The Abdus Salam
International Centre for Theoretical Physics

United Nations
Educational, Scientific
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International Atomic
Energy Agency

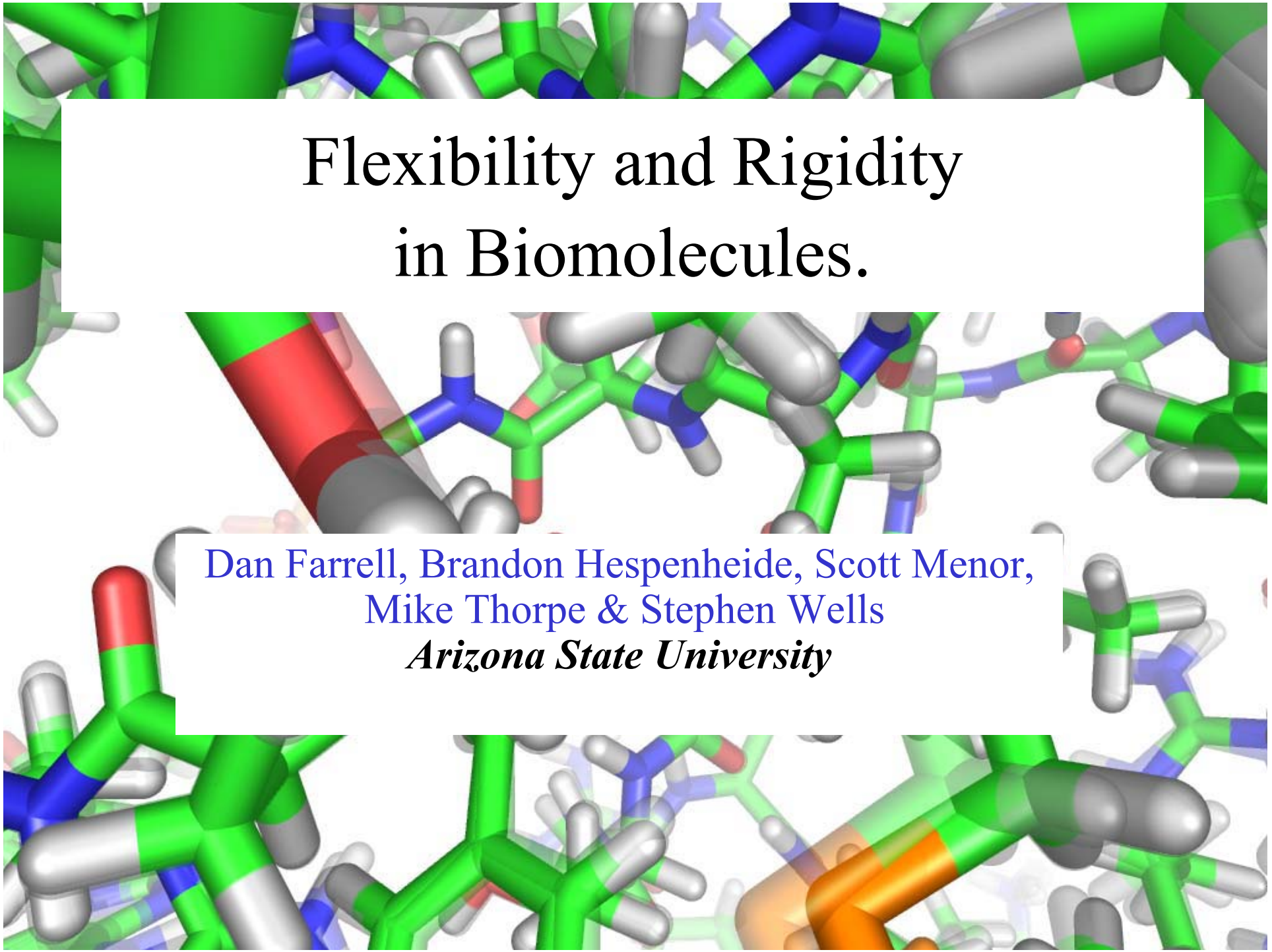
SMR.1759 - 17

**Fourth Stig Lundqvist Conference on
Advancing Frontiers of Condensed Matter Physics**

3 - 7 July 2006

Flexibility and Rigidity in Biomolecules

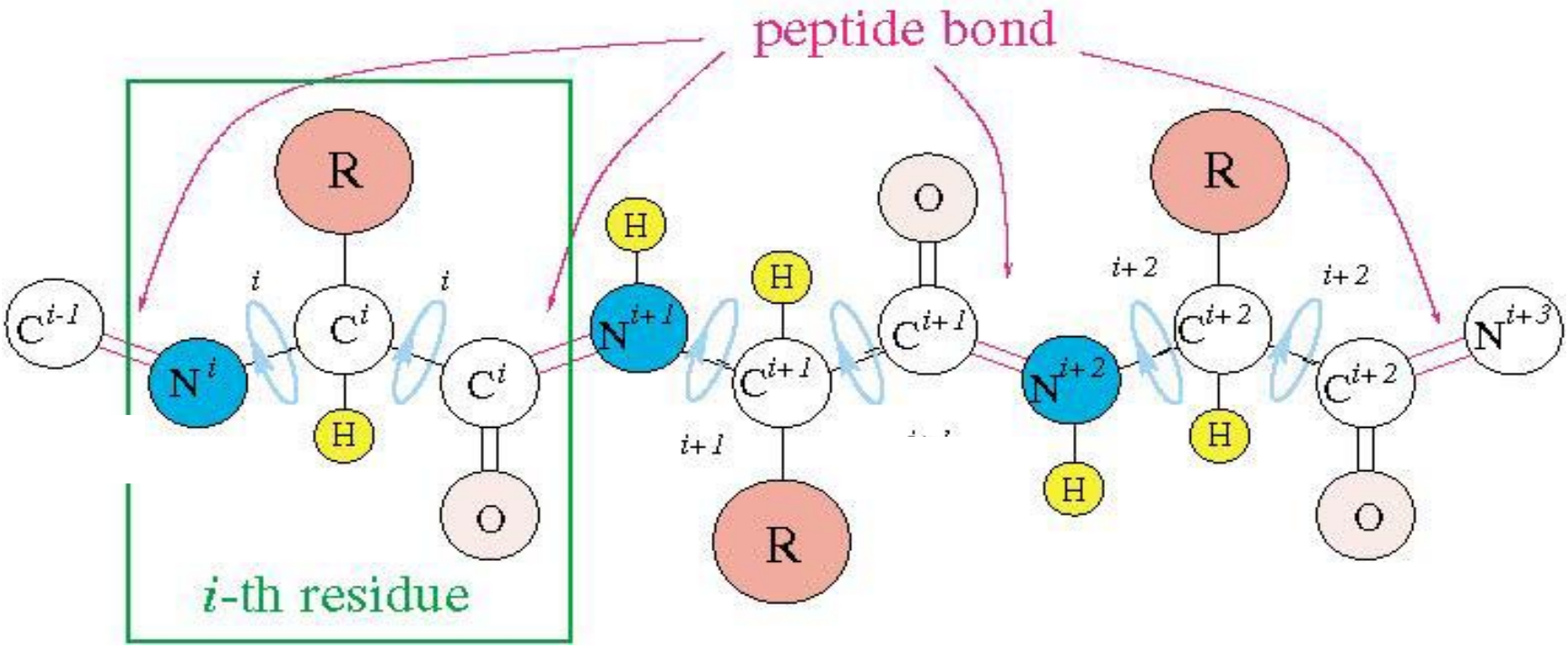
Mike THORPE
Michigan State University
Department of Physics & Astronomy
Biomedical Physical Building
East Lansing, MI 48824
U.S.A.



Flexibility and Rigidity in Biomolecules.

Dan Farrell, Brandon Hespenheide, Scott Menor,
Mike Thorpe & Stephen Wells
Arizona State University

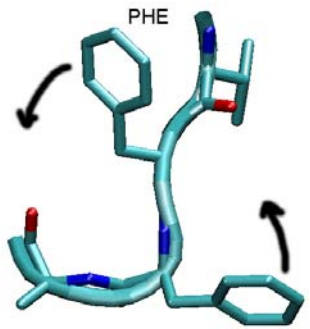
Proteins


peptide bond
R
H
O
i
i
i+2
i+2
i+1
C^{i-1}
N^{i}
C^{i}
C^{i}
N^{i+1}
C^{i+1}
C^{i+1}
N^{i+2}
C^{i+2}
C^{i+2}
N^{i+3}
i-th residue

