It is now clear that a significant part of eukaryotic genomes encode proteins with substantial regions of disordered structure. Several types of biological functions have been ascribed to these so-called natively unfolded proteins (NUPs), such as molecular recognition, signal transduction or neurodegenerative diseases. The existence of these systems questions one of the landmarks in protein chemistry claiming that the specific function(s) of a protein is determined by its unique 3D structure. The study of this amorphous class of proteins remains therefore out of reach by classical structural biology because of their conformational heterogeneity.

A new simulation strategy based on a stochastic process has been developed and tested to study at the atomistic level the structural properties of the unfolded state of proteins. The procedure combines a generation algorithm producing representative uncorrelated microstructures with an original relaxation method to minimize repulsive non-bonded interactions. Using this methodology, a set of 14 unfolded proteins including 7 NUPs as well as 7 “classical” proteins experimentally described in denaturing conditions, has been investigated, and calculated and experimental data used to describe the unfolded state are in very good agreement.

This new technique providing detailed characterizations of NUPs shall help understanding and controlling the protein-protein interactions based on disorder-to-order transitions involved in normal and pathological biological processes, and subsequently pave the way to several and essential therapeutic targets.