Molecular dynamics simulation of complex systems

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The investigation of mixed phospholipid bilayers using computer simulation methods is an ongoing research that gives a new and unique opportunity to study the membranes and their functions based on their natural lipid and fatty acid composition variations. These studies are of a vital importance in the field of cell membranes as the membranes of almost all cells across different organisms are made of lipid bilayers.

Our project aims to carry out molecular dynamics (MD) simulation of bilayers from a mixture of phospholipids. The method we developed is based on the biochemical data concerning the ratios and asymmetry of those phospholipids in the brain tissues of different vertebrates. The mentioned complex system consists of phospholipid bilayer and transmembrane integrin mixture, and is in a huge water bulk. In order to get a realistic model that mimics the natural systems, it is necessary to investigate and simulate the complex systems of millions of atoms in a nanosecond time-scale. In our case, the system with millions of atoms is assumed to be simulated for up to 100 ns. Moreover, after ~100 ns of a simulation run, we are planning to embed an obtustatin protein into the system and continue the simulation up to ~500 ns to fully understand the influence of obtustatin on our integrin-embedded mixed membranes model and assess some conformational features of proteins. Snake venom disintegrins are low molecular weight proteins that interact with certain integrins blocking their functional ability to bind endogenous ligands. The group of disintegrins - selective inhibitors of α1β1 integrin, which contain KTS motif in the active site was isolated from *Macrovipera lebetina obtusa* venom. Structurally, KTS-disintegrins belong to the monomeric short disintegrins, which resemble the previously reported short disintegrins such as echistatin or eristostatin. These disintegrins contain 8 cysteines in their polypeptide chain that are involved in creation of 4 intramolecular disulfide bounds. The 3D structure of obtustatin was recently designed based on NMR coordinates. It blocks the interaction of the α1β1 integrin with collagens IV and I *in vitro* with IC50s of 2 nM and 0.5 nM, respectively, and inhibits angiogenesis *in vivo*. All the proposed simulations are suggested to be carried out using the GROMACS MD simulation code. According to the benchmarks conducted on various platforms, we believe that in case of about 500 processors, the performance will be ~10-15 ns/day. This is why the usage of HPC resources is of the greatest importance for our longer simulations.

The mentioned method plays a crucial role offering a deep insight into the structure and dynamics of membranes as well as membrane-bound species that is likely to further not only our understanding of large spectra of biological processes but potentially provide solutions to their dysfunctions. Tumor growth and metastasis require angiogenesis, which is defined as the development of new blood vessels from a pre-existing vascular bed. Thus, obtustatin as the anti-angiogenic ligand may represent a lead molecule for the development of novel anti-angiogenic therapeutic strategies to treat aggressive cancers [14]. Studying the interactions between venom peptides and lipid membranes are of considerable theoretical interest for understanding the mechanisms and pathways of molecular evolution, designing novel therapeutic agents, and developing antivenom production strategies.