



JOINT INSTITUTE
FOR NUCLEAR RESEARCH



FRANK LABORATORY
OF NEUTRON PHYSICS

Small angle scattering and diffraction with pulsed reactor neutrons in structural biophysics

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Outline

- Historical Overview
- Sources and Properties of Neutrons
- Principles of Small-Angle Scattering
- Analysis of Small Angle Scattering Data + Examples
- Principles of Small Angle Diffraction
- Analysis of Small Angle Diffraction Data + Examples

Discovery and Utilization of X-rays

1920's

- 1895 – Wilhelm Röntgen – discovery of X-rays



Hand des Anatomen Geheimrath von Kolliker in Würzburg
Im Physikalischen Institut der Universität Würzburg
am 23. Januar 1896 mit X-Strahlen aufgenommen
von
Professor Dr. W. C. Röntgen.

X-RAY

CUSTOMERS

FITTING

EXPECT IT!

3. X-RAY FITTING TEST

X-RAY TEST

RIGHT WAY	LEFT	☐	GOOD	☐	RIGHT	☐	WRONG WAY
		☐	FAIR	☐		☐	
		☐	POOR	☐		☐	



Achievements with X-rays

7.1 A.1 Rosalind Franklin's and Maurice Wilkins' investigation of DNA structure by X-ray diffraction

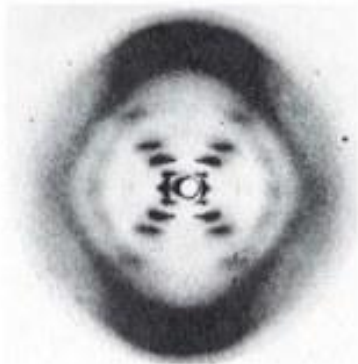
Rosalind Franklin (1950's)

- Worked with Maurice Wilkins
- X-ray crystallography = images of DNA
- Provided measurements on chemistry of DNA



(a) Rosalind Franklin

© 2011 Pearson Education, Inc.



(b) Franklin's X-ray diffraction photograph of DNA

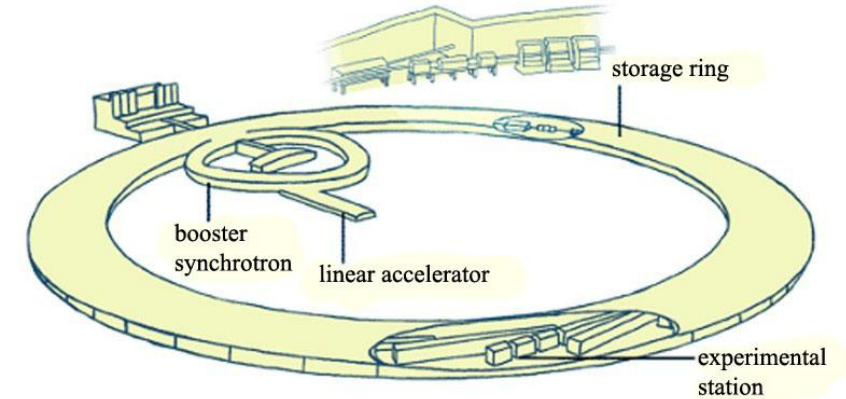
James Watson & Francis Crick (1953)

- Discovered the double helix by building models to conform to Franklin's X-ray data and Chargaff's Rules.



1950's

- 1944 – Vladimir Veksler – invention of synchrotron



Veksler V.I. and MacMmiller E. in Dubna (1963)

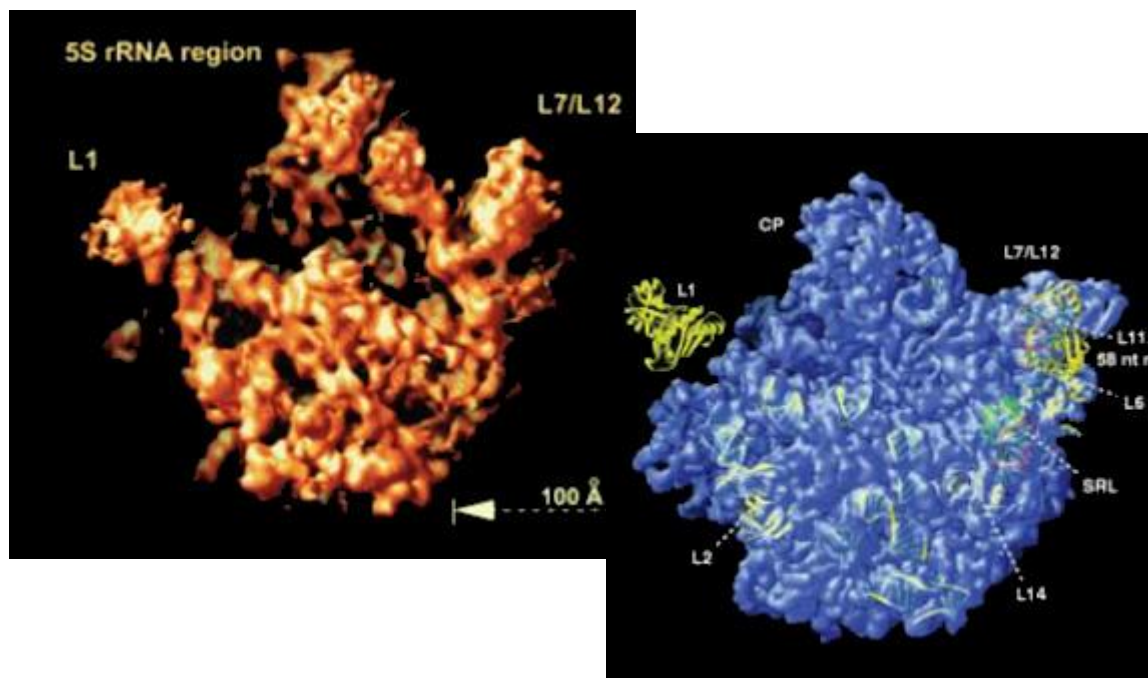


Achievements with High-flux Facilities

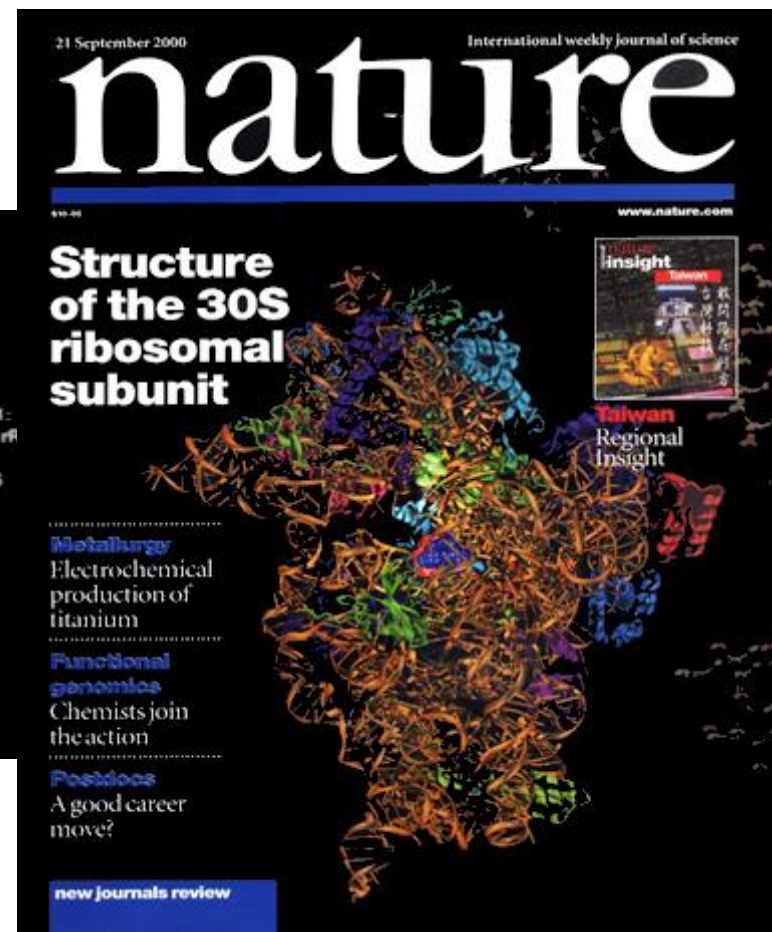
2000's

Access to synchrotron radiation has also contributed to **discoveries for which the Nobel prize was awarded**. One of them was in chemistry for the research on the structure and function of **the ribosome**.

Scientists explained what ribosomes look like and how they function at the atomic level, which has a crucial meaning to understand scientific foundations of life.



- 2009 - **Ada Yonath** sent X-rays through ribosome crystals that revealed the secrets of the ribosome

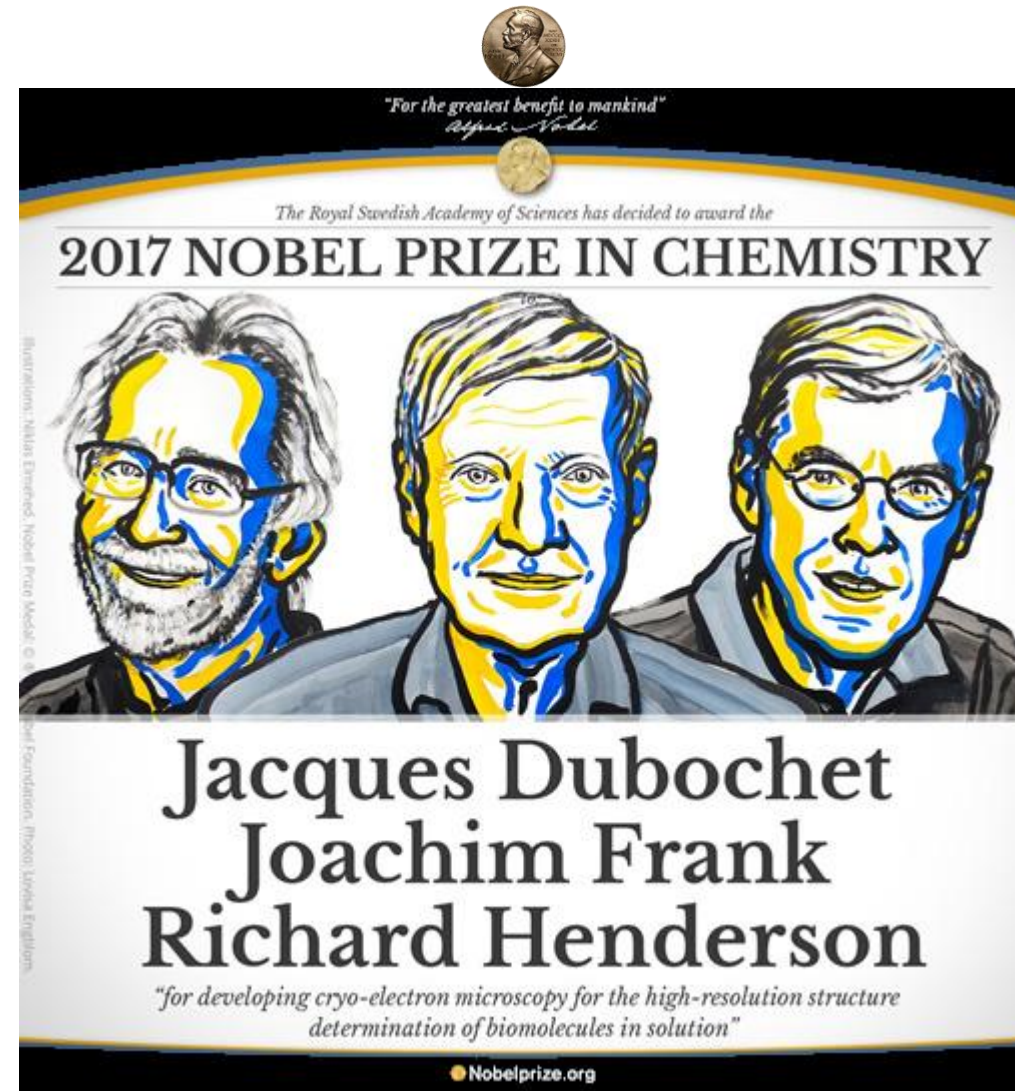
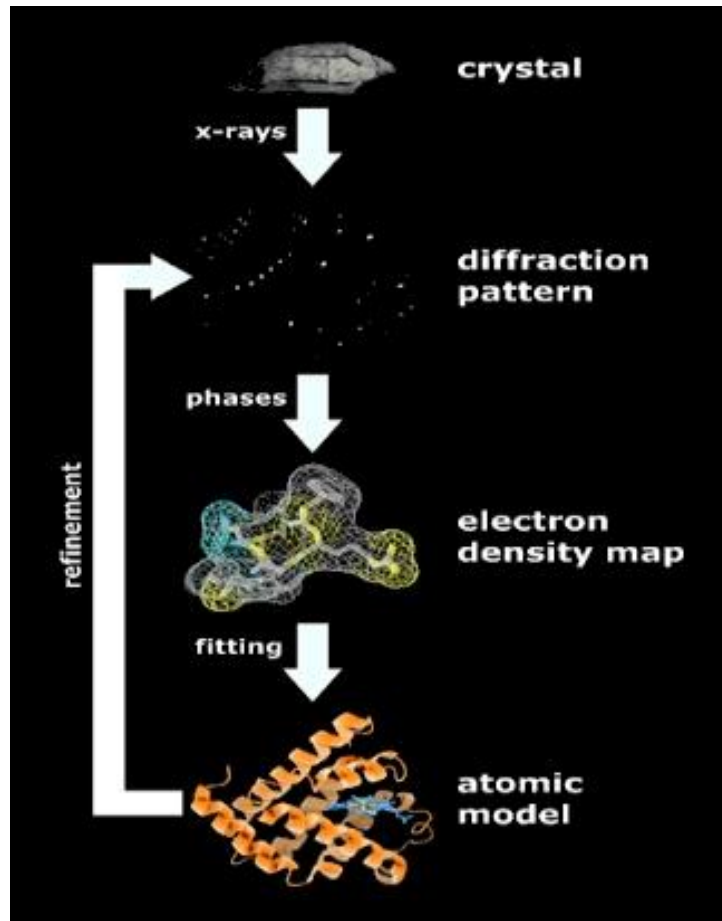




Further Achievements born by Diffraction

2017

- High resolution images from cryo-electron microscopy

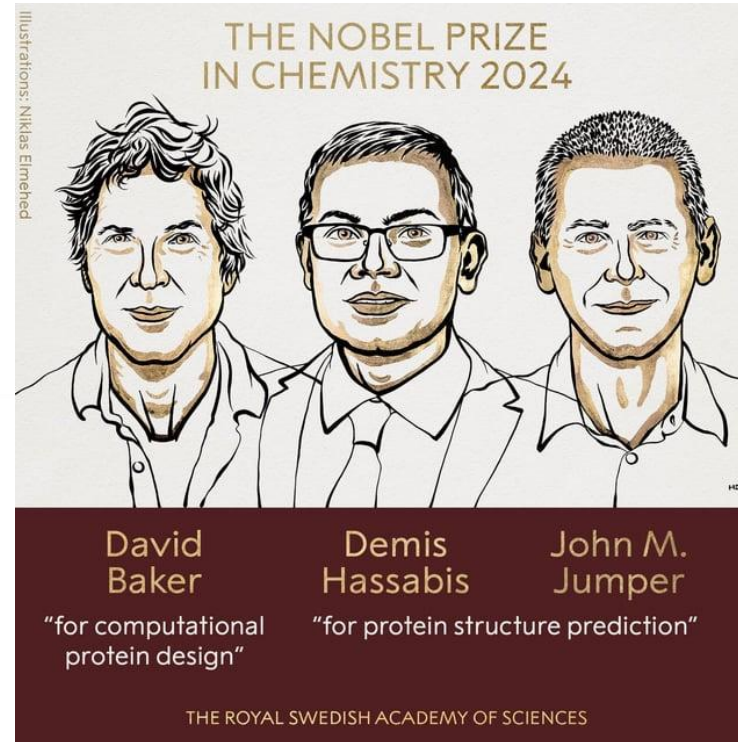
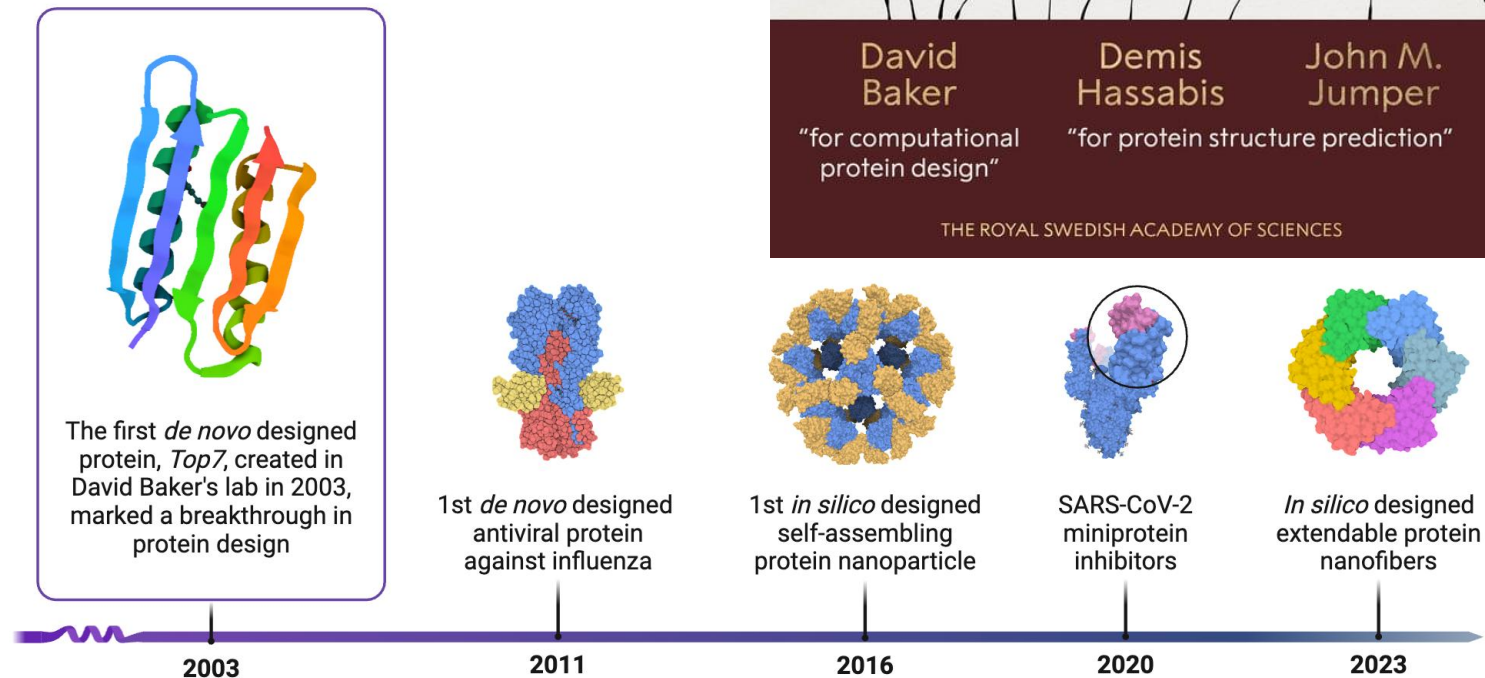




Protein Structure by Prediction

- Computational prediction of 3D protein structures

2024





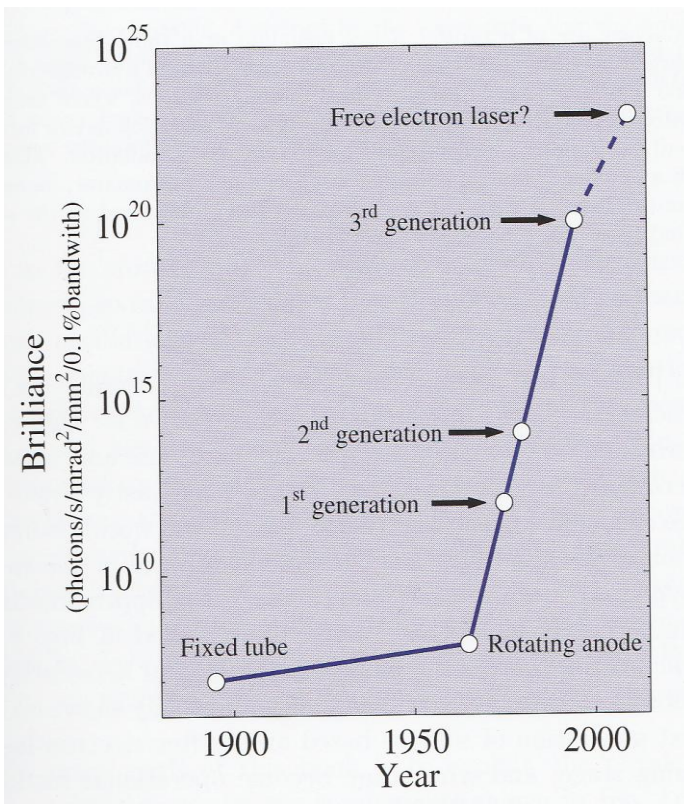
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Neutrons for Life Sciences

