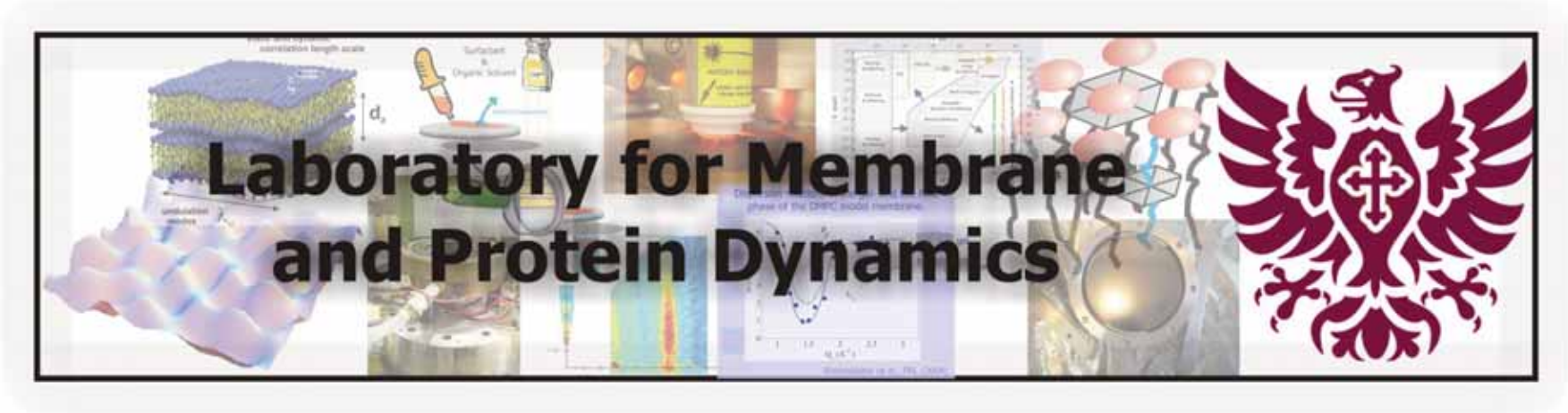
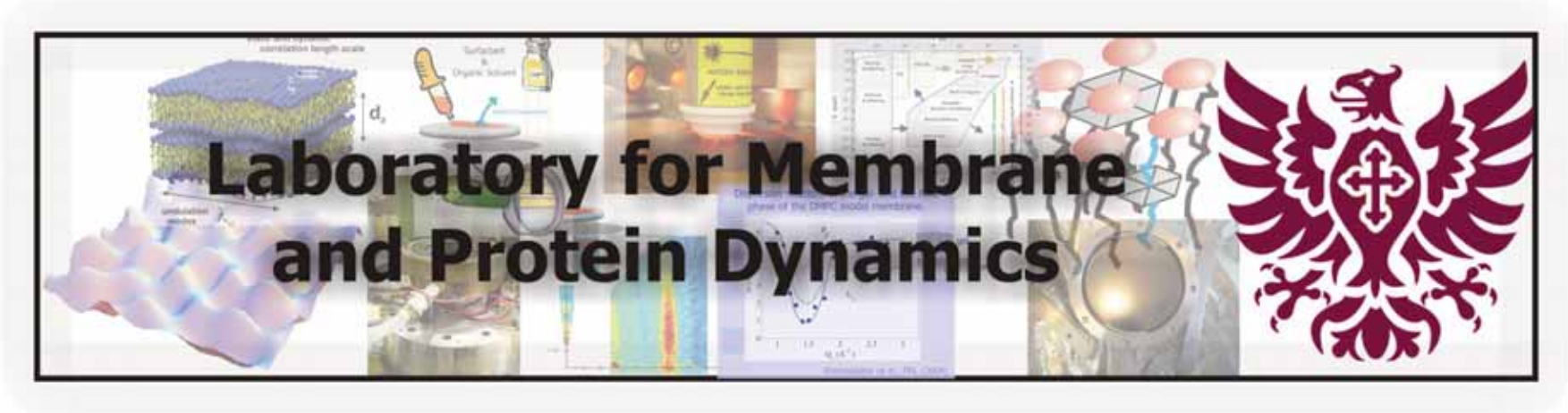


Maikel C. Rheinstädter
Laboratory for Membrane and Protein Dynamics
McMaster University, Hamilton ON
and
Canadian Neutron Beam Centre, NRC, Chalk River ON

XDL2011
Frontier Science with X-ray Correlation Spectroscopies using Continuous Sources
June 29-30, 2011
Cornell University, Ithaca NY

Nanobiology: Membranes and Proteins in Motion



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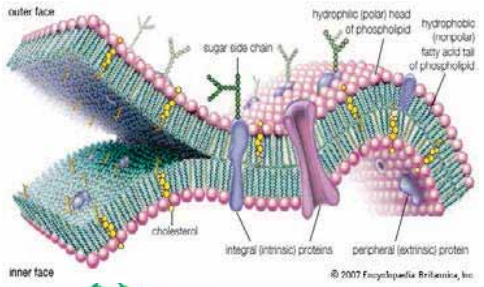
Scattering experiments outside of the comfort zone

Challenge

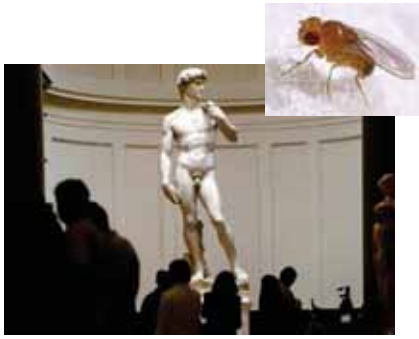


Hierarchy of biological systems:

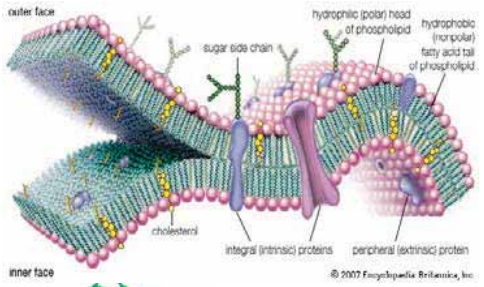
Organism
Organ
Cell
Organelle
Cytoskeleton
Functional Module
Biological Macromolecule
Molecule
Atom

years and meters

picoseconds and Angstroems



Challenge



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years and meters

picoseconds and Angstroems

NEUTRONS FOR SCIENCE

EUROPEAN SPALLATION SOURCE

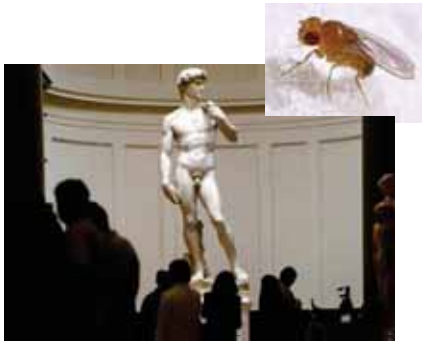
SPALLATION NEUTRON

CHESS

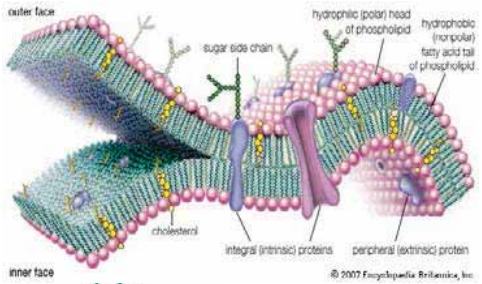
ties Council

Advanced Photon Source

Argonne National Laboratory



Challenge



Hierarchy of biological systems:

Atom
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Biological Macromolecule
Functional Module
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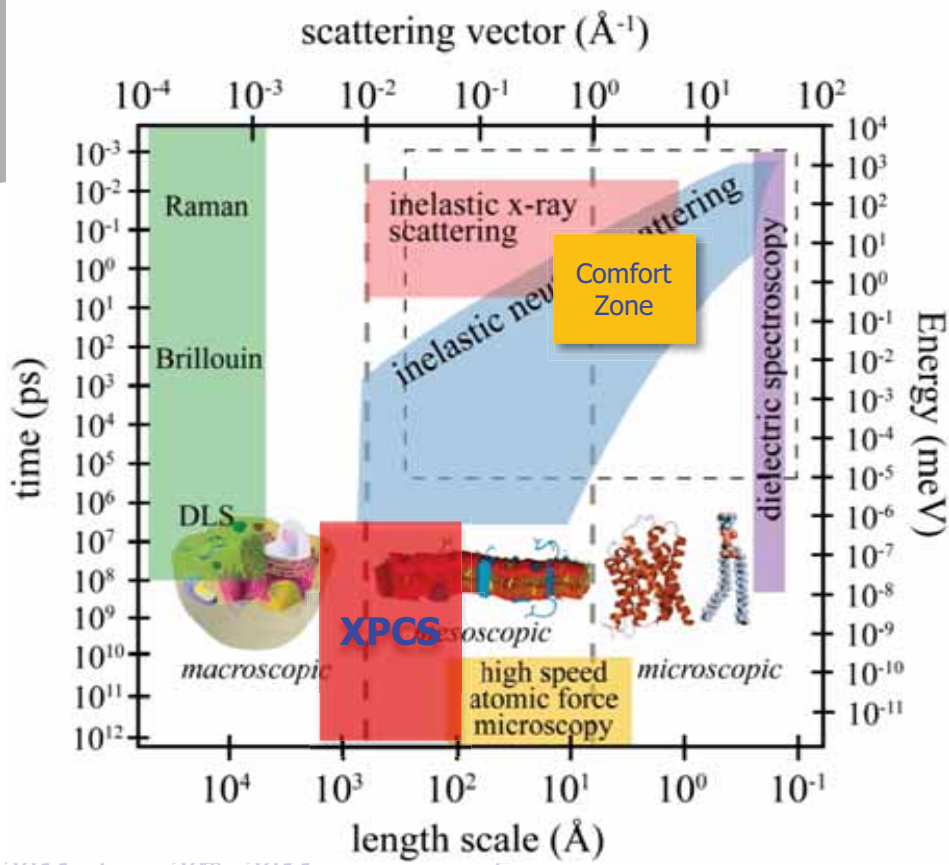
Organ
Organism

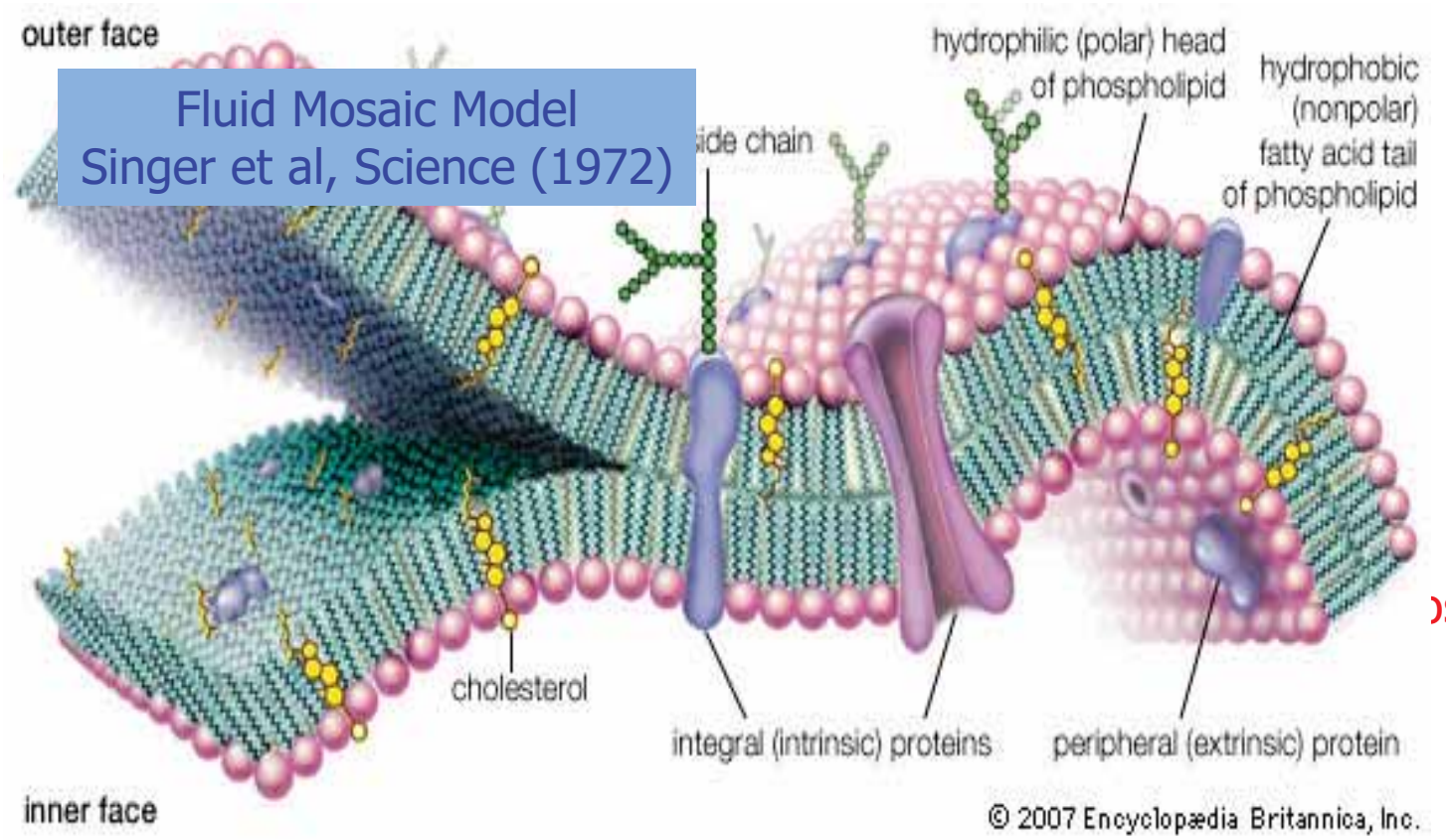
picoseconds and Angstroems

years and meters



Target: Molecular Biology and Nano Medicine

Laboratory for Membrane and Protein Dynamics



Fluid Mosaic Model
Singer et al, Science (1972)

osis

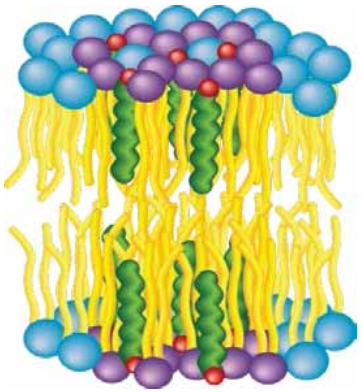
Target: Molecular Biology and Nano Medicine

