Network Rigidity; Donald J. Jacobs, University of North Carolina at Charlotte

Mechanical correlations between atoms in a molecule:

Atomic correlations can be quantitatively distinguished by identifying pairs of atoms that move in such a way that the distance between them remains fixed, while the distance between other atomic pairs is not fixed. This idea can be quantified using network rigidity.

Mechanical networks of bars and joints:

The basic idea is that a certain number of distance constraints are placed between mass points that are viewed as atoms to form a network. We can then ask the question which sets of atoms form rigid substructures. Rigid substructures (also called **rigid clusters**) link together at **flexible hinge joints**. The flexible hinge joints allow for various rigid clusters to have relative motions within the network. In addition to identifying all rigid clusters and all flexible joints, all independent constraints and degrees of freedom can be identified. All of this information is obtained through the concept of rigidity without simulating the motion of the network. Using the knowledge of the **rigid cluster decomposition**, and the location of the flexible hinge joints, protein motions can be simulated much faster than integrating equations of motion as typically done in a molecular dynamics simulation.

Rigidity algorithms:

Very fast graph algorithms can be employed to characterize network rigidity. There are ***pebble game*** algorithms for doing this in two and three dimensions, although they have certain limitations that are too technical to explain here. It suffices to realize that there is a certain range of **linear response** for which we are assuming holds. Moreover, the idea that the distance between a pair of atoms is precisely fixed is not realistic at the molecular level. This draconian concept of rigidity will be relaxed within the **Distance Constraint Model**. Rigidity theory provides the first step toward a quantitative characterization of the mechanical mechanisms within a molecule by identifying all rigid and flexible regions between all pairs of atoms, and thereby provides a precise description of static mechanical properties. That is, the information obtained from network rigidity tells what set of atoms are mutually rigid moving together as a rigid body, and which set of atoms can flex relative to one another. This information does not tell us about how much the amplitude of motion will be.

Network rigidity is a long-range interaction:

Below is a brief summary (in the form of pictures) describing what the rigidity calculation gives as an end result. It is important to realize that network rigidity is a long-range interaction. A single distance constraint placed in a critical region of a network can transform a region from being flexible (or floppy) to becoming rigid. Likewise, by removing a single distance constraint it is possible to shatter a large rigid structure into a large number of rigid substructures, similar to the way a house of cards collapses when a critical card is pulled out from underneath. In regions where there is higher density of distance constraints than is needed to keep the atoms mutually rigid, there will be strain energy. These regions are called **overconstrained** and are resistant to breaking apart upon the removal of a few distance constraints. If a region is rigid, but not overconstrained, it is called **isostatic** or **marginally rigid**.

Color rendering schemes:

One way to represent network rigidity properties is to color **flexible joints as green**, **isostatic rigid regions as red** and **overconstrained rigid regions as black**. A second coloring scheme is to color different rigid clusters connected by flexible joints differently. Pictures of both sorts are shown below.

Floppy Inclusion and Rigid Substructure Topography (FIRST):

An efficient way to calculate the network rigidity properties is through a pebble game algorithm that I developed. The FIRST software is available for such a task. I include a talk on how FIRST works after the brief summary of results. Note that FIRST has multiple implementations, but the most efficient way to represent rigidity information in 3D is in terms of the body-bar model for rigidity as described.

Constraint Theory

The long-range nature of network rigidity

2D Pebble Game Algorithm

1. Identification of independent constraints
2. Identification of rigid clusters
3. Identification of overconstrained regions
4. Identification of flexible regions

