Molecular biomechanics of the SARS-CoV-2 variants: The virus-host cell attachment and immune evasion

The proposed research will focus on the foundation of the molecular biomechanics of the SARS-CoV-2. Here we plan to investigate the spike (S) protein and its interaction with the human angiotensin-converting enzyme 2 (hACE2) receptor and neutralizing antibodies (Ab) responsible for the immune evasion. In these studies, we will consider several variants of concern (VoC) and the proper model of a viral lipid membrane. Our multiscale approach combines single molecule force spectroscopy (SMFS) data and molecular simulation. Our work aims to capture the biomechanics in evolution of the SARS-CoV-2. SMFS technique does not have access to molecular details at short time scales associated with the process of protein-protein recognition of quite relevance for cell attachment and in Ab recognition. This process will be only possible through the proposed research based on our multiscale approach. We aim to conduct exhaustive characterization for biomechanical parameters important for SARS-CoV-2 S VoCs attachment to host cells such as the mechanical stability of S/hACE2 and S/Ab complexes. Here we will consider the latest structural information deposited in Protein Data Bank. The primary hypothesis we will test whether the higher mechanical stability reported by us at the level of the receptor binding domain (RBD) in SARS-CoV-2 S protein has been fine-tuned by the emergence of new variants, increasing the strength of S/hACE2 binding and thus facilitating the spread of the disease in the world. Our approach will include the description of a viral cell membrane, which will provide a better representation of the typical S protein fluctuations under force deformation.

Our studies will have a direct impact on COVID-19 vaccine and therapeutics development. The proposed research makes our simulation studies on molecular biomechanics particularly attractive and powerful, by offering the ability of directly observing and monitoring molecular forces in the range of pN-nN. Several molecular details will correspond to structural changes in the presence of mechanical manipulation. Our multiscale approach will combine advanced SMFS methods and molecular dynamics simulation by enabling the monitoring of individual groups of atoms at any point during nanomechanical characterization. As a result, we plan to unveil the underlying mechanism for each process. Describing these processes will improve our understanding on the biomechanics of SARS-CoV-2 and its evolution. The proposed research will also lead to the development of a powerful computational tool in the field of biomolecular simulation. Furthermore, we plan to study the stability of complexes of the S protein and monoclonal Ab and estimate the regime of mechanical stability. The proposed research focuses on basic research, and it is based on some preliminary results of both experimental and numerical implementations that will facilitate the fast-paced development of the project. Therefore, we expect that many different scientific communities with broad focus on virus-cell interactions and viral respiratory infection will benefit by this project.