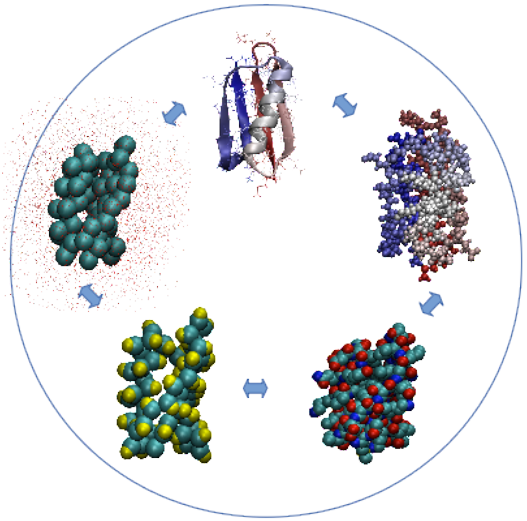
Coarse-grained computational study of interacting biomolecules

Tatjana Škrbić



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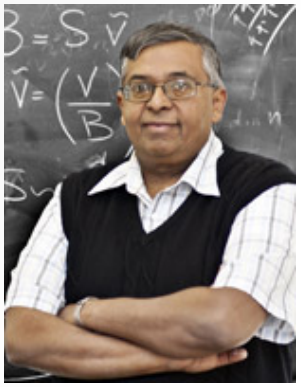
Collaborators



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Outline

- **Phases of matter**: symmetry is important
- **Emergent phases of biopolymers**: consequence of the removal of spurious symmetries in a homopolymer model
- **Elixir phase**: degeneracy as a consequence of 'helix-sheet' coexistence
- **Applications:**
  I) protein aggregation (amyloid formation)
  II) protein-DNA interactions

Proteins: difficult problem

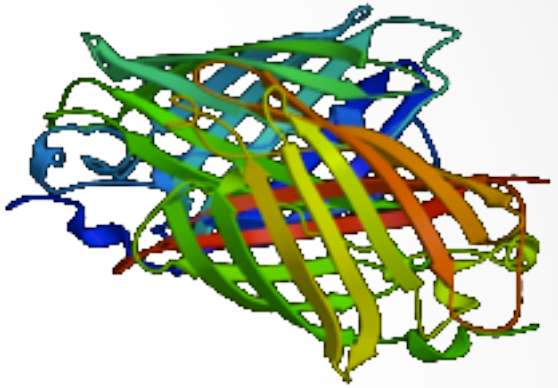
- Formidable complexity: 20 types of amino acids, role of water, huge number of degrees of freedom, steric constraints, chain connectivity
- Finite size
- Role of evolution

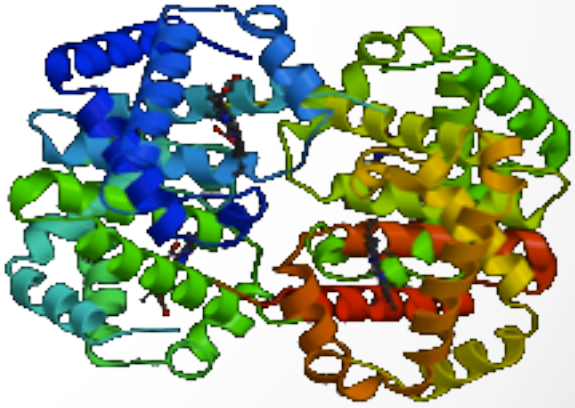
Standard approach: one protein at a time

"Any effective picture of protein structure must provide at the same time for the common character of all proteins as exemplified by their many chemical and physical similarities, and for the highly specific nature of each protein type." - *Bernal (1939)*

