Statistical Physics of the Transition State Ensemble in Protein Folding

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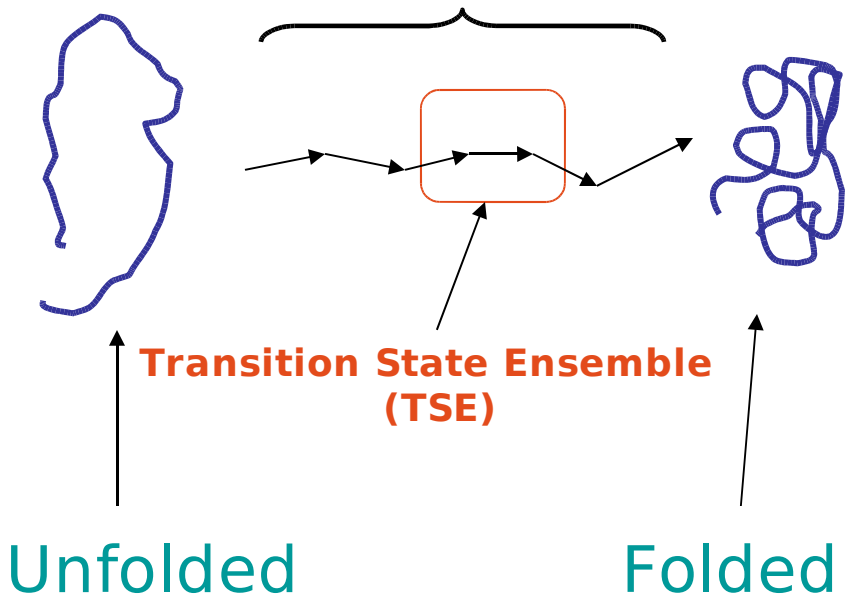
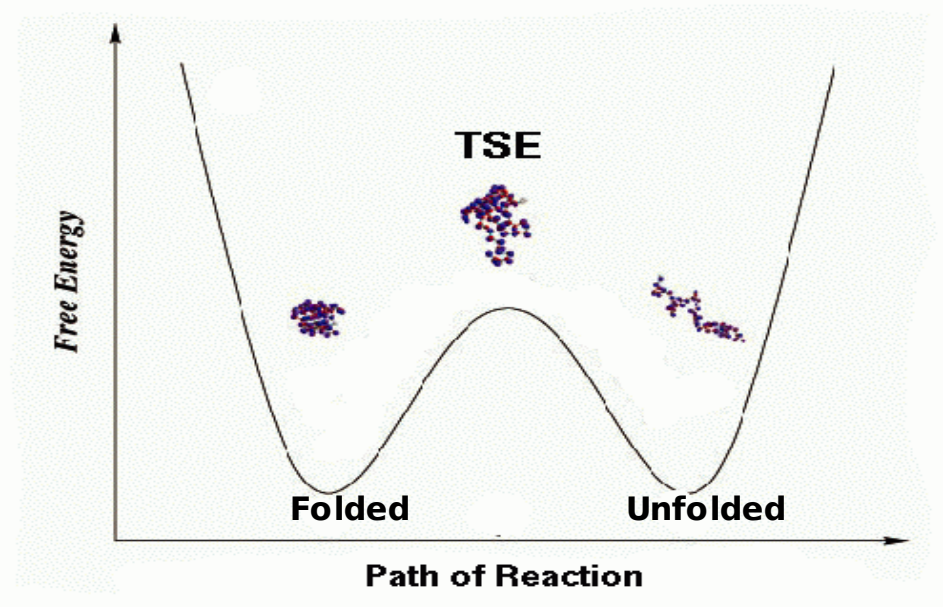
2004

The Protein Folding Problem

Protein Folding Process



At the Protein Folding Temperature T_F:



What is TSE?

Set of Protein Conformations located at the top of the free energy barrier that has the ***same probability*** *to fold or unfold*. (Du et al.,1998)

Purpose: *Characterize the structure of the TSE at the amino acid level.*

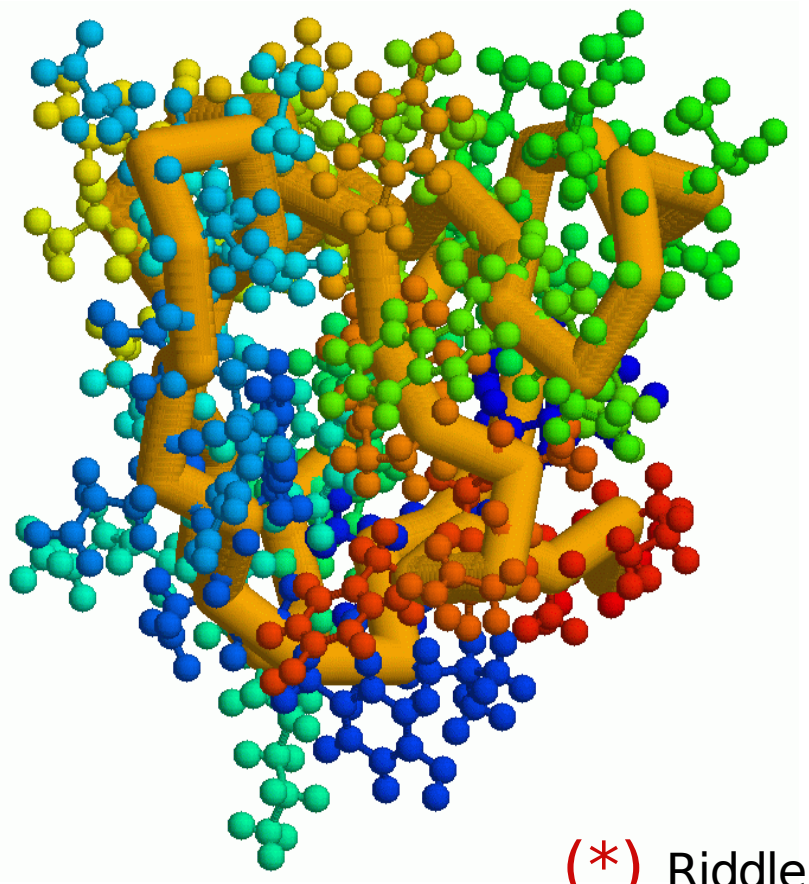
Why?: *Provide a guidance for amino acid substitution in experiments.(*)*

Our Results: *1.- The calculated TSE agrees with experimental data.*

2.- The TSE can be divided into a discre set of folding pathways.

