Morphological reorganization of lipid membranes induced by amyloid-beta peptides

S. Kurakin, O. Ivankov, T. Murugova, D. Badreeva, S. Efimov, T. Mukhametzyanov, N. Kučerka

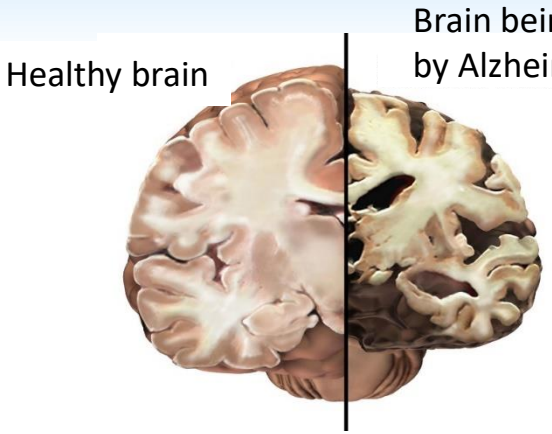
Kazan Federal
UNIVERSITY

Казанский федеральный
УНИВЕРСИТЕТ
ИНСТИТУТ ФИЗИКИ

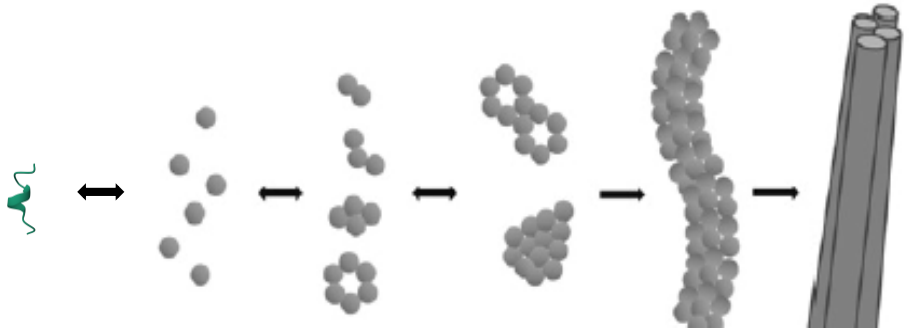
India-JINR workshop
Oct 16-19, 2023

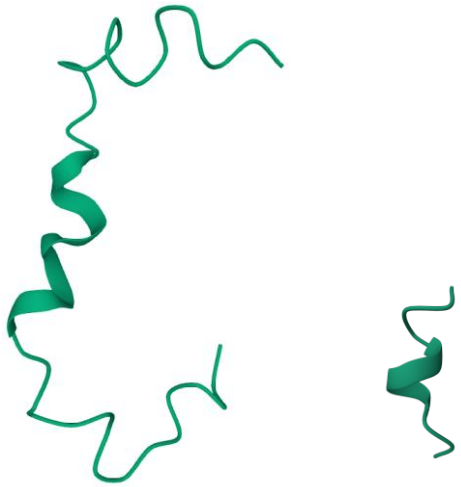
Relevance

Alzheimer's disease is a neurodegenerative disease that leads to dementia, memory loss, and death. No cure has been found so far.



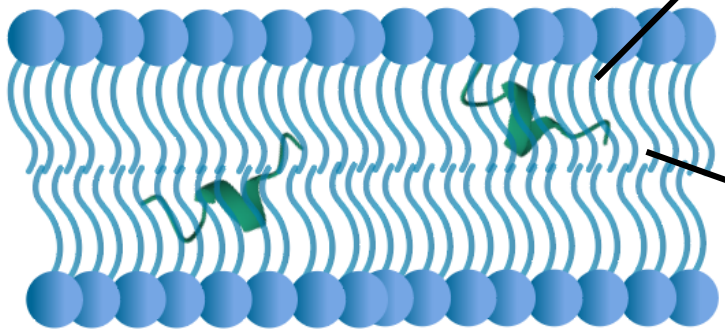
emergence of amyloid oligomers and fibrils