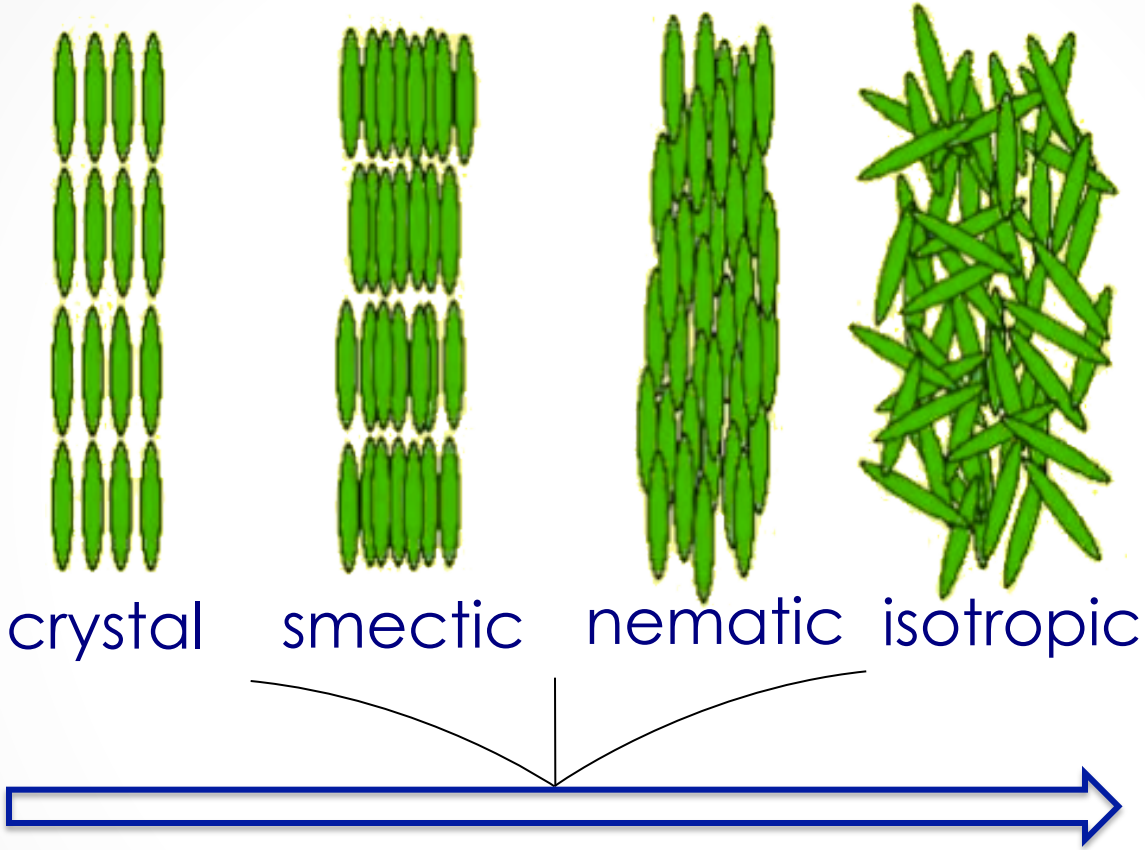
Proteins

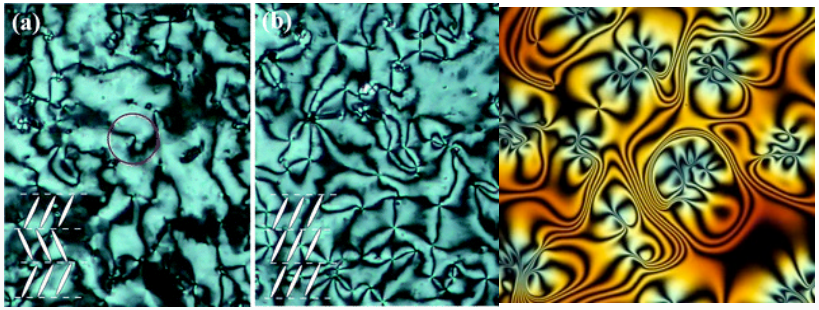
- Linear chains of amino acids
- Fold rapidly and reproducibly
- Few intermediate states
- Folding is driven by hydrophobicity
- Structures composed of helices and sheets compatible with sterics & hydrogen bonds
- Form determines function
- Only ~10^3 folds
- Powerful reactive properties
- Amyloid formation – Alzheimer's & mad cow diseases





