MS05-2-3 UBDB+EPMM approach as a tool for investigating electrostatic interactions between proteins and RNA #MS05-2-3

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Abstract
I would like to present the method for characterization of protein-RNA interaction on the example of IFIT-RNA complexes. IFITs proteins (Interferon-induced proteins with tetratricopeptide repeats) are expressed in cells infected by viruses and by binding foreign RNA they prevent synthesis of viral proteins in human host cell. They can bind different forms of RNA: with triphosphate group, guanine or cap at 5' end of RNA. I calculated electrostatic interactions in selected complexes of IFIT1 and IFIT5 proteins with RNA on the basis of the known structures deposited in Protein Databank and compared the results with experimental values of binding affinity.
I decided to focus on the electrostatic interaction energy because it has been shown, that electrostatic energy is a sufficient approximation of total interaction energy. Biomacromolecules (proteins, nucleic acids) are too complex systems for precise quantum mechanical computations and calculations of total energy are yet too demanding. Furthermore, electrostatic energy is the best component of total energy, because it is the least sensitive to errors in geometry of investigated systems. Such errors are often encountered while determining structures of big, biological complexes, for which it is very difficult to properly define position of all atoms. There are computational methods, which enable to estimate electrostatic interaction energy in macromolecules, however, most of them base on simplified methods taken from classical mechanic (force fields), where electrostatics is usually approximated by Coulomb interactions of point charges. I used the UBDB+EPMM approach, by which it is possible to compute electrostatic energies with similar accuracy as with quantum chemistry methods, for wide range of types of interactions (hydrogen bonds, π-π stacking) and distances (not only at equilibrium geometry but also below or above). University at Buffalo Pseudoatom DataBank (UBDB) enables reconstruction of charge density for macromolecules in quantitative manner. Exact Potential Multipole Method (EPMM) evaluates the exact Coulomb integral in the inner region (≤4.5 Å) and combines it with a Buckingham-type multipole approximation for long-range interatomic interactions, hence computational time is shortened. The UBDB+EPMM method has been successfully used in previous research to analyze interactions in peptides, proteins and various complexes e.g. aminoglycosides with RNA or proteins with DNA.
Energy calculations were based on the structures of IFIT5 proteins with pppRNA and IFIT1 with different 5'end of RNA deposited in PDB. The UBDB was transferred to reconstruct electron density distribution and thorough calculations of interactions between ligand and particular amino acids in the biding site were conducted to indicate significant residues influencing interaction energy. I showed that according to the calculations of electrostatic energy, the interactions of the IFIT5 protein with RNA do not depend on the sequence of the first three nucleotides of the RNA. Moreover, the IFIT1 protein should bind pppRNA with a similar strength as it binds cap0RNA. In addition, I identified energy-important amino acids, the mutations of which may affect the strength of RNA binding by the protein.
Project was financed from the grant PRELUDIUM11 of National Science Centre, Poland nr 2016/21/N/ST4/03722.

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