Simulating Alzheimer's on the XD1

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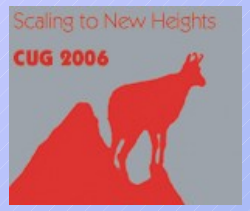
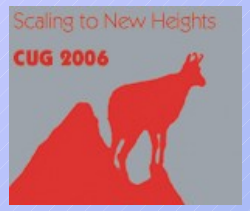


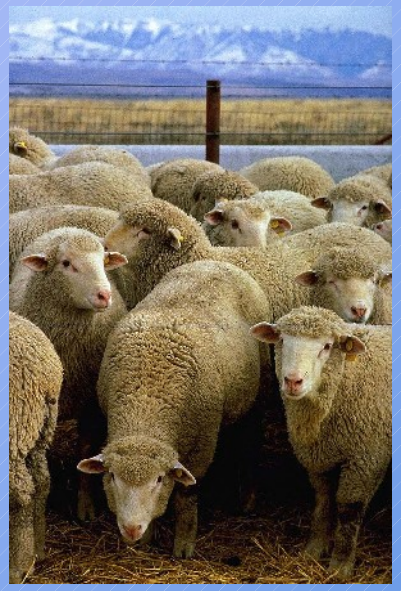
Alzheimer's Disease

Ronald Reagan, 1911–2004

Charles Bronson, 1921–2003

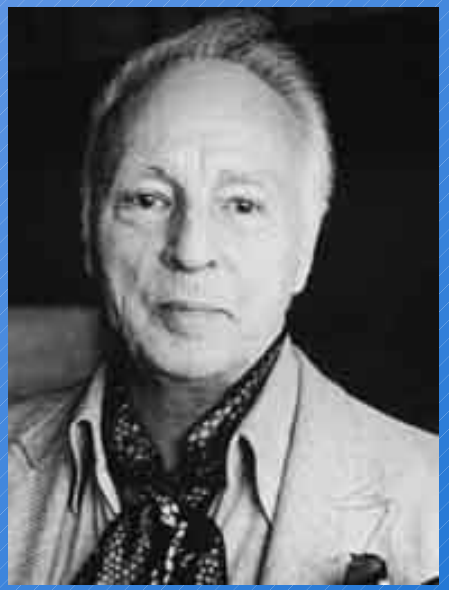


Prion Diseases

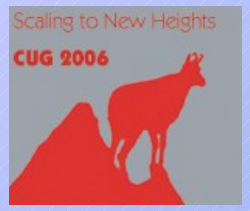


Scrapies

BSE



George Balanchine, 1904–1983
vCJD

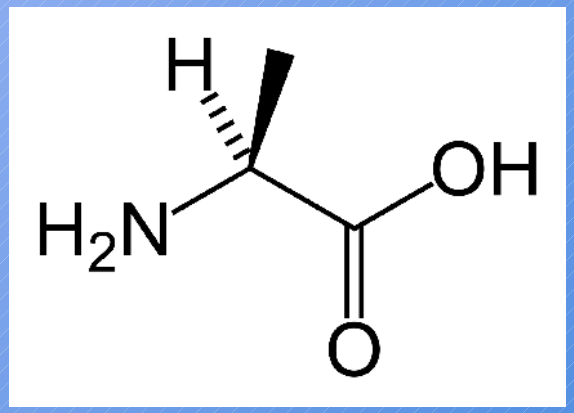


Proteins

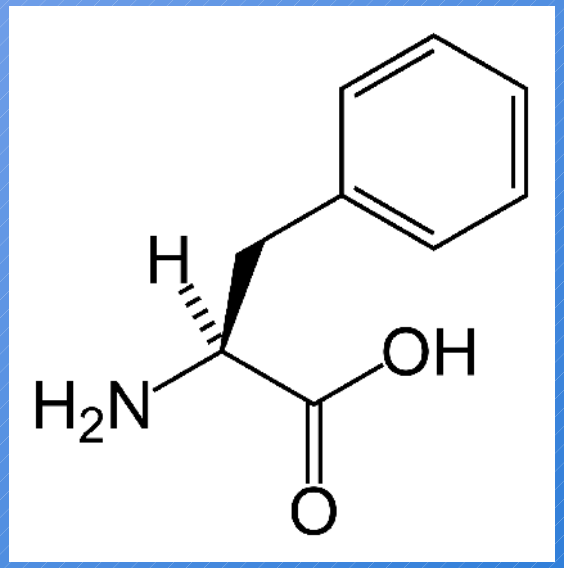
- Molecular work horses of our bodies
  - Catalyst (enzymes)
  - Transport (red blood cells)
  - Immune system (white blood cells)
- Form determines function

Proteins – Sequence

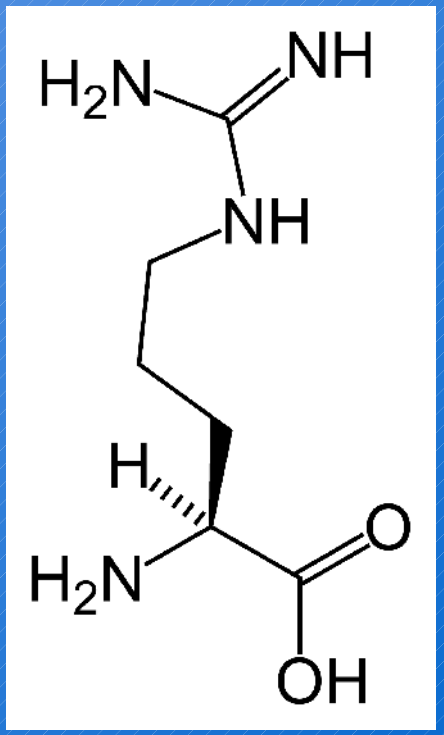
- 20 different amino acids
- Sequence encoded in DNA
- Sequence determines shape (single domain)
- Written down using 1- or 3-letter abbreviation



Alanine (Ala, A)



Phenylalanine (Phe, F)

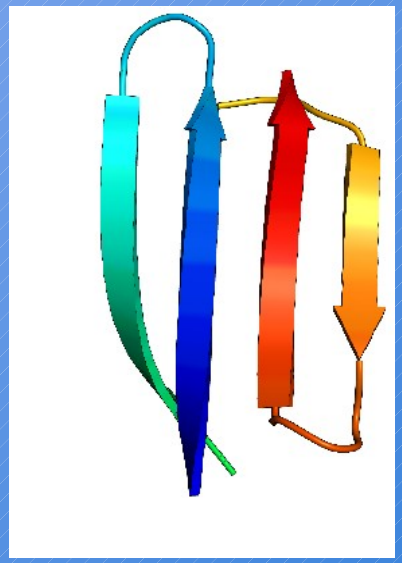


Arginine (Arg, R)