Laboratory for Membrane and Protein Dynamics

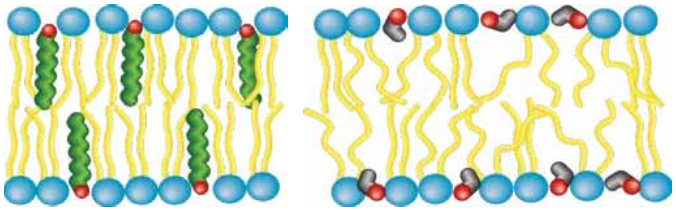
... are more than just passive barriers

Lipid Membranes

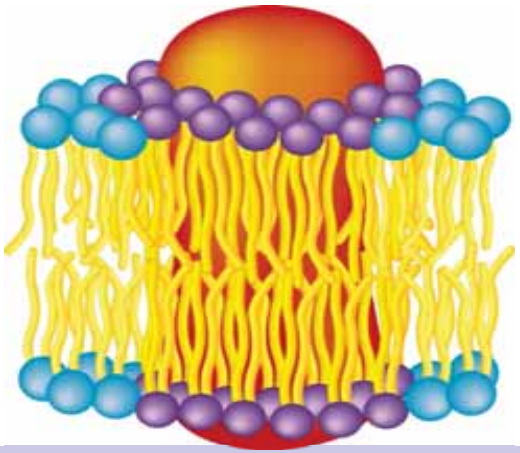
Rafts



Role of Macromolecules



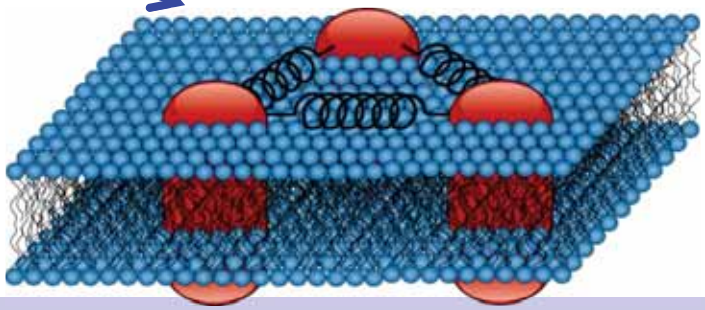
cholesterol



Creation of Protein Nano-environments

Alzheimer's

Apoptosis

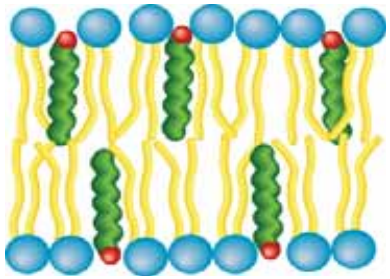


Membrane Mediated Protein Interactions

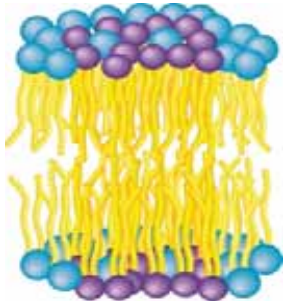
Overview of the LMPD

Laboratory for Membrane and Protein Dynamics

Dynamics of Lipid/Cholesterol Systems



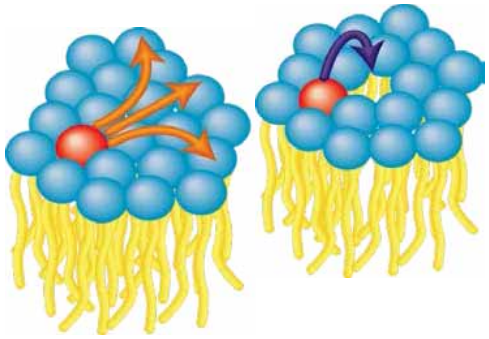
Nanodomains and Coexistant Phases in Lipid Membranes



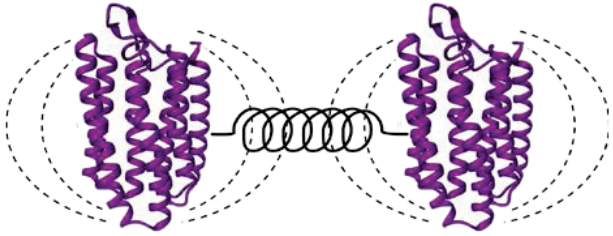
Structure and Dynamics of Model Brain Membranes

Biomedical Applications:
Neurodegenerative Disorders
Apoptosis

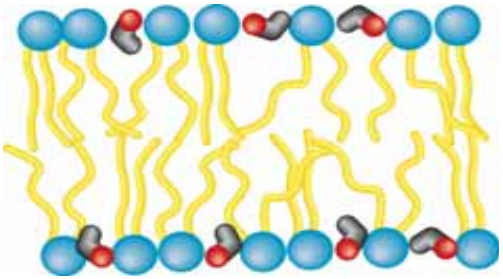
Lipid and Protein Diffusion



Protein-Protein Interactions



Drug Enhancers and Membrane Permeability

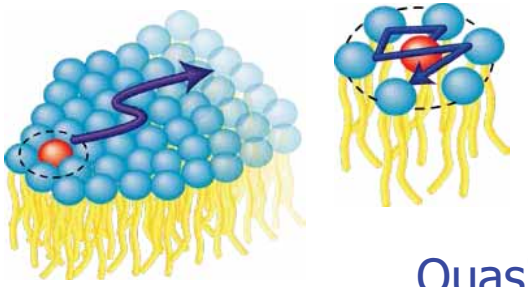


Diffusion in Membranes and Cells – Brownian Motion or Collective Transport?

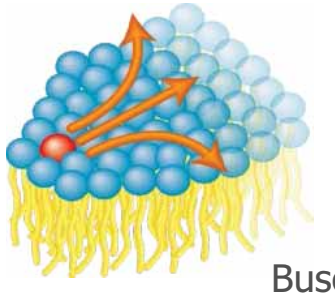
Laboratory for Membrane and Protein Dynamics

Previous Models

continuous diffusion with rattling in the cage



Recent Model (2010)

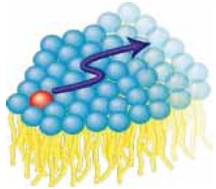


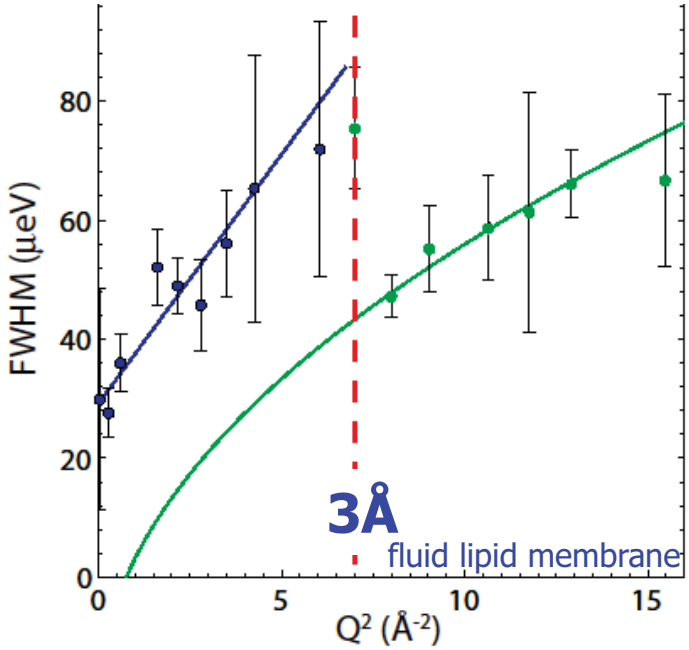
flow-like motion

Busch, *et. al., JACS*, (2010)

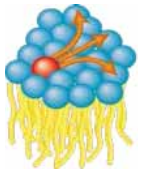
Quasi-elastic Neutron Scattering

continuous?





ballistic

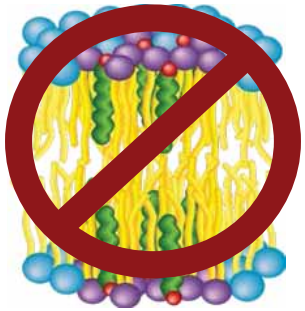


Armstrong, *et. al., Soft Matter* (2010)
Armstrong, *et. al.,* submitted
Rheinstadter *et al.*, **PRL** (2008)