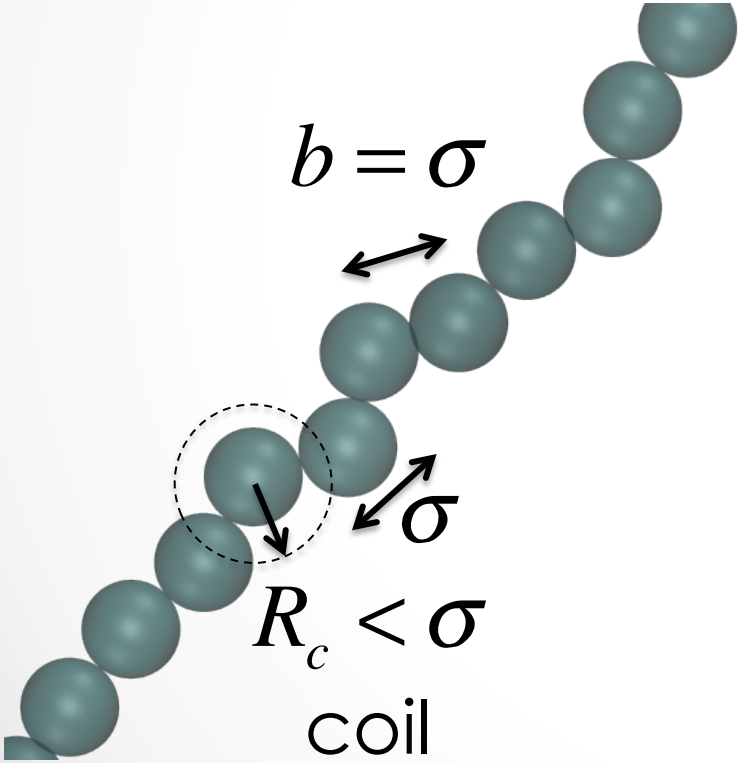
Liquid crystals – symmetry matters



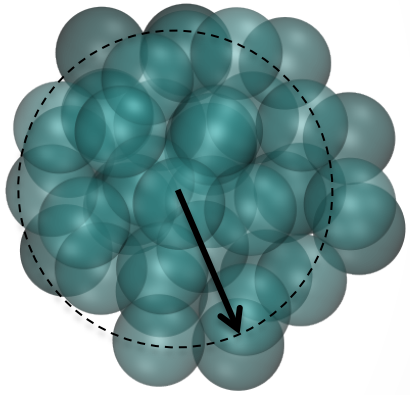


Standard polymer model

Ground state: state that maximizes the number of contacts (sphere centers within the range of attractive interaction R_c)



coil



$R_c > \sigma$

globule

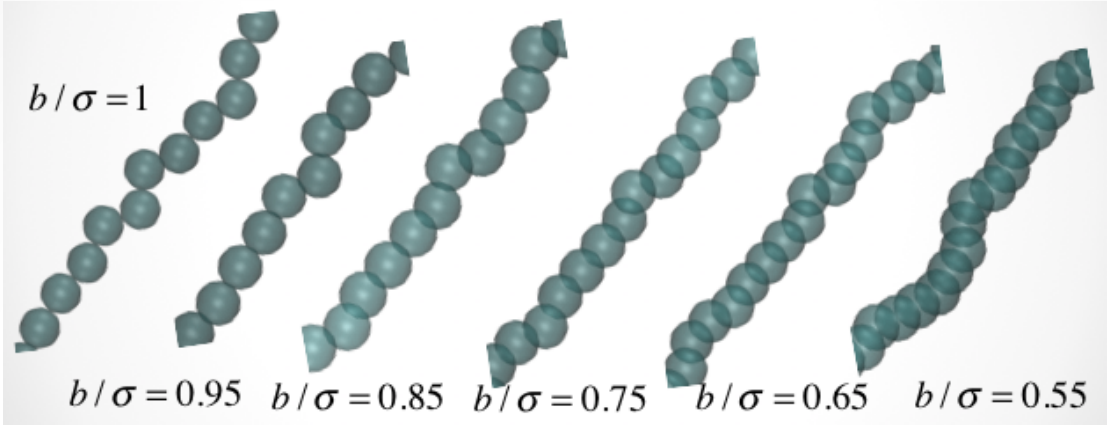
How does one capture the behaviour of proteins?

What is missing?

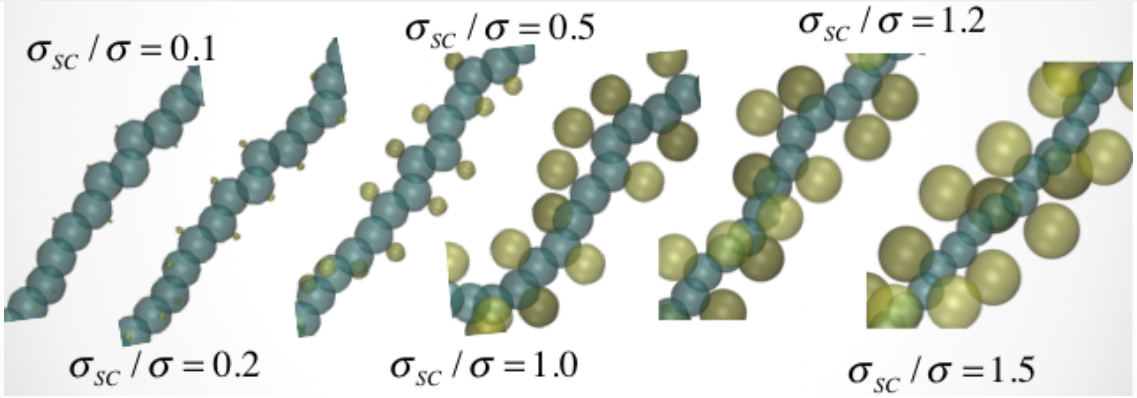
Amino acid heterogeneity? Chemistry?