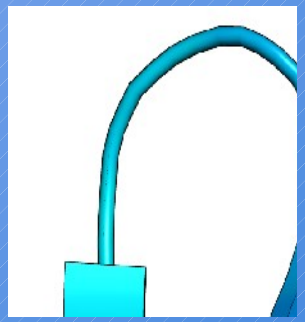
Proteins – Secondary Structure

- Helix
- Sheets
- Turns
- Coil

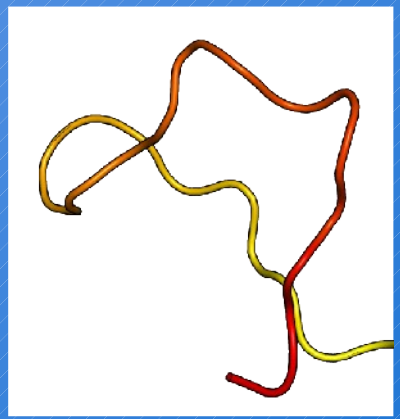
Helix



Sheets

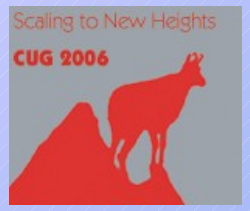


Turn



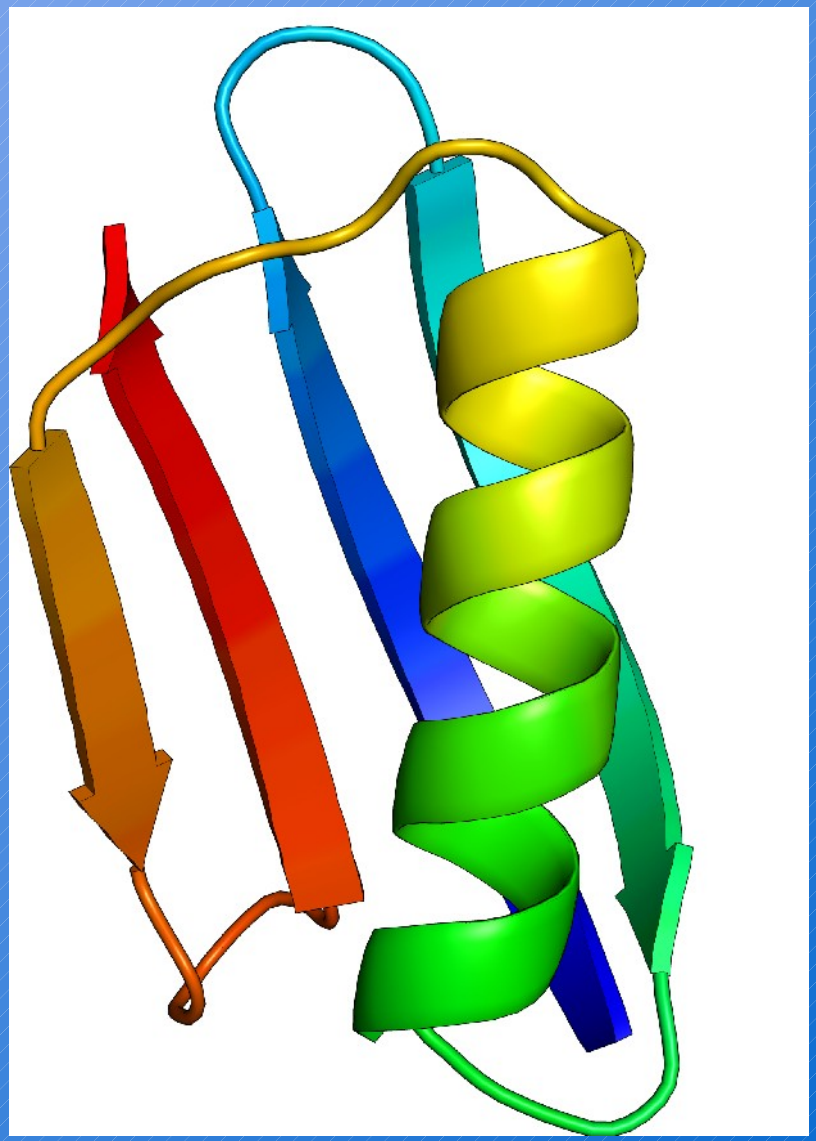
Random Coil

Graphics made with PyMOL



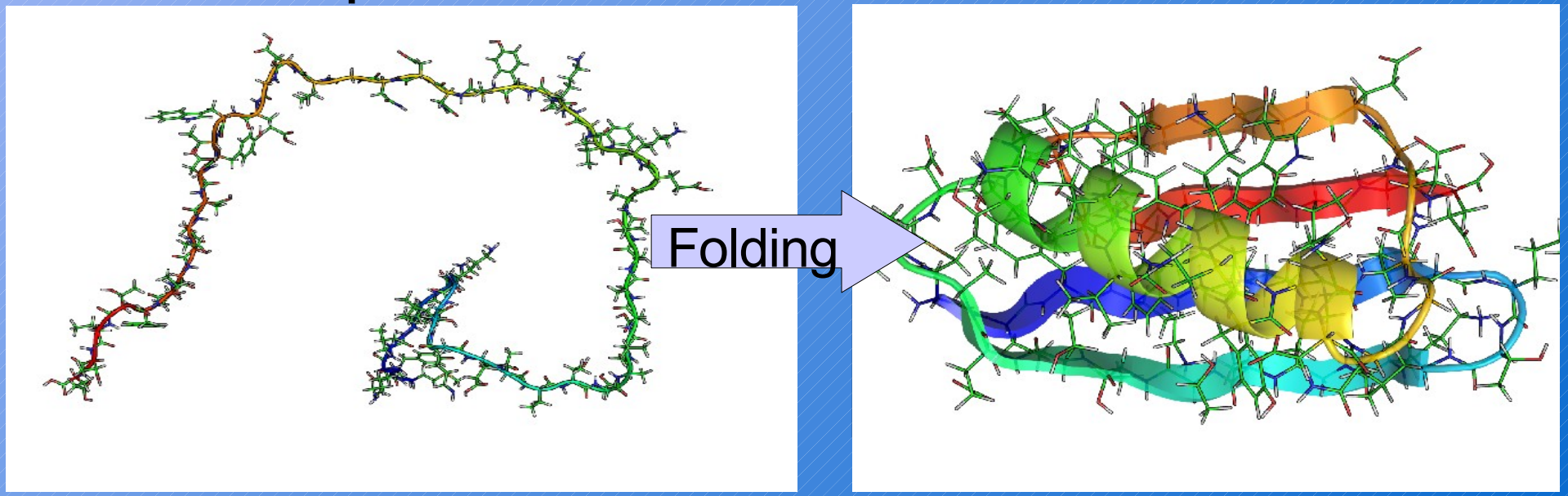
Proteins – Tertiary Structure

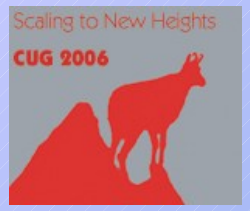
- Arrangement of secondary structure element into well defined 3d structure
- Functional unit
- Multiple domains possible



Protein Folding

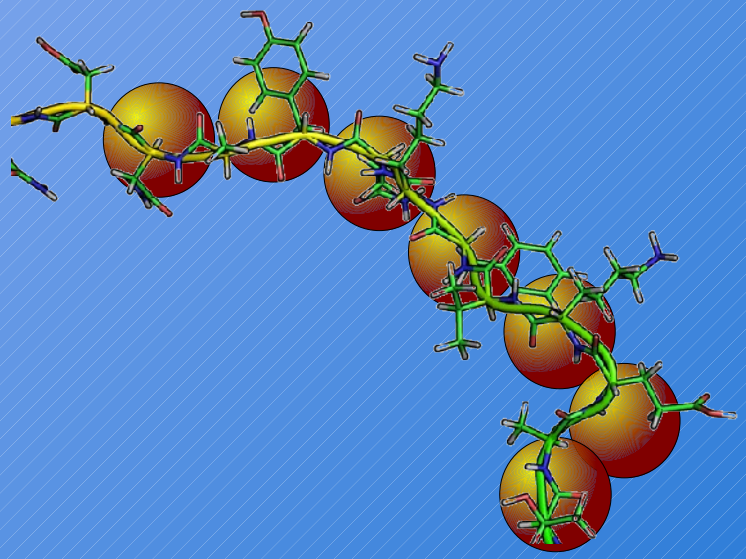
- Sequence uniquely determines shape
- Thousands of degrees of freedom
- Random sampling not feasible →Leventhal paradox
- Funnel picture





