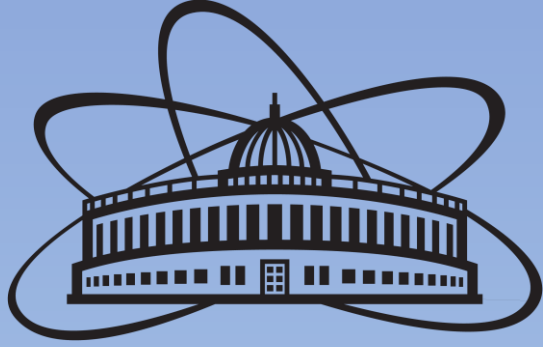

54th meeting of the PAC for Condensed Matter Physics

Effect of charged lipids on β-amyloid peptide interactions with a phospholipid membrane

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Objectives

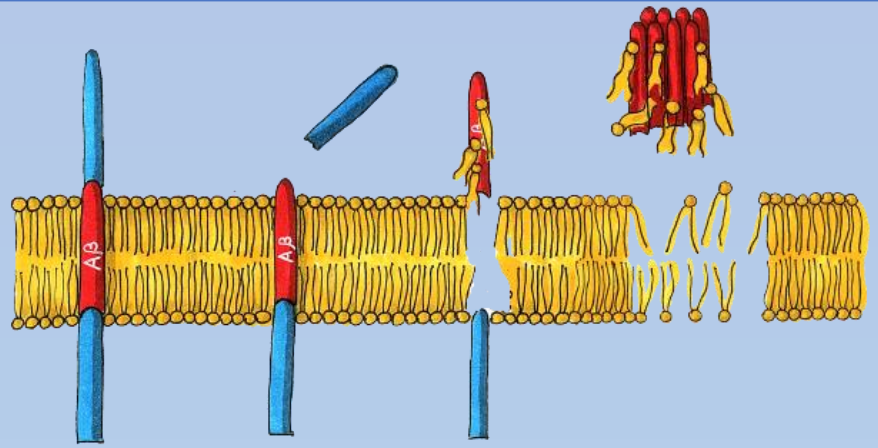
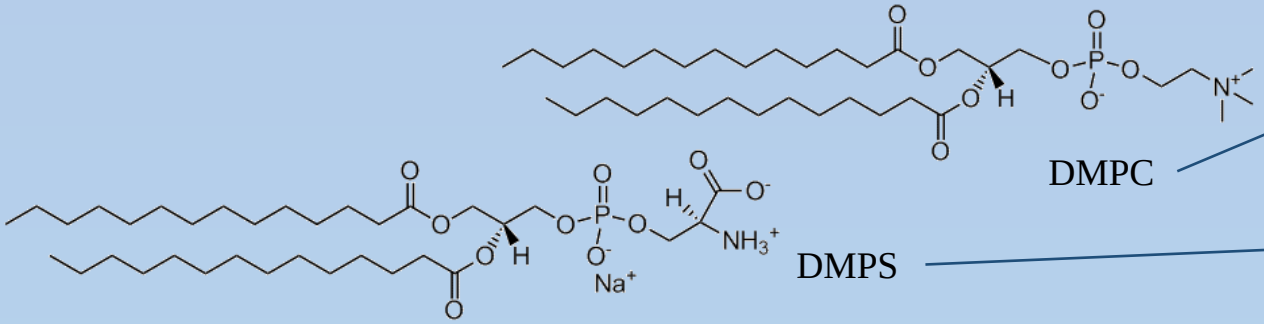


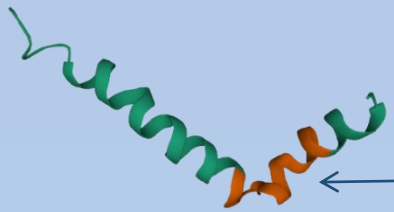
Fig. 1. The sketch of the amyloid hypothesis of Alzheimer's disease[1]



Questions:

- How do the Aβ(25-35) peptides affect the structure of the lipid membranes?
- Does the lipid charge affect the peptide-membrane interactions?
- Do Aβ(25-35) monomers form aggregates within the membrane?

