Normal-Mode Based Sampling of Pathways from Comparative Protein Models to the Native State

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In the computational determination of protein structures from sequence, approximate models of the native state are often obtained from comparison with known structures of proteins with related sequences. It remains challenging, however, to predict protein structures at near-experimental accuracy. This poses the question how approximate models with the overall correct topology but incorrect side chain packing and minor structural deviations can be refined to higher accuracy compared to an experimental structure. A related issue is how structures that are perturbed beyond the native basin may recover the native fold in vivo.

A sampling protocol is described where the native state is reached through iterative application of normal mode analysis. The results are compared to sampling based on all-atom molecular dynamics simulations as well as low-resolution lattice-based models. Results obtained so far demonstrate that low-energy pathways can generally be found that lead from approximate protein models directly to the native state without the need for unfolding and refolding. The combination of such sampling methods with suitable scoring function allows protein structure refinement. The requirements for the practical application of such a protocol are discussed and illustrated with successful and unsuccessful examples.