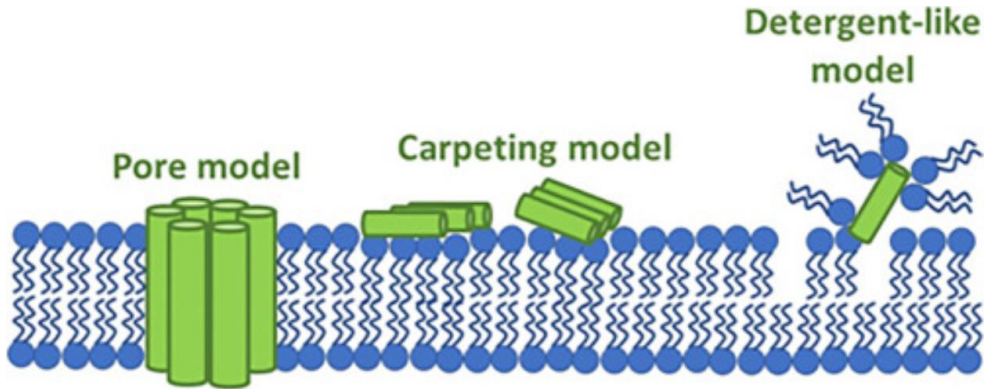




Aβ(1-40/42) Aβ(25-35)

Amyloid-beta peptide and one of its most toxic fragments



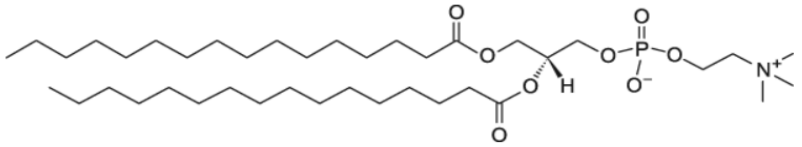


Press-Sandler et al. BBA-Biomembranes. 2018

Key roles leading to the emergence of oligomers and fibrils may belong to fatal changes in the interactions between the peptide and the lipid membrane

Research target and sample preparation

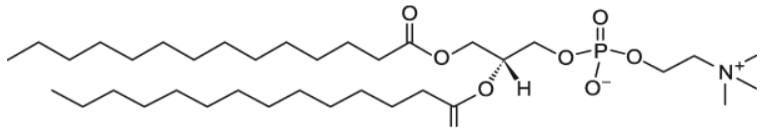
❖ **Effect of Aβ(25-35) peptides on the structure and morphology of lipid membranes**



DPPC molecule

1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine

or



DMPC molecule

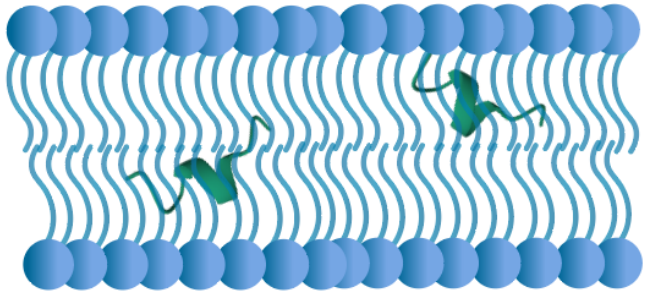
1,2-dimyristoyl-sn-glycero-3-phosphatidylcholine

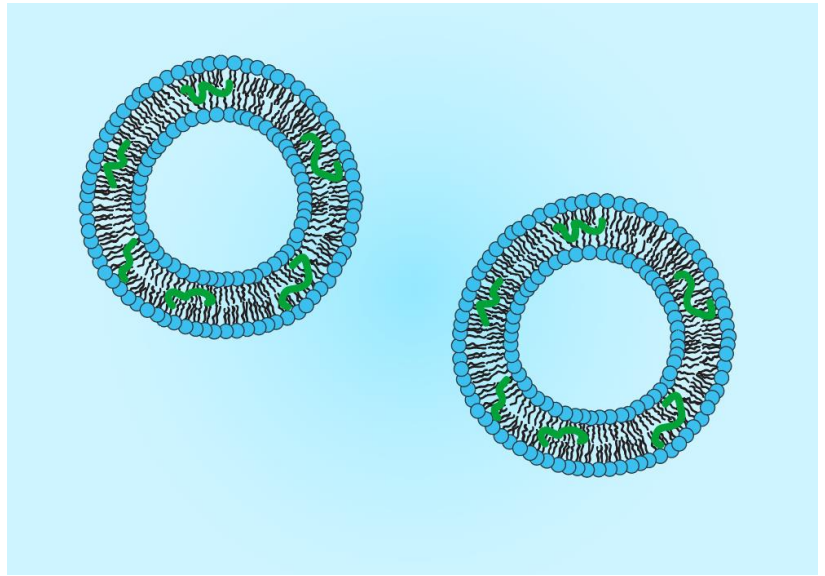
+

Amyloid-beta peptide Aβ(25-35)
(fragment of Aβ(1-40/42))