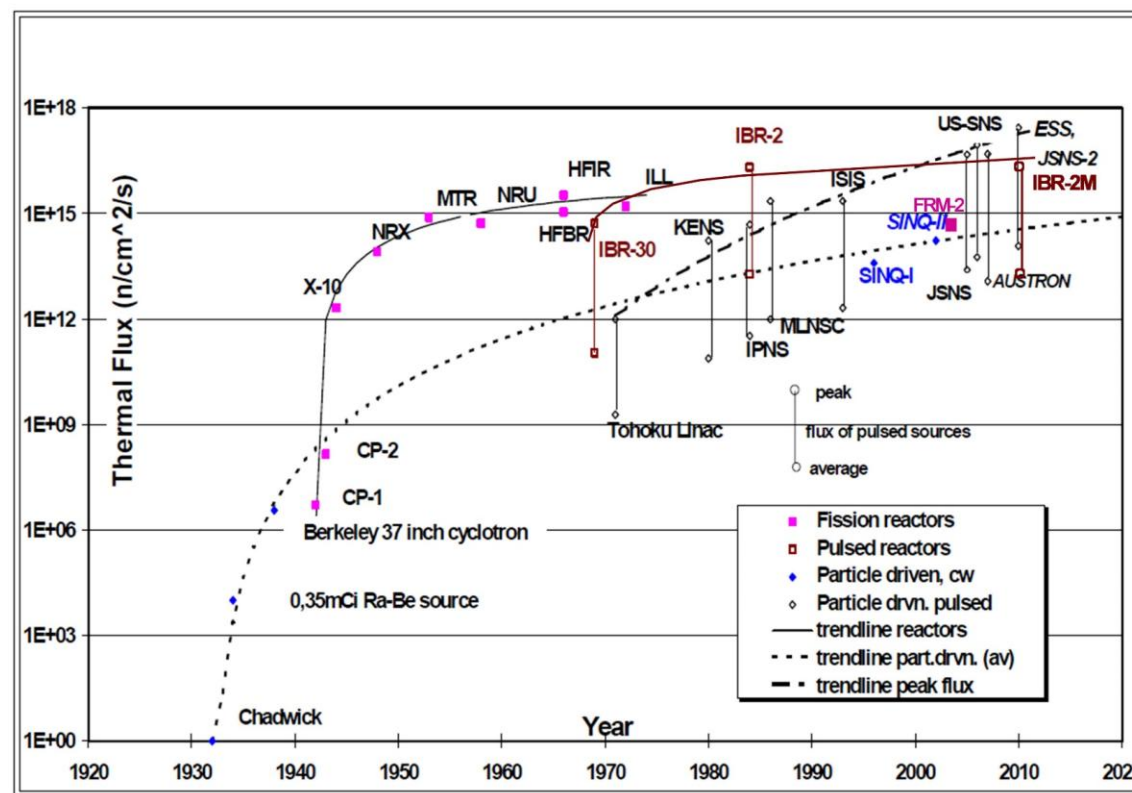
Neutron's sensitivity to H/D provide unique info on protein chemical state (protonation), its solvent accessibility, and H-bond networks



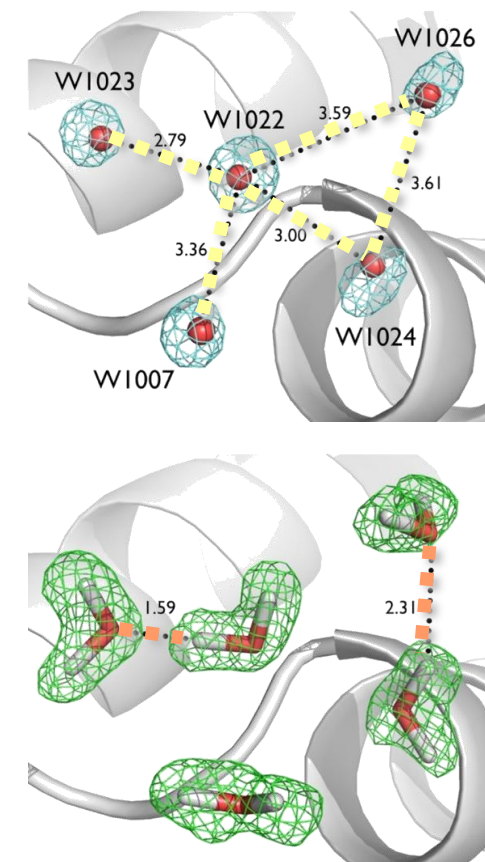
J. Als-Nielsen, D. McMorrow, Wiley (2001)

X-ray sources

Neutron sources



Report of a technical meeting in Vienna, IAEA-TECDOC-1439 (2005)



Chen et al. PNAS 109, 2012



Discovery and Utilization of Neutrons

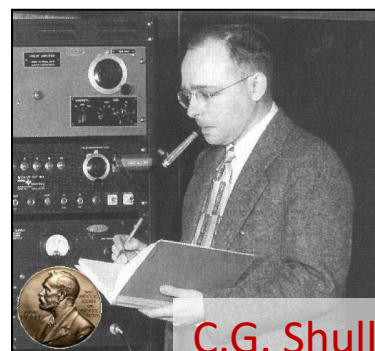
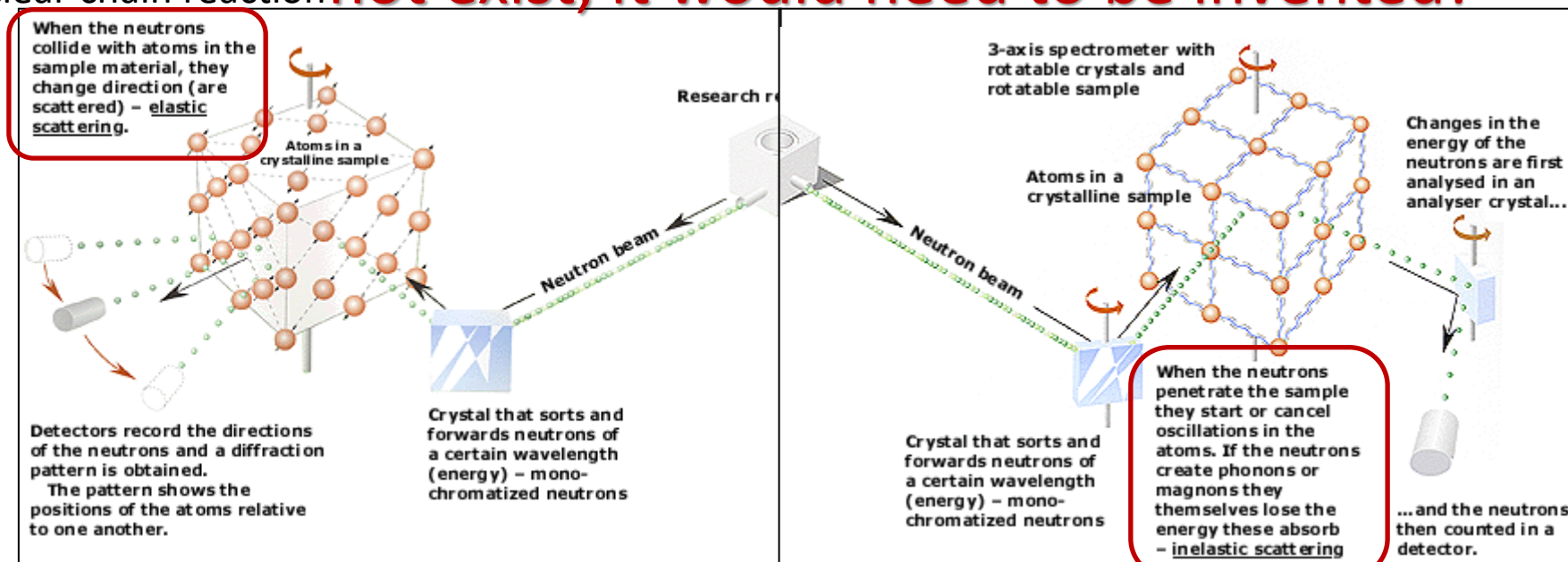
1960's

- 1932 – James Chadwick - discovery of neutron



- 1933 – Leó Szilárd – the idea of nuclear chain reaction

“It might well be said that, if the neutron did not exist, it would need to be invented!”



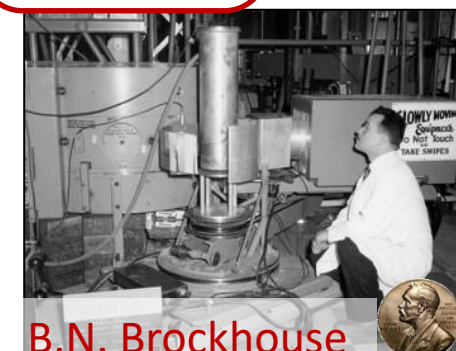
Neutrons show
where atoms are

Structure

Neutrons show
what atoms do

Dynamics

- The Nobel Prize in Physics 1994 -

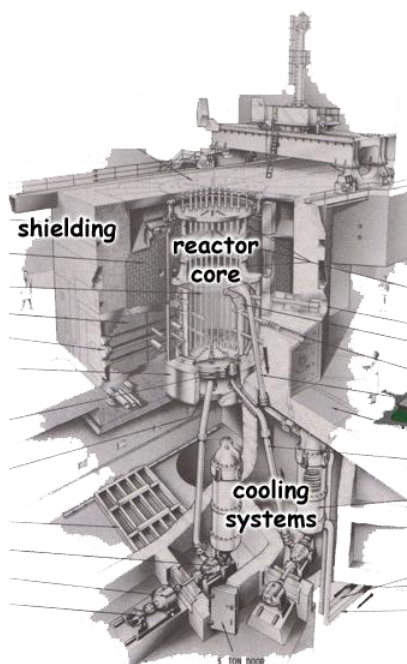




Advances in Neutron Sources Development

1980's

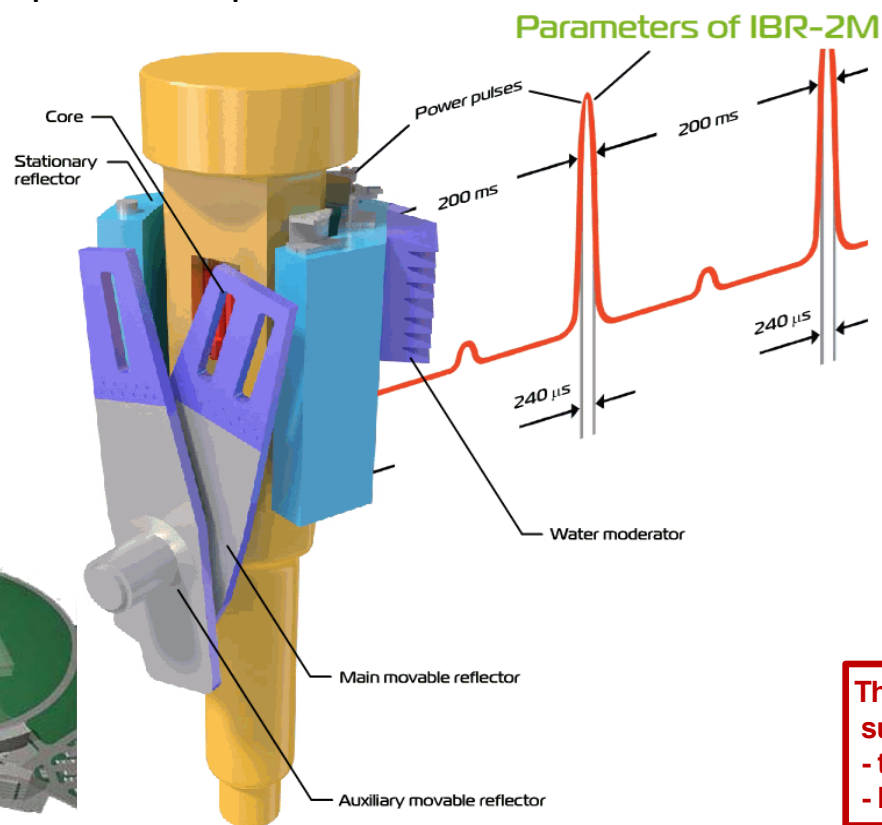
- 1942 – Enrico Fermi – the first artificial nuclear reactor Chicago Pile-1
- 1950-1954 – Ernest O. Lawrence – the first spallation source Materials Testing Accelerator
- 1955 – Dimitry I. Blokhintsev – the idea of pulsed reactor
- 1960-1968-2001 – Ilya M. Frank  & Fyodor L. Shapiro – the pulsed reactor IBR, IBR-30
- 1984-2010-204x – IBR-2, IBR-2M



NRU (1957)
Chalk River, ON



SNS (2006)
Oak Ridge, TN



Average power, MW	2
Burst power, MW	1850
Fuel	PuO ₂
Number of fuel assemblies	69
Maximum burnup, %	9
Pulse repetition rate, Hz	5; 10
Pulse half-width, μs: fast neutrons thermal neutrons	240 320
Rotation rate, rev/min: main reflector auxiliary reflector	600 300
MMR and AMR material	nickel + steel
MR service life, hours	55000
Background, %	7.5

Thermal neutron flux density from the surface of the moderator

- time average $\sim 10^{13}$ n/cm² s
- burst maximum $\sim 10^{16}$ n/cm² s

Monochromatizing vs. Time-Of-Flight

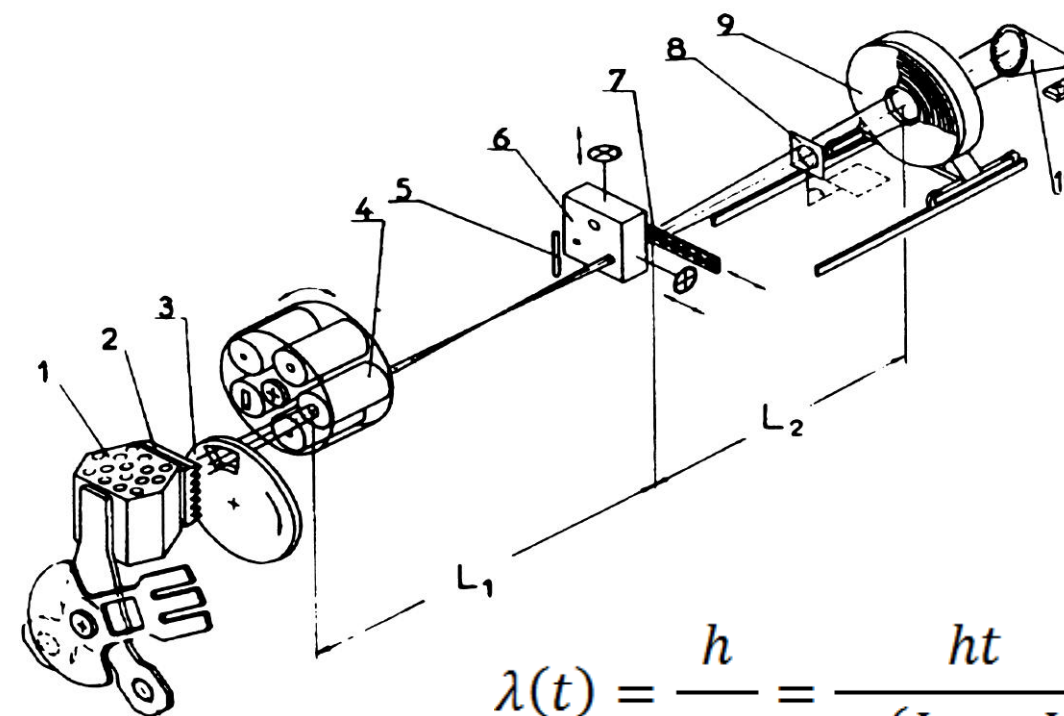
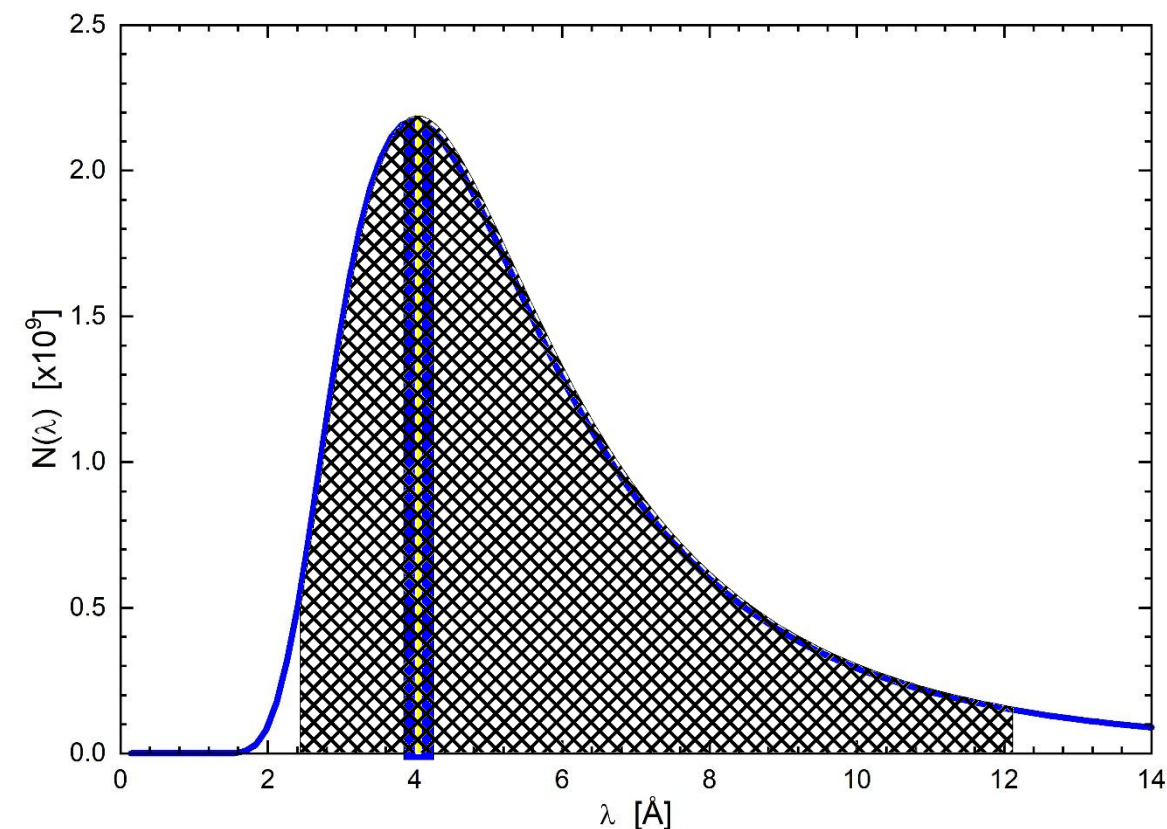
$$|\mathbf{q}| = q = \frac{4\pi}{\lambda} \sin \frac{\theta}{2}$$

Continuous sources

- velocity selectors (acceptance ~10%)
- monochromators (acceptance ~1% to 0.1%)

Pulsed sources

- choppers in time-of-flight method



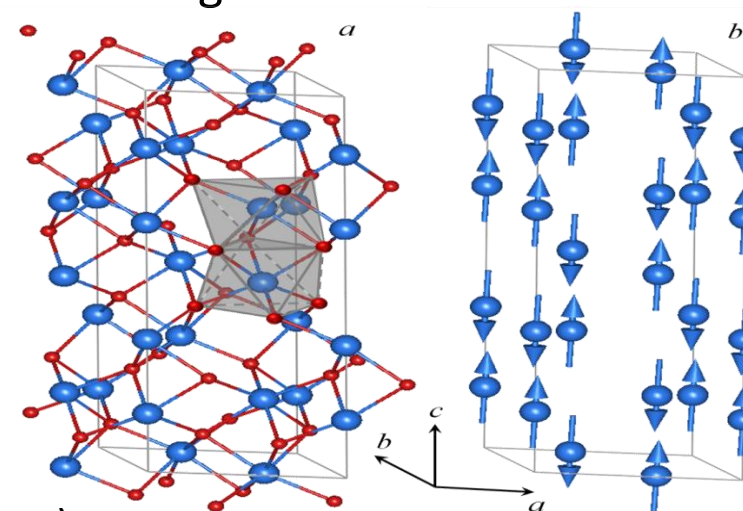
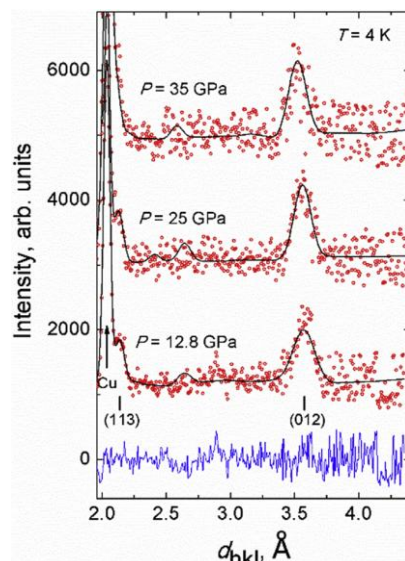
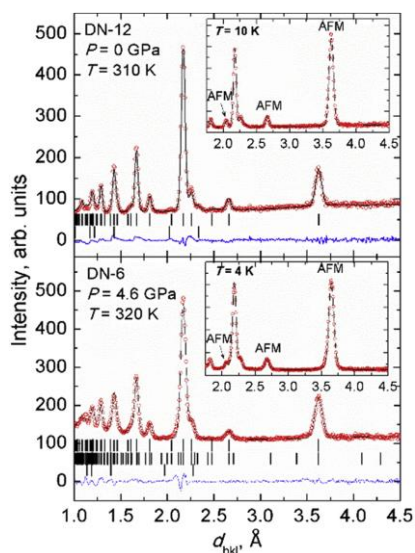
$$\lambda(t) = \frac{h}{mv} = \frac{ht}{m(L_1 + L_2)}$$

Advantages of Neutrons

- **Magnetic Moment:**  ==> the world smallest magnetometer

Crystal and Magnetic Structures of Novel Materials

Crystal and magnetic structures of Cr_2O_3 - one of the first discovered magnetoelectric materials with ferroelectric polarization induced by external magnetic field



Advantages of Neutrons

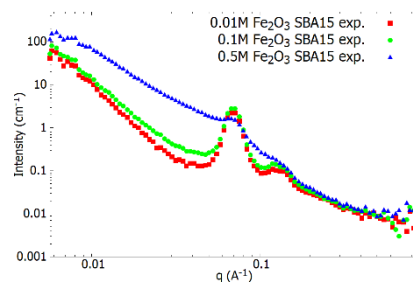
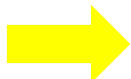
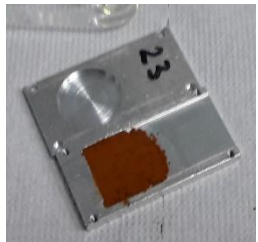
A neutron walks into a bar and asks how much for a beer.
Bartender replies: "For you,"

Sheldon Cooper
The Big Bang Theory

- Charge: **no charge**.