From Joan-Emma Shea

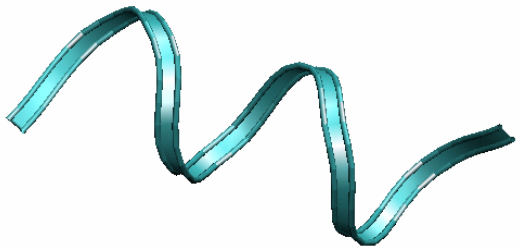
Time scales

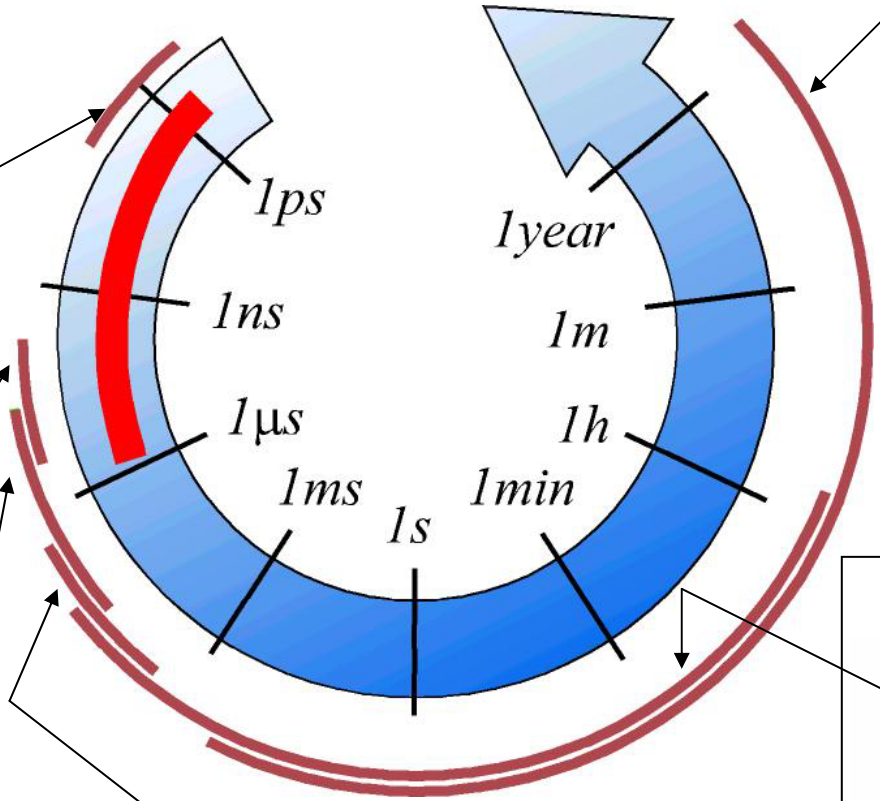
Side-chain rotations



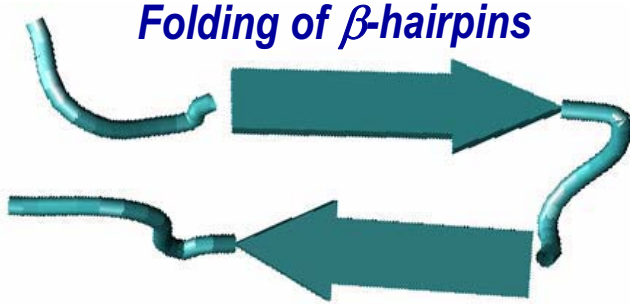
Loop closure

Helix formation

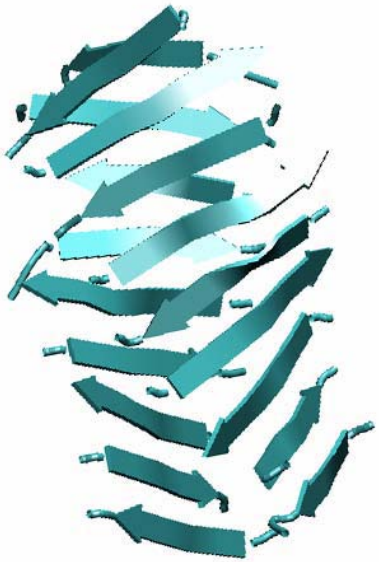




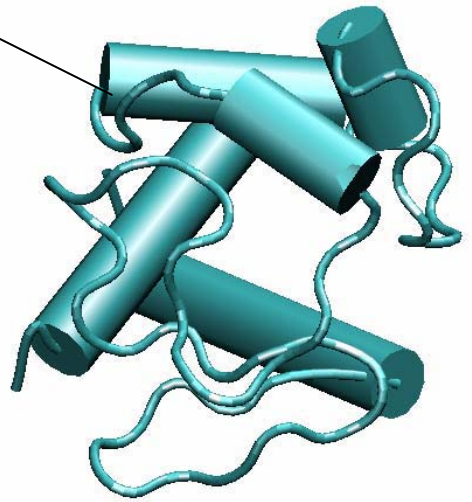
Folding of β-hairpins

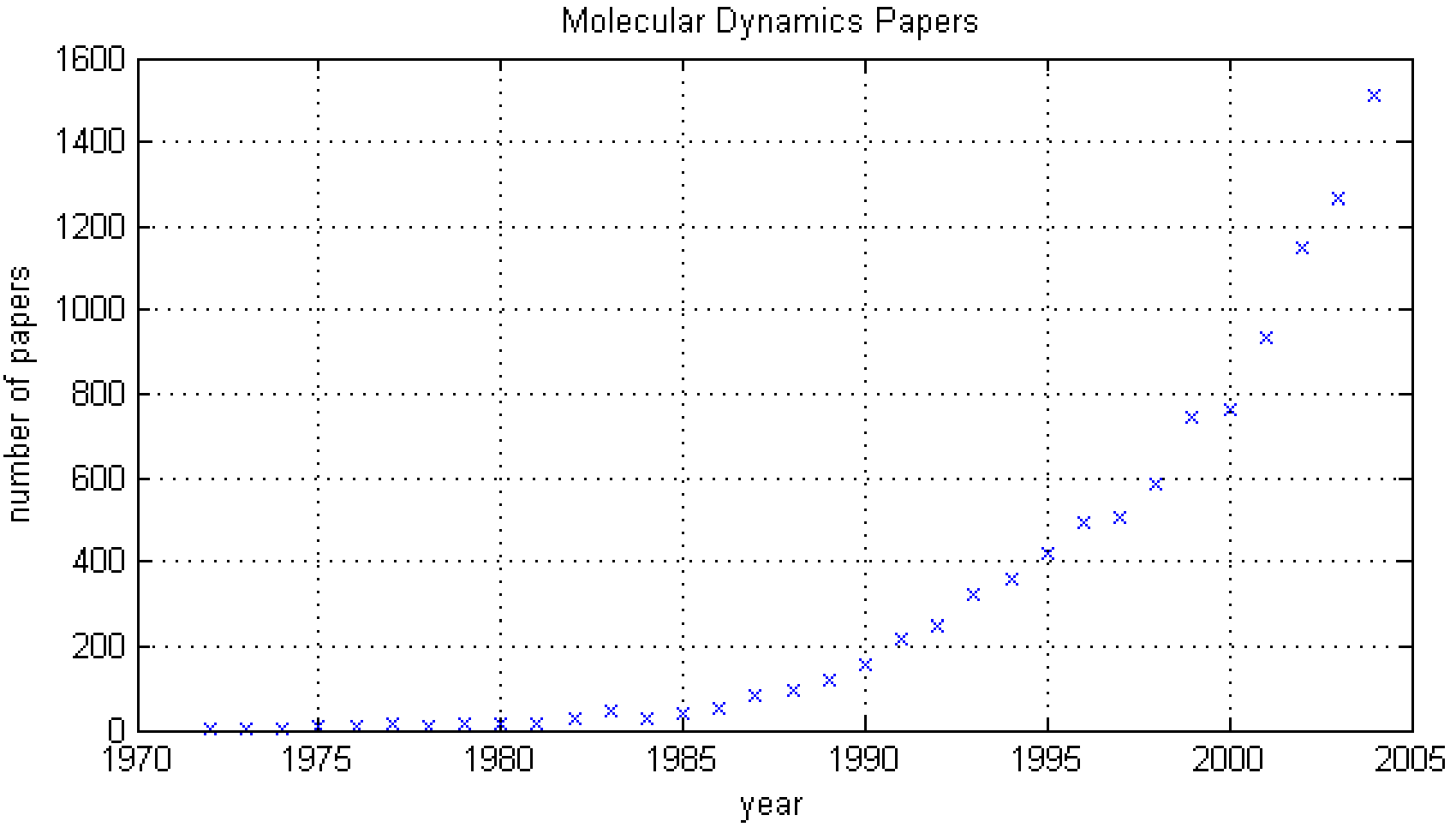


Protein aggregation



Protein folding





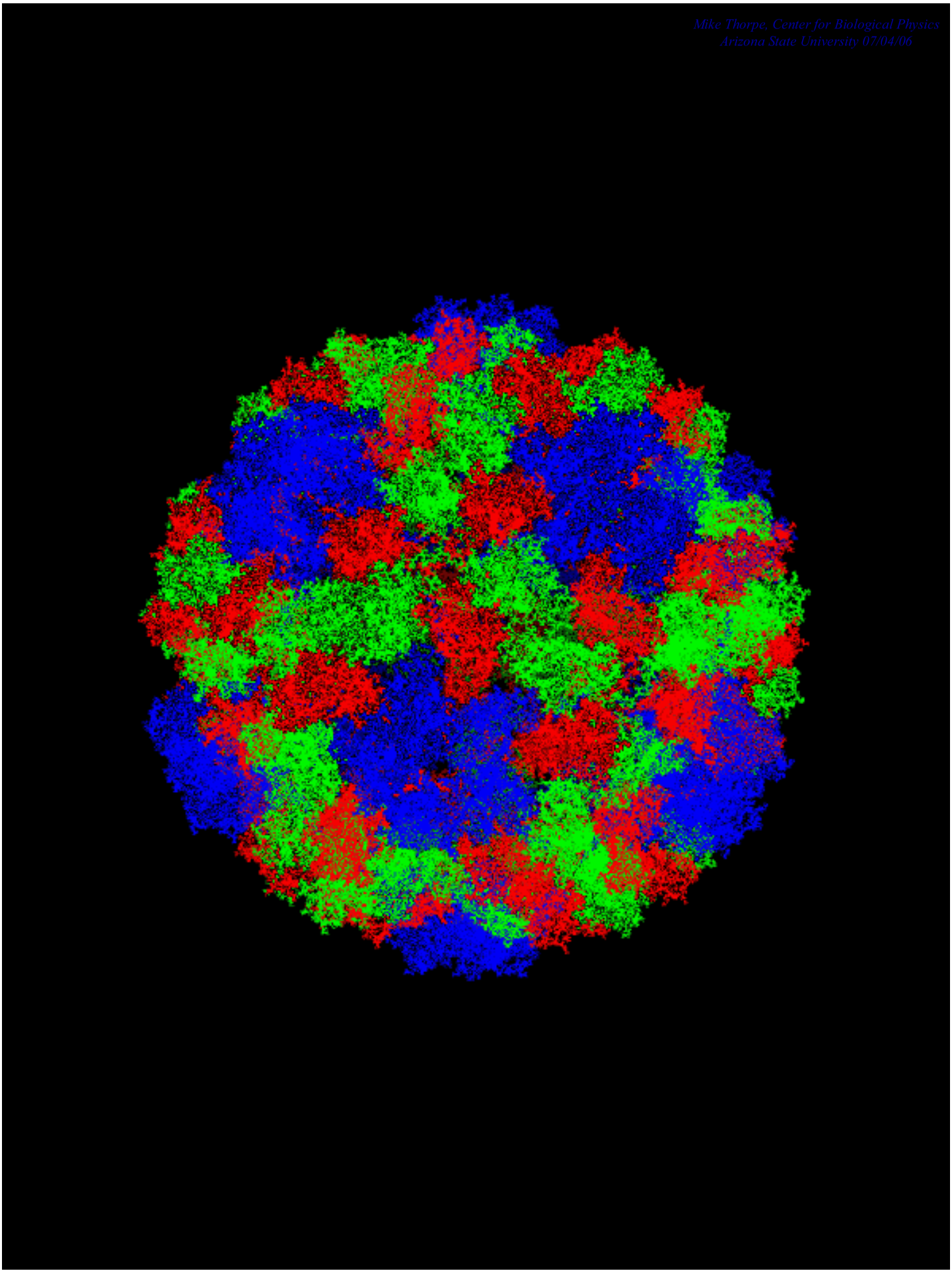
Search on molecular dynamics protein

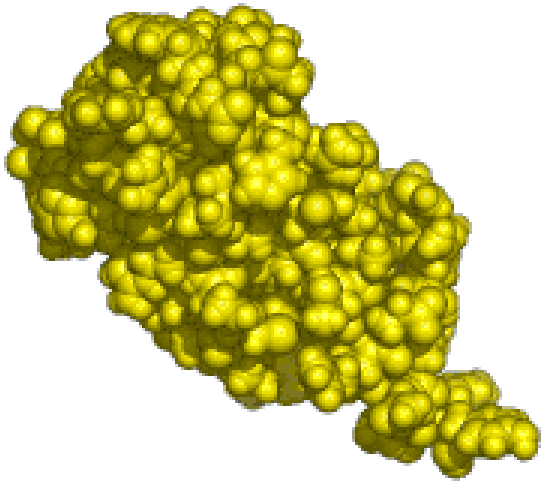
Mike Thorpe, Center for Biological Physics
Arizona State University 07/04/06

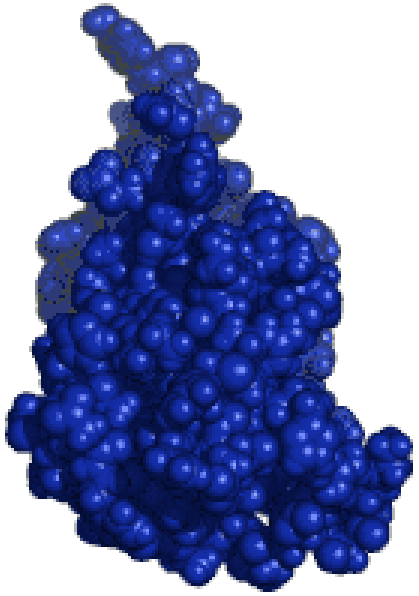
Molecular Dynamics

- F=ma
- Times to ~ 100 nanosecs, like ~ millisecs.
- Current improvements give factors of 10.
- Can't wait for Moore's law.

Coarse graining
Simplified potentials
Geometry


Mike Thorpe, Center for Biological Physics
Arizona State University 07/04/06



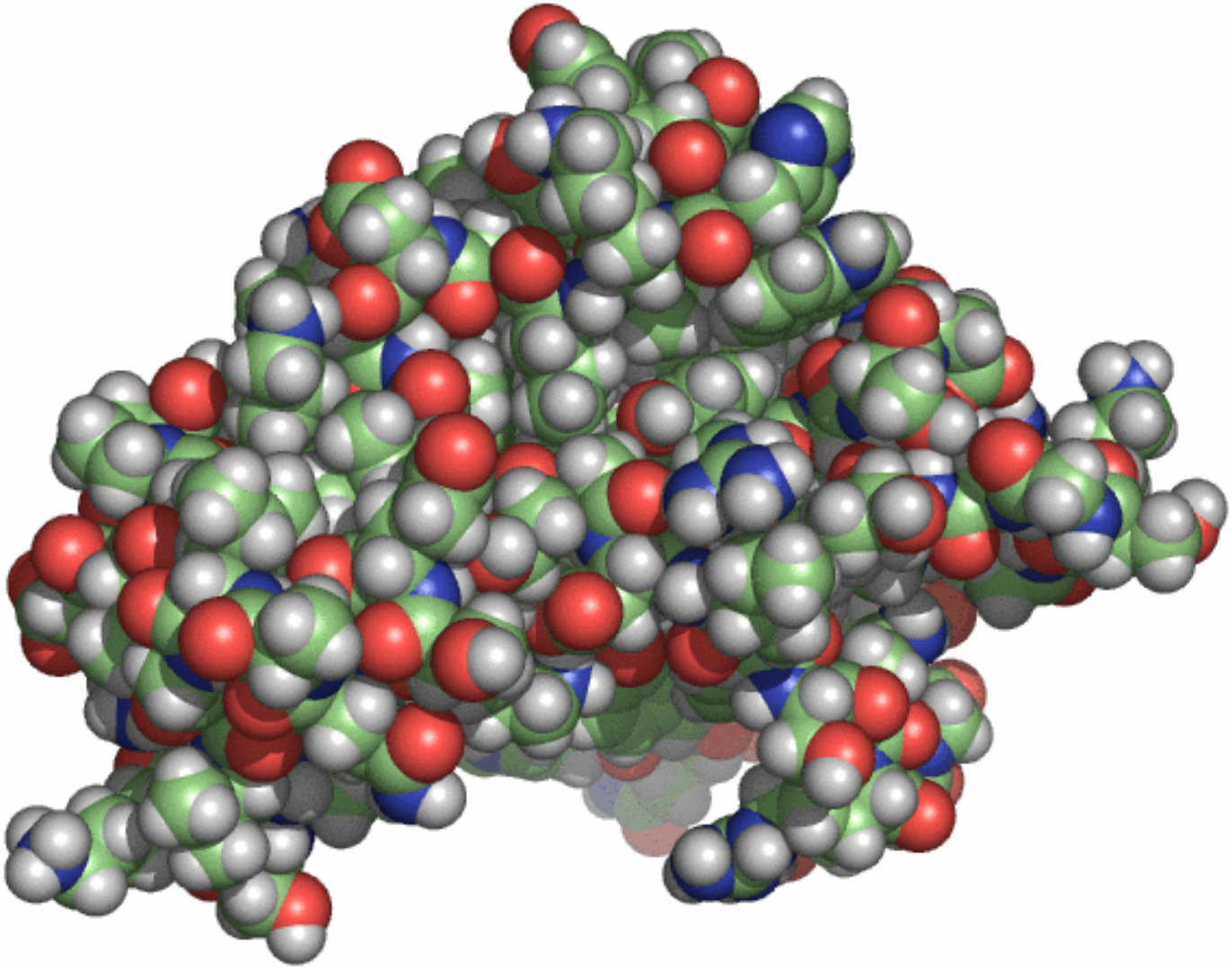


Motion Applet

- Audrey Lee, Aaron St John and Ileana Streinu
  (motion planning, robot arms etc.)

→Applet

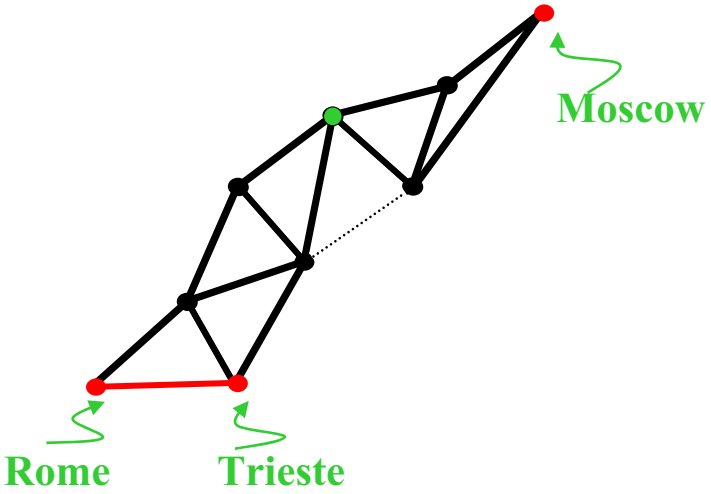
Barnase

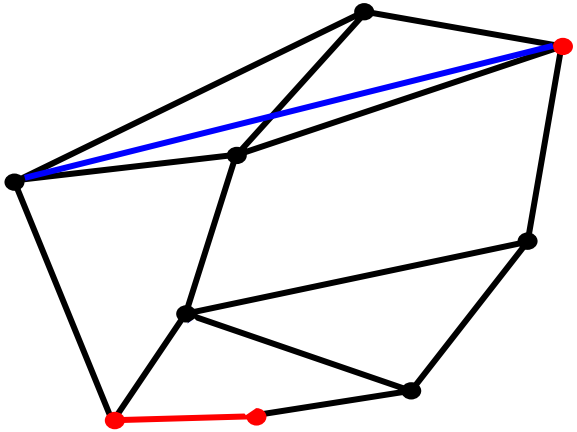


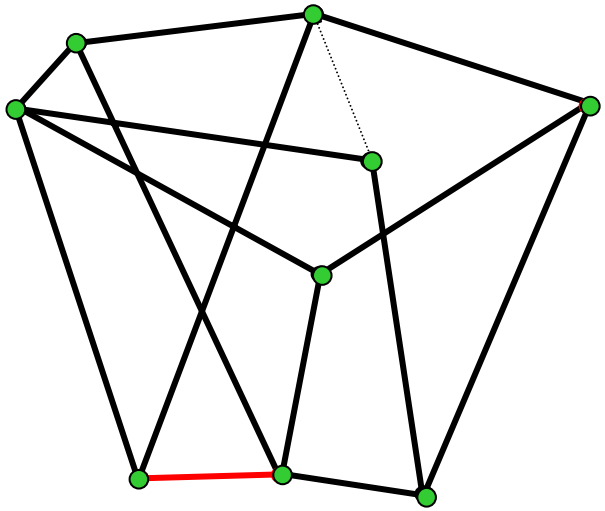
Statics

- Floppy Inclusions and Rigid Substructure Topography ***(FIRST)***
- *Don Jacobs and Brandon Hespenheide*

Surveying







$F = 2x9 - 15 = 3$

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Laman's theorem 1970

A generic network in 2d with N sites and B bonds (defining a graph) does not have a redundant bond iff no subset of the network containing n sites and b bonds defining a subgraph violates $b \leq 2n\text{-}3$.

Algorithmic realization – Pebble Game

Very fast – millions of sites
in a few seconds

- **Number of floppy modes**
- **Rigid clusters**
- **Stressed regions**
- **Flexible joints**

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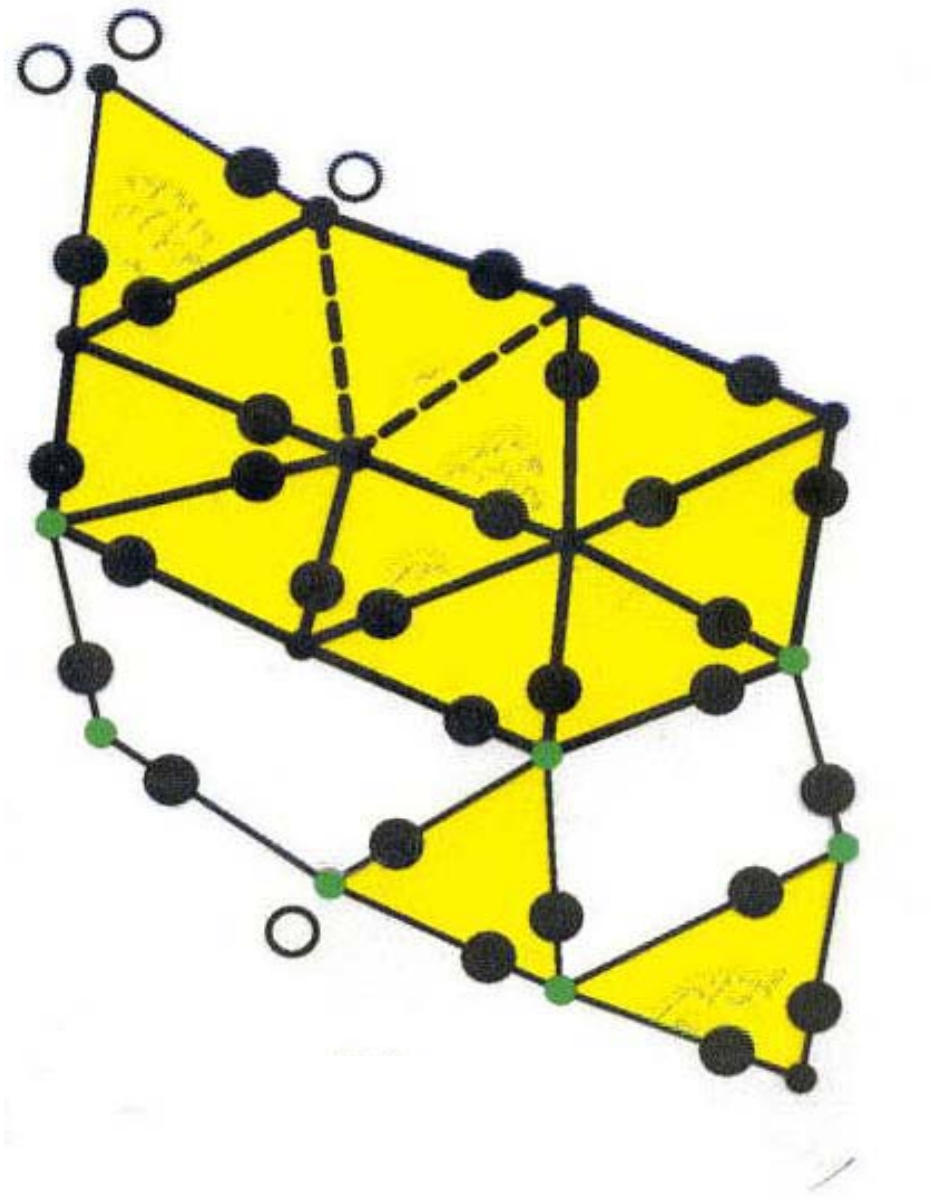
The Pebble Game



