60th meeting of the PAC for Condensed Matter Physics

The influence of phospholipid composition on membrane interaction with amyloid beta peptides within molecular dynamics simulations

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27th January 2025 Dubna, Russia

Motivation and Objectives

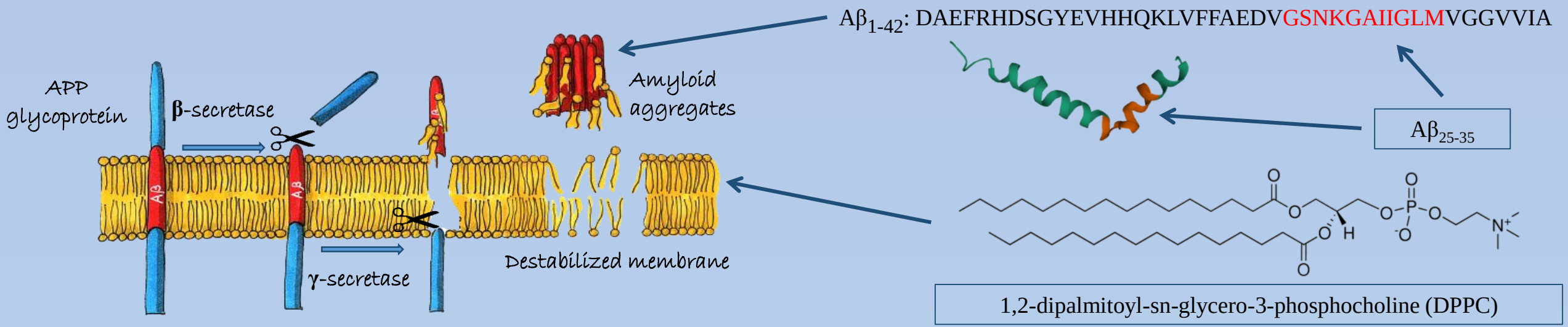


Fig. 1. The sketch of the amyloid hypothesis of Alzheimer's disease

Questions:

- How do the $A\beta_{25-35}$ peptides affect the morphology and structure properties of the lipid membranes?
- Where are the peptides located in membranes?
- How the membrane's complex composition affects its interaction with $A\beta_{25-35}$ in terms of the presence of two phases?

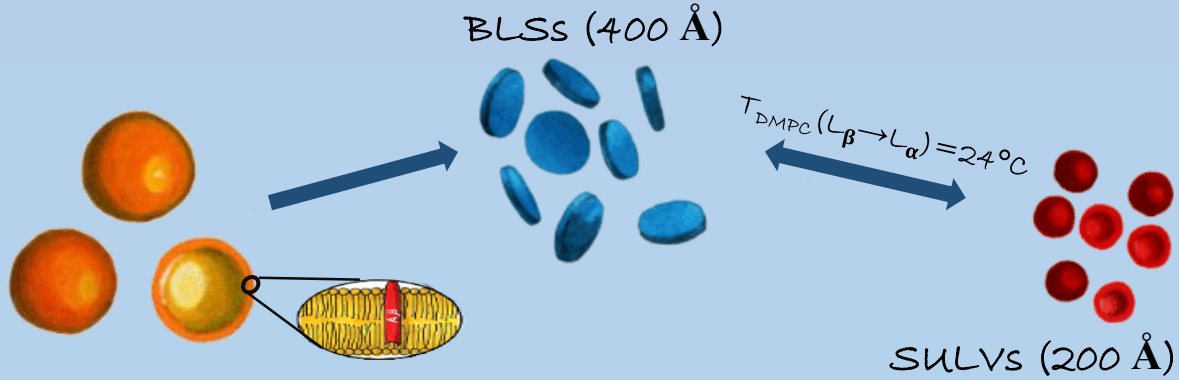


Fig. 2. The shape of the membrane changes with the temperature and in the peptide presence from the large vesicles to the vesicles of small sizes and bicelle-like structures[1] (SANS data)

[1] Ivankov O., et al. Amyloid-beta peptide (25–35) triggers a reorganization of lipid membranes driven by temperature changes. Scientific Reports 11.1 (2021): 21990.

