Copper induced Aβ aggregation upon synaptic excitation. Reaction - diffusion simulations in realistic 3D reconstruction of the synaptic cleft

Alzheimer Disease (AD) is one of the major challenges in modern science. In 2010 the estimated number of people suffering from this disease ranged from 21 to 31 mln worldwide. The scale of the problem is illustrated by the fact that until today we do not know the actual mechanism leading to pathology, although we all well aware of its symptoms. One of the most profound hallmarks of AD are so called „senile plaques", which are in fact aggregates of a single peptide – the Aβ peptide. At the same time plaques are disproportionally rich in copper (Cu(II)) and zinc (Zn(II)) ions. The importance of this observation is highlighted by the fact that these ions in the laboratory conditions accelerate the Aβ aggregation by three order of magnitude (from hours to seconds). This is one of the main reasons why dyshomeostasis of metal ions and their increased contribution to Aβ aggregation emerged as a fundamental hypothesis concerning the AD genesis.

The synaptic cleft is a place where all of this factors meet together. In the cleft, apart from the neurotransmitters responsible for signal transmission, Cu(II) and Zn(II) ions are also released and play significant role in signal modulation. At the same time Aβ peptide is also present in the synapse as a result of cleavage of membrane protein APP.

The goal of our research is to investigate possible interactions between Cu(II) and Aβ in conditions resembling the synaptic environment. Dimensions of the cleft are so small that performing a direct experiment is nearly impossible. On the other hand a numerical approach can be adopted, where considered mechanisms can be modeled with the use of simulations. Because synapse is a place with a complex geometry and distribution of particular species plays an important role, in simulations one has to take into account a morphological shape of modeled space.

In the project we will reconstruct a 3D fragment of brain tissue. This can be done on the basis of a series of electron microscope images. Using these images we are able to detect contours and consequently shapes of particular cells. The obtained reconstruction will serve as a matrix for simulations, where the Cu(II) ions and neurotransmitter can freely diffuse in the extracellular space, but receptors, transporters and other potential targets for Cu(II) ions are immobilized on the surface of various cells. In a series of simulations we will track the mechanisms occurring inside the synapse and establish a relation between the released concentrations of reagents and existence of complexes they form themselves.

The presented approach has a wide range of applications, including investigation of possible activities of copper chelating drugs in neurodegenerative diseases, but also in a number of other studies in general field of neuroinformatics.