=> deep penetration into matter

SANS experiments at YuMO



total SANS scattering = **regular matrix** + **polydisperse spheres**



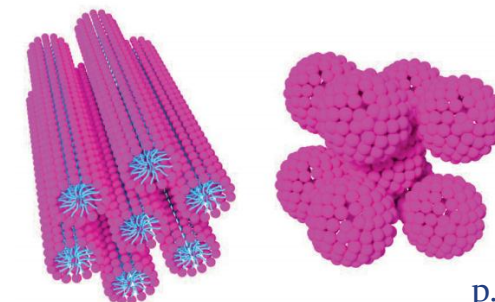
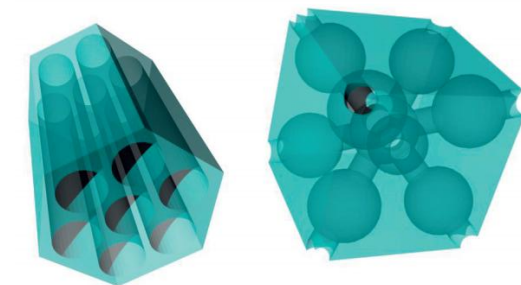
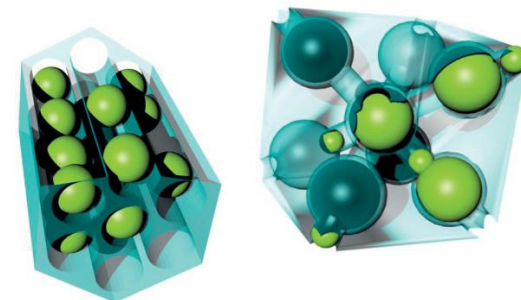
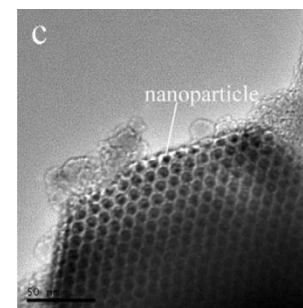
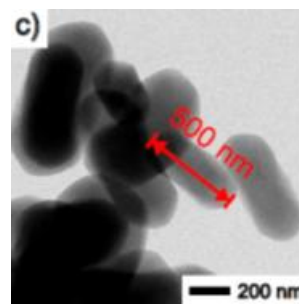
$$I(q) = K_C S(q) |F_C(q)|^2 + K_S |F_S(q)|^2 + I_d(q) + I_i$$

- pores - size & mutual distance
- NPs - size distribution & concentration

Material

Periodic nanoporous silica

- perfect regular structure
- biocompatibility
- thermal stability and durability
- high specific surface



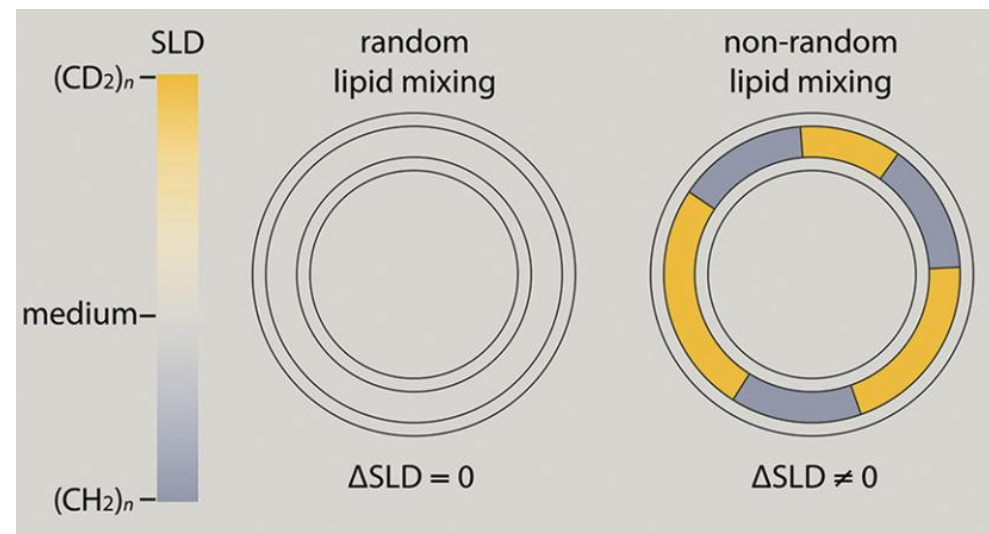
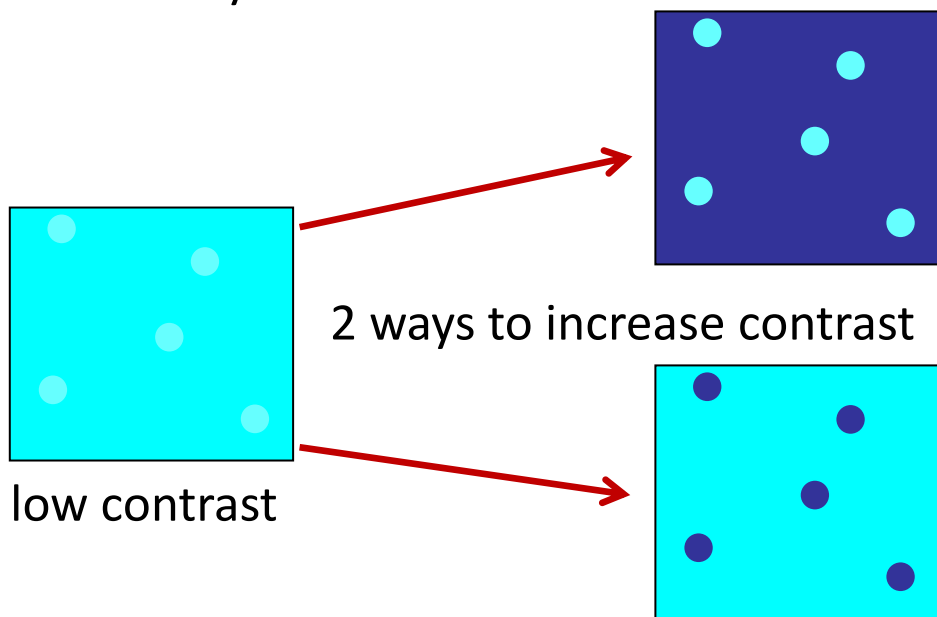
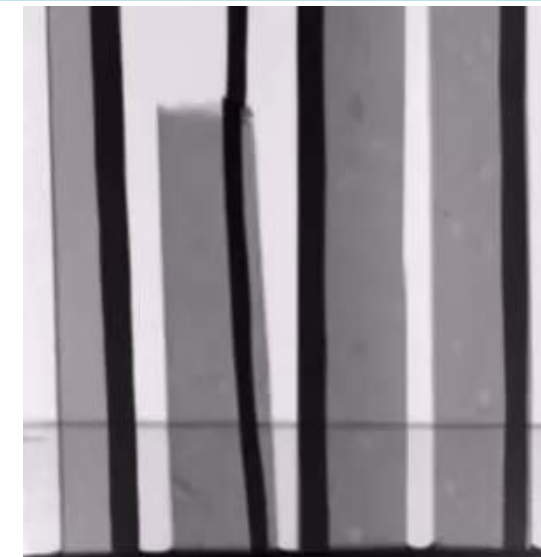
Advantages of Neutrons

- **Scattering Power:**

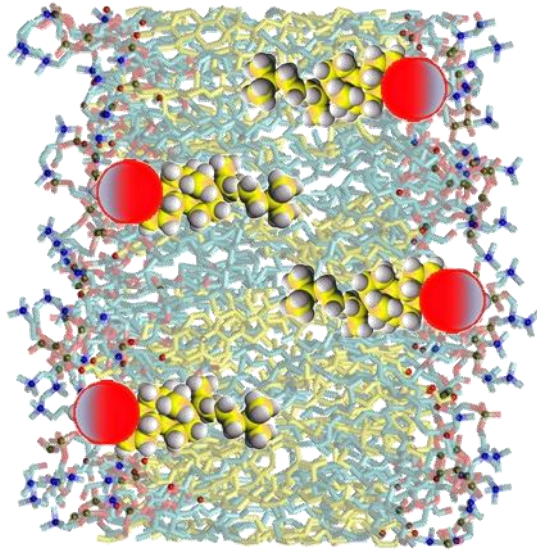
==> sensitivity to light elements

==> sensitivity to isotope exchange

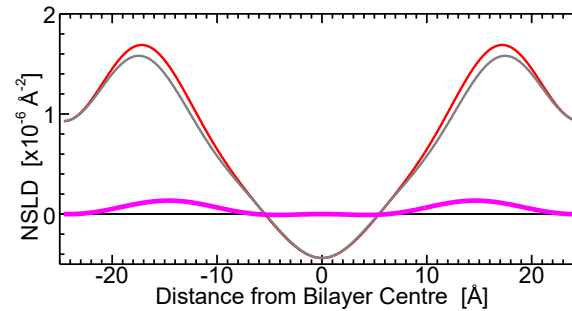
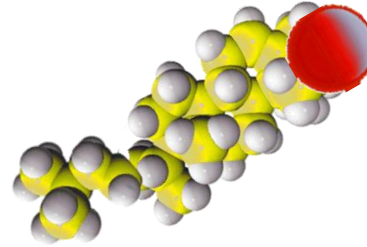
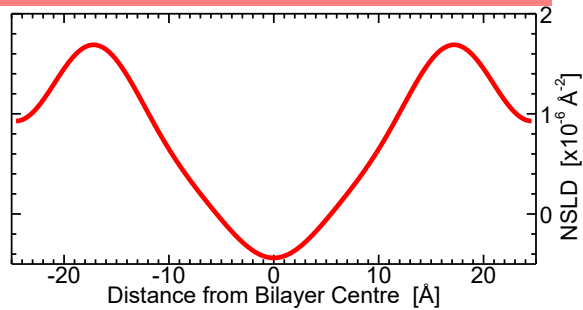
Neutron **contrast variation** can be done without changing the chemical properties of the system, because the neutron scattering lengths of isotopes can be very different.



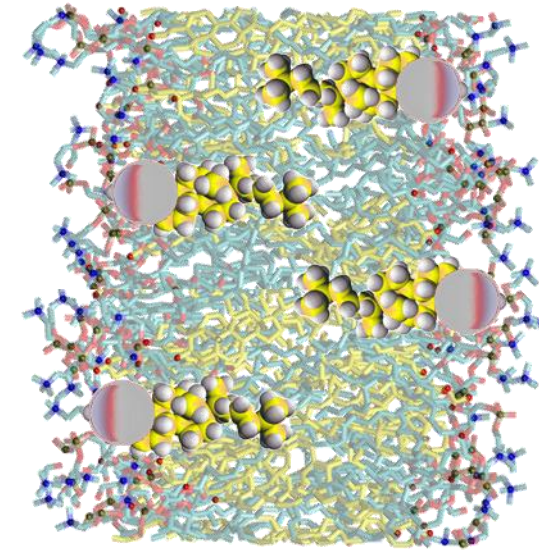
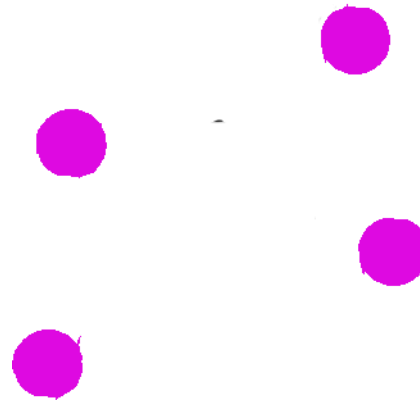
Label Distribution by Neutron Diffraction



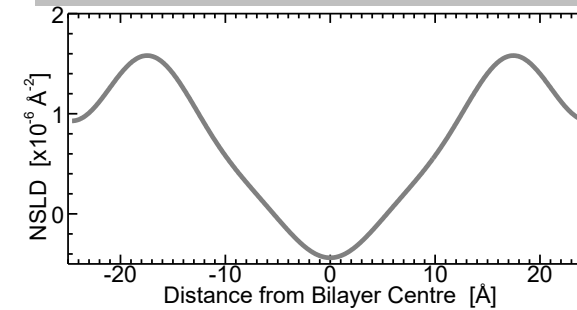
$$\rho_D(z) = \rho_B P_B(z) + \rho_W P_W(z) + \rho_{LD} P_L(z)$$



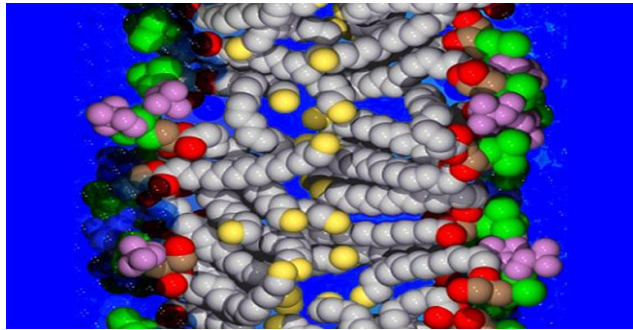
$$\rho_D(z) - \rho_H(z) = (\rho_{LD} - \rho_{LH}) P_L(z)$$



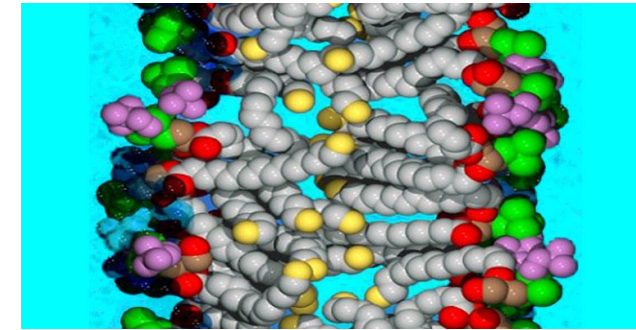
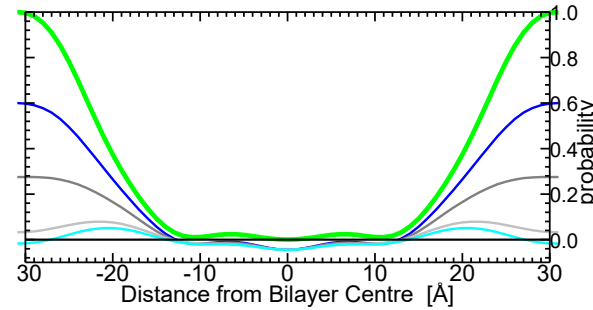
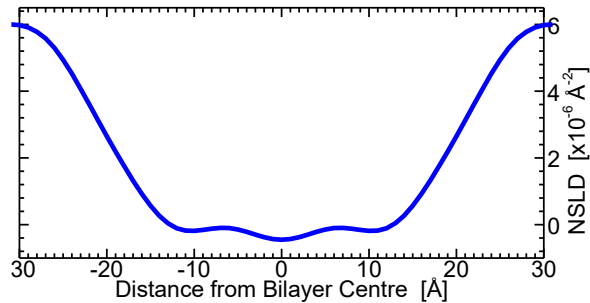
$$\rho_H(z) = \rho_B P_B(z) + \rho_W P_W(z) + \rho_{LH} P_L(z)$$



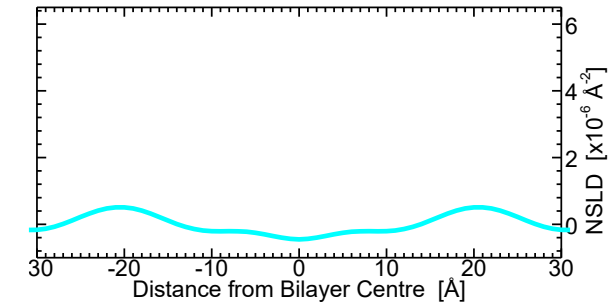
Water Distribution Across the Membrane



$$\rho_1(z) = \rho_{W1}P_W(z) + \rho_BP_B(z)$$



$$\rho_2(z) = \rho_{W2}P_W(z) + \rho_BP_B(z)$$

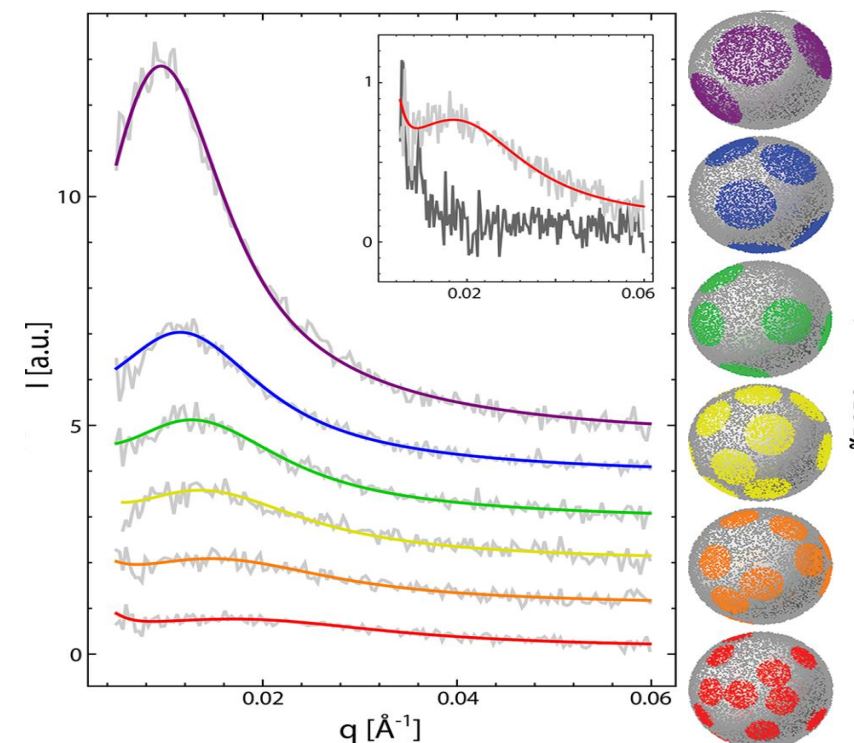
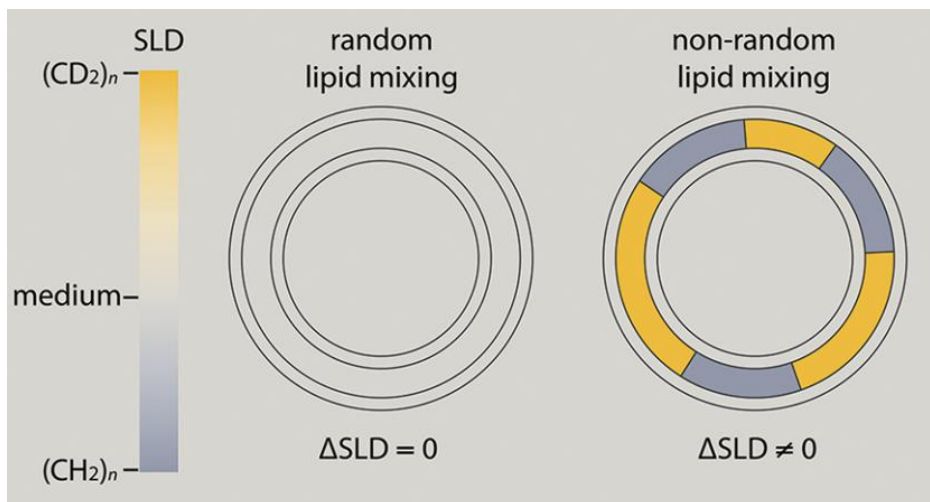


$$\rho_1(z) - \rho_2(z) = (\rho_{W1} - \rho_{W2})P_W(z)$$



Lipid Rafts by Neutron Scattering

Neutron scattering (via selective deuteration) is sensitive to nanometer-sized domains, previously not accessible by other methods.



