Determination of the influence of 5' end of RNA modifications and nucleotide or amino acid sequence on the electrostatic interaction energy of IFIT proteins with RNA

DESCRIPTION FOR THE GENERAL PUBLIC

Determination of structure and interaction energy is essential in the area of drug design, understanding mechanisms of biological processes and specifying structure-function relations in proteins.

An inhibitor is a compound (ligand), which after binding with protein, reduces its activity, hence it can be a potential drug. Searching for new drugs requires investigating how the character of interaction will change after modifying proteins or their ligands. Most informative would be testing all possible combinations of modifications. However, obtaining all mutated proteins and modified ligands and using them in experiments to determine the interaction strength will involve great expenses, a lot of effort and time. Luckily, theoretical methods can streamline this process. With molecular modeling and computational methods it is possible to estimate electrostatic interaction energy of chosen complexes and indicate areas, whose modifications can alter interaction strength.

In this project we aim to characterize electrostatic interactions in selected complexes of IFITs proteins with RNA. IFIT proteins are effectors of innate immune system, which are getting expressed in cells infected by viruses. By binding foreign RNA they prevent synthesis of viral proteins in human host cells and hence they block propagation of viruses. There is a few human IFIT proteins, which bind RNA with different forms at 5’ end. We plan to verify if RNA sequence influence on interaction energy in IFIT-RNA complexes and investigate how modifications at 5' end of RNA alter interaction strength.

Electrostatic energy has the most significant contribution to interaction energy (especially in the biological systems) thus it is the best tool for estimating interaction energy in biomacromolecules. Unfortunately, precise quantum mechanics calculations are not feasible not only for large biological systems, but also for chemical systems, hence simpler calculation methods are required. We propose method called UBDB+EPMM (University at Buffalo Pseudoatom DataBank + Exact Potential Multipole Moments). This hybrid method shortens computational time by combining two different approaches: calculating directs Coulomb integral of Exact Potential (EP) at short distances with evaluation of Multipole Moments (MM) in outer region. UBDB+EPMM method is developed in our group, however, this bank hasn’t been yet experimentally tested for calculations of proteins complexes with RNA. Thus prior validation of new atom types used to describe interactions of triphosphate group of RNA with proteins and magnesium ions will be needed. Validation of improved UBDB is additional goal of this project.

Calculated interaction energies of protein-RNA complexes will be compared with dissociation constants of complexes from literature. We also plan to conduct biophysics experiments by microscale thermophoresis method to verify experimental data. Describing the nature of IFIT proteins interactions can help to expand our knowledge about mechanisms of selective binding RNA and how human immune system recognizes and destroys viruses.