25	26	27	28	29	30	31	32	33	34	35
H_2N--Gly--	Ser--	Asn--	Lys--	Gly--	Ala--	Ile--	Ile--	Gly--	Leu--	Met--OH

Peptide/lipid ratio
0.5 mol% - 3 mol%

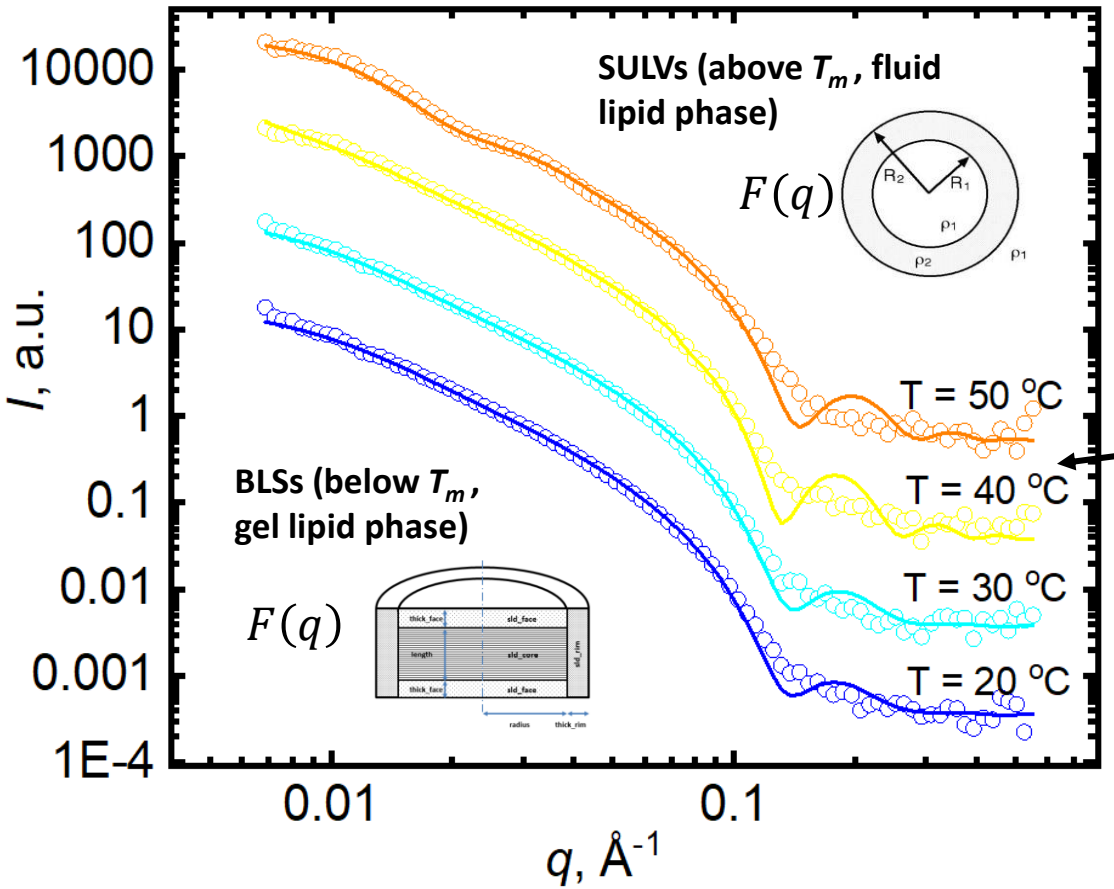




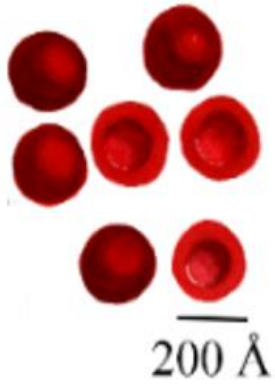
Morphological reorganization in DPPC + Aβ(25-35) and DMPC + Aβ(25-35) systems

Small-angle neutron scattering

$$I(q) = \text{const} \cdot |F(q)|^2 + \text{bkg}$$



Small-angle neutron scattering (SANS) curves obtained for DPPC + Aβ(25-35) systems in water



Small unilamellar vesicles (**SULVs**)