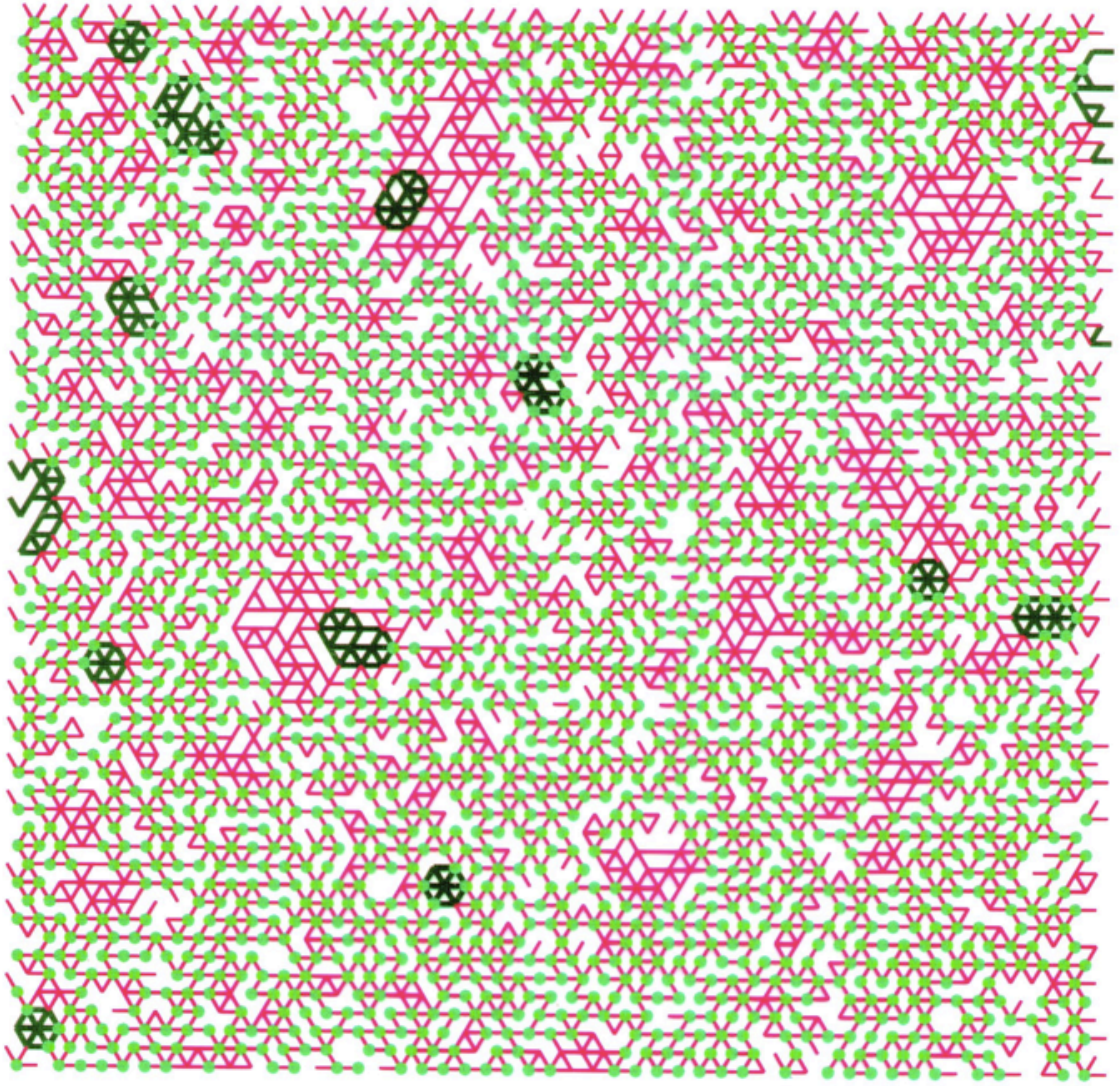
Jacobs & Hendrickson, J. Comput. Phys. 137, 346 (1997)
Jacobs & Thorpe, Phys. Rev. E 53, 3682 (1996)
Moukarzel, J. Phys. A: Math. Gen. 29, 8079 (1996)
Jacobs & Thorpe, Phys. Rev. Lett. 75, 4051 (1995)
Moukarzel & Duxbury, Phys. Rev. Lett. 75, 4056 (1995)

Two Dimensional Example: →

Constraint topology below rigidity transition

Globally floppy

Small section of a randomly bond diluted triangular lattice



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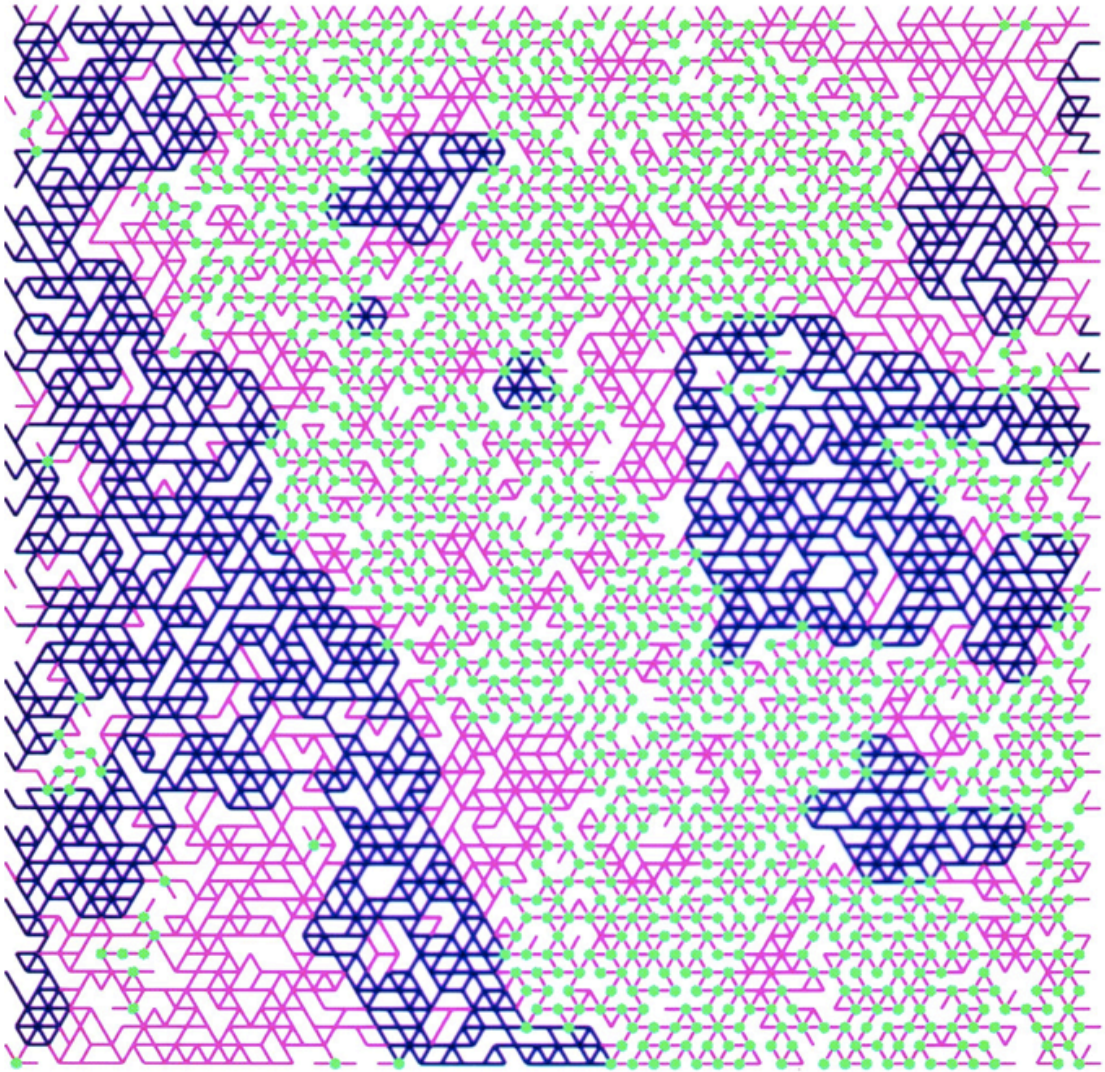
Two Dimensional Example: →