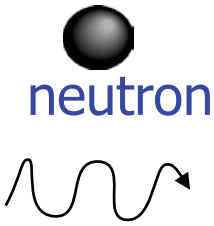
Nanodomains - Rafts

Laboratory for Membrane and Protein Dynamics

Nanometer sized structures that fluctuate on **nano-microsecond** time scales

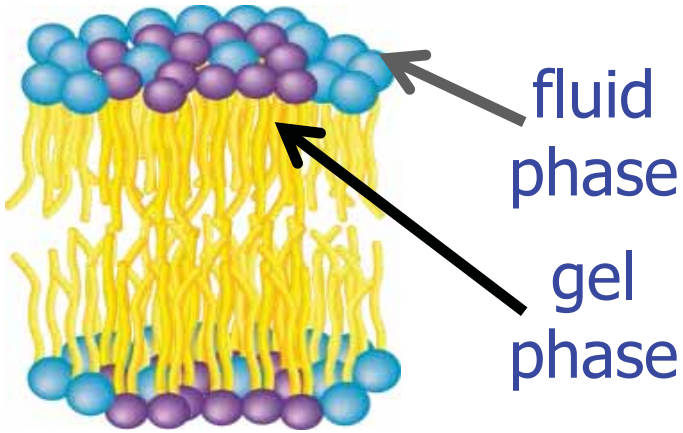


not been observed

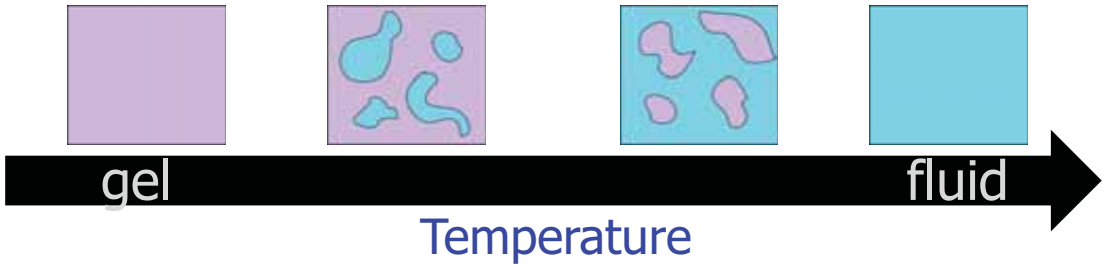


wave packet

coherence length ξ



Model system: single component membrane close to the phase transition

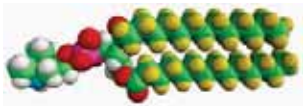


Nanodomains

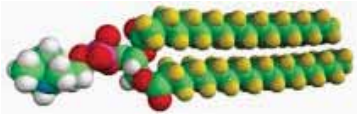
Laboratory for Membrane and Protein Dynamics

Neutron diffraction

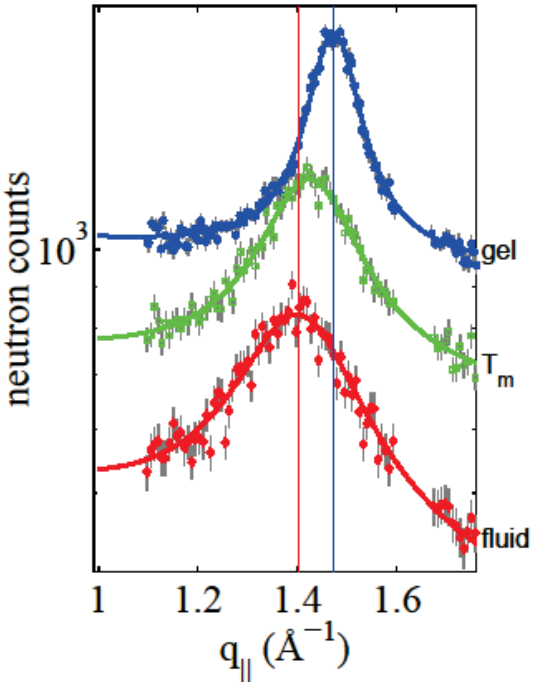
14 C atoms

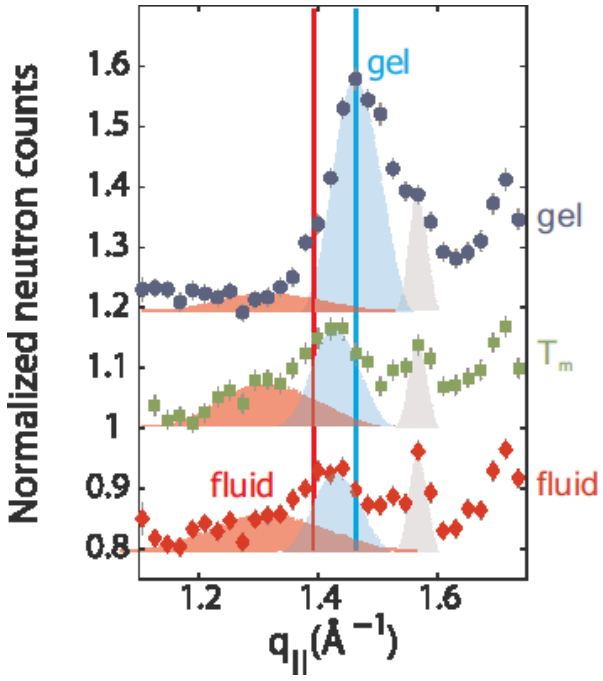


18 C atoms

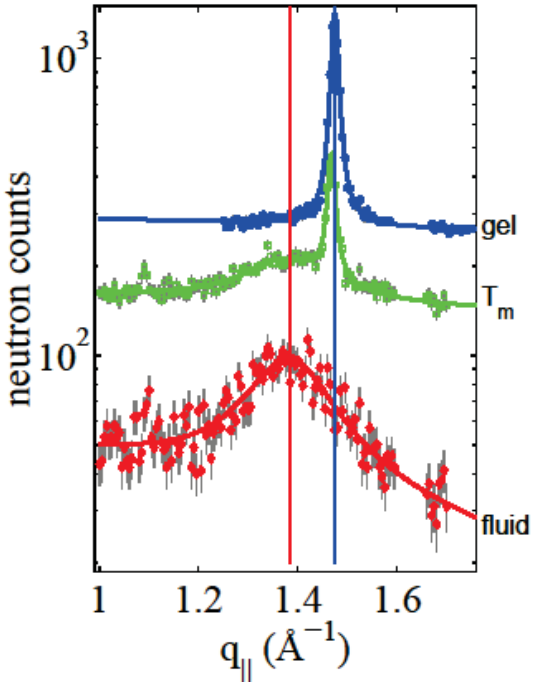


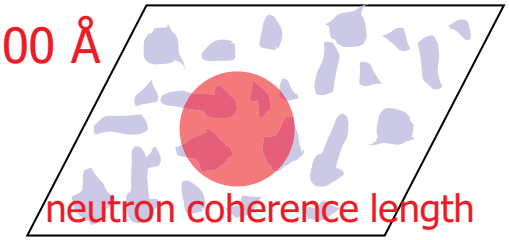
DMPC

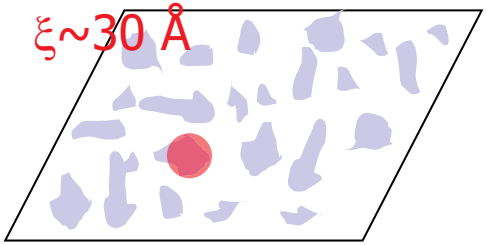


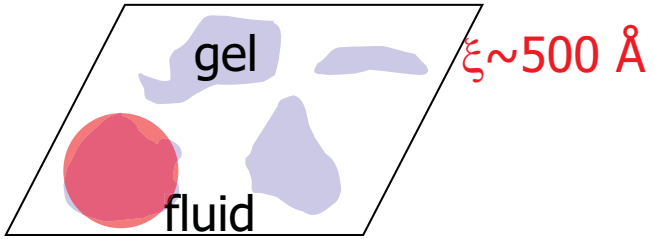


DSPC









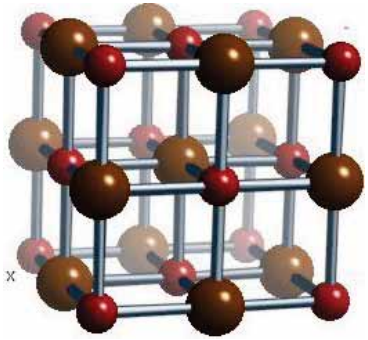
Coherence Length

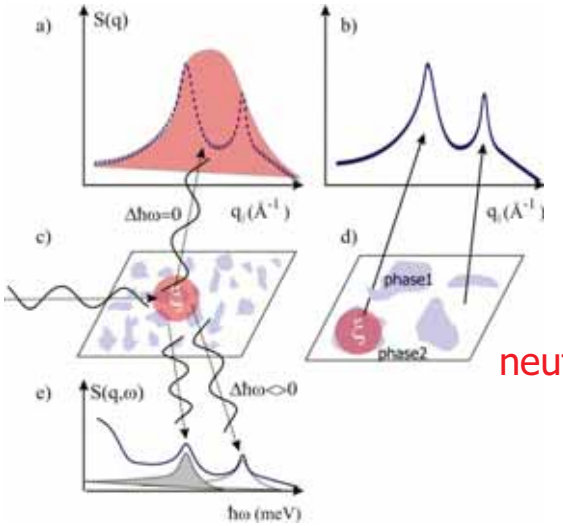
Laboratory for Membrane and Protein Dynamics