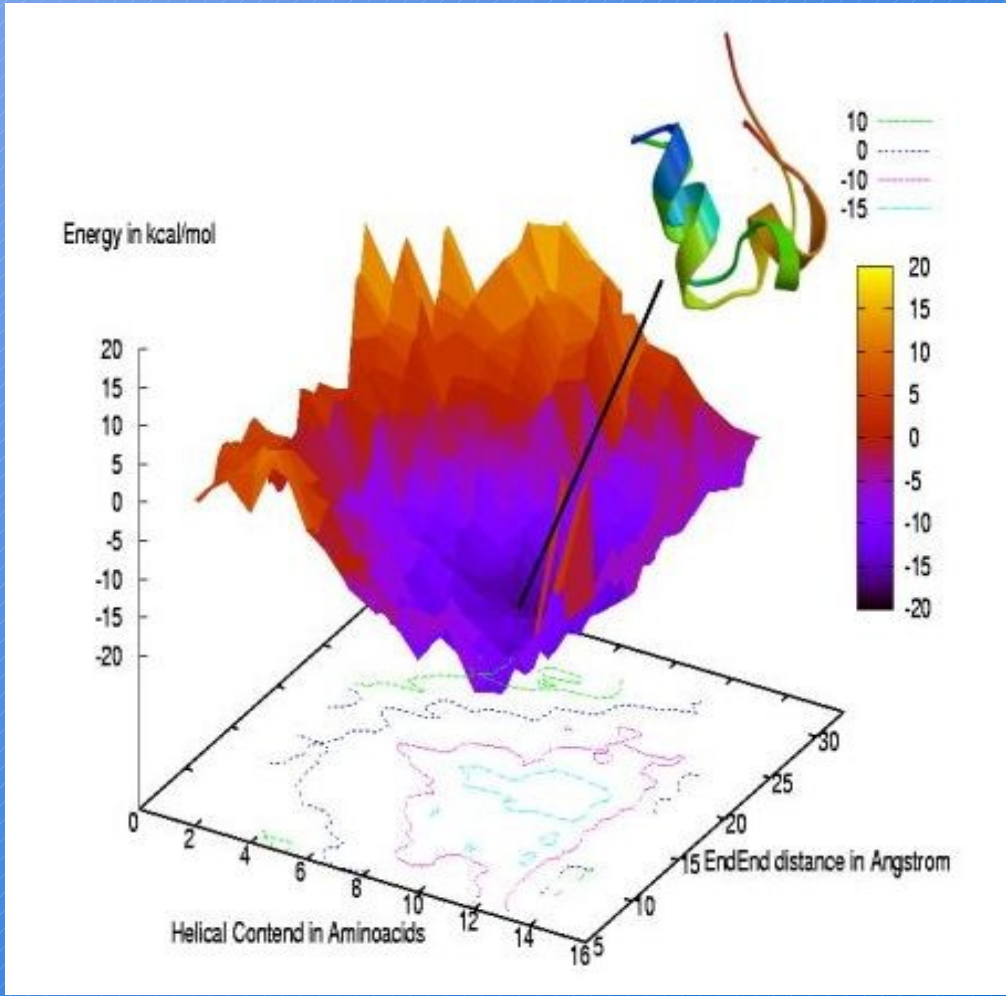
Simulating Proteins

- Representation
- Force fields
  - Describe interactions within protein
  - Describe interactions between proteins
- Methods
  - MD
  - MC
  - others



Force Fields

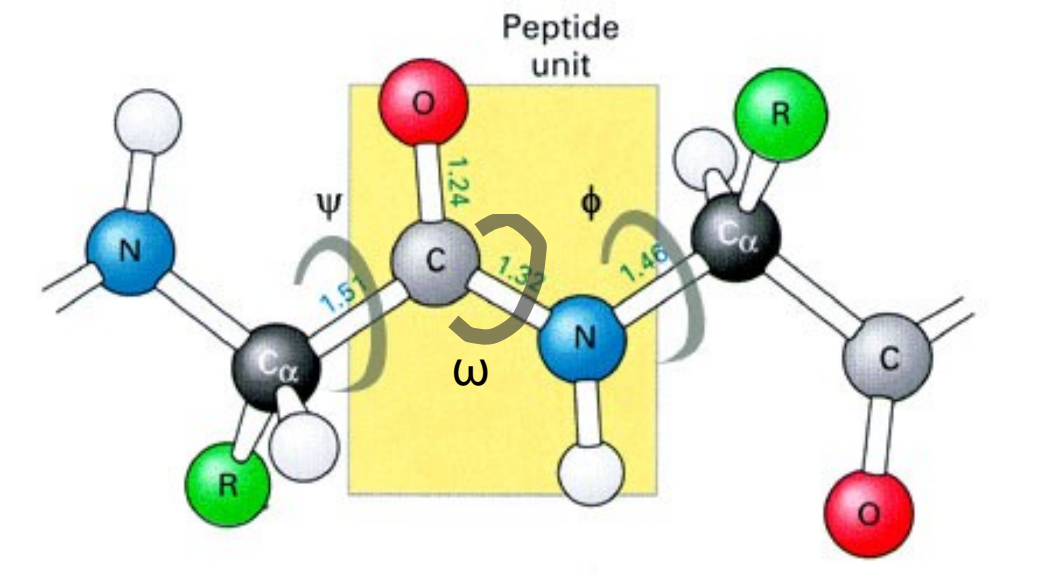
- Attractive terms + repulsive terms→rough energy landscape
- Many different parameterizations
  - Amber
  - Charmm
  - ECEPP
  - Gromacs



Schug, A. et al.
J. Chem. Phys.,
122(2005), 194711

Monte Carlo and SMMP

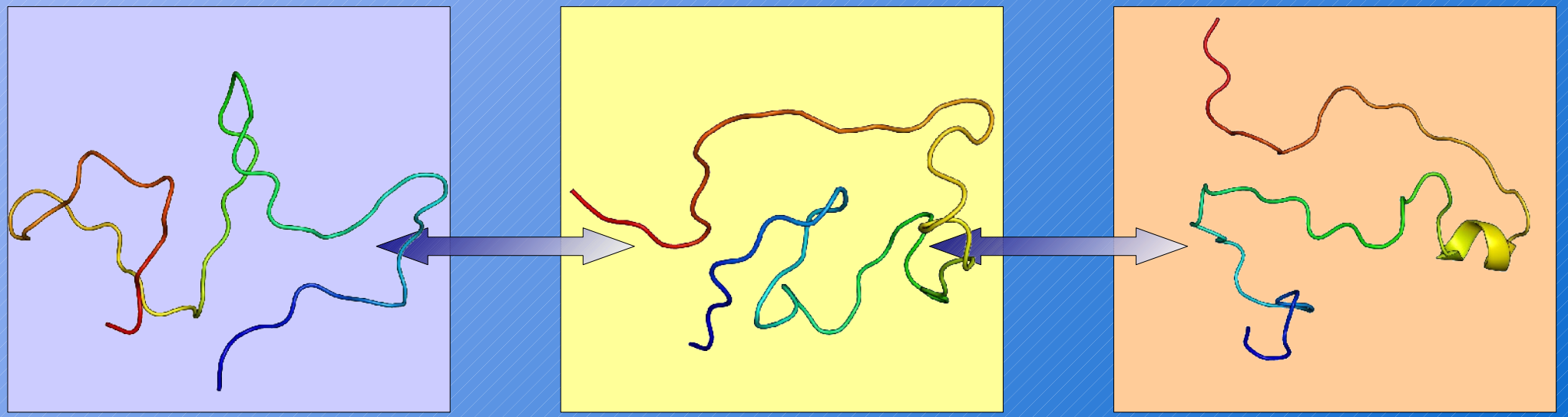
- Internal degrees of freedom (dihedral angles)
- Fixed bond lengths
- Random sampling of configurations