D. J. Jacobs and M. F. Thorpe
Generic Rigidity Percolation: The Pebble Game
Phys. Rev. Letts. **75**, 4051-4054 (1995).

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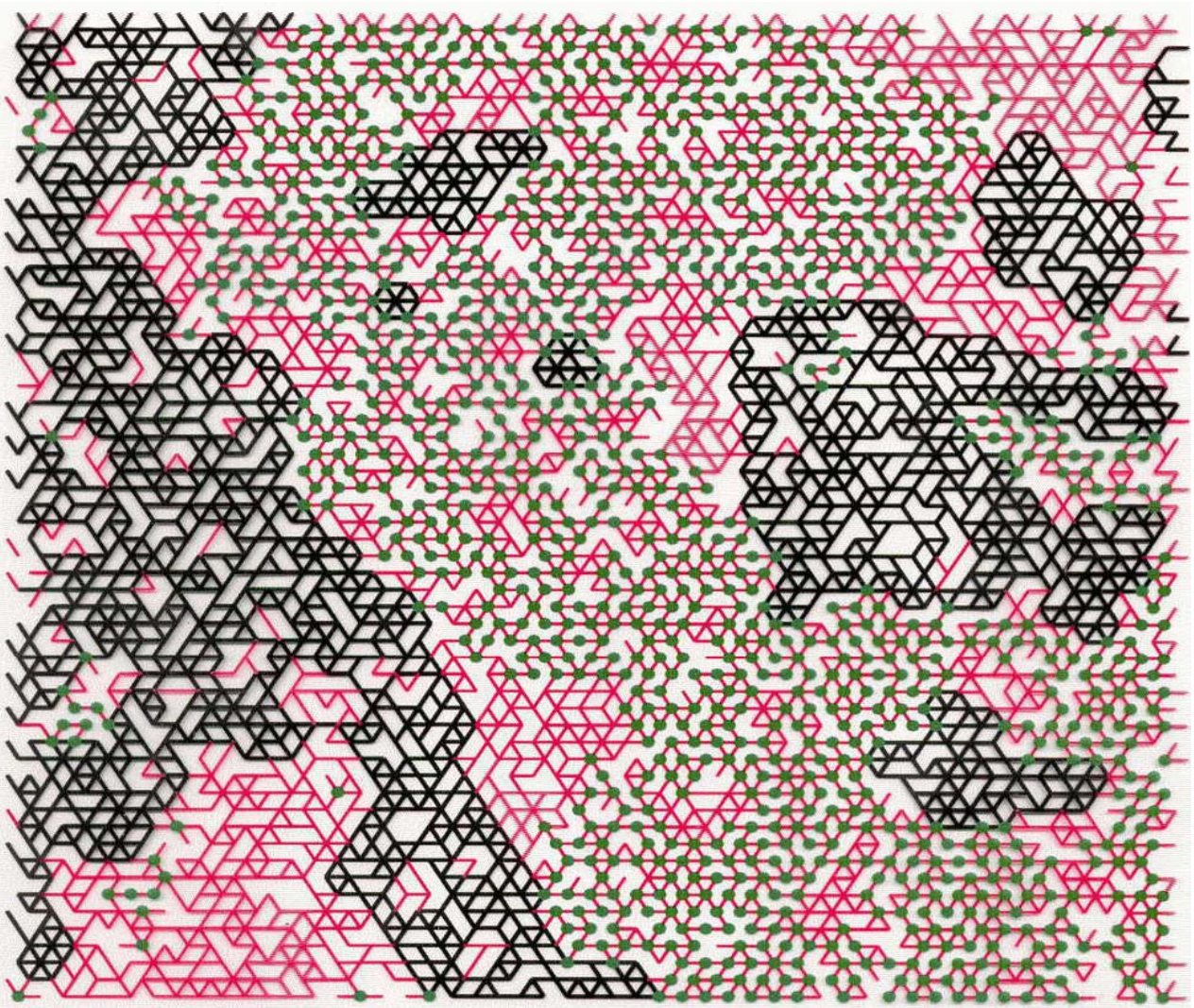
Arizona State University 07/04/06



A typical section from a bond-diluted generic triangular lattice near the rigidity transition. Local distortions are not shown. A bond concentration of 0.66 yields large floppy and rigid regions. Green circles show pivot joints, and the black bonds are stressed.

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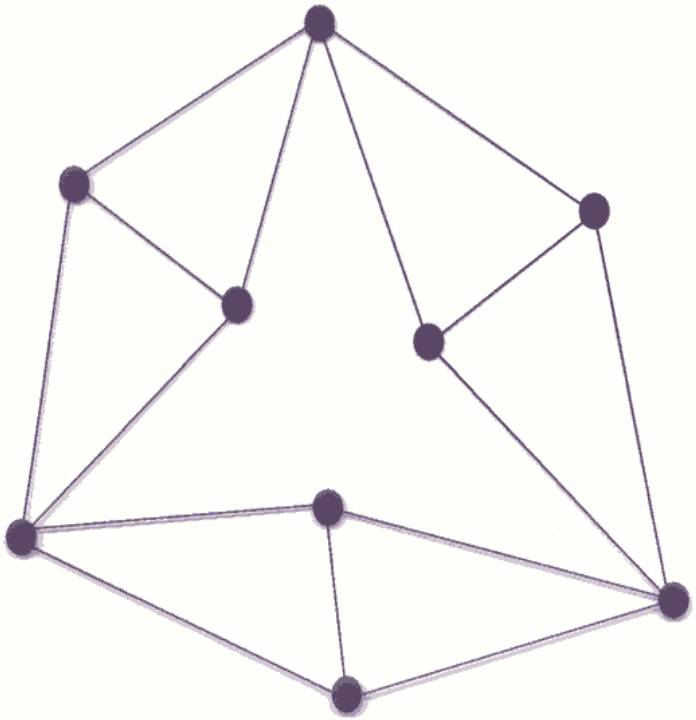
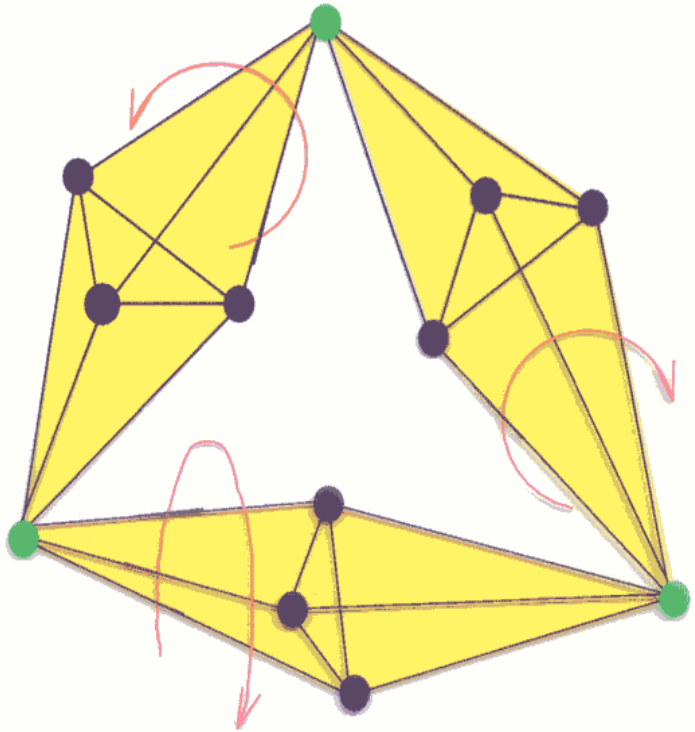
Two Dimensions



One rigid cluster

Three Dimensions



Four rigid clusters

Three internal floppy modes

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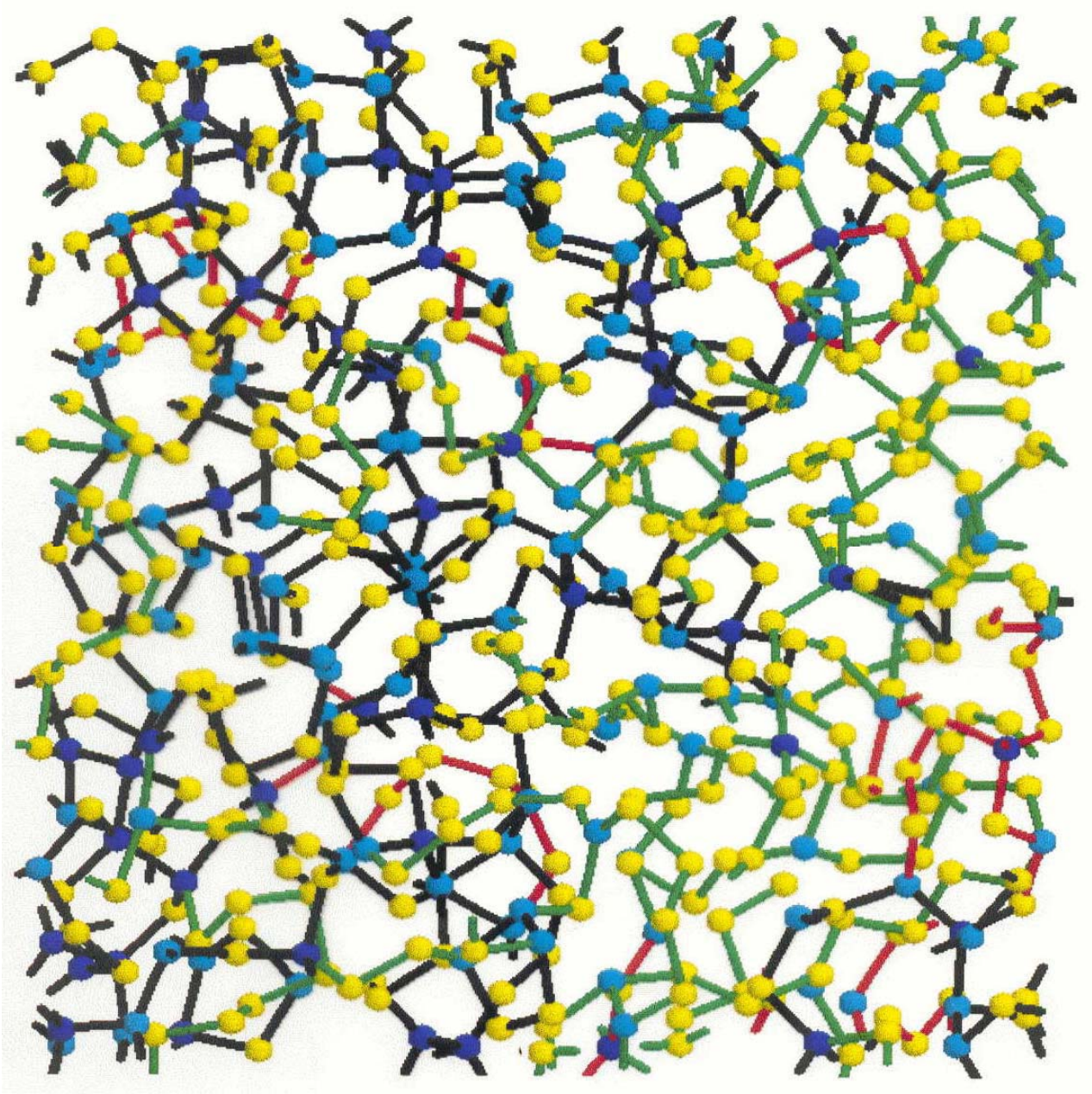

GeAsSe glass with $< r >= 2.4$

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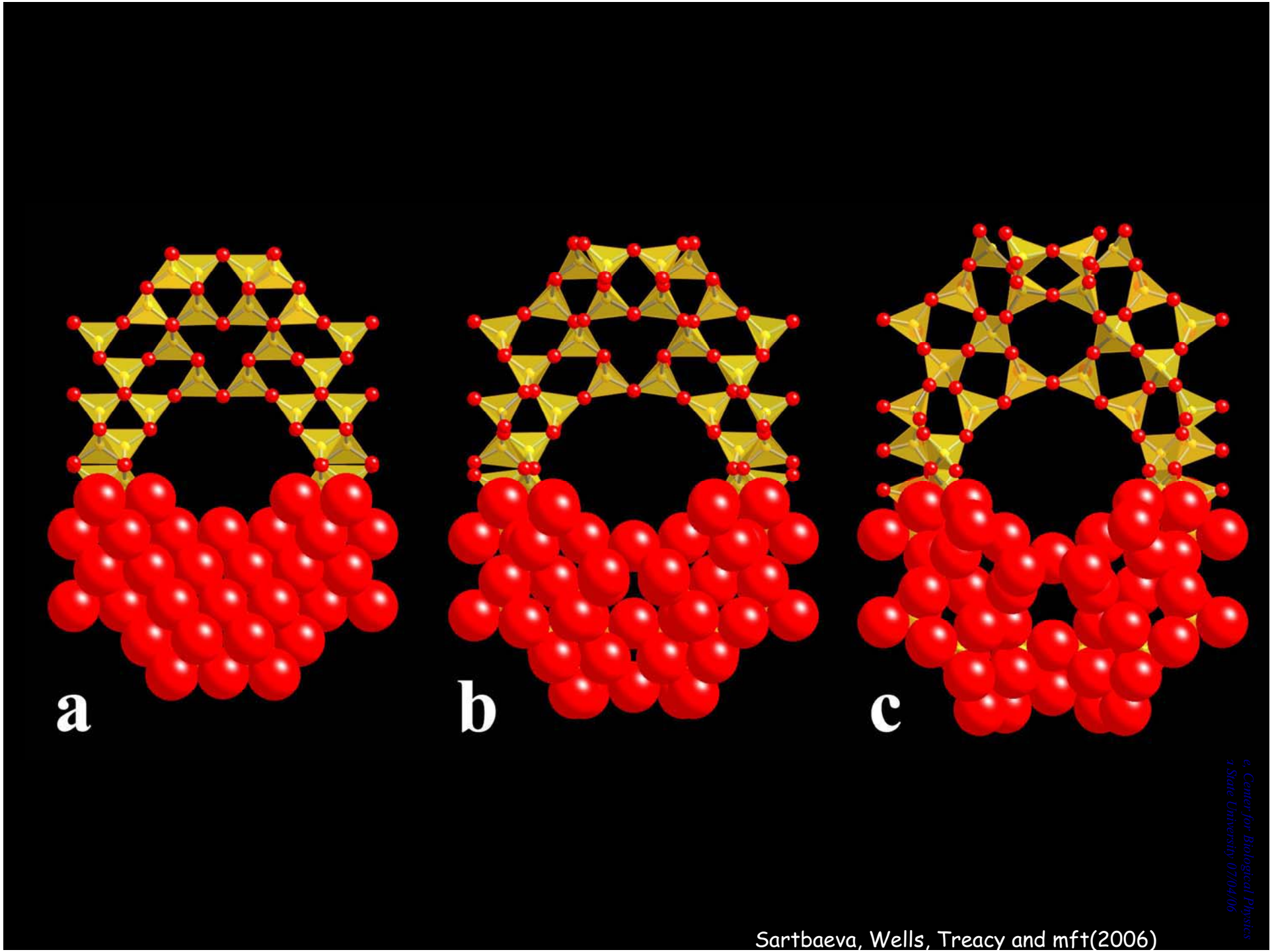
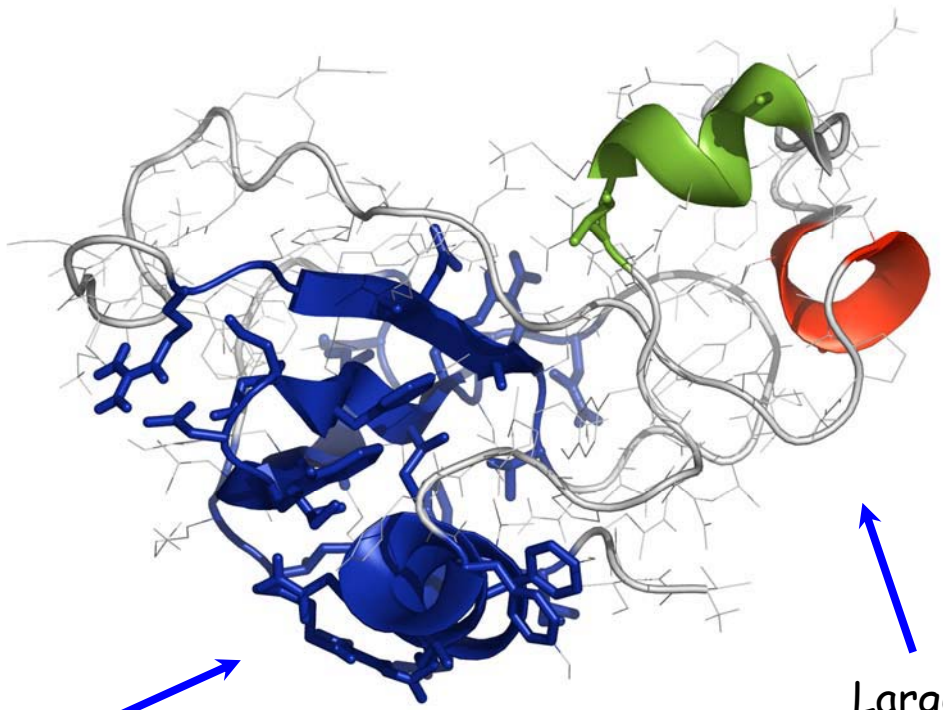

a
b
c
Sartbaeva, Wells, Treacy and mft(2006)
c Center for Biological Physics
Arizona State University 07/04/06

Rigid cluster decomposition of barnase

Flexible region composed of small mobile rigid clusters.



Large mobile rigid cluster.

Rigid core (immobile in simulations).