Neutron (longitudinal) coherence length:

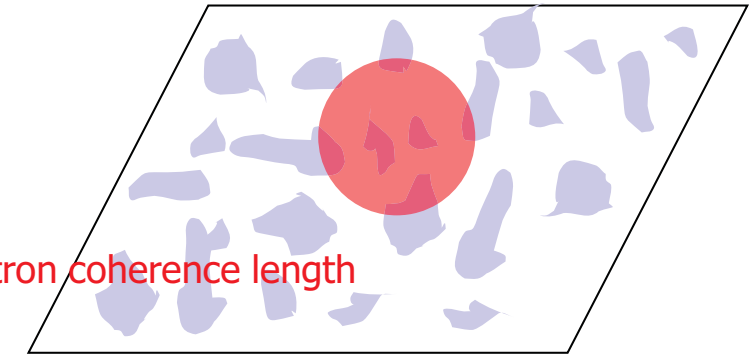
$$\xi \approx \frac{\lambda^2}{\Delta\lambda} \approx \frac{\sqrt{E}}{\Delta E}$$

well ordered





disordered



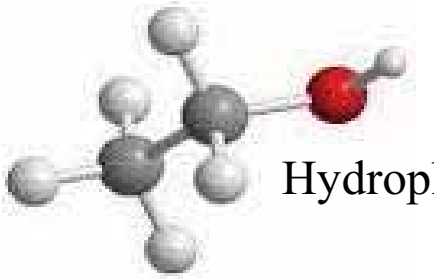
high spatial resolution ⟵ good $\Delta\lambda$ ⟶ '**poor**' spatial resolution

Membrane Properties

Laboratory for Membrane and Protein Dynamics

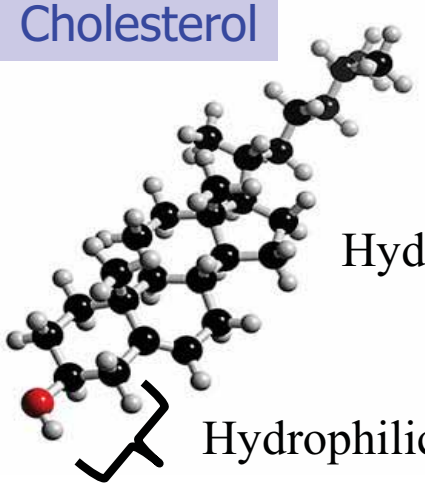
Membrane active molecules

Ethanol



Hydrophillic

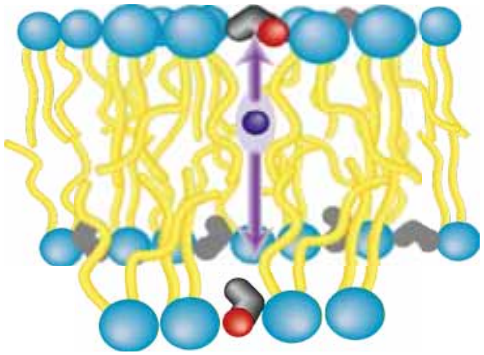
Cholesterol

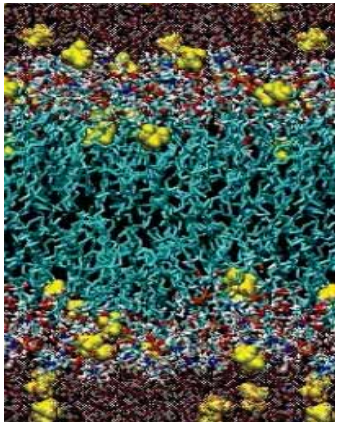


Hydrophobic body

Hydrophilic head

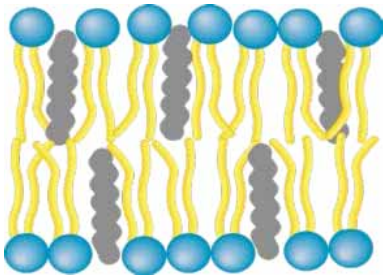
Model Drug Enhancer



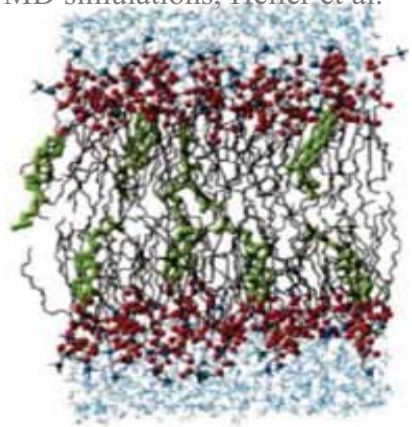


M. Tarek, University of Nancy

Controls Membrane Rigidity



MD simulations, Heller et al.

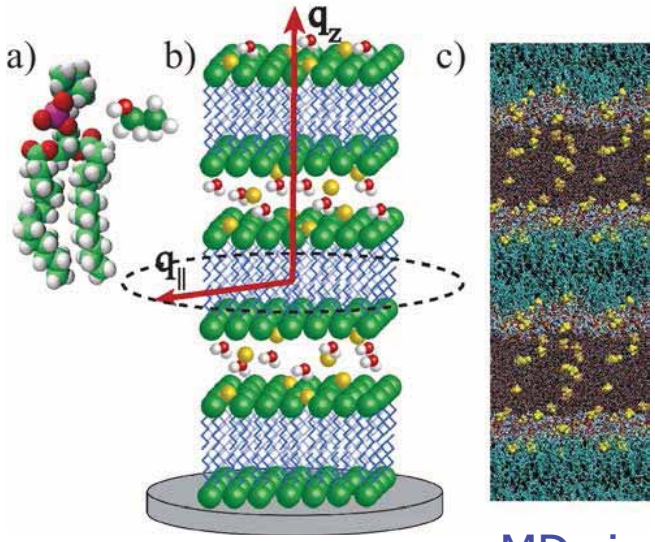


enhances → membrane fluctuations ← suppresses

Quantitative Molecular Biology – Drug Enhancer

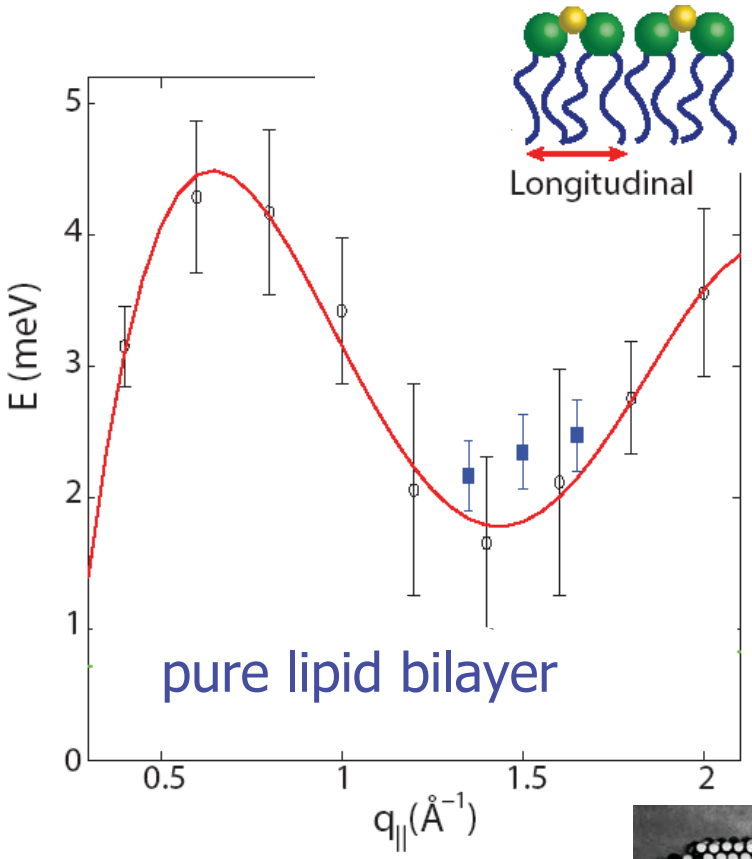
Laboratory for Membrane and Protein Dynamics