http://apple.sysbio.info/~mjhsieh/sstour/

Parallel Tempering

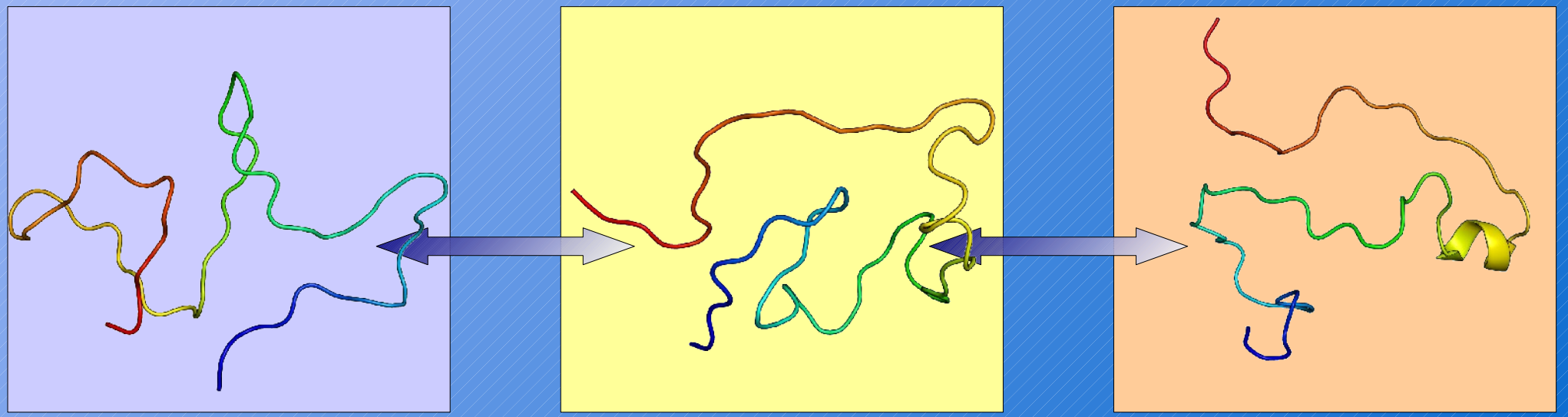
- Simulate the same system at different temperatures
- Exchange configurations between temperatures according to Metropolis criterion



$T_{i-1} < T_i < T_{i+1}$

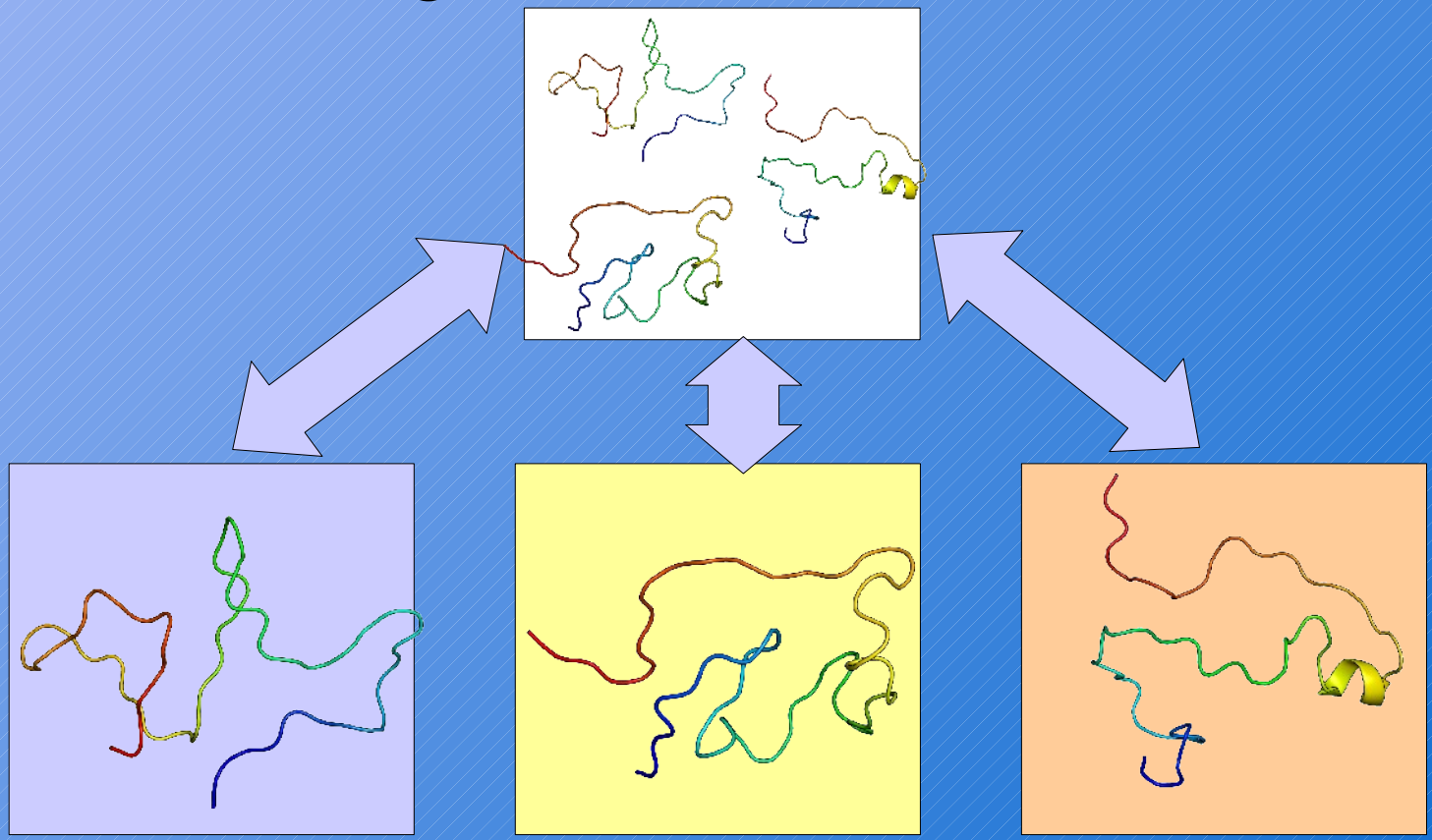
Scaling of Parallel Tempering

- n replicas produce n times the amount of data
- Exchange of configurations accelerates equilibration



