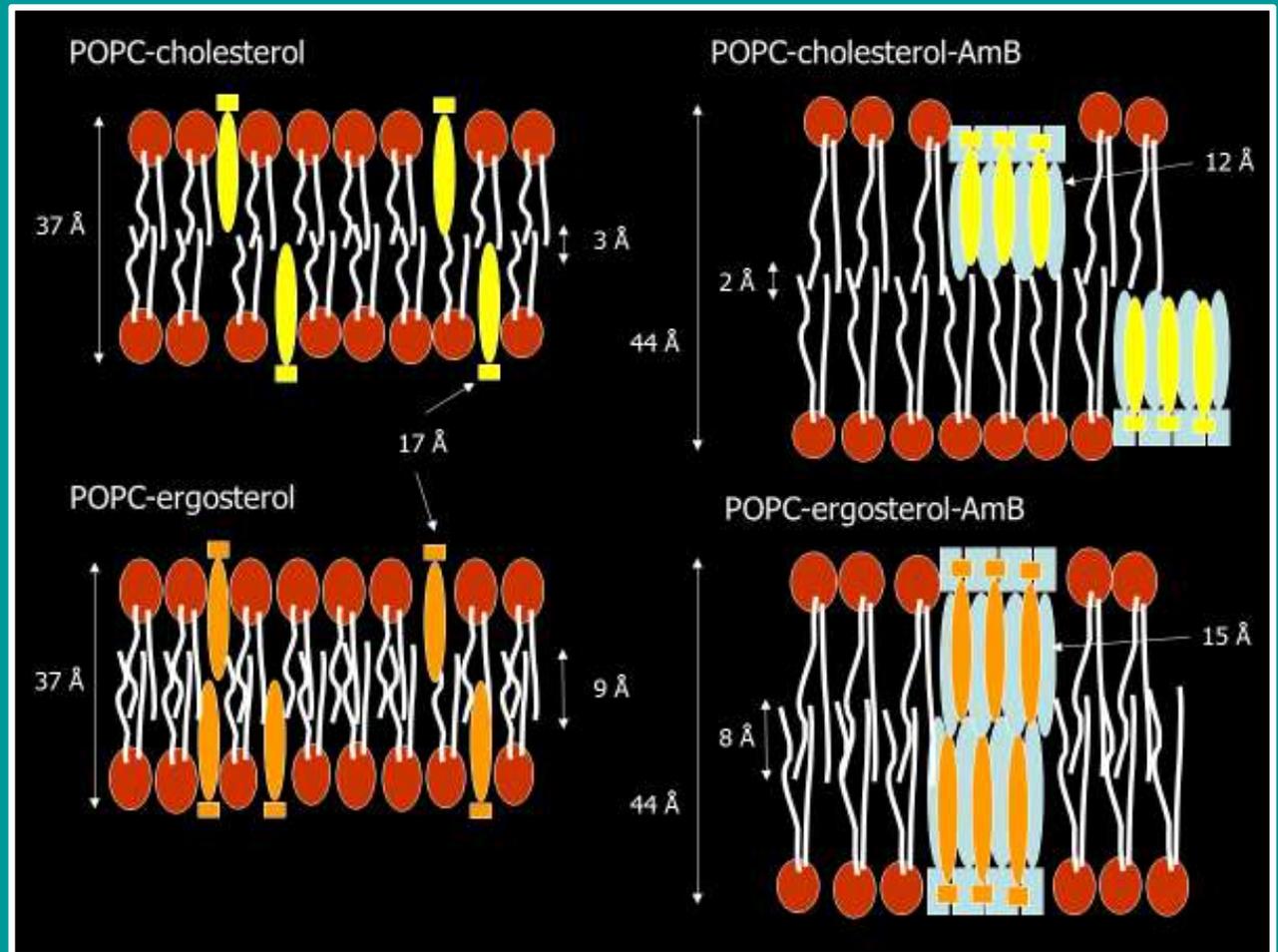
Different researchers, using different techniques, to investigate different systems ...