The study of complex membrane models, including functional domains, helps to further our understanding of how the cell may regulate critical biological process via the composition of lipid bilayers.

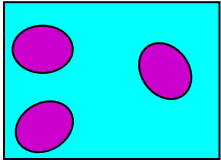
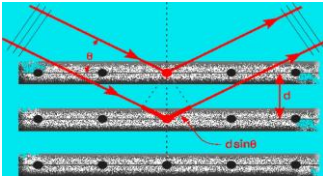


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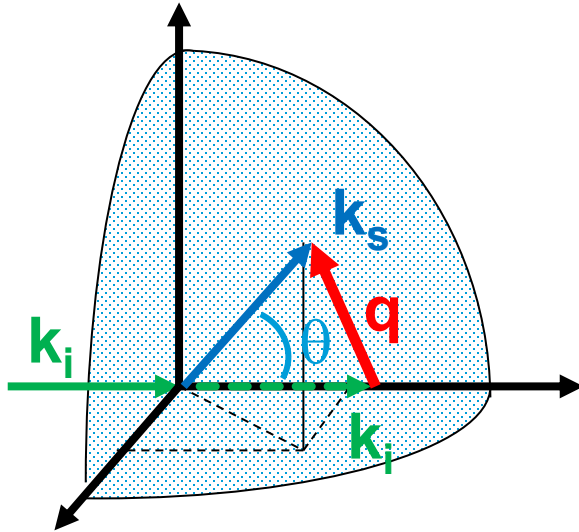
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Small Angle Scattering/Diffraction (SAS/D)

- radiation (e.g. **neutrons, X-rays, light**) is elastically scattered by a sample and the resulting scattering pattern is analysed to provide **details on the size, shape and location of components** within the sample
- Q range is usually between 0.003 and $0.6 \text{ \AA}^{-1}$ – providing a wide range of length scales (~ 10 to $2,000 \text{ \AA}$)
- powerful tool for investigating the average structure of the entire ensemble of particles **in solution (biologically relevant environment)**
- the studied structures can either be **isotropic (SAS)** or consist of repeating units that are **oriented (SAD)**
 - 
 - 
- **type of the sample**, sample environment and the information that can ultimately be obtained depend on the nature of the radiation, however **different radiations often provide complementary results**

Scattering Principles – Geometry



Scattering vector, q

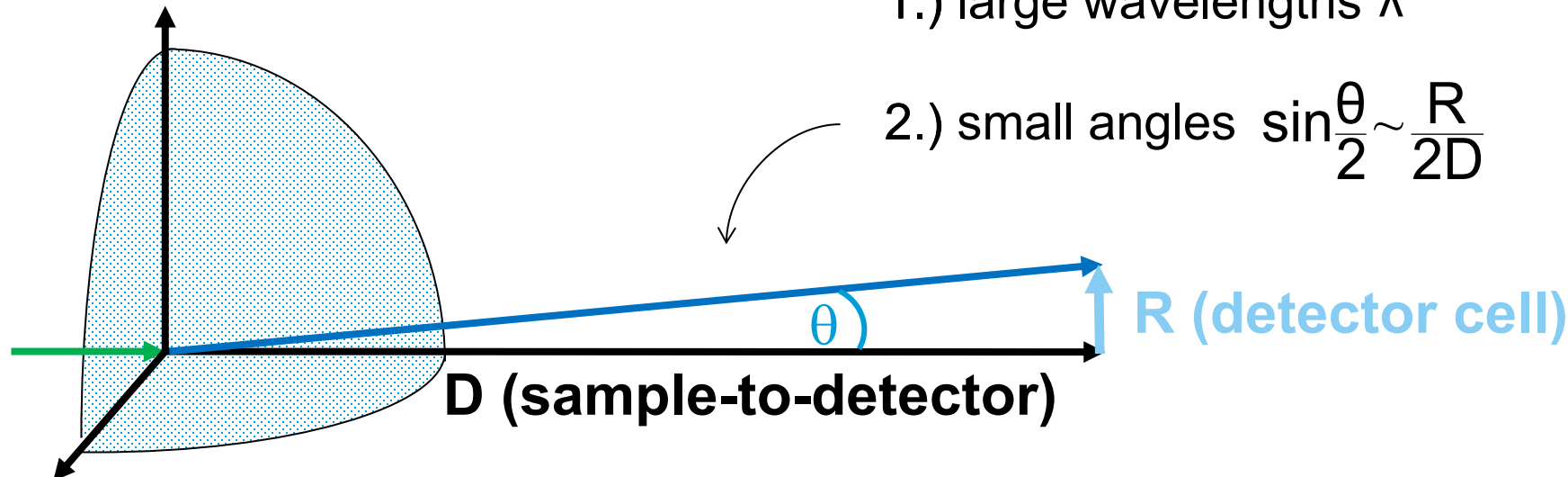
$$\mathbf{q} = \mathbf{k}_s - \mathbf{k}_i$$

$$|\mathbf{q}| = q = \frac{4\pi}{\lambda} \sin \frac{\theta}{2}$$

Two ways to get small scattering vectors:

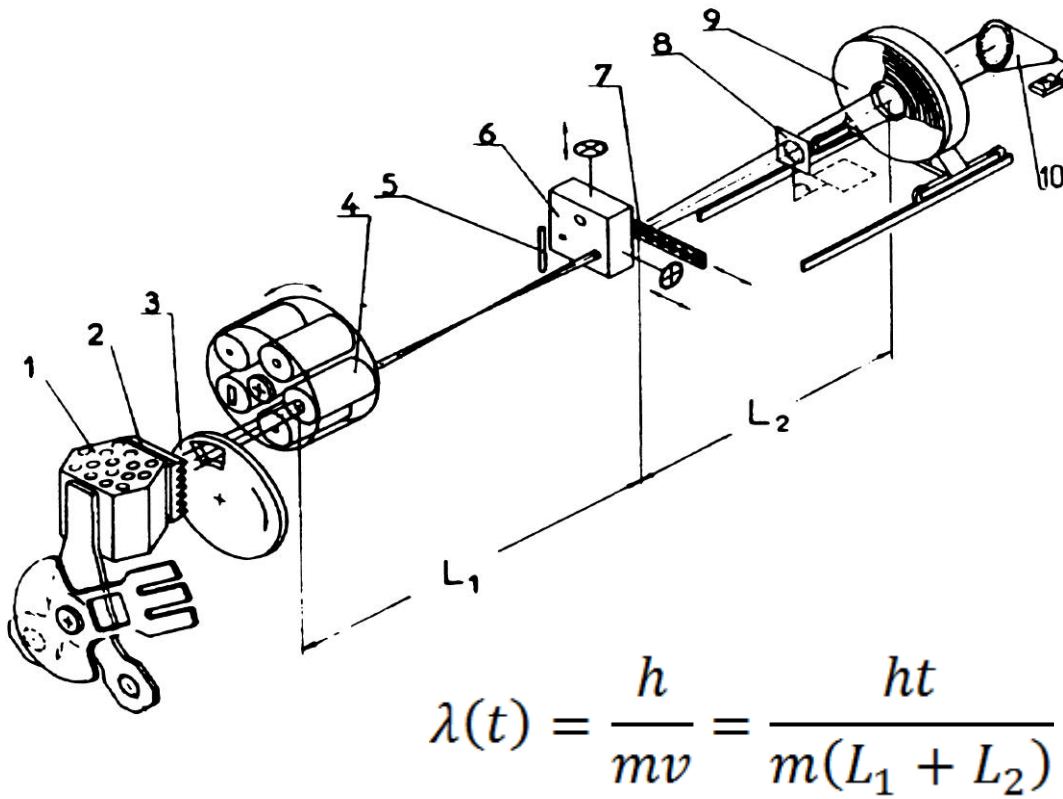
1.) large wavelengths λ

2.) small angles $\sin \frac{\theta}{2} \sim \frac{R}{2D}$





Scattering Principles – TOF SANS Instrument

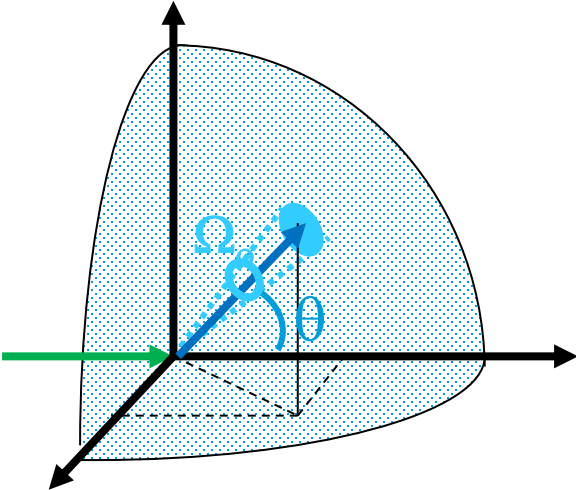


$$|\mathbf{q}| = q = \frac{4\pi}{\lambda} \sin \frac{\theta}{2}$$

Two ways to vary scattering vector:

- 1.) through angles θ = TAS
- 2.) through wavelengths λ = TOF

Scattering Principles – SAS Intensity



measured
intensity
at q (or θ)

$$I_m(q) = I_F \cdot \Omega_o \cdot \varepsilon \cdot T \cdot \left(\frac{d\sigma}{d\Omega} \right)_v \cdot A \cdot t$$

Flux Solid angle Detector efficiency Sample transmission Beam area on the sample Path length

Differential cross-section

$$\frac{d^2\sigma(\Omega, E)}{d\Omega dE} = \frac{\text{number of neutrons scattered per second into a solid angle } d\Omega \text{ with the final energy between } E \text{ and } E+dE}{\text{neutron flux of the incident beam} \cdot d\Omega dE}$$

For (quasi-)Elastic Scattering we assume no energy transfer

$$\frac{d\sigma}{d\Omega} = \int_0^\infty \frac{d^2\sigma}{d\Omega dE} dE = \frac{\text{number of neutrons scattered per second into } d\Omega}{\text{neutron flux of the incident beam} \cdot d\Omega}$$

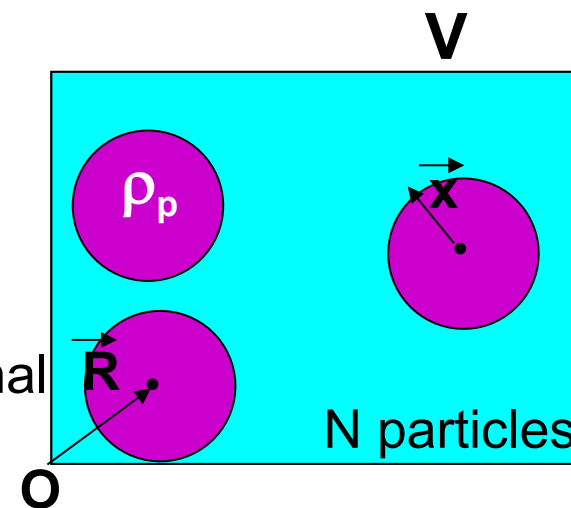
[time⁻¹] [area] [time⁻¹area⁻¹]

SAS Data Factorization

$$\frac{d\sigma}{d\Omega} = \sum_i \sum_j b_i b_j e^{i\vec{q} \cdot (\vec{r}_i - \vec{r}_j)} = \left| \sum_i b_i \langle e^{i\vec{q} \cdot \vec{r}_i} \rangle \right|^2$$

$$\left(\frac{d\sigma}{d\Omega} \right)_V = \frac{1}{V} \left| \sum_k \sum_i b_i \langle e^{i\vec{q} \cdot (\vec{R}_k + \vec{x}_i)} \rangle \right|^2$$

orientational average



$$\left(\frac{d\sigma}{d\Omega} \right)_V = \frac{1}{V} \left| \sum_k e^{i\vec{q} \cdot \vec{R}_k} \int \Delta\rho(\vec{x}) \langle e^{i\vec{q} \cdot \vec{x}} \rangle dV_P \right|^2; \quad \Delta\rho(\vec{r}) = \rho(\vec{r}) - \rho_s$$

$$\left(\frac{d\sigma}{d\Omega} \right)_V = \frac{N}{V} S(\vec{q}) P(\vec{q})$$

square of amplitude of (intra-)particle form factor

Inter-particle structure factor

$$|P(\vec{q})| = |F(\vec{q})|^2 = \left| \int \Delta\rho(\vec{x}) e^{i\vec{q} \cdot \vec{x}} dV_P \right|^2$$



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Model-Independent Analysis

(dilute system: $S(q)=1$)

$$\left(\frac{d\sigma}{d\Omega}\right)_V = \frac{N}{V} \left| \int \Delta\rho(\vec{r}) \langle e^{i\vec{q}\cdot\vec{r}} \rangle dV \right|^2$$

Assume a centro-symmetric particle with homogeneous ρ

$$\left(\frac{d\sigma}{d\Omega}\right)_V = \frac{N}{V} \left| \Delta\rho \int \langle \cos(\vec{q} \cdot \vec{r}) \rangle dV \right|^2 \rightarrow \frac{N}{V} \left| \Delta\rho V_P \left\langle 1 - \frac{(\vec{q} \cdot \vec{r})^2}{2} + \dots \right\rangle \right|^2$$

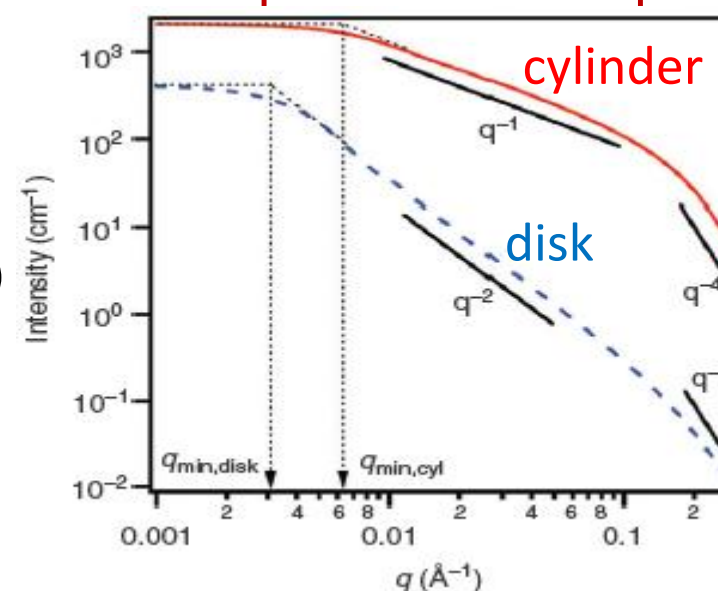
$$\left(\frac{d\sigma}{d\Omega}\right)_V = \frac{N}{V} \Delta\rho^2 V_P^2 \left[1 - q^2 \frac{R_G^2}{3} + \dots \right];$$

Guinier Approximation for
a spherical (3D) object

Decay of the scattering function depends on
the system's overall structure (dimensionality)

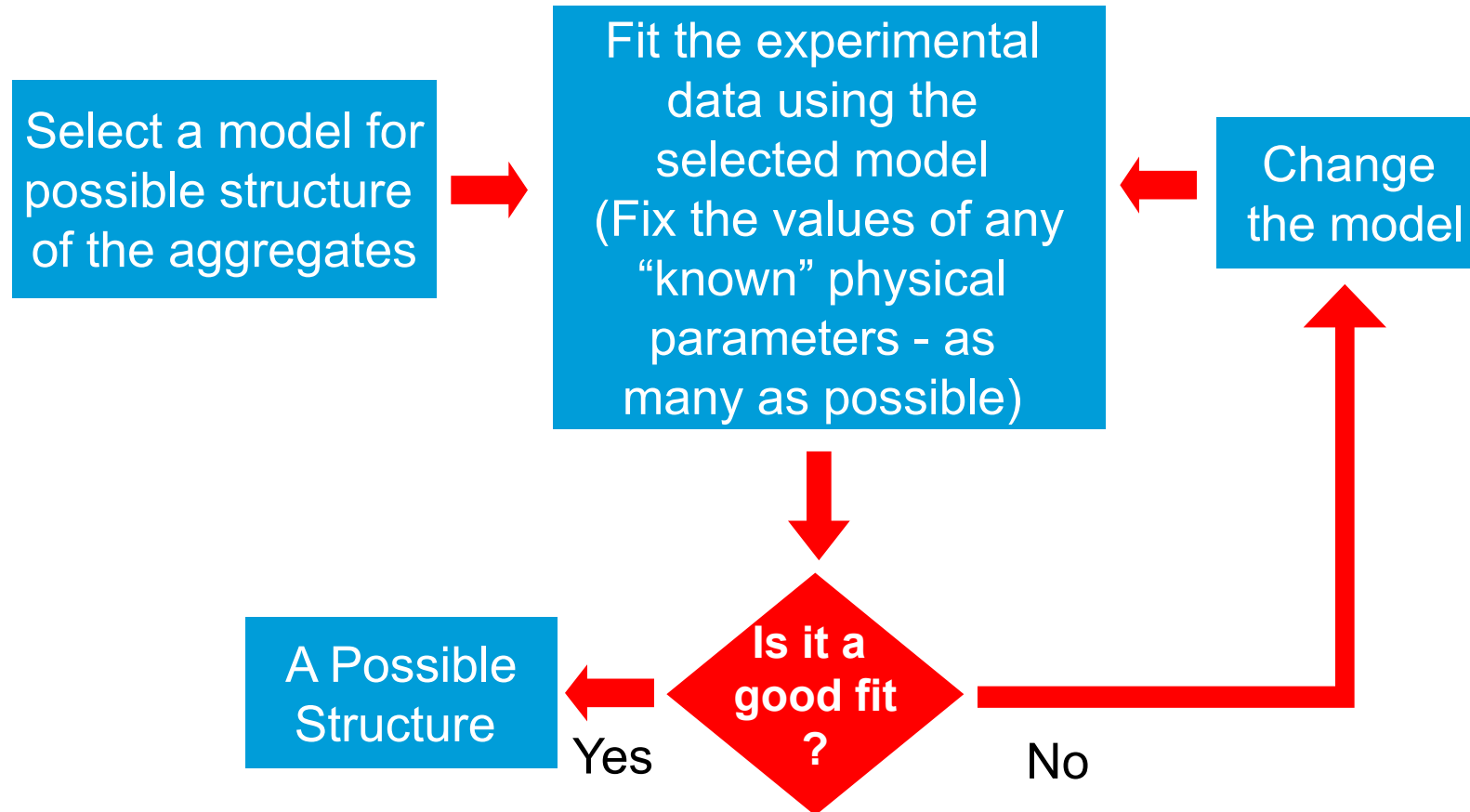
$\left(\frac{d\sigma}{d\Omega}\right)_V \sim q^{-m};$	$m=1$	- cylinders
	$m=2$	- disks, lamellae
	$m=3$	- fractals
	$m=4$	- sharp interfaces

Interpretation of Slopes





Model-Based Analysis

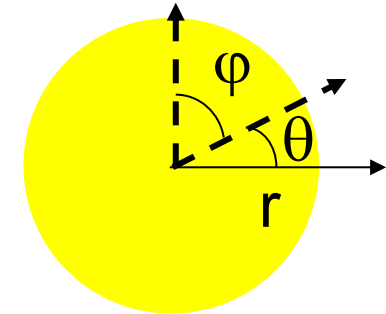


Scattering Form Factors – Spheres

$$P(q) = \frac{1}{V_{\text{sphere}}^2} \left| \iiint_{V_{\text{sphere}}} \rho(\vec{r}) \cdot e^{-i\vec{q} \cdot \vec{r}} d\vec{r} \right|^2$$

