Stochastic models for elastic and inelastic scattering data analysis of fluctuating membranes with embedded proteins

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Outline

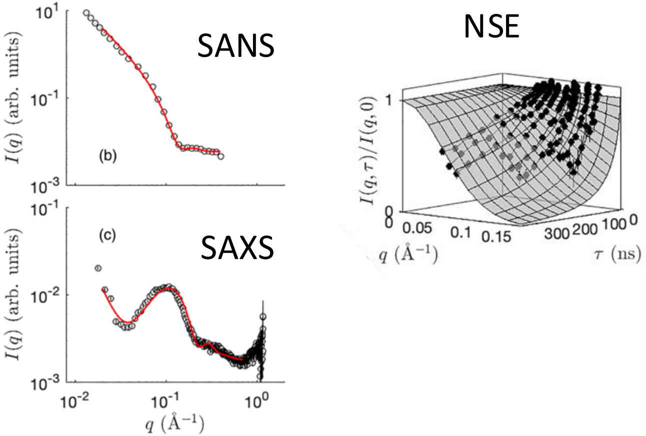
- Introduction (5 slides)
  - Context (SAXS, SANS & NSE of membranes)
  - Classical approaches for data analysis
- Stochastic models of fluctuating membranes (13 slides)
- Adding protein-like inclusions to these (and other) models (9 slides)

A bit of context, and the data at hand

PHYSICAL REVIEW E **110**, 034608 (2024)

Gaussian model of fluctuating membrane and its scattering properties

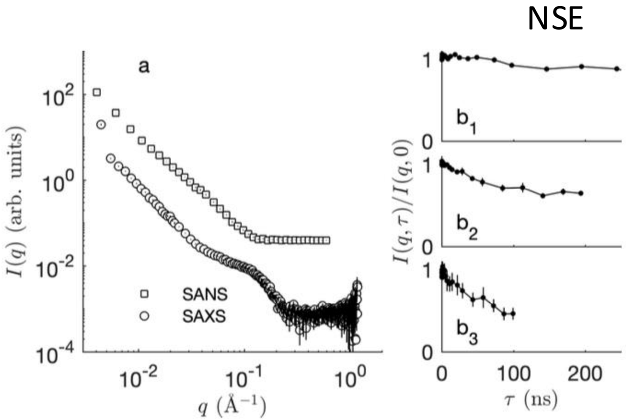
Cedric J. Gommes,[1,*] Purushottam S. Dubey,[2] Andreas M. Stadler,[3,4] Baohu Wu,[2] Orsolya Czakkel,[5] Lionel Porcar,[5] Sebastian Jaksch,[2,6] Henrich Frielinghaus,[2] and Olaf Holderer[2,†]



JOURNAL OF APPLIED CRYSTALLOGRAPHY
ISSN 1600-5767
J. Appl. Cryst. (2025). **58**

Model for small-angle scattering analysis of membranes with protein-like inclusions

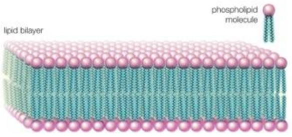
Cedric J. Gommes,[a*] Olga Matsarskaia,[b] Julio M. Pusterla,[c] Igor Graf von Westarp,[c,d] Baohu Wu,[e] Orsolya Czakkel[b] and Andreas M. Stadler[c,d*]

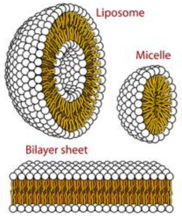


Unilamellar vesicles prepared from phospholipids extracted from porcine brain tissue

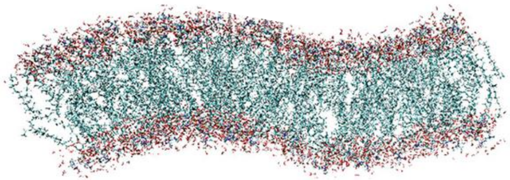
Red blood cells liposomes

Ideal and actual membranes

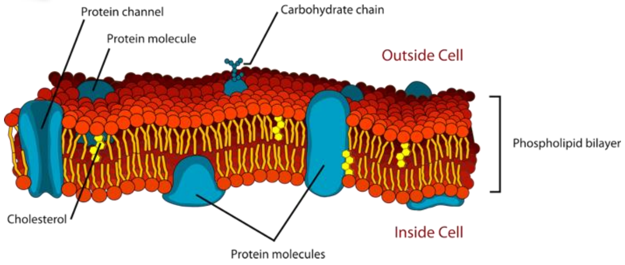


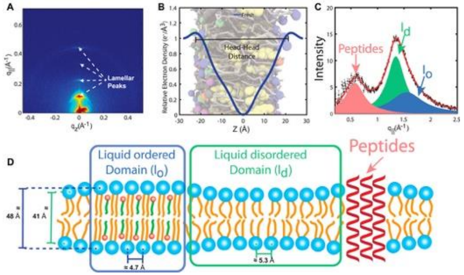


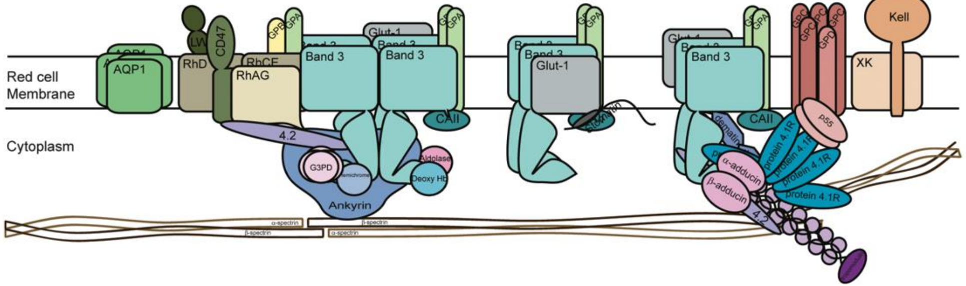
Phys Rev. E paper
(phospholipid vesicles)



J. Appl. Crystallography paper
(RBC liposomes)

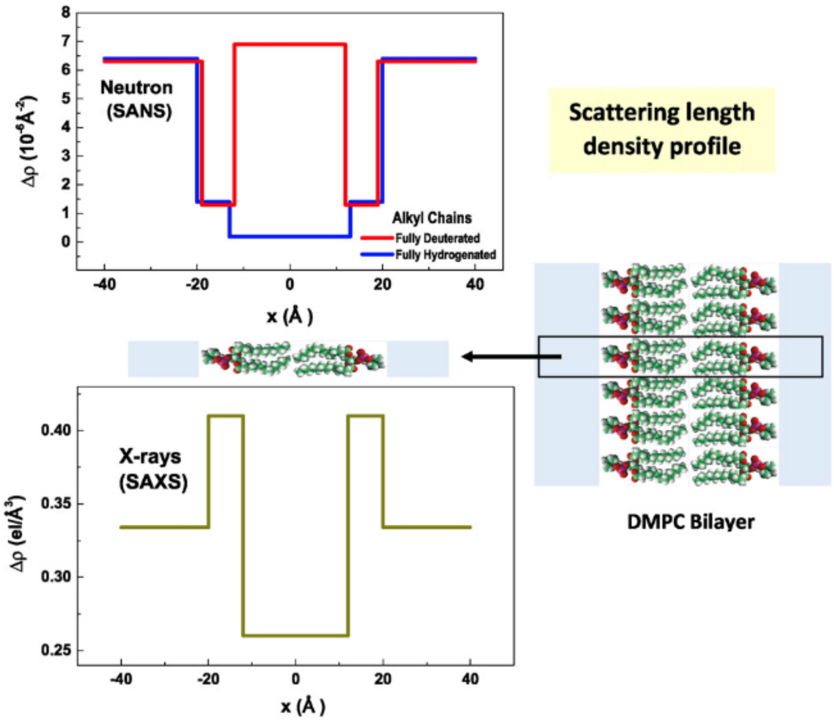


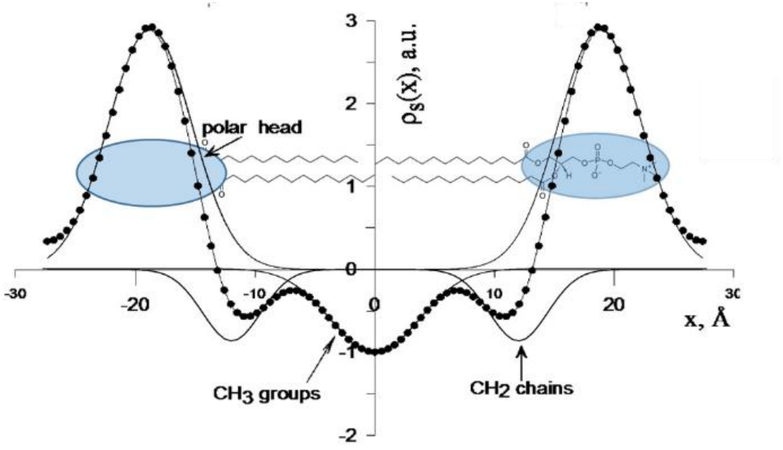




Slab-like models for SAXS/SANS analysis

M.A. Kiselev, D. Lombardo / Biochimica et Biophysica Acta 1861 (2017) 3700–3717





Dynamics of membrane bending fluctuations

VOLUME 77, NUMBER 23 PHYSICAL REVIEW LETTERS 2 DECEMBER 1996

Undulations and Dynamic Structure Factor of Membranes

A. G. Zilman and R. Granek

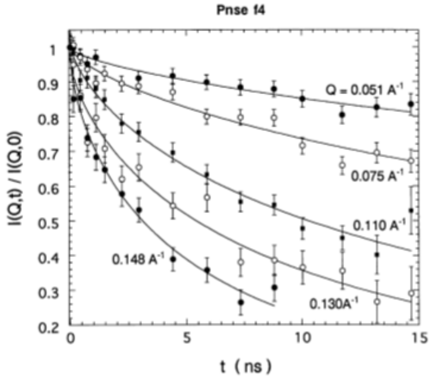
$$S(q,t) \simeq S(q) e^{-(\Gamma_q t)^{2/3}}$$