Methods: all-atom and coarse-grained molecular dynamics

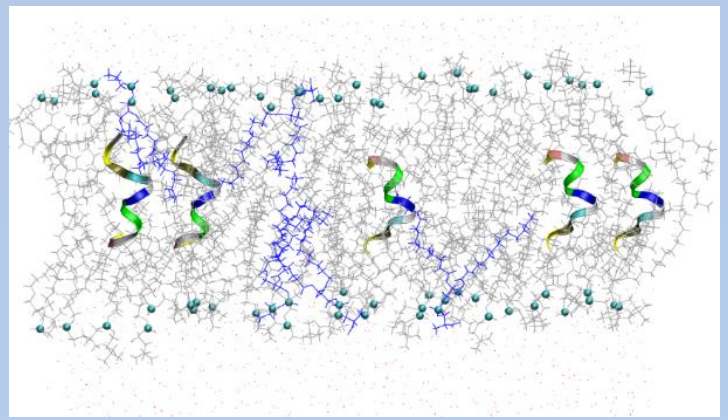


Fig. 3. The snapshot of one of the starting configurations (red points – water, cyan points – atoms of phosphorus, gray and blue lines – lipids)

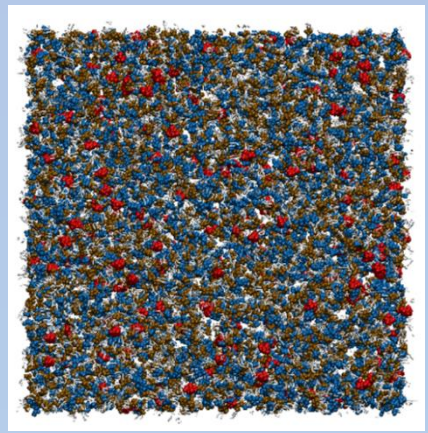


Fig. 4. The snapshot of the starting configuration of coarse-grained simulation

All-atom molecular dynamics details:

- **GROMACS 2019.3**;
- **"Govorun" supercomputer (MLIT, JINR)** (8 GPUs per run, multithreading, 1 μs – 7 days);
- Starting configuration: CHARMM-GUI Membrane Builder – 128 DPPC and 128 DOPC lipids;
- Force field: **CHARMM36m** with TIP3P water molecules (40 per lipid);
- NVT + NPT equilibrations: 50 ns for pure membranes, 100 ns for membranes with peptides;
- Nose-Hoover thermostat at 293 K and 323 K;
- Parrinello-Rahman barostat at 1 bar of pressure;
- MD run: **500 ns**;
- Integration: leapfrog algorithm with time step of 2 fs;
- Analysis: GROMACS tools.

Coarse-grained molecular dynamics details:

- **GROMACS** 2019.3;
- **"Govorun" supercomputer (MLIT, JINR)** (4 GPUs per run, multithreading);
- Starting configuration: in-house tools and CHARMM-GUI Membrane Builder;
- Force field: **MARTINI** v.2 with explicit water molecules;
- NPT equilibrations: 500 ns;
- Berendsen thermostat at 290 K and 323 K;
- Parrinello-Rahman at 1 bar of pressure;
- MD run: **5 μs**;
- Integration: leapfrog algorithm with time step of 20 fs;
- Analysis: GROMACS tools.

All-atom molecular dynamics results

Temperature, K	Thickness, Å		
	DPPC+DOPC	+ $A\beta_{25-35}$ in tails	+ $A\beta_{25-35}$ in heads
290	38.7	40.2	40.1
323	36.2	37.9	37.8

