

Description for the general public

Doubly knotted proteins – frontiers of topological complexity of proteins

Proteins are basic constituents of living organisms. Understanding how they function is crucial for a number of reasons – from trying to unravel conceptual and fundamental puzzles of life, to developing practical applications in medicine. Proteins are long chains made of amino acids, and to perform their function they should attain – in the process of folding – the so called native state, in which they form some particular shape. For many years it was believed that in the native state proteins cannot be knotted, because a folding process leading to such a configuration would be too complicated. However in the last two decades many knotted proteins have been discovered, and the study of knotted proteins has recently grown into an independent, rapidly developing subject. This research area is highly interdisciplinary and involves aspects of biophysics, mathematical knot theory, bioinformatics, structural biology, etc. It is worth stressing that the Principal Investigator in this project has made important, internationally recognized contributions to this research area.

The main aim of this project is to study most complex knotted structures in proteins, which we have discovered recently in the SpouT superfamily methyltransferase. These structures involve the presence of two knots, and we call such proteins as doubly knotted proteins. They are found in pathogens and in organisms living in extreme conditions.

In more detail, in this project we aim to determine how double knotting affects folding of proteins, biological activity, and proteasome degradation. Our analysis will be based on computer simulations and supported by experiments conducted in the laboratory of our collaborator.

Apart from purely scientific results of this project, its outcomes should also lead to new developments in medicine, which would then improve quality of our life. Indeed, some knotted proteins turn out to be antimicrobial drug targets – and this is so in particular for the TrmD protein from the SpouT family, which we will also analyze in this project, and which is present in all 12 drug-resistant bacteria recently ranked as high priority pathogens by the World Health Organization (WHO). Understanding properties of this protein should then lead to the development of a new antibacterial drug. Furthermore, understanding properties of doubly knotted proteins should lead to new developments in bioengineering – in particular it is known that knotting in proteins increases their stability, and taking advantage of doubly knotted proteins should enable to design yet more stable nano-structures.

This project will be conducted at the renowned Centre of New Technologies at the University of Warsaw, which is the best university in Poland. The Principal Investigator is an internationally recognized expert in topological properties of biomolecules, and the research conducted by our group will be supported by the top partner laboratory, experienced in conducting experiments with knotted proteins.

To sum up, this is an ambitious project that aims to unravel mysteries of most complex, doubly knotted proteins, identified recently by the Principal Investigator. It will lead to both conceptual understanding of knotting in proteins, as well as to applications in medicine and nanotechnology. Experience of the Principal Investigator, highly skilled research team, supporting experimental laboratory, and highly inspiring and motivating atmosphere of the Centre of New Technologies and the science campus of the University of Warsaw, ensure that the aims of the project will be reached.