Summary of the project for general audience

Proteins are one of the most important biologically active molecules. They play many functions in living organisms, such as scaffold, storage, enzymatic and regulation. However, proteins to play effectively their functions need to obtain a correct structure, which knowledge of is often needed in scientific investigations. In addition to experimental methods, scientific research can be performed also using computational methods, which often are significantly cheaper and allows to study phenomena not possible to study by experimental methods. For that reason, the main goal of this project is to extend and improve existing force fields and use them to study role of disulfide bonds in proteins. Disulfide bonds are common and are present in over 23% of proteins stored in Protein Data Bank, but their function in most of them is not fully understood. For a long time, it was believed that disulfide bonds are only stabilizing the protein structure, however, with advances in science it was found that they often can play much different roles, and sometimes their presence can even be lowering the stability of proteins, instead of increasing it. For example, many toxins have at least one disulfide bond, which main function is to prevent digestion by the organisms in which they are acting. In case of many peptides, which are ligands of the receptors, disulfide bonds are necessary to stiffen the polypeptide chain and allow it to form a particular shape. Only such molecules can bind to the receptor and be active. It was also found that in some cases disulfide bonds are necessary for proteins to form correct oligomeric structures, and that forming and disrupting disulfide bonds can be used to regulate biochemical cycles.

Because of the limited computational resources, which does not allow to simulate large biological systems in long enough time scale, coarse-graining is often used for the simulations. In coarse-grained methods, standard approach is to group atoms from polymeric unit, such as amino-acid residues in proteins, to one or multiple interaction centers to limit the number of calculations needed for the system and, therefore, significantly increasing capabilities of the simulation tools. Combining coarse-grained and all-atom methods allows not only to cross-check the results but also to perform investigations on different scales, from molecular one to atomistic, providing better understanding of studied phenomena. In this project, both all-atom and coarse-grained methods will be extended and enhanced to allow to perform simulations including disruption and formation of disulfide bonds to study role of disulfide bonds in selected proteins, such as ribonuclease A and lipid transfer proteins (LTPs). LTPs contain four disulfide bonds and are present in many plants. They have similar sequence and structure, however, their functions, usage and influence on other organisms is very different. For example, wheat proteins are the most allergenic and are believed to be main reason of Baker’s asthma, while barley proteins are used to stabilized beer foam.

Due to very complicated nature of protein folding, which is very time and computationally expensive to study, even using coarse-grained methods, in addition to conventional molecular dynamics (MD) simulations and replica-exchange variant, the steered MD will be used to study unfolding pathways in controlled way, significantly reducing computational cost. Such approach will allow also to study the most stable and the most flexible parts of the protein what is crucial to understand the way how they are functioning. Performed simulations will allow to understand molecular reasons of differences between LTPs and will determine exact roles of each of the disulfide bonds, as well as presence of stable intermediate structures and mechanism of folding and unfolding. Obtained results can be used to design proteins containing disulfide bonds and other types of bridges in medicine and industry.