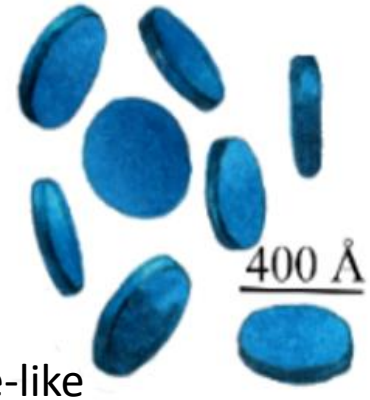
DMPC + Aβ(25-35)

DPPC + Aβ(25-35)

DMPC T_m = **24 °C**

DPPC T_m = **41 °C**

T_m **Main phase transition temperature**



Bicelle-like structures (**BLSs**)

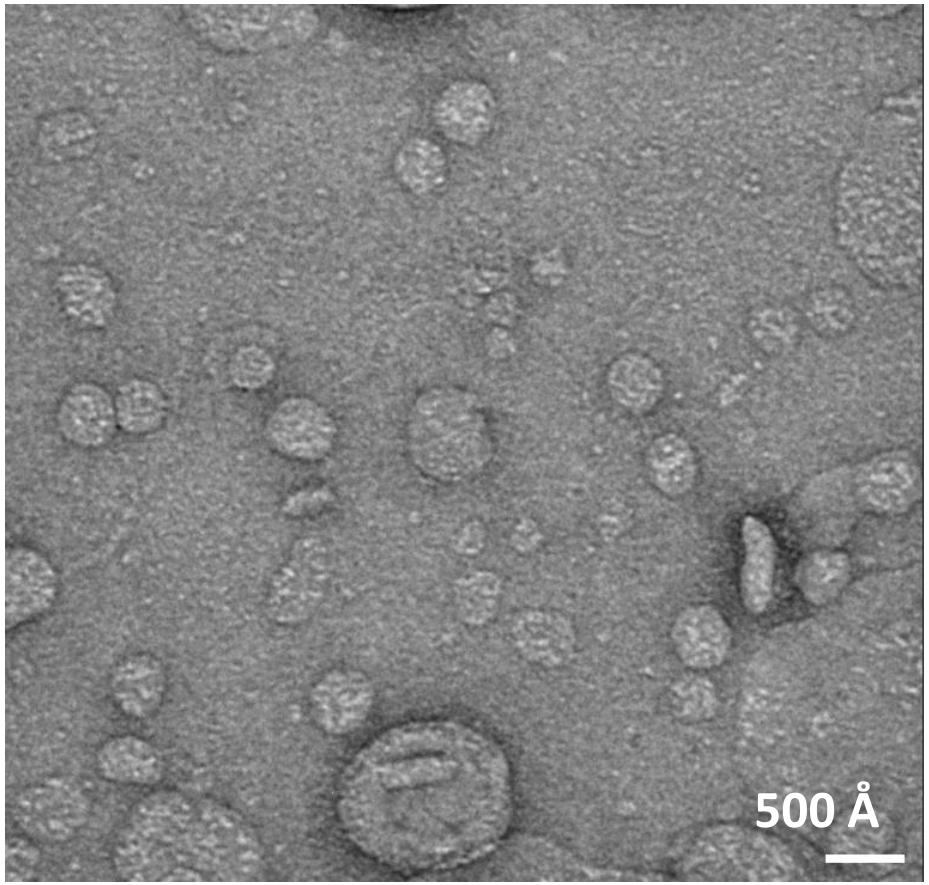
Bilayer thickness and diameter of the objects

