A HiCANS neutron reflectometer for small samples and biointerfaces

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Introduction We discuss a concept for a small-beam neutron reflectometer. Such an instrument may be used to study membrane physics and the structure and interaction of RNA-related phases with membranes. We propose to place such an instrument at one of the new accelerator-based sources, which have inherently smaller beams. These compact neutron sources are based on a high-current linear accelerator (HiCANS). We expect that such a reflectometer can record at least six orders of magnitude in signal to noise. We highlight some recent experiments with lipid membranes to show the potential of the instrument. Furthermore, we discuss instrument concepts.

Reflectometer Design Concept

Our instrument concept includes:

- A para-hydrogen cold neutron moderator
- Optimized neutron optics (mirrors, guides, chopper system)
- Time-of-flight (TOF) mode for a broad wavelength band (2–15 Å)
- Adjustable geometry: vertical and horizontal scattering configurations
- Lateral beam size <5 mm, footprint <1 cm², 6 orders of magnitude signal-to-noise
- 2D single-event neutron detector system (off-specular capable)

This compact layout reduces required sample amounts, enables highly localized measurements, and benefits from the ultra-low background of pulsed sources.

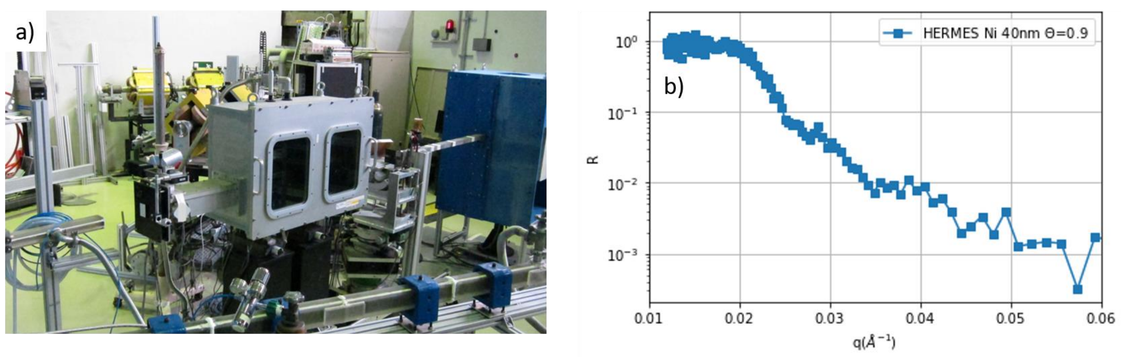
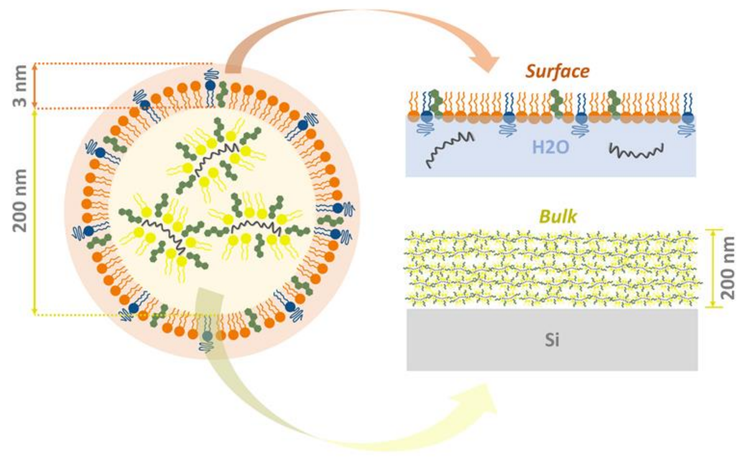


Figure 1: a) HERMES reflectometer installed at beamline 3 of the JULIC Neutron Platform. b) Neutron reflectivity measurement of a 40 nm thick Ni layer at this instrument covers 3 orders of magnitude. [2]

Motivation



RNA-based therapeutics, such as mRNA vaccines, rely on lipid-based carriers to protect and deliver genetic material [1]. These systems exhibit rich internal structures and complex interactions at interfaces — ideally suited for neutron reflectometry (NR). However, conventional NR requires milligrams of sample material, making it difficult to study novel formulations or scarce RNA complexes. We propose a neutron reflectometer design tailored for small samples. By leveraging the inherently small beam sizes of compact accelerator-based neutron sources (HiCANS), we aim to reduce required sample volumes while preserving analytical depth.

