LETTERS

Structural predictions for membrane proteins: the dilemma of hydrophobicity scales

Which hydropathy method is the best for predicting membrane-spanning helices? All researchers working on protein structure prediction would like an answer to this question. As previously evaluated in *TIBS*[1], there are several methodological aspects that affect the accuracy of transmembrane segment predictions. We would like to point out that the choice of an appropriate hydrophobicity scale is even more critical than is commonly believed[2]. For example, the procedures that Fasman and Gilbert[1] consider to be the most accurate, when applied to the structure of the bacterial reaction centre, all employ the same scale, that of Kyte and Doolittle[3,4]. This scale is the most widely used in the literature[1], but its popularity is clearly not sustained by its validity. It has led to wrong predictions for the folding of important families of proteins, such as cytochrome P_{450} and cytochrome *b* (Ref. 2).

The value of a hydrophobicity scale can also be assessed by its correlation with the distribution of residues inside and outside the membrane, either in the bacterial reaction centres or in bacterial rhodopsins[2] (the former system can be considered to be the standard of known structure for proteins with redox function, whereas the latter can be considered to be that for proteins with transport function). Table I lists a selection of hydrophobicity scales that best correlate with each of these standards. Empirically, it is found that the higher the correlation, the more accurate are the predictions of transmembrane folding obtained by the same optimized algorithm[2]. The linear correlation[2,5] is, therefore, a useful criterion for evaluating which scale is most suitable for proteins that are functionally similar to one or other of the standards. Strikingly, the scale that best correlates with bacterial rhodopsins, that of Sweet and Eisenberg[5], is the worst in correlating with the bacterial reaction centres – the different distribution of functional residues in redox and transport proteins is one reason for such a result[2]. Note also the low score of the Kyte and Doolittle scale with both standards. Hence, the data in Table I stress the importance of the choice of the scale that is most appropriate for the type of protein to be analysed.

The answer to the opening question remains debatable, but it is certain that a proper choice of the hydrophobicity scale (and method) will enhance the accuracy of the structural predictions for membrane proteins.

Table I. Percentage linear correlation of hydrophobicity scales

With five bacterial reaction centres[a]		With five bacterial rhodopsins[b]	
AMPO7[2]	88	OMH[5]	81
MPH89[2]	87	AMPO7[2]	77
Rao and Argos[6]	80	Rose *et al.*[7]	76
Rose *et al.*[7]	76	Rao and Argos[6]	72
Kyte and Doolittle[4]	72	MPH89[2]	71
GES[8]	68	Kyte and Doolittle[4]	69
OMH[5]	46	GES[8]	63

[a]Distribution factors in the aligned sequences of the L and M subunits of five reaction centres, that are 99% correlated with the distribution factors derived from only three reaction centres[2]. [b]Distribution factors in five bacterial rhodopsins (bR, sR, hR, aR and phR[9–11]) calculated from the recent alignment of Henderson[9], which is considerably different from that used previously for the standard scale of three rhodopsins in Ref. 2. However, the qualitative pattern of correlation resembles that of the latter scale. See the cited References for the acronyms of the scales.

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