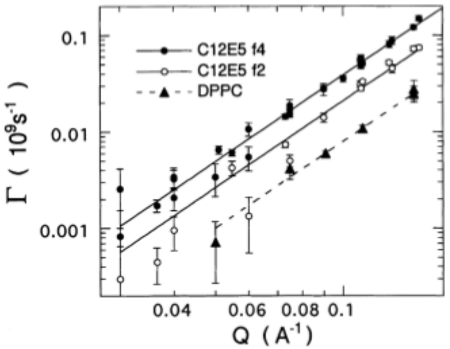
$$\Gamma_q = 0.025 \gamma_k \left(\frac{k_B T}{\kappa}\right)^{\frac{1}{2}} \frac{k_B T}{\eta} q^3$$

Journal of Physics and Chemistry of Solids 60 (1999) 1375–1377

Neutron spin–echo investigations of membrane undulations in complex fluids involving amphiphiles

T. Takeda[a,*], Y. Kawabata[a], H. Seto[a], S. Komura[b], S.K. Ghosh[a], M. Nagao[c], D. Okuhara[a]

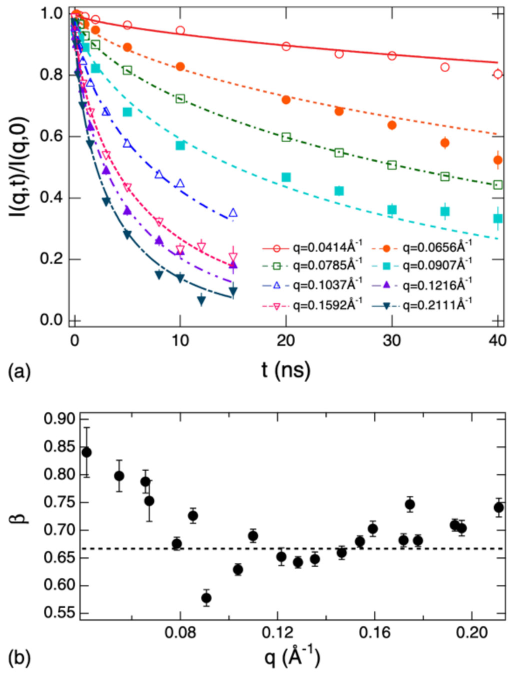


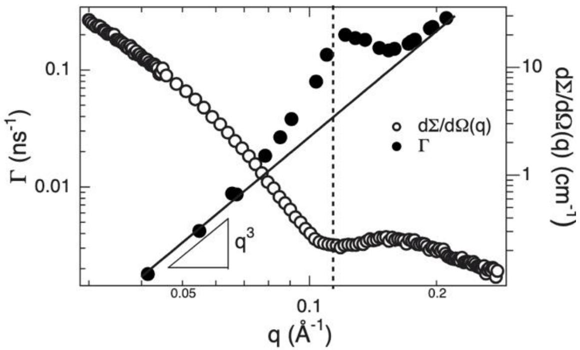


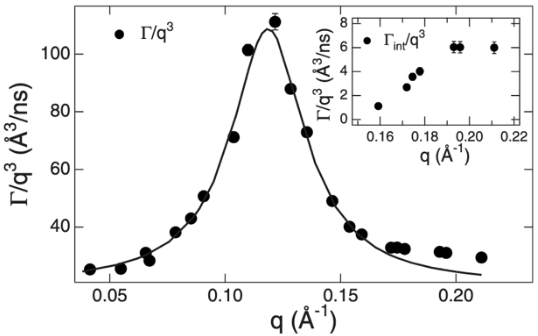
PHYSICAL REVIEW E **80**, 031606 (2009)

Observation of local thickness fluctuations in surfactant membranes using neutron spin echo

Michihiro Nagao*
NIST Center for Neutron Research, National Institute of Standards and Technology, Gaithersburg, Maryland 20899-6102, USA and Cyclotron Facility, Indiana University, Bloomington, Indiana 47408-1398, USA





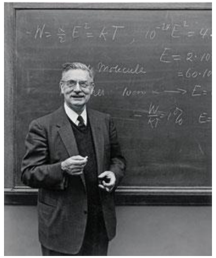


(Experiments with deuterated tails so-called head-contrast)

Outline

Two-point correlation functions

For elastic scattering



Peter Debye (1884-1966)

JOURNAL OF APPLIED PHYSICS VOLUME 28, NUMBER 6 JUNE, 1957

Scattering by an Inhomogeneous Solid. II. The Correlation Function and Its Application*

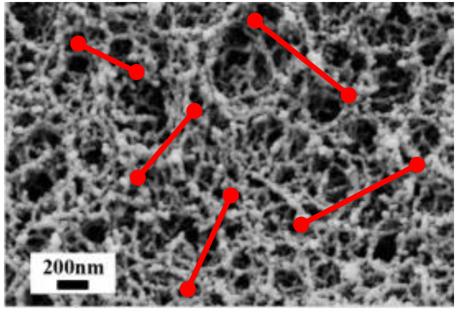
P. DEBYE, H. R. ANDERSON, JR.,† AND H. BRUMBERGER
Baker Laboratory of Chemistry, Cornell University, Ithaca, New York

(Received January 2, 1957)

$$\gamma(r)\langle\eta^2\rangle_{\mathrm{Av}} = \langle\eta_A\eta_B\rangle_{\mathrm{Av}}, \qquad (1)$$

$$i = 4\pi\langle\eta^2\rangle_{\mathrm{Av}} V \int_0^\infty \gamma(r) r^2 \frac{\sin ksr}{ksr} dr. \qquad (4)$$

* This research was supported by the Esso Research and Engineering Company, Elizabeth, New Jersey.



$$C(r) = \mathrm{Prob}\left\{ \begin{array}{l} x \text{ in the Solid} \\ x + r \text{ in the Solid} \end{array} \right\}$$

Van-Hove correlation functions

For inelastic scattering

Leon van Hove (1924-1990)

PHYSICAL REVIEW VOLUME 95, NUMBER 1 JULY 1, 1954

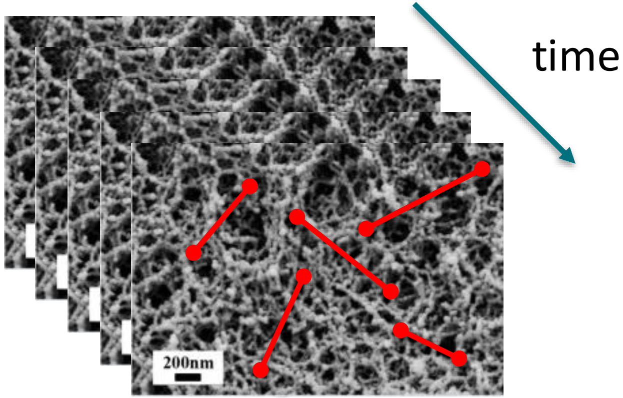
Correlations in Space and Time and Born Approximation Scattering in Systems of Interacting Particles

LÉON VAN HOVE
Institute for Advanced Study, Princeton, New Jersey

(Received March 16, 1954)

$$G(\mathbf{r},t)=N^{-1}\left\langle \sum_{l,j=1}^{N} \int d\mathbf{r}' \cdot \delta(\mathbf{r}+\mathbf{r}_l(0)-\mathbf{r}')\delta(\mathbf{r}'-\mathbf{r}_j(t)) \right\rangle, \tag{10}$$

$$\frac{d^2\sigma}{d\Omega d\epsilon}=\frac{a^2N}{2\pi\hbar}\frac{k}{k_0}\int \exp[i(\boldsymbol{\kappa}\cdot\mathbf{r}-\omega t)]\cdot G(\mathbf{r},t)d\mathbf{r}dt. \tag{26}$$



$$C(r,\tau) = \text{Prob}\left\{ \begin{array}{l} x \text{ in the Solid at time } t \\ x + r \text{ in the Solid at time } t+\tau \end{array} \right\}$$