... get different results, and infer different mechanisms

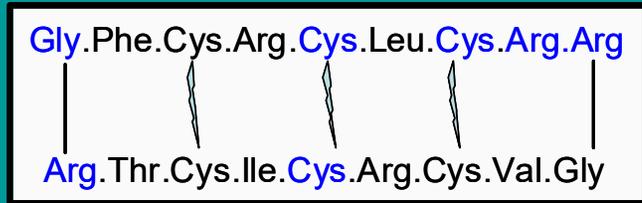
Through a combination of static and dynamic SANS, neutron reflectivity and neutron lamellar diffraction experiments

Foglia *et al.* (2011) *Biochim Biophys Acta* **1808**:1574
Foglia *et al.* (2012) *Sci Rep* **2**:778
Foglia *et al.* (2014) *Langmuir* **30**:9147
Foglia *et al.* (2015) *Langmuir* **31**:8042

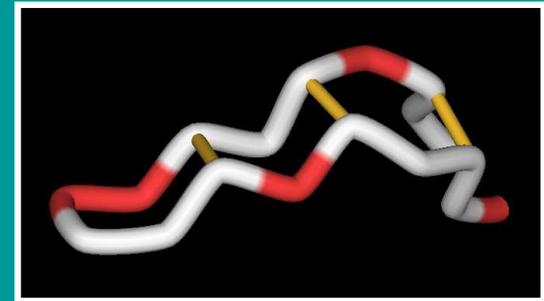




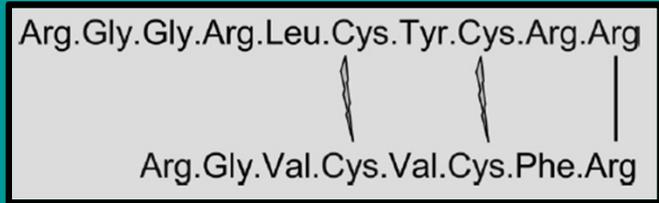
Rhesus θ -Defensin (RTD-1)



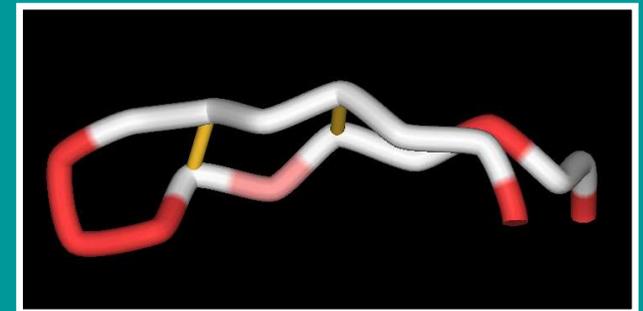
Not cytotoxic, not haemolytic

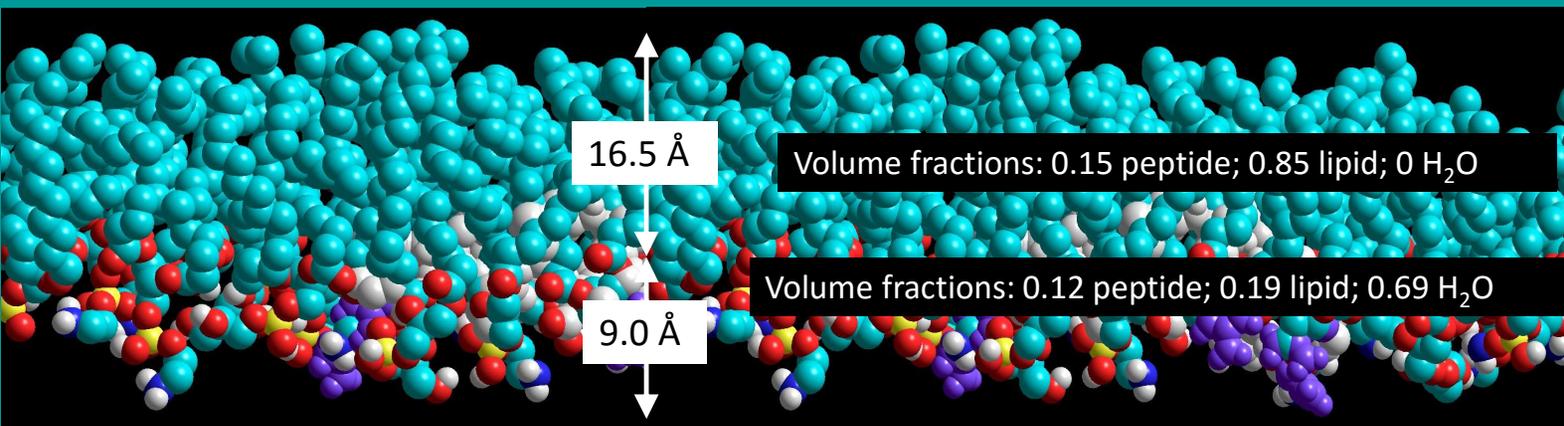


Porcine Protegrin-1 (PG-1)