Or does one need to remove spurious symmetries?

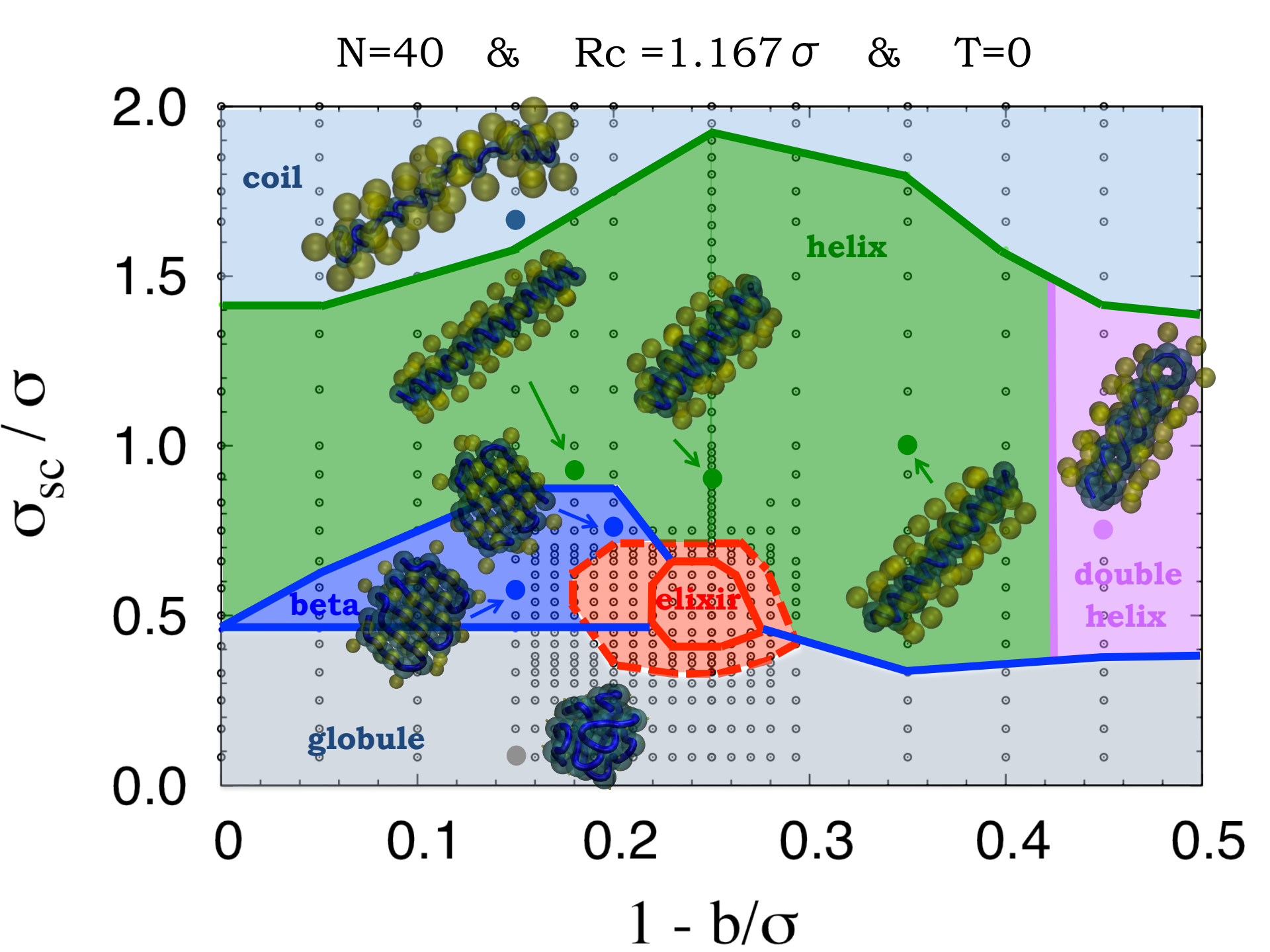
Sphere overlap (breaking spherical symmetry)



