The Prediction of Lateral and Rotational Positioning of α-Helices in a Membrane Protein

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Introduction

A new method for the prediction of the lateral and the rotational positioning of transmembrane helices was developed[1] and applied to the amino acid sequence of bacteriorhodopsin. The basic assumptions of the method are the followings:

1. The positioning of transmembrane helices is determined by the interaction between continuum rods of helices. Namely the averaging of inter atomic interactions is possible in the problem of helix positioning.
2. The dominant interaction for the tertiary structure formation is the polar interactions.
3. The distance between a pair of helices is determined by two factors: the length of the linking segment and the average strength of polar interactions.
4. The orientation of helices is determined due to the polar interactions.

The helix positioning of bacteriorhodopsin was predicted according to two method. The result showed good agreement with the experimental structure by Henderson et al.[2]

Lateral and Rotational Positioning of Helices

The lateral position of helices is determined by the two factors: the rotational average of binding energy and the length of the linking segments between transmembrane helices. To estimate the strength of the binding of two helices, the polar interaction field is calculated by a probe helix method, using copolymer of serine and alanine as probe helices. Then 48 polar indices (24 directions around a helix par both terminal side of it) were assigned to the surfaces of transmembrane helices. Using the polar interaction indices the simplified binding energy was estimated, which is the function of rotational angle of two helices and the distance between the pair helices.

We consider an index I_{ij} that characterizes the tendency of a pair of i-th and j-th helices to approach each other, as.

$$I_{ij} = g(B_{ij}, L_{ij}) \tag{1}$$

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in which B_{ij} is the minimum value of the binding energy and L_{ij} is the number of residues of the segment linking the two helices. When the binding energy B_{ij} or/and the length of a linking segment L_{ij} decrease, the magnitude of I_{ij} should increase.

The problem of the lateral positioning of helices may be restated as the assignment of the hydrophobic helical segments in an amino acid sequence, $A, B, C \ldots$, to the peaks of high electron density, $1, 2, 3 \ldots$ of two-dimensional electron density map of low resolution. We assume that, the nearer two helices with large I_{ij} come, the smaller the configuration energy is. The problem may be solved by calculating a function $G(D_{ij}, I_{ij})$ for all possible assignments of the helical segments to the peaks, as.

$$G(D_{ij}, I_{ij}) \; = \; - \sum_{i,j=A,B,C\ldots} D_{ij} * I_{ij} \; , \tag{2}$$

where, D_{ij} is weight for the distance between helices i and j. The structure with the smallest value of the lateral-positioning function should be the preferable configuration in terms of energetic.

The rotational positioning is determined by the polar interaction field, assuming the most preferable lateral configuration. Using the binding energies for all helix pairs, the total binding energy of the whole molecule is calculated. Rotating the helices independently by 30 degrees in this work, the total binding energy of 12^N structures are obtained. A set of helix angles, that corresponds to the minimum of the total binding energy, is the final result of the rotational positioning. The structural change due to the binding of a prosthetic group is calculated, fixing the rotational freedom of a helix that is connected to the prosthetic group.

Result

We have calculated the lateral-positioning function $G(D_{ij}, I_{ij})$ for all possible configurations (7!) of the seven helices of bacteriorhodopsin. Here, the two best configurations; the native lateral location and its mirror image are obtained. After the performance of rotational positioning, assuming the two configurations, it was shown that the native location was more preferable.

In the predicted structure the polar arcs of helices C, F and G are oriented to the center of the helix bundle, which was different from the experimental configuration by Henderson et al.[2] While, considering the binding of prosthetic group to the helix G, a structure that was very similar to the experimental configuration was obtained as the most preferable structure.

References

[1] Suwa, M. Hirokawa, T. and Mitaku, S. Proteins, 1994 submitted.

[2] Henderson, R., Baldwin, J. M., Cheka, T. A., Zemlin, F., Beckman, E., Downing, K. H. J. Mol. Biol. 213 : 899–929, 1990.