(*): Martinez and Serrano, Nature Structural Biology,1999.
Riddle et al, Nature ,1999,
Gsponer et al, PNAS,2002,
Vendruscolo et al, Biophysical Journal.,2003

Our Protein: SH3



1.- Small Protein: 56 amino acids

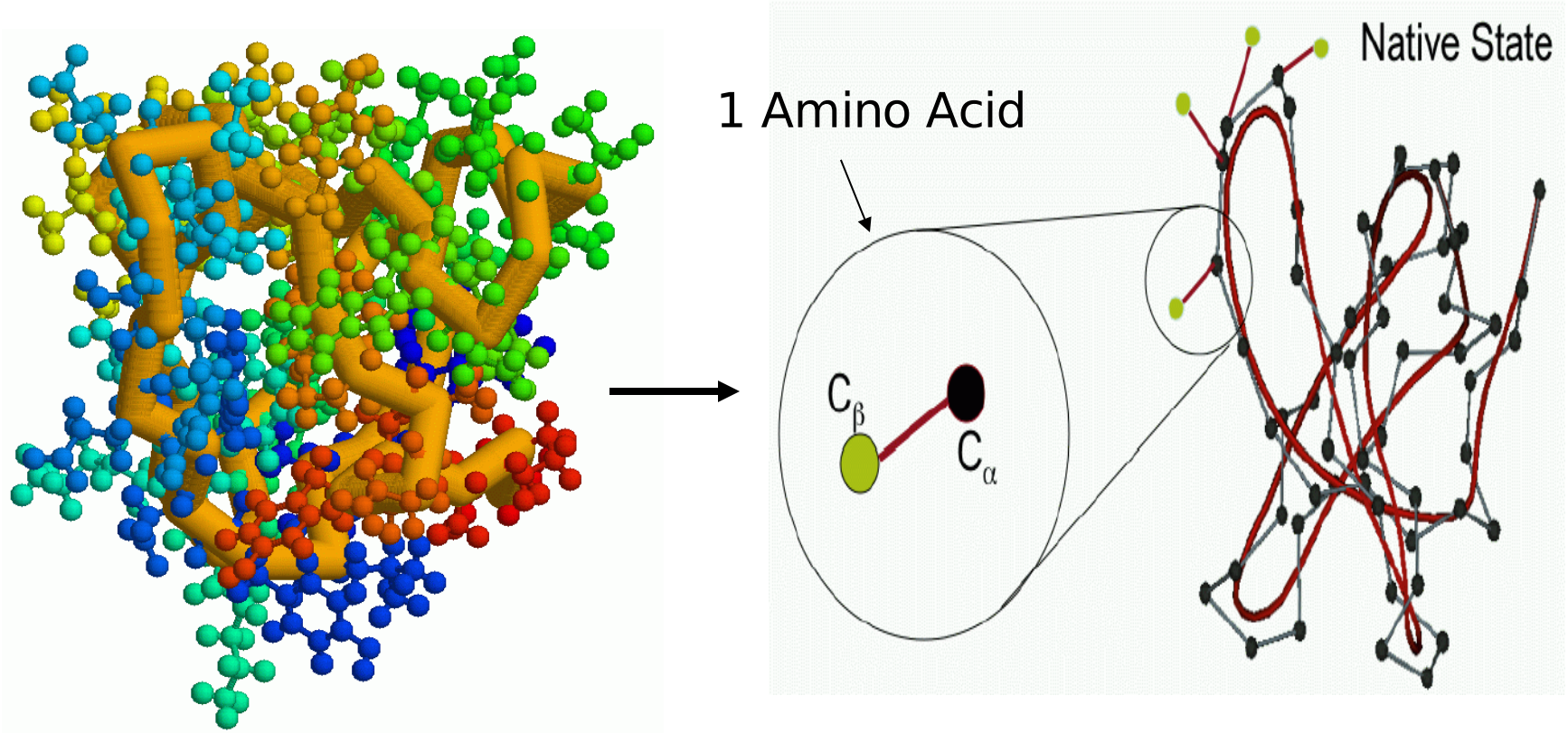
2.- Folds quickly.

3.- Well studied by experiments.

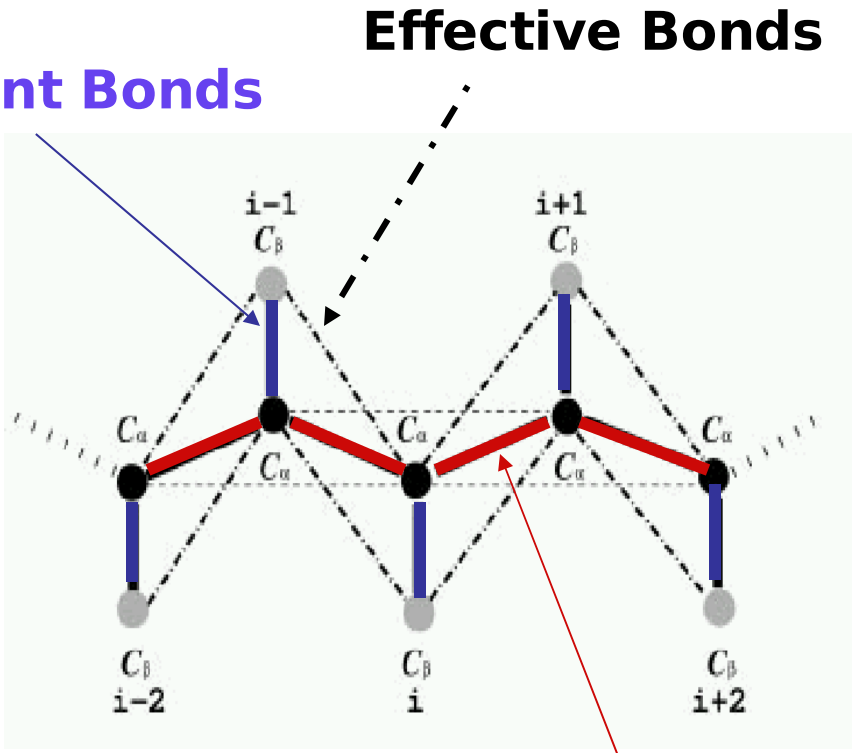
(*) Riddle et al, Nature ,1999.
Martinez and Serrano, Nature Struct. Bio.,1999.

The Two-Bead Representation

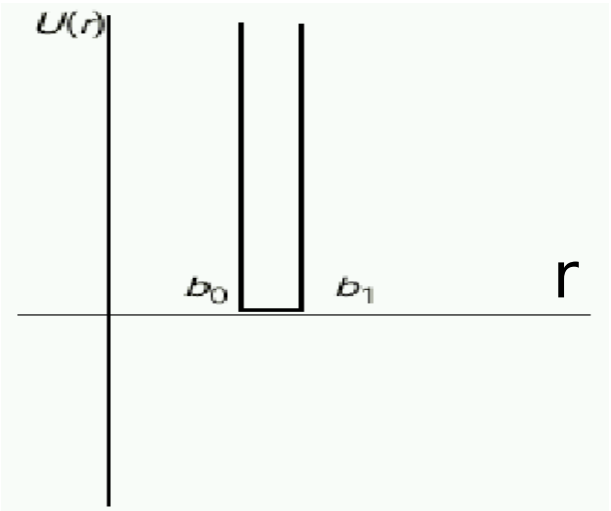
From its atomic structure to a coarse grained model



The Two-Bead Model



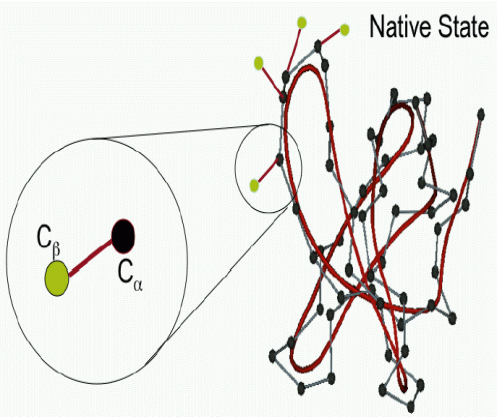
a) C_α - C_α and C_α - C_β Interactions:

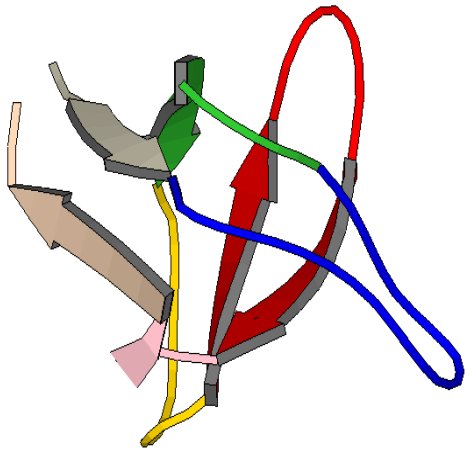


Bond	Bond length (Å)	Deviation (%)
$C_{\alpha i}$-$C_{\beta i}$	1.55	2.4
$C_{\alpha i}$-$C_{\alpha(i\pm1)}$	3.82	3.1