IN12@ILL (triple-axis)



DMPC/5% Ethanol

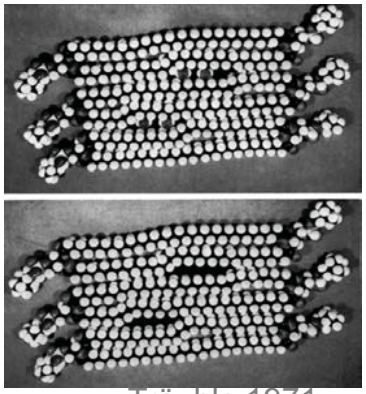
MD simulations



longitudinal phonon

transverse phonon

Quantitative access to membrane properties
- drug development and sensor applications



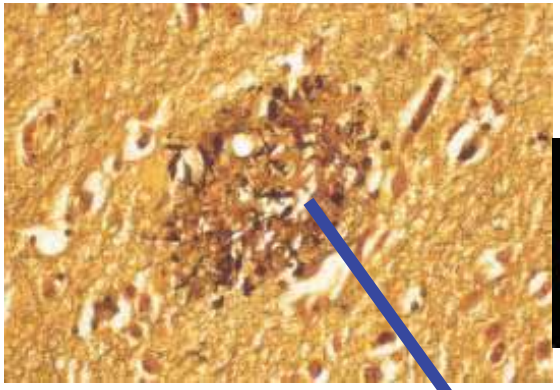
Träuble 1971

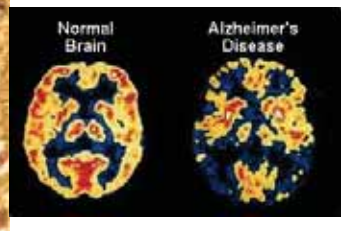
Kaye et al., PRE (2011)

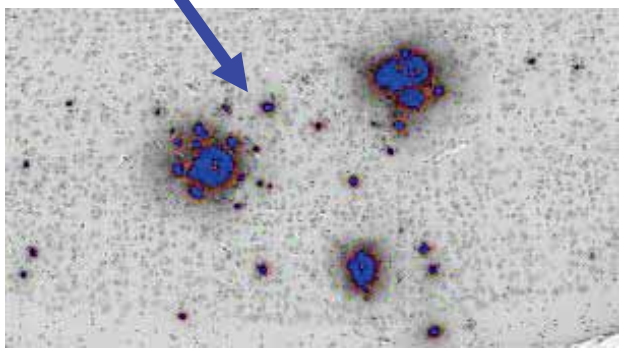
Protein-Protein Interactions

Alzheimer's Disease

Neurotoxic senile plaques



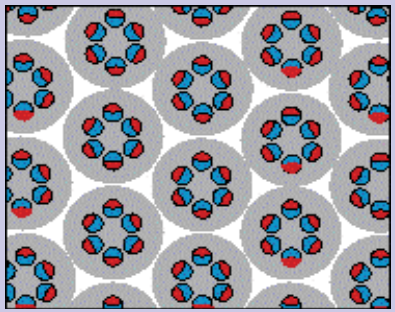


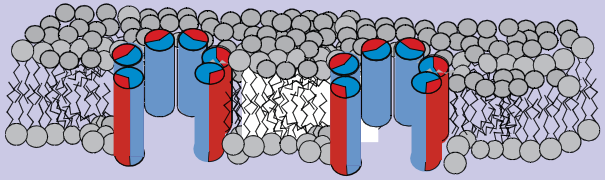


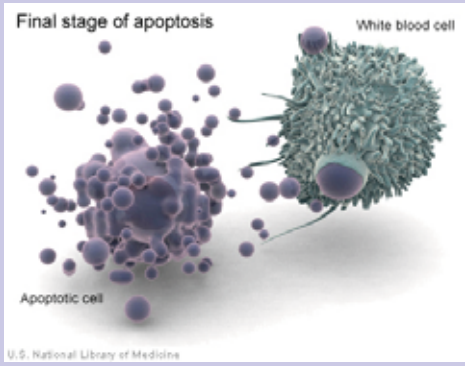
Aggregation of amyloid proteins

Cancer Research

Apoptosis – Programmed Cell Death







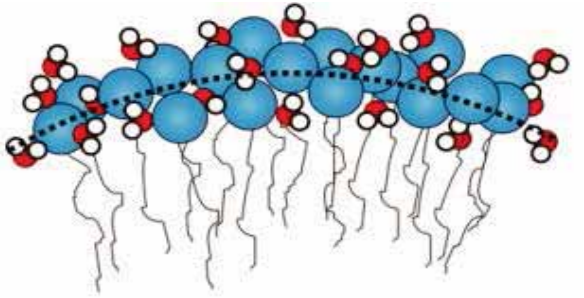
"Cancer's self destruct button"