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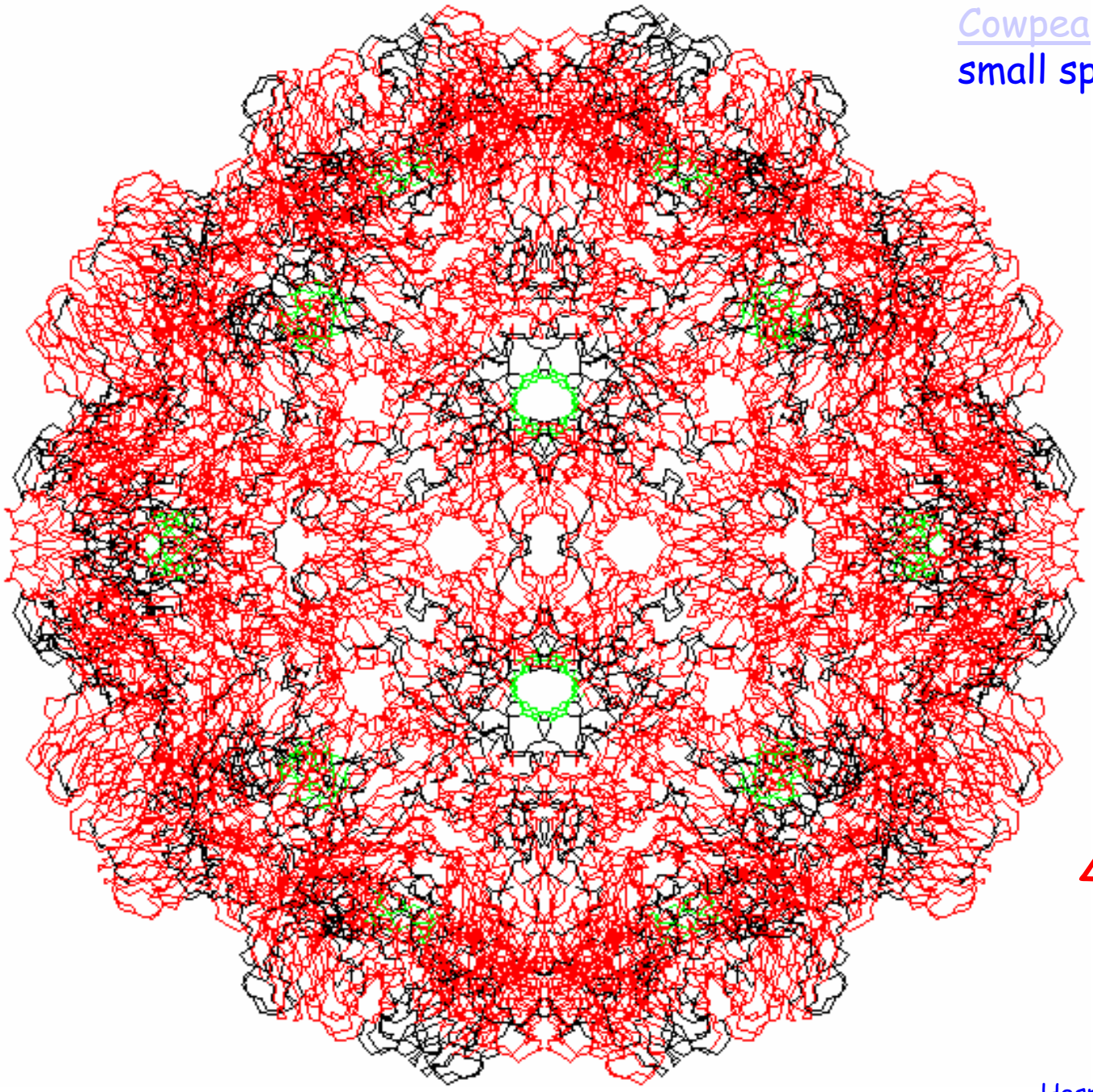

Cowpea Chlorotic Mottle Virus
small spherical plant virus

430,000 atoms

Hespenheide/Douglas/mft 2004

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Arizona State University 07/04/06

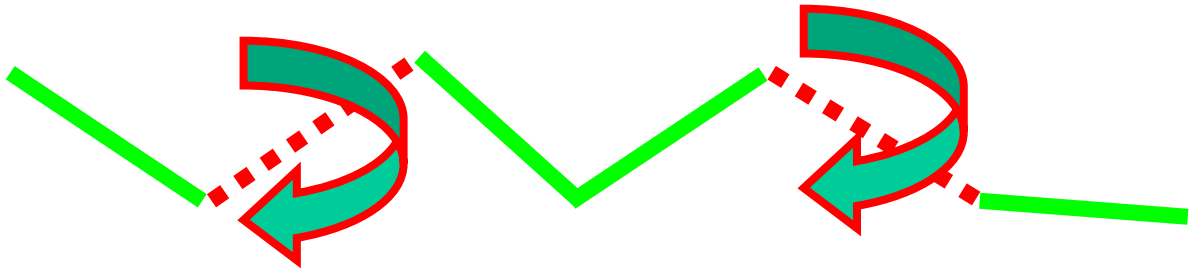
Geometrical Simulation

- *FRODA* (***F***ramework ***R***igidity ***O***ptimized ***D***ynamics ***A***lgorithm)

Stephen Wells

Mike Thorpe, Center for Biological Physics
Arizona State University 07/04/06

Rigid clusters as templates for motion



… templates overlap at hinges.

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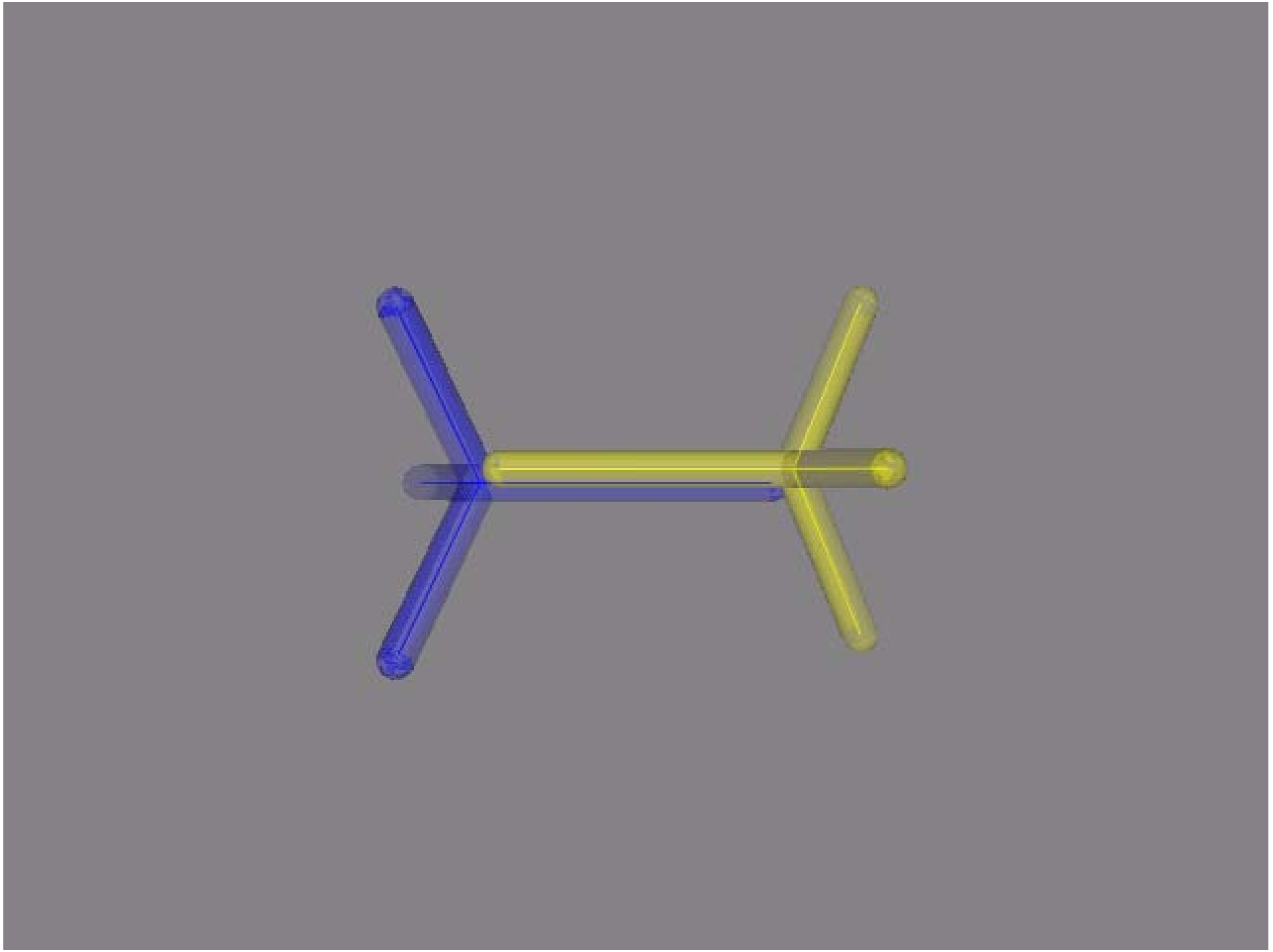
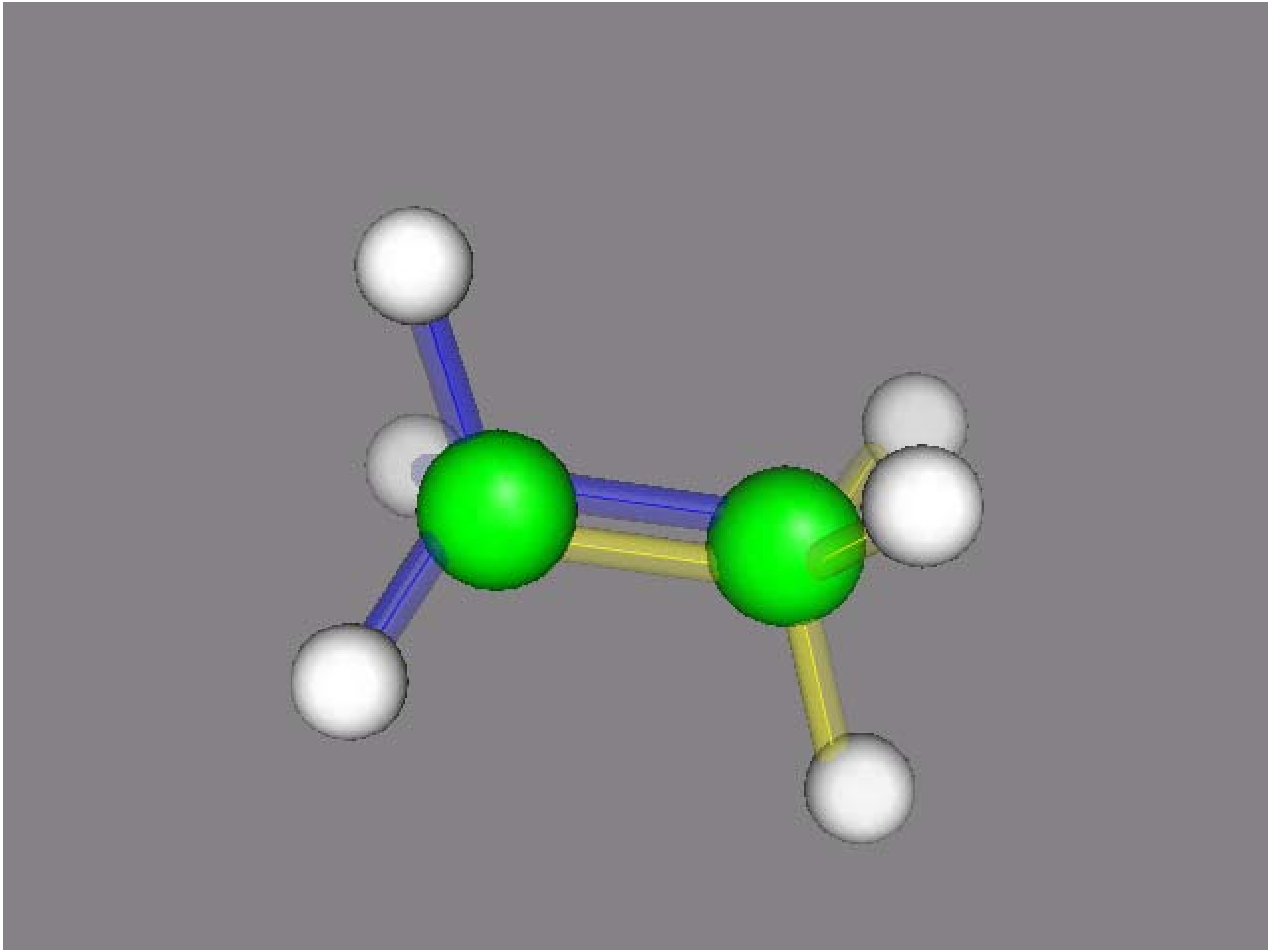
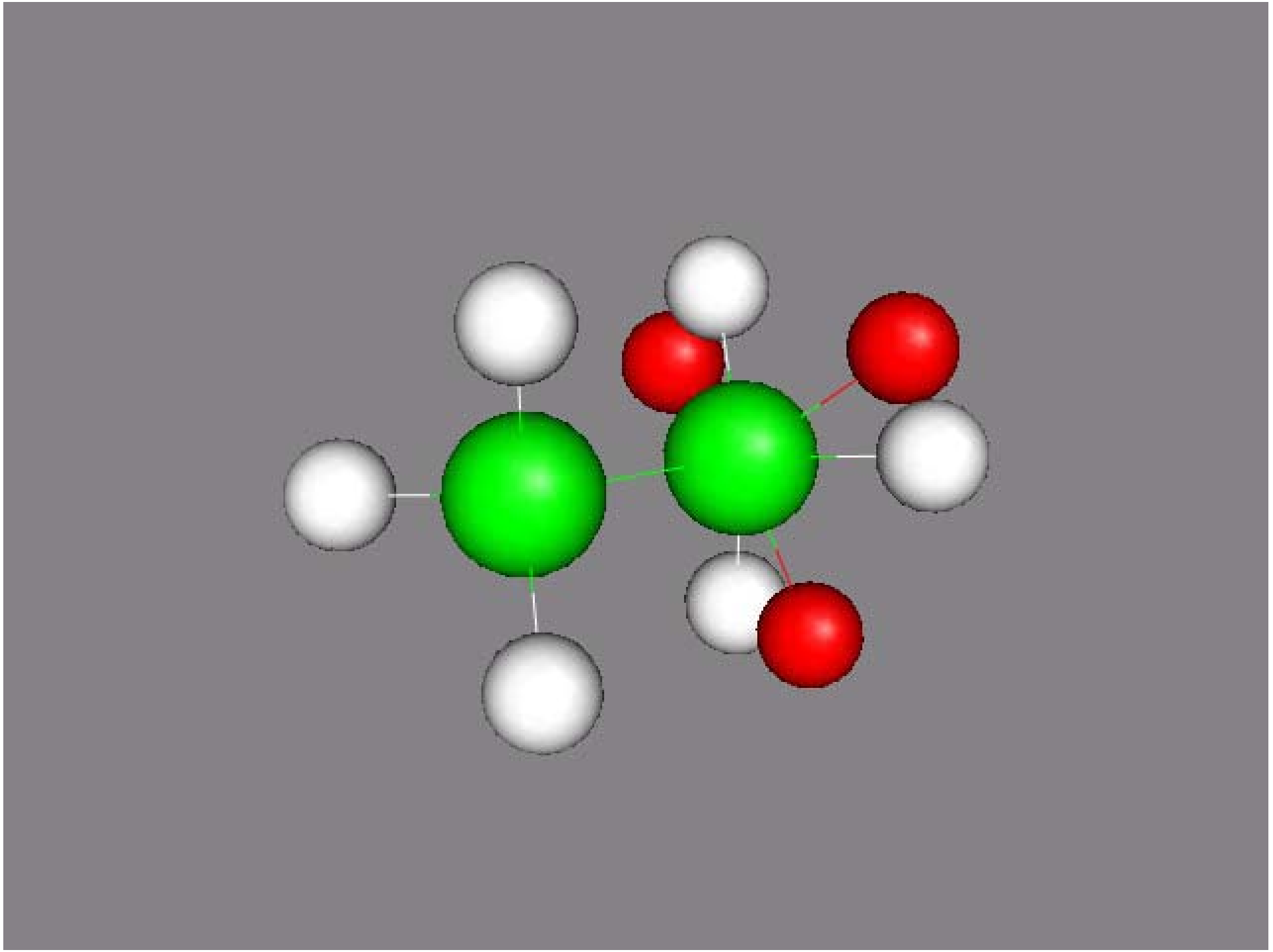


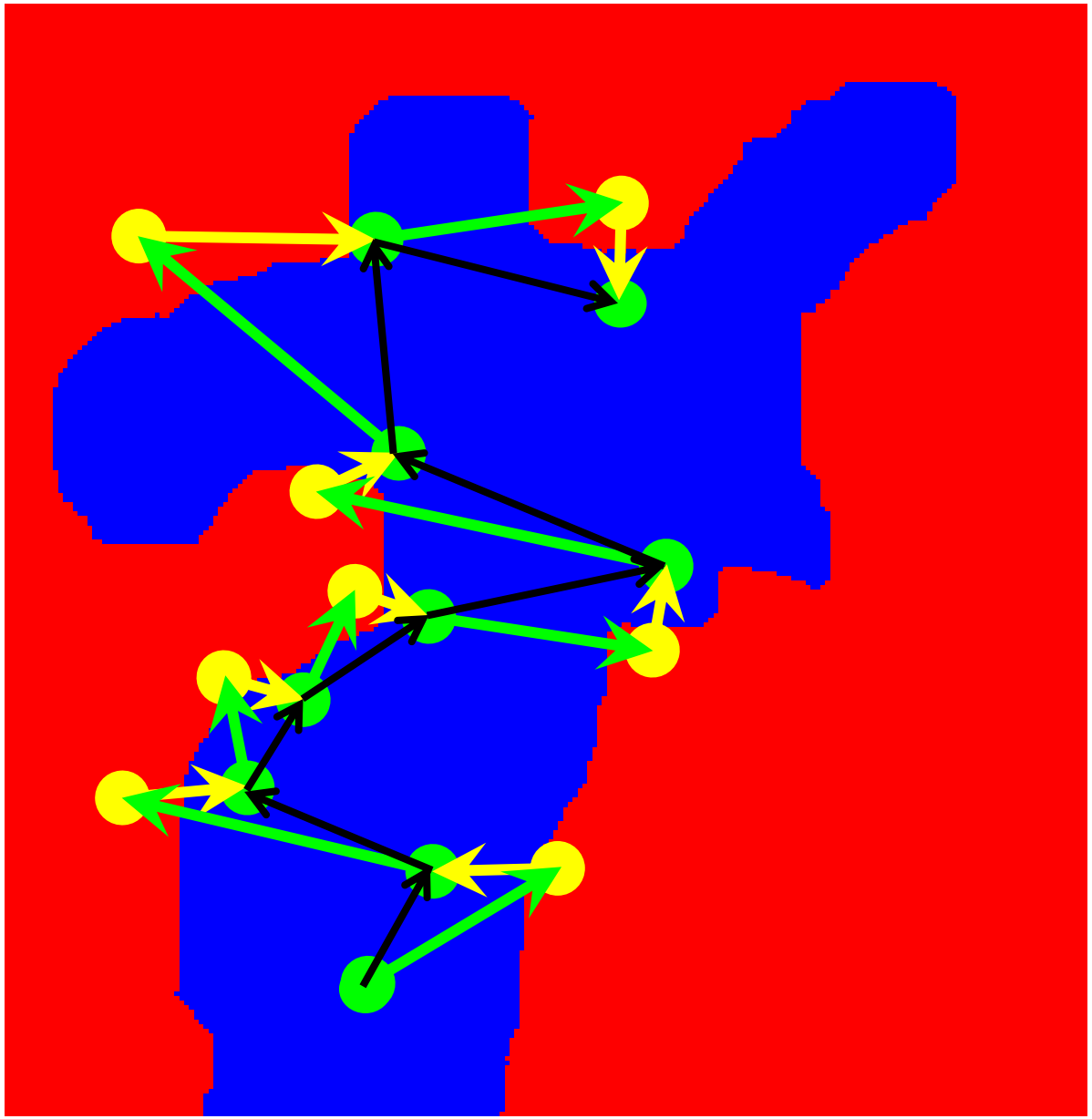




Monte Carlo search with geometric simulation

Red regions are forbidden

Blue regions are accessible.