Since spheres are isotropic, there is no need to do orientational average

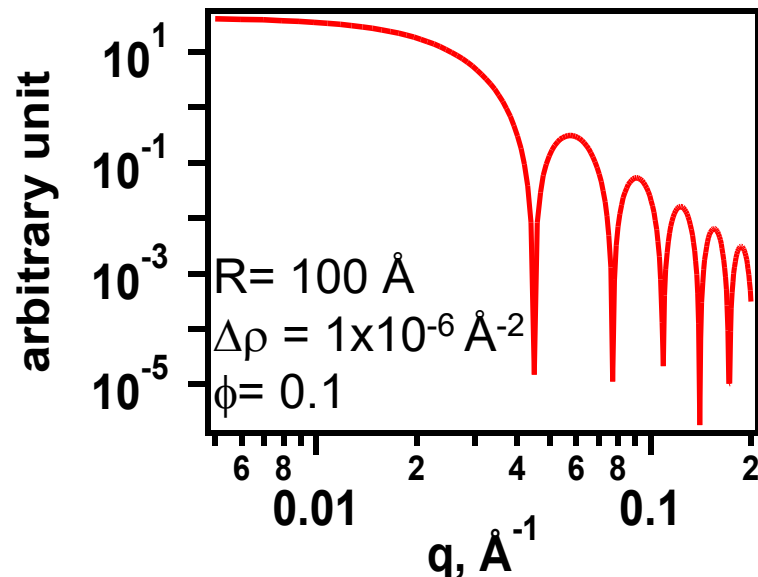
$$= \frac{1}{V_{\text{sphere}}^2} \left| \int_{r=0}^R \int_{\theta=0}^{\pi} \int_{\varphi=0}^{2\pi} e^{-iqr \cos \theta} r^2 \sin \theta d\varphi d\theta dr \right|^2$$



$$= \frac{9}{(qR)^6} [\sin(qR) - qR \cdot \cos(qR)]^2$$

$$\left(\frac{d\sigma}{d\Omega} \right)_v = \frac{N}{V} (\rho_{\text{sphere}} - \rho_o)^2 \cdot V_{\text{sphere}}^2 \cdot \vec{P}(\mathbf{q})$$

$$= \phi_{\text{sphere}} V_{\text{sphere}} \Delta \rho^2 \frac{9}{(qR)^6} [\sin(qR) - qR \cdot \cos(qR)]^2$$



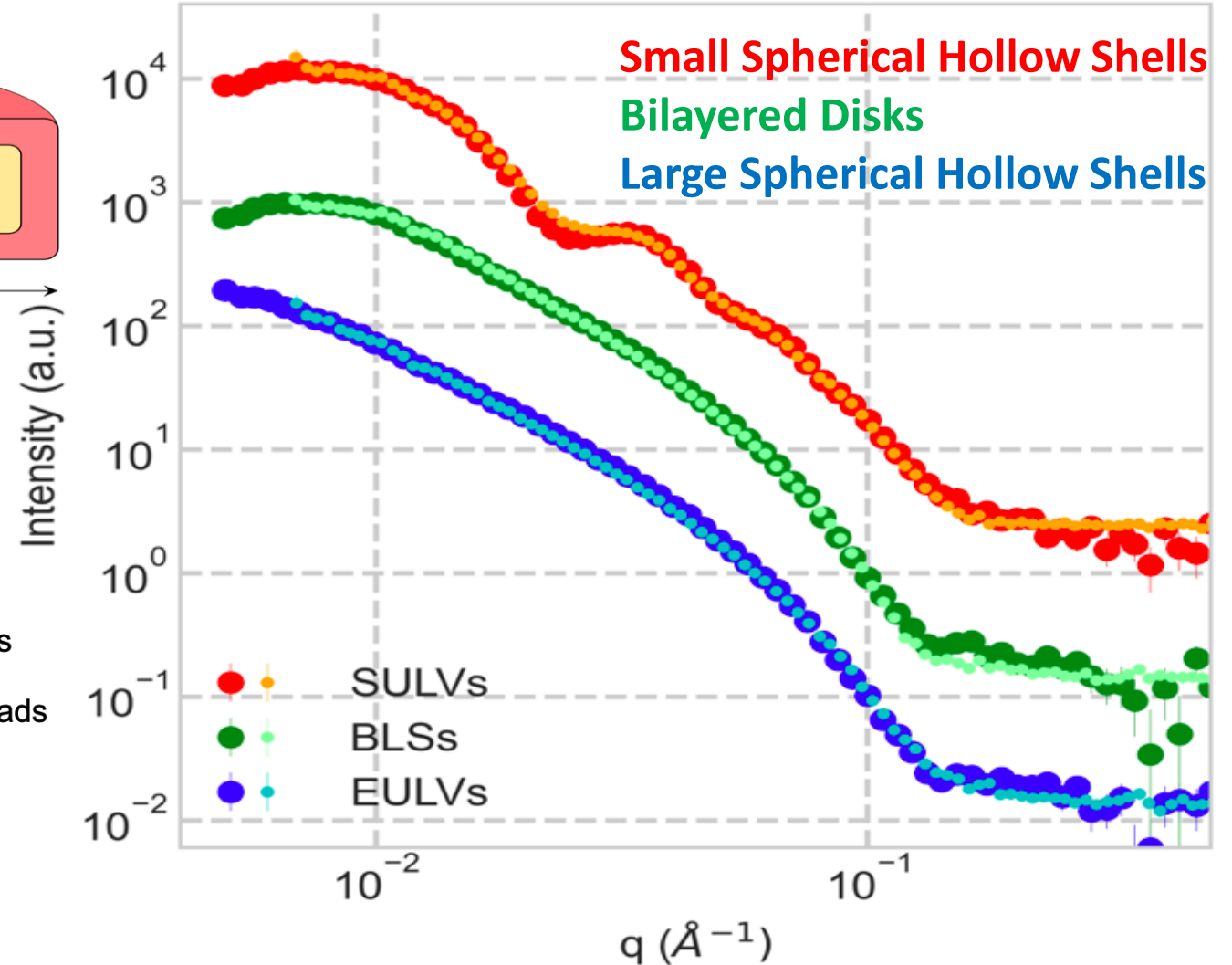
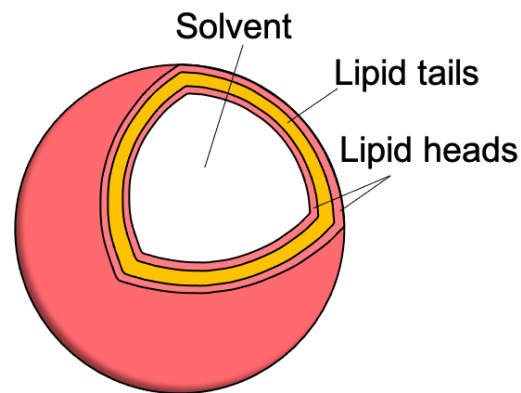
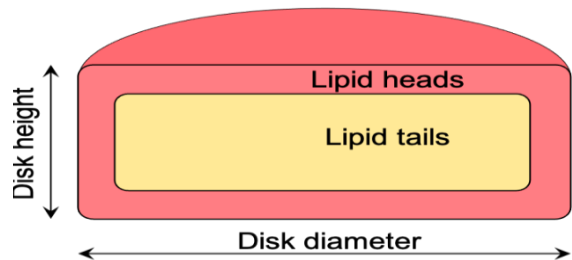
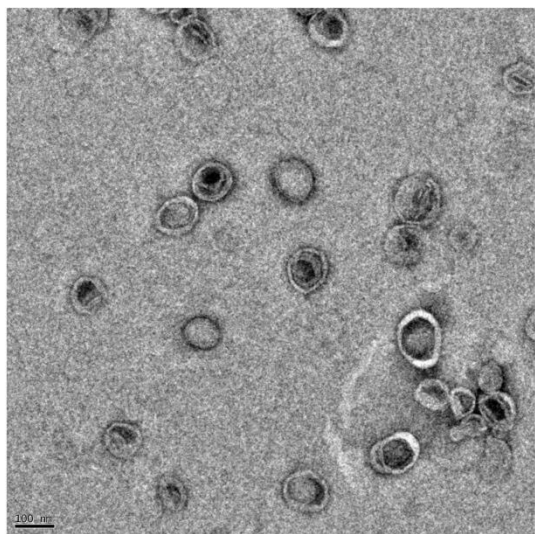
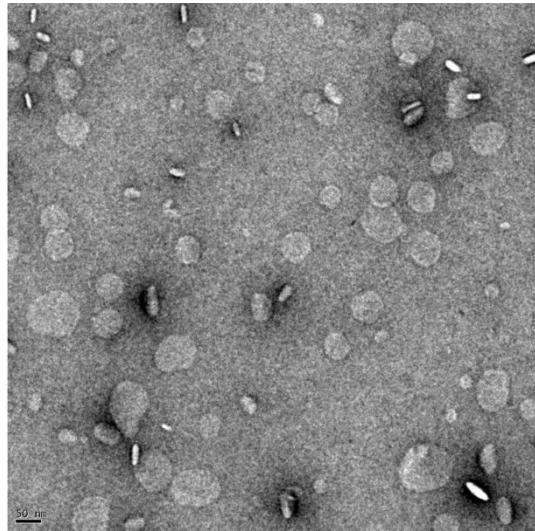


Scattering Form Factors

Common form factors of particulate systems

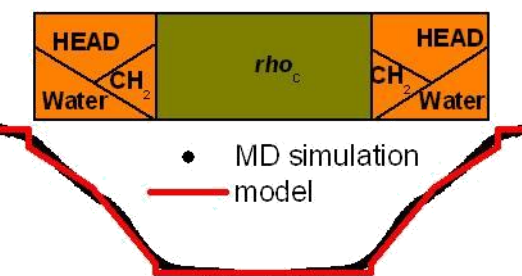
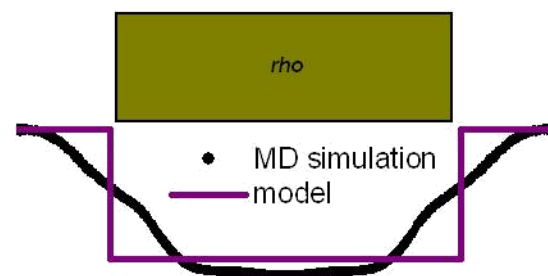
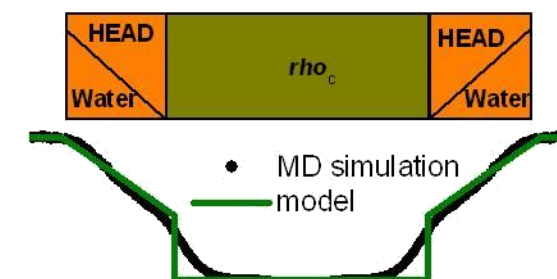
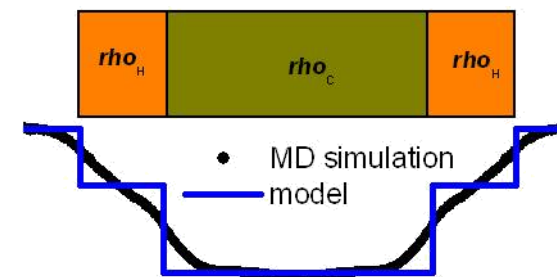
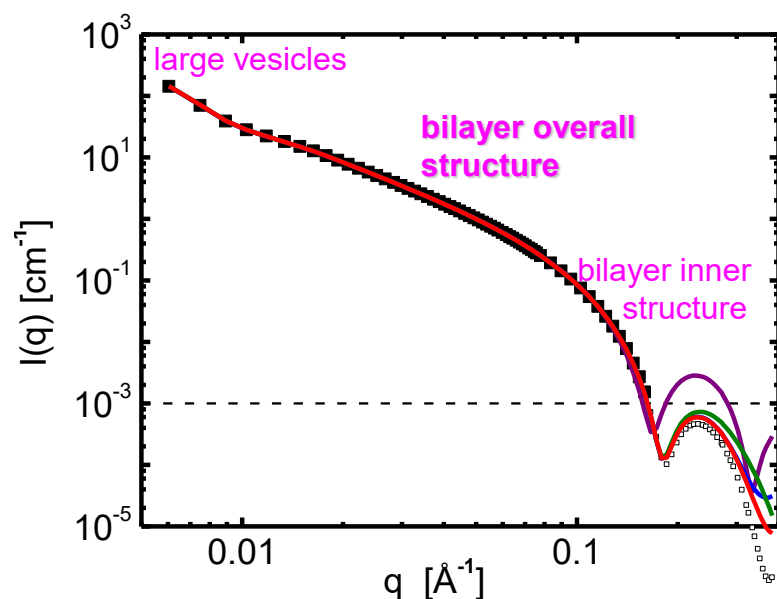
Morphologies	P(q)	Remarks
Spheres (radius :R)	$\frac{9}{(qR)^6} [\sin(qR) - qR \cdot \cos(qR)]^2 = A_{\text{sph}}^2(qR)$	- Integration of x and y are for orientational average. $J_1(x)$ is the first kind Bessel function of order 1
Spherical shells (outer radius: R_1 inner radius: R_2)	$\frac{[R_1^3 \cdot A_{\text{sph}}(qR_1) - R_2^3 \cdot A_{\text{sph}}(qR_2)]^2}{(R_1^3 - R_2^3)^2}$	
Triaxial ellipsoids (semiaxes: a,b,c)	$\int_0^1 \int_0^1 A_{\text{sph}}^2 [q \sqrt{a^2 \cos^2(\pi x/2) + b^2 \sin^2(\pi x/2)(1-y^2)} + c^2 y^2] dx dy$	
Cylinders (radius: R length: L)	$4 \int_0^1 \frac{J_1^2[qR \sqrt{1-x^2}]}{[qR \sqrt{1-x^2}]^2} \frac{\sin^2(qLx/2)}{(qLx/2)^2} dx$	
Disk (radius: R infinitely thin)	By setting $L = 0$	
Rod (length: L infinitely thin)	By setting $R = 0$	
	$\frac{2 - J_1(2qR)/qR}{q^2 R^2}$	
	$\frac{2}{qL} \int_0^{qL} \frac{\sin(t)}{t} dt - \frac{\sin^2(qL/2)}{(qL/2)^2}$	

Model Analysis of Scattering Experimental Data



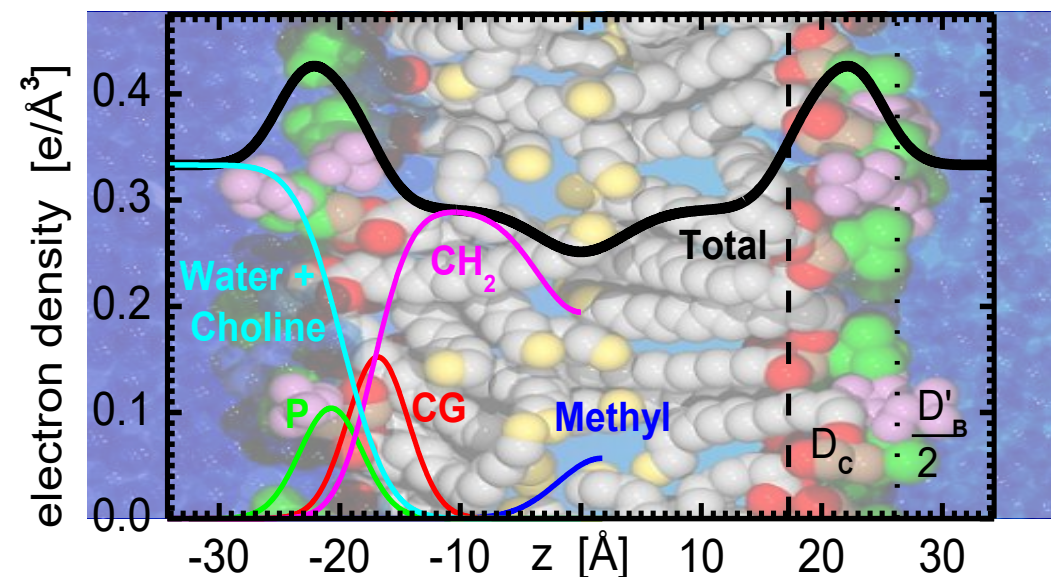
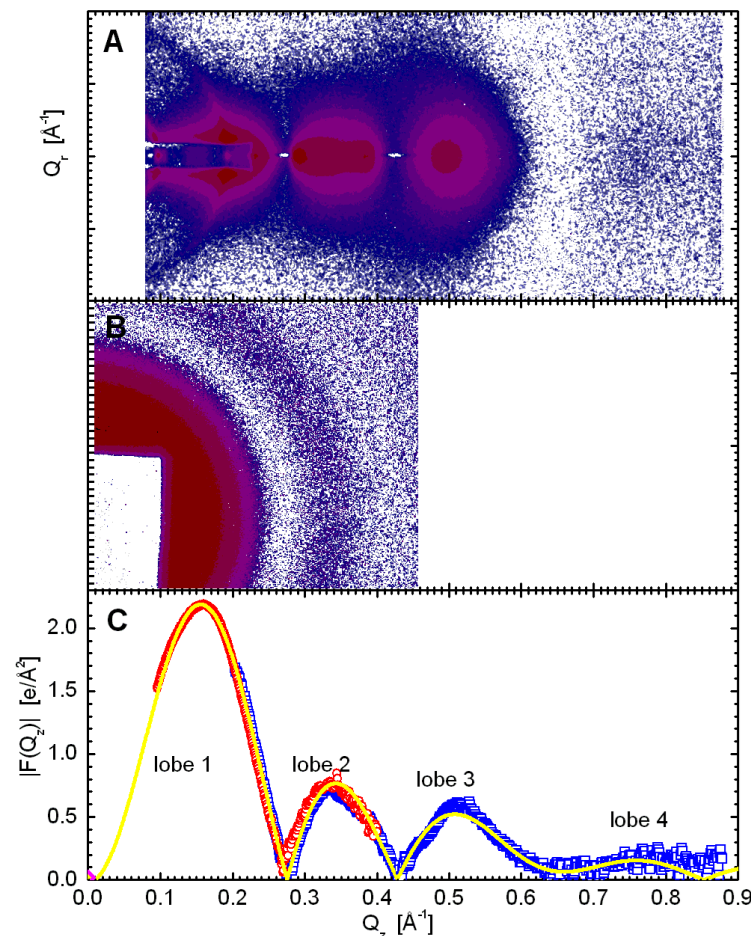
Neutron Scattering = Simple Models

- neutron scattering data are inherently featureless
- however, the mid- q region provides strong information on bilayer overall structure, reflecting the large scattering contrast between the lipid bilayer (a lot of H) and solvent (D_2O)



X-ray Scattering = Complex Models

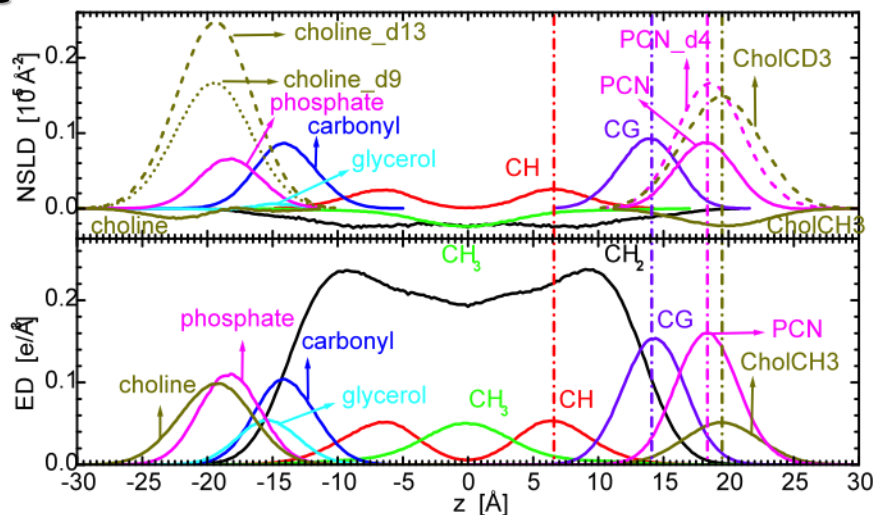
- high resolution X-ray scattering data allows for using complex models, thus enhancing the spatial resolution of the bilayer structure



