ticular, the presence of the non-standard purine–purine base pairs substantially widens the major groove. In normal A-form helical RNA, the major groove is too deep and narrow to accommodate an α-helix. Although the α-helical Rev-peptides were not explicitly modelled or considered in the calculations, the unusual structure adopted in the internal loop region of the *RBE* can readily accommodate a helical peptide ligand (Fig. 2). The unusual structure adopted by the internal loop of the *RBE* may only be one of many ways that RNA structure plays a role in forming a specific binding site for proteins.

The *RBE* is a good test for the MC-SYM algorithm, because it is essentially an elaborate secondary structure, apparently without tertiary interactions. The structure of the internal loop must fit between the two boundaries of A-form helical segments, and maintain all of the base pairing implied by the phylogenetic restraints. As the results would indicate, this is a realistic goal, and the predicted *RBE* structure is an appealing one.

The similarity of the family of predicted *RBE* structures based on base pairing suggests that base–base hydrogen bonding and stacking are the prevalent interactions that shape RNA structure. Understanding the hydrogen-bonding pattern for a given sequence has proved a potent first step toward understanding the 3D structure. Biochemical information obtained from chemical probing, and co-variation deduced from phylogeny or aptamer pools are both methods for deducing the pattern of base–base interactions. Clearly this type of information is extremely useful for understanding RNA folding.

The proof of the structure prediction method lies, of course, in its comparison with the actual structure, but this will have to wait for the structural biologists to catch up. A correct prediction will be a triumph for aptamers and MC-SYM. A less than perfect prediction will permit some retrospective analysis of the modelling that will surely benefit future predictions. In either case, the work of Leclerc *et al.*[1] is a bold step, merging these two new methodologies toward a solution of the RNA folding problem.

1. Leclerc, F., Cedergren, R. & Ellington, A.D. *Nature struct. Biol.* **1**, 293–300 (1994).
2. Major, F. *et al. Science* **253**, 1255–1260 (1991).
3. Freier, S.M. *et al. Proc. natn. Acad. Sci. U.S.A.* **83**, 9373–9377 (1986).
4. Holley, R.W. *et al. Science* **147**, 1462–1465 (1965).
5. Woese, C.R. *et al. Nucleic Acids Res.* **8**, 2275–2293 (1980).
6. Noller, H.F. *et al. Nucleic Acids Res.* **9**, 6167–6189 (1981).
7. Michel, F., Jaquier, A. & Dujon, B. *Biochimie* **64**, 867–881 (1982).
8. Davies, R.W., Waring, R.B., Ray, J.A., Brown, T.A. & Scazzocchio, C. *Nature* **300**, 719–724 (1982).
9. Michel, F. & Westhof, E. *J. molec. Biol.* **216**, 585–610 (1990).
10. Stern, S., Weiser, B. & Noller, H.F. *J. molec. Biol.* **204**, 447–481 (1988).
11. Bartel, D.P., Zapp, M.L., Green, M.R. & Szostak, J.W. *Cell* **67**, 529–536 (1991).
12. Giver, L. *et al. Nucleic Acids Res.* **21**, 5509–5516 (1993).

Groovy Water

IMAGE
UNAVAILABLE
FOR COPYRIGHT
REASONS

The structure of the trp repressor/operator complex caused something of a stir when it was published over five years ago. Of the four base-specific hydrogen bonds between a repressor monomer and operator DNA, three are indirect, being mediated through water molecules: a thoroughly unexpected result at the time. Now Shakked and colleagues (Nature 368, 469-473) demonstrate that the position of 10 waters (red spheres) — including the three that mediate critical base contacts — are conserved between the complex (right; DNA alone, shown in green) and the naked operator sequences (left). These waters are effectively an intrinsic part of the operator DNA structure and are used by the repressor to recognise the target sequences buried beneath. (Figure provided by Z. Shakked)