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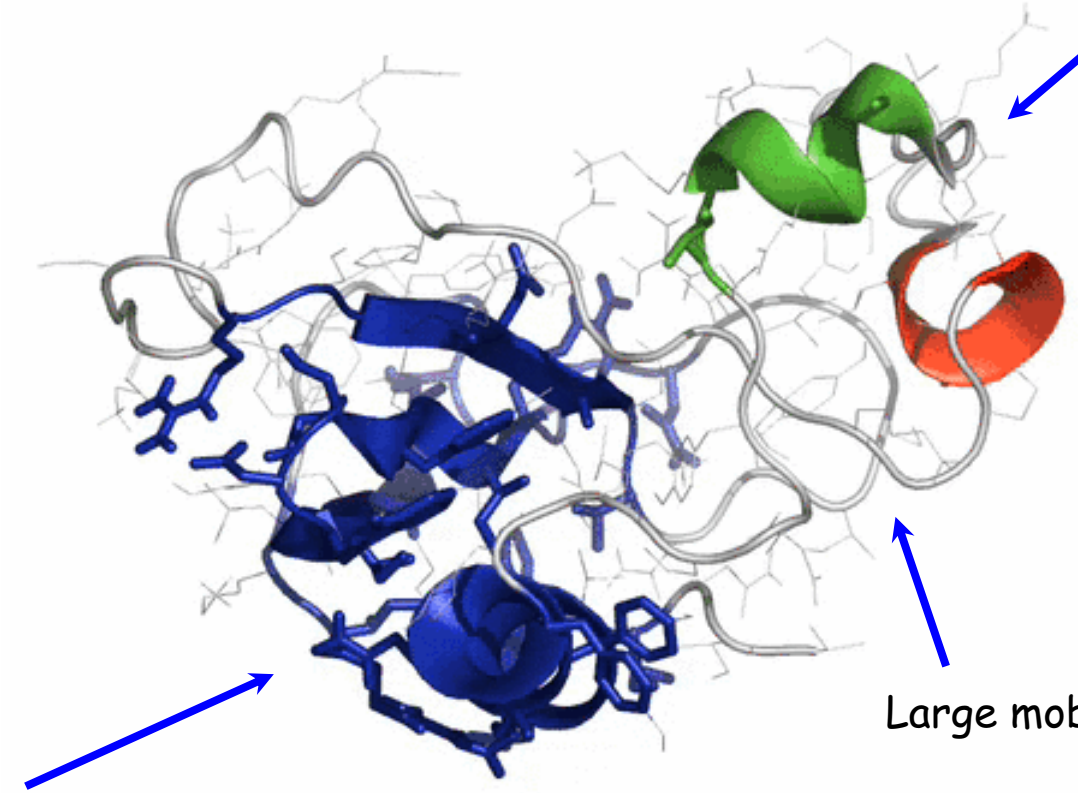
barnase

Flexible region composed of small mobile rigid clusters.



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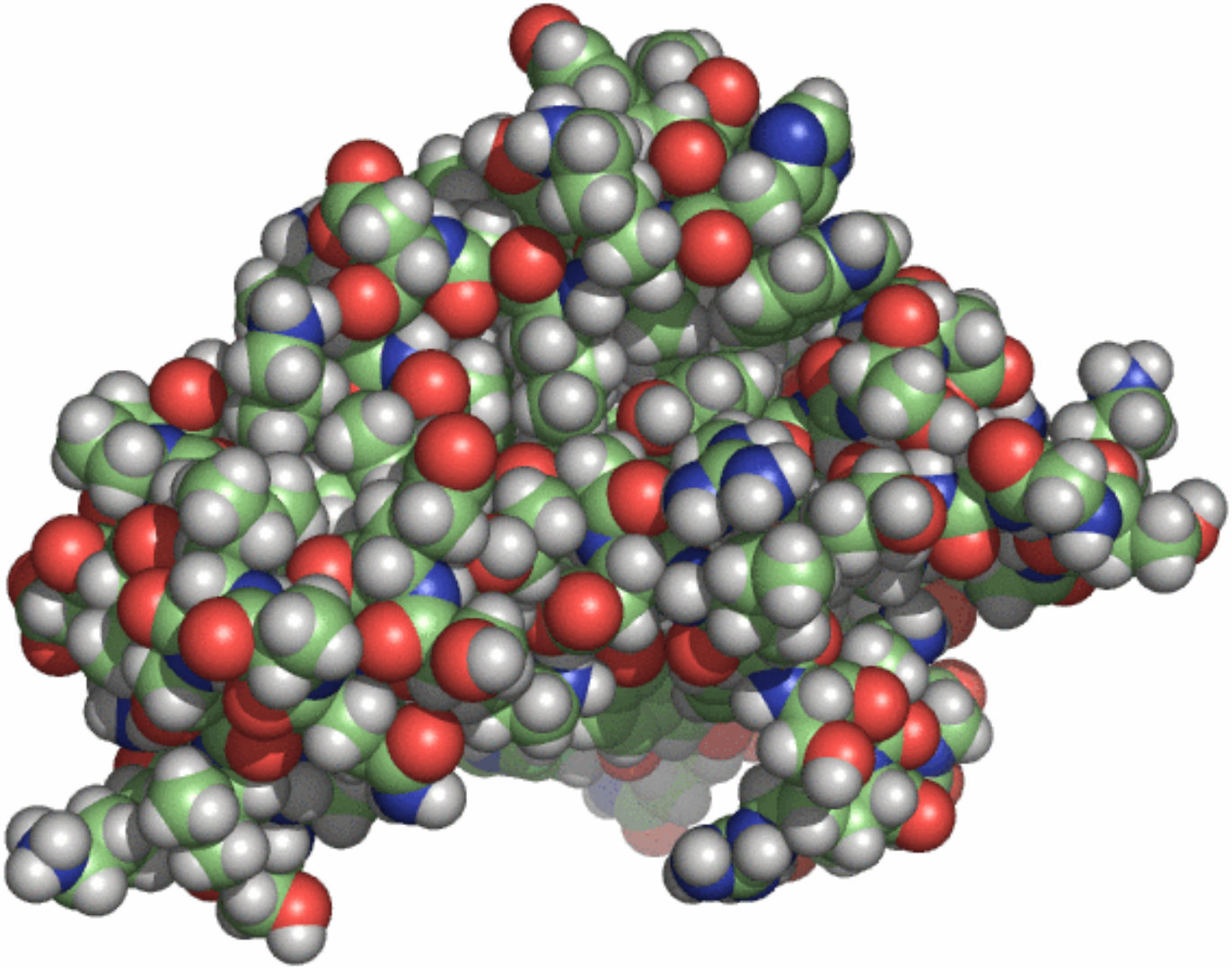
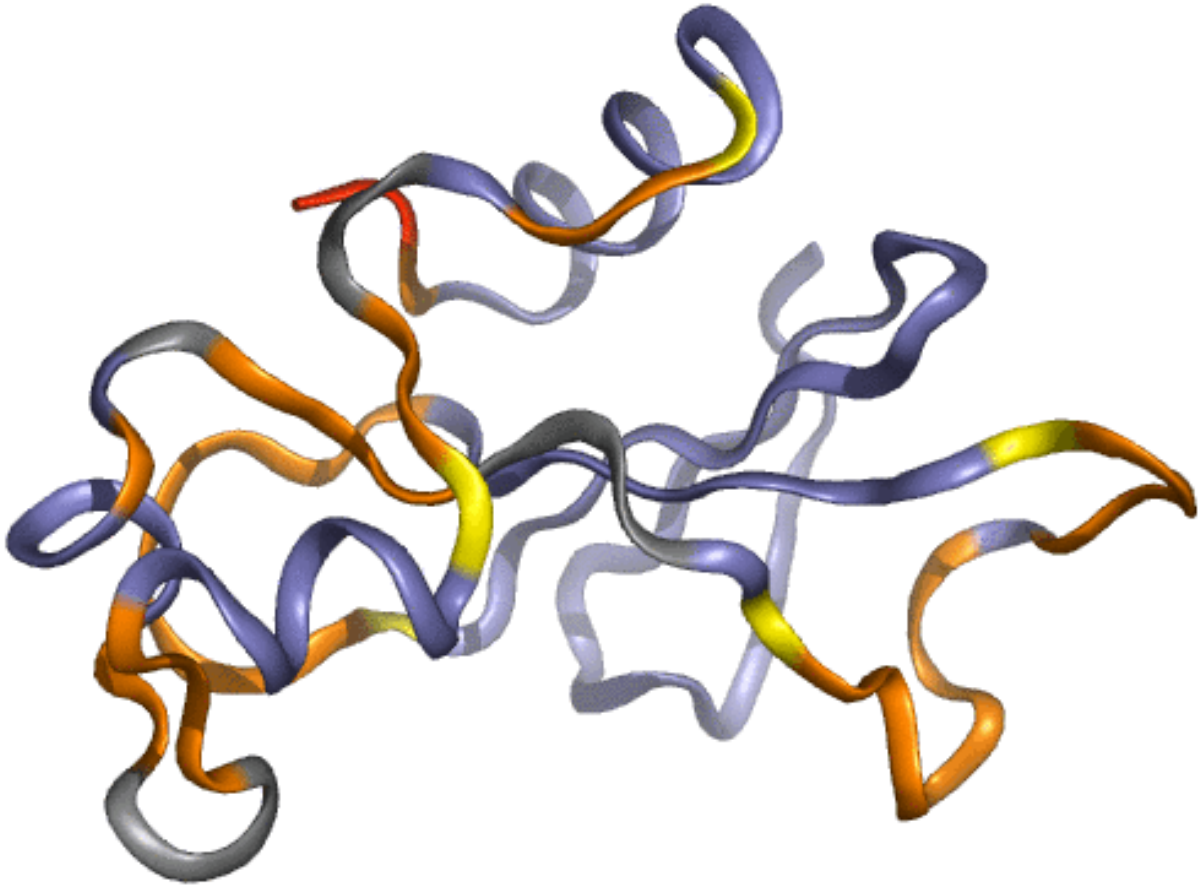
Barnase



Barnase



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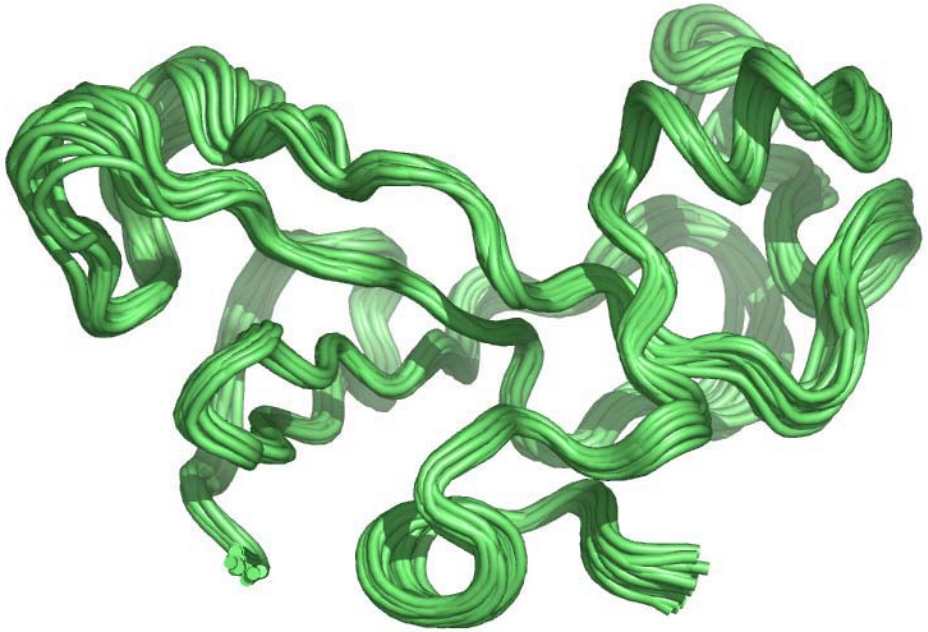
FRODA

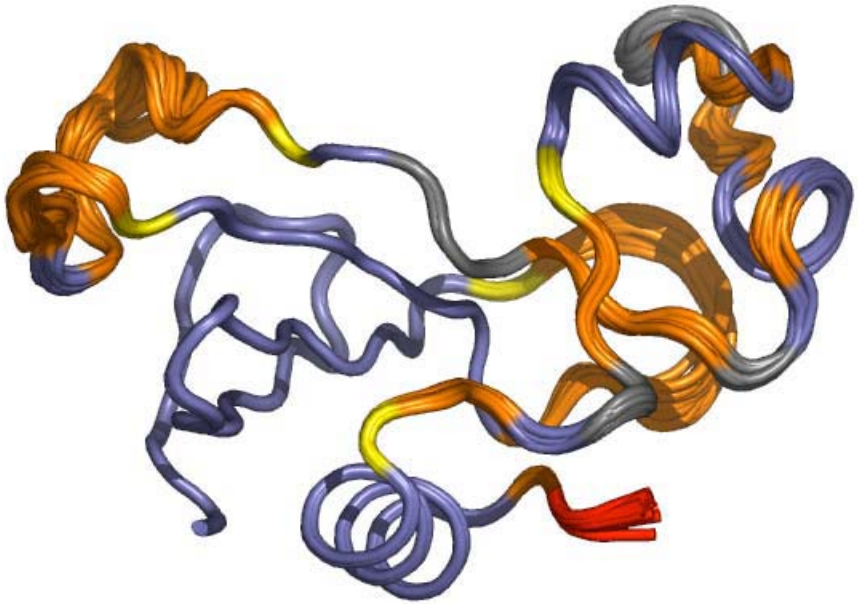
- Maintain constraints at each step (covalent, hydrophobic and hydrogen bonds)
- Rigid clusters stay rigid
- Avoid van der Waals clashes
- Ramachandran constraints obeyed
- Side groups mobile