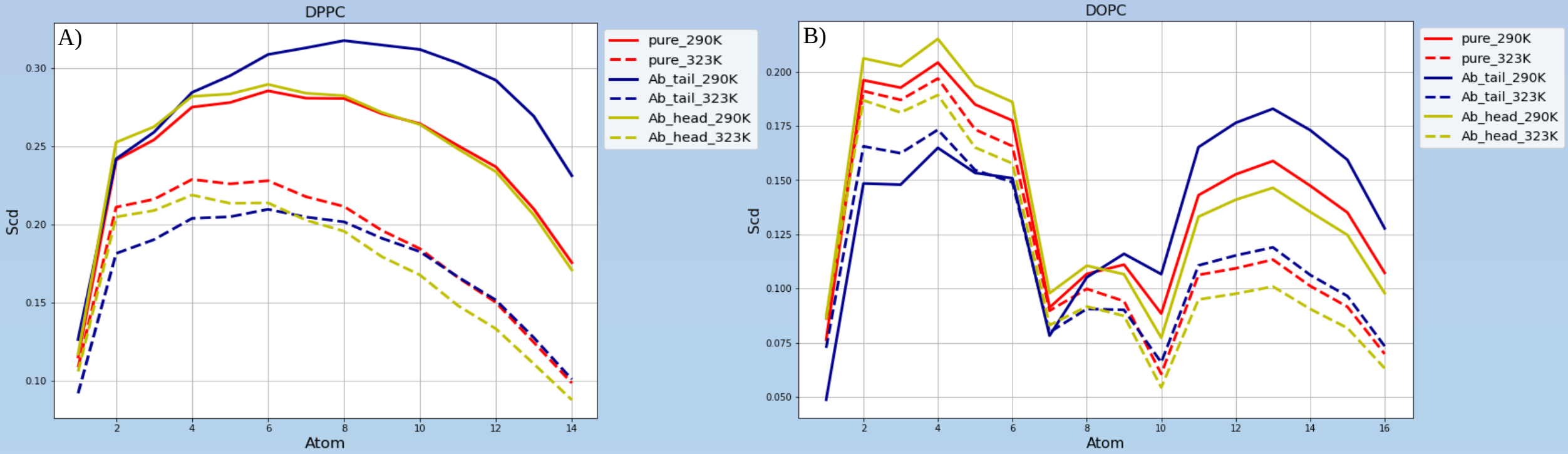


Fig. 5. Order parameters of lipid chains ($\mathbf{S_{cd}=(3\cos^2\theta_{cd}-1)/2}$) of A) DPPC and B) DOPC

