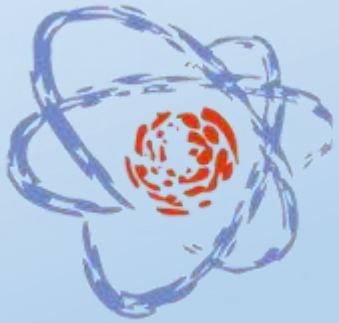


The XXVII International Scientific Conference
of Young Scientists and Specialists (AYSS-2023)

Coarse-grained molecular dynamics simulation of DPPC membrane self-assembly in the presence of amyloid beta 25-35 peptides

Dina Badreeva

Meshcheryakov Laboratory of Information Technologies, JINR

31st October 2023 Dubna, Russia

Motivation

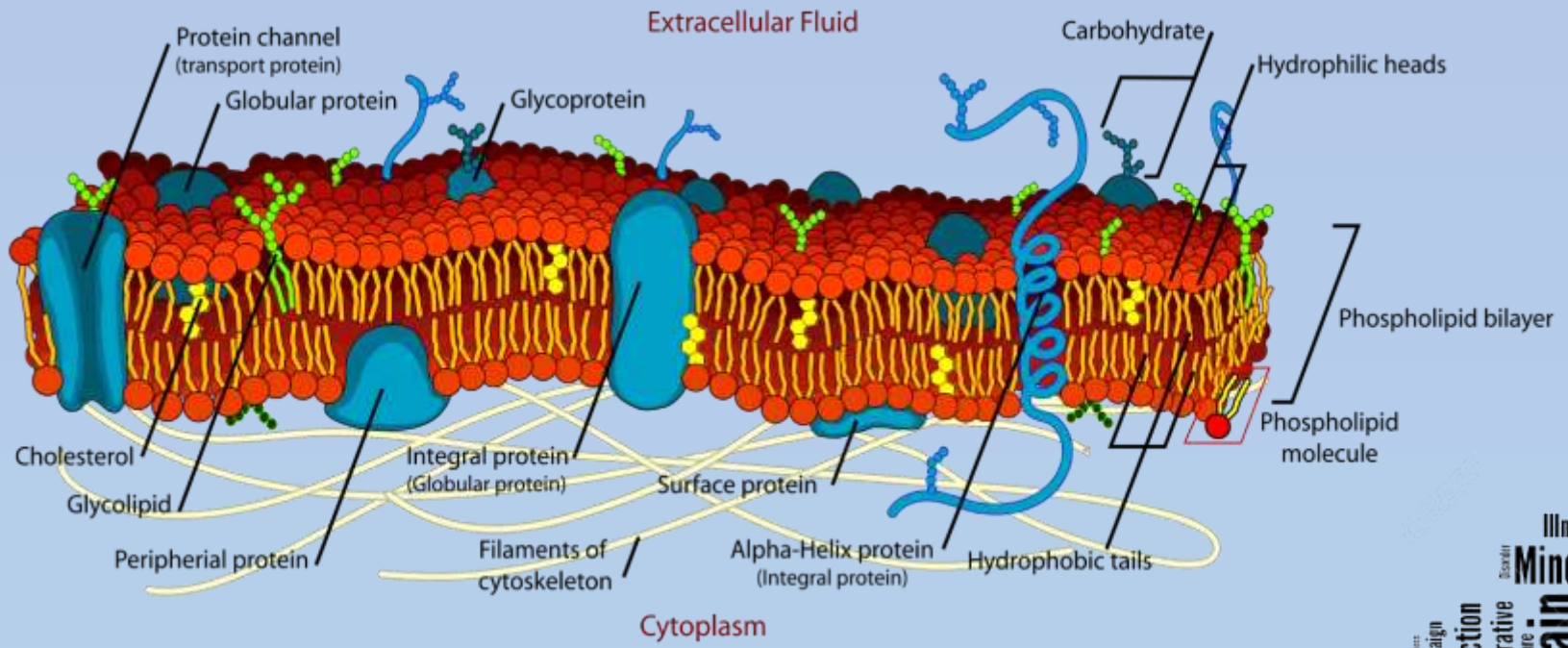


Fig. 1. The model of membrane structure[1]