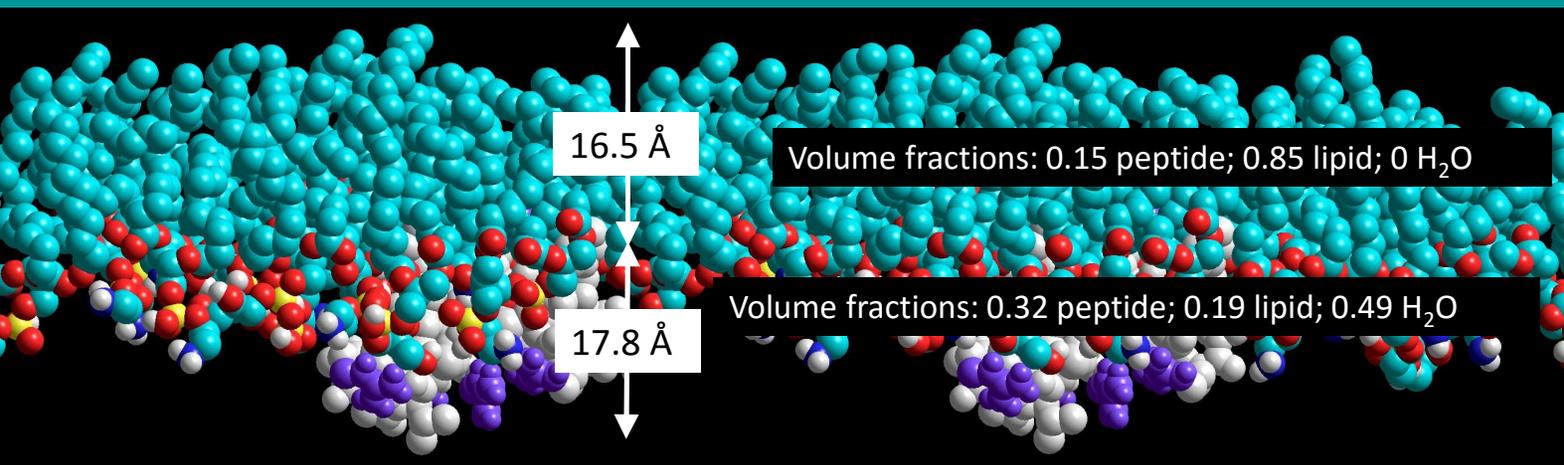
Toxic to fibroblasts; lyses erythrocytes





PG-1

Neutron reflectivity experiments show that PG-1 sits more favourably at the air-water interface
 - and so more readily forms transmembrane pores and is more haemolytic