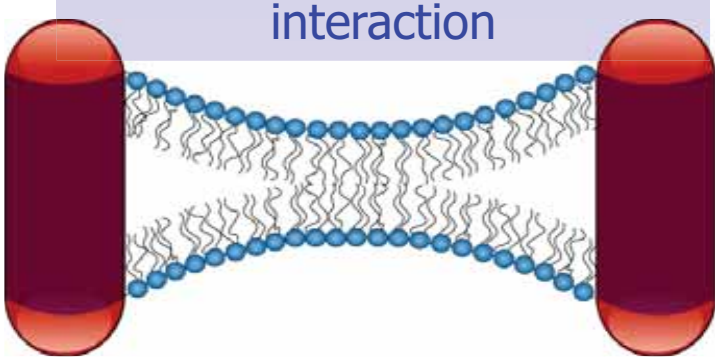
Protein-Protein Interactions

Laboratory for Membrane and Protein Dynamics

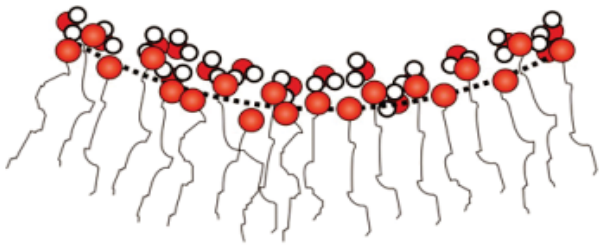
Membrane mediated elastic interaction

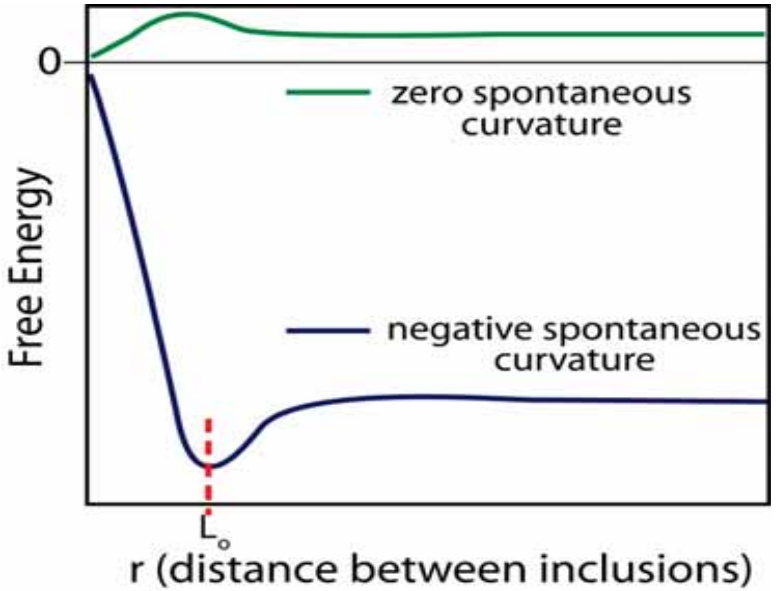
Positive Curvature

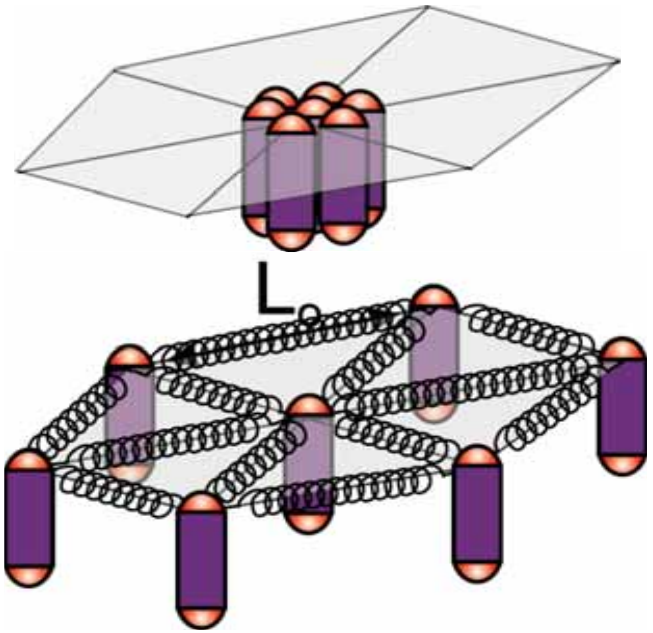




Negative Curvature





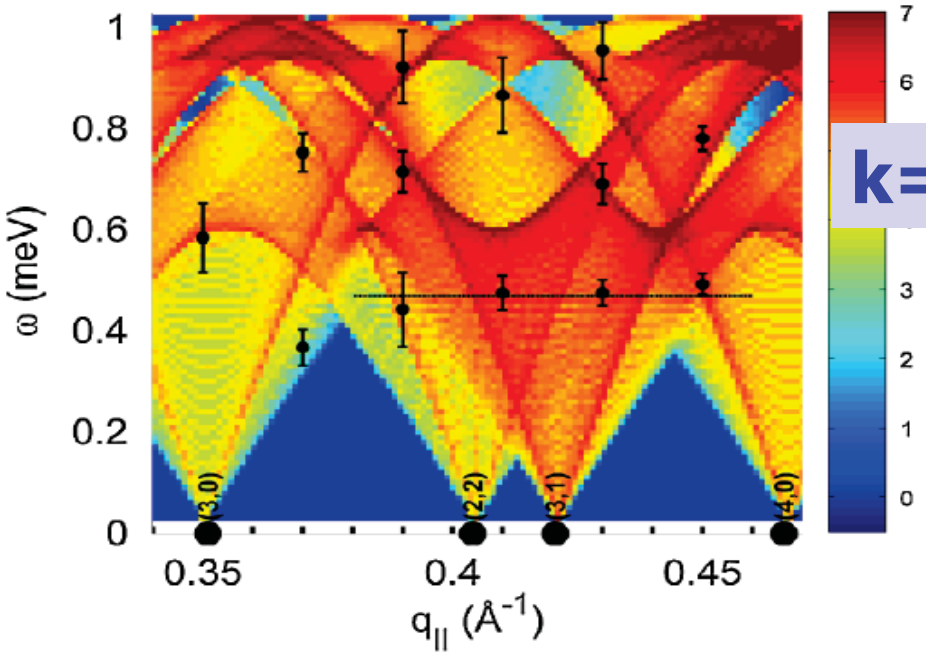


Armstrong et al., Protein and Peptide Letters (2010)

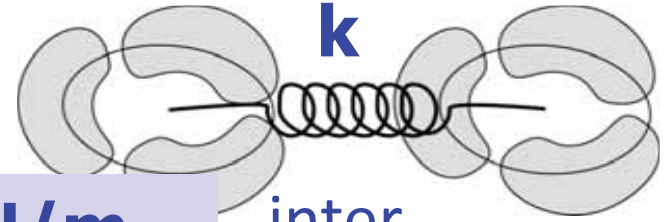
Protein-Protein Interactions

Laboratory for Membrane and Protein Dynamics

Fluctuation spectrum of the 2d protein lattice



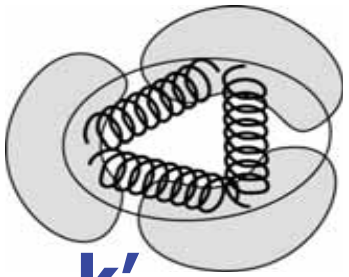
k=50N/m



inter

protein dynamics

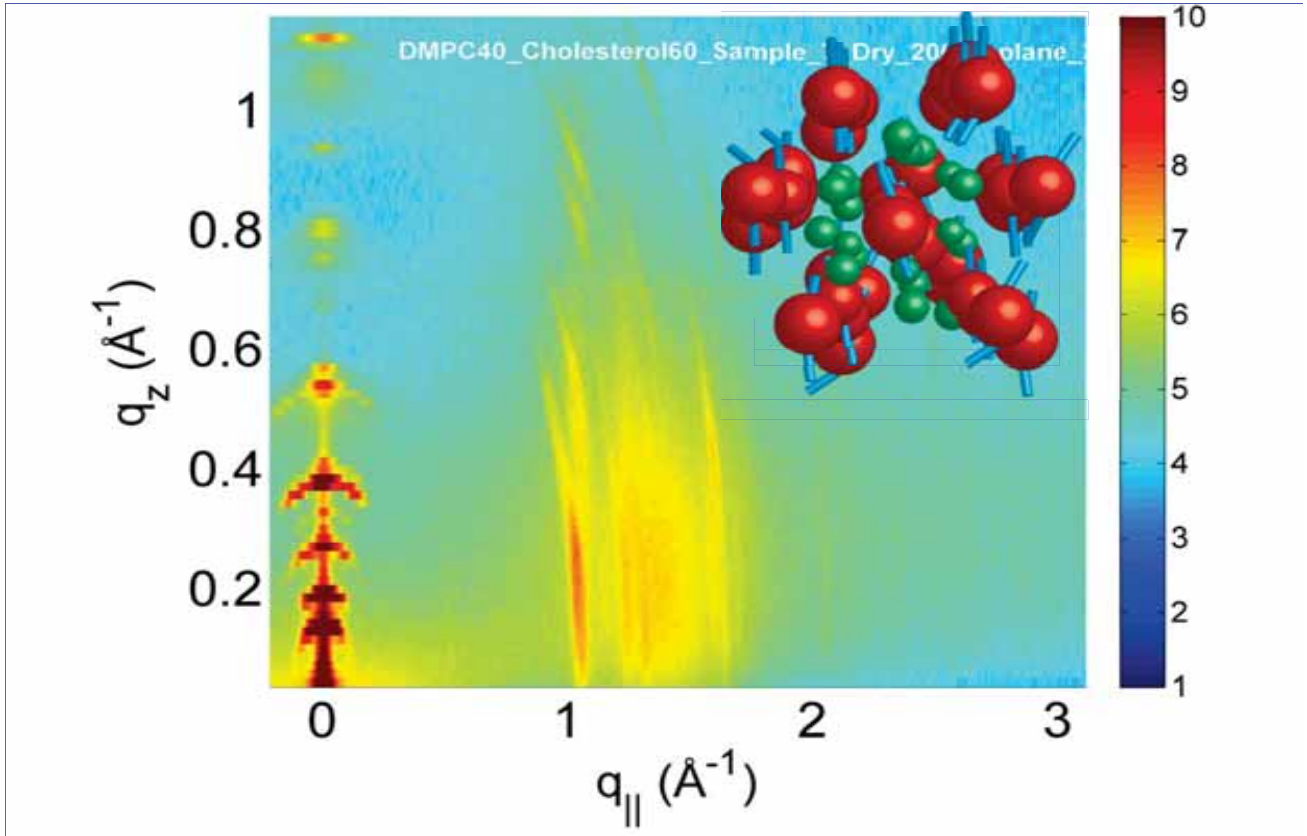
intra



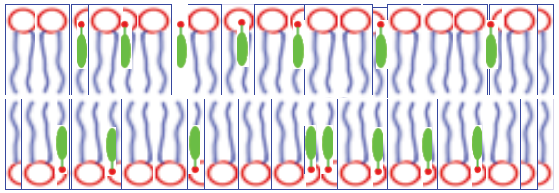
Neutrons and X-Rays measure protein-protein interactions in-situ under physiological conditions