Scientific Use Cases

This platform enables novel NR studies on:

- **Lipid bilayer sandwich architectures** interacting with RNA
- **Photoswitchable multilayers** and their light-triggered transitions
- **Free-standing films**: hydration, curvature, and phase behavior
- **Blodgett films**: vertical hydration gradients and endosomal mimicry
- **Monolayers** at air/water interfaces with controlled surface pressure

These investigations are relevant to RNA delivery, membrane biophysics, and nanoscale drug release mechanisms. Contrast variation and small beam size provide structural insights previously inaccessible

Sample Environments

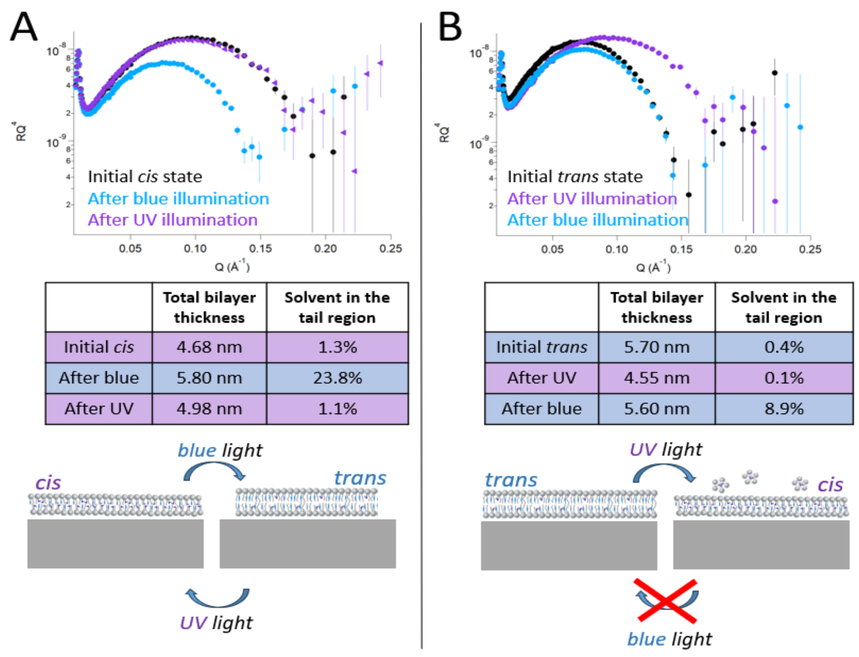
To fully exploit small beam sizes, we are propose to develop specialized environments:

- **Humidity chamber**: for lipid-RNA films under controlled RH and pH
- **Mini Langmuir trough**: for amphiphilic monolayers at liquid interfaces
- **Free-standing film cell (TFPB)**: to study lamellae with disjoining pressure control
- **Vertical solid/liquid cell**: for supported lipid bilayers and wetting films
- **Optical access**: for light-activated lipid systems (photopharmacology)

Each environment is designed to be low-volume, thermally stable, and compatible with sub-mm neutron beams.

Example: lipid photoswitches (BN with V. Reisner, T. Kammerbauer and E. Kostyurina, LMU)

Neutrons reveal pore formation in SLBs upon isomerization



	Total bilayer thickness	Solvent in the tail region
Initial *cis*	4.68 nm	1.3%
After blue	5.80 nm	23.8%
After UV	4.98 nm	1.1%

	Total bilayer thickness	Solvent in the tail region
Initial *trans*	5.70 nm	0.4%
After UV	4.55 nm	0.1%
After blue	5.60 nm	8.9%

Neutron Reflectometry (ILL FIGARO) measurements of azo-PC SLBs prepared from the cis state (B) and trans state (C) and after switching two times. The tables show the values for the bilayer thickness and solvent penetration to the tail region obtained from the three-contrast fits.

[1] J. Philipp, A. Dabkowskab, A. Reiser, K. Frank, R. Krzysztoń, C. Brummer, B. Nickel et al, *pH- dependent structural transitions in cationic ionizable lipid mesophases are critical for lipid nanoparticle function,* PNAS Vol 120 p 502023 (2023)
[2] M.A. Paulin, I. Pechenizkiy, P. Zakalek, K. Lieutenant, P. Kämmerling, A. Steffens, H. Kleines, U. Rücker, T. Gutberlet, S. Gautrot, A. Menelle, F. Ott, *Development of neutron reflectometry for a HiCANS: The HERMES instrument at the JULIC Neutron Platform*, EPJ Web of Conferences **298**, 01001 (2024)