Prediction of the three-dimensional structures of proteins by Homology Modelling

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Our work is based on the prediction of the protein structure by computational methods, mainly by Homology Modelling, currently considered the most reliable predictive method. The need of a suitable reference model appears the main limit to the application of this method, being commonly accepted that good models are obtained when the target and the reference protein share high sequence identity, whereas sequence identity of 20-40% represents the threshold to apply the Homology Modelling. In our studies, we applied the Homology Modelling to different proteins: in some cases the sequence identity between the target protein and the reference structure(s) resulted higher than 40%, in other cases the identity was lower, and it was needed to assess accurate sequence alignments, based on multiple alignments of sequences and comparisons of predicted secondary structures. This was the case of the human eIF-5A model (Facchiano et al., 2001), created by using two reference proteins having 34% and 32% identity of sequence to the target, and of the sea bass interleukin-1beta (IL-1beta) model, with sequence identities of 37% and 32% to the selected reference proteins. These two predicted models were created working at the limits of applicability of Homology Modelling, and our experience suggests to apply an homology modelling strategy based on the comparison of predictions by different methods, as well as on accurate refinement of the sequence alignment. The comparison with experimental information about protein structure, as an example secondary structure content by circular dichroism, is very useful to validate the models, as well as it is needed an accurate computational analyses of conformational features.

Facchiano et al., Protein Eng. 2001 Nov;14(11):881-890.