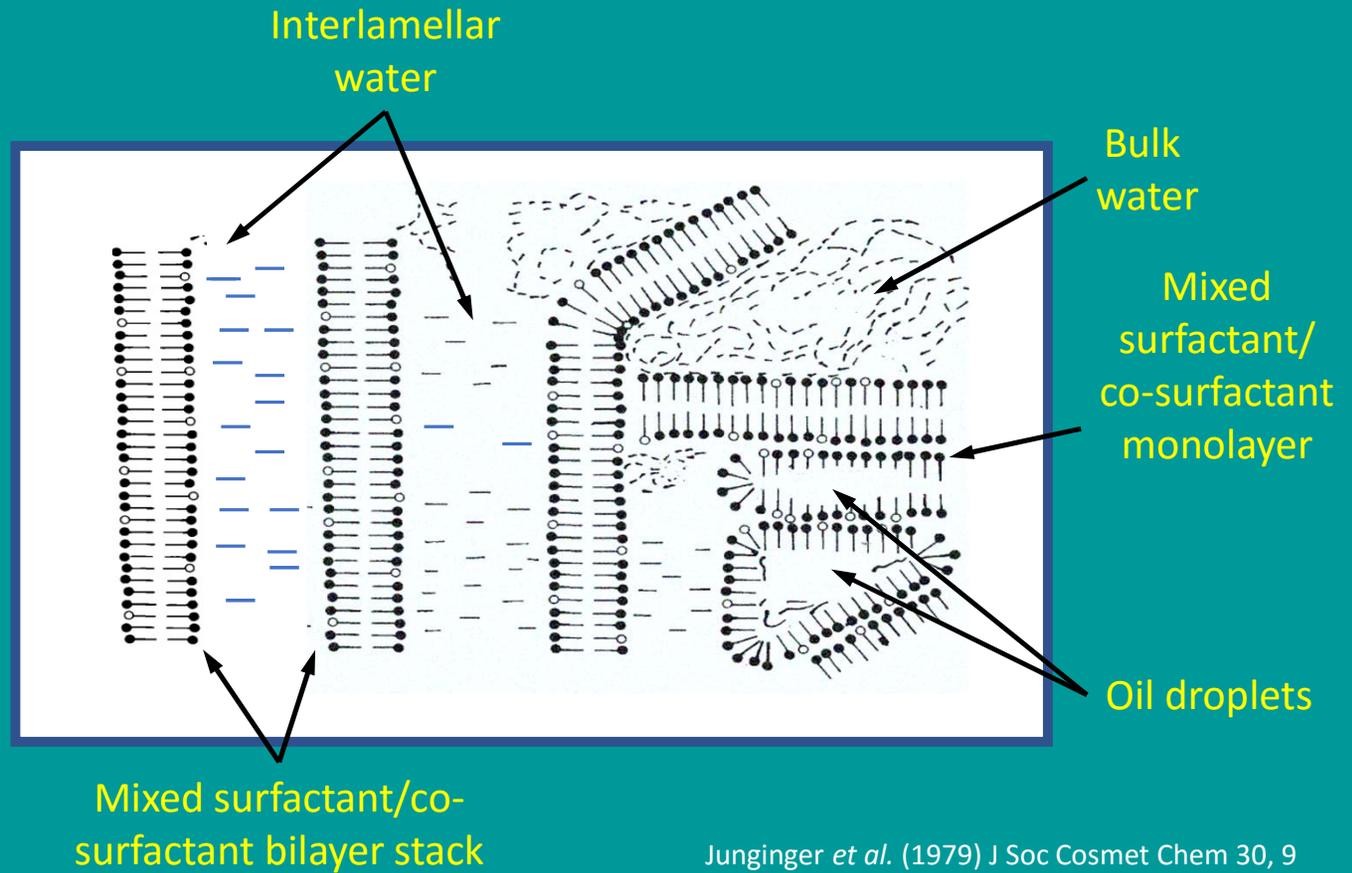
RTD-1



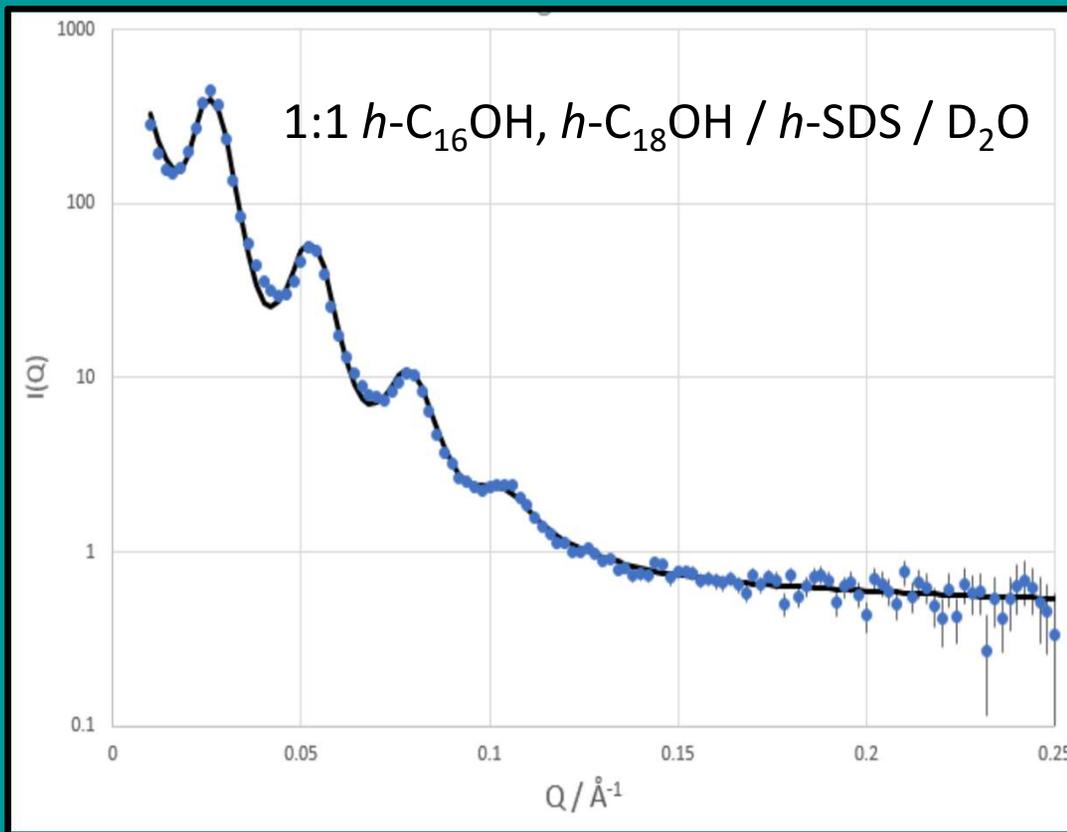
Pharmaceutical Creams

Textbook Picture of an Aqueous Cream

Oil (20%)
Water (70%)
Surfactant
Co-surfactant(s)



SANS Studies of Protiated Systems



FISH Model-fitting
Kotlarchyk & Ritzau (1991)