cholinergic hypothesis

tau hypothesis

amyloid-beta hypothesis

[1] Figure has been reproduced from wikipedia.org/wiki/Cell_membrane

Objectives

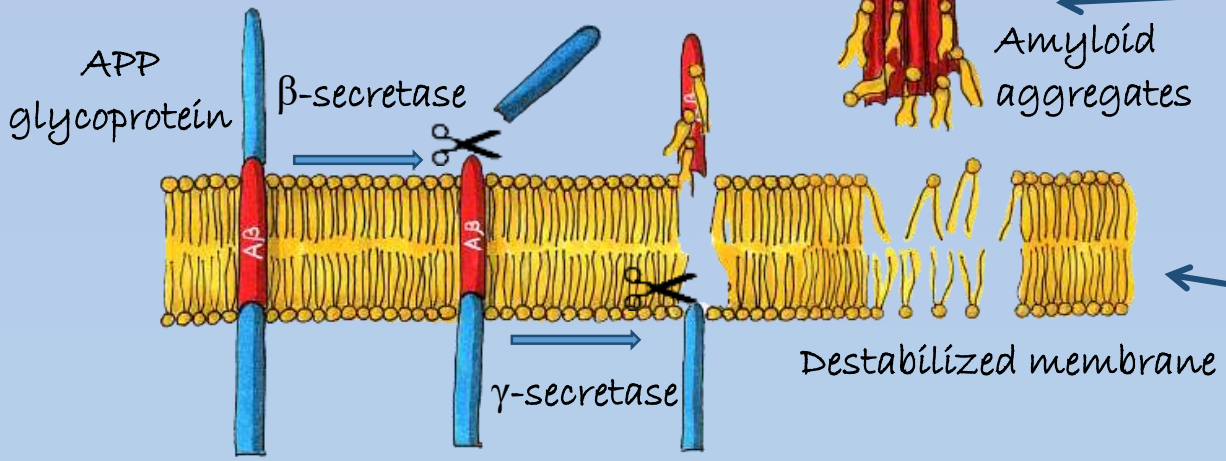
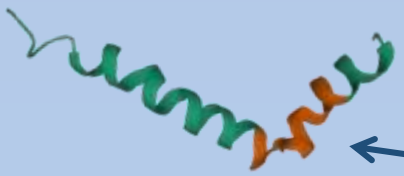
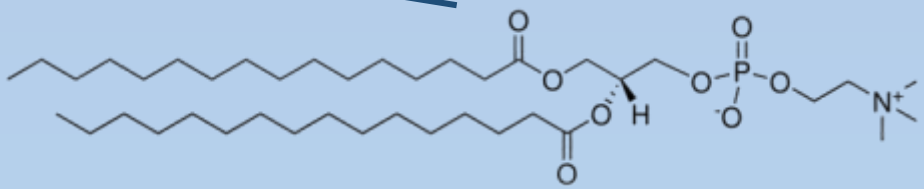


Fig. 2. The sketch of the amyloid hypothesis of Alzheimer's disease[1]

$A\beta_{1-42}$: DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA



$A\beta_{25-35}$



1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)

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?

[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//)

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.