Barnase

NMR

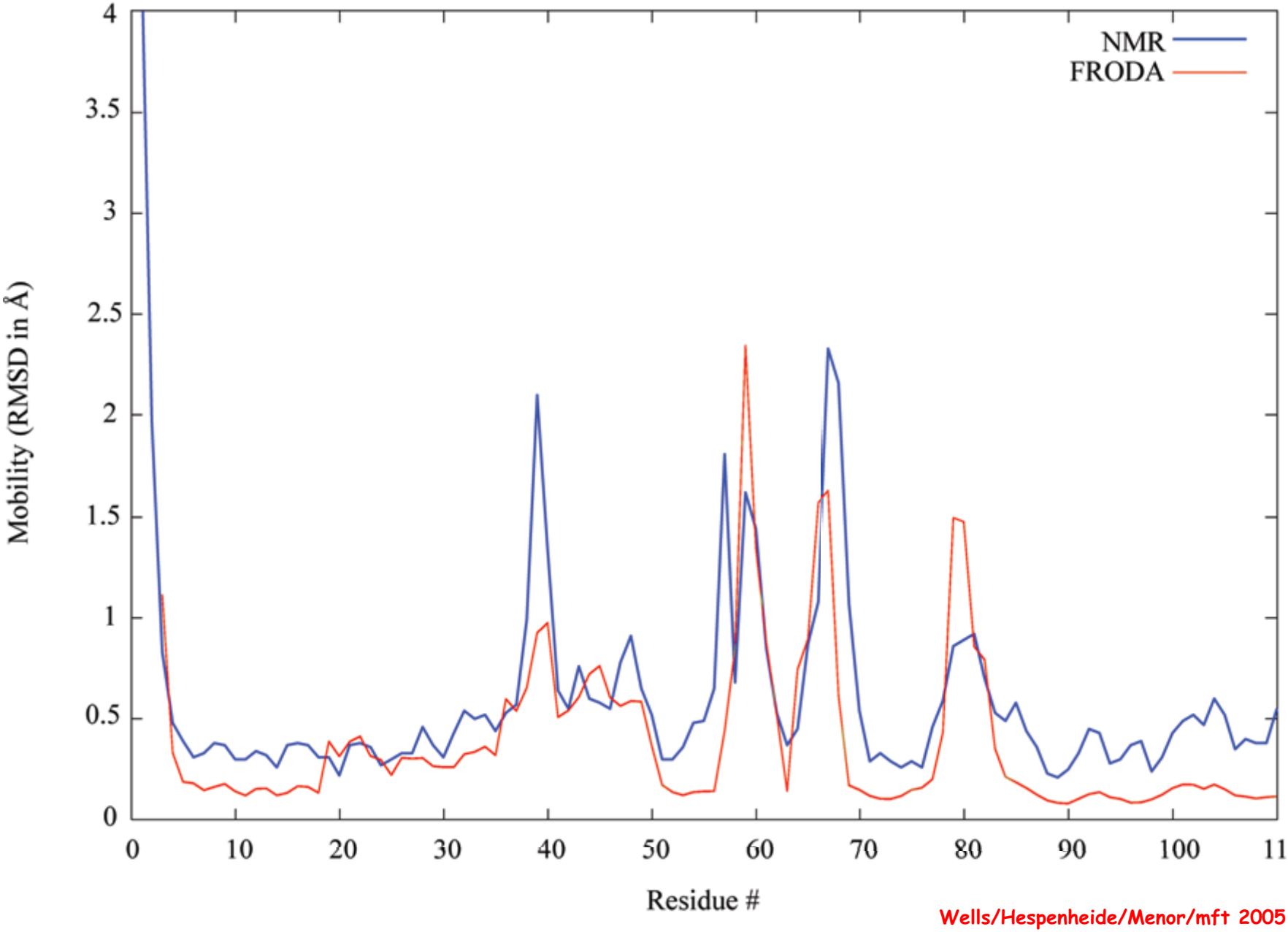


X-ray + FRODA



Wells/Hespenheide/Menor/mft 2005

Barnase



Wells/Hespenheide/Menor/mft 2005

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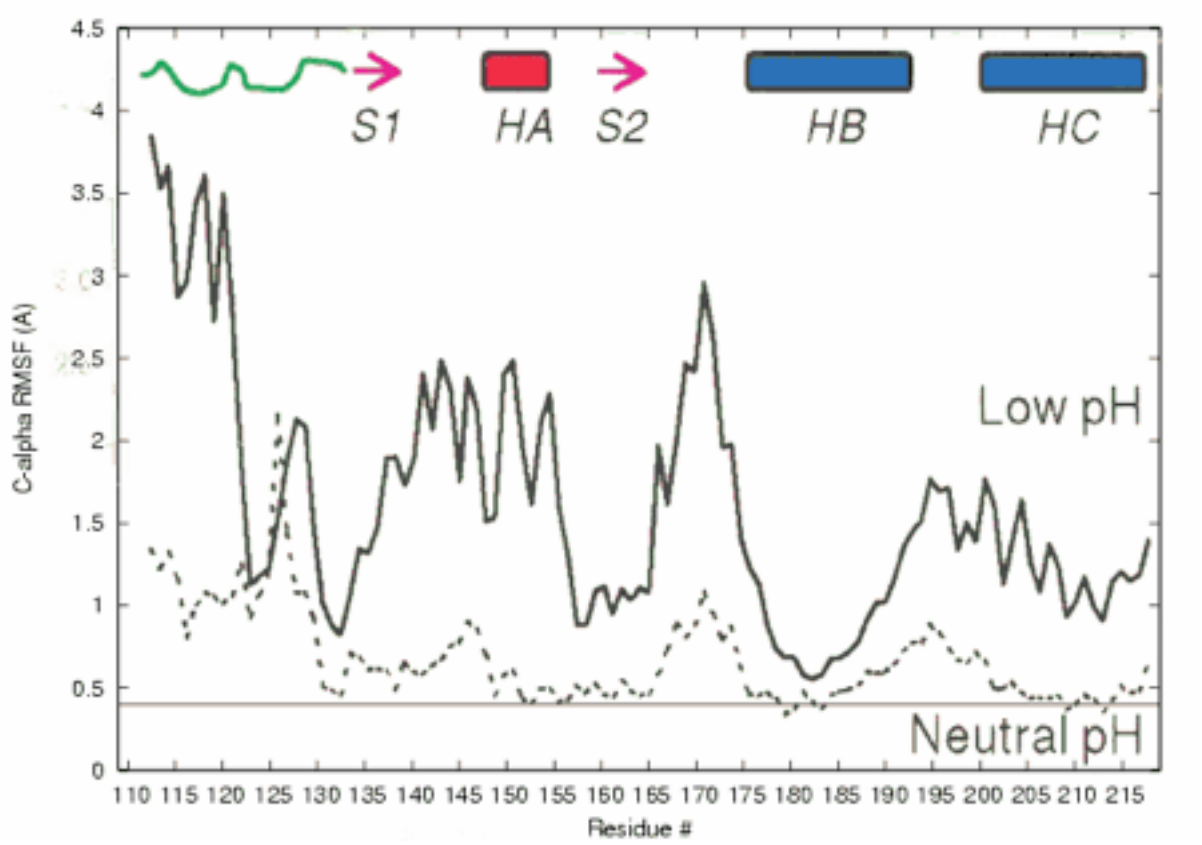
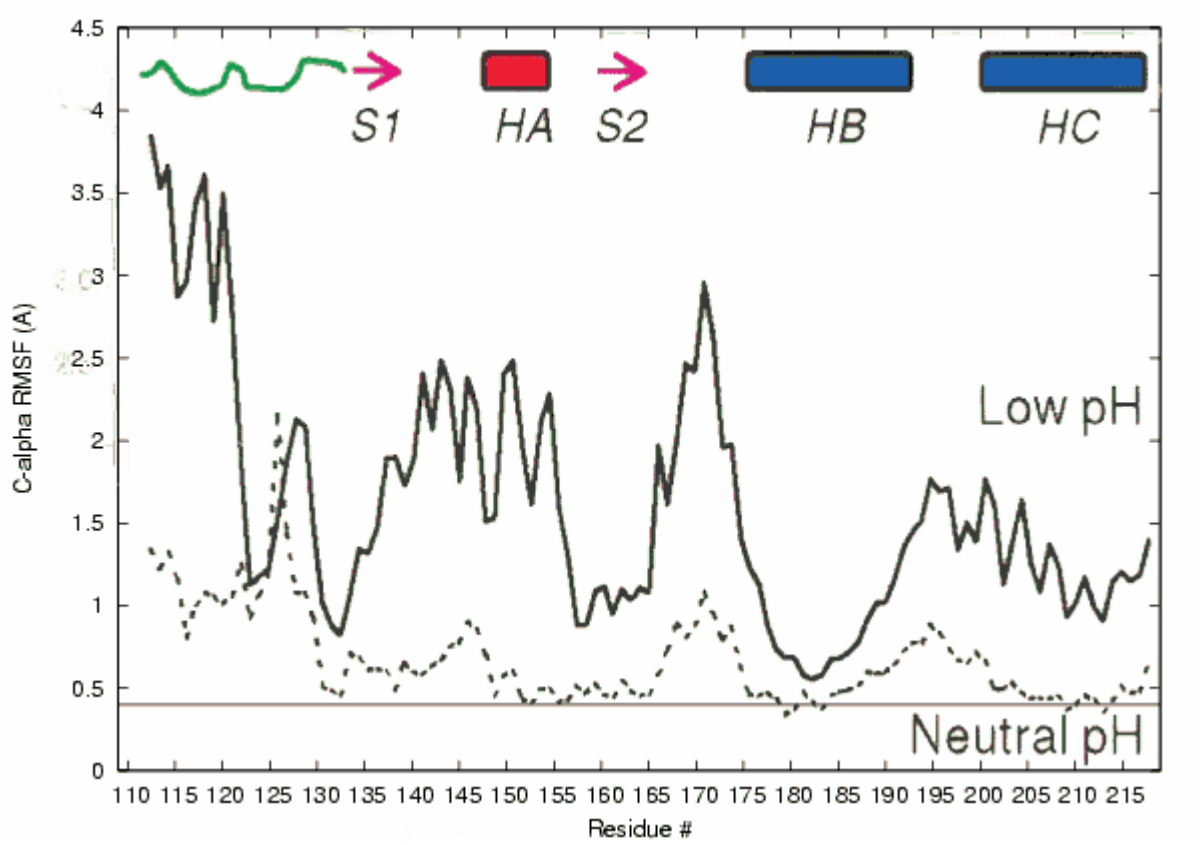
Growth of FRODA mobility, low pH



Alonso D O, DeArmond S J, Cohen F E and Daggett V 2001 *Proc Natl Acad Sci U S A* **98** 2985-9

Growth of FRODA mobility, low pH



Alonso D O, DeArmond S J, Cohen F E and Daggett V 2001 *Proc Natl Acad Sci U S A* **98** 2985-9

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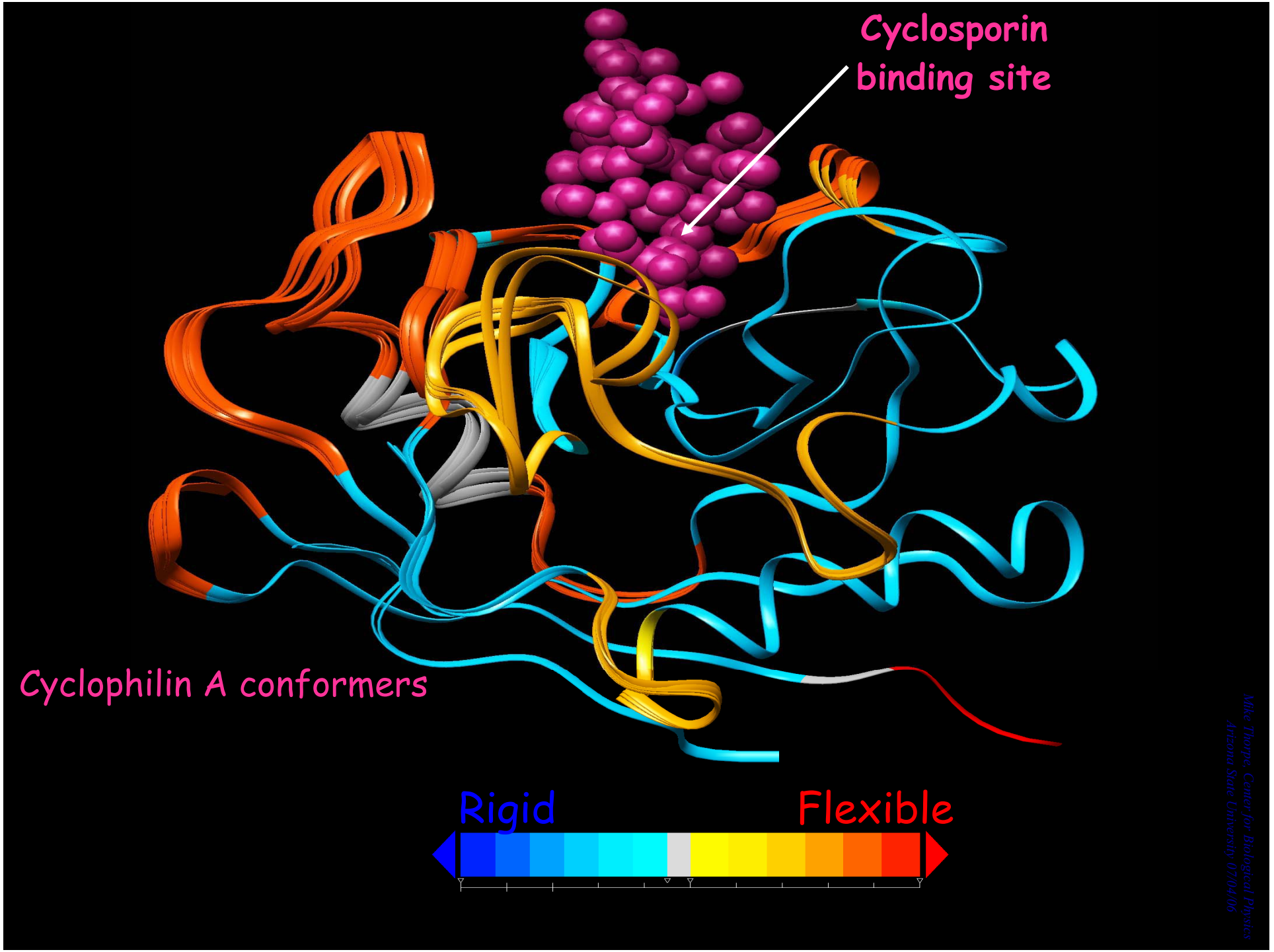
Cyclosporin
binding site
Cyclophilin A conformers
Rigid
Flexible
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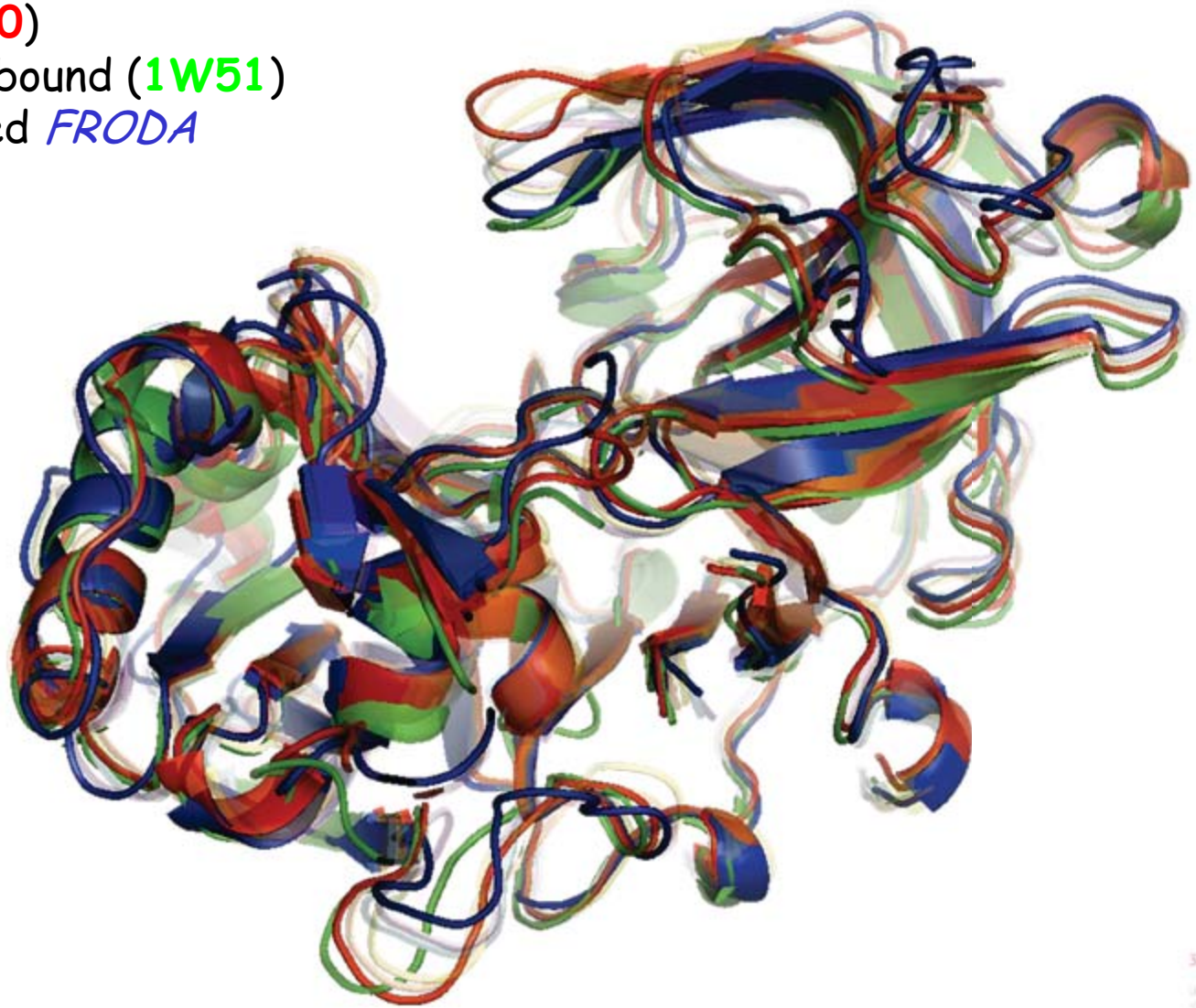
Arizona State University 07/04/06

Beta-secretase

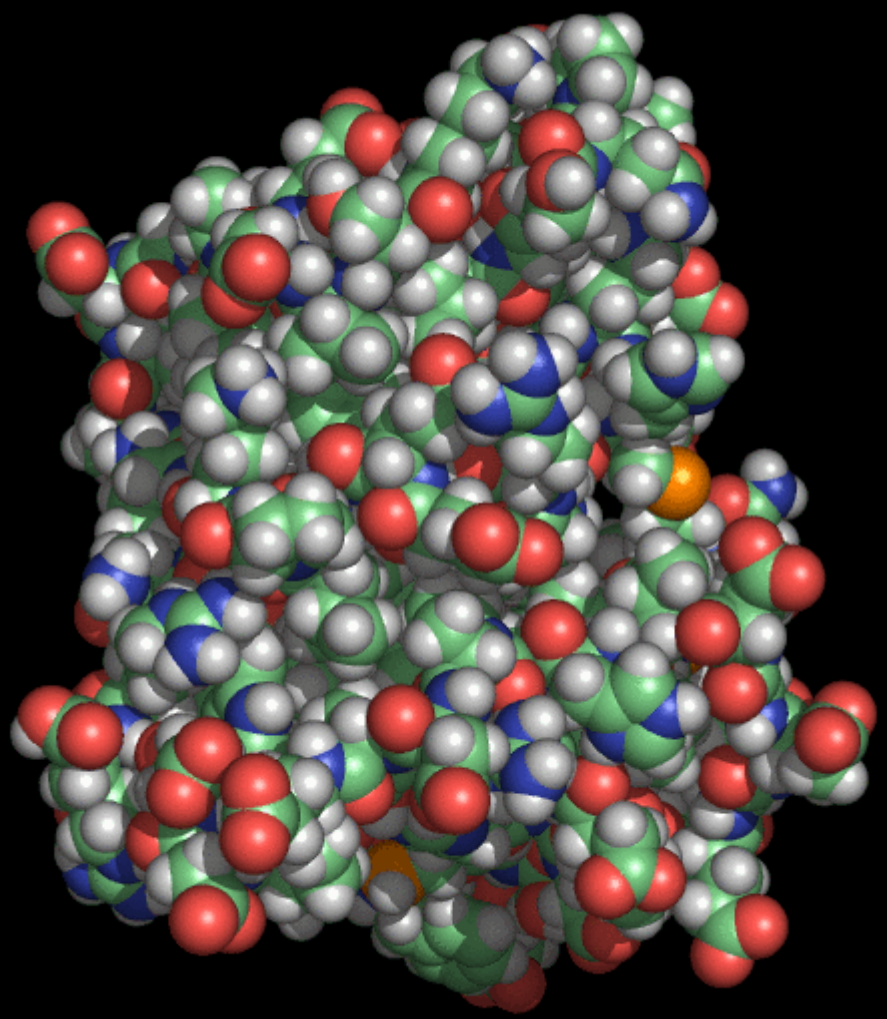
apo (1W50)
inhibitor-bound (1W51)
Undirected *FRODA*