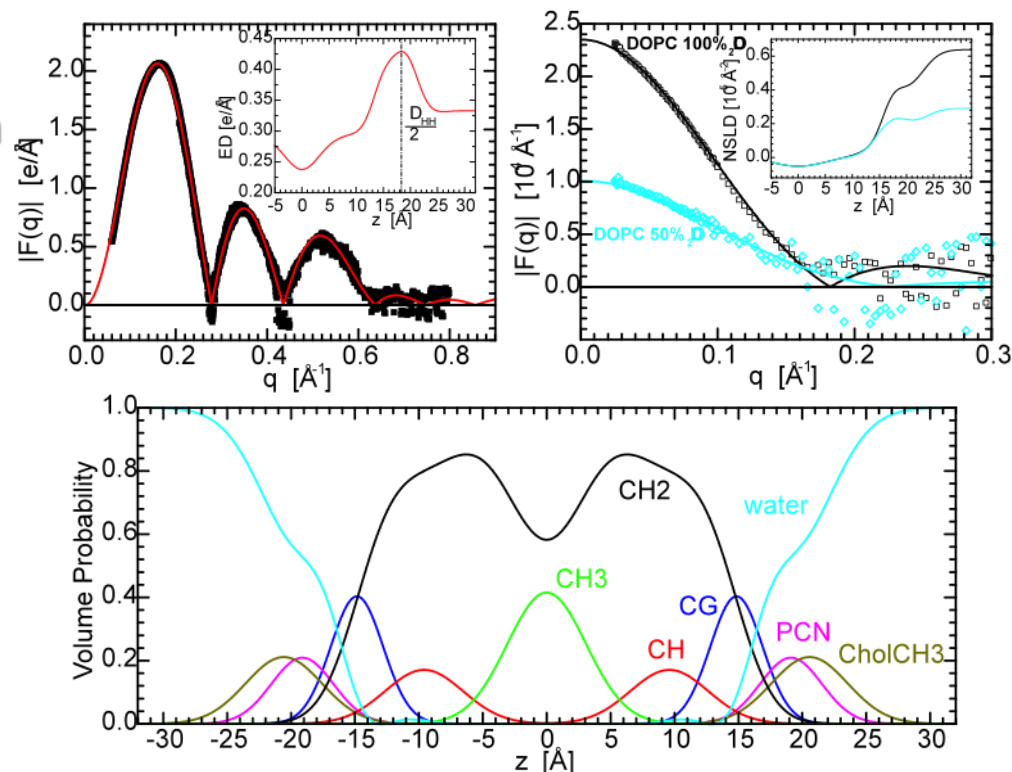
Joint Refinement = Advanced Models

Scattering Density Profile analysis

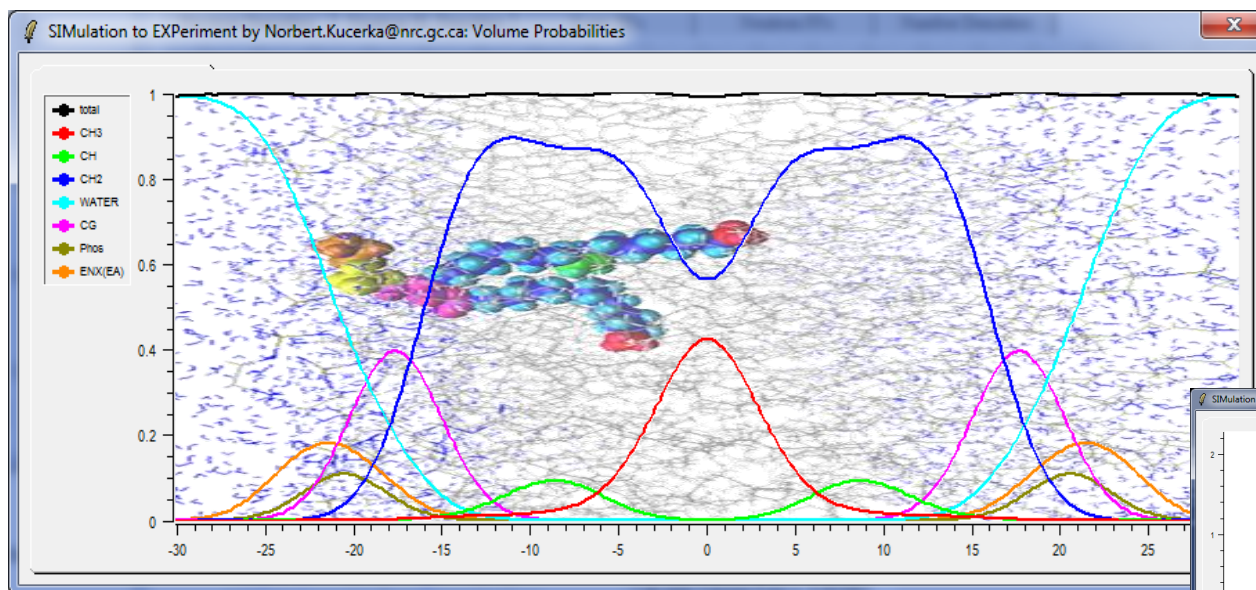
- The same functional form for all of the different contrast conditions (X-rays and neutron contrast variation)
- Volume distributions satisfy a spatial conservation principle



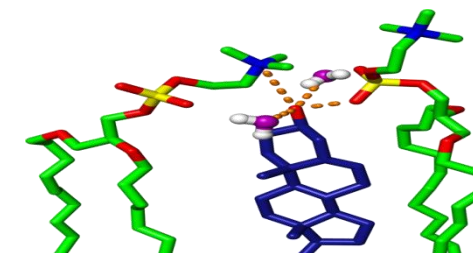
The SDP model is fit simultaneously to the different contrast conditions.



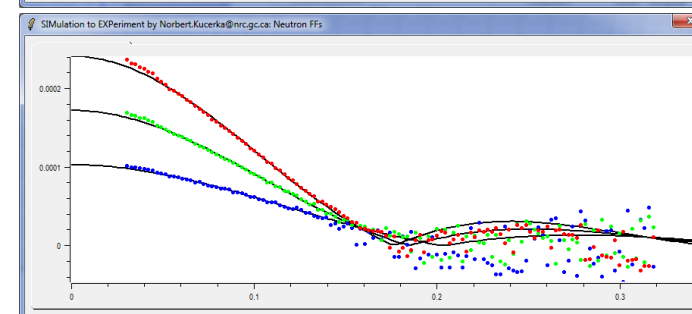
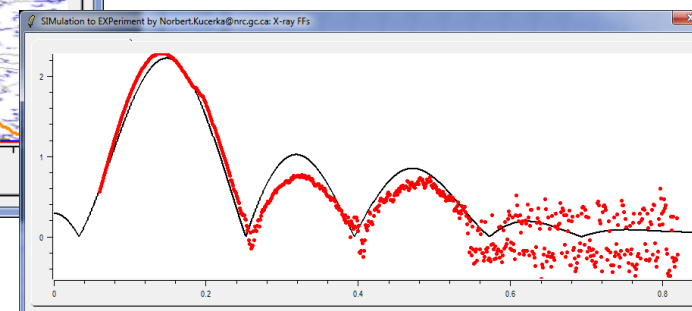
MD Simulations + Experiment = beyond advanced



detailed structural information



hydrogen bonding interactions
lipid - cholesterol - water



SIMulation to EXperiment analysis

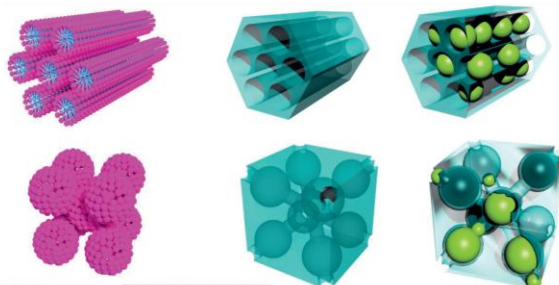
- MD simulations aid the analysis of experiment
- experimental results help to improve simulations
- direct comparison reconciles simulation and experiment



SAS and low-resolution techniques

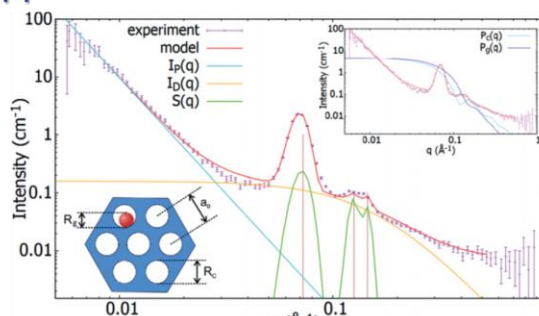
Nanopores for Magnetic and Biomedical Applications

- Periodic nanoporous material on the basis of amorphous silica
- Neutrons reveal the inside of **composites with nanoparticles**

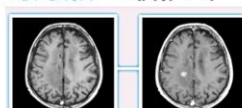


Applications

- Therapeutic agents in tumor treatment and drug delivery
- MRI contrast media (Gadovist)



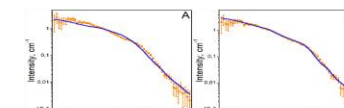
$$I(q) = K_C S(q) |F_C(q)|^2 + K_S |F_S(q)|^2 + I_d(q) + I_i$$



- Magnetic refrigeration due to the large magnetocaloric effect

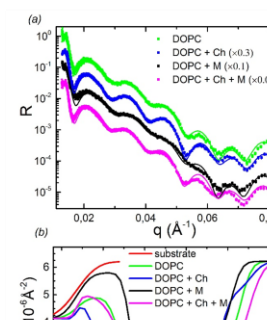
Superstructure of Signaling Systems

- Two-component systems** (transmembrane proteins in general) are responsible for the communication of microorganisms with their environment



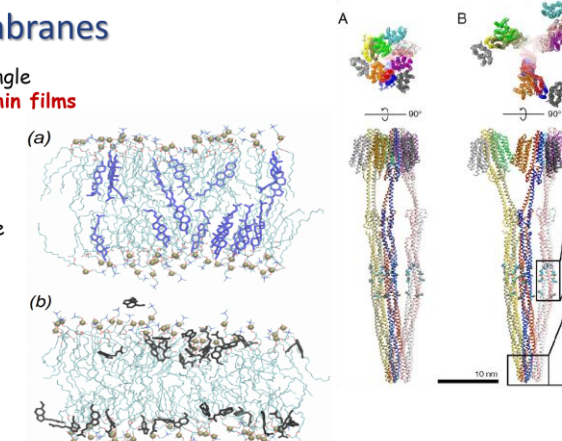
Reflectometry of Model Lipid Membranes

Neutron reflectometry experiments performed with single supported membranes reveal the structures of these **thin films**



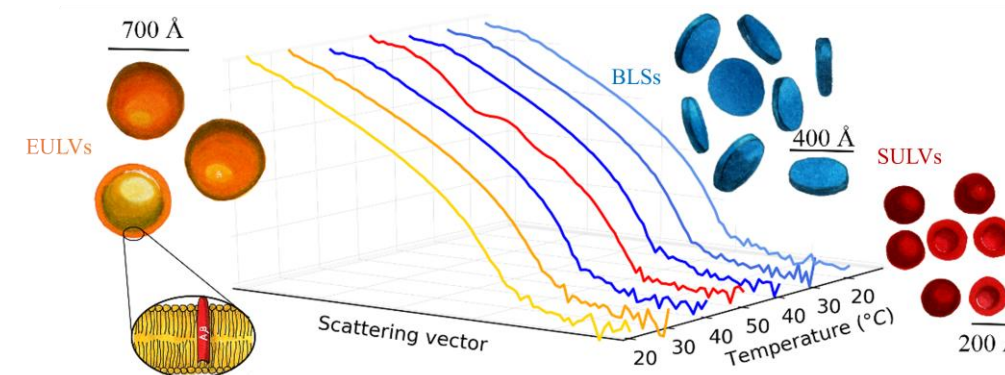
Cholesterol increases the membrane thickness

Melatonin decreases the membrane thickness



Understanding the Mechanism of Alzheimer's Disease

- Neutron scattering allows to study model membranes that replicate **pre-clinical** stage of AD

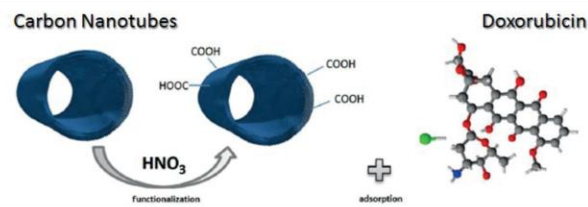


Changes in the membrane self-organization happen during the thermodynamic phase transitions of lipids and are interpreted as the **peptide driven membrane breakage**.

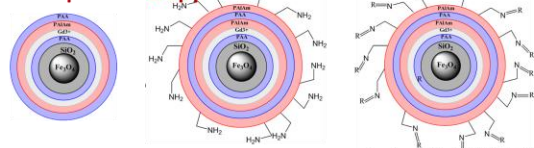
Ivankov, Murugova, Ermakova, Kondela, Badreeva, Soloviov, Kuklin, Kučerka, Sci Rep 11, 21990 (2021)

Drug Delivery Systems

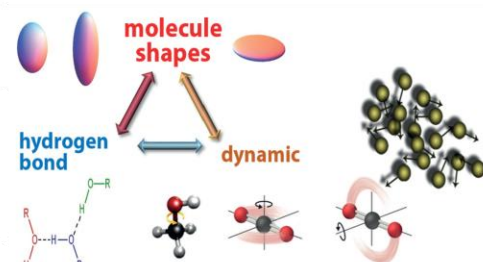
- Carbon nanoplatforms** for molecular imaging, tissue engineering, biosensors, and **targeted drug delivery** in cancer treatment



- Superparamagnetic Fe₃O₄ core-shell nanoparticles for **boron neutron capture therapy**



- Isomeric forms** of antiepileptic drug ETX was studied by **inelastic neutron scattering**
- Due to different pharmacological activity, enantiomers may differ in **toxicity**





Outline

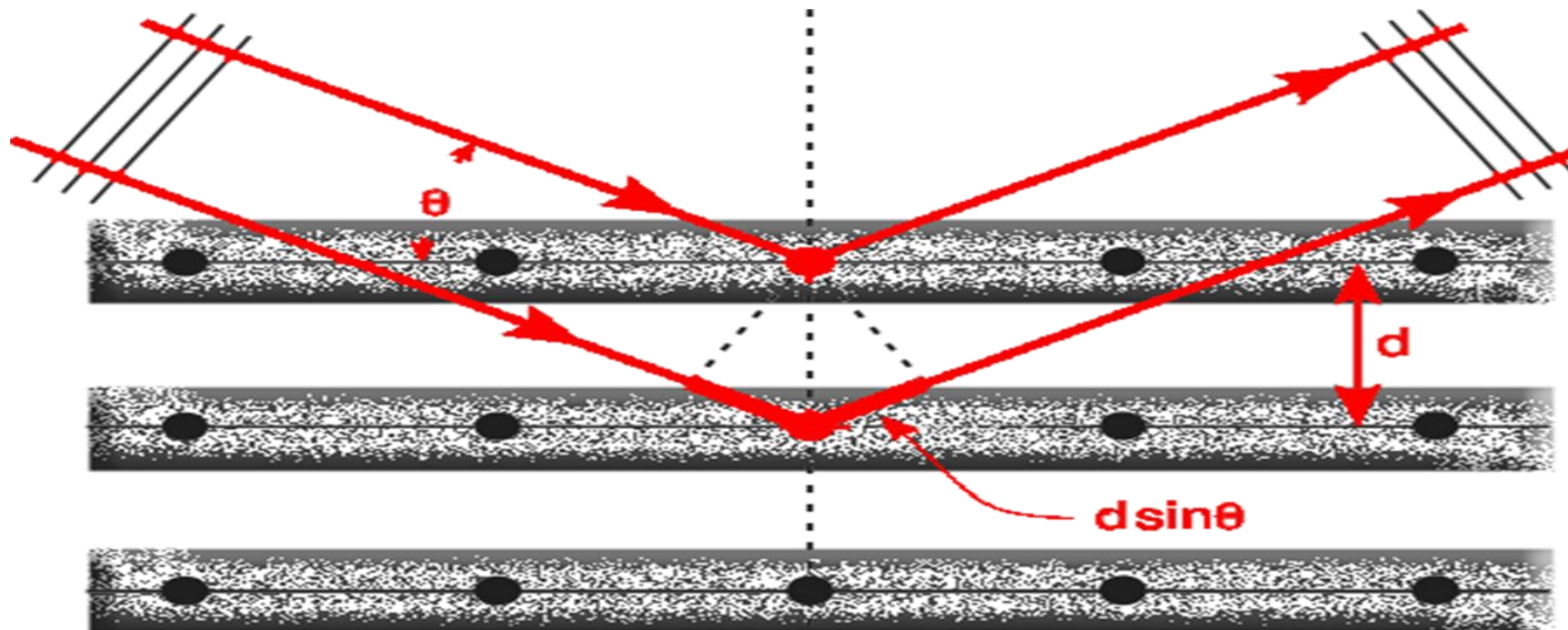
- Historical Overview
- Sources and Properties of Neutrons
- Principles of Small-Angle Scattering
- Analysis of Small Angle Scattering Data + Examples
- **Principles of Small Angle Diffraction**
- Analysis of Small Angle Diffraction Data + Examples



The Bragg's Law

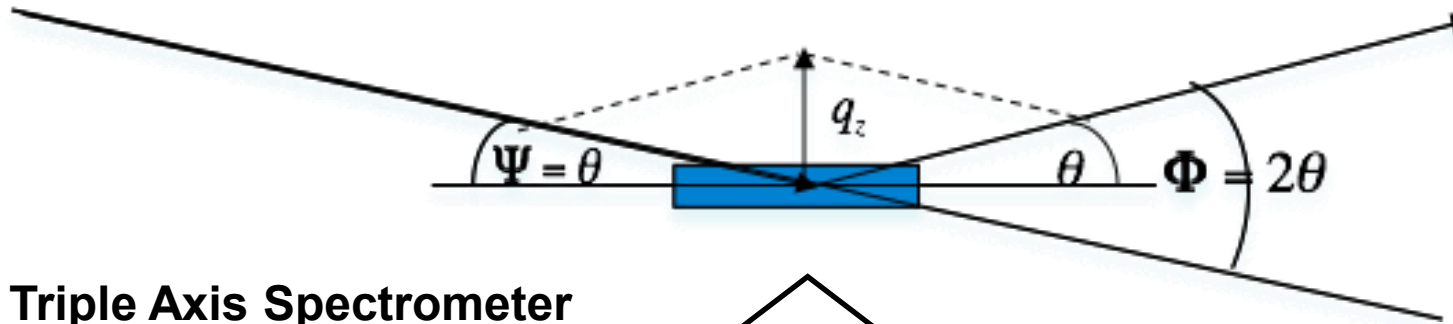
The two planes will scatter in phase if the path difference ' $2d\sin(\theta)$ ' is a whole number of wavelengths ' $n\lambda$ '

$$n\lambda = 2d\sin(\theta)$$

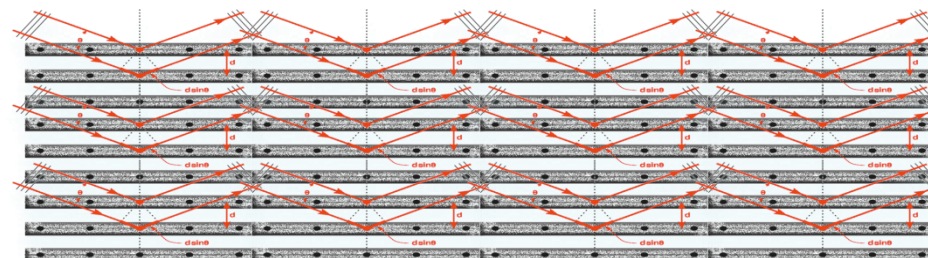
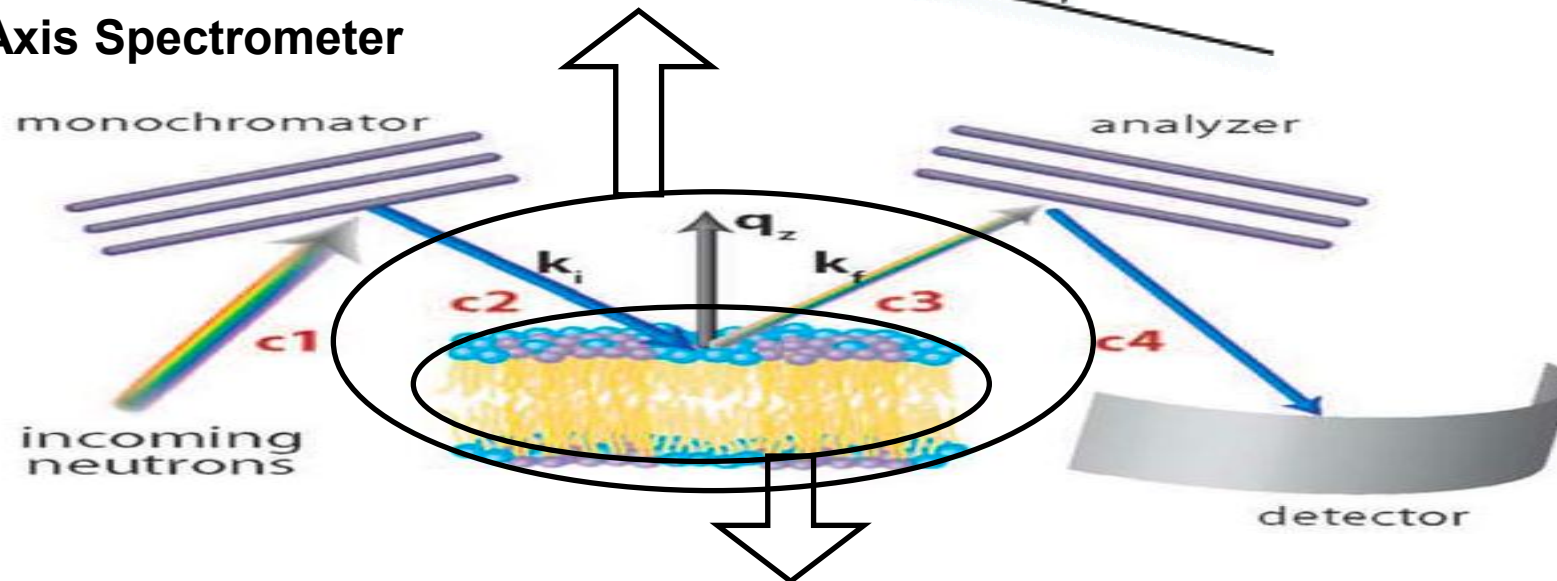