BLSs (T = 20 C)	SULVs (T = 50 C)
d_b = 55 Å	d_b = 50 Å
D = 400 Å	D = 200 Å

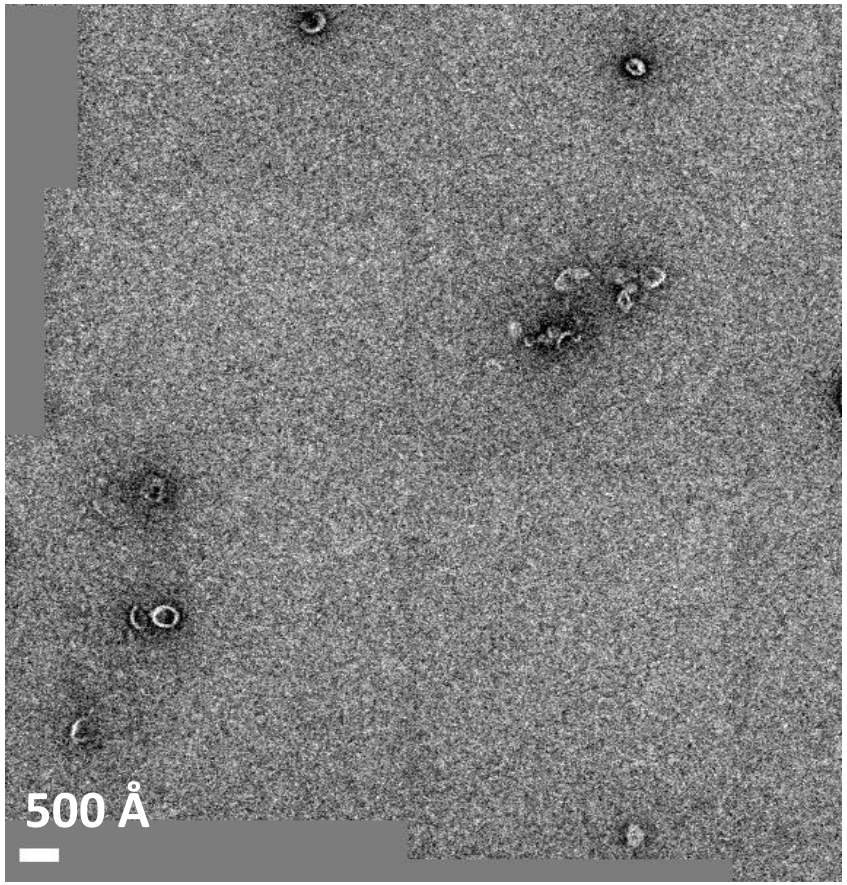
Ivankov et al. Sci Rep. 2021

Morphological reorganization in DPPC + Aβ(25-35) and DMPC + Aβ(25-35) systems

Electron microscopy



$< T_m$



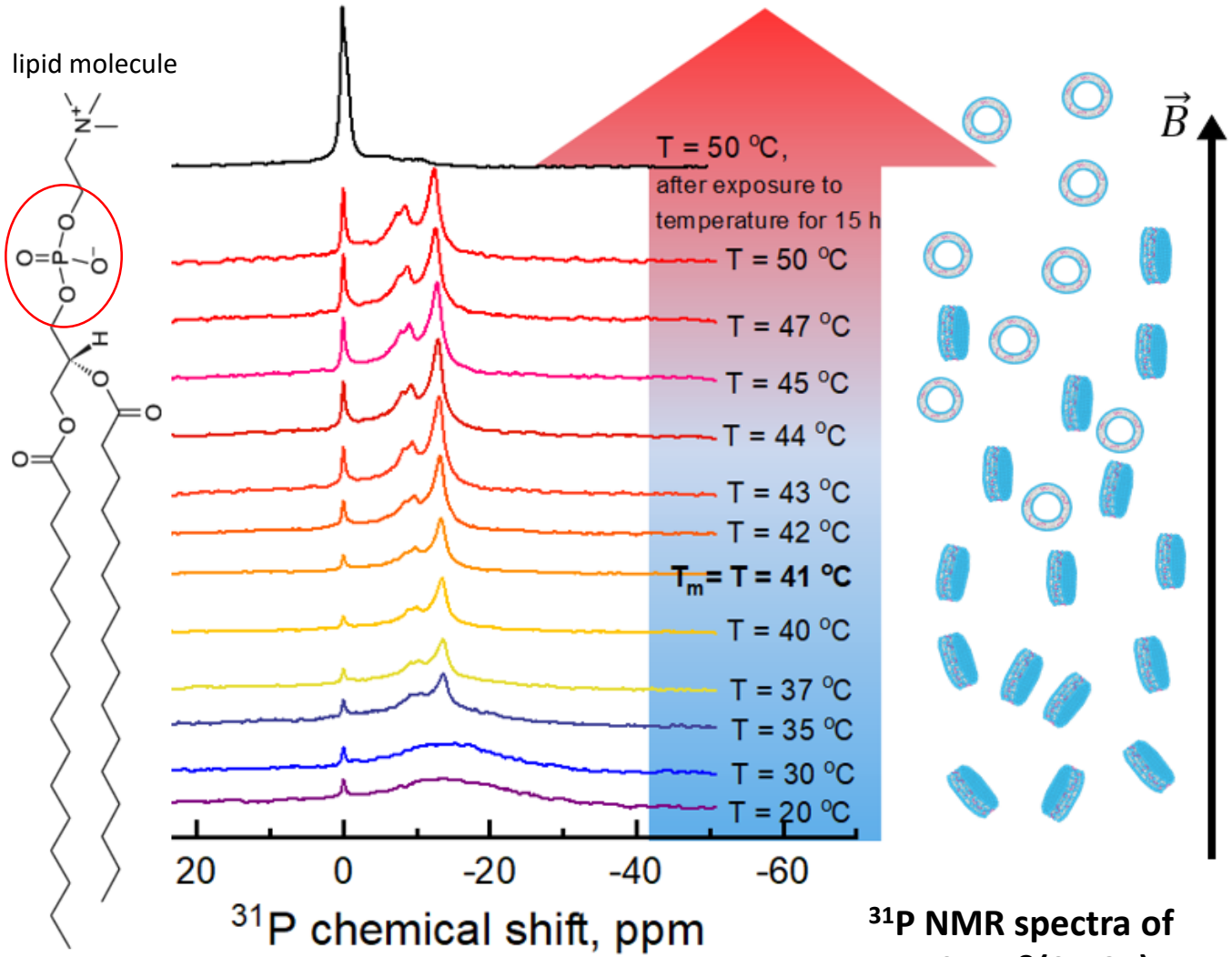
$> T_m$