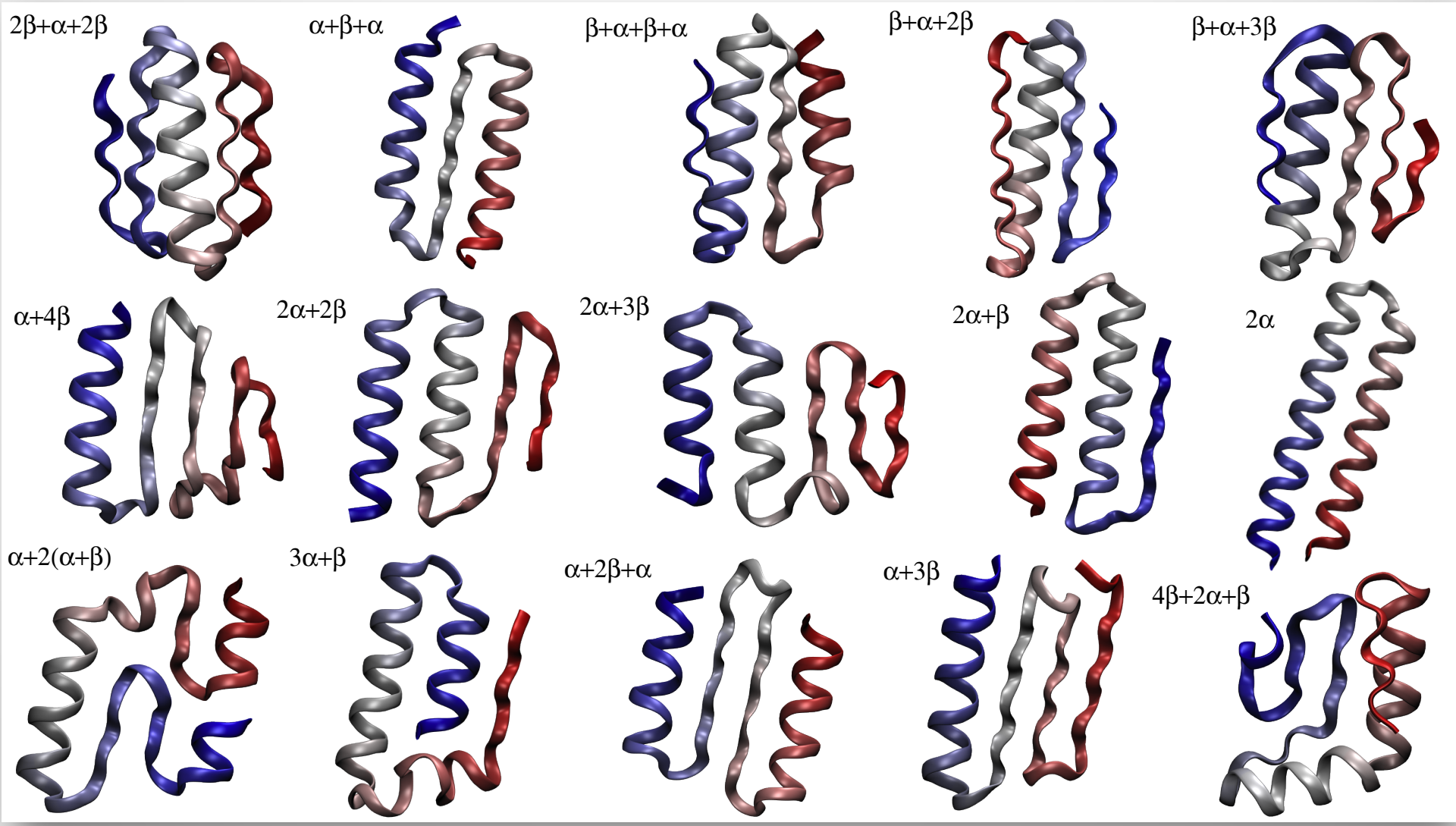
Side spheres (breaking cylindrical symmetry)



