Structure Prediction of Proteins with Transmembrane Helices

Takatsugu Hirokawa[1] hiro@cubs.bio.rsi.co.jp
Makiko Suwa[2] suwa@hri.co.jp
Seah Boon-Chieng[3]
Shigeki Mitaku[3] mitaku@cc.tuat.ac.jp

[1] Ryoka Systems Inc., 1-5-2, Irifune, Urayasu City, Chiba Pref. 279-0012, Japan
[2] Helix Research Institute, 1523, Yana, Kisarazu City, Chiba 292-0812, Japan
[3] Tokyo University of Agriculture and Technology, 2-24-16, Nakacho, Koganei City, Tokyo 184-8588, Japan

Keywords: structure prediction, transmembrane helix, physicochemical interaction

1 Introduction

Many sophisticated methods have been applied to the prediction of structure and function of protein sequences which are derived from the genome projects. However, difficulties of prediction for some protein types, e.g., membrane proteins, are not still resolved due to the lack of their 3D structure information. Although membrane proteins are minor fraction of the genome, the biological function of membrane proteins are extremely important in the pharmacogenomics area. Therefore, developing a new computational systems for structural and functional prediction of proteins is one of urgent issues in the post genome era. In this work, we developed a protein structure prediction system comprised of two modules: (1) classification and secondary structure prediction of membrane proteins, and (2) the determination of lateral and rotational positioning of transmembrane helices (TMH) in proteins, based on the physicochemical consideration.

2 Method and Results

The first modules, we have used three parameters: average hydrophobicity of TMH, size of proteins and the effect of distribution of amphiphilic residues in TMH ends, which were assumed the important factors by the statistical analysis with non-redundant data sets of the both soluble and membrane proteins [2]. The evaluation results using the discriminant analysis and the cross-validation test indicated that the accuracy of classification and secondary structure prediction by three parameters are 99% and 96%, respectively. This module was also released as internet based prediction system, called SOSUI (http://azusa.proteome.bio.tuat.ac.jp/sosui/) [1]. The second problem, tertiary structure prediction of membrane proteins, we developed a new method for exhaustive search of lateral and rotational positioning of seven-TMH without structural templates derived from experimental studies, based on a previous method, which is reconstructing approach of seven-TMH bundle on electric density map based on polar interaction energy by Suwa *et al.* [3]. In stead of structural templates, triangle lattice models having twelve and eleven nearest neighbor pairs were adopted for surveying the available conformations of TMH. This method was divided into four steps: (1) characterization of polar interaction energy of TMH by probe helix method, (2) lateral and rotational positioning of TMH on lattice models are determined by the potential function consist of polar interaction energy and loop constraint terms, (3) refinement of the energetically lowest 100 structures with tilting motion around the lattice frame, and (4) analyzing of reformation of structure with ligand-binding environment. When this method was applied to bacteriorhodopsin, the most preferable structure was similar to the experimental structure.

References

[1] Hirokawa, T., Boon-Chieng S. and Mitaku, S., SOSUI: classification and secondary structure prediction system for membrane proteins, *Bioinformatics*, 14(4):378–379, 1998.

[2] Mitaku, S. and Hirokawa, T., Physicochemical factors for discriminating between soluble and membrane proteins: hydrophobicity of helical segments and protein length, *Protein Eng.*, 12(11):953–957, 1999.

[3] Suwa, M., Hirokawa, T. and Mitaku, S., A continuum theory for the prediction of lateral and rotational positioning of alpha-helices in membrane proteins: bacteriorhodopsin, *Proteins*, 22(4):363–377, 1995.