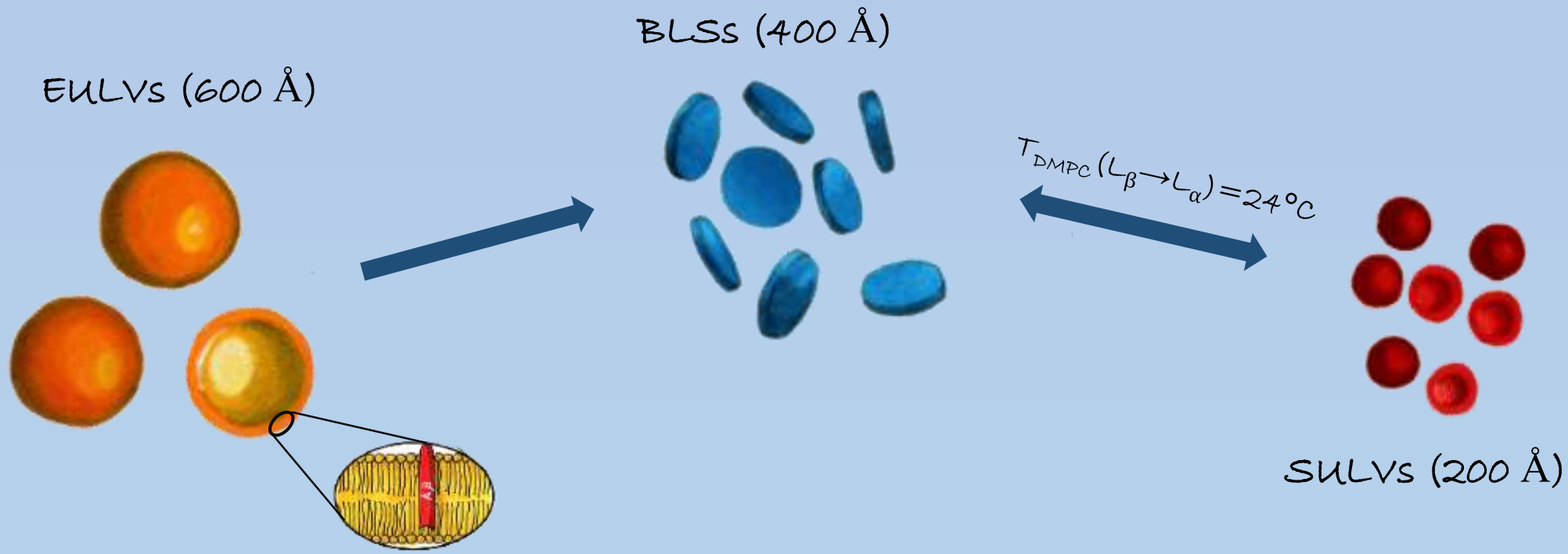


Fig. 3. The shape of the membrane changes with the temperature and in the peptide presence from the large vesicles to the vesicles of small sizes and bicelle-like structures[1]

[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//)

Molecular dynamics is a simulation method based on the calculation of the evolution of a system of interacting particles (atoms, molecules...) by solving the equations of their motion:

$$\begin{cases} \vec{v}_i = \dfrac{d\vec{r}_i}{dt}, \\ m_i \dfrac{d\vec{v}_i}{dt} = \vec{F}_i, \end{cases} \quad i = 1,\ldots N.$$