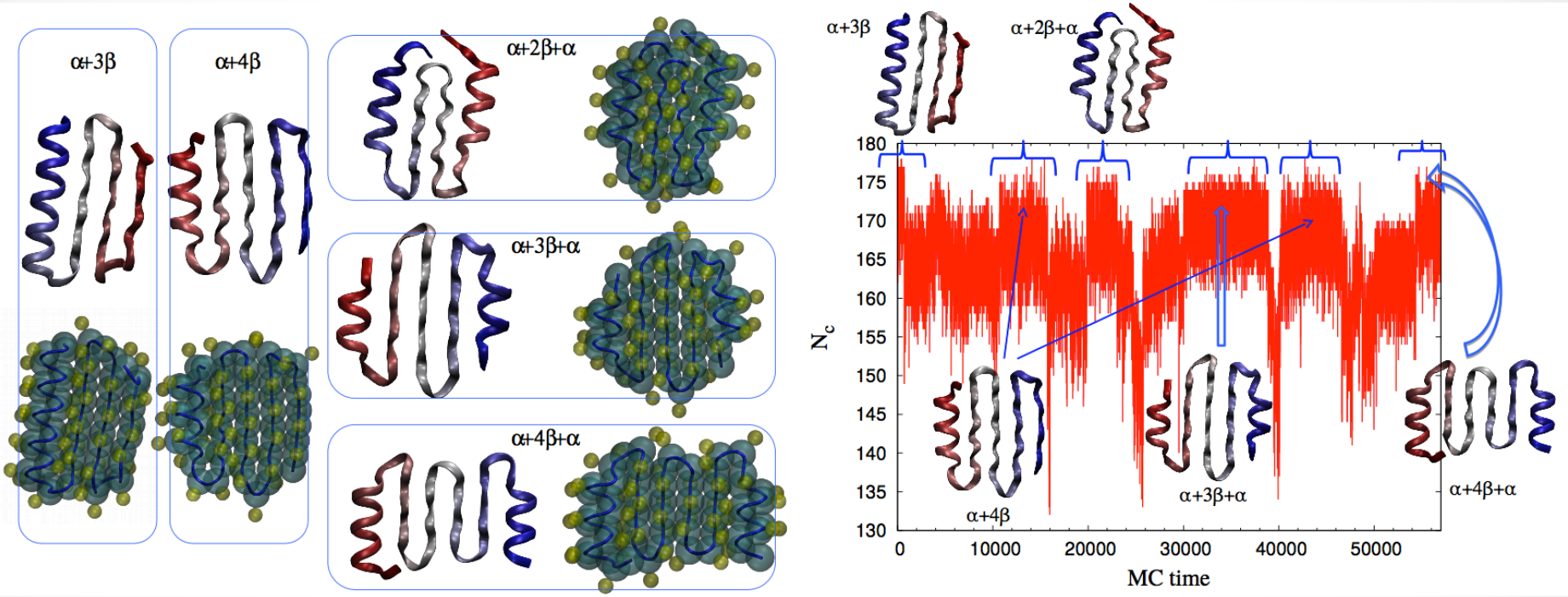
Attractive square-well interactions among the main chain spheres: ground state maximizes number of contacts


N=40 & Rc =1.167 σ & T=0
coil
helix
beta
elixir
double
helix
globule
2.0
1.5
1.0
0.5
0.0
σsc / σ
0
0.1
0.2
0.3
0.4
0.5
1 - b/σ