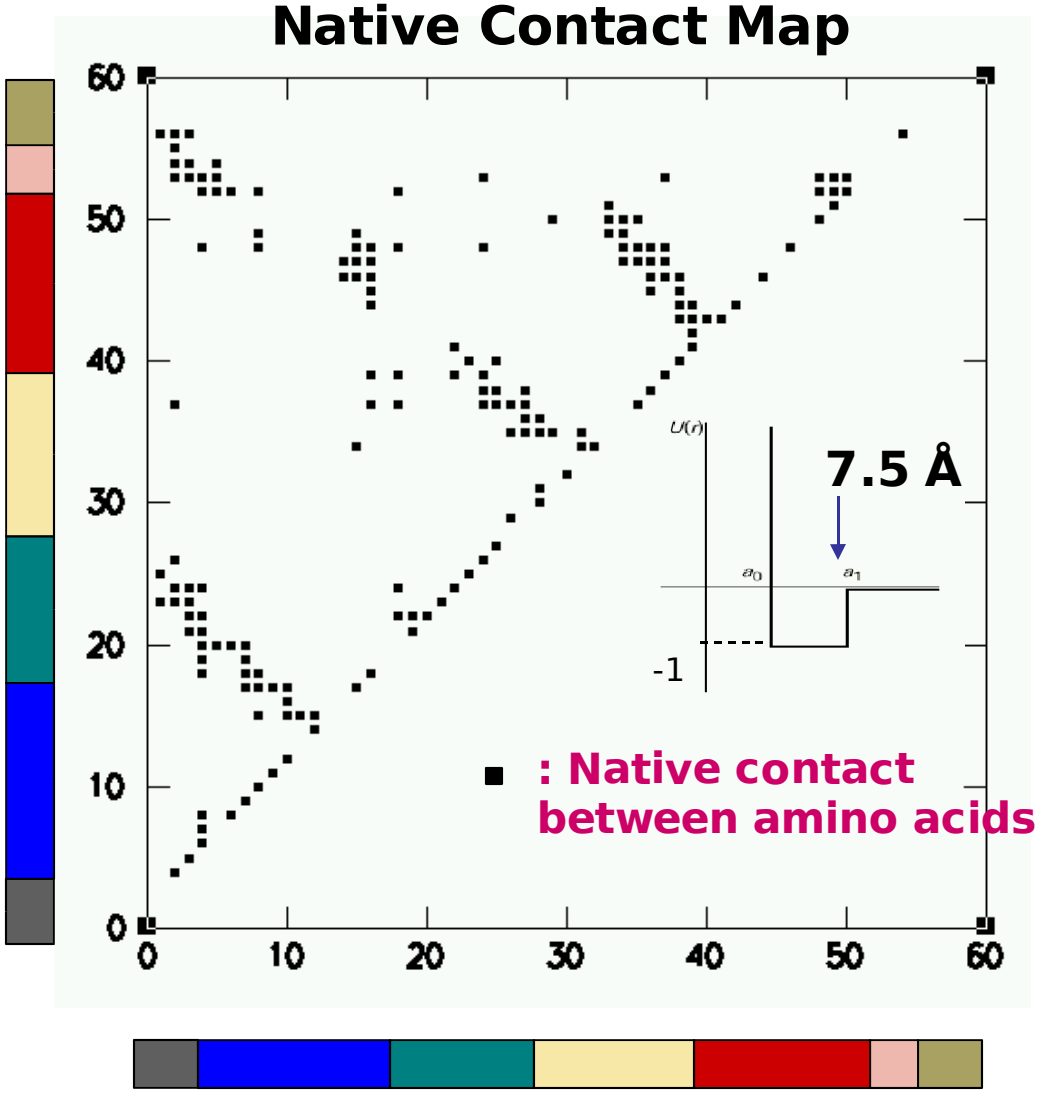
Feng Ding et al., Biophysical Journal,2001

b) C_β - C_β Interactions:





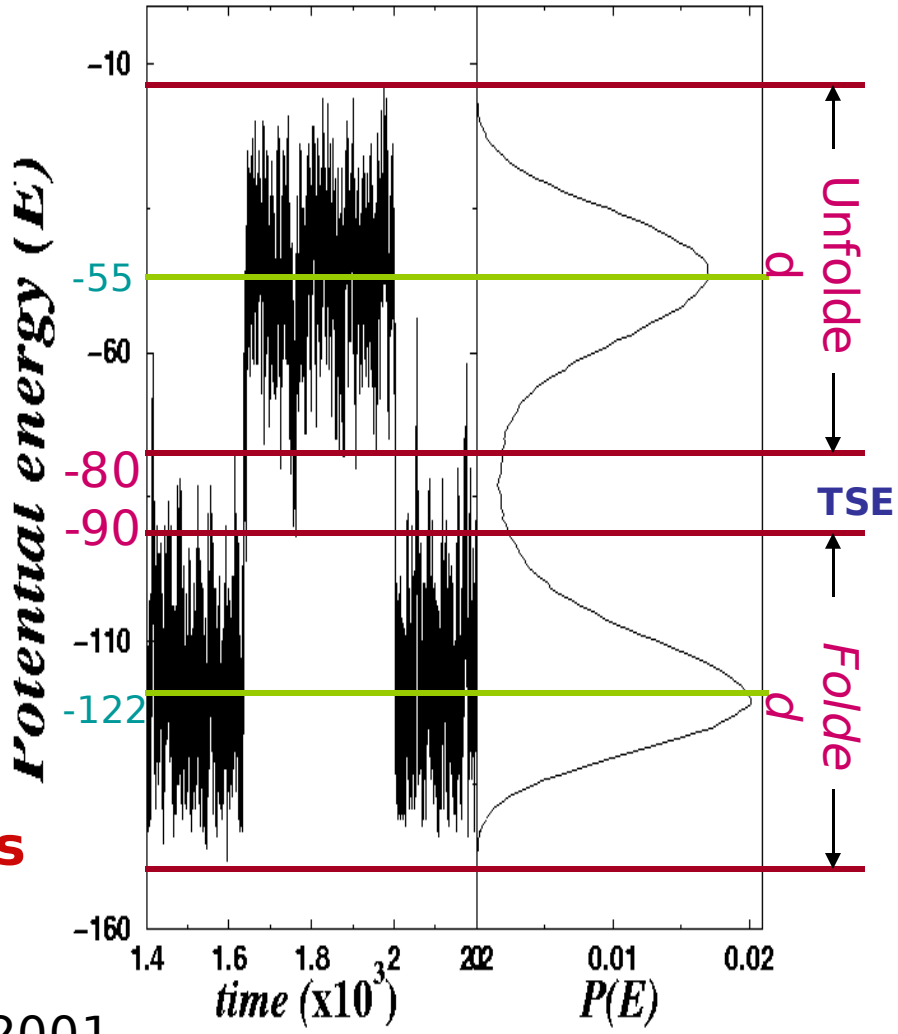
Cutoff = 7.5 Å



Obtaining the TSE

- *Run Long Time DMD Simulation at T_F=0.91.*
- *Select the Potential Energy as the approximate Path of Reaction.*
- *Energy window between -90 and -80 to locate the TSE (*).*
- *Record conformations within the energy window.*

