Rigid body constraints can thus be satisfied exactly, rather than by strong restraining forces. 2) Minimization is carried out in any subset or linear combination of these variables. The user's job is to choose intelligently the minimal combination of degrees of freedom appropriate for the problem at hand. Only the chosen degrees of freedom are varied, while all others remain unchanged. The practical advantages of this approach can be considerable. For example, an entire domain of a globular protein can be treated efficiently as a rigid unit, with all surface sidechains freely mobile and interdomain hinges completely flexible. Full flexible geometry is available when needed, e.g. to regularize unreasonable stereochemistry or to extricate the molecule from local minima traps. Workers with experience of protein folding will recognize shades of classical torsion minimizers. In fact, MaxTwist is derived from F32FKMNM incorporating a tree data structure of molecular conformation in terms of bond lengths, bond angles and dihedral angles written in 1972. Energy-minimized and initial structures are compared using the fast superposition algorithm U3BEST. Conformational changes are dramatically displayed in a movie-like manner alternating between different 3D views. This is done with a new molecular graphics program, MacCello, on the vector calligraphics display Wirrwarr. (See abstract 21.)

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Determination of 3D molecular structures from NMR/NOE distance data: application to nucleic acids

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One of the long time goals of NMR spectroscopy has been to determine the 3D structure of macromolecules in solution. Crystals are sometimes very hard to obtain, and in cases where a high resolution X-ray structure is available it is still desirable to know the native solution structure, which may not be the same as in the crystal. The technique which can give the most direct and detailed geometric information about macromolecules in solution is NMR, especially the Nuclear Overhauser Effect (NOE). NOE is a measure of how much a resonance peak belonging to a given nucleus is affected by strong irradiation at the resonance of another nucleus. The main interaction mediating the effect is dipole–dipole coupling, which gives a very strong dependence on the distance between the two nuclei, $N = C\, r^{-6}_{ij}$, so in practice it can only be observed for nuclei that are closer than $\approx$5Å. To reconstruct a structure from a set of distances there are several possible strategies, with the triangulation methods based on a distance geometry algorithm being the conceptually most straightforward. We have chosen to use a molecular dynamics program, complemented with a restraining energy term $E_R(r_{ij}) = K_{ij} \cdot (r_{ij} - r^0_{ij})^2$ which serves the purpose of forcing the atoms i and j close to their observed distance r^0_{ij} during the course of the simulation; at the same time all the other energy terms, describing the covalent structure and van der Waals characteristics, keep the system in a stereochemically reasonable conformation. Molecular dynamics (MD) in this application has the advantage over energy minimizations that a larger fraction of conformational space is searched, which makes MD less sensitive to the choice of starting conformation. The method has been applied to the determination of the 3D structure of a short piece of DNA, $d(CGTACG)_2$, for which 190 interproton distances had been estimated in NOE experiments. It is possible to show that irrespective of whether the simulations were started from a classical A-DNA or a B-DNA, the resulting conformations after a few picoseconds were essentially the same in the two cases: a structure of the B type, but with more local structure variations than in the ideal structure from fibre data.

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Simulation and 3D display of DNA–histone complexes

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Recent developments in equipment and software make possible the interactive display of more than 10 000 atoms so that specific features of large macromolecules may be simulated to investigate long-range spatial relations, correlations of binding sites and dynamic effects. The first step towards these goals is the creation of structures that simulate macromolecules while preserving their most essential structural features, nevertheless allowing, whenever possible, the use of simple mathematical procedures for their construction. An acceptable balance between the need for structural fidelity and the requirement for simplicity in construction must be aimed at. This problem is particularly acute for all those structures which are known to occur in several slightly different conformations or in minor variants of chemical composition. The work to be presented shows simulations of DNA and histones which serve as the basis for structural refinements and investigations of their interactions. A program has been developed which constructs nucleic acid superhelices of variable pitch and radius. This program does not simply bend a straight piece of nucleic acid by applying a geometric transformation to all atoms[1,2], but rather it projects individual basepairs without distortions to their positions in the superhelix. Therefore, the coordinates of the nucleotides are preserved in their standard configuration[3] and it is only necessary to refine the backbone linkage. The program allows the computer controlled simulation of any type of DNA sequence bent along any desirable radius without distortion of internal bonds or angles. It thus becomes possible to study the effect of smooth bending of DNA on the width of its grooves,