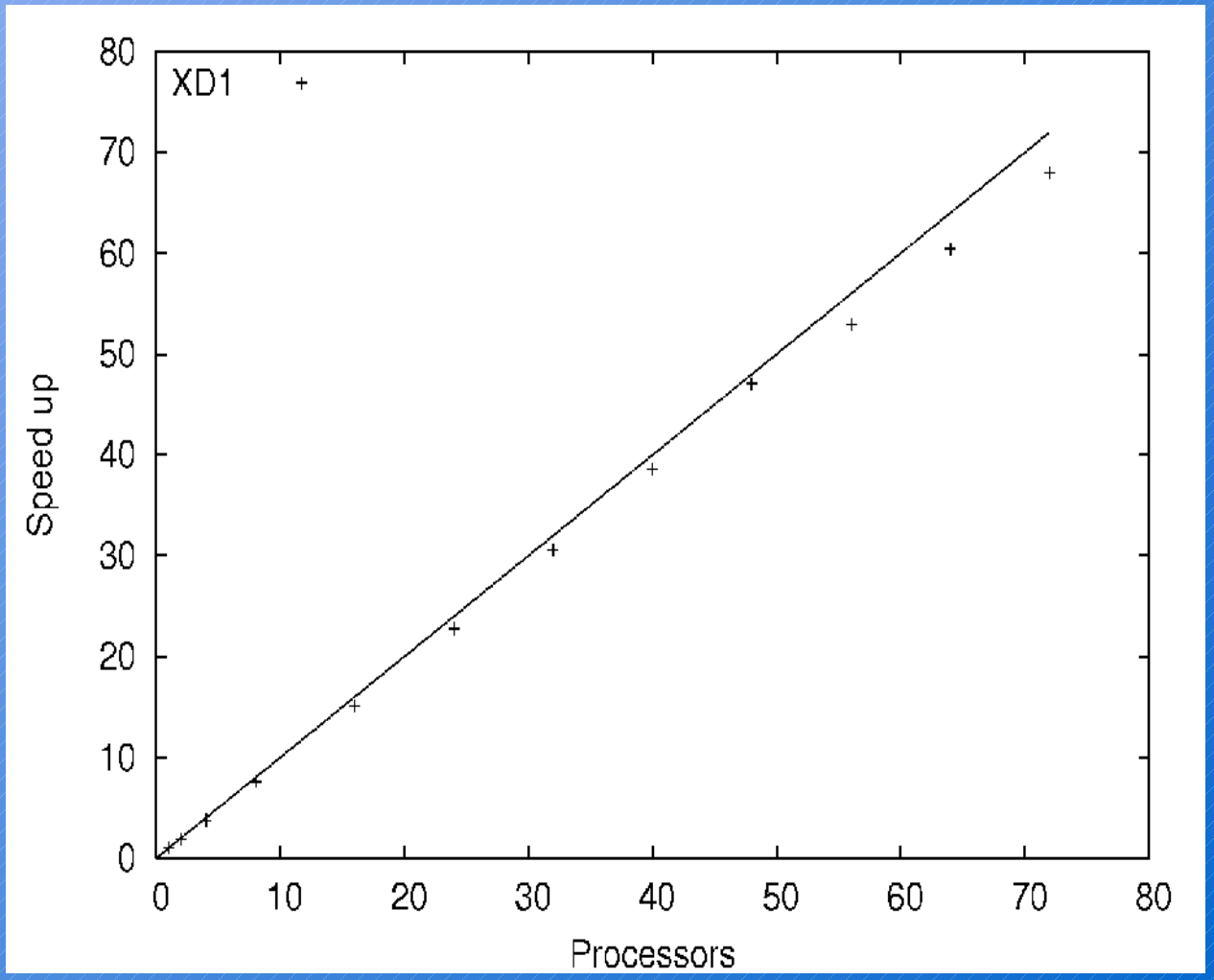
Some Implementation Details

- Exchanging temperatures vs. exchanging configurations
- Replica exchange done on Master node



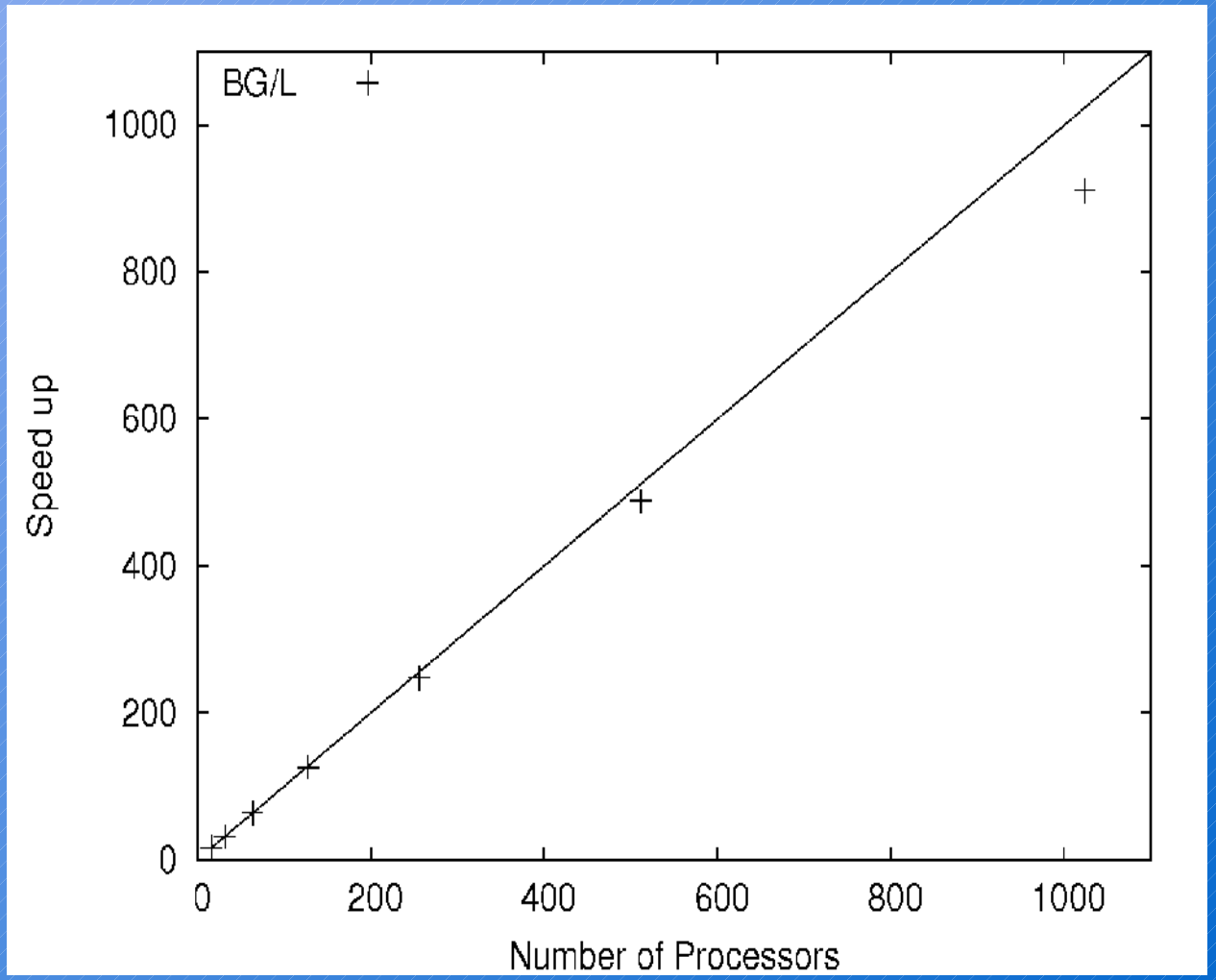
Scaling on the XD1

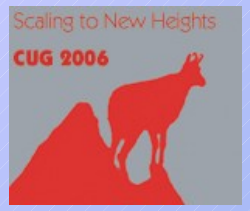
- Speed on a single node
  - time for an energy calculation vs. system size
  - time for a sweep vs. system size
- Parallel scaling