The effect of morphological reorganization is explained by toxic behavior of the Aβ(25-35) that leads to a temporary membrane disintegration during lipid phase transitions

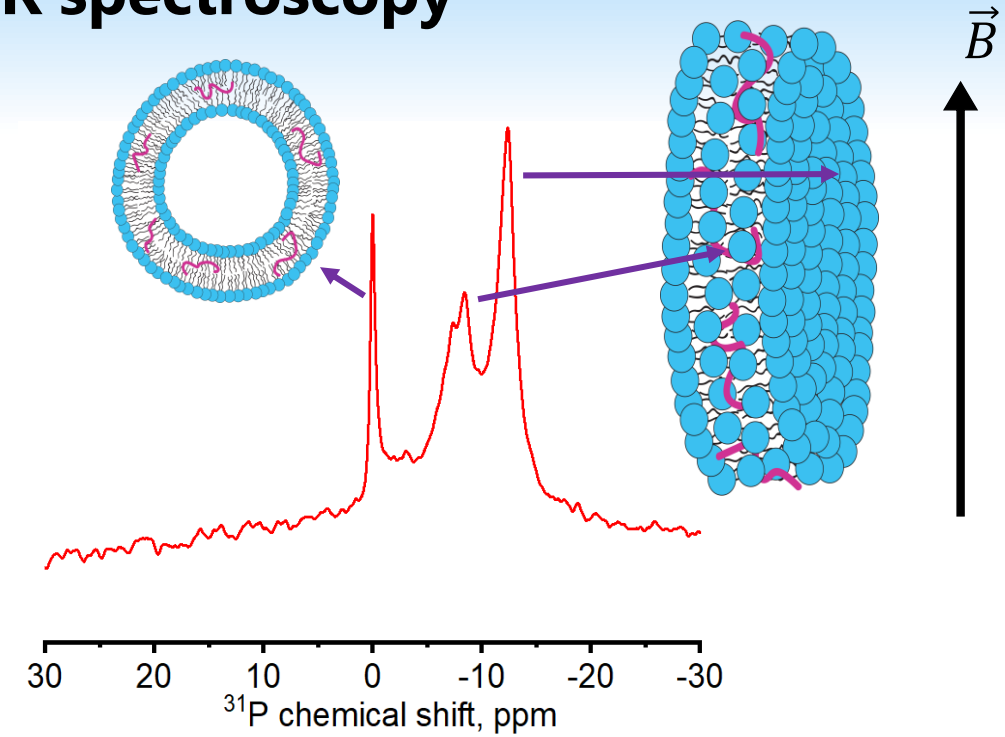
Structure of BLSs

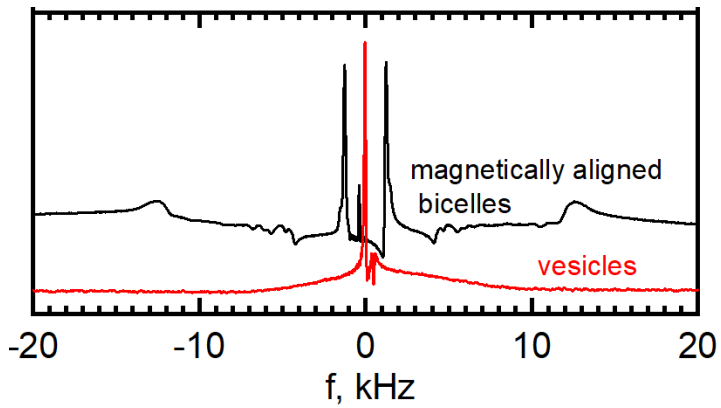
Solid-state ^{31}P and ^{2}H NMR spectroscopy

