An Automated Structure Prediction System by Lattice Model for Seven-Helix-Type Membrane Proteins

Junichi Uechi [1] uechi@cc.tuat.ac.jp
Takatugu Hirokawa [2] takatsugu@din.or.jp
Makiko Suwa [3] suwa@hri.co.jp
Shigeki Mitaku [1] mitaku@cc.tuat.ad.jp

[1] Tokyo University of Agriculture and Technology, Department of Biotechnology, Tokyo 184-5855, Japan
[2] Ryoka Systems Inc., Computational Science and Technology Division, Irifune, Urayasu, Chiba 279-0012, Japan
[3] Helix Research Institute, 1532-3 Yana, Kisarazu-shi, Chiba 292, Japan

1 Introduction

Bacteriorhodopsin (bR) is a light-driven proton pump, which is a membrane protein with seven transmembrane helices and a prosthetic group of retinal. The structure of bR has been determined at high resolution, and the homology modeling of G-protein coupled receptors, which have seven transmembrane helices, is usually carried out based on the structure of bR as the structure template. However, the structure of receptor proteins is not necessarily the same as that of bR. Therefore, we previously developed a structure prediction system for seven-helix-type membrane proteins, using a lattice model [1]. The principle of the method is that the dominant interaction between helixes is the polar interaction [3], which was estimated by a probe helix method [2]. This system showed very good performance, when it was applied to bR [1]. However, the system had several disadvantages: (1) Calculation time was very large. (2) Manual procedures were inevitable. (3) The information about important helices in the bR structure could not be extracted from the calculation.

In this work, we developed an automated version of the tertiary structure prediction system for seven-helix-type membrane proteins, based on the previously reported system [1]. The new system is completely automated and provides helix triangles which may contain functionally active sites.

2 Methods

The method is divided into the following two steps:

(1) The probe helix method [2] is employed for characterizing the polarity of the surface of each helix, in which the polar interaction energy between a transmembrane helix and a probe helix of serine-alanine copolymer by an energy calculation software (CHARMm-QUANTA, Molecular Simulation Inc.). Regarding a transmembrane helix as a continuum rod, 48 values of polar index are given to a helix by this calculation.

(2) Total energy of a system with seven transmembrane helices is calculated for all lateral and rotational positioning of TM helices. In order to reduce the calculation time, a triangle lattice model is adopted and helices are rotated in the interval of 15 degrees.

The calculation time became as short as 45 hours by the automation of the system, as compared to about 5 days in the previous system (Indy RS6000/590, Silicon Graphics). Furthermore, the prediction became more reliable than the previous method because of the automation of the system.

3 Analysis of top hundred predicted structures

The predicted structures contain the information of structurally robust substructures, when the top hundred structures are analyzed. We counted the numbers of all helix triangles. Every triangle consists of three helices (for example, helix C, helix F and helix G). The number of combination is ${}_7C_3$ (= 35), and there are their mirror images. Therefore, the total triangle number is 70. The dependence of the number of triangles on the number of predicted structures from the top was analyzed.

4 Results and discussions

The structure of bR was predicted by applying the present system to the amino acid sequence of bR. The predicted energetically lowest structure was very similar to experimental structure of bR. The helices was positioned clockwise and the helix was located in the center of the protein. Furthermore, the orientational angles of transmembrane helices were almost the same as the experimental values. The analysis of helix triangles showed that a triangle of helices C-F-G of the clockwise configuration, which is functionally very important, was the most robust in the bR structure. Consequently, this system automatically provided the most preferable structure, which is very similar to the experimental structure and the most important site in the protein.

References

[1]

[2] Hirokawa, T., Suwa, M., and Mitaku, S., Theoretical prediction of positioning, orientation and tilt angles of helices of a small membrane protein without structural template, *Genome Informatics Workshop 1995*, Universal Academy Press, 128–129, 1995.

Mitaku, S., Suzuki, K., Odashima, S., Ikuta, K., Suwa, M., Kukita, F., Ishikawa, M., and Itoh, H., Interaction stabilizing tertiary structure of bacteriorhodopsin studied by denaturation experiments, *Proteins*, 22:350–362, 1991.

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