Molecular-dynamic simulations of β-amyloid peptide in the presence and absence of inhibitors of its aggregation

Salamanova E, Atanasova M, Dimitrov I, Doytchinova I.
Faculty of Pharmacy, Medical University of Sofia

Alzheimer's disease is a neurodegenerative disease with an asymptomatic onset, a slow but irreversible development of dementia and a fatal outcome. One of the main features of the disease is the amyloid plaques, which are formed by misfolded amyloid peptides in blood vessels. The plaques clog the vessels that feed the nerve cells, and the neurons die.

The aim of the present study is to simulate the interactions between the β-amyloid peptide (Aβ) and an inhibitor of the aggregation and to elusidate the mechanism of inhibition. As inhibitors of Aβ are used curcumin (CU, strong inhibitor with IC_{50} = 0,8 μM) and ferulic acid (FA, weak inhibitor with IC_{50} = 5,5 μM).

❖ MD protocol

For this purpose, three systems are modeled: 1 molecule Aβ, 1 molecule Aβ + 1 molecule CU and 1 molecule Aβ + 1 molecule FA. The inhibitors are randomly positioned near the peptide.

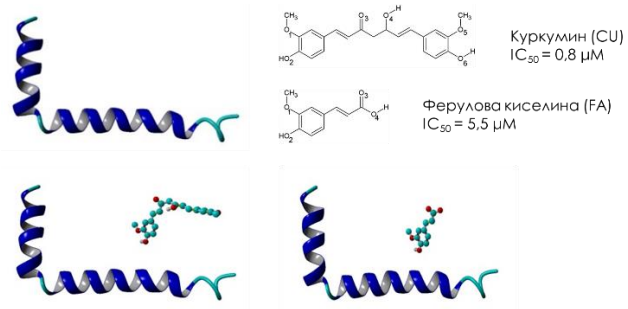

Figure 1: Modelled systems: Aβ (upper left), Aβ + CU (lower left) и Aβ + FA (lower right).

The systems are placed into truncated octahedron, solvated with isotonic NaCl solution. Initially, the energy of the systems is minimized by 5000 steps, followed by heating to 310 K (37°C) for 1 ns and equilibration at constant pressure. The movement of the systems is simulated for 1000 ns at constant pressure and temperature with a step of 2 fs. The coordinates of the systems are recorded every ns (1000 frames).

❖ Results and Discussion

The analysis of the trajectories shows that the helical structure of the peptide is destroyed in the absence of inhibitors and is preserved relatively in their presence.

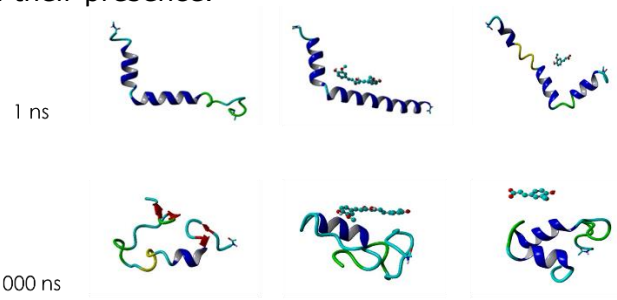

Figure 2: Systems coordinates in the beginning (1-st ns, upper) and in the end of the production phase (1000 ns, lower)

The average fluctuations (RMSF) of peptide residue show that in the absence of an inhibitor, the fluctuations are almost evenly distributed along the entire length of the peptide. In the presence of CU, Aβ is stabilized between the 9th and 32nd aa, and both ends remain mobile. In the presence of FA, stabilization covers shorter sections: between the 9th and 21st aa and between the 28th and 34th. Over 400 intramolecular hydrogen bonds in the Aβ peptide are detected during the simulation. In the presence of inhibitors, this number is not only maintained, but 94 hydrogen bonds between CU and Aβ are added, and there are 55 between FA and Aβ. In 65% of them, CU acts as a donor, in 75% FA acts as an acceptor. The average duration of the hydrogen bonds between CU and Aβ is 5.5 ns and is 2 times longer than the average duration of the bonds between FA and Aβ.

In conclusion, the MD simulations of the modelled systems show that the antiaggregation effect of the inhibitors is due to the relative preservation of the helical structure of Aβ and the plurality of hydrogen bonds between the peptide and the inhibitors.