Nuclear Magnetic Resonance (NMR) spectroscopy is widely used technique for investigation of molecular properties based on the interaction of external magnetic field with nuclear magnetic moments. The key advantage of NMR, making it in certain situations superior in comparison to other tools of structural biology, is the ability to describe at the atomic level not only the molecular structure, but at the same time, their dynamics and interactions. The range of applications of NMR vary from small molecules to complex biomolecules like proteins and nucleic acids, and from the solutions to solid state. Therefore, NMR spectroscopy is considered as one of basic tools in contemporary chemistry and molecular biology.

In 2019 a new virus emerged in China and very quickly has spread around the world. To combat a new disease, many strategies are being proposed, a new vaccine development among others. The virus form a nanoparticle size molecular machinery. Therefore, molecules that would inhibit SARS CoV-2 virulence by affecting the viral metabolic pathways at molecular level are being searched. Or, in other words, the molecules that potentially could deteriorate viral replication machinery and function are indispensable.

Solution NMR spectroscopy is especially well suited to study dynamics over a broad spectrum of time-scales, and to obtain information about molecular interactions and plasticity. The research described in this proposal will employ the NMR technique as we focus on the key protein molecules and their interactions with regulatory particles, and other binding partners that control function and substrate protein and RNA targets. On the other hand, the aim of the project is to develop and optimize new methods of NMR spectroscopy for the investigation of large protein molecules in solution. The realization of the project will require the development, implementation, and optimization of NMR techniques (pulse sequences), as well as improvement of existing methods.

The main motivation of the whole project is to get insight into a behavior and properties of large protein molecules at the atomic level and to identify hot-spots on their structure that could serve as potential binding sites for drug candidates. We plan to trace allosteric pathways leading from the effector binding sites to the catalytic centers. For example the hydrolases the 3CLpro and the NSP15 are believed to act in a cooperative way. It is our intention to verify this hypothesis and, if possible, identify the mechanism of communication between the individual protomers within the multimeric molecules. Taken together, our data will help to understand how their function is regulated through binding. Building on our work, possible strategies on how to dysregulate the catalytic activity will be proposed. In our opinion, such approach at the interface of the chemistry, biology and physics will lead to the highest quality data providing a very detailed picture of the SARS CoV-2 hydrolases at work.

The outcome of the project is essential for a better understanding of processes occurring at the molecular level during virus replication. The project addresses problems relevant from the viewpoint of fundamental science. However, we strongly believe, with this knowledge in hand many new possibilities for structure-based drug design will open up.