age' secondary structure prediction for the family.

The prediction of Benner *et al.* was in the event disappointing in some respects[8]. But other predictions have been better. The recent publication of tertiary structures for SH2 domains from *src* (ref. 9), *abl* (ref. 10) and p85α (ref. 11), for example, has confirmed our previously published analysis of this family[7] in which we aligned 67 SH2-domain sequences and used this information to predict the secondary structure and position of buried residues. The prediction was performed by combining two-turn and three secondary-structure prediction algorithms, and was augmented by the identification of residue conservation patterns characteristic of helix, loop and strand. The experimentally determined structures confirm our secondary-structure prediction within the conserved core, although we failed to identify a small surface sheet in a variable part of the domain. The overall accuracy of the prediction on a residue-by-residue basis was 78, 76 and 76% when compared to the secondary structures of *src*, *abl* and p85α SH2-domains, respectively. Furthermore, analysis of the *src* SH2-domain coordinates[9] shows that the 22 positions predicted to be buried are inaccessible to solvent.

We, in common with most people developing methods for protein-structure prediction, welcome challenges to predict the structures of other proteins that are soon to be experimentally determined.

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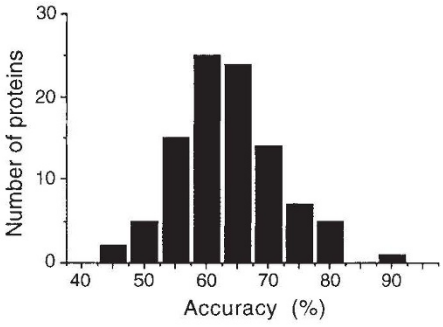
SIR — Benner *et al.*[1] appear to have fallen foul of the classic mistake of so many architects and analysts of protein secondary-structure prediction. They forget that "one swallow does not make a summer".

Benner *et al.* consider a single protein as a test case when comparing protein secondary-structure prediction methods. But all these methods are directly or indirectly statistical in nature, and as such can be assessed only over applications to many proteins. The figure shows the distribution of the quality of results for predictive success using our GOR method[2], which Thornton *et al.*[3] took as the standard comparison when reviewing the method of Benner *et al.* in News and Views. The results in the figure are on a three state (α-helix, β-strand and coil) basis for 98 proteins. The fair and proper



Histogram of the accuracy of secondary-structure predictions (α-helix, β-strand and coil) by the GOR method including directional amino-acid pair frequencies[2]. Note that before prediction, each protein is removed from the database for calculating the pair frequencies.

measure of predictive success or accuracy (not always used) is that a residue is either right or wrong in its assignment to one and only one of the three states. Note that there is a broad spread of predictive capability with a standard deviation of the accuracy per protein of 6–8%, depending on the method. Some proteins are easy to predict and some are very difficult, so we emphasize the spread rather than the mean of 65%. Although a level of accuracy of 65% is useful, it could well be that the particular protein of interest is one of those which predict at the 45% level (close to random at 38%), or indeed at 90%!

In attempting to predict the structure of SH3 (a small protein domain homologous to various signal transduction proteins) the dice have fallen badly for Benner *et al.* Our analysis of their prediction shows that they predicted only 46% of residues correctly, and Rost and Sander[4] found 56% accuracy. Either way, an earlier comparison of the method[3] (again on a single protein) seemed to promise a more satisfactory 63%. We have found that most secondary-structure prediction methods (except perhaps those based on homology to other proteins[4]) seem to fare badly with SH3, perhaps a consequence of dominance of three-dimensional 'tertiary' effects over local, secondary structure effects.

We agree with Benner *et al.* that if several homologous proteins are known, secondary-structure prediction based on analysis of the similarities[5] should bring the average accuracy to much higher values. M. E. Sternberg and others suggested early on that a 4% improvement may be possible, and J. M. Levin (in J. G.'s laboratory) has shown that, providing poorly matching sequences are not included, an average 7% point improvement can be obtained following automatic multiple alignment.

We disagree with Benner *et al.* that other methods are not credible if they are applied after the experimental results are obtained. Statistically, one can and should test performance on the broadest possible number of test cases, providing the method is objective, programmable, fully automatic and well-described in the literature, and providing that the performance in terms of percentage residues correct is based on the (laborious but fair) operation of re-calibrating the parameters or rules with every protein removed from the database when its secondary structure is to be predicted. The GOR methods have survived for more than a decade because of their formal correctness, ease of reproduction and various methods of objective testing. By seeking to incorporate intuition, insight and expertise interactively, Benner *et al.* do not satisfy these criteria, and they admit there is a subjective element[6]. Then, 'blind' prediction tests become the only acceptable route, but these then run into the dangers of assessing quality from a very small sample. Reproducibility is the cornerstone of science, and although that may appear hampering to the creative, it does have very considerable benefits.

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■ Another method which may not be widely known to *Nature*'s readers is that of B. V. Shestopalov (*Molec. Biol.*, Moscow **24**, 900–927; 1990; Engl. transl.), which predicts the SH3 domain structure to a similar degree of accuracy as the other methods discussed in this debate. Dr Shestopalov, of the Institute of Cytology, Russian Academy of Sciences, St Petersburg 194064, fax 247 0341, would appreciate receiving protein sequences for secondary structure prediction by his method. □