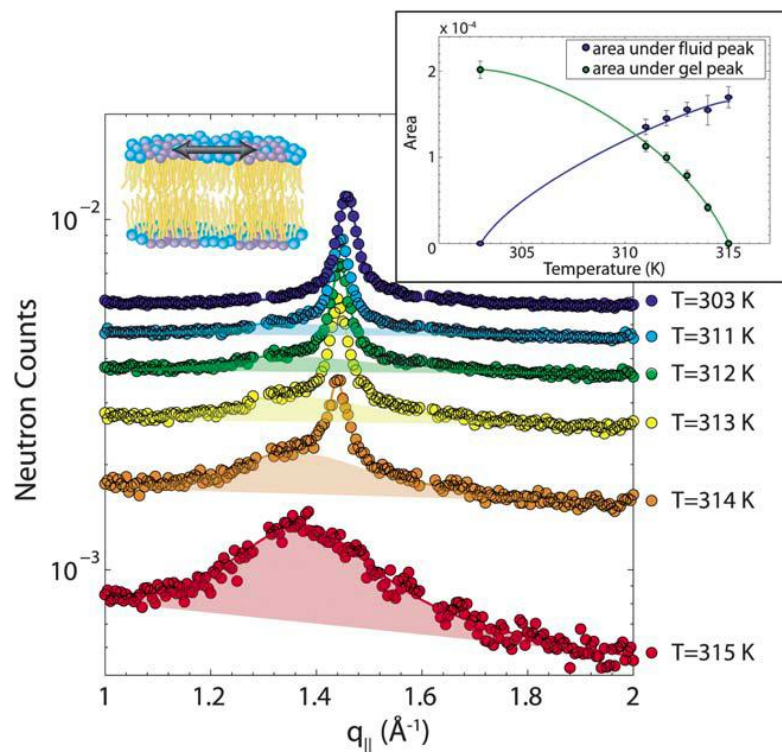
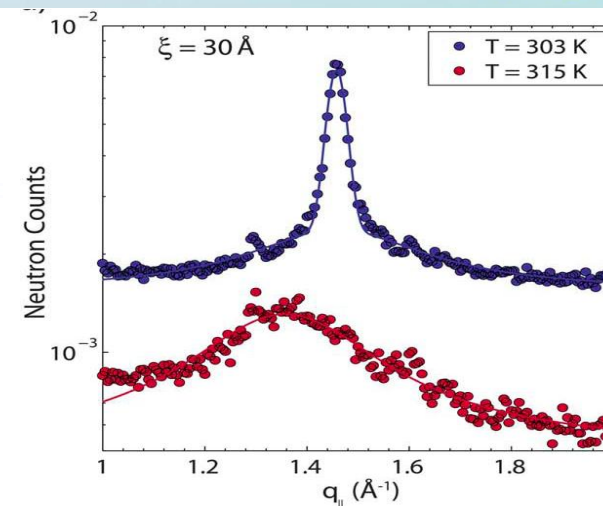
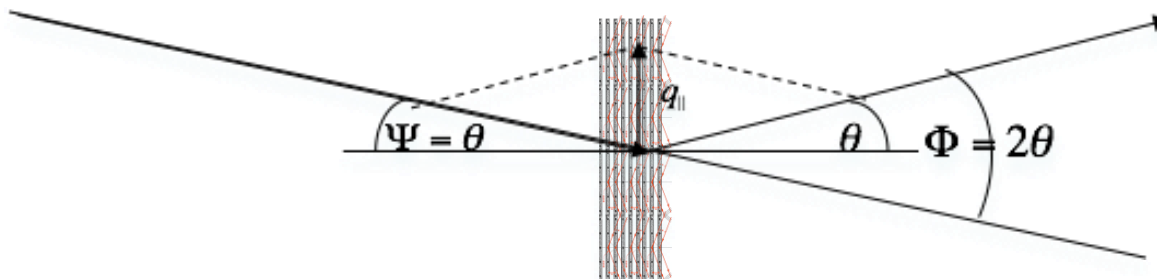
Scattering Angles in Diffraction



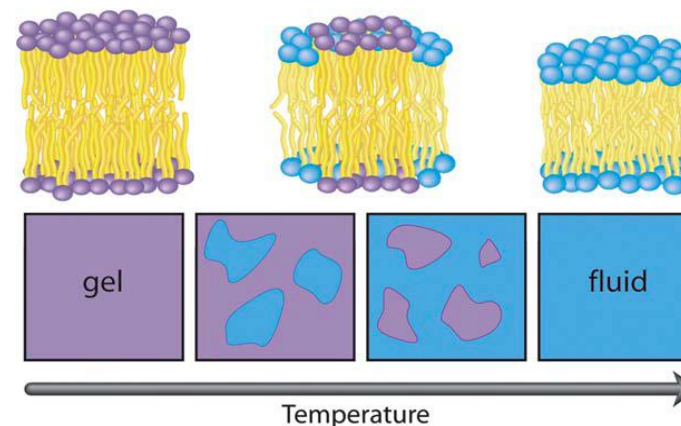
Triple Axis Spectrometer



In-plane Scattering

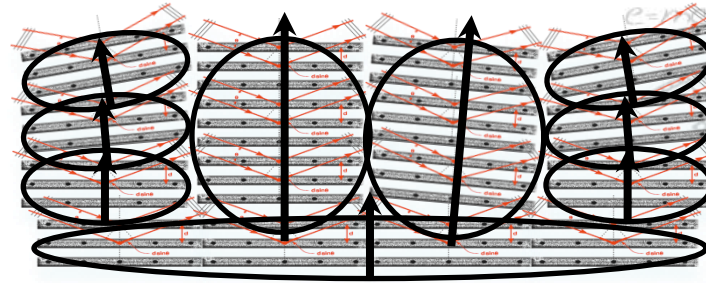
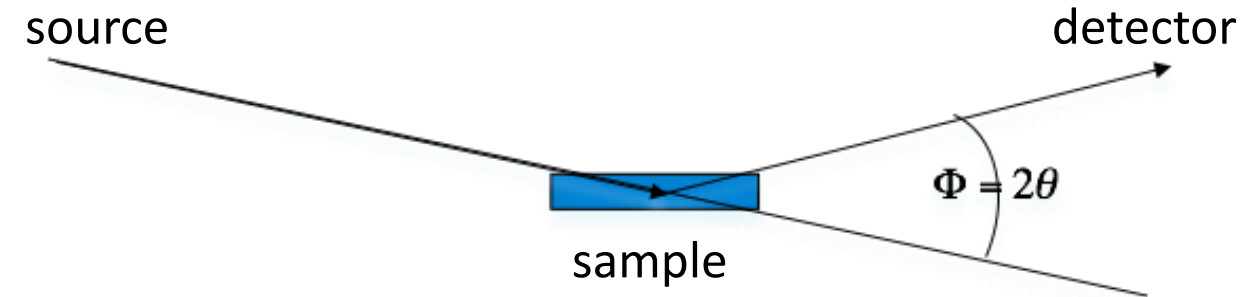


Instead of a continuous phase transition from the well ordered gel into the fluid phase, which adheres to a well-known critical behaviour, **neutron diffraction shows** a first order transition with a **co-existence of gel and fluid domains**.

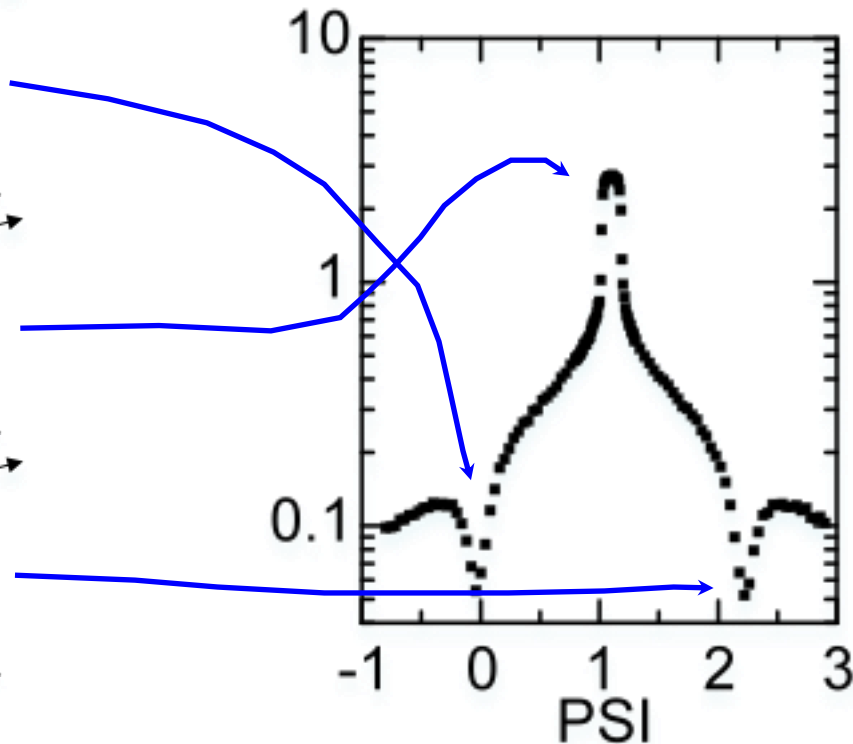
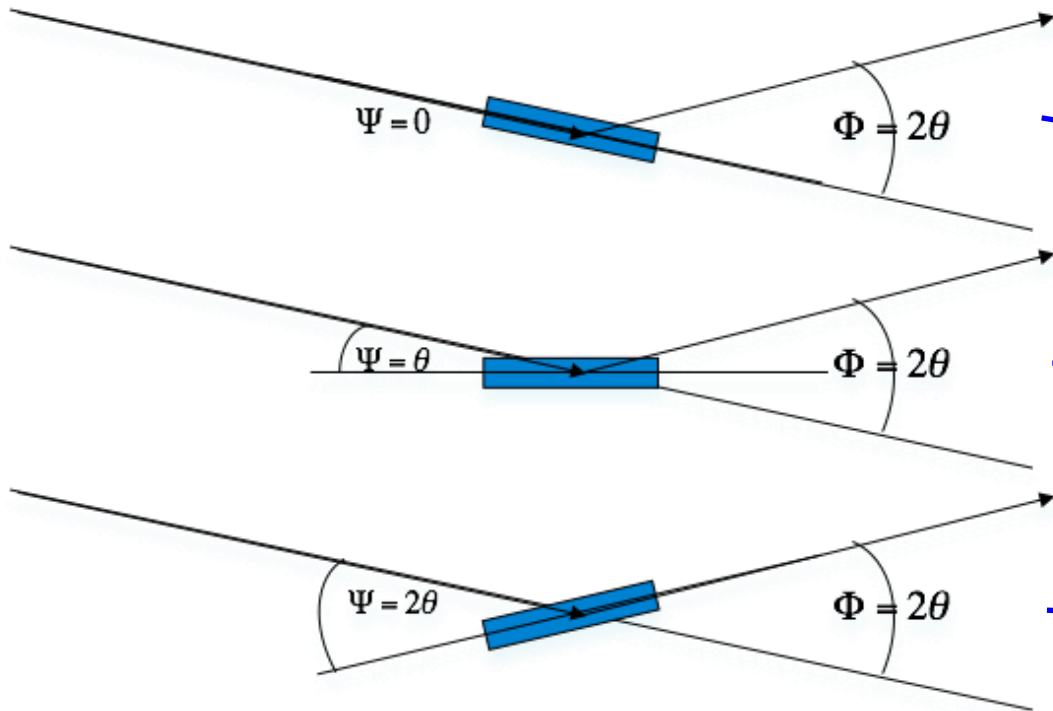




Non-qz Component in Rocking Curve



READY FOR A
QUIZ?

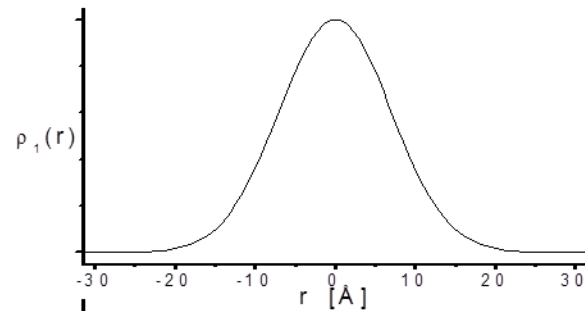




Scattering & Real Space – Fourier Transform

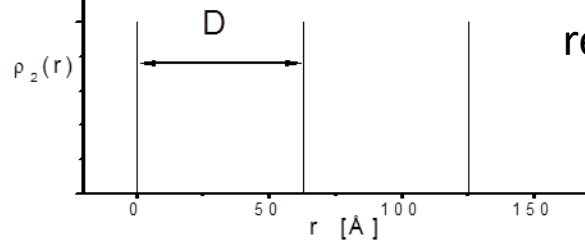
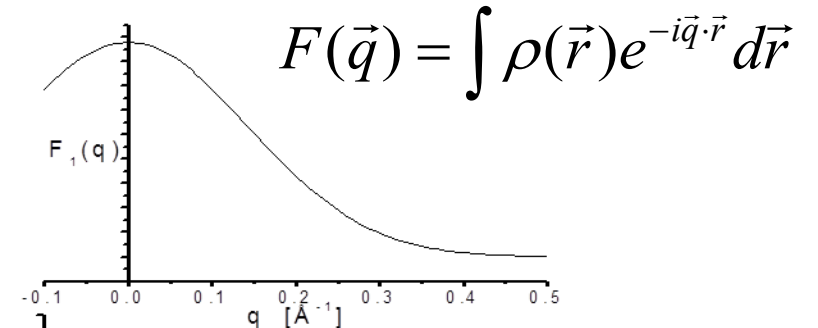
$\rho(r)$ - scattering density profile

Scattering amplitude = FT of SDP



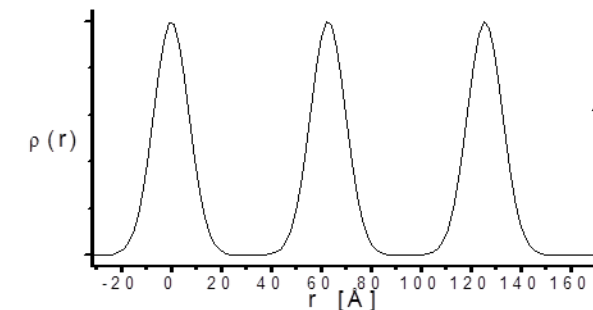
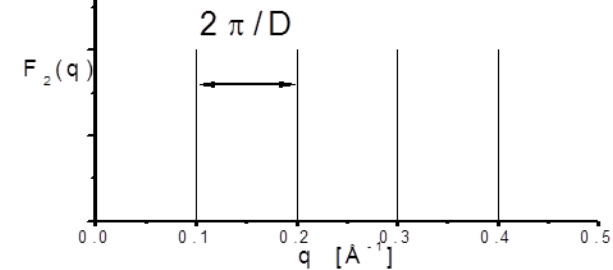
$$\exp\left(-\frac{x^2}{2\sigma^2}\right)$$

$$\sqrt{2\pi\sigma} \exp\left(-\frac{q^2\sigma^2}{2}\right)$$



repeat spacing D

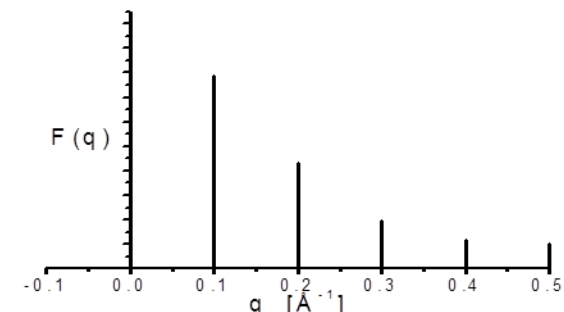
repeat spacing $2\pi/D$



$$\rho_1(\vec{r}) * \rho_2(\vec{r})$$

$$F_1(\vec{q}) F_2(\vec{q})$$

$$FT(\rho_1(\vec{r}) * \rho_2(\vec{r})) = FT(\rho_1(\vec{r})) FT(\rho_2(\vec{r}))$$





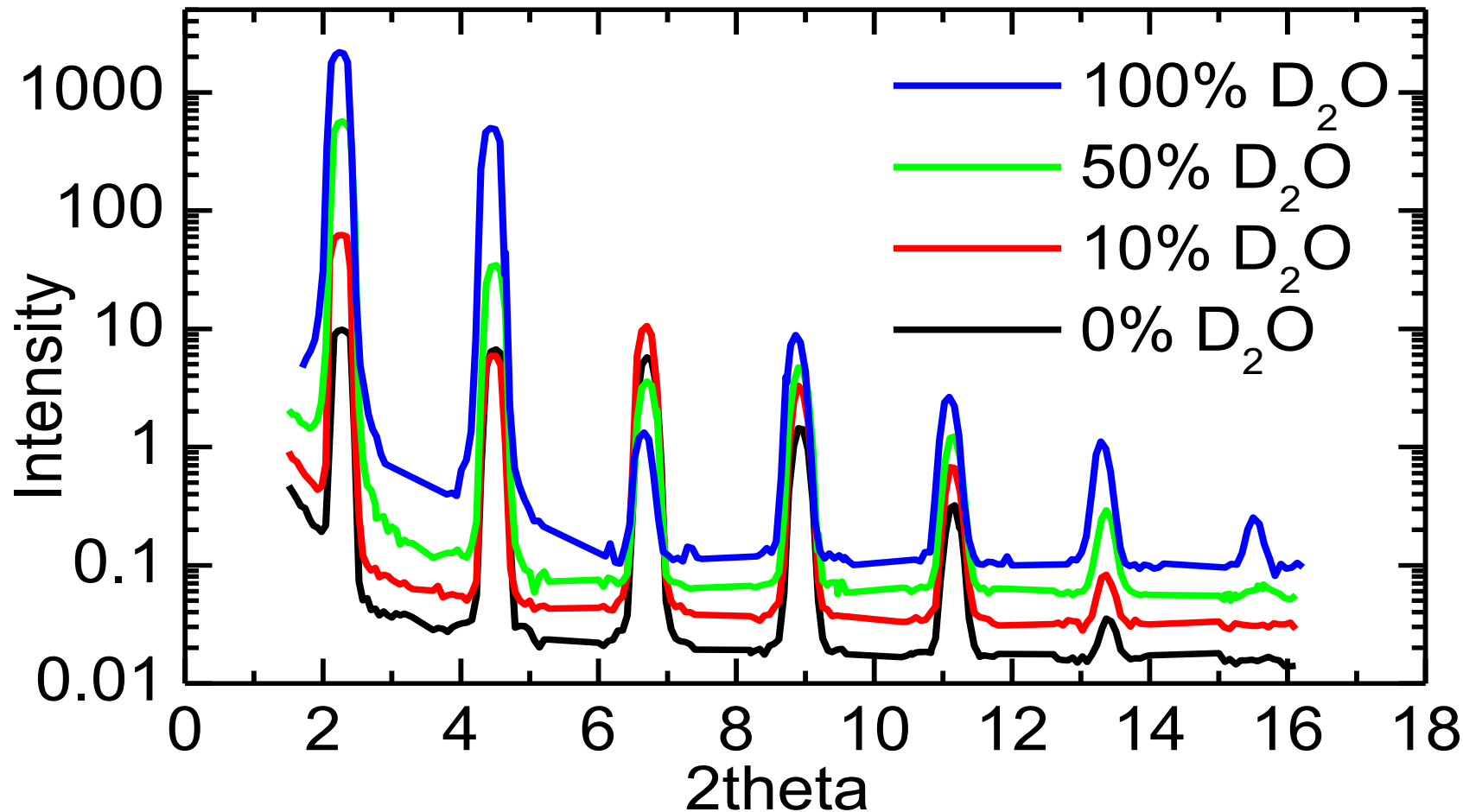
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- Analysis of Small Angle Diffraction Data + Examples