Elastic & inelastic scattering by multiphase structures

$$\rho(\mathbf{x}, t) = \sum_n \rho_n \mathcal{I}_n(\mathbf{x}, t)$$

$$\rho_n = \text{SLD of phase } n$$

$$\mathcal{I}_n(\mathbf{x}, t) = \begin{cases} 1 & \text{if } \mathbf{x} \text{ in phase } n \text{ at time } t \\ 0 & \text{if not} \end{cases}$$

$$\begin{aligned} C_\rho(\mathbf{r}, \tau) &= \langle \rho(\mathbf{x}, t) \rho(\mathbf{x} + \mathbf{r}, t + \tau) \rangle \\ &= \sum_m \sum_n \rho_n \rho_m C_{mn}(\mathbf{r}, \tau) \end{aligned}$$

$$I(\mathbf{q}, \tau) = \int \mathrm{d}V_r \, e^{-i\mathbf{q}\cdot\mathbf{r}} C_\rho(\mathbf{r}, \tau)$$

$$\text{SANS/SAXS} : I(\mathbf{q}, 0)$$

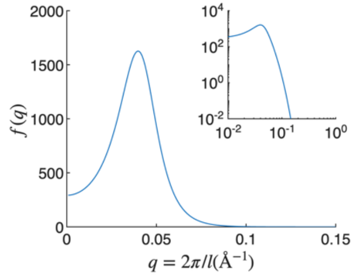
$$\text{NSE} : I(\mathbf{q}, \tau)/I(\mathbf{q}, 0)$$

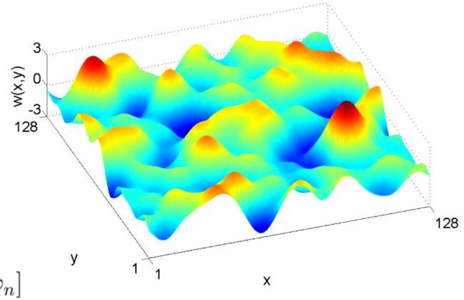
Gaussian fields : a well-defined type of disorder

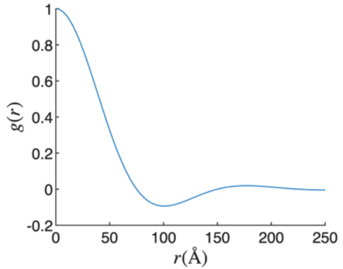
Power spectral density

Fourier

Field correlation function

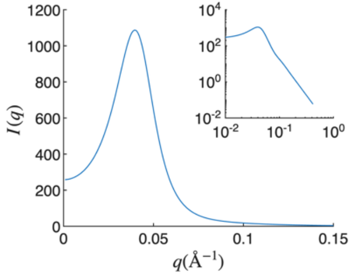


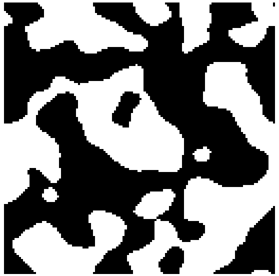


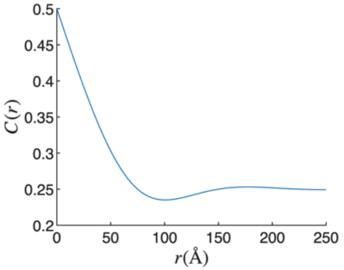


$$W(\mathbf{x}) = \sqrt{\frac{2}{N}} \sum_{n=1}^{N} \sin\left[\mathbf{q}_n \cdot \mathbf{x} - \varphi_n\right]$$

« some mathematics »





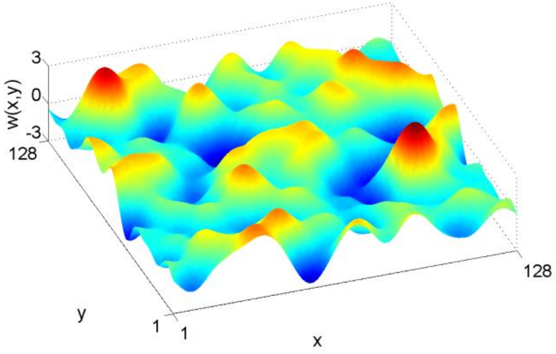


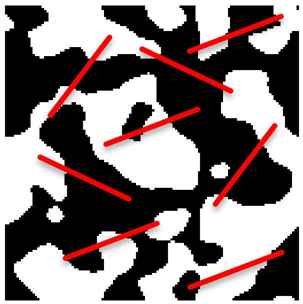
Scattered intensity

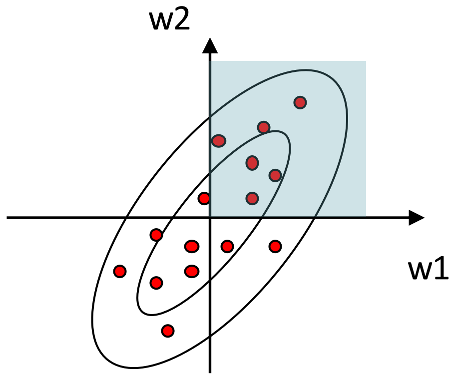
Fourier

Correlation function

The type of mathematics in Gaussian-field models





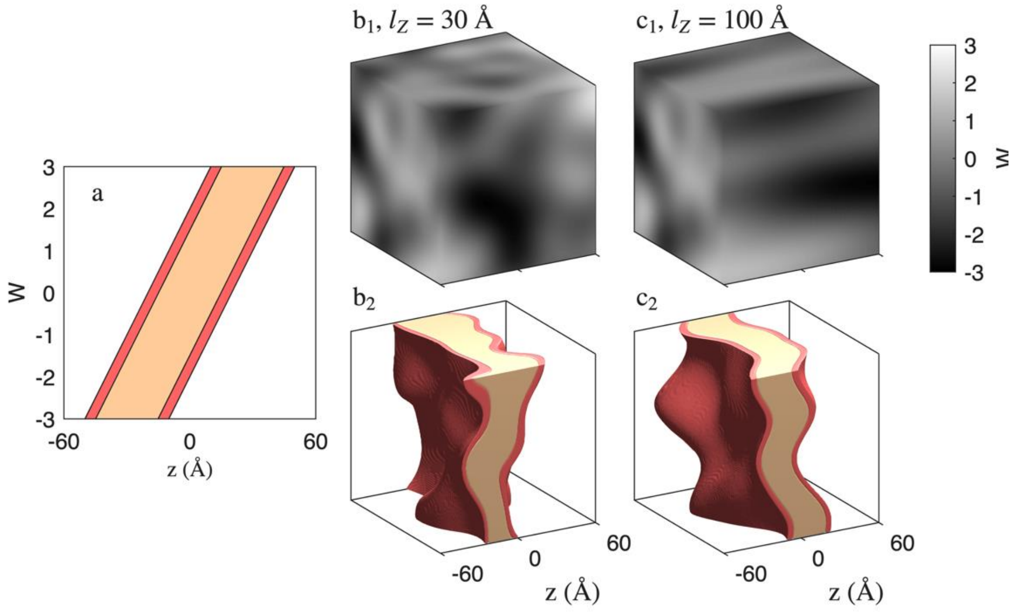


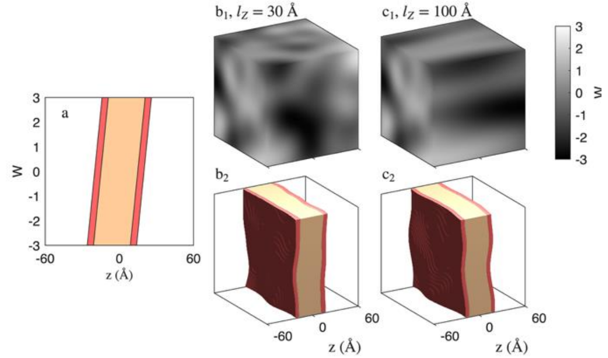
C(r) = probability for the two ends of a random stick with length r to be in the white phase

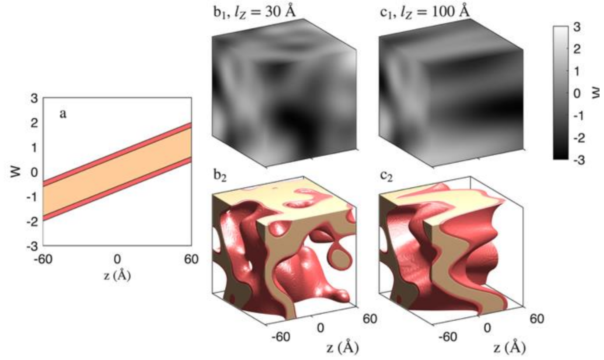
same as " to have a W > threshold "

Modelling membranes with Gaussian fields

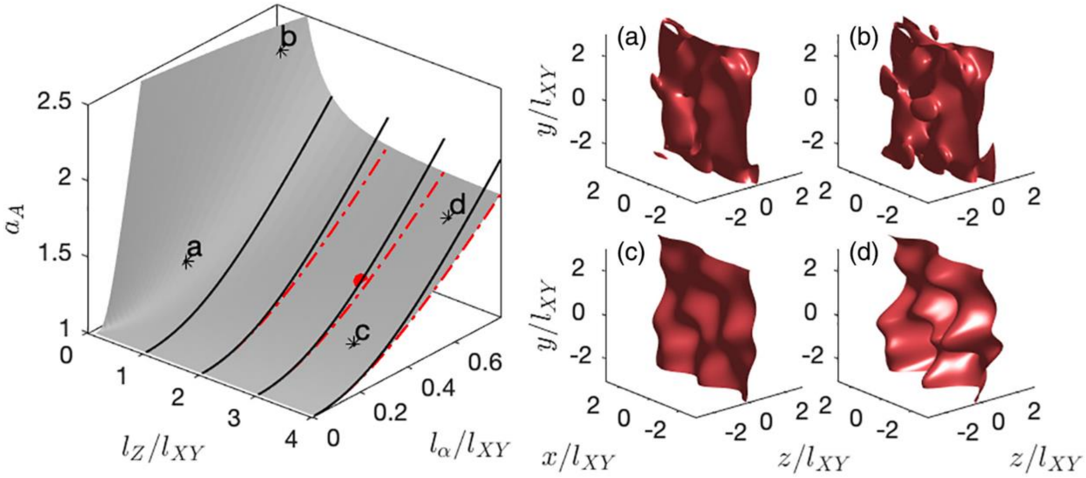
$$g_W(\mathbf{r}, 0) = \exp\left[-\frac{r_x^2 + r_y^2}{l_{XY}^2} - \frac{r_z^2}{l_Z^2}\right]$$