Scaling on IBM BlueGene/L

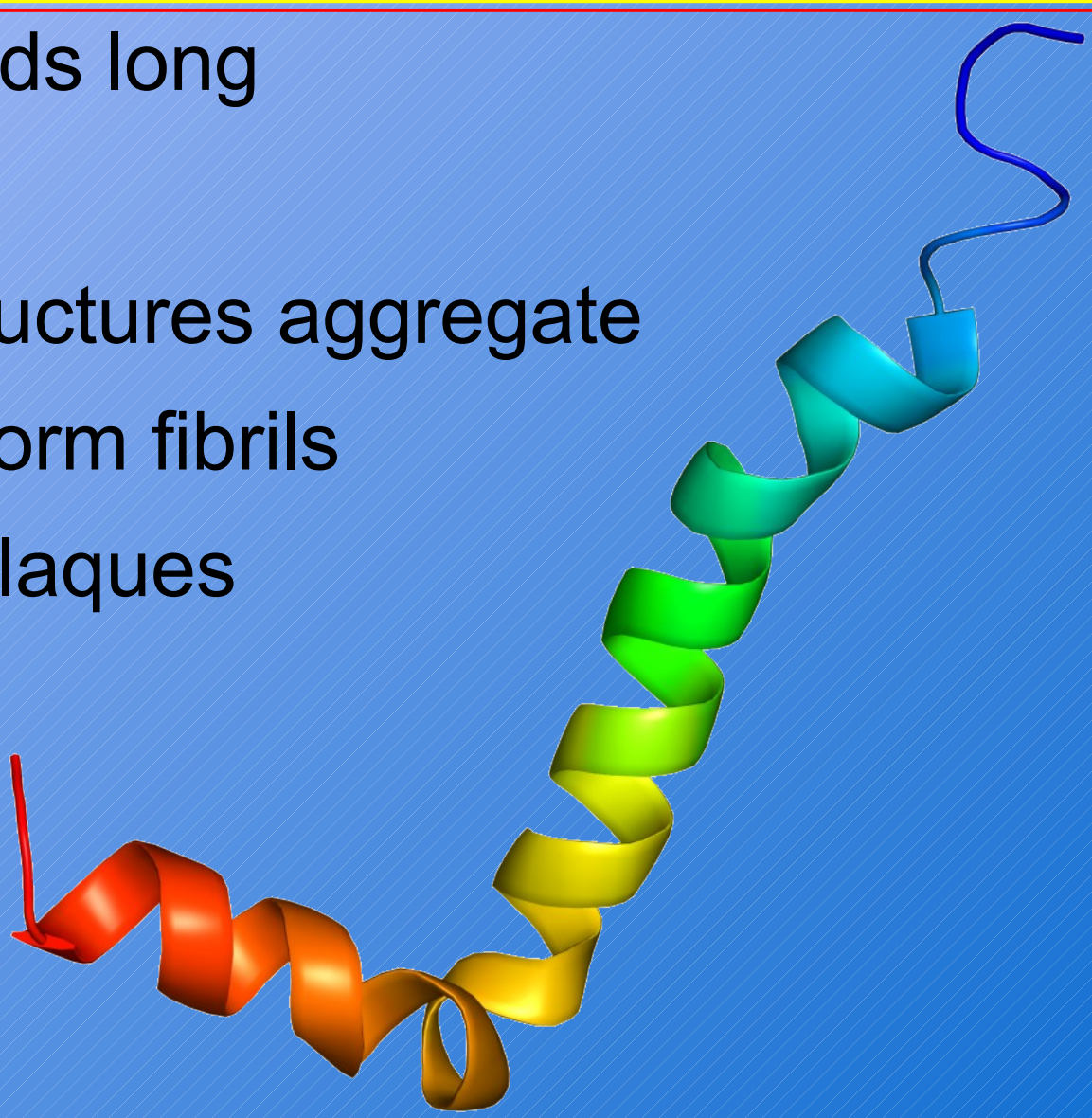
- Speed on a single node
  - time for an energy calculation
  - time for a sweep 7 times longer than XD1
- Nearly linear up to 1024 processors

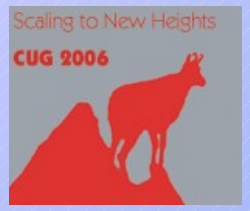




Alzheimer's β-amyloid

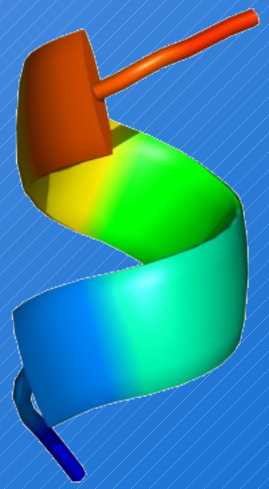
- 42 Amino acids long
- Misfolds
- Misfolded structures aggregate
- Aggregates form fibrils
- Fibrils form plaques
- Neurotoxic

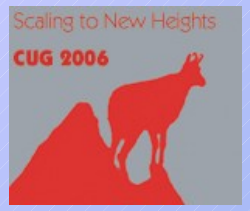




Studying Aggregation in Silico

- Alzheimer's β-amyloyd is already a large protein for all-atom simulations
- Simulating multiple proteins of that size is beyond our computational abilities
- Study aggregation of fragment