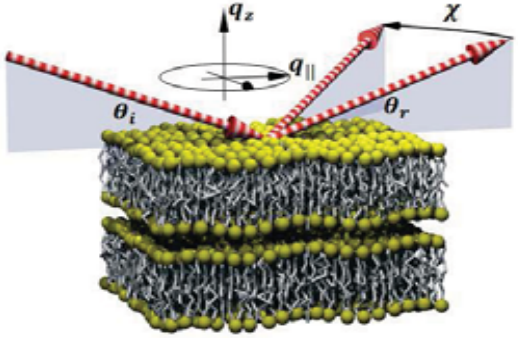
Rheinstadter et al., Physical Review Letters (2009)

Effect of Cholesterol on Membrane Structure



40% DMPC
60% Cholesterol

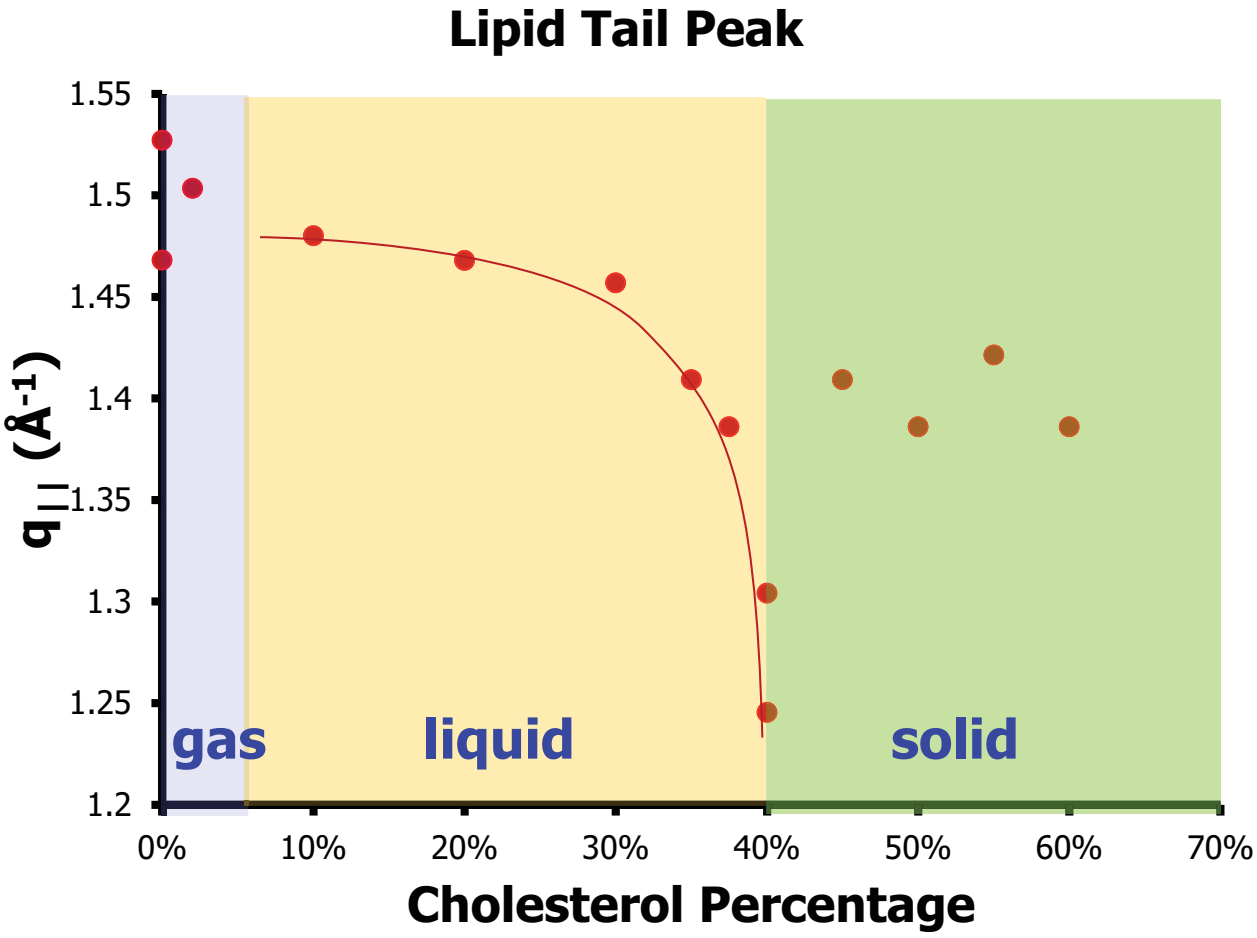




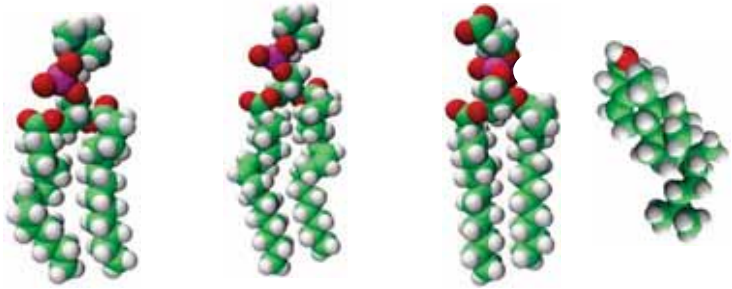
Cholesterol %

0 10 20 30 40 50 60 70 80 90 100

Artificial Brain Membranes



Mixture of 3 lipid molecules and varying levels of cholesterol



saturated unsaturated charged cholesterol

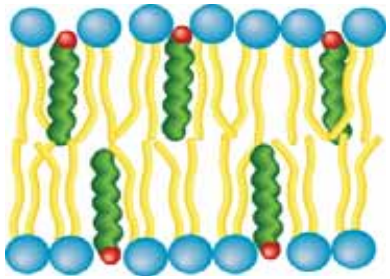
Amyloid-β protein

Study protein-protein interactions in model brain membranes

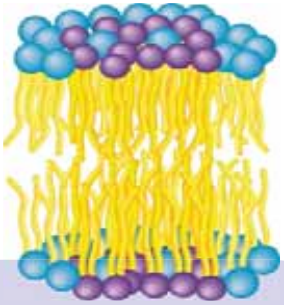
Summary

Laboratory for Membrane and Protein Dynamics

Dynamics of Lipid/Cholesterol Systems



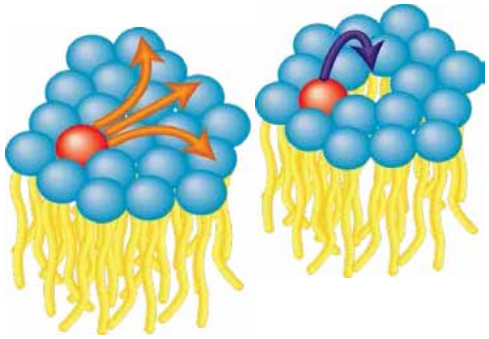
Nanodomains and Coexistant Phases in Lipid Membranes



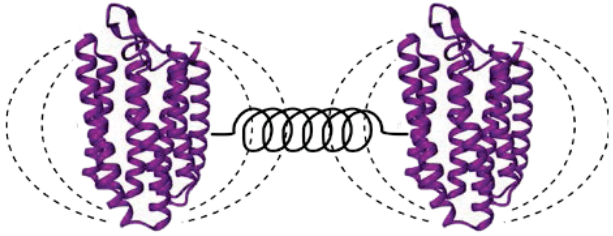
Structure and Dynamics of Model Brain Membranes

Biomedical Applications:
Neurodegenerative Disorders
Apoptosis
using X-Ray (XPCS?) and Neutron Scattering

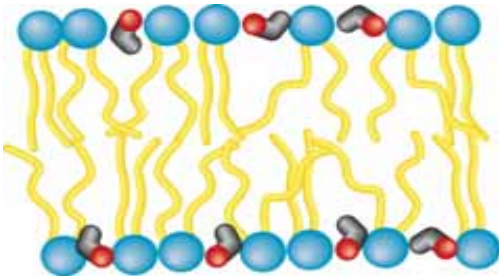
Lipid and Protein Diffusion



Protein-Protein Interactions



Drug Enhancers and Membrane Permeability



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