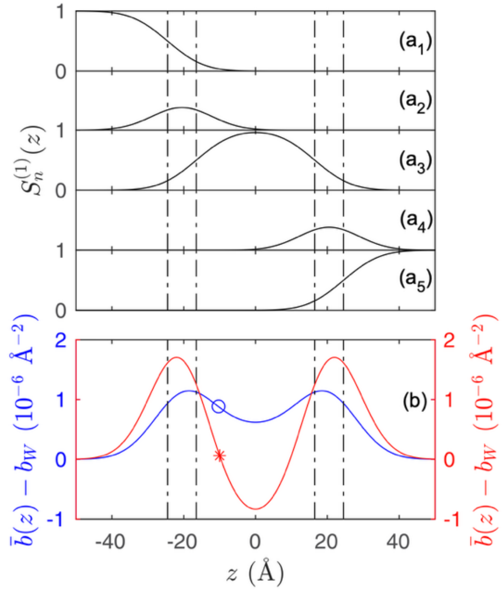
The big picture: the surface area



$$a_A = \frac{2}{\sqrt{\pi}} \frac{l_\alpha}{l_{XY}} \left\{ \exp\left[-\left(\frac{l_{XY}}{2l_\alpha} \right)^2 \right] + \sqrt{\pi} \left(\frac{l_{XY}}{2l_\alpha} + \frac{l_\alpha}{l_{XY}} \right) \mathrm{erf}\left[\frac{l_{XY}}{2l_\alpha} \right] \right\}$$

The scattering by Gaussian membranes

$$I(\mathbf{q},\tau) = \bar{I}(\mathbf{q}) + \tilde{I}(\mathbf{q},\tau)$$



Average SLD profile

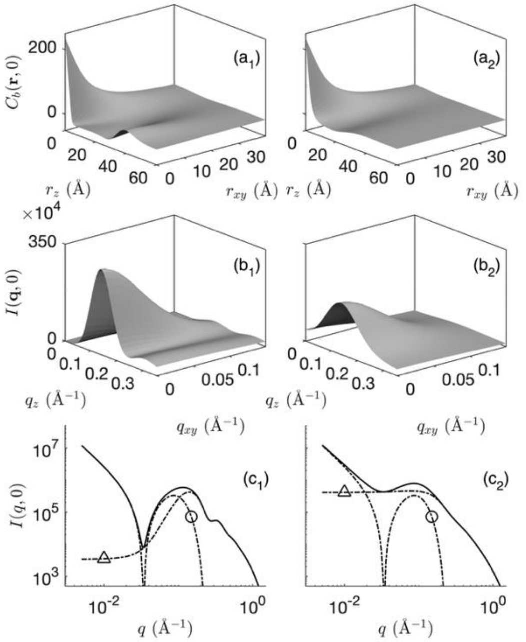
$$\tilde{C}_b(\mathbf{r},\tau) = \left[\sum_{n=0}^{N}(b_n - b_{n+1})^2\right]\Gamma_0(\mathbf{r},\tau) + \sum_{m>n}(b_n - b_{n+1})(b_m - b_{m+1}) \times \left[\Gamma_{Z_m - Z_n}(\mathbf{r},\tau) + \Gamma_{Z_n - Z_m}(\mathbf{r},\tau)\right]$$

$$\Gamma_L(\mathbf{r},\tau) = l_\alpha G\left[\frac{|r_z - L|}{l_\alpha}, g_W(\mathbf{r},\tau)\right]$$

$$G[\eta, g] = \frac{1}{\sqrt{\pi}}\left(\exp\left[-\frac{\eta^2}{4}\right] - \exp\left[-\frac{\eta^2}{4(1-g)}\right]\sqrt{1-g}\right) + \frac{\eta}{2}\left(\operatorname{erf}\left[\frac{\eta}{2}\right] - \operatorname{erf}\left[\frac{\eta}{2\sqrt{1-g}}\right]\right). \quad (28)$$

incompressible

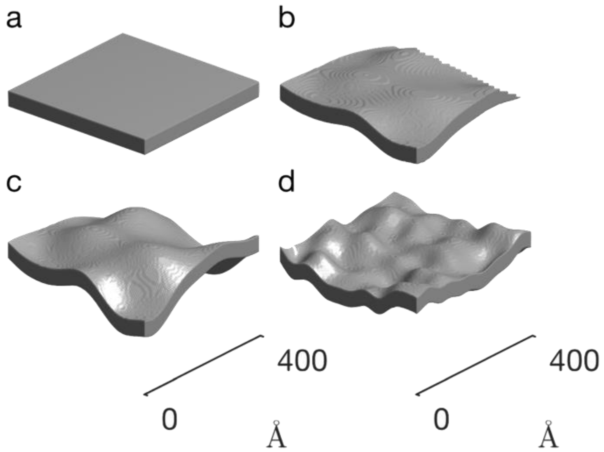
compressible

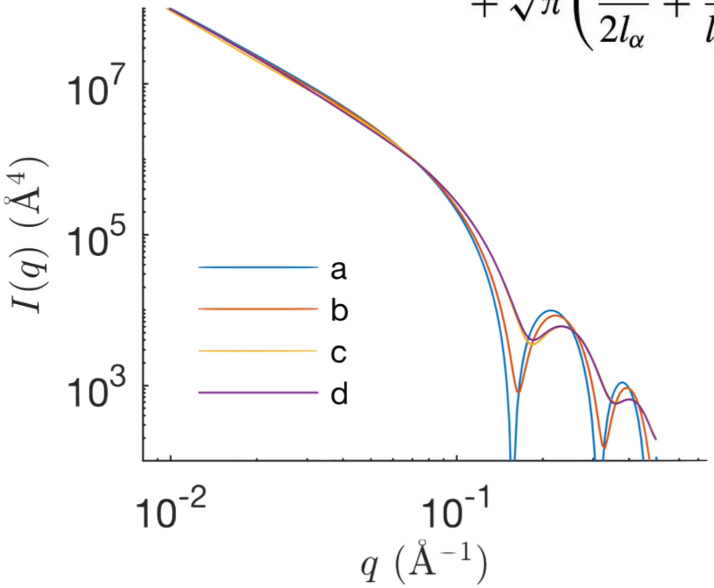


Fluctuations

Effect of bending fluctuations on scattering: l_α and l_{XY}

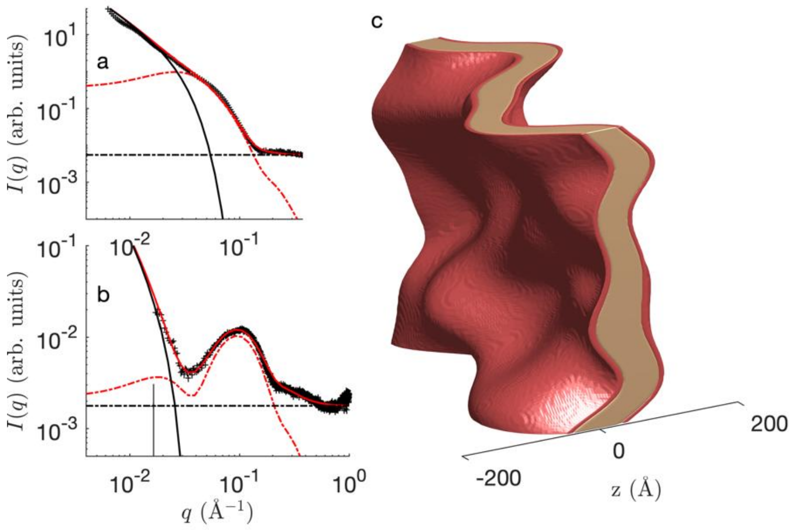
$$a_A = \frac{2}{\sqrt{\pi}}\frac{l_\alpha}{l_{XY}}\left\{\exp\left[-\left(\frac{l_{XY}}{2l_\alpha}\right)^2\right] + \sqrt{\pi}\left(\frac{l_{XY}}{2l_\alpha}+\frac{l_\alpha}{l_{XY}}\right)\mathrm{erf}\left[\frac{l_{XY}}{2l_\alpha}\right]\right\}$$