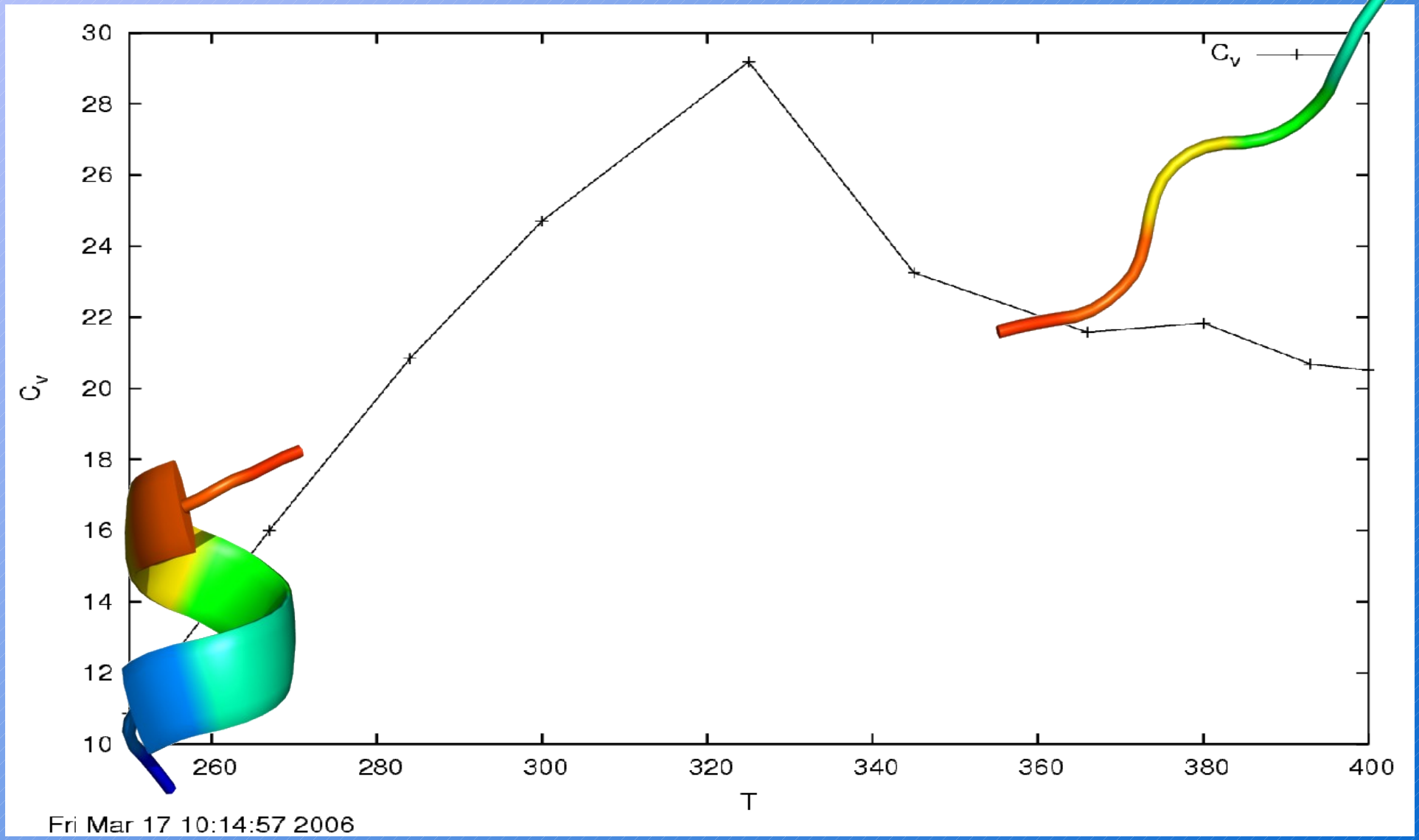


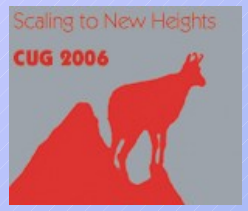


Alzheimer's β-amyloyd$_{16\text{-}22}$

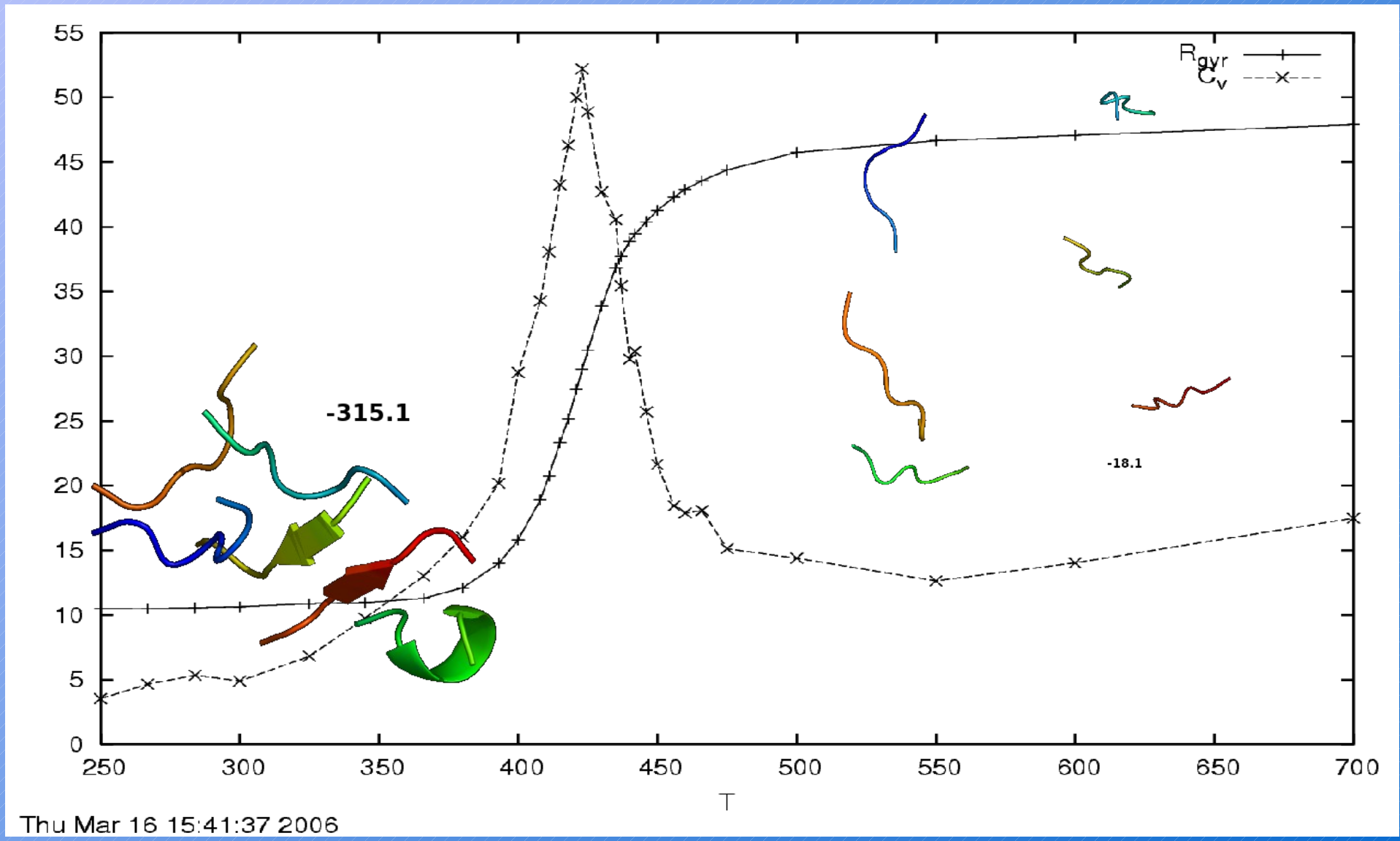
- Experimental evidence for importance of Aβ$_{16\text{-}22}$ in aggregation
- Aβ$_{16\text{-}22}$ aggregates by itself
- Previous simulations showed aggregation with simpler force field.