Elixir phase: degeneracy



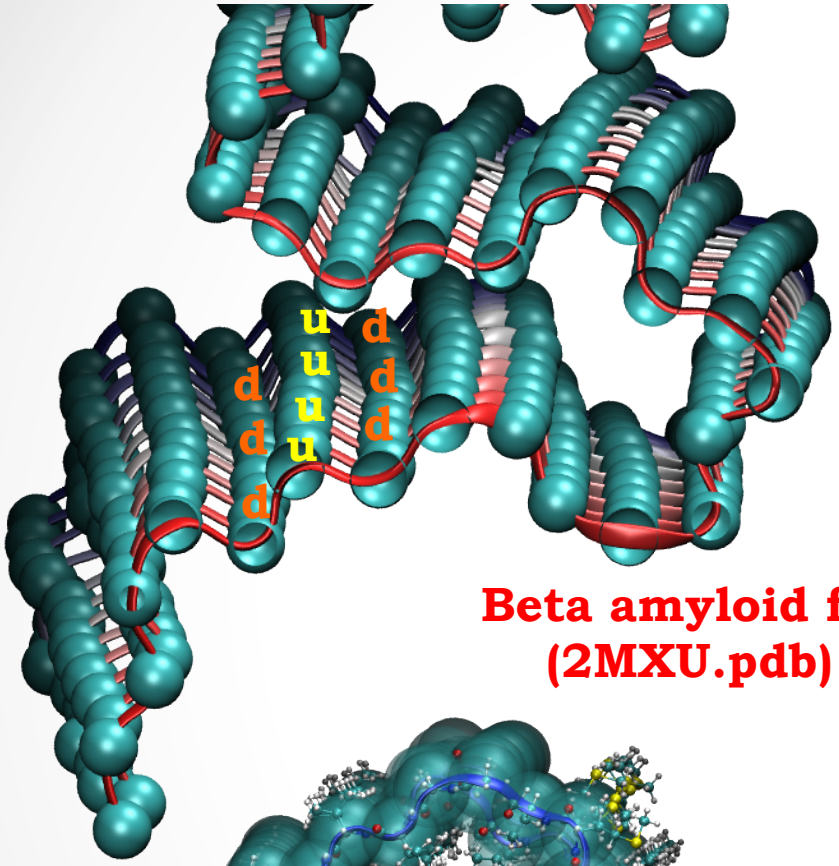
Thermal switching in the elixir phase

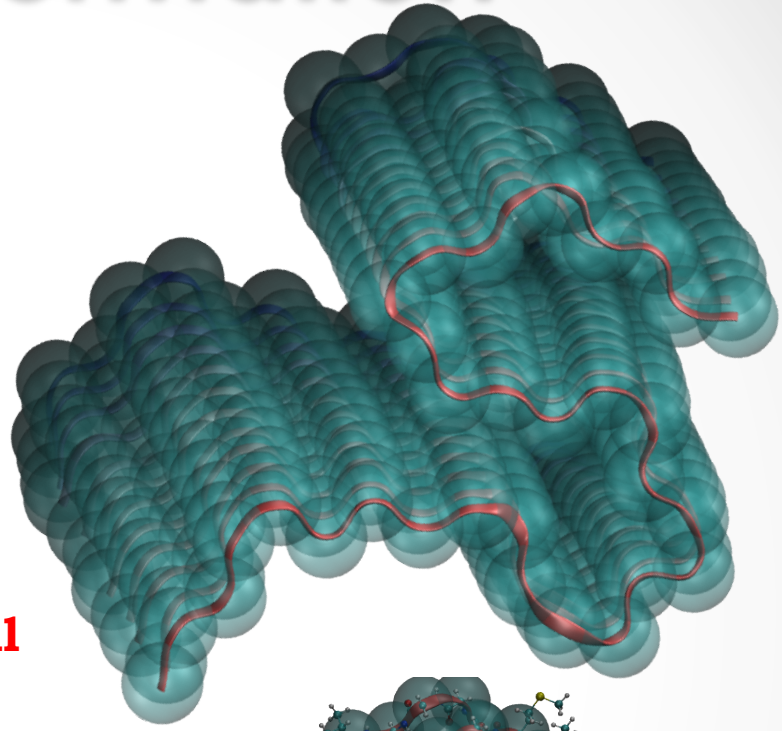


Skrbic et al. *Proteins* (2019)

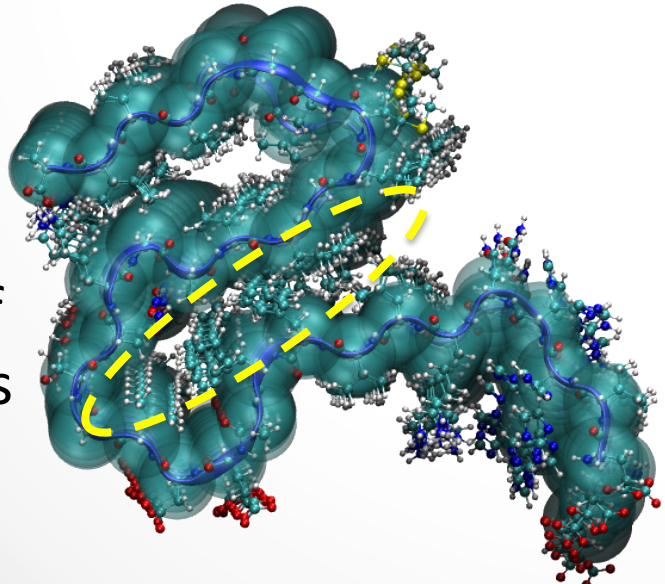
Skrbic et al. *Soft Matter* (2019)