$$\vec{F}_i = -\frac{\partial U}{\partial \vec{r}_i}$$

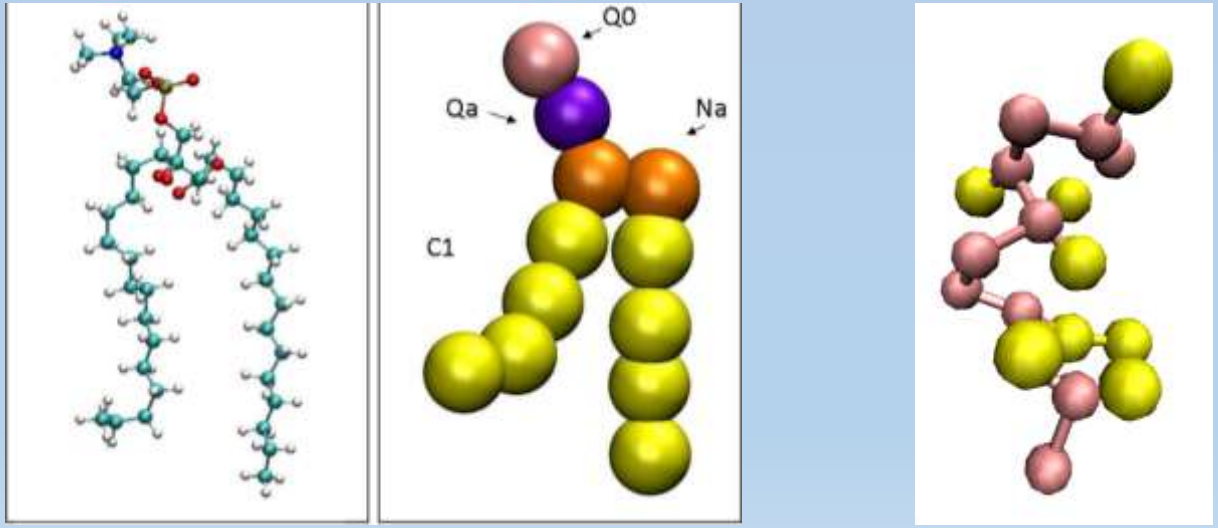


Fig. 4. All-atom and coarse grained DPPC and coarse grained $A\beta_{25\text{-}35}$