Wells, 2006

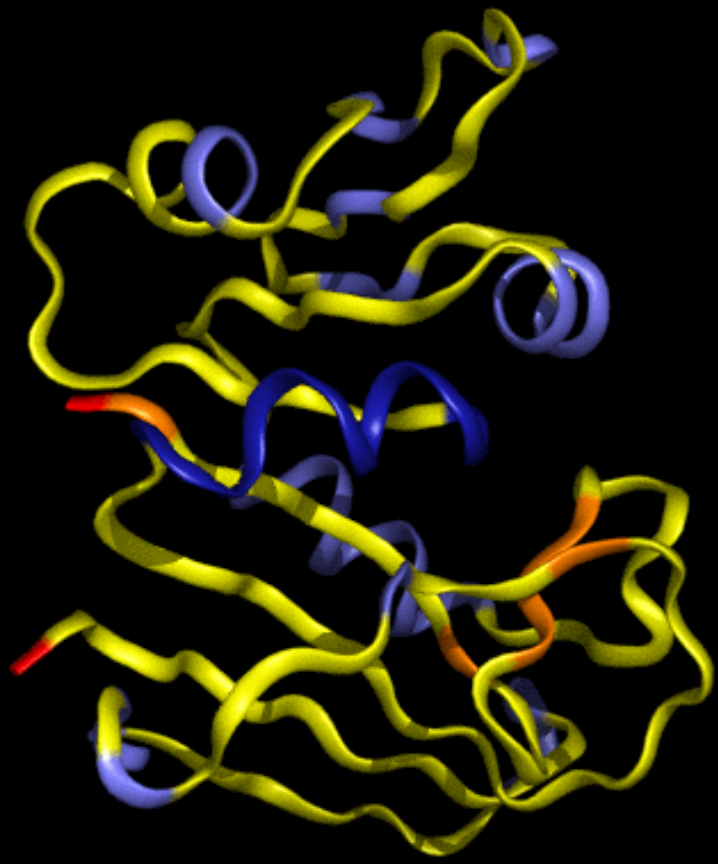
Directed dynamics

DHFR

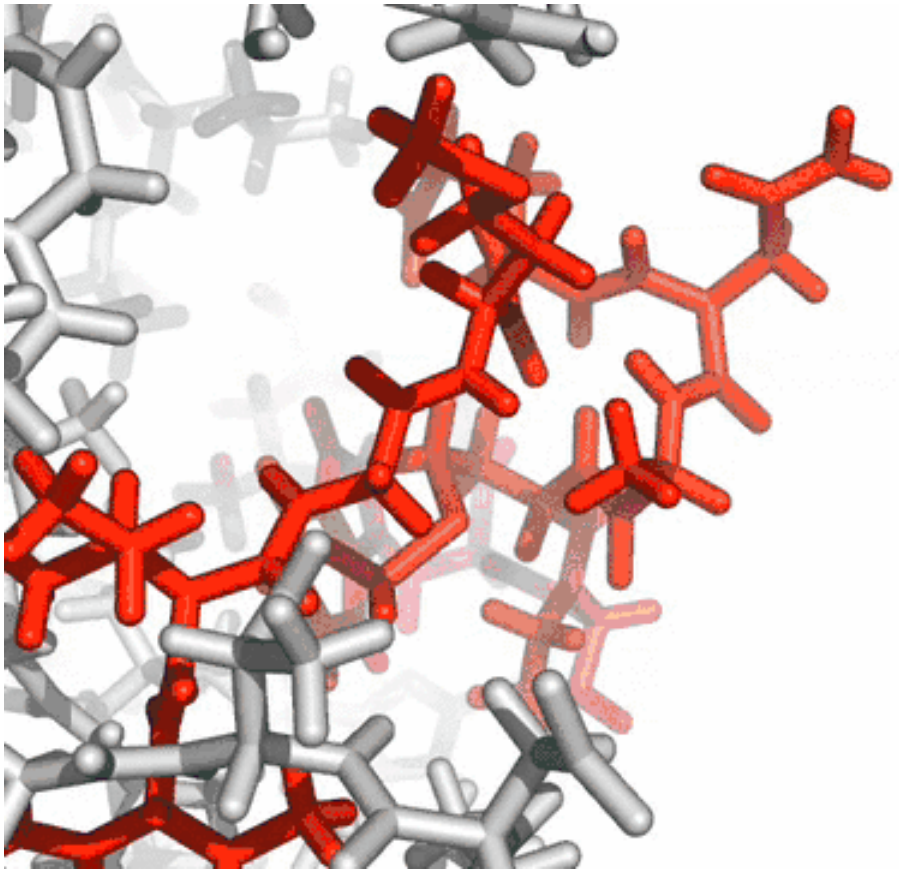


Directed dynamics

DHFR



Directed dynamics
DHFR



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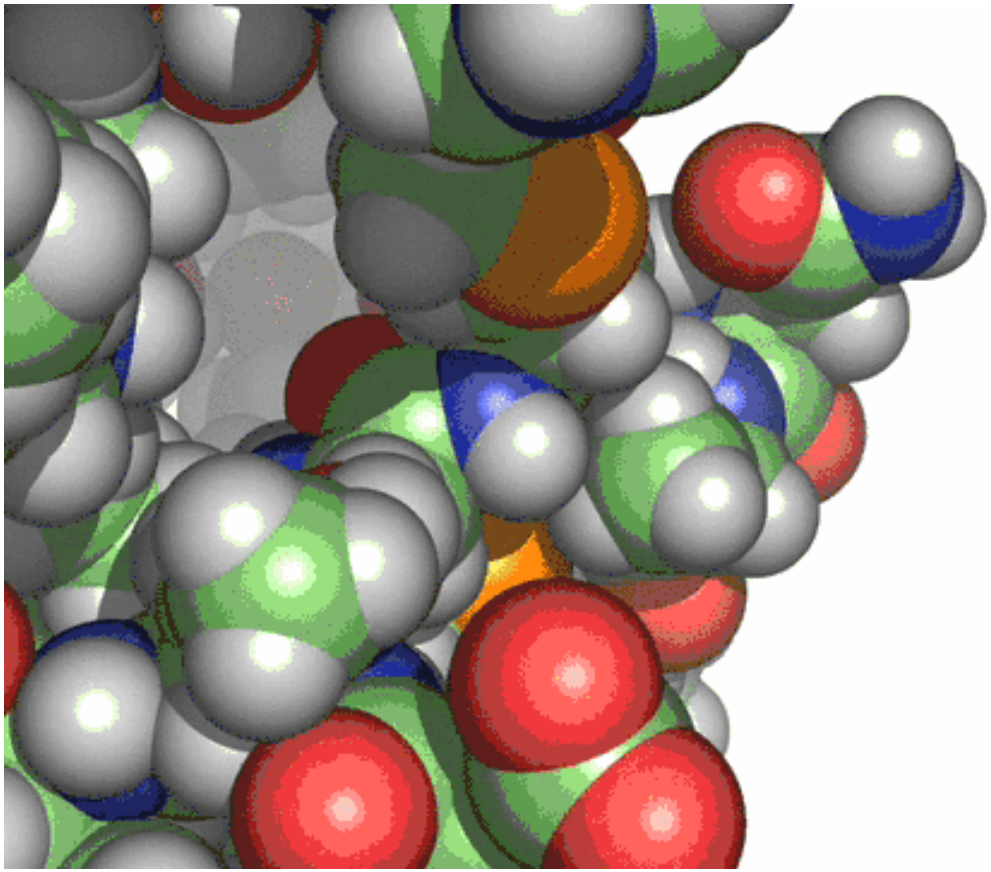
Directed dynamics
DHFR



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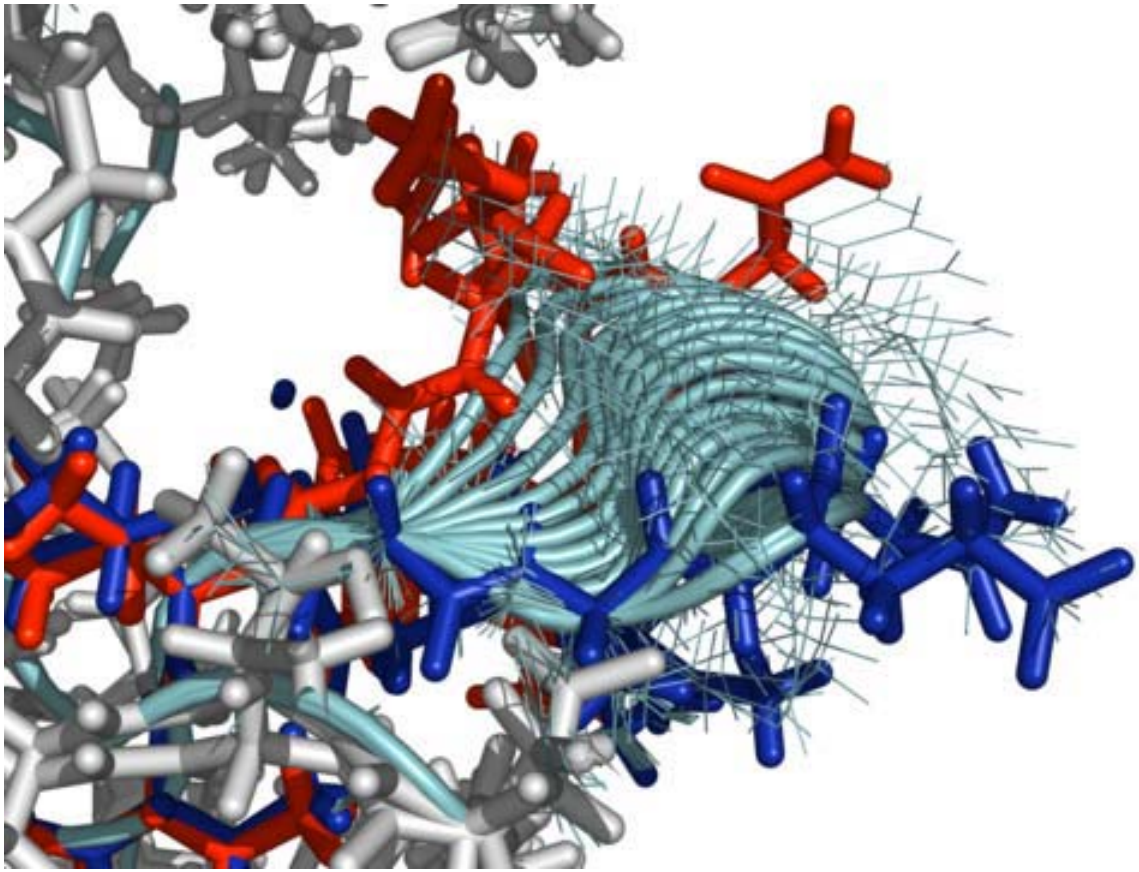
Directed dynamics
DHFR



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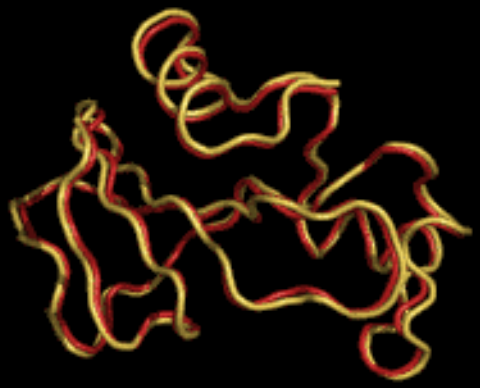
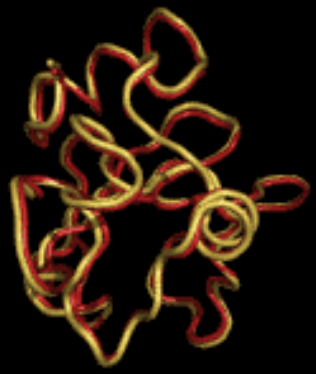
Barnase
"exploded"





Hespenheide 2005

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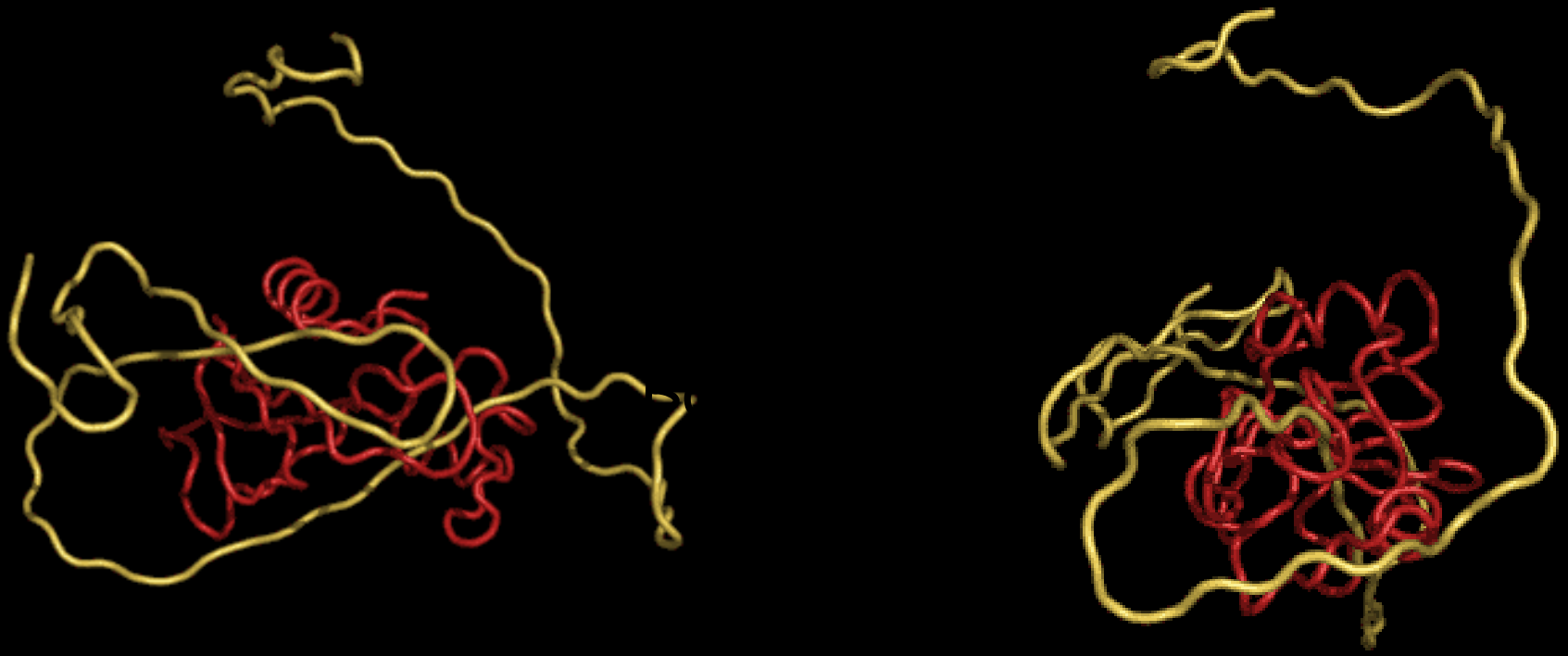
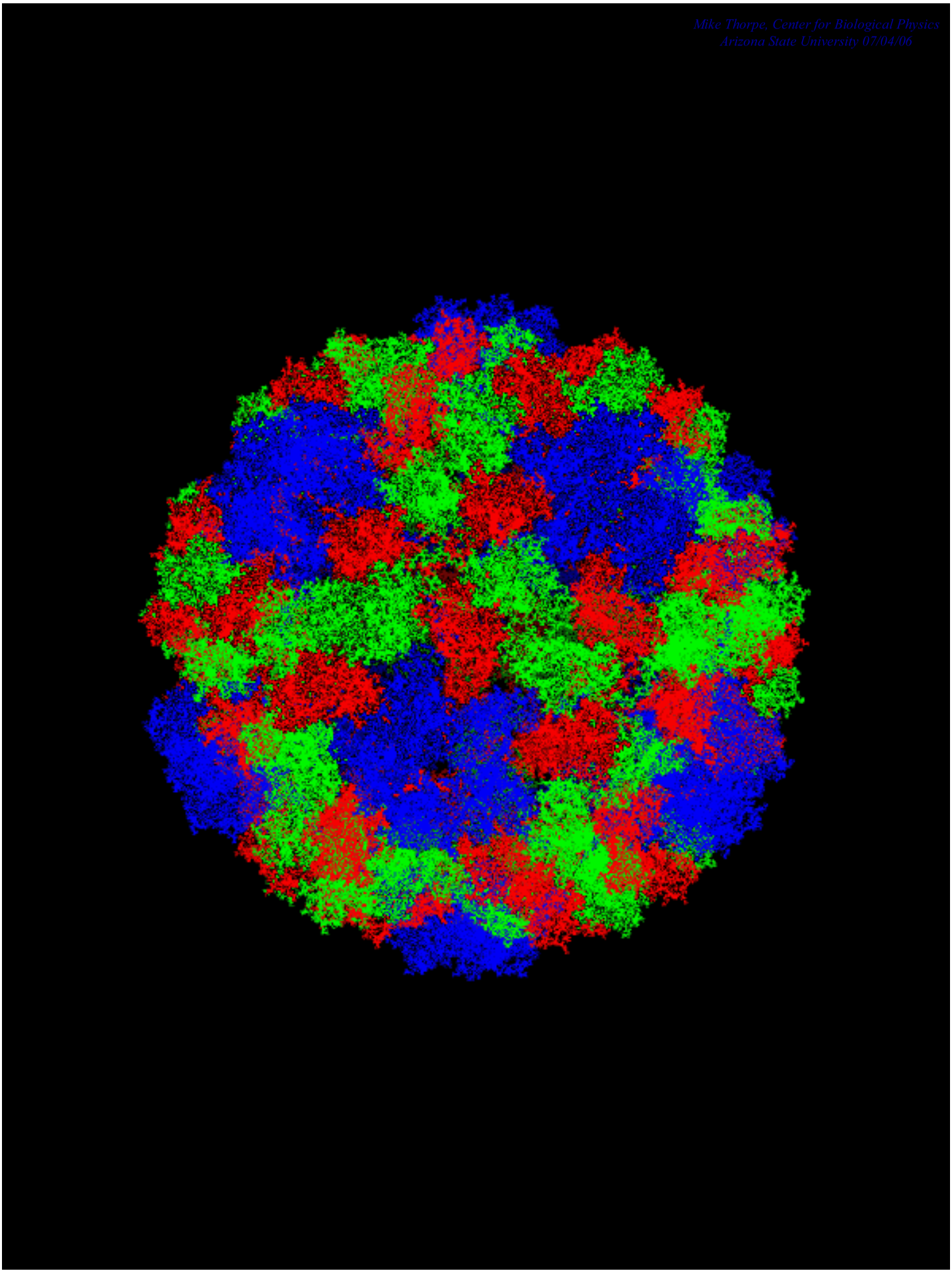
Arizona State University 07/04/06

