Systematic Analysis of Structure-Stability Relationship for Proteins and Mutants

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1 Introduction

In order to understand the function of proteins, it is necessary to analyze the relationship among sequence, structure and thermodynamic property of proteins. Such analyses have been carried out mostly for individual proteins. However, rapid increase in sequence, structural and thermodynamic data of proteins enables us to make systematic analysis of their relationship. Unfortunately, these kinds of data are scattered among different databases, and there are few databases integrating all of them. Thus, it is rather difficult to utilize the information efficiently for the study of proteins. We have developed thermodynamic database for proteins and mutants (ProTherm) and integrated the thermodynamic data with sequence and structural information. Here, we try to utilize this integrated database to analyze the relationship between the stability and structural features for wild-type and mutant proteins in a systematic way.

2 Methods and Results

We have developed thermodynamic database for proteins and mutants, ProTherm [1], which contains over 17,000 numerical data of several thermodynamic parameters along with experimental methods and conditions, and structural, functional and literature information. STING is a comprehensive java-based analysis tool for proteins with many structural descriptors [2]. It includes information about graphical amino acid contact, Ramachandran plot, surfaces, sequence neighbors and other features. Parsing data from relevant databases (e.g., HSSP, SwissProt) is one of the key features of this integrated tool. This tool is developed by Bioinformatics Laboratory of Embrapa in Brasil.

Those entries of ProTherm with corresponding structural information of mutants are linked to STING through PDB code, chain ID, and residue number of the mutation site. Structural and physico-chemical information of mutation site and surrounding residues are visualized by STING as well as visualization tool in ProTherm. We have also created links from given protein mutations searched within STING to available thermodynamic information of mutant proteins in ProTherm. These cross-references help users to analyze the thermodynamics-structure relationship.

We have extracted 1,325 proteins which have both wild-type and mutant structures, together with the corresponding thermodynamic data (stability changes in terms of transition temperature, ΔT_m, or free energy of unfolding, $\Delta\Delta G$) in ProTherm. Mutations usually affect both the structure and stability of proteins. We have compared the structures of wild-type and mutant proteins. Table 1 shows the RMSD (in Å) between the wild-type and mutant structures. The RMSD was calculated by DaliLite [3]. As seen in the table, mutations cause a wide range of structural changes.

Table 1: Distribution of RMSD between wild-type and mutant structures.

RMSD (Å)	Number of structures
0.0∽0.1	118
0.1∽0.2	512
0.2∽0.3	450
0.3∽0.5	120
0.5∽1.0	59
1.0∽2.0	38
2.0∽5.0	28

We are also calculating detailed structural parameters for wild-type and mutant proteins such as: accessible surface area (ASA) of mutation residue; secondary structure; hydrogen bonding with distant information; other types of contacts with surrounding residues and contact energy. Then, we will correlate those structural parameters with the stability data in ProTherm. We try to identify those structural descriptors which most correlate with the thermodynamic data. By using multiple regression analysis, we also try to derive a formula to predict stability change for a given mutation in proteins.

3 Discussion

We have integrated thermodynamic data of proteins and mutants with the corresponding structural information by using ProTherm and STING tools. We have collected proteins with wild-type and mutant structures and compared many structural features. So far, we have made a preliminary analysis of these structures, and plan to conduct a comprehensive analysis of structural features and compare them with the thermodynamic data. Such analysis would provide insight into the relationship between structure and stability of proteins, and resulting knowledge would help designing proteins with enhanced stability.

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