Coarse-grained MD input

System	1
DPPC	10000
$A\beta_{25-35}$	300 (3%)
Water	50 per lipid

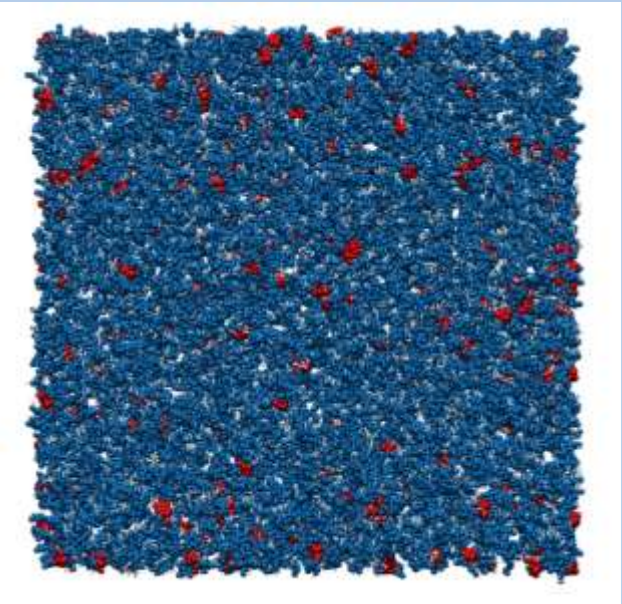
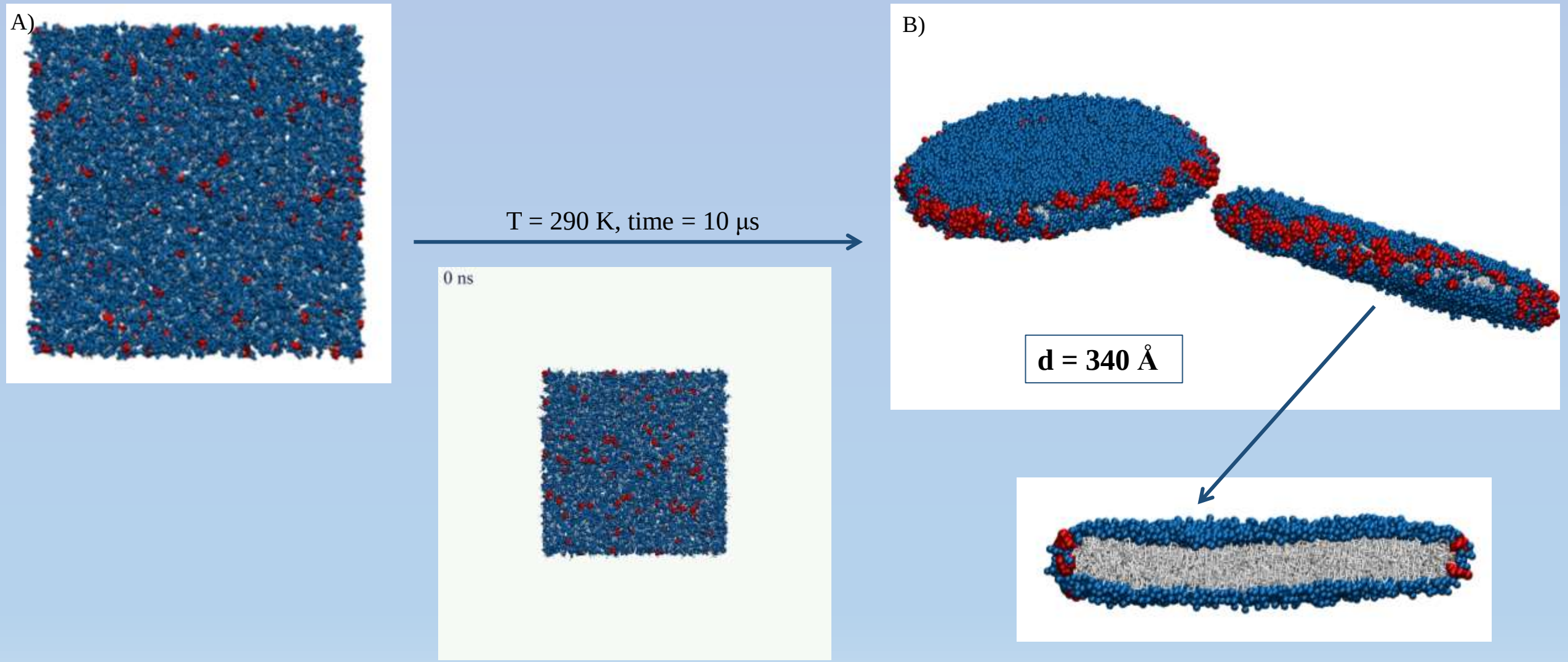