Fig. 2. Aβ(1-42): DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA



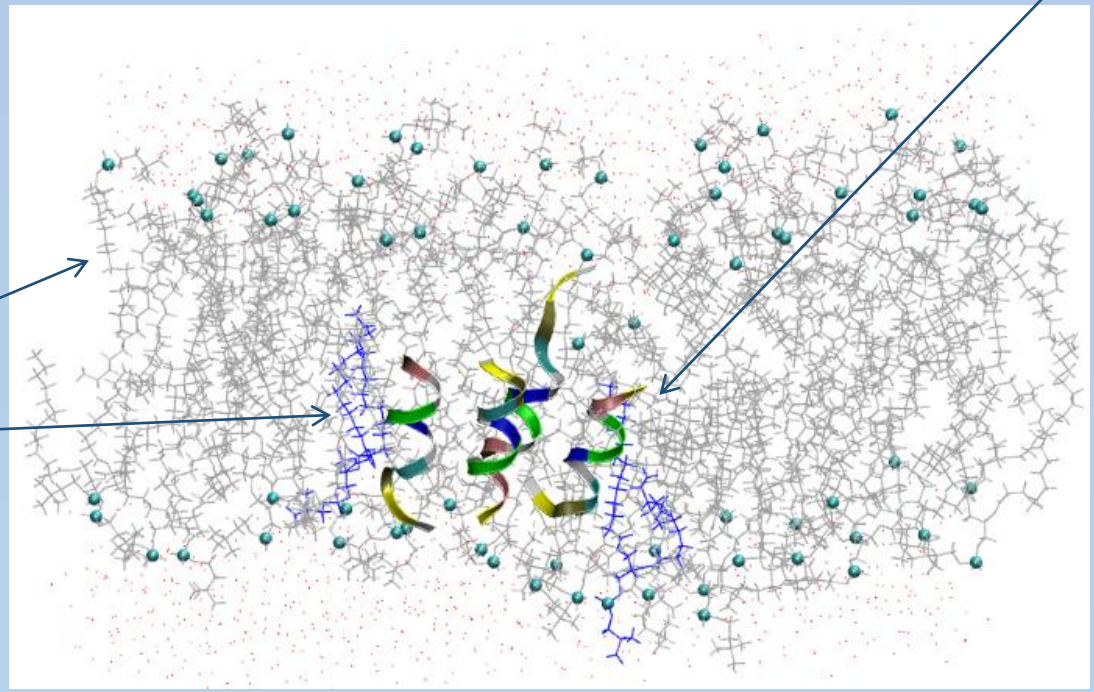


Fig. 3. The snapshot of Aβ(25-35) positions in a model phospholipid membrane after 1 μs run (red points – water, cyan points – atoms of phosphorus, gray lines – DMPC lipids, blue lines – DMPS lipids)

[1] Figure has been reproduced from JINR news (15.02.2021// D.R. Badreeva, P. Hrubovčák, E.B. Dushanov, E.V. Ermakova, O.I. Ivankov, T. Kondela, A.I. Kuklin, S.A. Kurakin, T.N. Murugova, V.V. Skoi, D.V. Soloviov, Kh.T. Kholmurodov and N. Kučerka, Neutrons and molecular simulations: scrutinizing the neural membranes damage caused by amyloid beta peptide//)

Methods: molecular dynamics and umbrella sampling

System	1	2	3	4	5	6
DMPC	256		252		248	
DMPS	0		4 (1.5%)		8 (3%)	
Aβ(25-35)	-	8 (3%)	-	8 (3%)	-	8 (3%)

Molecular dynamics details:

- GROMACS 2019.3;
- Starting configuration: CHARMM GUI Membrane Builder and InflateGRO script;
- Force field: CHARMM36m with TIP3P water molecule;
- NVT + NPT equilibrations: 50 ns for pure membranes, 100 ns for membranes with peptides;
- Nose-Hoover thermostat at 293 K, 303 K, 323 K;
- Parrinello-Rahman barostat at 1 bar of pressure;
- MD run: 500 ns for pure membranes, 1 μs for membranes with peptides;
- Constraints: LINCS algorithm;
- Integration: leapfrog algorithm with time step of 2 fs;
- Long-range electrostatic interactions: the smooth particle mesh Ewald algorithm;
- PBC in three dimensions;
- Analysis: GROMACS tools;
- “Govorun” supercomputer (4 GPUs, 6 OpenMP threads).