Layer thickness (L): $47 \pm 1 \text{\AA}$

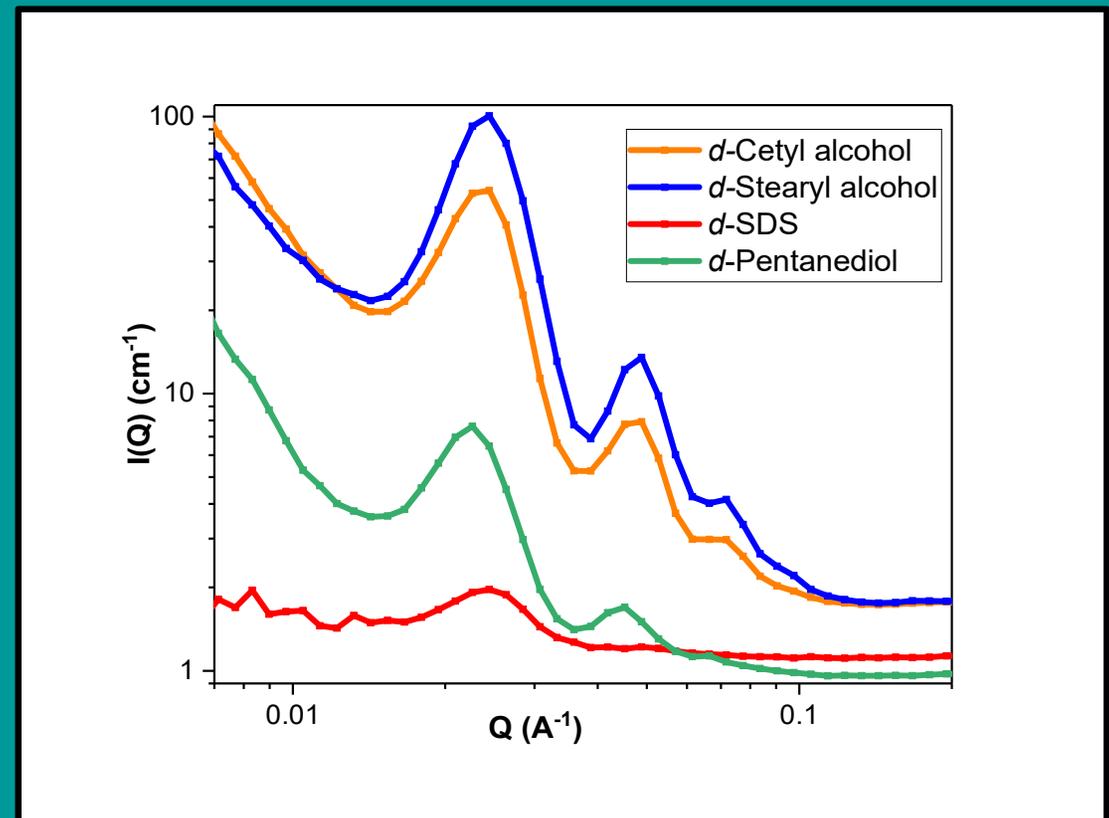
d -spacing (D): $237 \pm 2 \text{\AA}$

Lamellarity (M): 4

SANS Studies of Selectively Deuterated Systems

SANS for $d\text{-C}_{16}\text{OH}$, $d\text{-C}_{18}\text{OH}$ and (surprisingly) $d\text{-pentanediol}$ creams show clear Bragg peaks with the same d -spacing (263 Å) – all three components thus co-located in the lamellae

SANS for $d\text{-SDS}$ cream (surprisingly) lacking in Bragg peaks – located outside the lamellae?
SDS micelle-like aggregates?



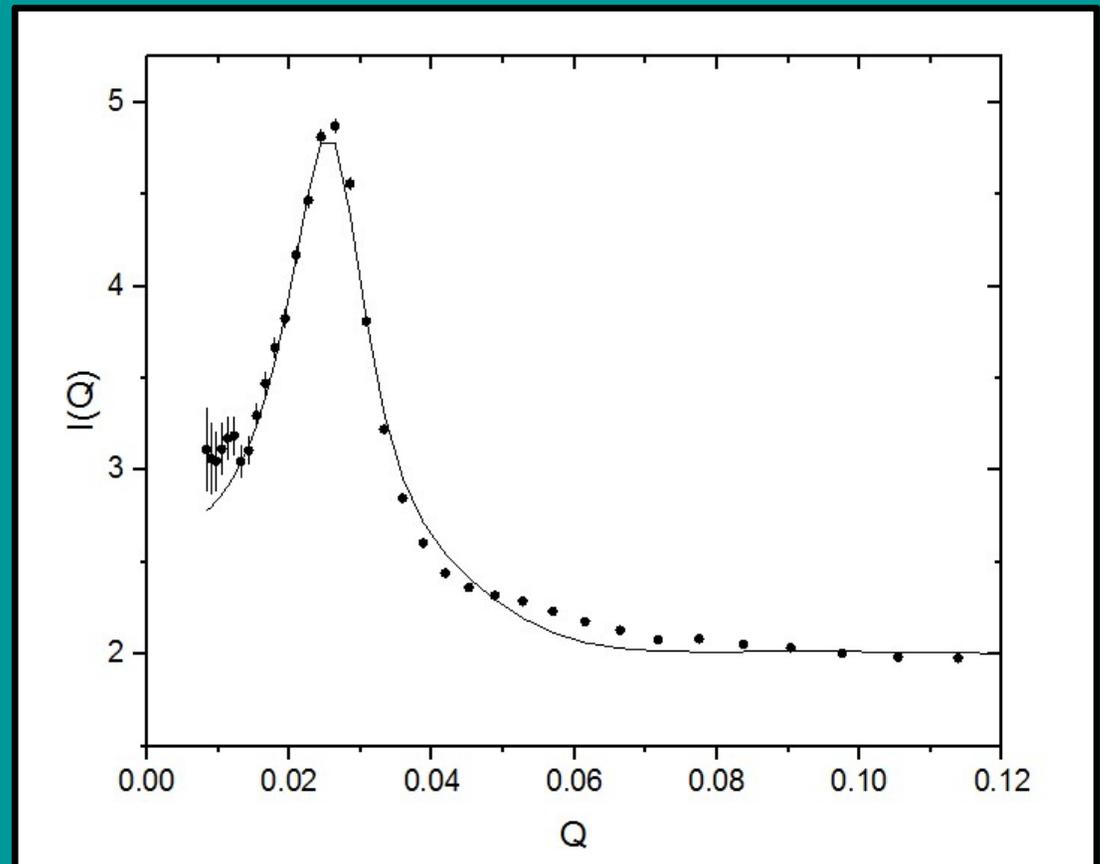
SANS Studies of Selectively Deuterated Systems

FISH model fit:

Highly charged prolate ellipsoids, with
semi-axis lengths: $56 \text{ \AA} \times 56 \text{ \AA} \times 134 \text{ \AA}$