SAXS & SANS fitting

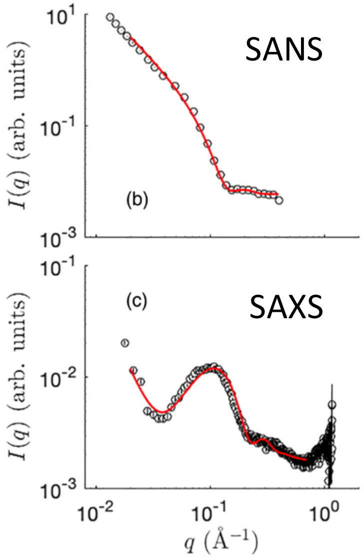
1D slab model



$$l_C \simeq 16.3Å \quad l_H \simeq 5.2Å$$

$$l_{xy} \simeq 80Å \quad l_\alpha \simeq 38Å$$

$$\sigma_t/t \simeq 0.23$$



$$l_C = 17.0Å \quad l_H = 4.5Å$$

polydispersity 15%

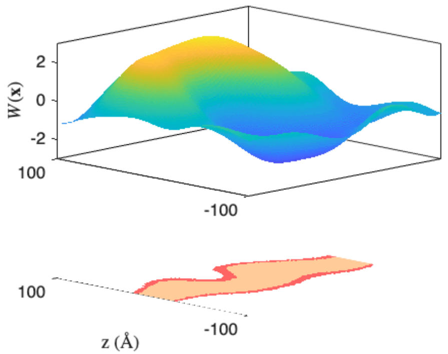
Time-dependent Gaussian fields

« jump »

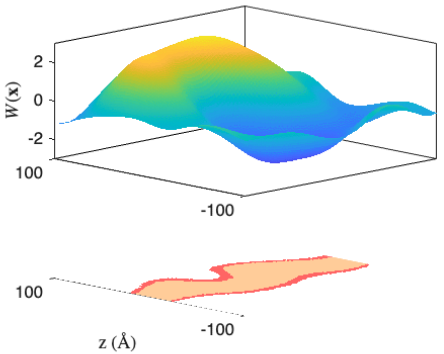
$$W(\mathbf{x}) = \sum_s A_s w(\mathbf{x} - \mathbf{x}_s) \qquad w(\mathbf{x}) = \exp\left[-2\left(\frac{x^2+y^2}{l_{XY}^2} + \frac{z^2}{l_Z^2}\right)\right]$$

$$W(\mathbf{x}, t) = \sum_s A_s w[\mathbf{x} - \mathbf{x}_s - \mathbf{j}_s(t)]$$

Ballistic
with velocity c



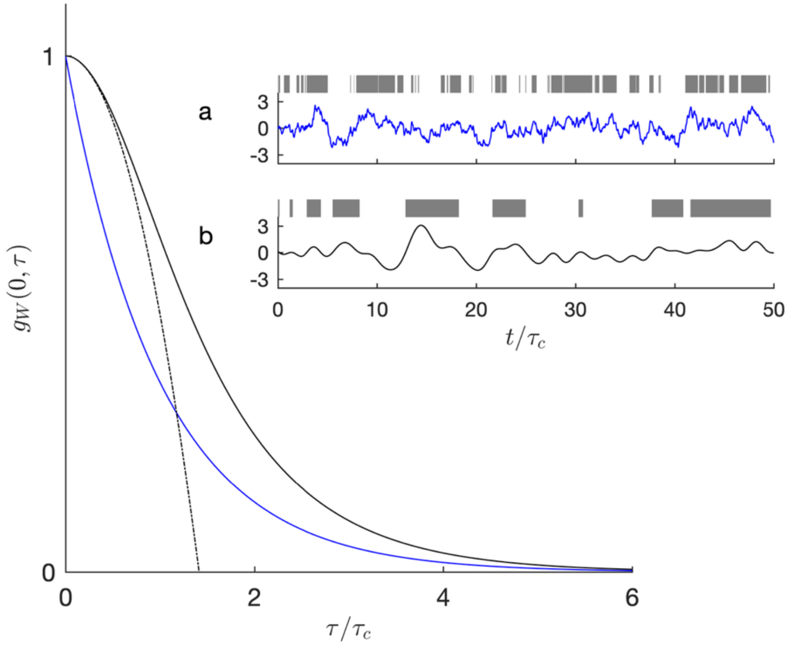
Diffusive
with coeff D



$$g_W(\mathbf{r}, \tau) = \exp\left[-\frac{r_z^2}{l_Z^2}\right] \exp\left[-\frac{(r_{xy} - c\tau)^2}{l_{XY}^2}\right] \times \exp\left[-\frac{2r_{xy}c\tau}{l_{XY}^2}\right] I_0\left[\frac{2r_{xy}c\tau}{l_{XY}^2}\right],$$

$$g_W(\mathbf{r}, \tau) = \left(1 + \frac{4D\tau}{l_{XY}^2}\right)^{-1} \exp\left[-\frac{r_{xy}^2}{4D\tau + l_{XY}^2}\right] \exp\left[-\frac{r_z^2}{l_Z^2}\right]$$

Timely crossing rate (Rice's formula)



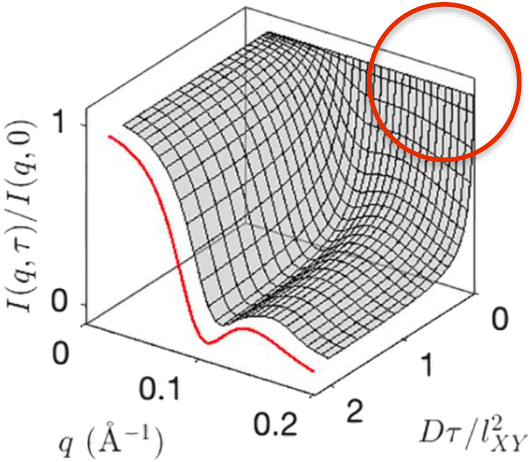
$$n_t = \frac{\sqrt{2}}{\pi} e^{-\alpha^2/2} \lim_{\tau \to 0} \frac{\sqrt{1 - g_W(0,\tau)}}{\tau}$$

$$g_W(0,\tau) \simeq 1 - (\tau/\tau_W)^2$$

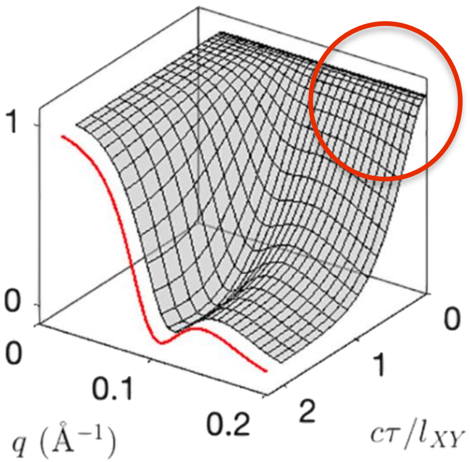
Intermediate scattering functions

(in)finite slope ?