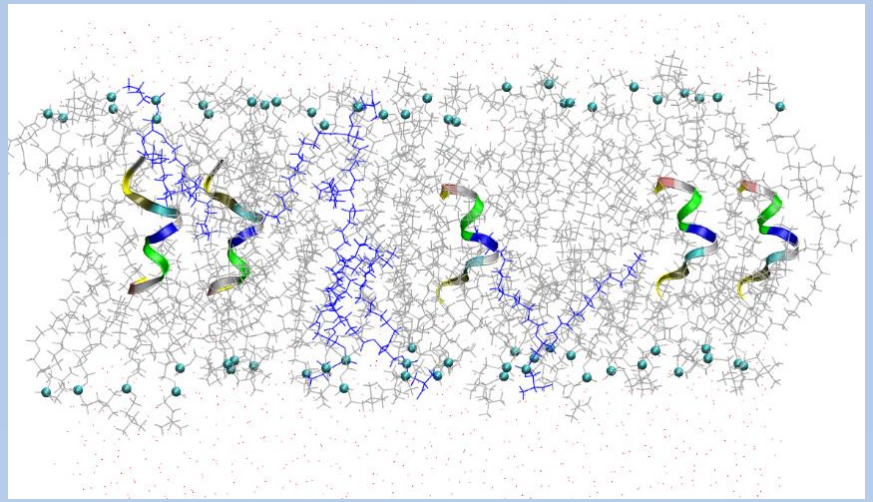


Fig. 4. The snapshot of one of the starting configurations (red points – water, cyan points – atoms of phosphorus, gray lines – DMPC lipids, blue lines – DMPS lipids)

Umbrella sampling details:

- Reaction coordinate: distance between the centers-of-mass of the peptide and the membrane;
- 12 windows spaced every 2 Å;
- 1 ns NPT equilibration;
- 100 ns run;
- The force constant: 1000 kJ/mol/nm^2;
- The pulling rate: 0.02 nm/ns;
- Analysis: the weighted histogram analysis method.

