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Introduction

The development of energy functions and force fields for studying the behaviour of molecular systems is a major goal in physical chemistry. Prediction of native structures of proteins from amino acid sequences, simulation of the folding process, and calculation of protein stabilities are among the most ambitious goals of contemporary research in biomolecular theory [1].

Research on these topics already has a respectable history, and the difficulties encountered over the past two decades seemed to indicate that they might be intractable because of our lack of a suitable theory of molecular interactions, and because of the computational complexities involved. We now, however, have computational tools at hand that enable the recognition of errors in experimentally determined and model structures. Furthermore, fold-recognition techniques are enabling molecular architectures of proteins to be correctly predicted, before the experimentally determined structures are

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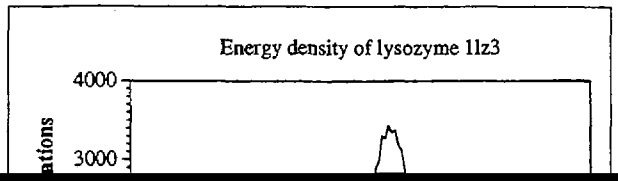
Scheraga [11], and many others have reported subsequent attempts in the intervening period (see e.g. [12–16] and [17–24] for more recent developments).

A characteristic feature of molecular force fields

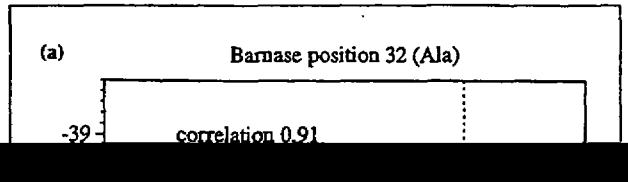
The detailed features of molecular energy functions that



Cβ pairwise and −6.2 for protein–solvent interactions), but when the two terms are combined the scores increase significantly to −9.66 (M Jaritz, MJ Sippl, unpublished data). In other words, the information contained in intramolecular pair interactions is quite different from protein–solvent interactions and both components are

actions in this molecule are unfavourable. The z-scores and energy graphs were calculated using the program PROSA II [26••] (PROtein Structure Analysis), which

There are three critical components of fold recognition techniques: first, energy functions or parameter sets providing a reasonable description of protein–solvent



Protein stabilities

A vital requirement for rational protein engineering and design is the ability to predict the effect of amino acid replacements on the stability of proteins. In some cases experimental results are well documented. In the case of

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