Constraint topology at the rigidity transition

Globally rigid

Small section of a randomly bond diluted triangular lattice



Constraint Theory

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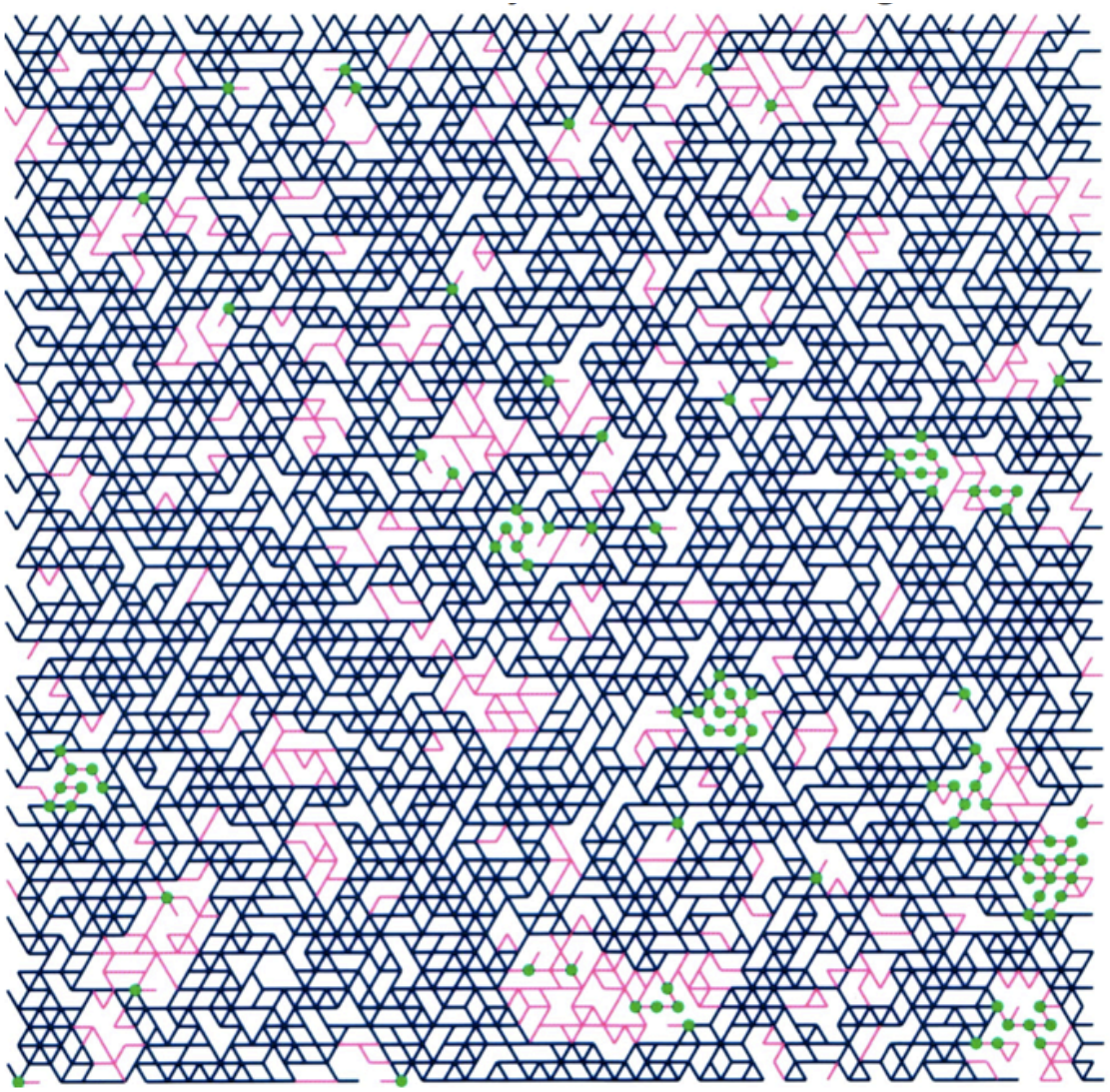
Moukarzel & Duxbury, Phys. Rev. Lett. 75, 4056 (1995)

