The function of a protein usually stems from its spatial structure. However, about 33% of eukariotic proteins lack a well defined structure in extended parts of their sequences. These are IDPs: intrinsically disordered proteins. Despite the lack of stationary structure, they play important functional roles in the cell. Compared to the structured proteins, the IDPs have fewer hydrophobic residues and may form complexes with different partners. The objective of the proposed research is to study relevant examples of the IDPs in a systematic way and to develop novel molecular-dynamics (MD) methods for their analysis. Insights into the behavior of biomolecules can be obtained through all-atom (AA) MD simulations or by solving equations of motion for effective particles (e.g. one per residue) representing the molecules in a coarse-grained (CG) description. The CG models eliminate details that should not be relevant for long processes with large conformational changes, and allow for a major extension of the simulation time and system size.

The IDPs have been studied by AA approaches but the CG models in this context need to be developed. Recently, we have generalized the CG α-C based description of the structured proteins to the case of the IDPs. For structured proteins, the most effective model involves introducing contact interactions between pairs of residues that are bound in the native state. The presence of a native contact is determined based on a criterion related to the existence of an overlap between effective spheres associated with the heavy atoms. In the case of the IDPs, the idea of the contacts is still valid but they are defined dynamically. This involves residue-dependent characteristic distances (and directions) at which a contact may arise through, e.g., sidechain-sidechain interactions. The model yields a correct description of average geometrical parameters of various IDPs such as polyglutamines, but we plan to develop it further and to make improvements, especially in the context of aggregation.

We plan to perform systematic studies of single- and multiple-chain IDPs by a combination of the CG and AA methods (with various force fields) to understand mechanisms of aggregation and tendencies to generate temporary secondary structures. The focus will be on proteins involved either in neurodegenerative diseases (alpha-synuclein, protein tau) or in the memory consolidation (hCPEB3, Orb2). The ultimate goal of the CG-based studies will be systems of many IDPs . One example of such systems is gluten (in bread). There are experiments on the rheology of gluten but no MD work. Thus molecular-level understanding is missing.

Another example of systems containing many IDPs are proteinaceous liquid droplets. The droplets arise under the conditions of large concentration through the liquid-liquid phase separation. The resulting compartmentalization into the so called membraneless organelles is necessary for the organization of vital processes. Examples include stress bodies, inflammasomes, signalling complexes, and nucleoli (within the nucleus) in which ribosomes are formed. The droplets have received little theoretical analysis, because of the large number of molecules they involve. The droplets in the cell usually combine IDPs with the nucleic acids but there are also *in vitro* studies which show that it is possible to form droplets with just one kind of IDPs: protein tau or hCPEB3. We shall understand these simpler droplets through the CG MD in a close collaboration with the experimentalists in Madrid. We plan to map out the fluid-fluid coexistence curves, determine the fluid parameters (surface tension, viscosity), and to explain differences in properties for droplets made of different IDPs.