Preface

PROTEIN FOLDING: SOLUTION IN SIGHT?

The five papers contained in this special issue on Protein Folding review novel theoretical approaches to predict three-dimensional structures of proteins from the sequence of amino acids and to do computer simulation of the folding pathway.

In spite of the sophistication of theoretical work and the dramatic increase of computing power now available, the complexity of the problem has hindered real progress over many years. The use of detailed atomic force fields and the method of conventional molecular dynamics, being very successful in many other fields, appeared not to be appropriate to attack the protein folding problem.

The new strategies developed in different research groups are turning away from merely first-principle approaches and are now also exploiting sequence–structure relationships derived from the growing number of experimentally determined protein structures. The underlying idea is to combine knowledge-based methodologies, which have their own traditions in secondary structure predictions and homology-modelling, with methods of computational chemistry and statistical physics. This allows introduction of simplified descriptions and in particular derivation of experimentally based mean force-field potentials by using the inverse Boltzmann principle. As compared to the force fields used by molecular dynamics methods, the empirical mean force fields are superior for scoring sequence–structure alignments and may also be used as the driving forces to simulate the folding pathway.

The results obtained for solutions of the inverse folding problem, i.e. the prediction of a sequence compatible with a known protein fold, are very promising. By using simplified models to describe protein structures and corresponding mean force-field potentials, it is also shown that the ultimate goal of tertiary structure predictions for sequences not relying on known protein folds will soon be in reach. Thus, at least in principle terms, one can be confident that the solution of the protein folding problem is now in sight.

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E.W. Knapp
H. Sklenar