Amyloid formation

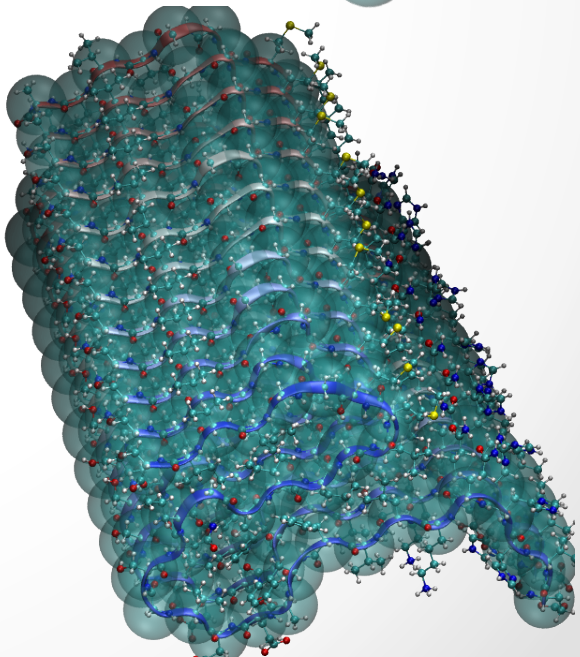




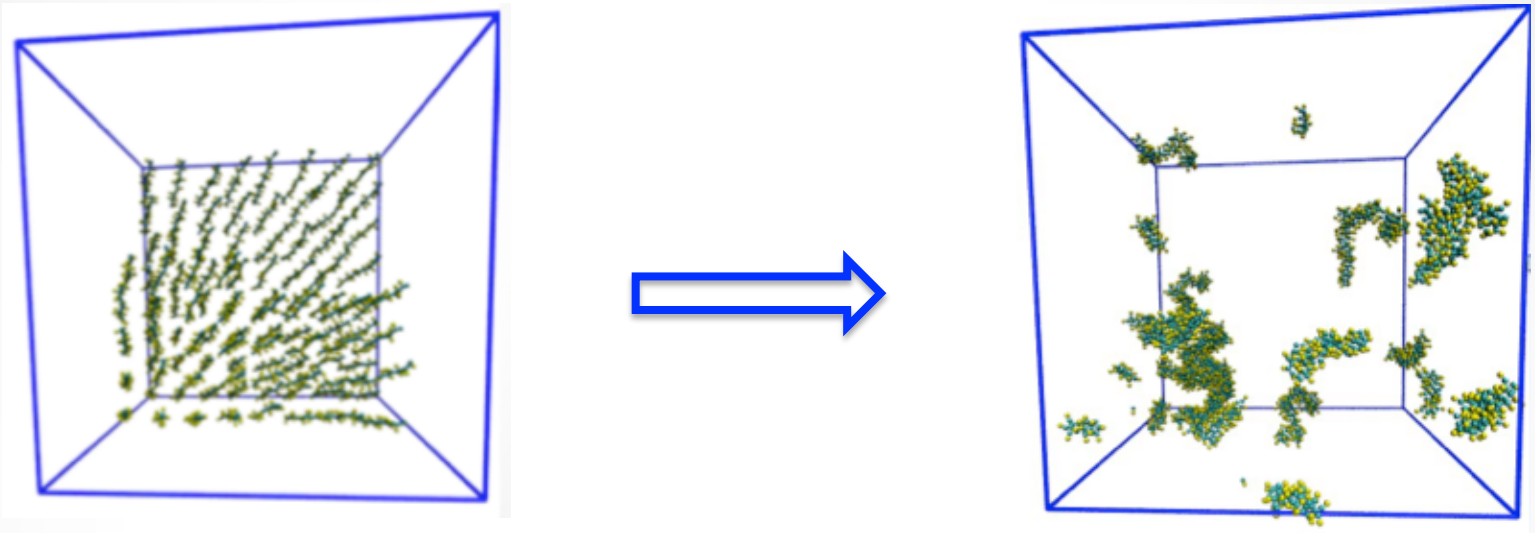
Beta amyloid fibril (2MXU.pdb)

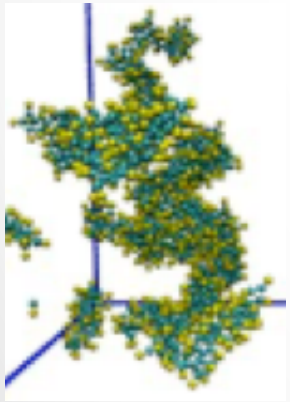


stacking of side-chains



Preliminary results: multichain annealing simulations at 10 mM





- Large number of detailed computationl studies: aimed at understanding and prevention of the degenerative amyloid formation
- *Our simple polymer model with correct symmetries captures the onset of β-sheet aggregation*
- *Protein-DNA interaction (unifying with the coarse-grained model of DNA developed by Flavio Romano)*