Small-Angle Diffraction – Diffraction Curve

$$I(q) \sim F^2(q)$$

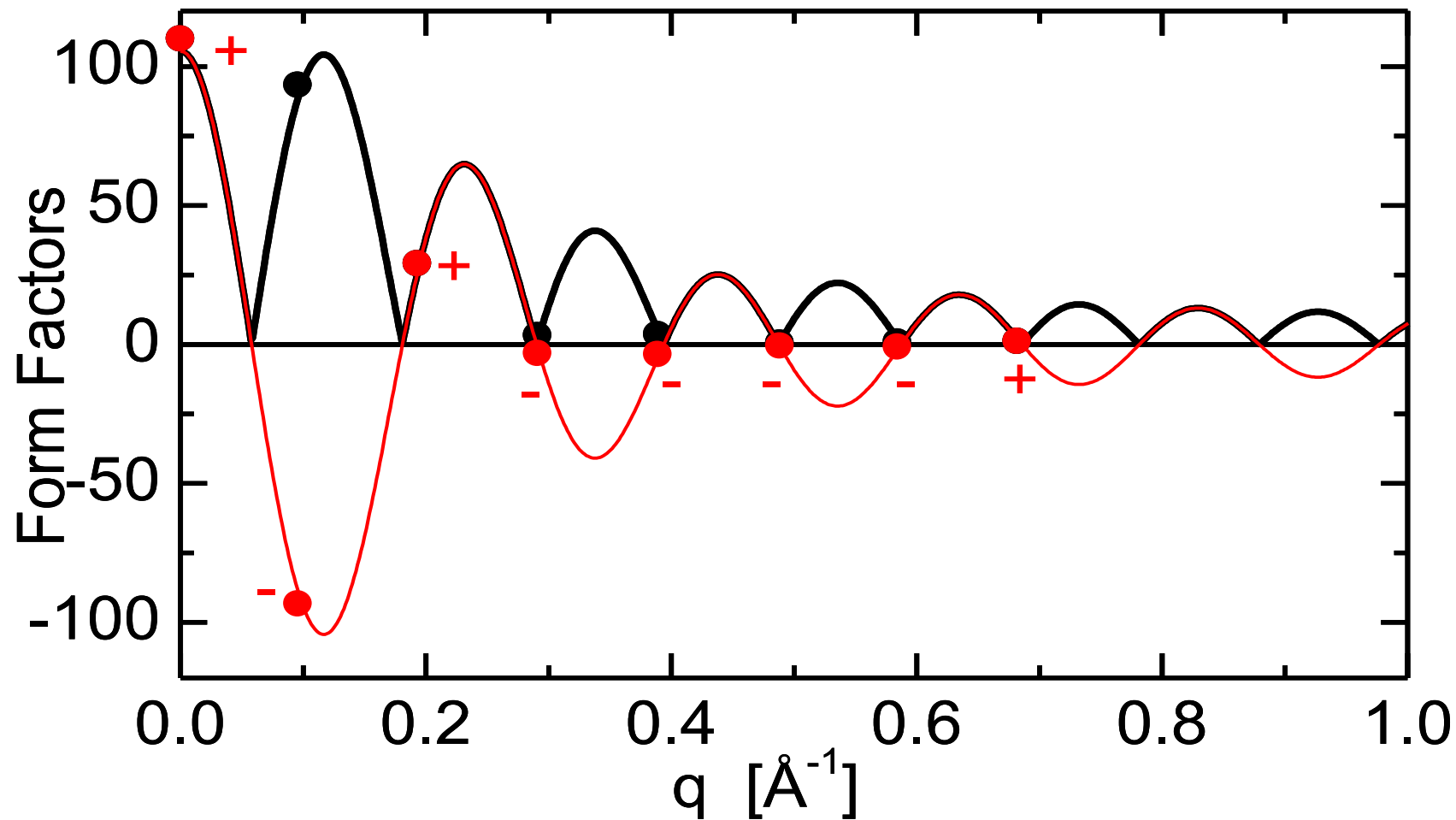
$$F(q) \sim FT(\rho(z))$$



Phase Problem

$$\rho(z) \sim FT(F(q))$$

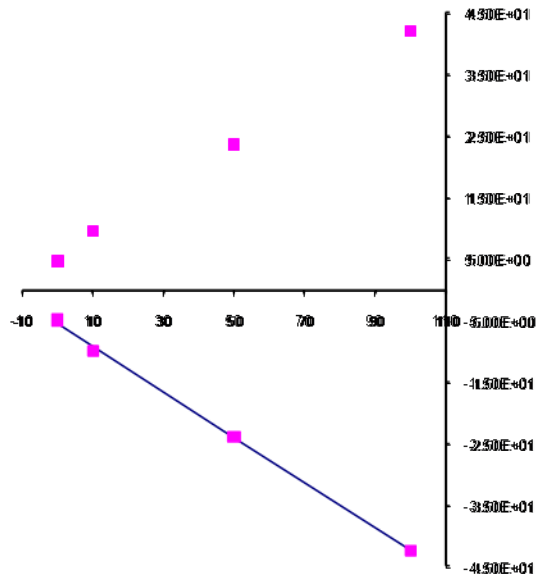
$$|F(q)| \sim \sqrt{I(q)}$$



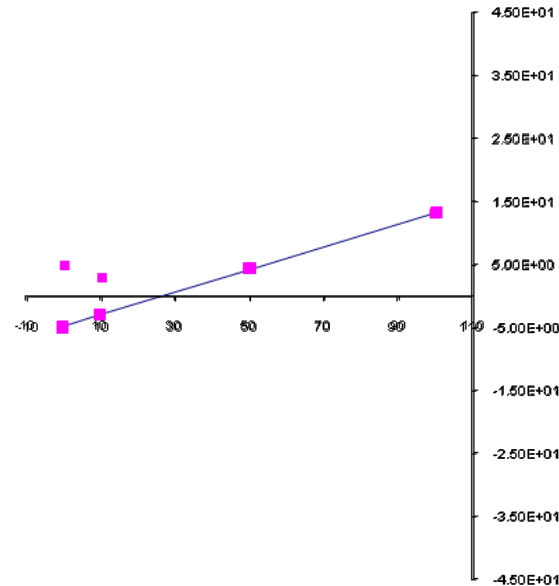


Phase Determination

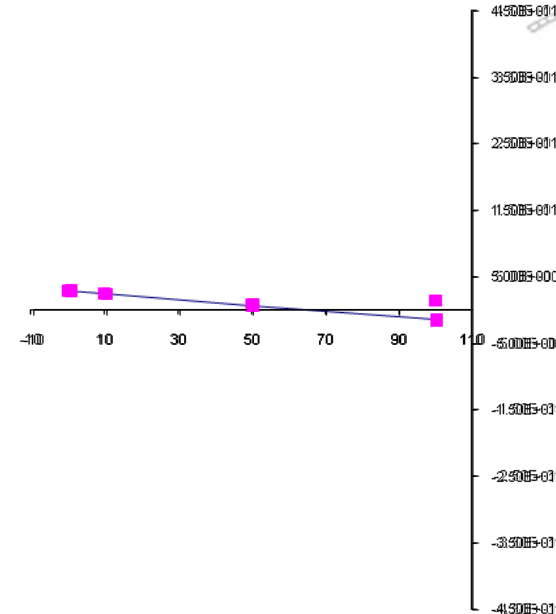
1st order



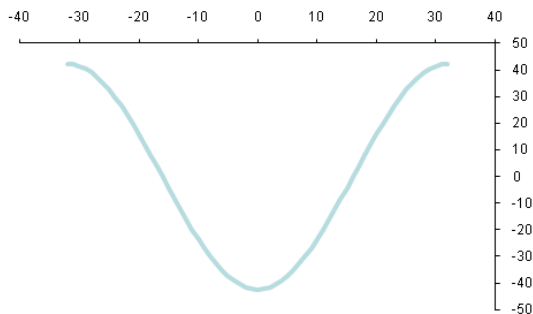
2nd order



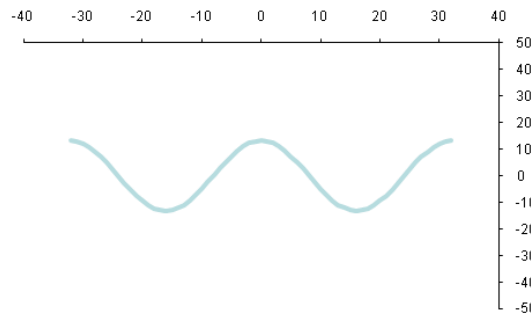
3rd order



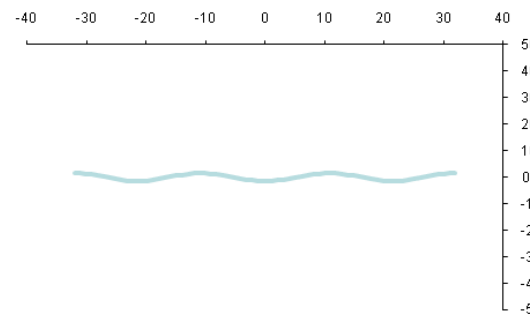
100% D₂O



100% D₂O



100% D₂O

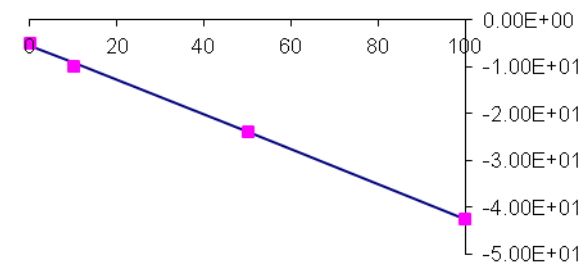


READY FOR A
QUIZ?

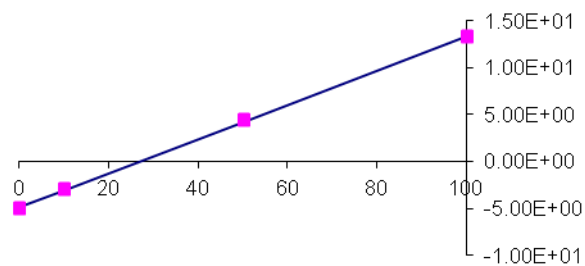


Phase Determination

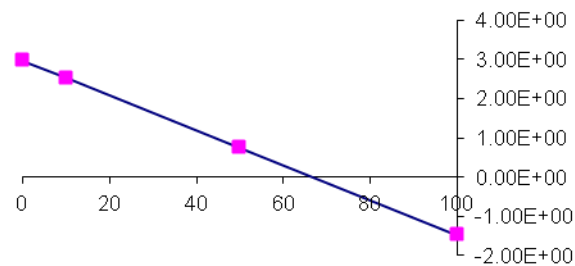
1st order



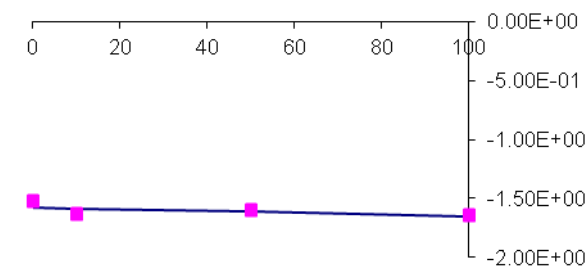
2nd order



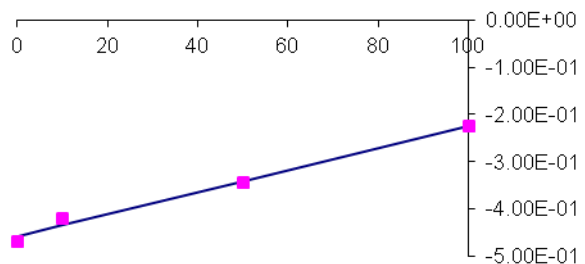
3rd order



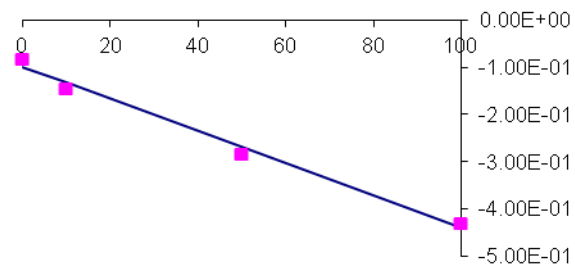
4th order



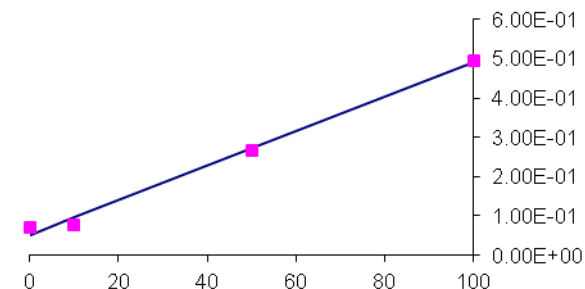
5th order



6th order

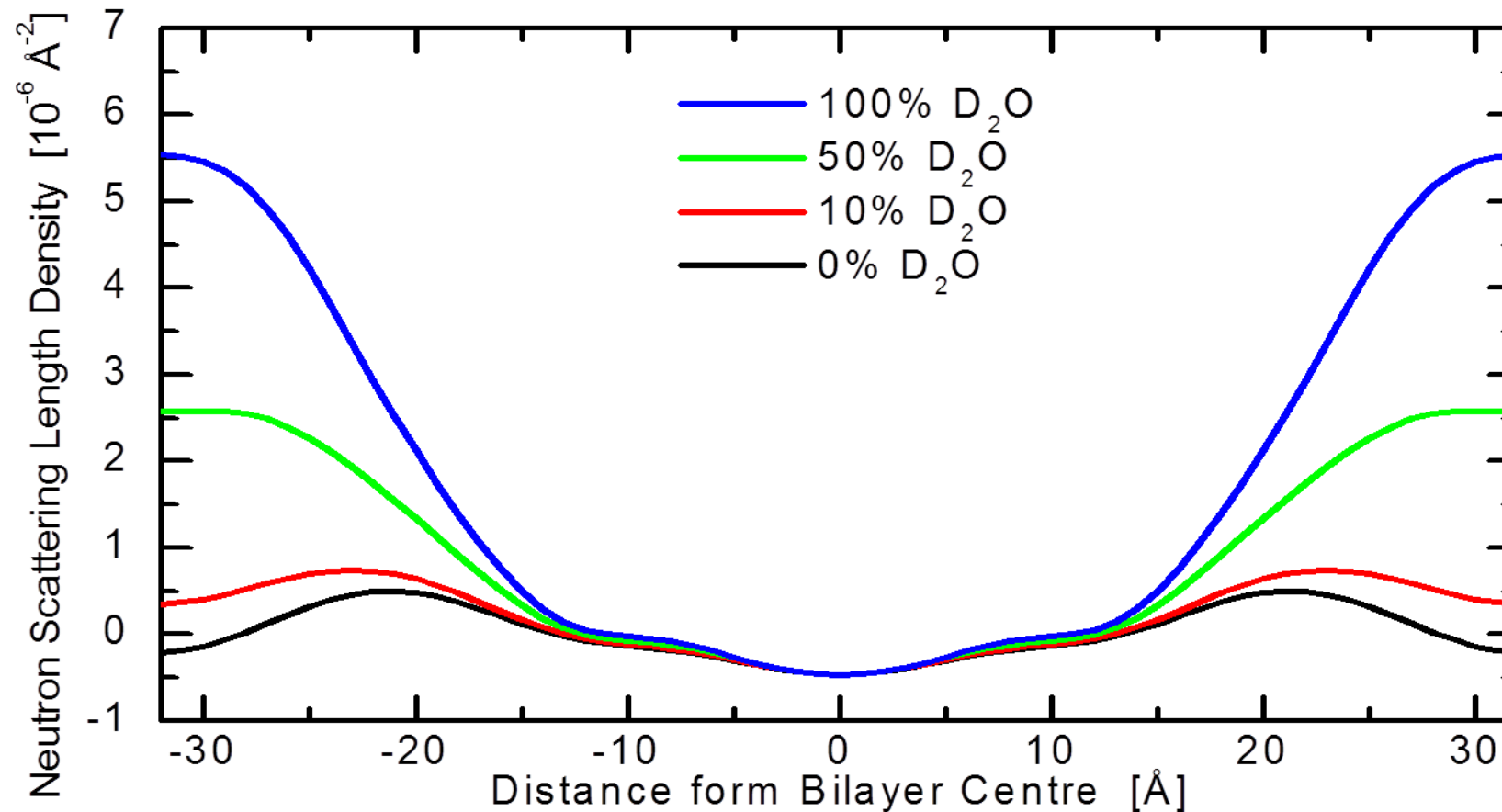


7th order



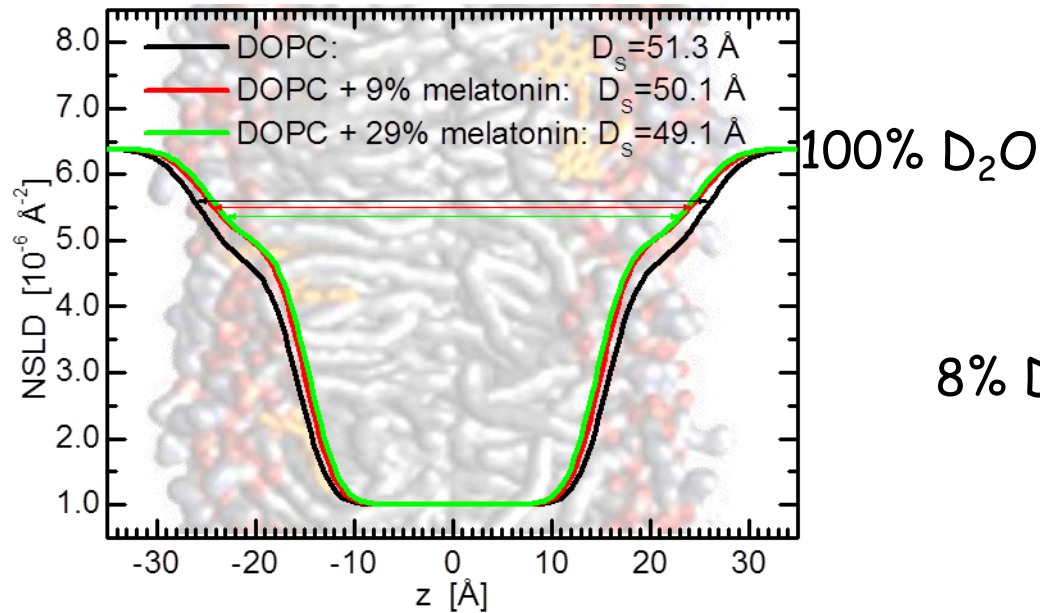
Bilayer Structure Reconstruction

$$\Delta\rho(z) = \frac{1}{D} F_0 + \frac{2}{D} \sum_{h=1} F_h \cos\left(\frac{2\pi h z}{D}\right)$$

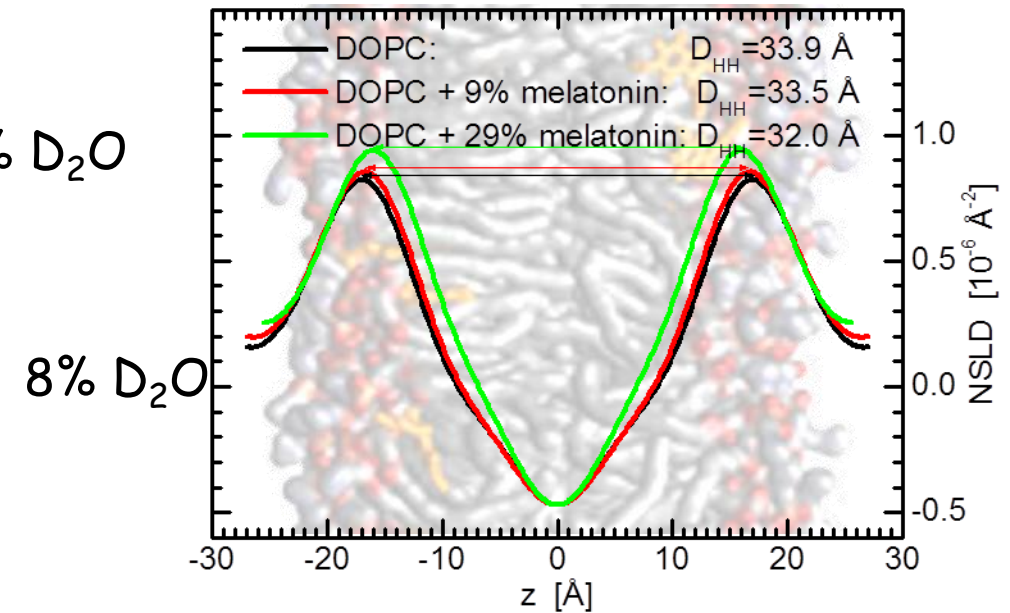


Bilayer Thickness

NSLD profiles provide a measure of various bilayer thicknesses



Interface between bilayer and surrounding 100% D₂O provides a steric (total) bilayer thickness



Lipid head-to-head distance is revealed for bilayers dispersed in 8% D₂O (NSLD of solution is zero)



Summary

- Small-Angle Scattering is a valuable tool for structural biophysics allowing the *in situ* measurements of systems between 10 to 1000 Å
- The scattering function is proportional to the product of form factor (intraparticle scattering function) and **structure factor** (interparticle interactions)
- Small-Angle Diffraction allows to **uncouple** information according to the **orientation** planes
- Contrast variation offers the solution of scattering **phase problem**
- Solvent contrast variation provides **water distribution** profiles
- Specific labeling enhances **resolution** of determined structures
- Bilayer structure reveals the link between the **structure and function** taking place in biological membrane