Barnase
refolded



Hespenheide 2005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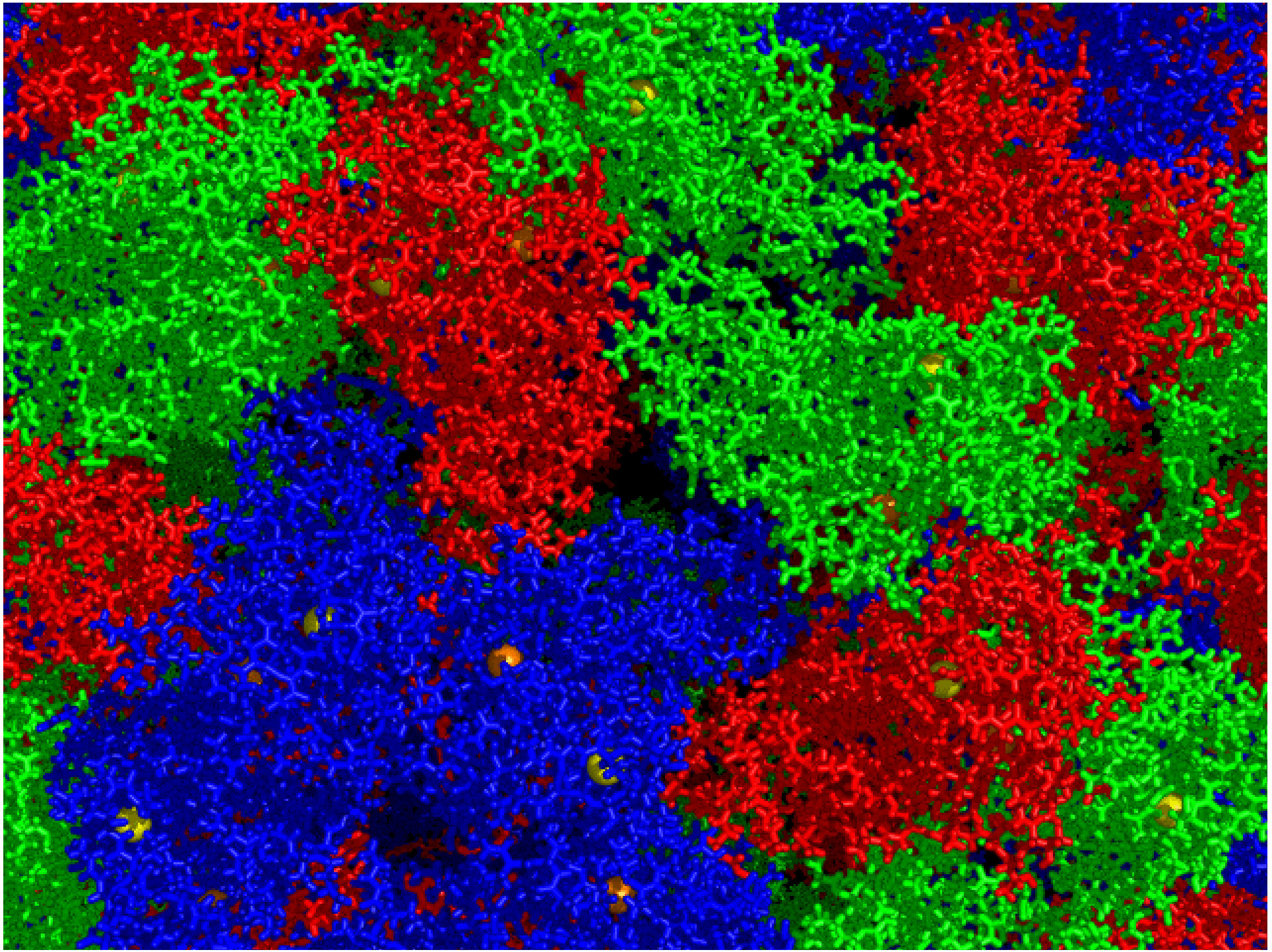
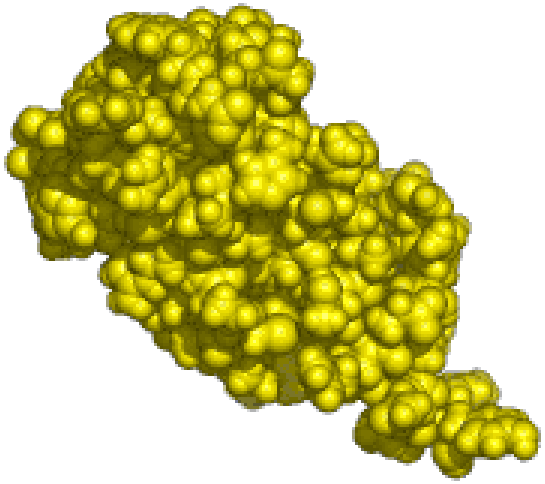
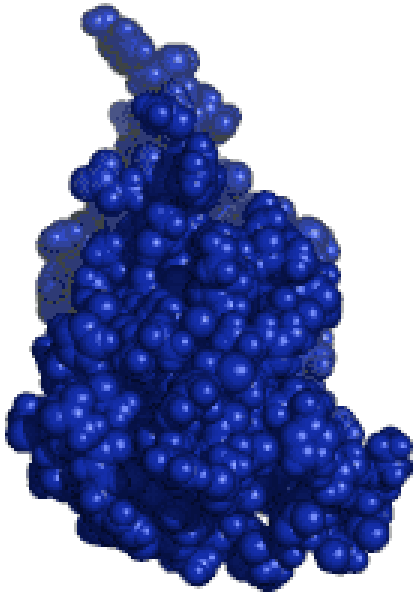


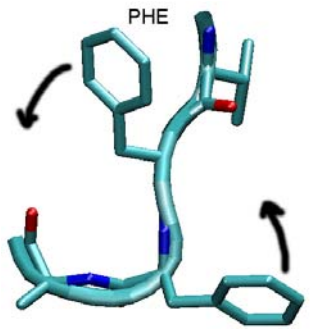




From Joan-Emma Shea

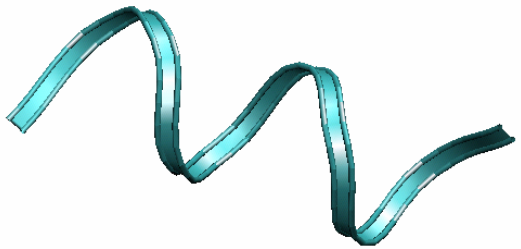
Time scales

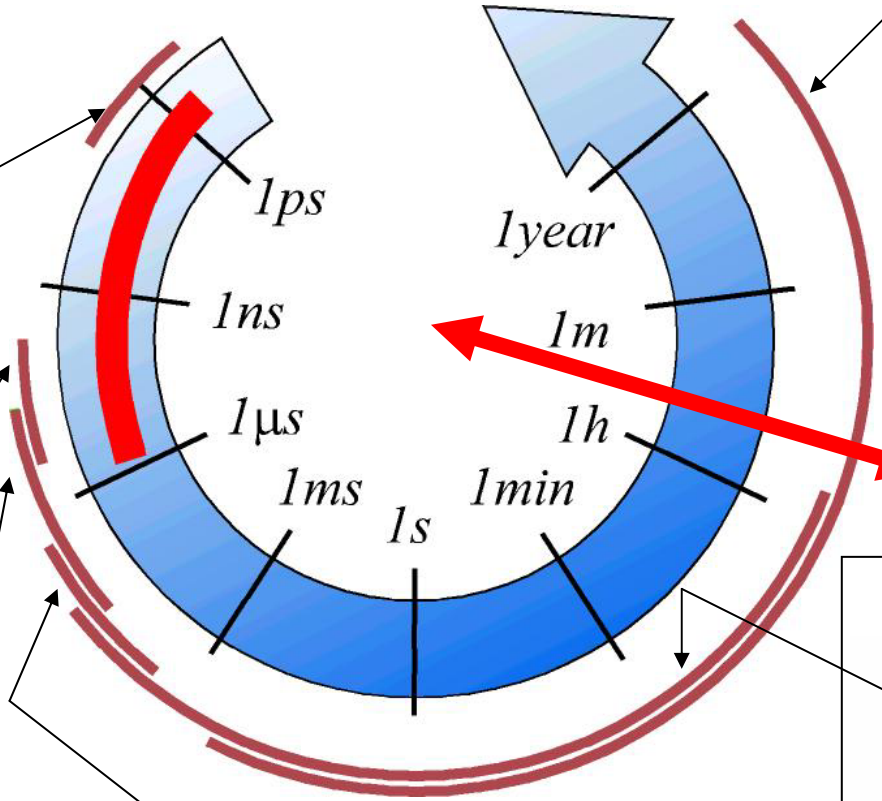
Side-chain rotations



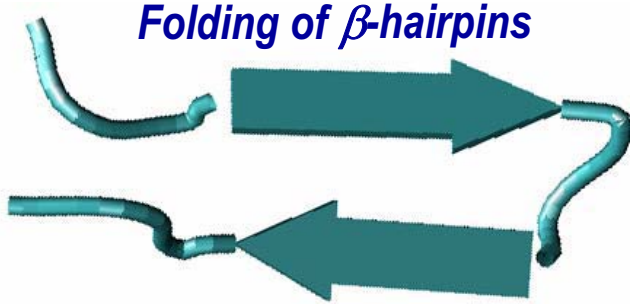
Loop closure

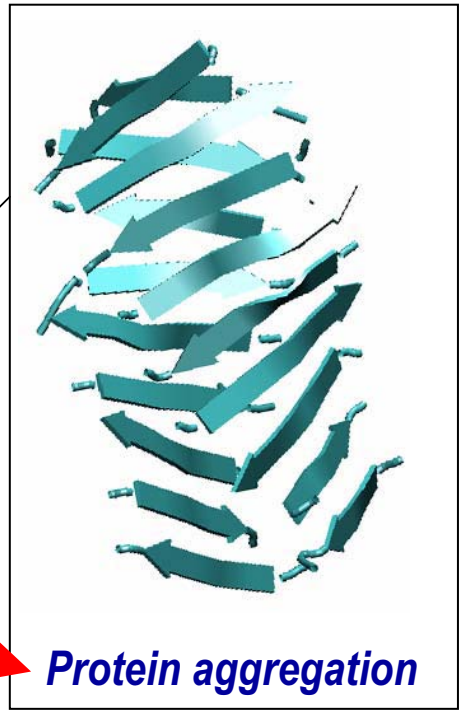
Helix formation





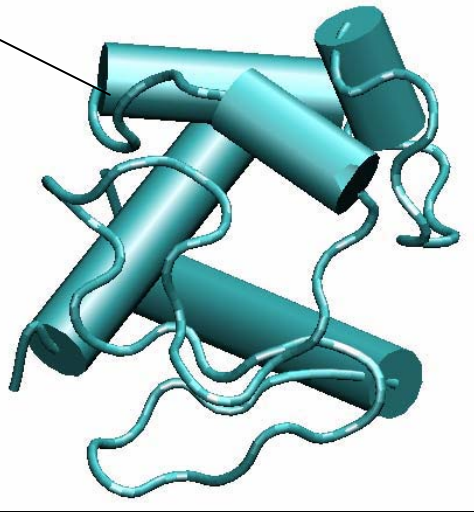
Folding of β-hairpins





Protein aggregation

Protein folding



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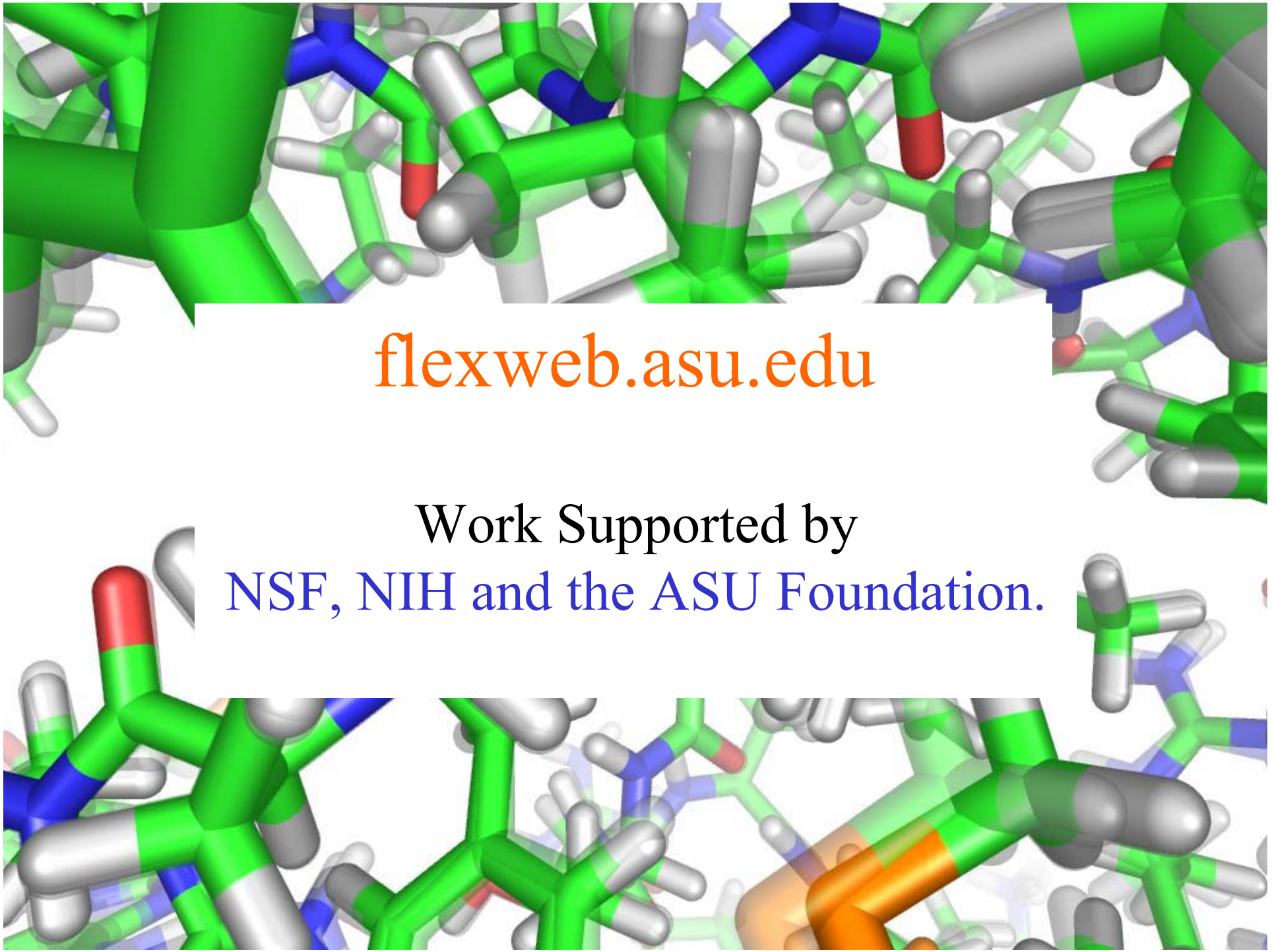

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