Two Dimensional Example: →

Constraint topology above rigidity transition

Globally overconstrained

Small section of a randomly bond diluted triangular lattice



Constraint Theory

Application to covalent bond network glasses

3D Pebble Game Algorithm

1. Identification of independent constraints
2. Identification of rigid clusters
3. Identification of overconstrained regions
4. Identification of flexible regions

Jacobs, J. Phys. A: Math. Gen. 31, 6653 (1998)
Whiteley, Contemp. Math. 197, 171 (1996)
Tay and Whiteley, Structural Topology 9, 31 (1984)
Tay, J. Comb. Theory B 26, 95 (1984)

Three Dimensional Example: →

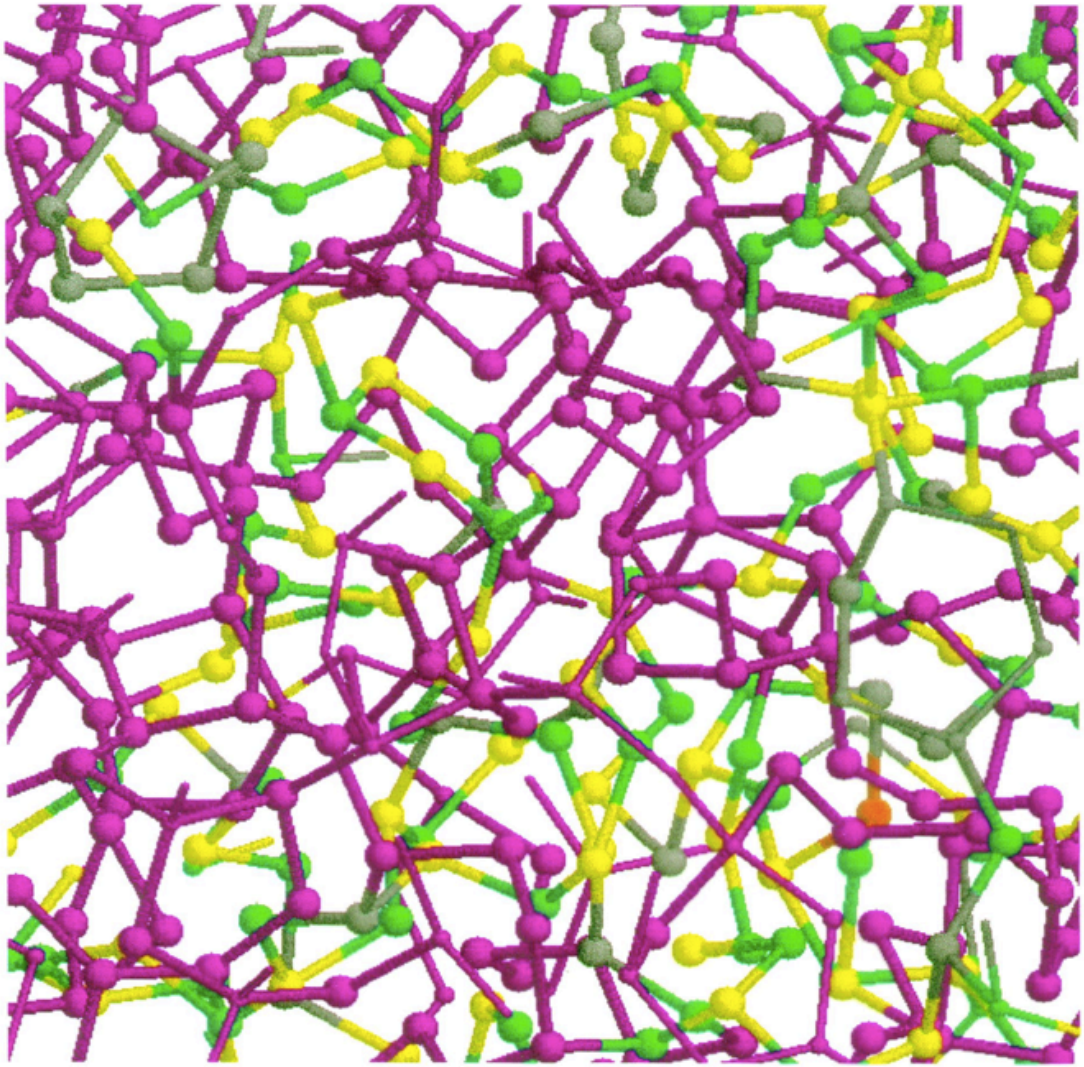
Constraint topology above rigidity transition

