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Explorations in Conformational Space: Revealing Inaccuracy and Heterogeneity in Crystal Structures. N. Furnham, T.L. Blundell, Dept. of Biochemistry, Cambridge Univ., Cambridge, UK.

It still remains a challenge to produce reliable high quality models of proteins from medium and low resolution crystals, despite significant progress in developing model building and refinement techniques for structure determination by X-ray crystallography. This is primarily due to the difficulty in adequately exploring the large and complex energy landscape and determining the set of conformers that best describes the experimental data. We have developed and applied a restraint based conformational search engine called RAPPER to this problem, using electron density as a restraint in the building process. By coupling this with traditional molecular dynamics/simulated annealing techniques we can explore unconnected local minima in the energy landscape. Thus we generate ensembles of solutions where all the members are equally compatible with original experimental data. Depending on how the models are generated this may either reflect the experimental uncertainty or also the spatial heterogeneity or dynamics. This has been applied to both high and medium resolution data and most recently to low resolution data. We have shown that there can be significant heterogeneity in protein structures. Ignoring this can lead to overestimation of the accuracy of crystallographic models.