Molecular dynamics and umbrella sampling results

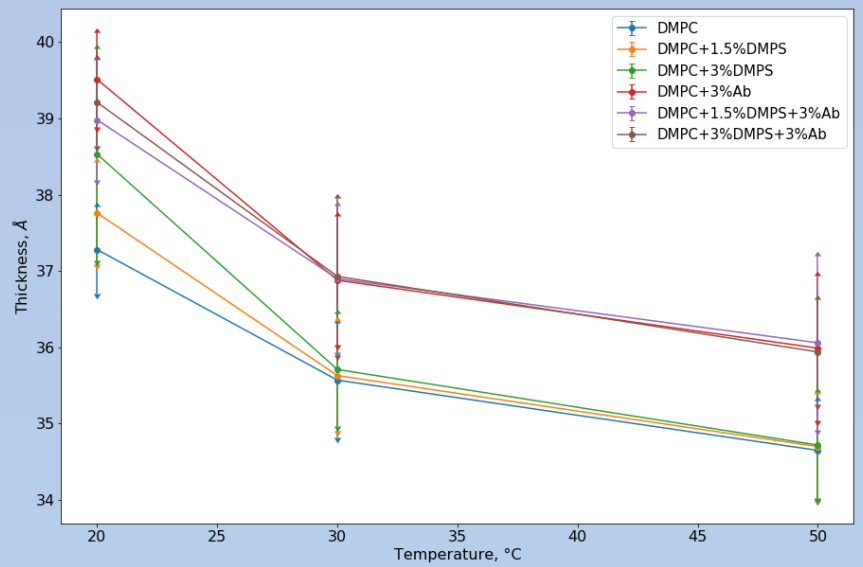


Fig. 4. Dependence of membrane thickness on temperature and its composition

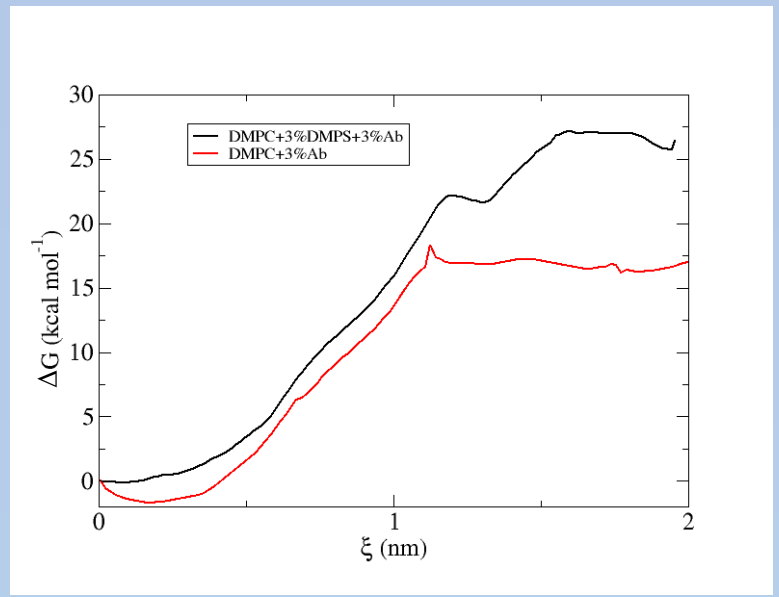


Fig. 6. Free-energy profiles of Aβ peptide binding to the DMPC and DMPC+1.5%DMPS membranes at 30°C

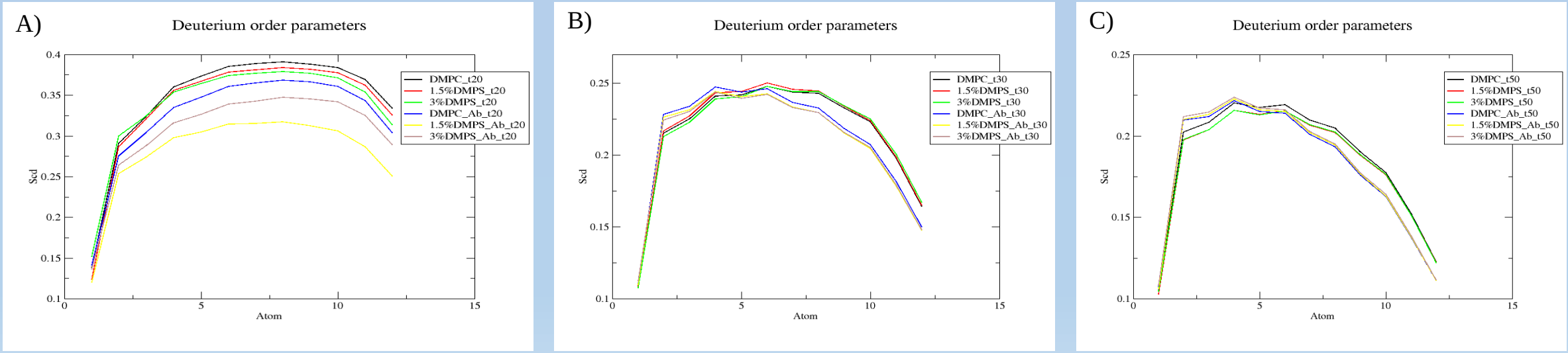


Fig. 5. Order parameters of lipid chains at temperatures of A) 20°C, B) 30°C, C) 50°C