M.F. Thorpe, J. Non-Cryst. Solids 57, 355 (1983)
J. C. Phillips, J. Non-Cryst. Solids 34, 153 (1979)

Macroscopic concepts applied to atomic structure

Requires separation of hard & soft forces

Small section of a randomly bond diluted diamond lattice



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Rigidity percolation:

Similar to standard "connectivity" percolation theory, the rigidity percolation problem deals with finding a rigid path across a sample. If the sample is homogeneous in nature, and infinite in extent, a well-defined rigidity threshold can be defined related to the density of constraints that are laid randomly in the network. This is a mechanical transition where the global properties of the network will be flexible below a critical threshold in the density of constraints, and rigid above the threshold. At and near the constraint density threshold, the network generally shows characteristics of large fluctuations of rigid and flexible regions. For a first order transition, change in global character (**flexible ⇔ rigid**) is made suddenly, while for a second order transition, the fluctuations extend to infinity at the transition point.

Rigidity transition:

In 3D networks, rigidity transitions tend to be first order in nature. This means there is a nucleation process occurring where the system will be globally flexible and then rapidly become globally rigid with just the addition of an infinitesimal increase in constraint density. The ideas of rigidity percolation can be applied to proteins. In proteins, it makes sense to model all the covalent bonds as rigid bars. However, if those are the only interactions modeled as constraints, the protein is just a floppy polymer chain even in its folded state. If all torsion forces and hydrogen bonds are modeled as distance constraints, the entire protein will be rigid. Initially, when rigidity theory was applied to proteins, only the covalent bonds and a subset of hydrogen bonds (and salt bridges, viewed as a special type of hydrogen bond) were modeled as distance constraints. By adding more distance constraints one at a time in the order of strongest to weakest hydrogen bond strength (based on an energy scale, corresponding to the depth of the potential well) one can create a rigidity percolation problem.

Rigid cluster susceptibility (RCS):

To characterize the degree of mechanical fluctuations within a network, the fluctuations in the size of the rigid clusters in a network is monitored. If the network is far below the rigidity threshold where it is mostly floppy, there will mainly be small rigid clusters, and rare to find large rigid clusters. Conversely, if the network is far above the rigidity threshold, there will be a very large rigid cluster, and rare to find floppy regions consisting of smaller rigid clusters. In either limit, the rigid cluster susceptibility (RCS) will be low. However, near the rigidity threshold, fluctuations in the rigid cluster decomposition will be greatest, and the peak in the RCS identifies the location of the rigidity transition (in terms of density of constraints). This is analogous to using the peak in heat capacity that monitors energy fluctuations to locate the thermodynamic transition (in terms of temperature) between two phases, such as a folded and unfolded protein.

Applying rigidity percolation theory to proteins:

In the FIRST software, the flexibility of a protein is interrogated by sweeping across different degrees of rigidity based on an energy cutoff that determines how many hydrogen bonds are modeled as distance constraints. This approach (shown below) gives insight into mechanical stability of a protein, but it does not reflect thermodynamic stability. In this approach, "constraint density" is mapped to adding more constraints by changing which hydrogen bonds are modeled as a constraint. Also, a protein is not a homogeneous system of infinite extent. In fact, it is a highly inhomogeneous finite system with surface effects. Nevertheless, rigidity percolation theory has proved useful to understand mechanical properties of proteins, and the results obtained provide insight into the allowed dynamics.