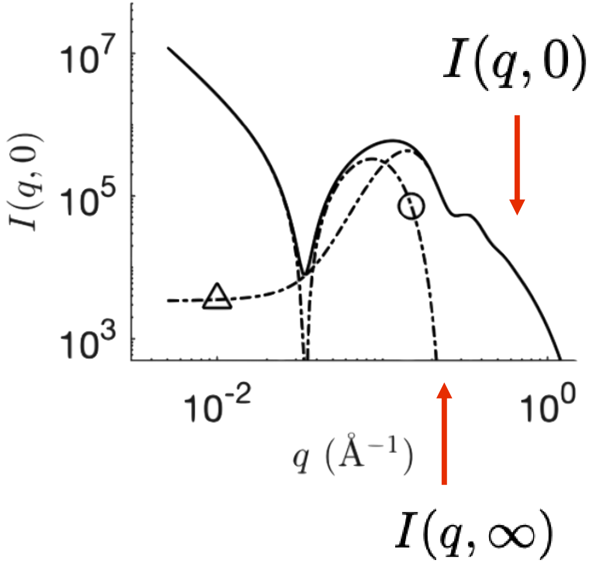
Quadratic



Diffusive

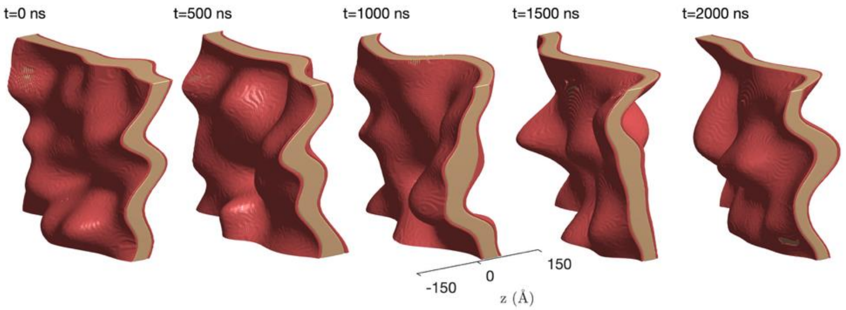


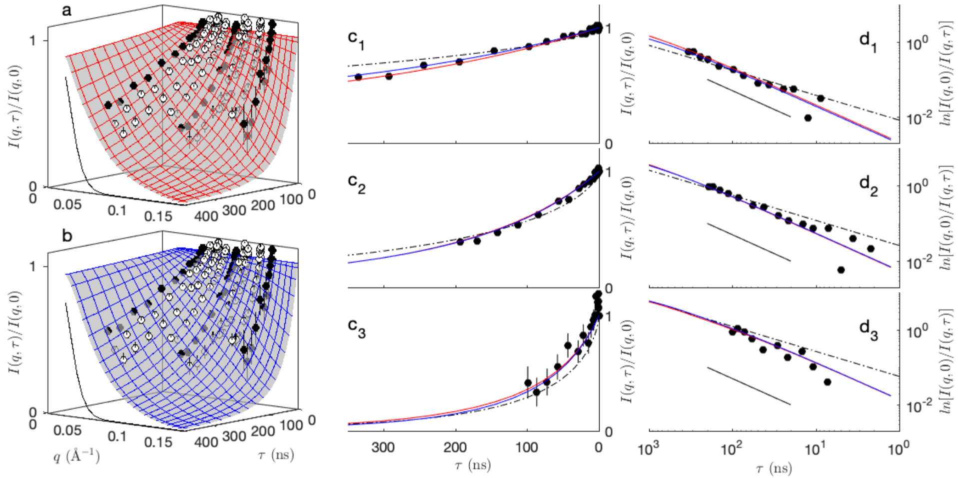
Ballistic



NSE data analysis

One-parameter fits





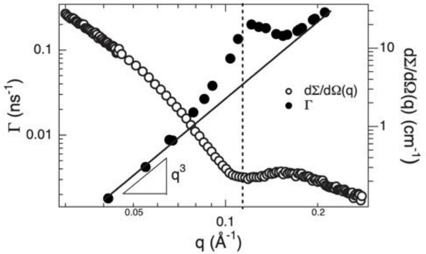
Dash: Zilman-Granek (streched exp)

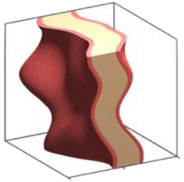
Red: diffusive model
(same parameters as SAXS/SANS
+ D = 1.65 A^2/ns)

Blue: another diffusive-like model
(same parameters as SAXS/SANS
+ τ_c= 975 ns)

Thickness fluctuations

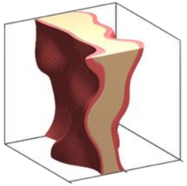
& ZG relaxation rate ?





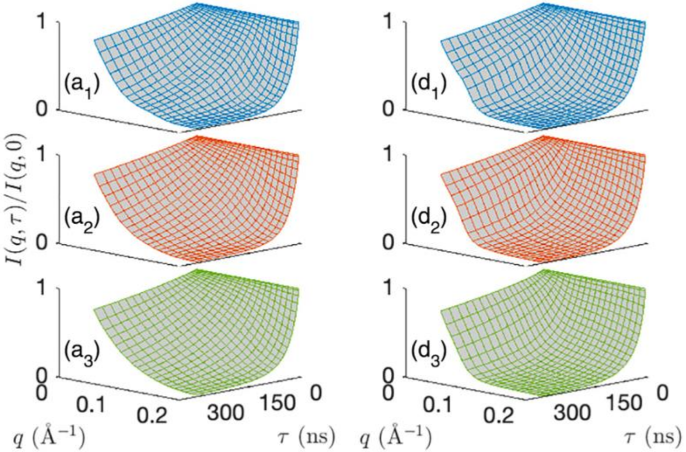
Decreasing

l_Z



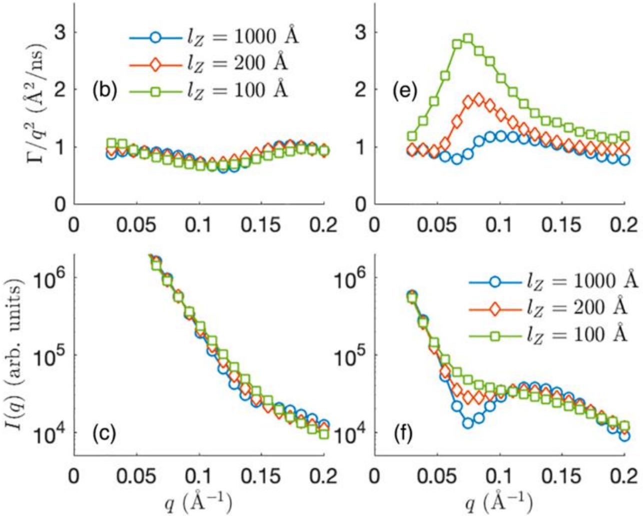
Chain contrast

Head contrast

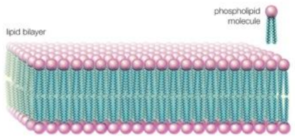


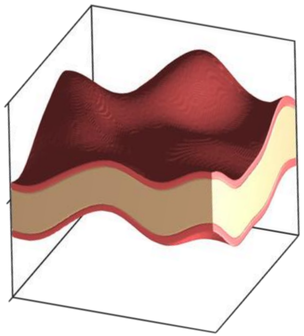
Chain contrast

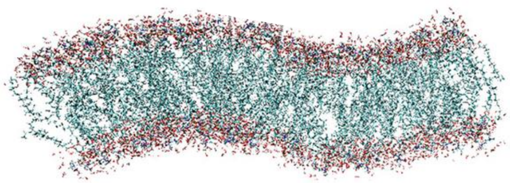
Head contrast



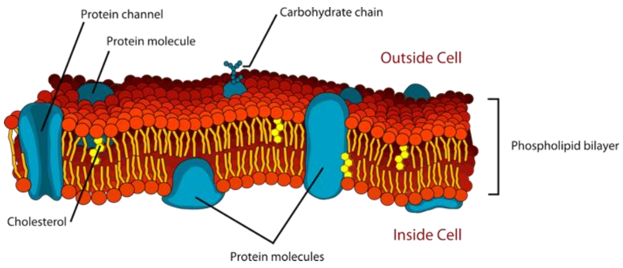
Outline


phospholipid
molecule
lipid bilayer

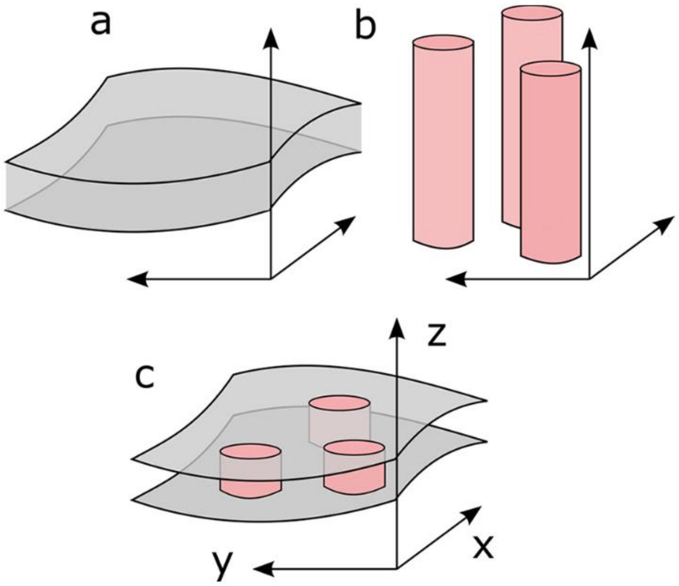




?


Protein channel
Carbohydrate chain
Protein molecule
Outside Cell
Phospholipid bilayer
Cholesterol
Inside Cell
Protein molecules

A cookie-cutting approach



$$\rho(\mathbf{x},t) = \rho_\mu \mathcal{I}_\mu(\mathbf{x},t) \times [1 - \mathcal{I}_p(\mathbf{x},t)] + \rho_p \mathcal{I}_\mu(\mathbf{x},t) \times \mathcal{I}_p(\mathbf{x},t)$$

$$\mathcal{I}_{\mu/p}(\mathbf{x},t) = \begin{cases} 1 & \text{if } \mathbf{x} \text{ in } \mu/p \text{ at time } t \\ 0 & \text{if not} \end{cases}$$

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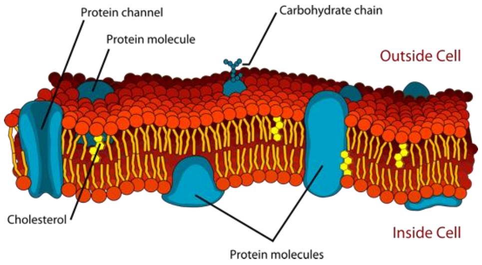
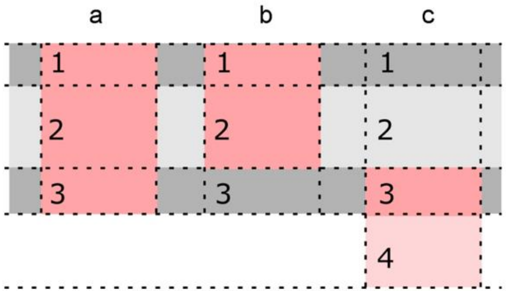
It is more flexible than it seems

