An Overview of the Protein Thermostability Prediction: Databases and Tools

Abstract

Thermostable proteins are characterized as high thermal stability proteins while mesophilic proteins are stable at lower temperatures. These types of proteins have numerous applications regarding protein engineering, drug design and industrial processes. Studies showed that thermal stability is strongly related to structural and sequential properties in thermophilic proteins. Some computational studies were being taken to identify the mentioned properties in heat resistant proteins. This paper reviews the studies of protein thermostability prediction and gives an introduction to the thermal stability related tools and databases.

Keywords: Protein thermostability; Thermophilic proteins; Mesophilic proteins; Databases; computational methods; Bioinformatics

Introduction

Environmental temperature plays an important role in the cell life [1]. There are four classes of organism in relation to their optimal growth temperature namely hyperthermophile (>80°C), thermophile (45-80°C), mesophile (20-45°C) and psychrophile (<20°C) [2]. Thermal stability is defined as the ability of material to resist changes in physical structure or chemical irreversibility, or spatial structure stability of polypeptide chains at high temperatures [3]. Studies showed that thermal stability of thermophilic proteins is related to a series of protein sequential and structural properties [4]. A small number of these mentioned properties are going to be introduced in this paper. Also, the amino acid compositions difference had been studied in mesophilic and thermophilic proteins [3,5-7]. For instance, Zhang and Gromiha research shows that Lys, Arg, Glu and Pro were higher and Ser, Met, Asp and Thr were lower in number of thermophilic than the number of mesophilic proteins [6,8] (Figure 1). Protein secondary structure stability like alpha-helix is considered as a necessary factor for thermal stability [6]. Studies suggested that thermal stability is increased by certain characteristics in proteins. These characteristics are: increased number of hydrogen bonds [7], salt bridges, ion pairs [9], aromatic clusters [8], sidechain-sidechain interactions, electrostatic interactions of charged residues [9] and hydrophobic interactions [5].

Protein’s Thermal Stability Prediction Methods

Protein’s thermal stability can be predicted based on sequence or structure. Both mentioned methods and their corresponding advantages and limitations have been discussed here in further detail. Table 1 demonstrates an overview of the thermal stability prediction methods.

Sequence based prediction

This method utilizes sequence information of proteins; for instance, distribution of amino acid and di-peptide composition for discrimination of thermophilic and mesophilic proteins. Studies revealed the differences between amino acid and di-peptide composition in thermophilic and mesophilic proteins. For example, the frequency of Lys, Arg, Glu and Pro was higher and Ser, Met, Asp and Thr were lower in number of thermophilic than the number of mesophilic proteins [6,8] (Figure 1). Protein secondary structure stability like alpha-helix is considered as a necessary factor for thermal stability [6]. Studies suggested that thermal stability is increased by certain characteristics in proteins. These characteristics are: increased number of hydrogen bonds [7], salt bridges, ion pairs [9], aromatic clusters [8], sidechain-sidechain interactions, electrostatic interactions of charged residues [9] and hydrophobic interactions [5].

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Table 1: An overview of protein thermostability prediction studies.

| Sequence/Structure Feature       | Algorithm                  | Reference |
|----------------------------------|----------------------------|-----------|
| Amino acid sequence              | Support vector machine     | [10]      |
| Primary structure                | LogitBoost                 | [12]      |
| Amino acid sequence and residues and dipeptide composition | Neural network | [8] |
| Primary, secondary and tertiary structure information | Decision tree | [11] |
| Amino acid distribution and dipeptide composition | Support vector machine     | [13]      |
| Amino acid composition-based similarity distance | KNN-ID                      | [1]       |
| Dipeptide composition            | Statistical Methods        | [14]      |
| Amino acid sequence              | Genetic Algorithm          | [15]      |
| Thermodynamic parameters         | Statistical Potentials     | [16]      |

Structure based prediction

The studies of protein thermostability prediction are based on protein structures utilized protein secondary and tertiary information for discrimination of thermophilic and mesophilic proteins. Important features considered in these studies include amount of secondary structure, ion pairs, hydrogen bonds, disulfide bonds and accessible surface area [11]. Although the thermal stability is directly related to the protein structure stability [11]. Regarding the fact that structural and sequential features affect the thermal stability, applying the both mentioned features at the same time leads to a more accurate, precise prediction. The protein structural information may not be always available; This restrains structure based protein thermostability prediction.