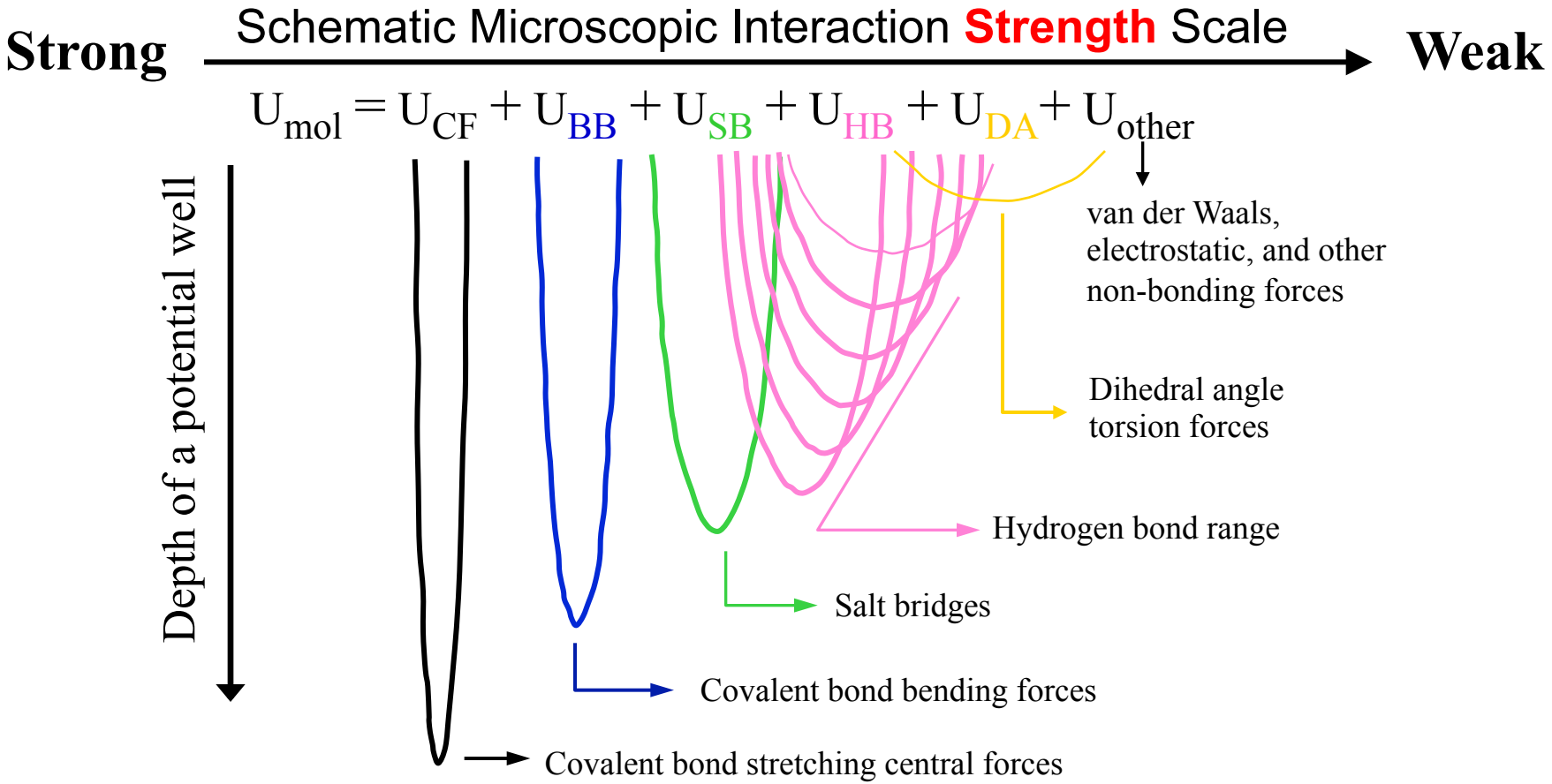
To be or not to be a constraint:

A problem with the initial approach of using an energy cutoff for determining which hydrogen bond to model as an infinitely strong constraint, versus no constraint is that in reality there is a continuum of strength, not just on/off. The on/off problem is resolved using the Distance Constraint Model where the strength of a constraint is set by the curvature in the restoring potential energy for an interaction.

How can constraint theory be applied to proteins?

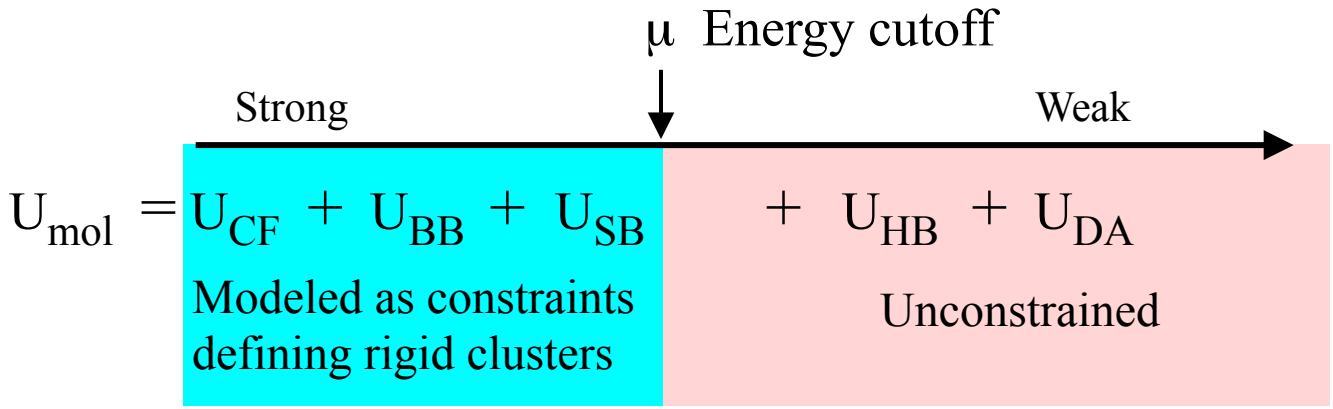
Microscopic interactions do not cleanly separate into strong and weak

Jacobs, et. al., p357 in "Rigidity Theory and Applications",
Eds. M.F. Thorpe and P.M. Duxbury, Kluwer-Academic (1999).