Molecular dynamics results

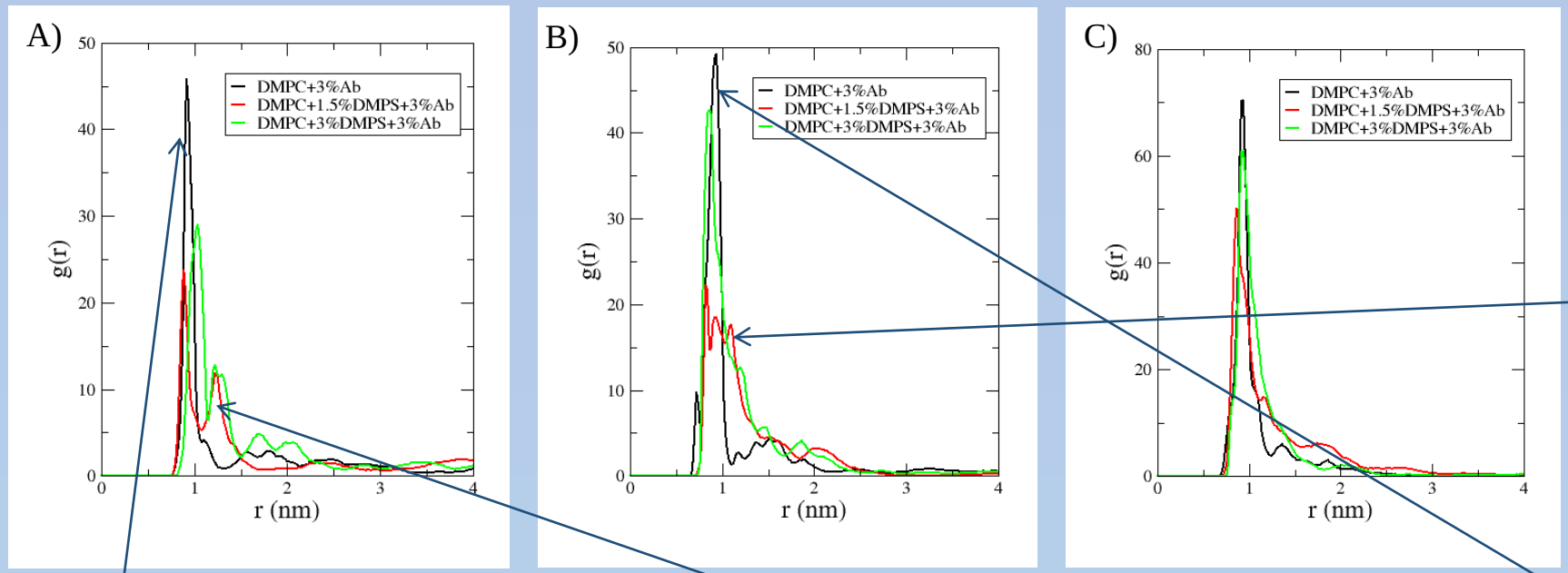


Fig. 7. Radial distribution function of peptide-peptide COM at temperatures of A) 20°C, B) 30°C, C) 50°C

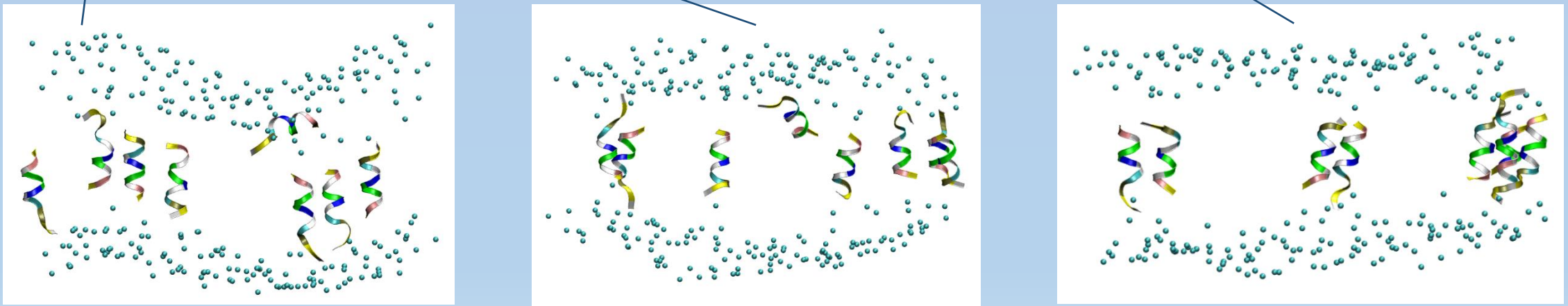


Fig. 8. The snapshots of Aβ(25-35) positions in A) DMPC, B) DMPC+1.5%DMPS, C) DMPC and D) DMPC+1.5%DMPS membranes at 20°C and 30°C accordingly after 1 μs run (cyan points – atoms of phosphorus, water and lipids are omitted)

Conclusions

- The presence of Aβ(25-35) peptides affects the structural properties of the zwitterionic and anionic membranes:
  - Aβ(25-35) peptides embedded in the hydrophobic part of the membrane increase the total membrane thickness by 1-2 Å, although the thickness decreases at the site of peptide aggregation;
  - Also, peptides reduce the order parameter of lipid tails and increase disorder in the organization of lipid molecules; however, with an increase in temperature, this effect disappears due to an increase in the peptides aggregation;
- Interpeptide and charge head groups-peptide interactions help part of peptides to overcome the potential barrier and move from the hydrophobic tail of the membrane to the hydrophilic heads;
- It can be assumed, that the ability of Aβ to aggregate can be expressed as a function of potential of hydrogen and electrostatic bonding between the peptides and the surrounding lipids: lipids with greater numbers of hydrogen bonding and anionic groups such as DMPS reduced Aβ aggregation and the structural destabilization caused by Aβ;
- Aggregated Aβ did not exit any of the studied membranes, in agreement with experimental results that suggest Aβ aggregation within membranes is favored over the monomeric state in solution.

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