DPPC + Aβ(25-35)



^{31}P NMR spectra of DPPC + Aβ(25-35)





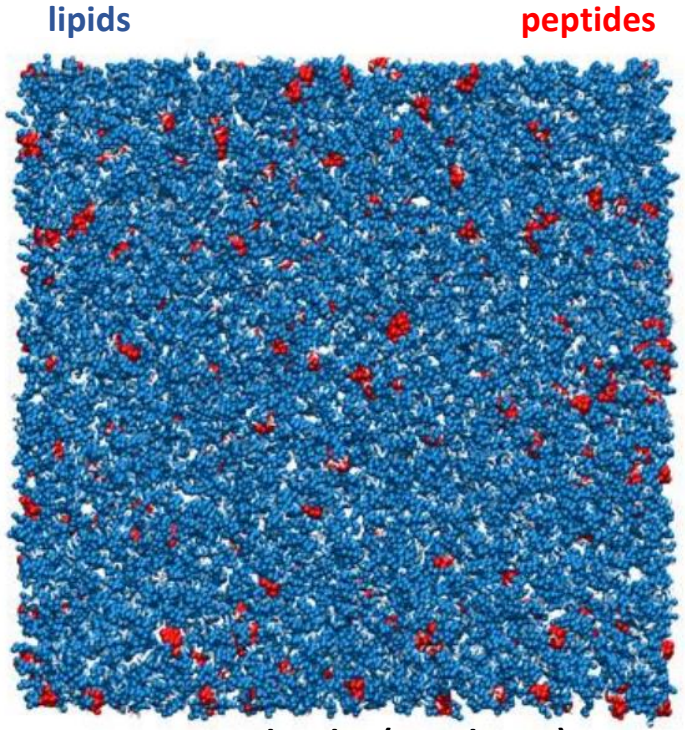
^{2}H NMR spectra at 40°C and 50°C

Kurakin et al. BBA-Biomembranes. 2023

Structure of BLSs and SULVs

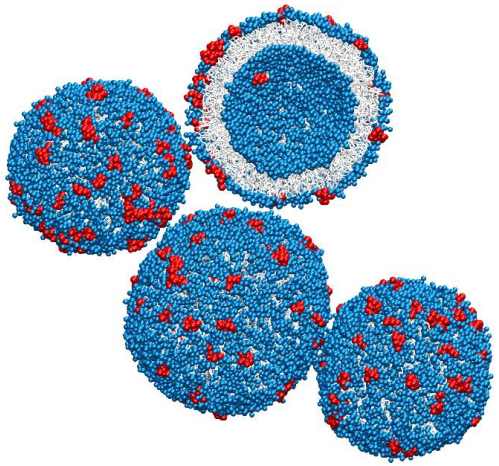
Coarse-grained molecular simulations

- **Self-assembling**



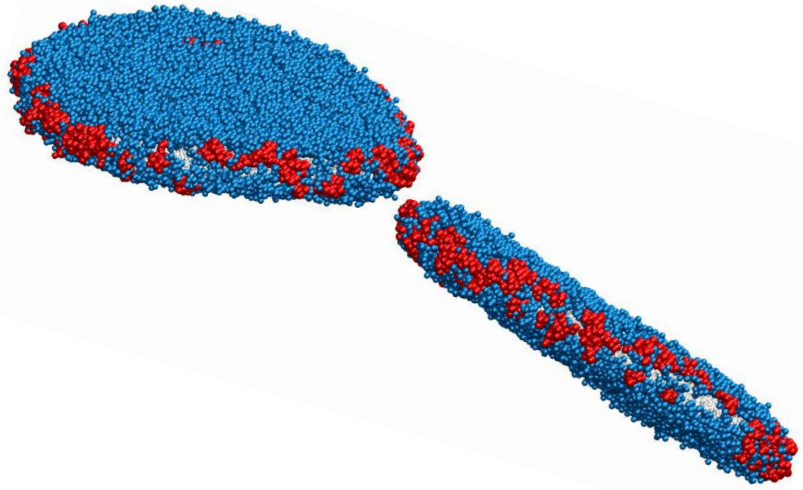
7 µs

Above T_m



11 µs

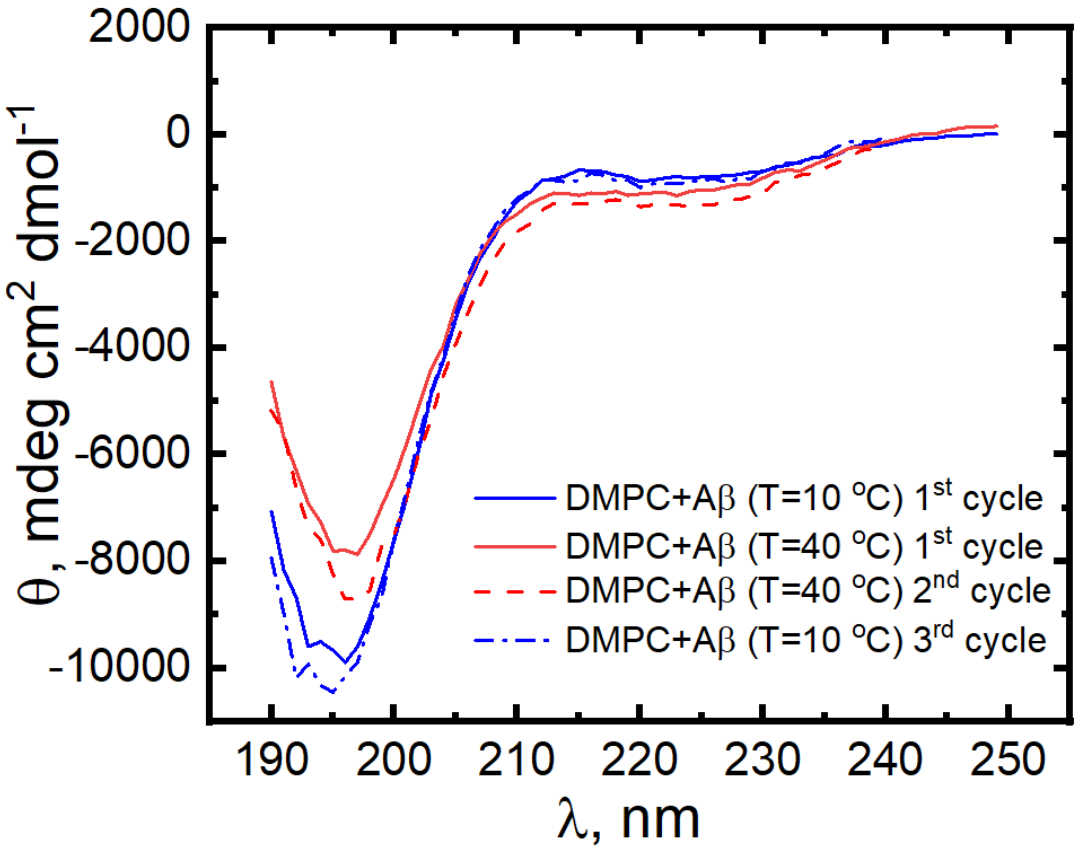
Below T_m



Kurakin et al. BBA-Biomembranes. 2023

Secondary structure of Aβ(25-35) in BLSs and SULVs

Circular dichroism



Circular dichroism spectra of the DMPC+Aβ(25-35) system at different heating-cooling cycles.

DMPC + Aβ(25-35)

	α-helices	β-sheets	β-turns	Random coils
BLSs (T = 10 °C)	3%	22%	21%	54%
SULVs (T = 40 °C)	5%	28%	20%	47%

DMPC lipid: T_m = **24 °C**

Conclusions

- Transitions between bicelle-like structures and small vesicles have been observed. This effect is explained by toxic behavior of the Aβ(25-35) peptides that cause a temporary membrane disintegration during its phase transitions

- In bicelle-like structures, peptides are localized on the BLS rim covered with lipids, while peptides reside predominantly in the outer leaflet in SULVs

- The secondary structure of the Aβ(25-35) peptide is predominantly unordered and it does not change significantly in BLSs and SULVs

Acknowledgement

JINR

KFU

The work is partly supported by:
- RSF №19-72-20186
- JINR AYSS-2022 №22-402-02
- JINR AYSS-2023 №23-402-06

Thank you for attention!