Single molecule behavior



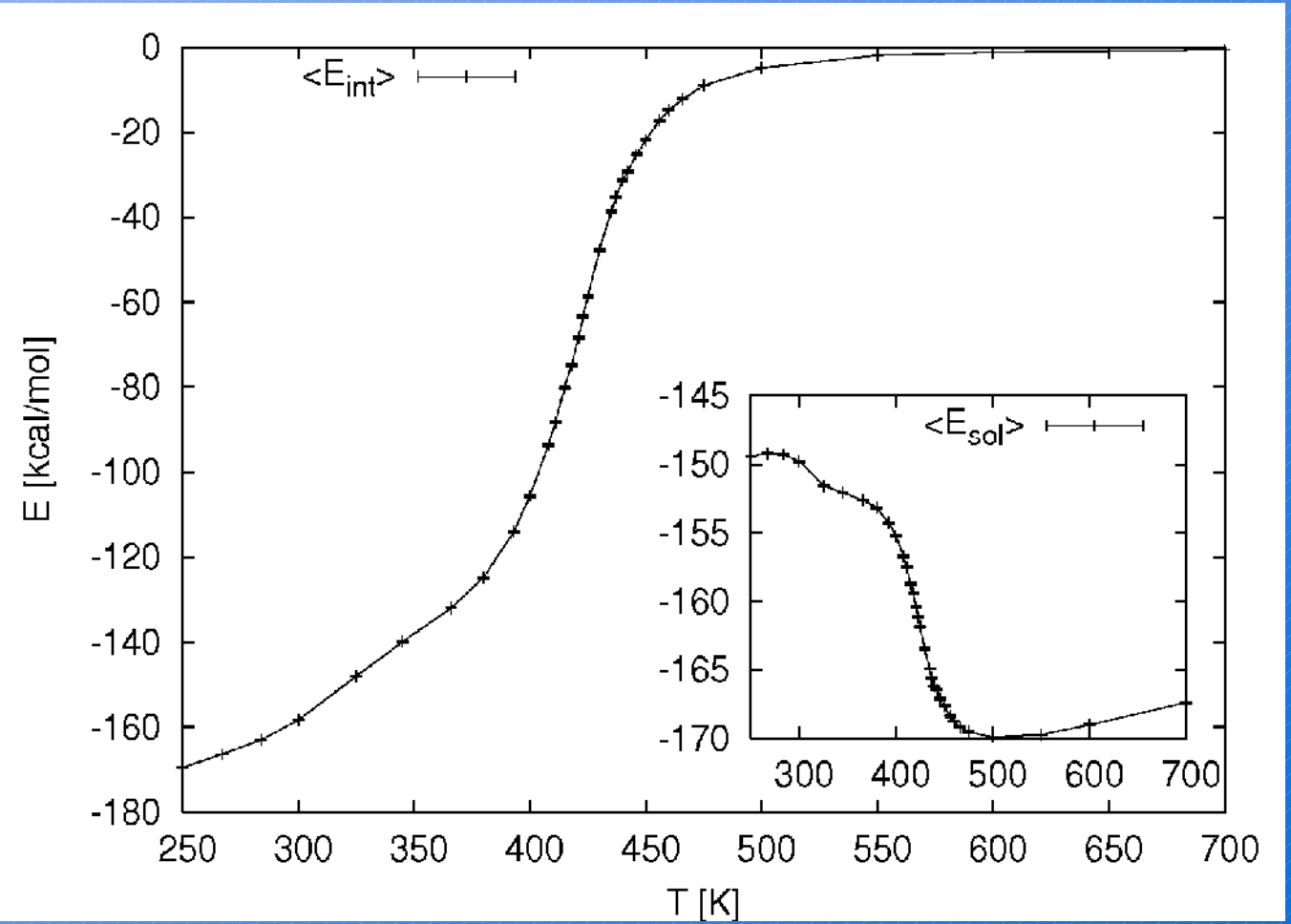


Aggregation



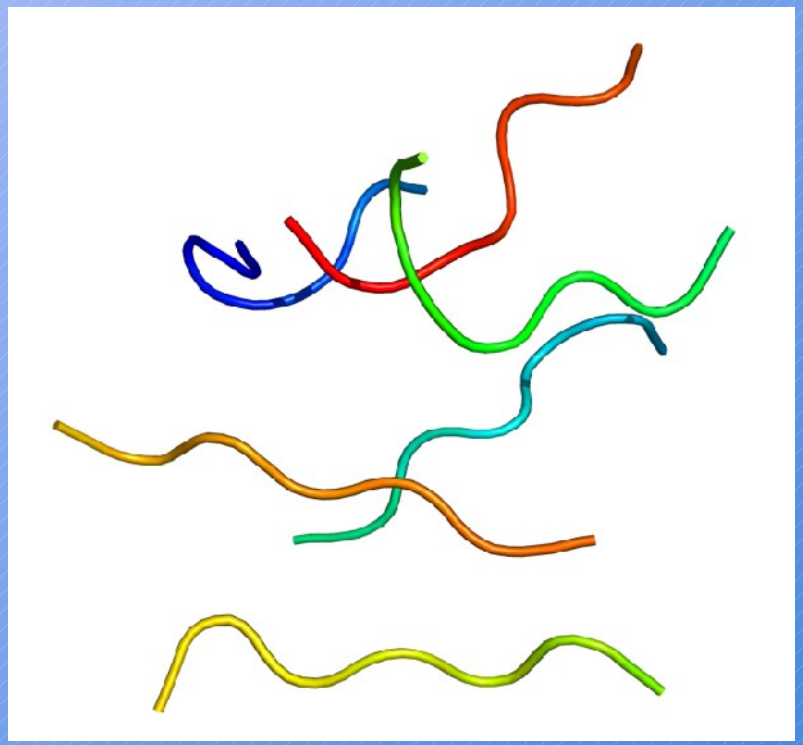
Energies

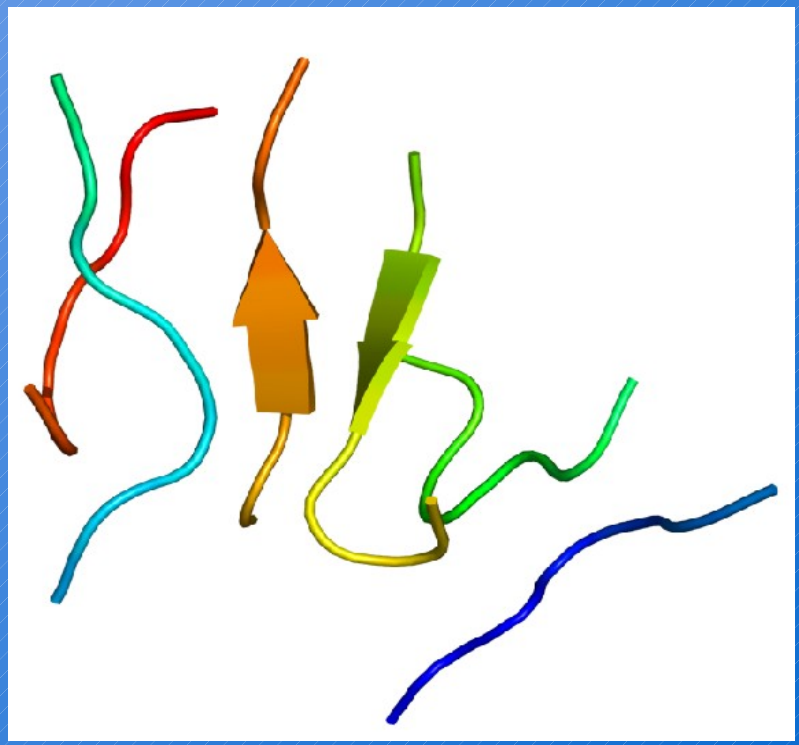
- Interaction drives aggregation
- Collapse despite solvent term

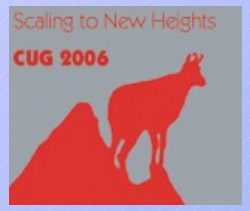


Organization of aggregate

- Start as random aggregates
- Sheet formation
- Parallel vs. anti-parallel







Summary

- Parallel tempering scales very well
- Energy calculation may profit from FPGA
- Successful first steps
- Still a long way to go