Flexibility and Rigidity in Biomolecules

M.F. THORPE
Center for Biological Physics
Biodesign Institute, Bateman Physical Sciences PSF 359
Arizona State University, Tempe AZ 85287, U.S.A.

Abstract:

Molecular dynamics is unable to explore the conformations of large protein complexes, viral capsids etc. Using Lagrange constraints for covalent bonds, hydrogen bonds, hydrophobic tethers, the rigid regions and the flexible joints between them can be found using graph theory. This input is then used as the basis for a geometric based simulation using a Monte Carlo dynamics that uses ghost templates to efficiently guide rigid clusters through conformational space via the flexible joints between them. This approach also incorporates van der Waals overlaps to maintain good local stereochemistry. The generation a new protein conformation typically requires about 100 milliseconds CPU time [1].

Input from a single X-ray crystallographic structure can generate an ensemble of structures remarkably similar to those observed in NMR. Further applications are pathways for ligand docking, misfolding proteins and viral-capsid swelling. The software used for this work is available either interactively or for downloading via http://flexweb.asu.edu . Rigidity analysis also provides a natural basis for coarse graining that can be used to limit to size of conformational space to be explored. An example is given using the Gaussian network model, where it is shown that improved results using less CPU can be obtained using this kind of coarse graining [2].

Geometrical simulation can also be used for targeted dynamics either in a lite mode [3] where only covalent constraints and van der Waals overlaps are included, or in a full mode where all constraints are included [1].

References:

[1] Stephen Wells, Scott Menor, Brandon Hespenheide and M. F. Thorpe, *Constrained Geometric Simulation of Diffusive Motion in Proteins,* Physical Biology 2, S127-S136 (2005)

[2] Holger Gohlke and M.F. Thorpe, *A Natural Coarse Graining for Simulating Large Biomolecular Motion,* Biophysics Journal (submitted).

[3] Samuel Flores, Nathaniel Echols, Duncan Milburn, Brandon Hespenheide, Kevin Keating, Jason Lu, Stephen Wells , Eric Z. Yu, Michael Thorpe and Mark Gerstein, *The Database of Macromolecular Motions: new features added at the decade mark,* Nucleic Acid Research, 34, D296 - D301 (2006).