All-atom molecular dynamics results

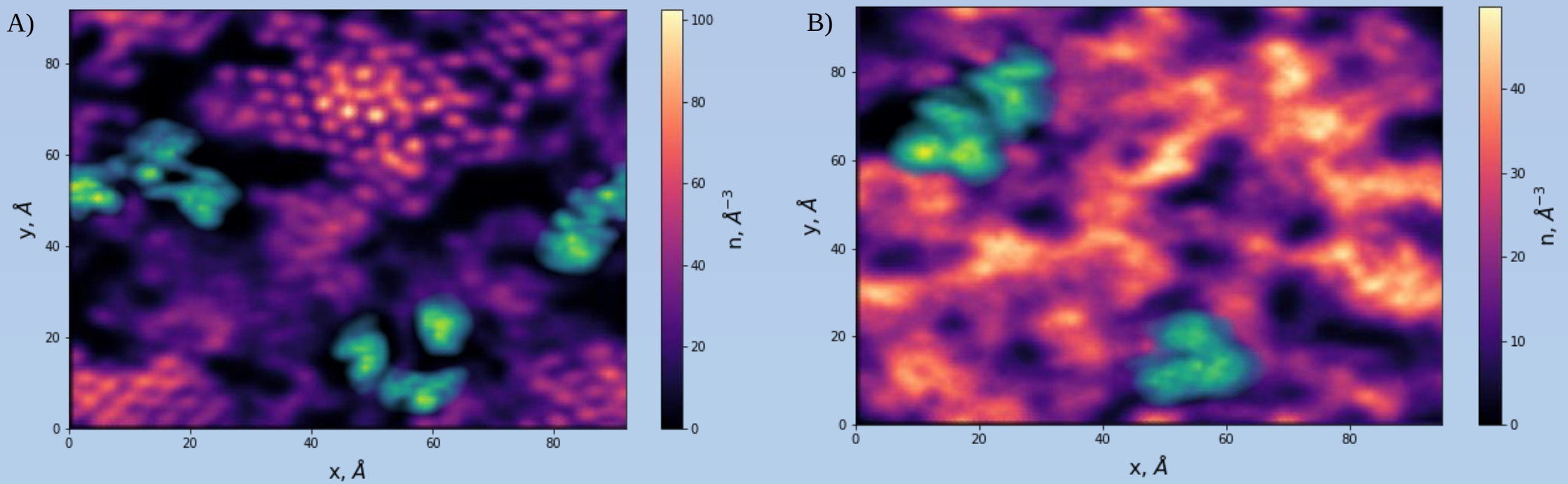
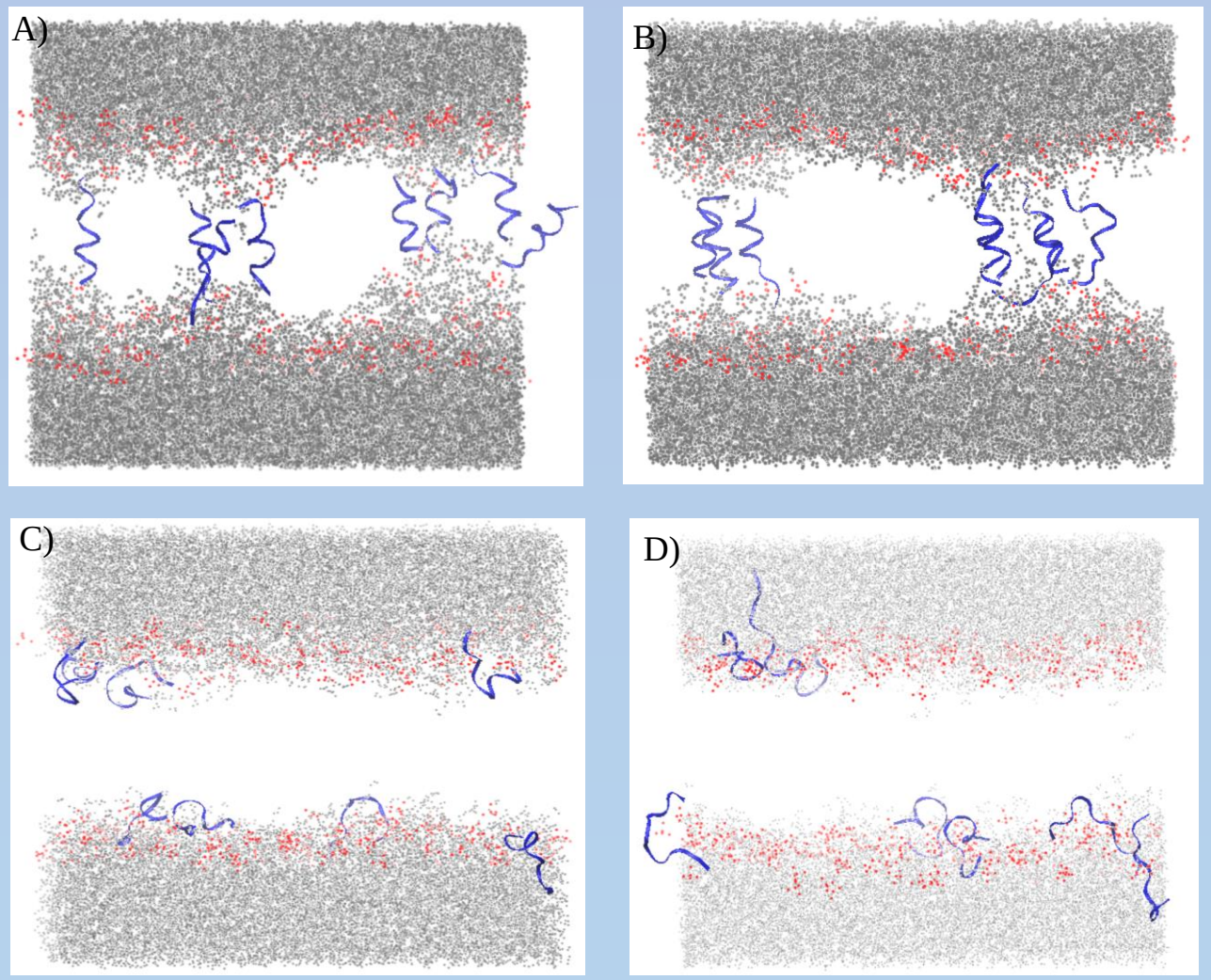


Fig. 6. Density map of DPPC lipids (orange-purple), DOPC (black) and $A\beta_{25-35}$ (green) at temperatures of A) 290 K and B) 323 K

Lipid type	Number of contacts			
	+ $A\beta_{25-35}$ in tails		+ $A\beta_{25-35}$ in heads	
DOPC	641	455	485	414
DPPC	422	326	395	344
Temperature, K	290	323	290	323

