The goal of this project is improvement the UNRES (UNited RESidue) force field developed in our laboratory with regard to the accuracy of the modeled protein structures and extension of its applications to model very large protein systems and to take into account the change of amino-acid-residue chirality. The last process, albeit slow, has important implications in the functioning of human body. For example, the degeneration of αA-crystallin from eye lens is the main cause of senile cataract.

The coarse-grained approach is based on the partition of a system into well-defined groups (coarse-grained centers), each of which contains many atoms but is considered as a single object. Such an approach is commonly applied in everyday life. For example, we refer to "a grain of sand" or "a grain of wheat", not necessarily taking into account their complex atomic or molecular structure. In the UNRES model, the united side chains (which are centers of solvent-mediated hydrophobic interactions) and united peptide groups (which are hydrogen-bonding centers) are considered as "grains". Additionally, to take into account the elasticity of the chain, which is determined by local interactions (between close neighbors), the α -carbon (C^{α}) atoms are present. This substantial simplification (from 20 atoms per residue on average to 2 centers only) results in a quantum jump of the capability of the modeling of protein structure and dynamics, which can be compared to the difference between the possibility of computing the trajectory of a thrown stone with considering all its individual atoms and computing stone's trajectory assuming that it is a rigid body subjected to Newton's laws. The equations of motion for the UNRES model are more complicated because the anchor points are not located in the centers of masses of the coarse-grained sites, which results in a quadratic increase of the memory required to numerically solve them with protein-chain length and, consequently, limits the size of simulated systems to 1300 amino-acid residues.

Application of a coarse-grained model to study a system requires the definition of an effective energy function. In the UNRES model we apply statistical mechanics to achieve this goal which, thanks to the Boltzmann law, enables us to average the energy over the details that are omitted from the coarse-grained model (such as, e.g., the positions of the water molecules, locations of the peptide groups with respect to the C^{α} atoms, etc.). Such average energy function is termed the *potential of mean force*. Because the coarse-grained centers are sitting on the same polypeptide chains, the averaging is restricted, depending on the location of a group's neighbors. Consequently, the energy function cannot be expressed as a sum of contributions from pairs of centers but includes correlation terms as essential components. These contributions are mandatory for the description of regular α-helical and β-sheet structures of proteins. The mathematical formalism of the UNRES force field takes into account the correlation contributions in a straightforward manner, because the potential of mean force is expressed by Kubo's cluster cumulants, each of which describes the interactions within its particular fragment. Owing to this unique feature, UNRES has already scored considerable success in the prediction of protein structures and dynamics, and simulations of biological processes; however, it still provides only medium resolution of the simulated structures.

The cumulant-based expressions can be derived given the all-atom energy function. However, full dependence of the energy on system's geometry must be taken into account in the process. Only recently we developed a unique theory which fulfills this condition. From the theory it follows that the torsional potentials, which account for the dependence of the average energy on the torsional angles for the rotation about the C^{α}... C^{α} virtual-bond axes, and which are a very important factors determining local chain geometry, depend not only on the the torsional angles but also on the adjacent planar angles. A similar dependence on planar angles is obtained for the correlation contributions. Therefore, introducing the new potentials should result in a major improvement of the performance of the UNRES force field. Using the newly developed formalism, we will also introduce local potentials of the united side chains that will take residue racemization into account. To improve the description of the orientation and packing of side chains, we will also extend the UNRES model to introduce C^{β} atoms and multiple interaction centers on the side flat side chains of tryptophan, tyrosine, and phenylalanine. The new potentials will be parameterized by computing potential-energy surfaces of systems modeling the respective fragments of polypeptide chains and the whole force field will be calibrated to reproduce the structures and thermodynamic properties of selected model proteins. The optimized force field will be tested with regard to reproducing protein structures and thermodynamic properties, including the participation in the upcoming Community Wide Experiment on the Critical Assessment of Techniques for Protein Structure Prediction (CASP; www page: predictioncenter.org).

We expect that successful completion of the project will result in a major improvement of the capacity of the UNRES force field to model protein structure, both on the global and local level, and in the extension of the scope of its application to very large systems and to amino-acid-residue racemization. The UNRES package will be available at its current address, www.unres.pl, and through the PL-GRID system. The results of project's research will also be published in international scientific journals and presented on national and international scientific conferences.