5200 Candidate Conformations obtained.



(*) Feng Ding et al., Biophysical Journal,2001

Filtering the TSE Candidates

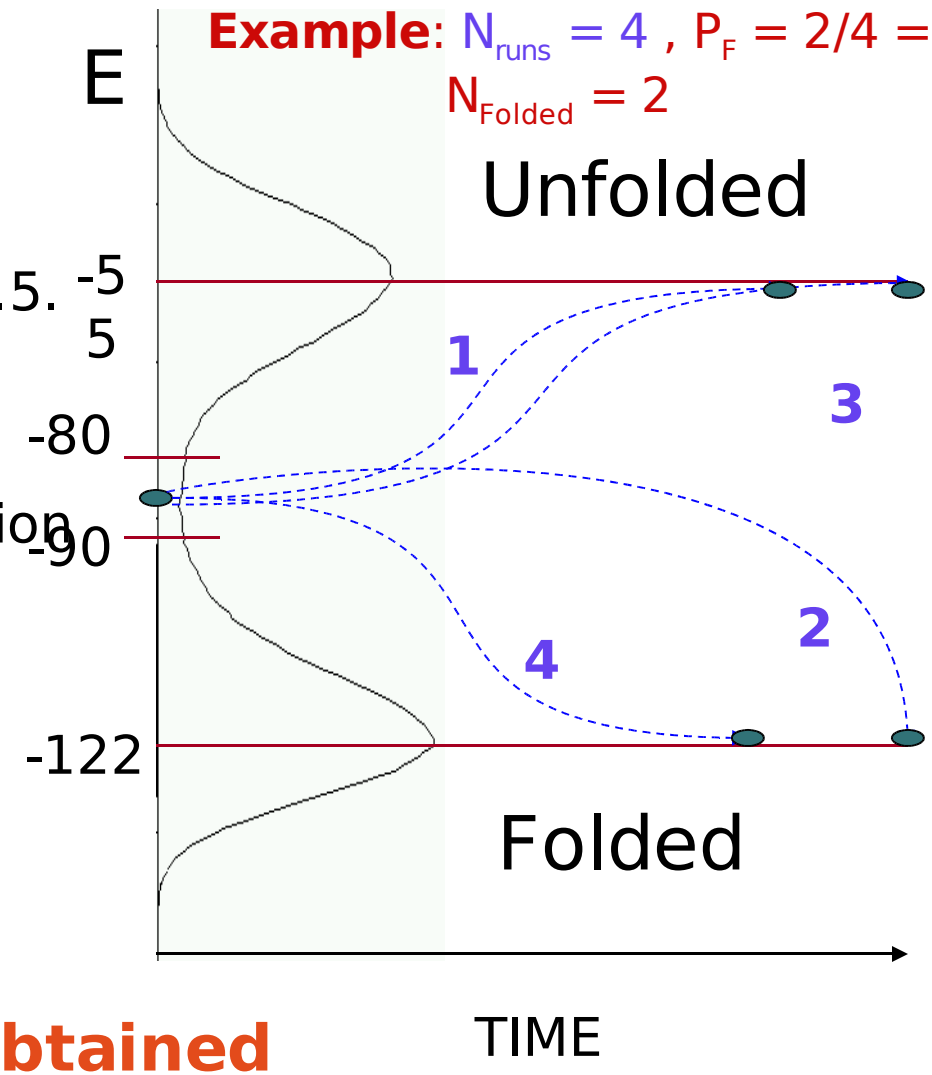
Calculating Folding Probability P_F

1.- TSE conformation has $P_F \sim 0.5$.

2.- Run N_{runs} of DMD simulations for each candidate conformation at T = 0.91.

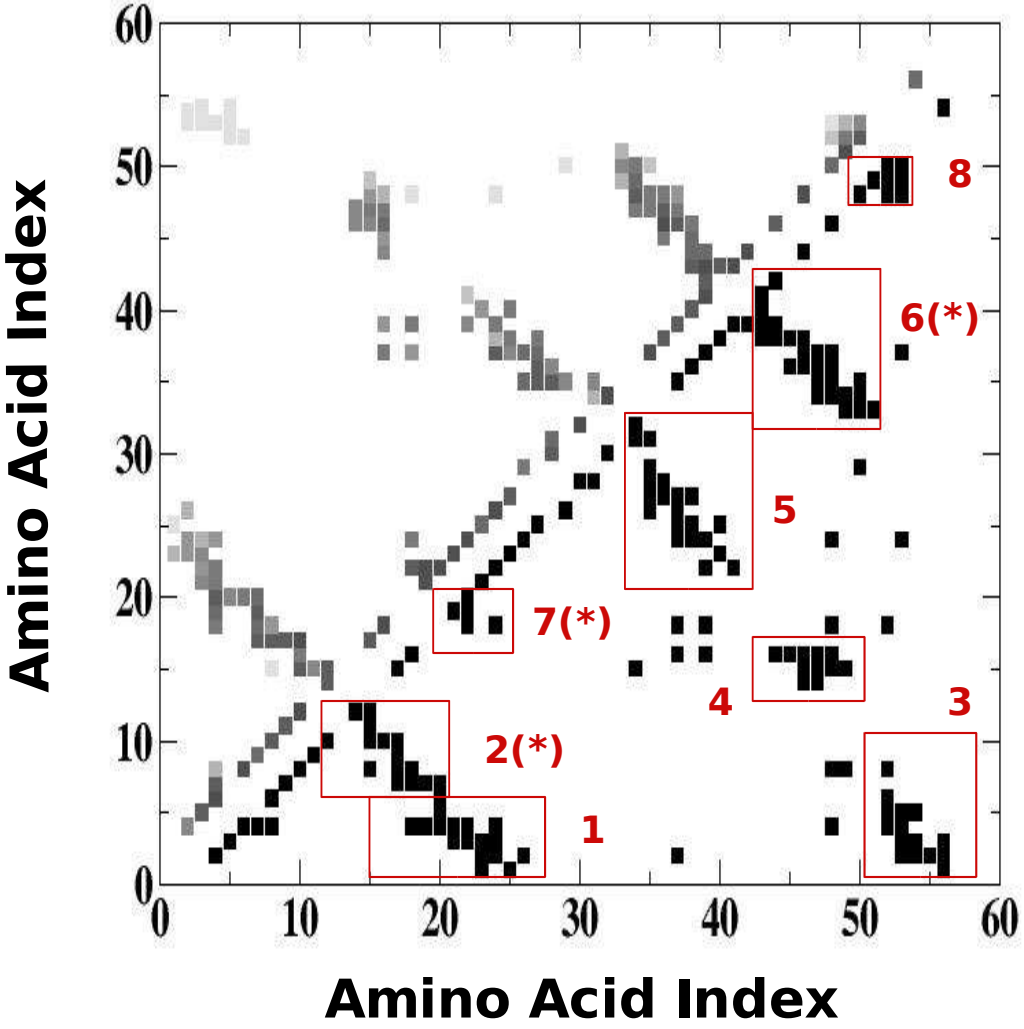
3.- Calculate P_F with:

$$P_F = N_{Folded}/N_{runs}$$

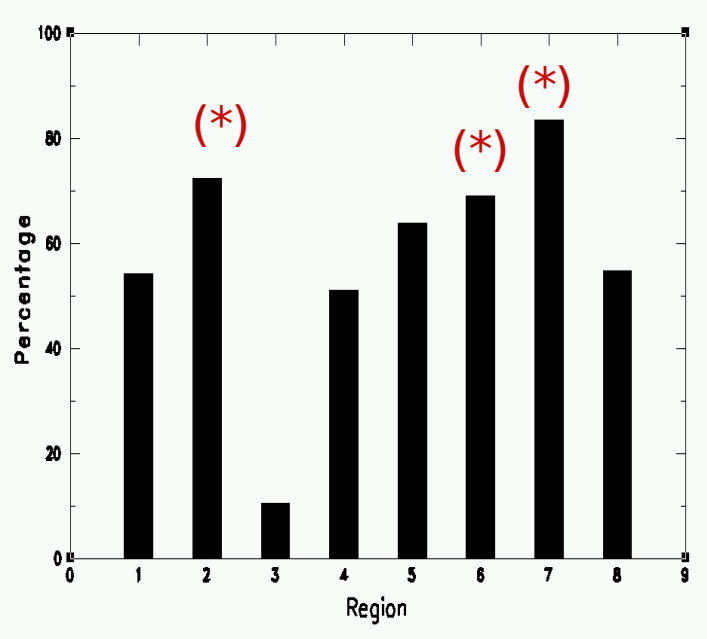


1525 Members of TSE obtained

The TSE Average Contact Map



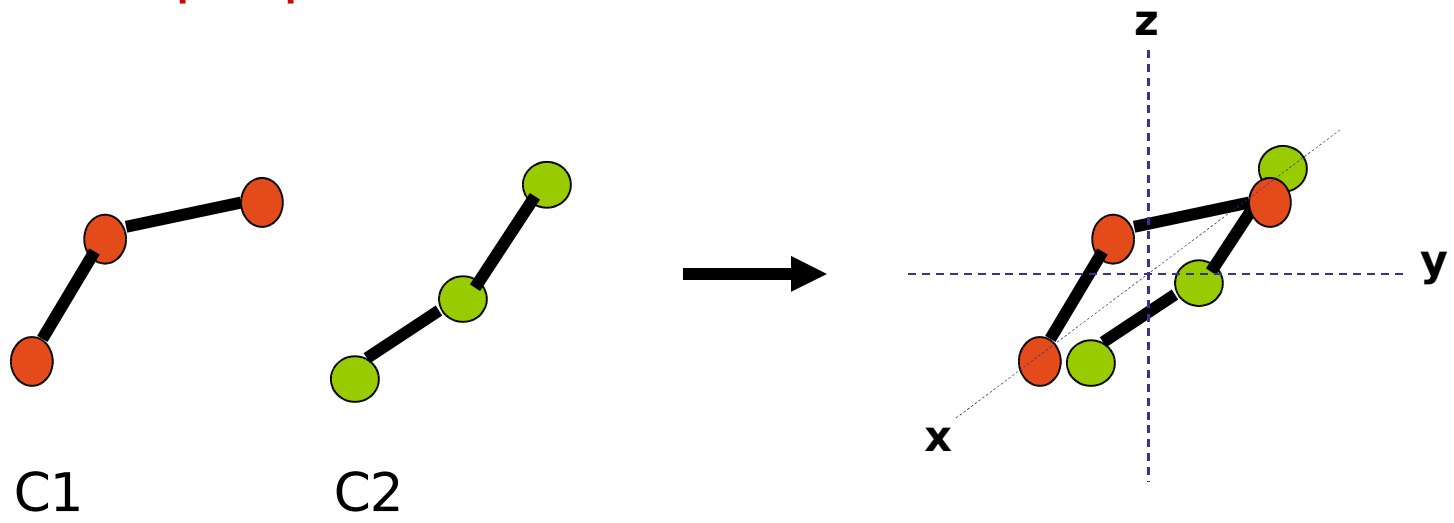
Frequency



(*): Martinez and Serrano, Nature Structural Biology,1999

Root Mean Square Distance (rmsd)

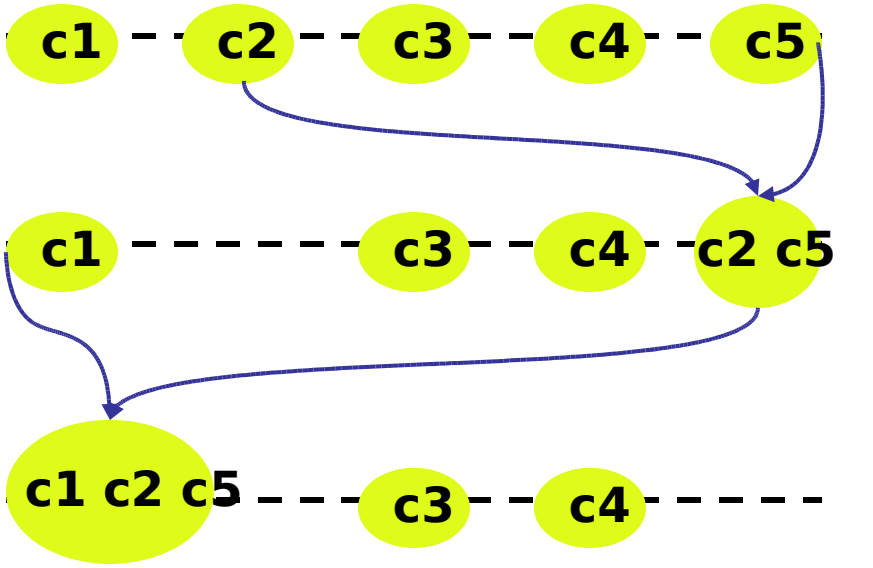
1.- Take two protein conformations C1 and C2 and superpose the centers of mass.



2.- Find the rotation $\Re$ that minimizes the function:

$$\mathbf{rmsd}(C_1, C_2) = \sqrt{\left(\sum_{k=1}^{N} (\mathbf{r}_k^{(C1)} - \Re \mathbf{r}_k^{(C2)})^2 \right)}$$

The Clustering Algorithm(*)



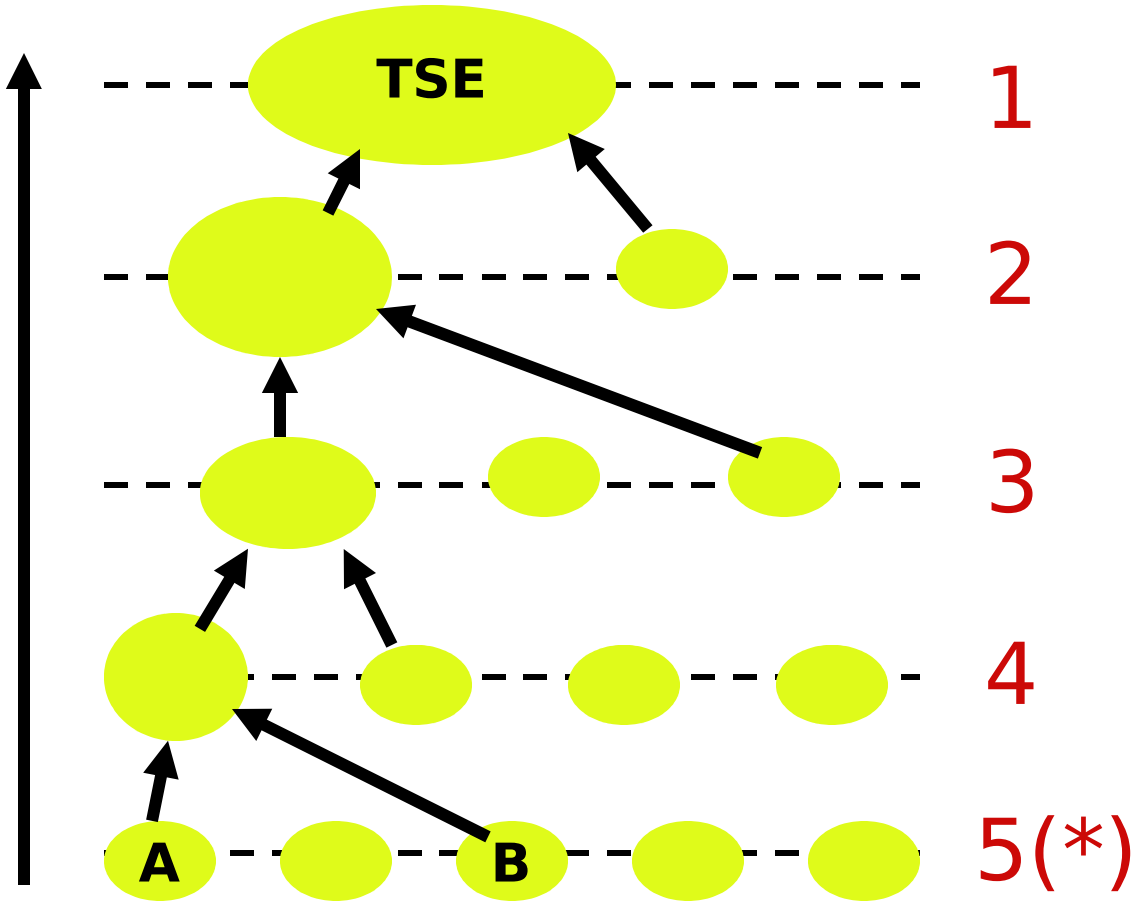
1.- Find pair of clusters with minimal root mean square distance (rmsd).