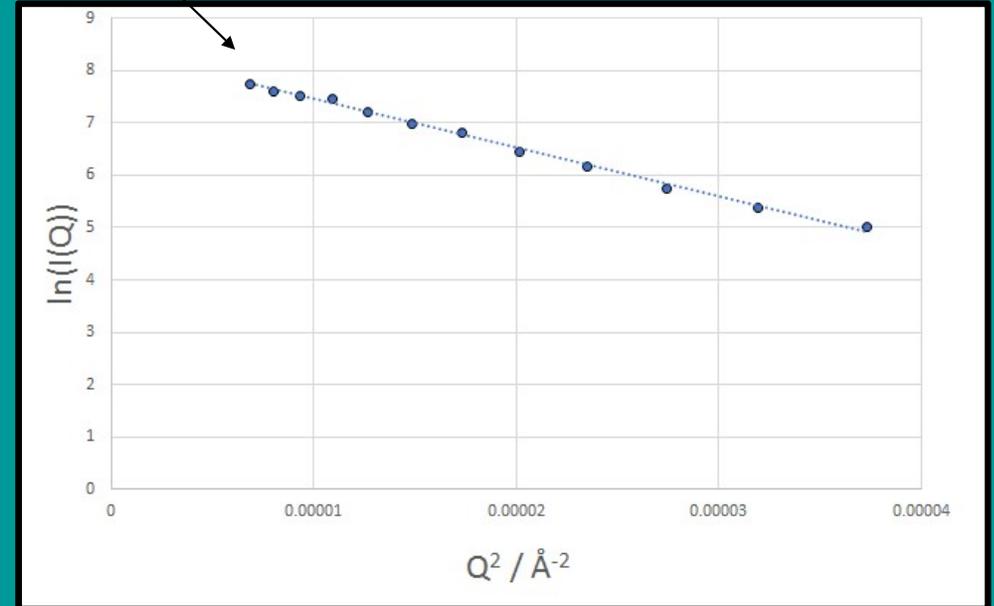
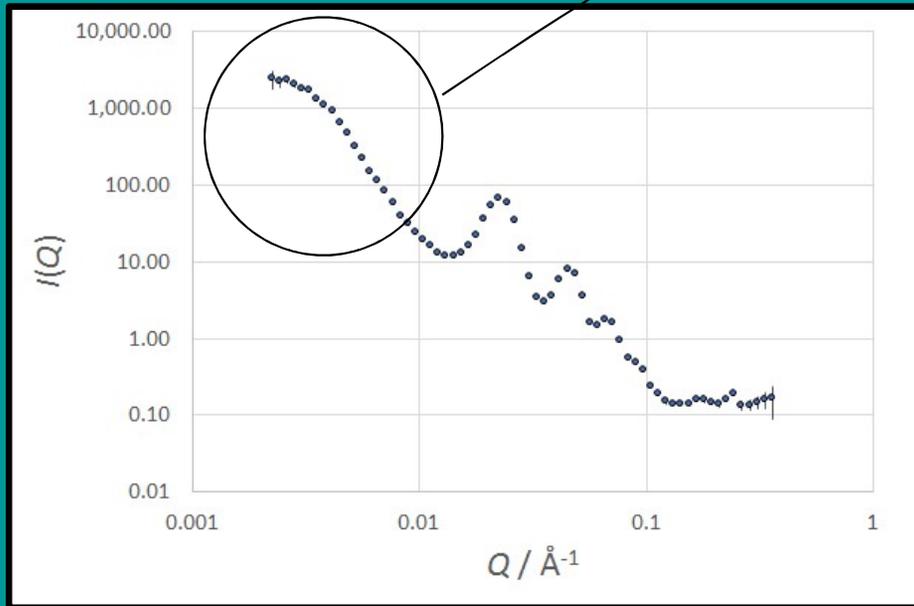
Strong interparticle interaction (modelled
with Hayter-Penfold structure factor)

Mixed SDS / cetyl alcohol micelles?



VSANS Studies of Protiated Systems (on Zoom)

Spherical aggregates of $R_g = 527 \text{ \AA}$
Assuming homogenous sld, $D \approx 0.1 \text{ \mu m}$



100 nm oil droplets? Crystallites of C16/C18 alcohols?

Simple Pharmaceutical Creams?

- Excipients are *not* located where expected
- Colloidal nature *not* as presented in text books
- More to creams than meets the eye; Not so simple after all!

Thank you for listening!