All-atom molecular dynamics results



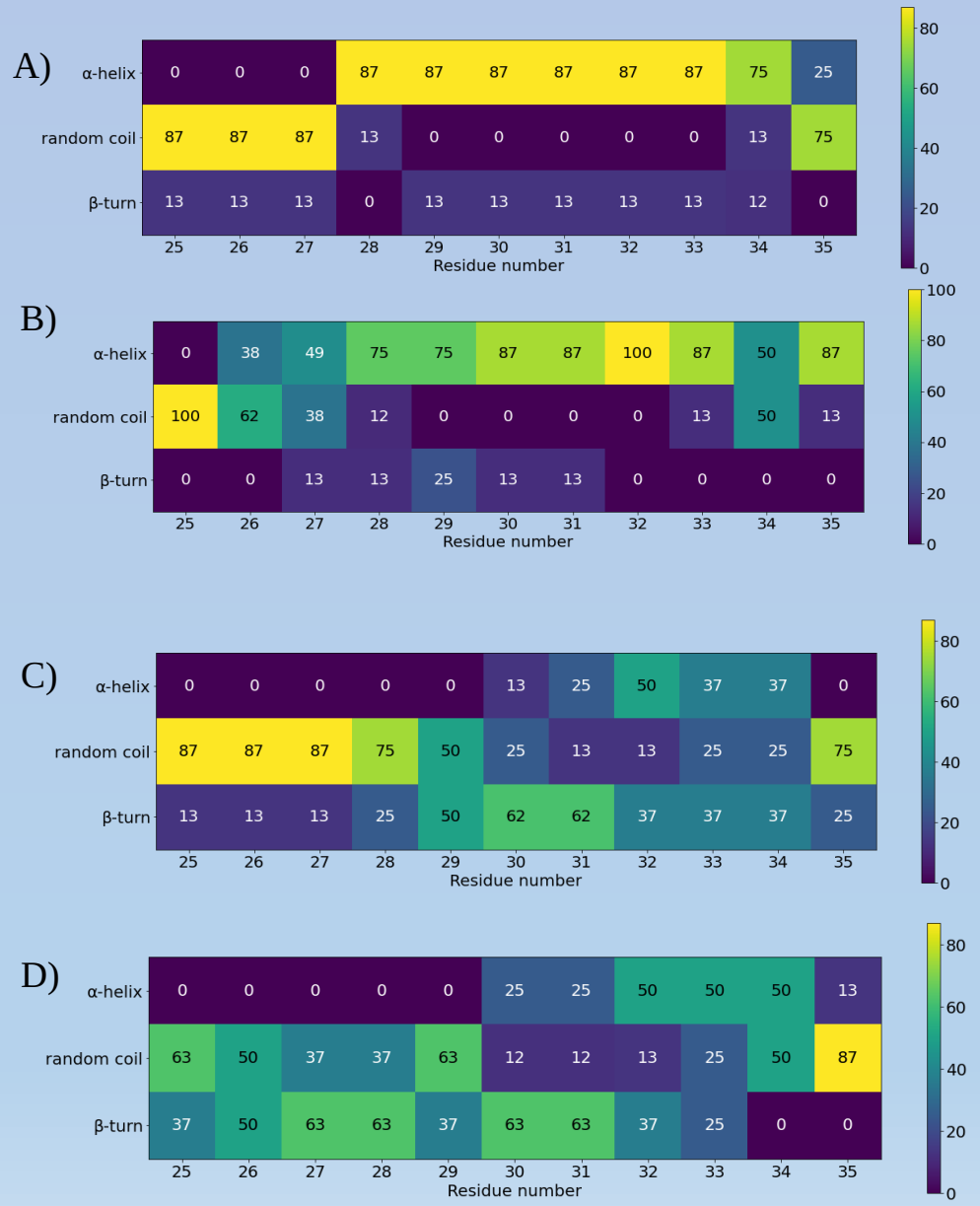
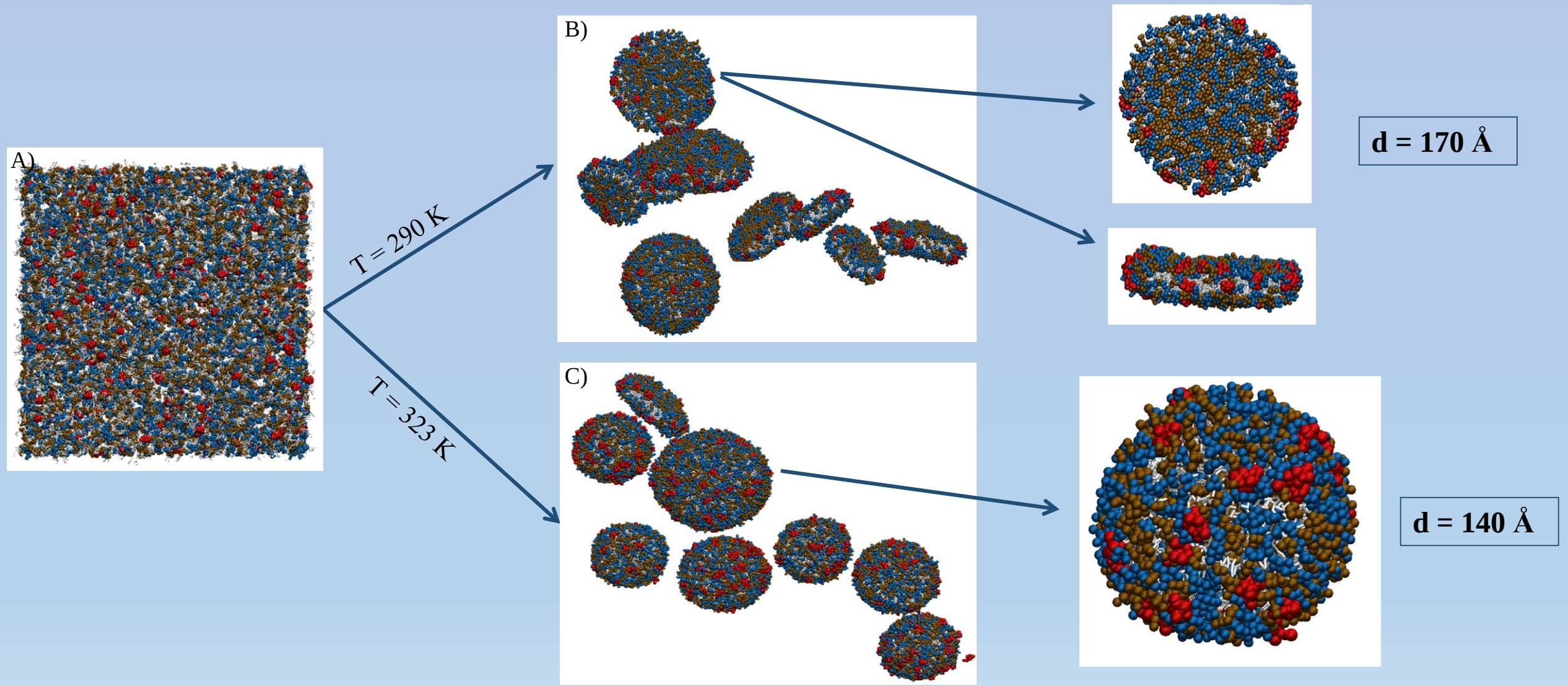