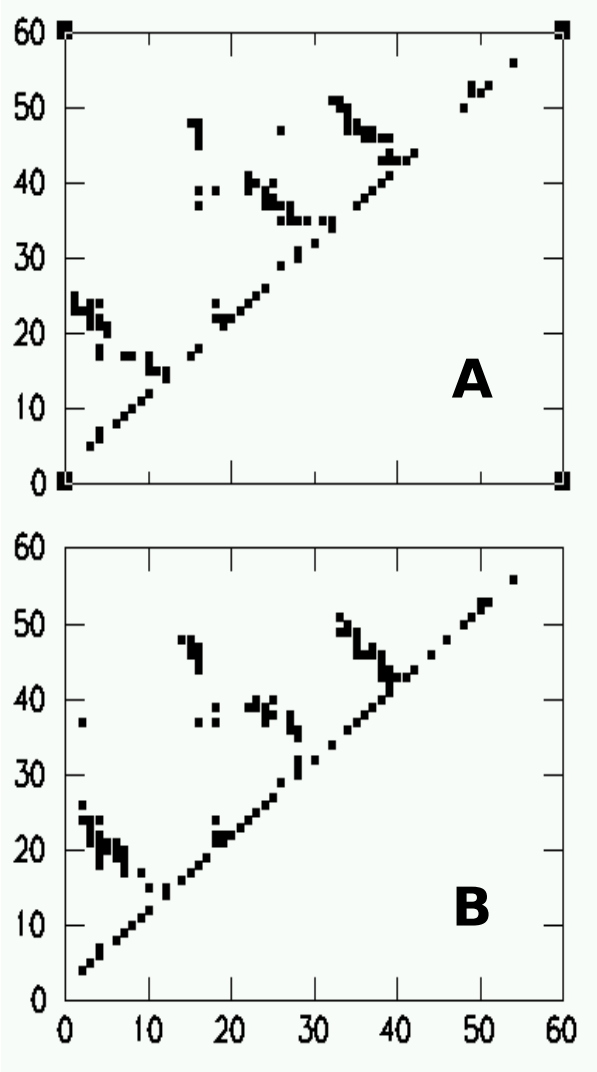
$$\mathrm{rmsd}_{ij} = \frac{1}{\mathrm{N}_i.\mathrm{N}_j} \sum_{C_i} \sum_{C_j} \mathrm{rmsd}(C_i, C_j)$$

2.- Join them. Go to next stage and repeat procedure.

(*): Sneath,P.H.A., Numerical Taxonomy,1973

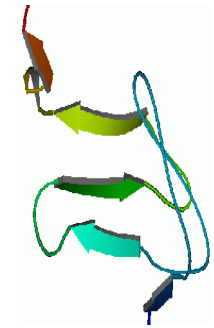
Clustering Tree

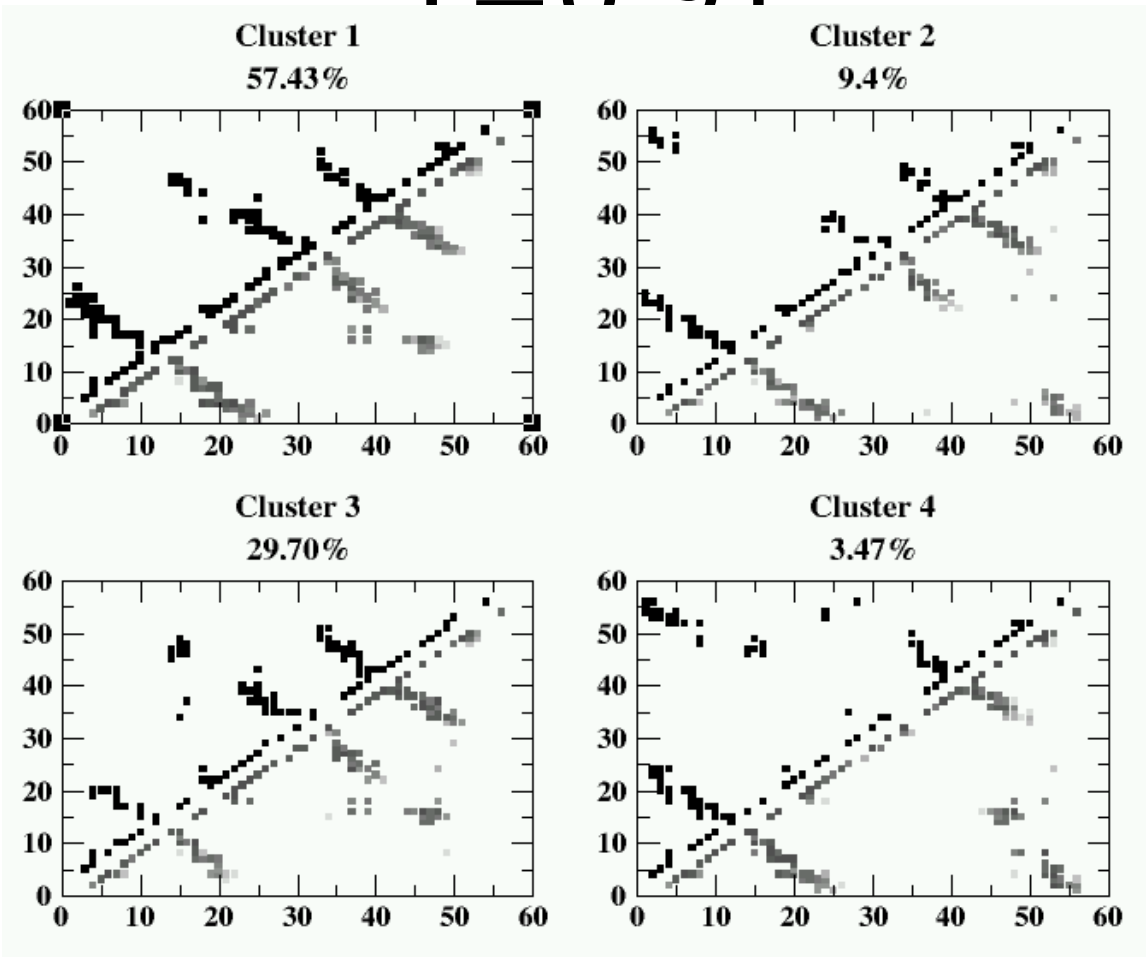


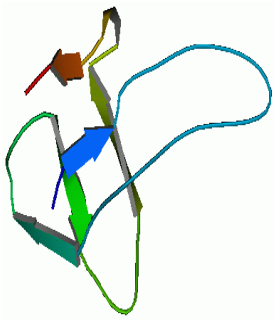


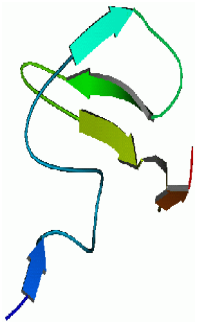
(*)Two similar Folding Pathways when we have 5 Clusters.