Fig. 5. The snapshot of the starting configuration

- **GROMACS** 2019.3;
- **“Govorun” supercomputer (MLIT, JINR)** (4 GPUs per run, multithreading);
- Starting configuration: in-house tools and CHARMM-GUI Membrane Builder, Martinize python script;
- Force field: **MARTINI** v.2 with explicit water molecules;
- NPT equilibrations: 500 ns;
- Berendsen thermostat at 290 K - 313 K;
- Parrinello-Rahman at 1 bar of pressure;
- MD run: **10 μs**;
- Integration: leapfrog algorithm with time step of 20 fs;
- Cutoff of 12 Å for LJ potential and electrostatic interactions;
- LJ potential was smoothly shifted between 9 and 12 Å;
- Coulomb potential was shifted between 0 and 12 Å;
- PBC in three dimensions;
- Analysis: GROMACS tools.

Coarse-grained MD results

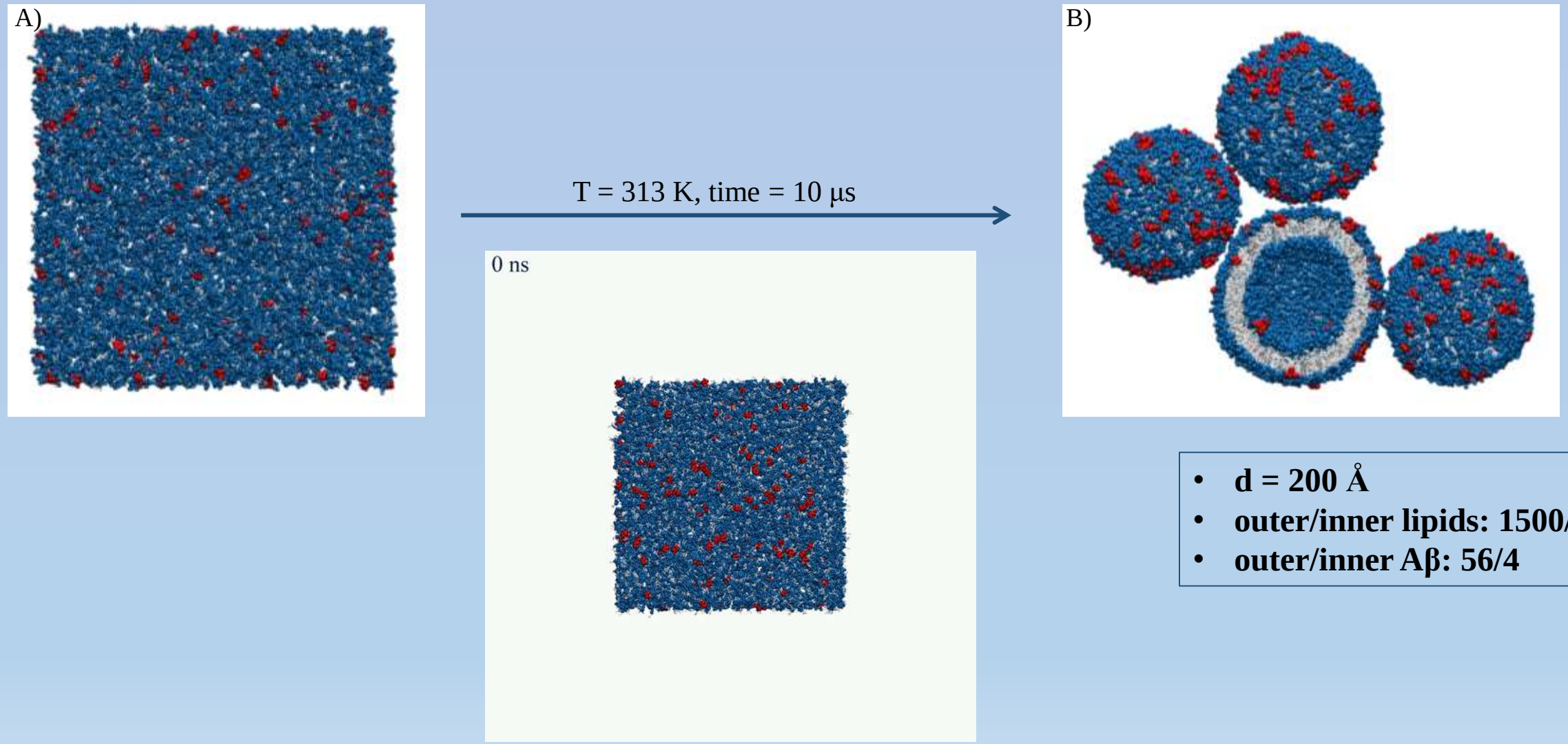
Fig. 7. The snapshots of A) the starting configuration and B) after 10 μs at the temperature below T_m of the DPPC lipid



Kurakin S., et al. Arrangement of lipid vesicles and bicelle-like structures formed in the presence of Aβ (25–35) peptide. BBA-Biomembranes 1866.1 (2024): 184237.

Coarse-grained MD results

Fig. 8. The snapshots of A) the starting configuration and B) after 10 μs at the temperature above T_m of the DPPC lipid



- **d = 200 Å**
- **outer/inner lipids: 1500/900**
- **outer/inner Aβ: 56/4**

Conclusions

- **Coarse-grained** molecular dynamics simulation showed **good agreement** with experimental results;
- **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 and with a significantly **asymmetric distribution** between the outer and inner leaflets due to the defects in lipids packing;
- Coarse-grained molecular dynamics does **not** allow **achieving** the reverse transition from vesicle to bicelle-like structures only in the presence of Aβ$_{25-35}$ peptides.

The following steps:

- To carry on 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 look towards the antimicrobial peptides (melittin, alamethicin..).

Acknowledgments

Thank you for your attention!

Our group:

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E.V. Ermakova (FLNP, JINR, Russia)

O.I. Ivankov (FLNP, JINR, Russia)

A.I. Kuklin (FLNP, JINR, Russia & MIPT, Russia)

S.A. Kurakin (FLNP, JINR, Russia & KFU, Russia)

T.N. Murugova (FLNP, JINR, Russia)

V.V. Skoi (FLNP, JINR, Russia)