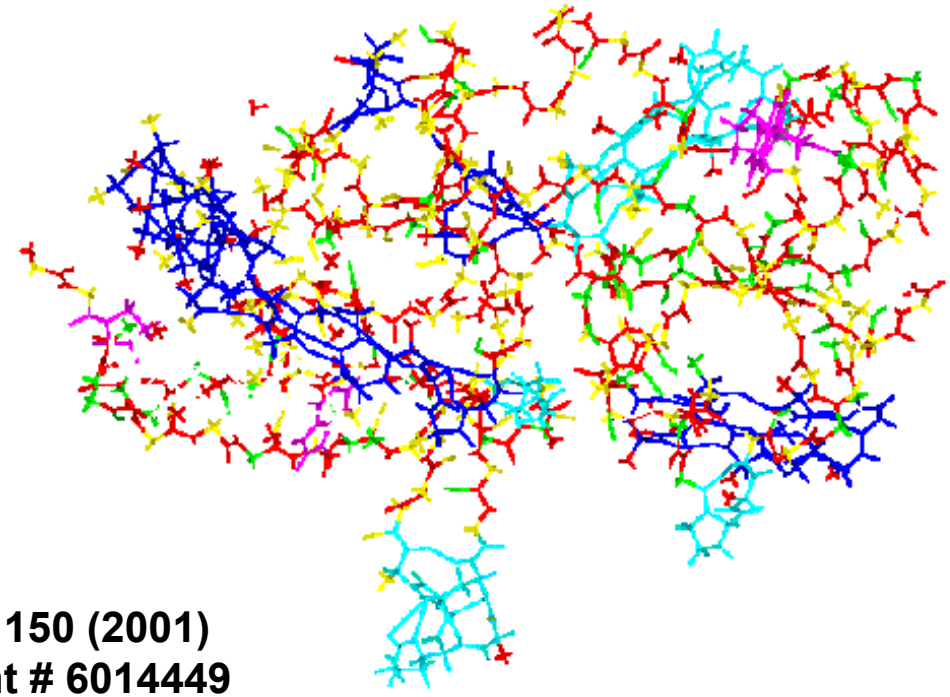
Network Rigidity: Applied to Proteins

To be or not to be a constraint?



μ = -1.80 kcal/mol

246 hydrogen bonds modeled as a constraint



Jacobs, et. al., Proteins 44, 150 (2001)
Jacobs & Thorpe, US Patent # 6014449

Network Rigidity: Applied to Proteins

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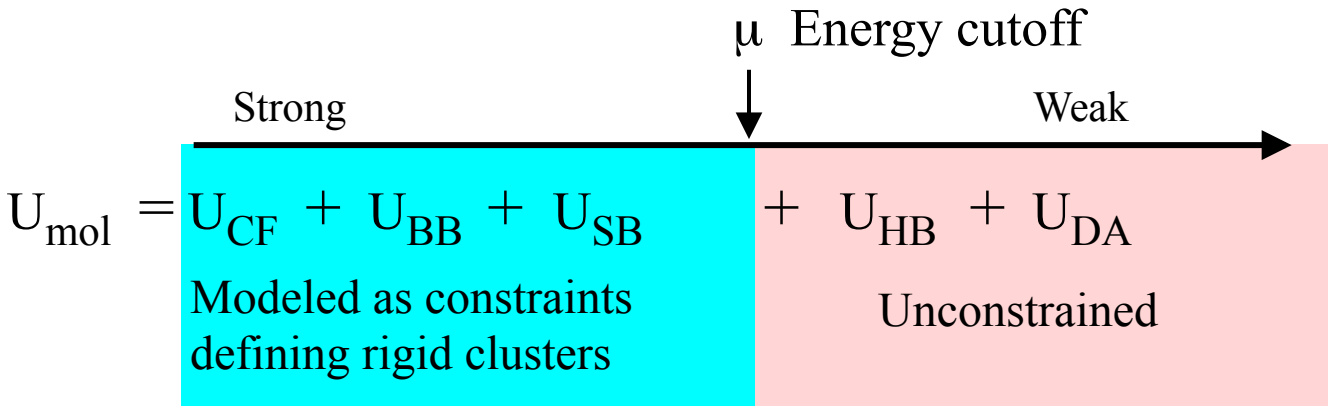
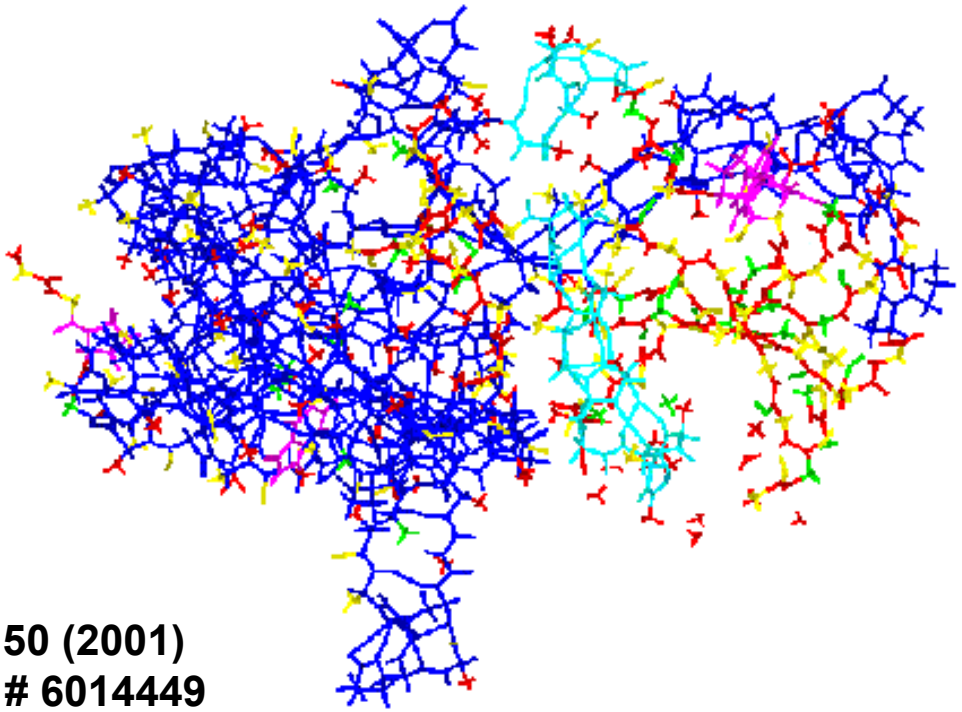