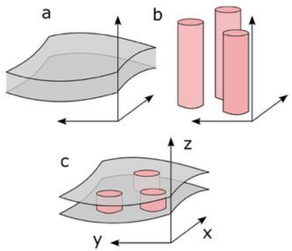




$$\rho(\mathbf{x}, t) = \left[\sum_{n=1}^{N} \rho_{\mu}^{(n)} \mathcal{I}_n(\mathbf{x}, t)\right]\left[1 - \mathcal{I}_{\mathrm{p}}(\mathbf{x}, t)\right] + \left[\sum_{n=1}^{N} \rho_{\mathrm{p}}^{(n)} \mathcal{I}_n(\mathbf{x}, t)\right]\mathcal{I}_{\mathrm{p}}(\mathbf{x}, t),$$

J. Appl. Cryst. (2025). **58**

Correlation function & scattering



Assuming statistical independence of the membrane and protein

$$C_\rho(\mathbf{r},\tau) = C_\rho^{(\mathrm{a})}(\mathbf{r},\tau) + C_\rho^{(\mathrm{c})}(\mathbf{r},\tau)\, C_\mathrm{p}(\mathbf{r},\tau)$$

Membrane structure with adjusted SLDs

Protein structure

Average SLD (membrane+protein)

$$C_\rho^{(\mathrm{a})}(\mathbf{r},\tau) = \sum_{n=1}^{N}\sum_{m=1}^{N}\left[(1-\phi_\mathrm{p})\,\rho_\mu^{(n)} + \phi_\mathrm{p}\rho_\mathrm{p}^{(n)}\right] \times \left[(1-\phi_\mathrm{p})\,\rho_\mu^{(m)} + \phi_\mathrm{p}\rho_\mathrm{p}^{(m)}\right] C_{m,n}(\mathbf{r},\tau)$$

SLD contrast (membrane - protein)

$$C_\rho^{(\mathrm{c})}(\mathbf{r},\tau) = \sum_{n=1}^{N}\sum_{m=1}^{N}\left[\rho_\mu^{(n)} - \rho_\mathrm{p}^{(n)}\right]\left[\rho_\mu^{(m)} - \rho_\mathrm{p}^{(m)}\right] C_{m,n}(\mathbf{r},\tau)$$

A simple particular case

Slab membrane model

$$I_\mu(\mathbf{q}) = (2\pi)^2 \left|\rho(q_z)\right|^2 \delta(q_x)\delta(q_y)$$

$$\rho(q_z) = 2(\rho_H - \rho_S)\frac{\sin[q_z(l_H + l_C)]}{q_z} + 2(\rho_C - \rho_H)\frac{q_z l_C}{q_z}$$

Hard-disk protein model

$$I_p(\mathbf{q}) = (2\pi) I_p(q_{xy})\delta(q_z)$$

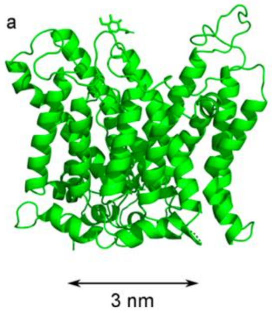
$$P_{\mathrm{p}}(q_{xy}) = \left[\frac{2J_1(q_{xy}R_{\mathrm{p}})}{q_{xy}R_{\mathrm{p}}}\right]^2$$

$$S_{\mathrm{HD}}(q_{xy}) \simeq \left\{1 + 4\frac{J_1(q_{xy}R_{\mathrm{p}})}{q_{xy}R_{\mathrm{p}}}\left[\frac{1}{(1-\phi_{\mathrm{p}})^2} - 1\right]\right\}^{-1}$$

$$\bar{I}(q,\tau) = \frac{2\pi}{q^2}|\rho^{(\mathrm{a})}(q)|^2 + \int_0^1 \mathrm{d}\mu\ |\rho^{(\mathrm{c})}(q\mu)|^2 I_{\mathrm{p}}(q\sqrt{1-\mu^2},\tau)$$

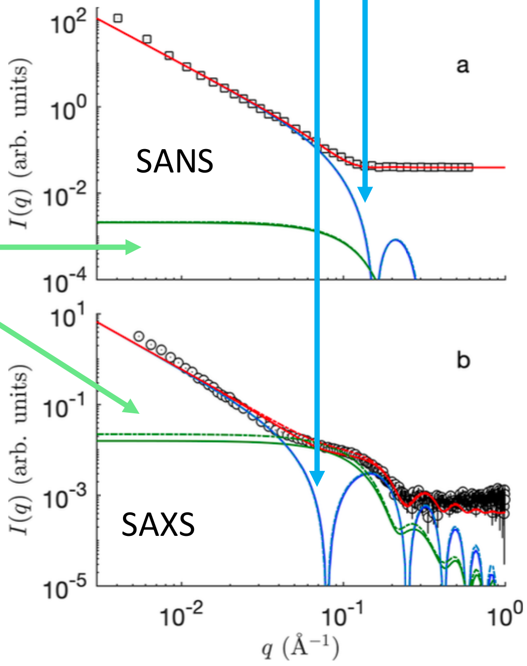
SANS & SAXS of red blood cells liposomes (25 % proteins)

slab & hard disk model



Protein scattering

Membrane scattering

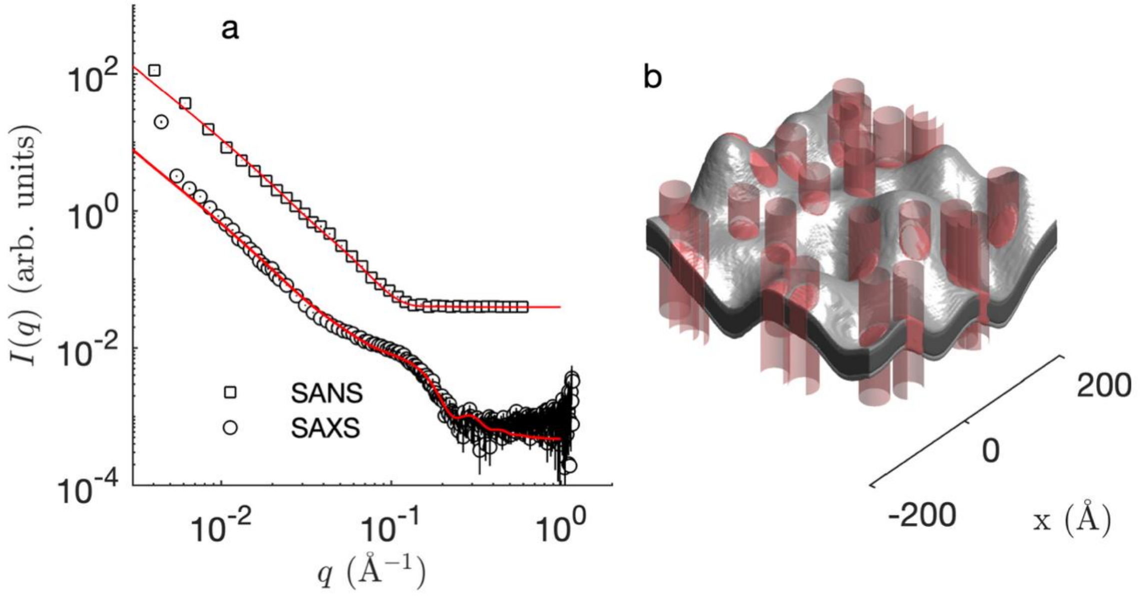


$$C_\rho(\mathbf{r},\tau) = C_\rho^{(a)}(\mathbf{r},\tau) + C_\rho^{(c)}(\mathbf{r},\tau)\,C_p(\mathbf{r},\tau)$$

			a_P (Å)	b_P (Å)	l_C (Å)	l_H (Å)	χ^2 (-)
Disks	Monomer	Boolean	21.4	21.4	16.3	5.0	0.35
		Hard-disk	21.4	21.4	16.6	4.5	0.35
	Dimer	Boolean	28.4	28.4	16.0	5.6	0.45
		Hard-disk	28.4	28.4	16.6	5.1	0.42
Ellipses	Monomer	Boolean	29.5	15.5	16.4	5.0	0.38
		Hard-disk	29.5	15.5	16.8	4.5	0.43
	Dimer	Boolean	52.5	15.5	16.3	5.1	0.49
		Hard-disk	52.5	15.5	16.6	5.1	0.37

SANS & SAXS of red blood cells liposomes (25 % proteins)

