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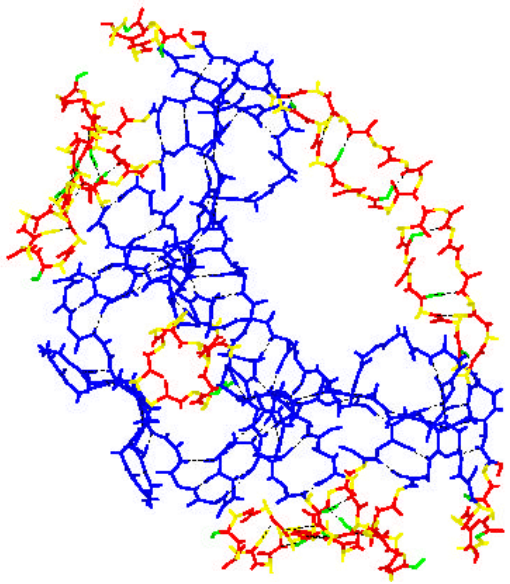
PROTEIN FLEXIBILITY

Presenter: M. F. Thorpe

The theory of rigidity and its application to large networks has been developed at MSU over the last decade and applied to the study of network structures [1] and glasses [2]. For the past two years, we have been extending this work to the study of proteins [3].

A protein is regarded as a collection of atoms held together by covalent and hydrogen bonds. By using a new *graph–theoretic algorithm* [3], it is possible to identify the flexible and rigid regions in even the largest protein in under a second of CPU time on a workstation. The resultant maps show the rigid regions in the protein and the flexible joints between them. We can use this technique to quantify the flexibility of a protein by defining a density of local floppy modes.

This new approach to protein flexibility will be illustrated using HIV protease, where we correctly predict the flexibility associated with the main flaps, which determines the functionality of this protein. In the figure below, the blue region is rigid and the multicolored regions are flexible and contain many rotatable dihedral angles



We are also studying the *protein unfolding* problem. We postulate that the folded structure contains information about its folding pathway, encoded within the hydrogen bonds. By analyzing the strength and density of the hydrogen bonds, we are studying how a protein unfolds as the temperature is raised. We find that the tertiary structure of a single protein decomposes in a collective way via a global breakdown in rigidity caused by the removal of a few key hydrogen bonds. We are currently studying this important application of the non-local character of rigidity. We can identify *critical hydrogen bonds* – those that cause a large change in the flexibility of the protein. Modifying these critical bonds by mutagenesis of the associated side group(s) would probably result in seriously degraded functionality in the protein.

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[1] P.M. Duxbury, D.J. Jacobs, M.F. Thorpe, C. Moukarzel
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[2] M. F. Thorpe, D. J. Jacobs, N. V. Chubynsky and A. J. Rader
Generic Rigidity of Network Glasses in ***Rigidity Theory and Applications***
Edited by M. F. Thorpe and P. M. Duxbury (Plenum Press, New York, 1999).

[3] D. J. Jacobs, L. A. Kuhn and M. F. Thorpe
Flexible and Rigid Regions in Proteins in ***Rigidity Theory and Applications***
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