μ = -0.50 kcal/mol

366 hydrogen bonds modeled as a constraint



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Network Rigidity: Applied to Proteins

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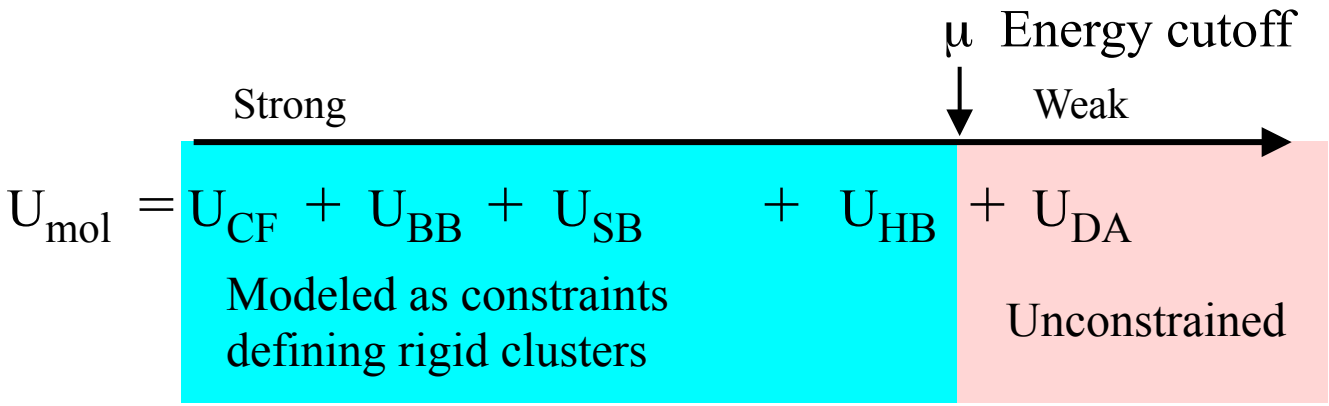
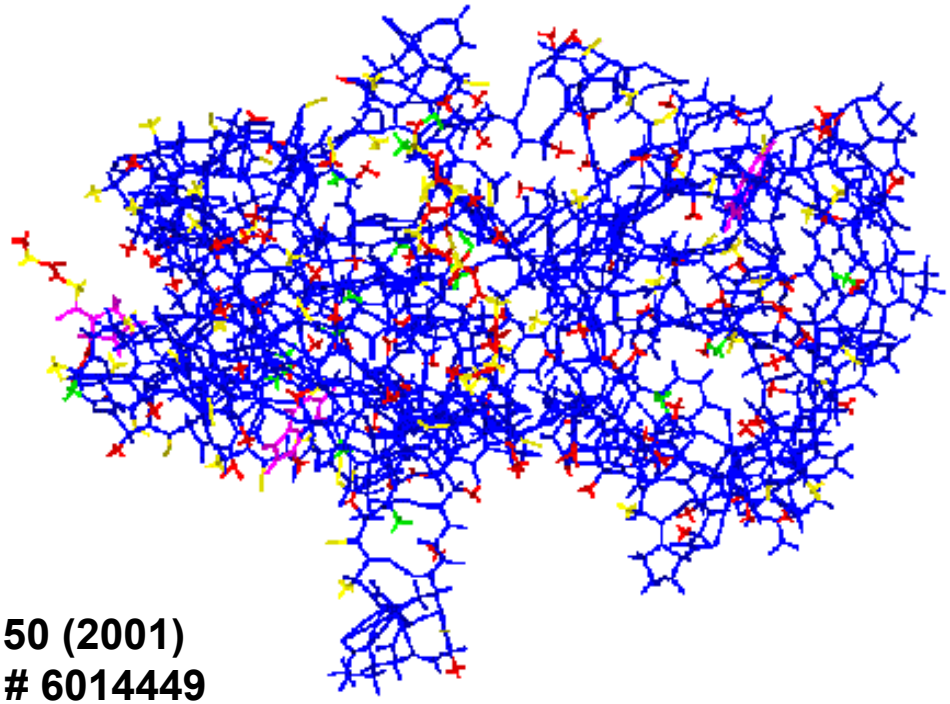


μ = -0.01 kcal/mol

461 hydrogen bonds modeled as a constraint



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