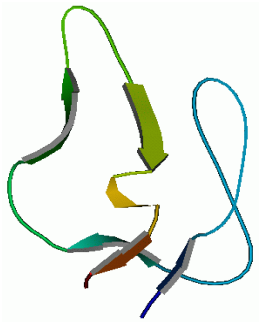
The Clusters Set of TSE for T=0.91











The TSE can be divided into a discrete set of Folding Pathways

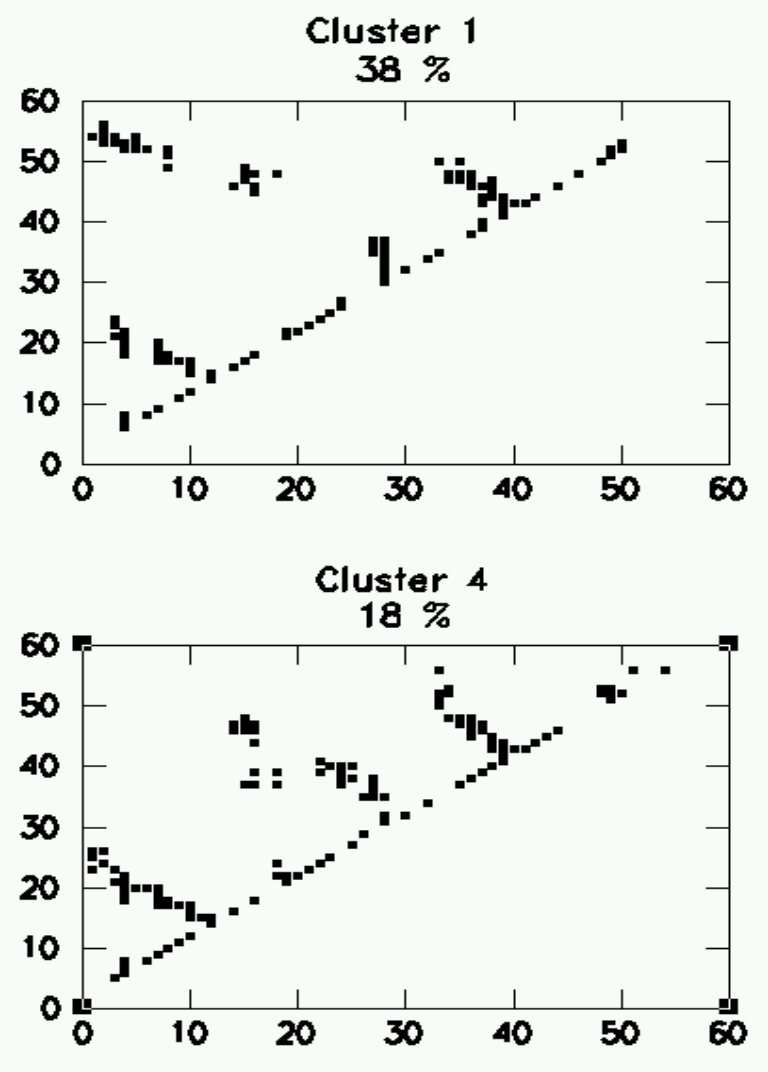
Changing Pathways Preferences

1.- Increase the intensity of contacts for cluster 4 and reduce the intensi of contacts for cluster 1 by using **E’ = E(1-δ).**

2.- The new conformations are used as starting point in our analysis.

3.- Repeat all steps to get the TSE members and make clustering.

Results: The majority of the conformations changes their pathway.

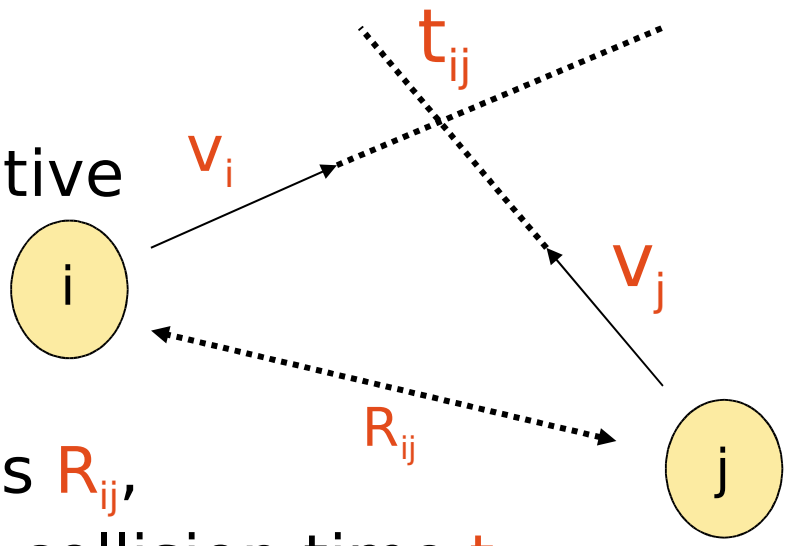


Summary

- TSE structure can be described through a finite number of folding pathways.
- The preference of a conformation to follow a folding pathway can be manipulated by changing the intensity of the contacts present in a pathway.

Discrete Molecular Dynamics (DMD)

Two particles moves with velocities v_i and v_j with relative position r_{ij}.