Fig. 7. The snapshots of $A\beta_{25\text{-}35}$ positions and their secondary structures A), C) at 290 K and B), D) at 323 K (red points – atoms of phosphorus, gray points – atoms of water, lipids are omitted)

Coarse-grained molecular dynamics results

Fig. 8. The snapshots of A) the starting configuration, B) the system after 3 μs at the temperature below T_m of the DPPC lipid and B) the system after 5 μs at the temperature above T_m of the DPPC lipid



Conclusions

From **all-atom** molecular dynamics simulations:

- **Aβ$_{25-35}$** peptides embedded into the membrane **increase** the membrane **thickness** in both types of insertion, peptides **increase** the **order** parameter of lipid tails and **reduce** disorder in the organization of lipid molecules in the case of insertion into the tails; however, with an increase in temperature and insertion into heads, this effect is reduced;
- **Aβ$_{25-35}$** peptides do not assemble at the phase interface but **prefer** regions consisting of lipids in the **liquid phase**;
- In the case of initial incorporation of peptides into the **hydrophobic tails** of lipids, they prefer to **remain in this region** of the membrane with a predominance of **helices** in the secondary structure; with initial insertion into the **hydrophilic heads** of lipids, peptides **remain on the surface** of the membrane with partial exit to the water;
- Due to the complex composition of the membrane (possibly the presence of two phases or significant heating of the DOPC lipid), **pores** in the bilayers formed by peptides **were obtained** with the possibility of water movement through them, which is perhaps the first step towards membrane destabilization.

From **coarse-grained** molecular dynamics simulations:

- **Aβ$_{25-35}$** peptides prefer to be located **at the rim** of the bicelle-like structures, but they are not able to form the stable belt typical for nanodisc; **lipid heads** were also found to be located **at the BLS rim**, helping Aβ cover the hydrophobic part of membrane;
- **Aβ$_{25-35}$** peptides prefer to be inserted into the **hydrophilic** region of **vesicles** with their partial incorporation into hydrophobic region.

The **following** steps:

- To carry on all-atom and coarse-grained molecular dynamics simulations of lipid membranes with different additional conditions (pH, ions, charges) in order to reach the changes in vesicles structure (pore formation, lipid extraction);
- To simulate coarse-grained systems with different secondary structures of peptides (obtained from all-atom MD) or all-atom system of bilayer with half vesicle.