Palaeocene therapsid debate

SIR — Sues[1] contests our identification of *Chronoperates* as a Palaeocene mammal-like reptile of the Order Therapsida[2], an identification which extends the temporal range of therapsids over 100 million years. Sues implies that *Chronoperates* is instead a mammal, but presents no synapomorphies that it shares with mammals, nor does he tell us what he conceives a mammal to be. The dimensions specified for the Class Mammalia differ widely and, because we do not know which alternative Sues prefers, we are unable to evaluate the features of *Chronoperates* that he thinks are mammalian. Sues, following Novacek[3], suggests that the differences between the teeth of *Chronoperates* and symmetrodonts (early therian mammals restricted to the Mesozoic) are 'subtle'. However, neither of them has accounted for the lack in *Chronoperates* of several fundamental features that are seen in the cheekteeth of all symmetrodonts (for example, double roots, anterior peg and posterior recess interlocking mechanism, basal cingulum or well-defined shearing surfaces).

Sues identifies several features of *Chronoperates* which demonstrate that it is not one of several already known Triassic cynodonts, and we agree completely. Nonetheless, we still maintain, and Sues has not shown otherwise, that the structure of the teeth and dentary of *Chronoperates* is more similar to that of Triassic cynodonts than to that of any other known vertebrate, including any Mesozoic mammal. Further, Sues states that we distinguished between *Chronoperates* and Mesozoic mammals on differences in enamel microstructure and were incorrect in doing so; however, our comparison was not with Mesozoic mammals, but with two Cenozoic eutherian groups, Edentata and Mesonychia, both of which have teeth which superficially resemble those of *Chronoperates*. As we stated originally, the enamel of eutherians is fully prismatic, not pseudoprismatic as in *Chronoperates*.

Sues implies, misleadingly, that the therapsid features of the dentary of *Chronoperates* are probably artefacts of preservation and not original anatomical structures. In reply, we simply note that Sues has never observed the original specimens or casts of them, with or without magnification. Although breakage and crushing may obscure demonstration of a shallow Meckelian groove

(as we explicitly noted), there is no evidence that the other features in question (such as the presence of a groove for postdentary bones and scar for coronoid bone, inferior limit of masseteric fossa) are artefacts resulting from breakage, crushing or some combination that affected the specimen after death. We therefore maintain that our original interpretations were correct and invite Sues and others to examine the specimens. Our only deficiency seems to be our failure to interpret the evidence according to Sues's expectation of what it 'should' be. In concluding from the evidence that *Chronoperates* is a Palaeocene therapsid, we think we have done substantially better than that.

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Jury returns on structure prediction

SIR — The jury on structure prediction has returned. The witnesses: the experimental structure of the Src-homology 3 (SH3) domain by Musacchio *et al.*[1], solved by X-ray crystallography, and the accompanying theoretical structure by Benner *et al.*[2], predicted from the amino-acid sequence. The case: how well did the ETH (see figure) structure-prediction method work in this blind test, performed before the structure became available?

First, the bad news: the tertiary structure prediction was wrong. Benner *et al.*[2]

structure, the answer is yes: our novel prediction method[3], also tested on the SH3 domain without knowledge of the structure, reached not only 80% for segments, but also 70% for single residues, a good result by current standards. This new method (PHD in the figure) uses information from multiple sequence alignments (as does the ETH method), but has the added advantage of being fully automatic (the ETH method relies in part on human intuition).

We agree with Benner *et al.* that blind predictions should be made before ex-

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........1.........2.........3.........4.........5.......
AA   KELVLALYDYQEKSPREVTMKKGDILTLLNSTNKDWWKVEVNDRQGFVPAAYVKKLD
EXP     EEEE    B      B B     EEEEE       EEEEEE   EEEEEEGGGEEEE

ETH     EEEEEEE     EEEEE HHHHHHHH    EEEE      EEE   EEEEE
PHD     EEEEE         EEE EEEEEEE     HHHHH     EEEE  HEEE
MUS     EEEEE       EEEEE EEEEEE    EEEEEEEE
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Comparison of the secondary structure of the SH3 domain, determined experimentally and predicted on the basis of multiple sequence alignments by three different methods. AA, amino acid sequence; EXP, crystal structure[1]; ETH, *de novo* prediction of conformation[2]; PHD, profile neural network prediction (jury of 12 networks)[3]; MUS, partial prediction by Musacchio *et al.*[5]; E, β-strand (extended); H, α-helix; G, 3_{10}-helix; B, isolated β-bridge.

predicted a structure "built from β-strands with a single turn of α-helix lying on one face". The crystallographers[1], instead, find that "the five strands form two orthogonal β-sheets, as in a β-sheet sandwich". The only similarity between the predicted and experimental tertiary structures is the presence of β-strands, and that is merely a statement about secondary structure.

Second, the good news: the secondary structure prediction was quite accurate. The protein is correctly predicted to consist mainly of β-strands. Of the five β-strands, four are correctly predicted in about the right sequence position, and one is predicted incorrectly as a helix, a neat 80% success rate for segments (ETH in the figure). The success rate is less good when counting how many residues are predicted correctly as helix, strand or loop: only 56%.

Can one do better? For secondary

perimental structure solution. To make such tests independent of human intervention, we have installed an electronic mail server to which academic researchers can submit sequences (send 'help' to PredictProtein@Embl-Heidelberg.De on Internet). The secondary structure prediction will be sent by return mail. With the steady stream of structures now appearing almost weekly, we will know in a year's time the true accuracy of "prediction of progress at last"[4].

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