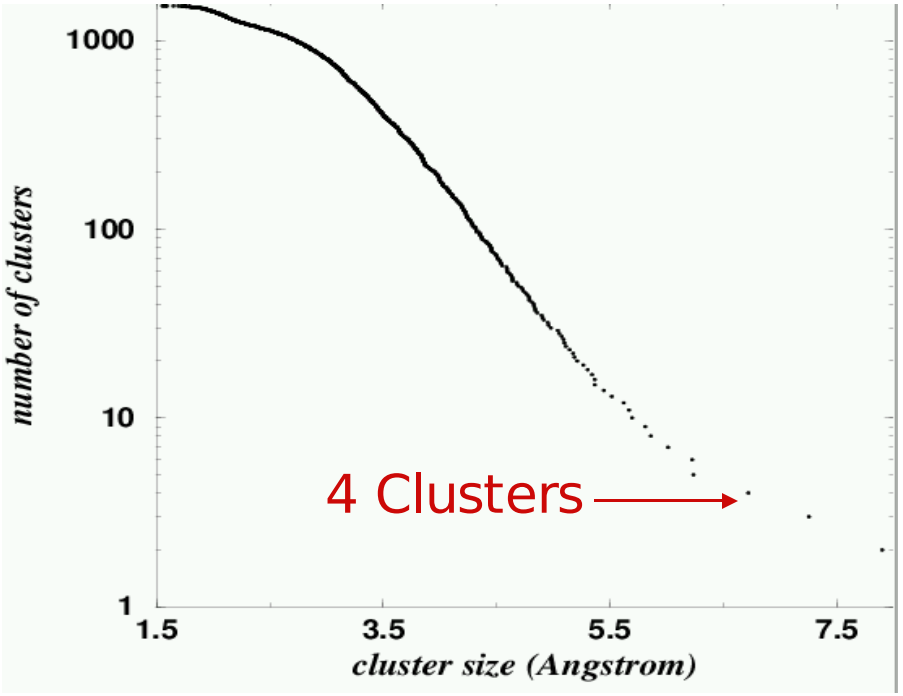


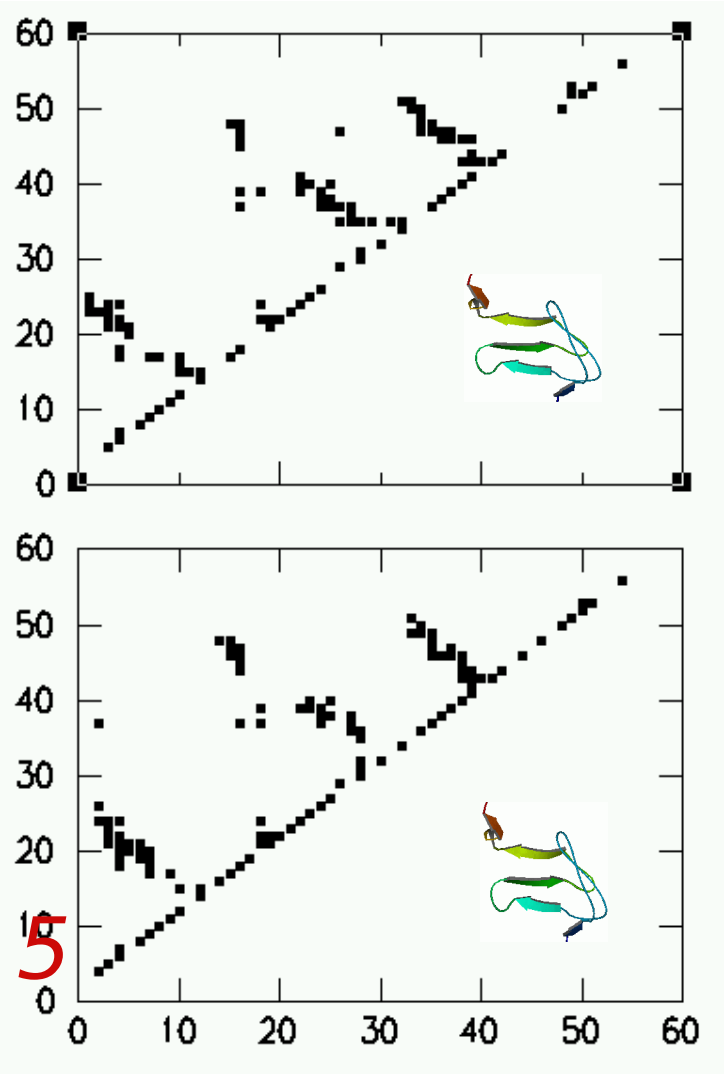
When distance between these two particles becomes R_{ij}, a collision happens and the collision time t_{ij} satisfies: $(r_{ij} + t_{ij}v_{ij})^2 = R_{ij}^2$

Select the pair with minimum t_{ij} and repeat.

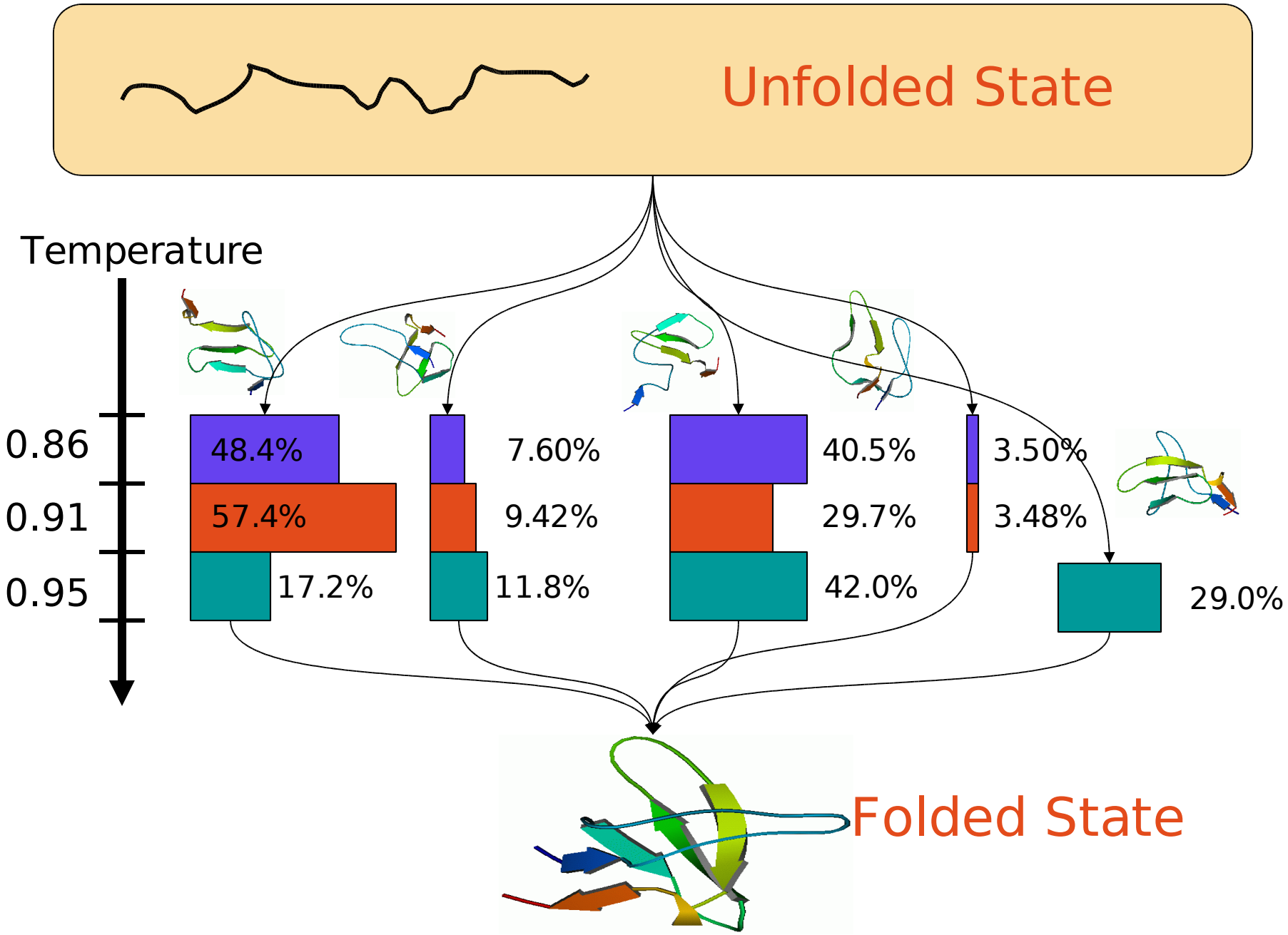
These quantities are conserved: $E_i + E_j$, $P_i + P_j$ and

Why 4 Clusters?





Two similar Folding Pathways when we have 5 Clusters.


Unfolded State
Temperature
0.86
0.91
0.95
48.4%
57.4%
17.2%
7.60%
9.42%
11.8%
40.5%
29.7%
42.0%
3.50%
3.48%
29.0%
Folded State