Gaussian membrane model



$l_C \simeq 16.1\text{Å} \quad l_H \simeq 5.0\text{Å}$

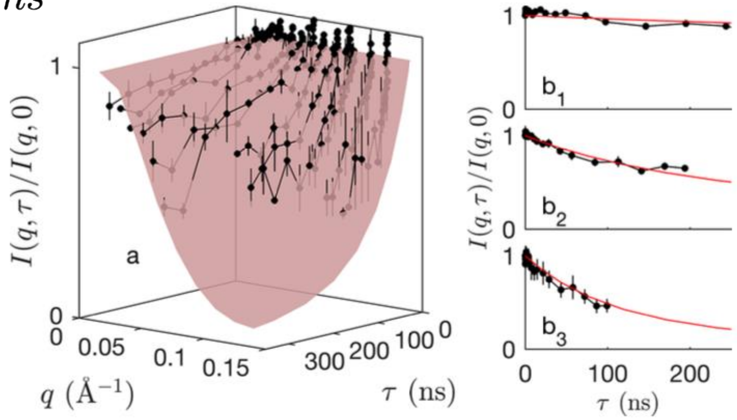
$l_{xy} \simeq 63\text{Å}$

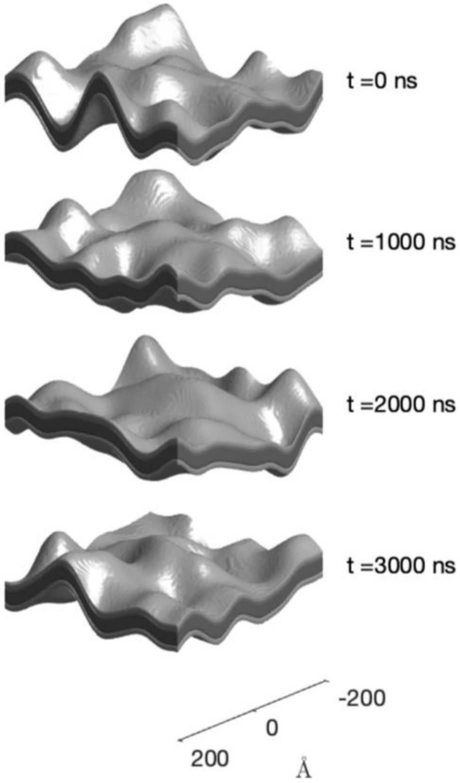
$l_\alpha \simeq 23\text{Å}$

NSE of red blood cells liposomes (25 % proteins)

Gaussian membrane model

$D \simeq 1.85 \mathring{A}^2/ns$



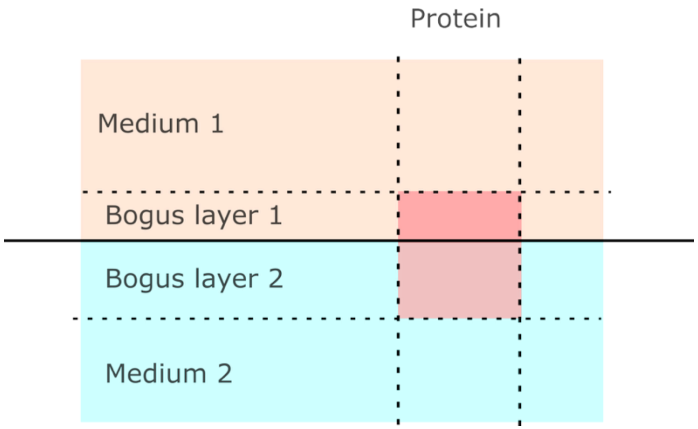


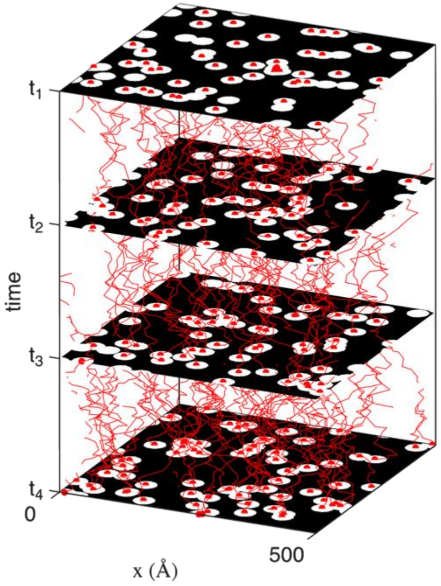
$$C_\rho(\mathbf{r}, \tau) = C_\rho^{(a)}(\mathbf{r}, \tau) + C_\rho^{(c)}(\mathbf{r}, \tau) C_p(\mathbf{r}, \tau)$$

The second protein contribution is negligible in our neutron experiments.
We could not probe the protein diffusion within the membrane

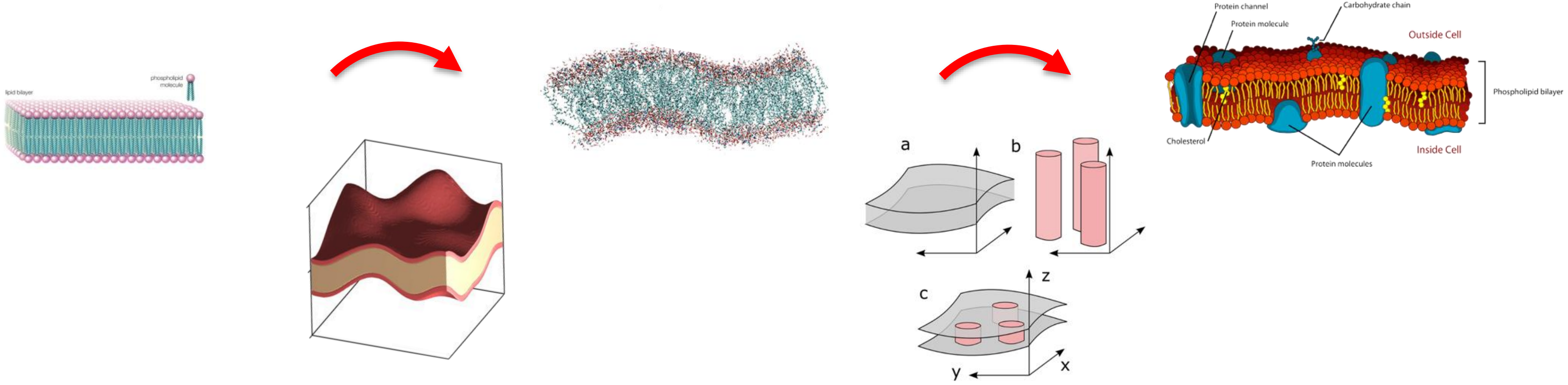
Ideas for future work (emulsions)

Discriminating interface fluctuations
from in plane protein diffusion





Conclusions : parcimonious models

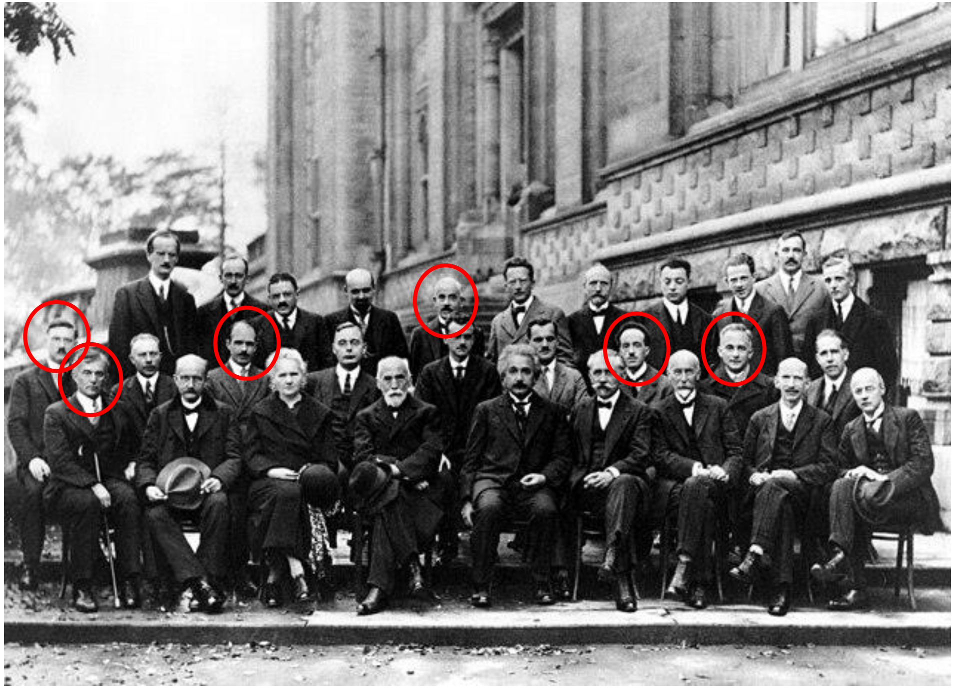


- Qualitative aspects : validate data analysis procedures with an exact model (Cf compressibility, SAXS & NSE)

- Quantitative: fitting all the data with a single model

- Very transparent contributions to scattering (average SLD & constrast)

- Can experiments be designed to discriminate membrane fluctuations from protein diffusion?



Solvay conference (1927)

P. Debye

W. Bragg

T. De Donder

L. de Broglie

M. Born

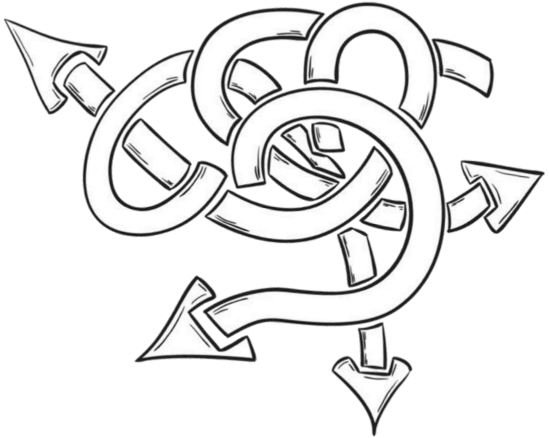
I. Langmuir

Leon van Hove (1924-1990)

Ilya Prigogine (1917-2003)

Thank you
for your attention

and for your questions



A metaphor about models and reality

Fred Astaire & Ginger Rogers
Swing Time (1936)

Marx Brothers
A Night at the Opera (1935)