a. Protein’s thermal stability prediction procedure: Several machine learning methods have been applied to predict protein thermostability. Here, we briefly review these methods. Figure 2 provides an illustration of these methods. As illustrated in the figure, in order to predict the thermal stability of proteins, at first, a dataset of thermophil and mesophil proteins is collected from the related databases. Then, proteins are analyzed based on their sequential and structural characteristics. The goal in this stage is to select those features which are significantly important regarding protein thermostability prediction. It should be noted here that considering the structural and sequential features at the same time can produce more precise results. In the next stage, the dataset is going to be divided into the train and test datasets. The train dataset is then used for learning the machine learning algorithm while the test dataset is used to evaluate the model.

Prediction algorithms based on machine learning methods

The following section introduces a few machine learning algorithms. The selected algorithm is going to distinguish the thermophile from mesophile proteins.

a. Support vector machines (SVMs): Support vector machines is an machine learning method for classification two classes of data and many kind of kernel functions can be used for classification in this algorithm [17].

b. Artificial Neural Networks (ANN): The ANN concept is inspired by the neural structure of the brain. In this model of prediction, the system is supposed to learn from data - a large number of inputs and solve a wide variety of tasks. ANN software packages can be downloaded from Open NN (Available online: http://www.cimne.com/flood/download.asp)[15].

c. Decision Tree: A decision tree is popular machine learning algorithm in bioinformatics and computational biology. It uses a tree-like graph or model of decisions and their possible consequences to classify input instances.

Performance Measures

Assessing a prediction tool is a critical task. Table 2 describes commonly used measures for performance prediction assessment: accuracy, sensitivity, specificity, strength, MCC, precision, F-measure and area under the ROC curve (AUC). These measures based on the following four basic parameters:

a. True positive (TP): The number of thermophile proteins, which have been correctly predicted as thermophile.

b. True negative (TN): The number of mesophile proteins, which have been correctly predicted by the prediction method as mesophile.

c. False positive (FP): The number of mesophile proteins, which have been incorrectly predicted as thermophile.

d. False negative (FN): The number of thermophile proteins, which have been incorrectly predicted by the prediction method as mesophile.
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Table 2: Commonly used measures for performance assessment in protein thermostability prediction.

| Expression | A Brief Description |
|------------|---------------------|
| Accuracy   | \[
\frac{TP + TN}{TP + TN + FP + FN}
\] percent of correct prediction |
| Sensitivity| \[
\frac{TP}{TP + FN}
\] percent of correctly predicted positive |
| Specificity| \[
\frac{TN}{TN + FP}
\] percent of correctly predicted negative |
| Precision  | \[
\frac{TP}{TP + FP}
\] Positive Predictive Value |
| F - measure| \[
\frac{2 \times \text{Precision} \times \text{Sensitivity}}{\text{Precision} + \text{Sensitivity}}
\] The harmonic mean of sensitivity and specificity |

Databases

To build a model capable of predicting the proteins thermal stability; at first, a dataset is created using the related databases.

Table 3: List of databases in protein thermostability prediction.

| Data bases | Note | Ref. Num |
|------------|------|----------|
| UniProt    | The Universal Protein Resource (UniProt) provides a stable, comprehensive, freely accessible, central resource on protein sequences and functional annotation. This DB is used to extract the sequential information of thermophilic and mesophilic proteins. Availability: http://www.uniprot.org. | [18] |
| PDB        | The Protein Data Bank contains information of the 3D structures of large biological molecules, including proteins and nucleic acids. This DB is used to extract structural information of thermophilic and mesophilic proteins. Availability: http://www.rcsb.org. | [19] |
| ProTherm   | ProTherm is a thermodynamic database that contains experimentally determined thermodynamic parameters of protein stability. This DB is specifically used to predict the thermal stability. Availability: http://gibk26.bse.kyutech.ac.jp/jouhou/Protherm/protherm.htm | [20] |
| PGT        | PGT contains Prokaryotic Growth Temperature database (PGTdb). This DB is specifically used to predict the thermal stability. Availability: http://pgtdb.csie.ncu.edu.tw | [2] |

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