Towards identification of a hydrophobic core in globular proteins

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ICT PRAGUE

Hydrophobic core (HC) concept:

- HC is a set of hydrophobic amino acid residues buried inside the protein.
- These amino acids significantly contribute to stability of the protein
- HC is often conserved in proteins with similar structure
- HC has evident correspondence with folding nucleus
- Destruction of HC is often critical step of protein denaturation
- Prediction of HC architecture is a critical step towards solution of protein folding problem

BUT:

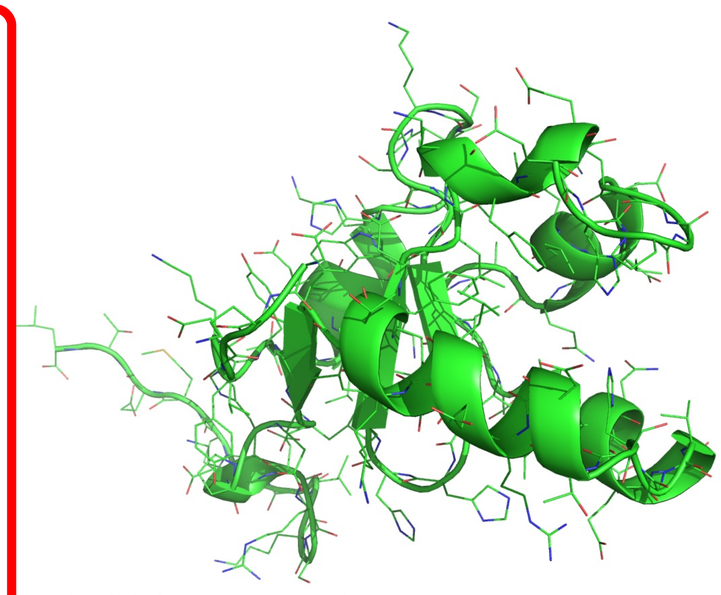
- There is no algorithm for HC identification which would lead to reliable, quantitative and transferable methodology of core search.

Interaction energy matrix (IEM) concept:

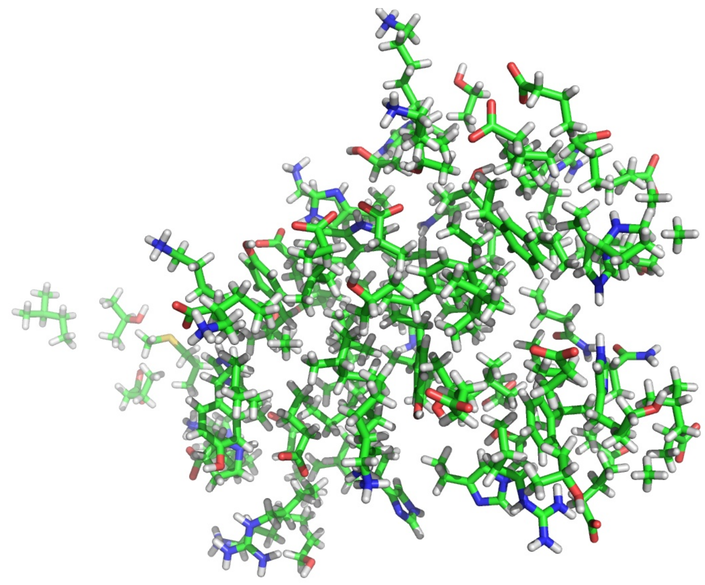
- Interaction energy matrix is a computational tool that allow us to evaluate amino acid side chains contribution to intramolecular stabilisation energy of a protein and to assess importance of the contact.
- Our analysis are based on Amber03 empirical force field calculations.
- Interaction energies between uncharged residues are similar to benchmark values determined by CCSD(T)
- To evaluate only side chain contribution to the stability we remove backbone atoms of amino acids by replacing C alpha atoms by methyl CH3 groups.

The amino acid contact definition:

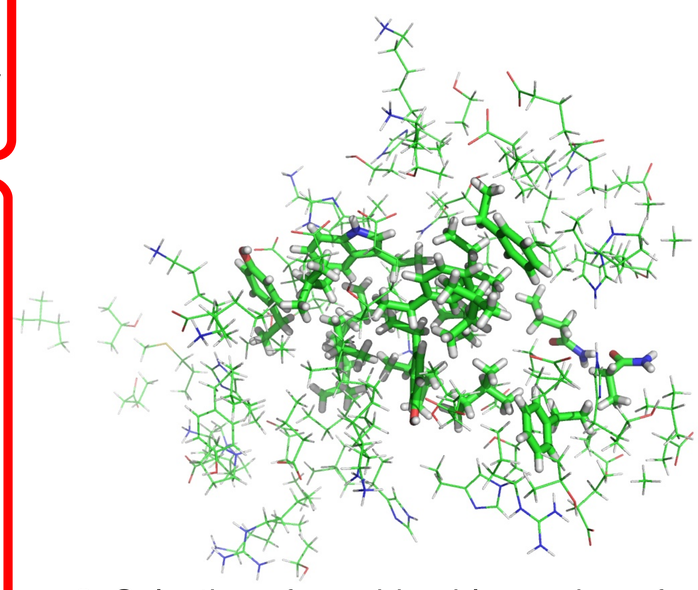
- To determine whether two residues are in contact we define treshold of 0.5 kcal/mol. to fall into this category
- In a parallel study we show that this definition of contact is reasonable and most convenient.
- Following this value, number of contacts of particular residue very well correlates with sum of interaction energies of with its neighbors. The slope of this linear function is for all proteins from dataset almost the same.



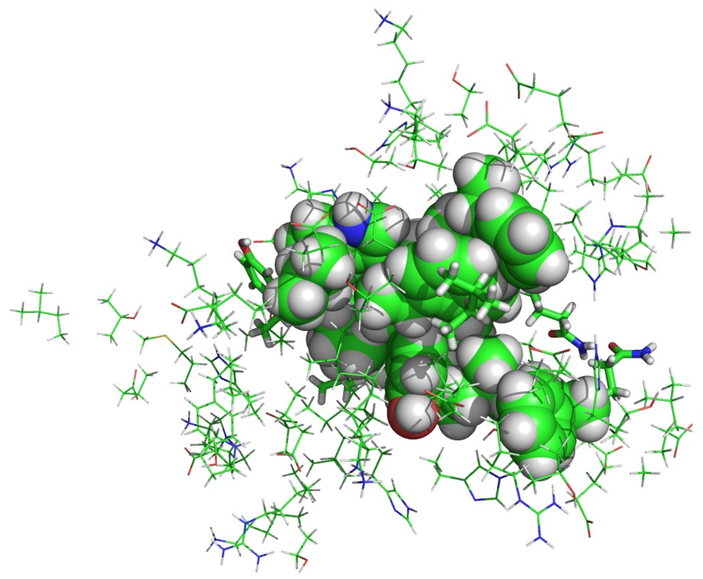
1. PDB structure of globular protein with or without hydrogens



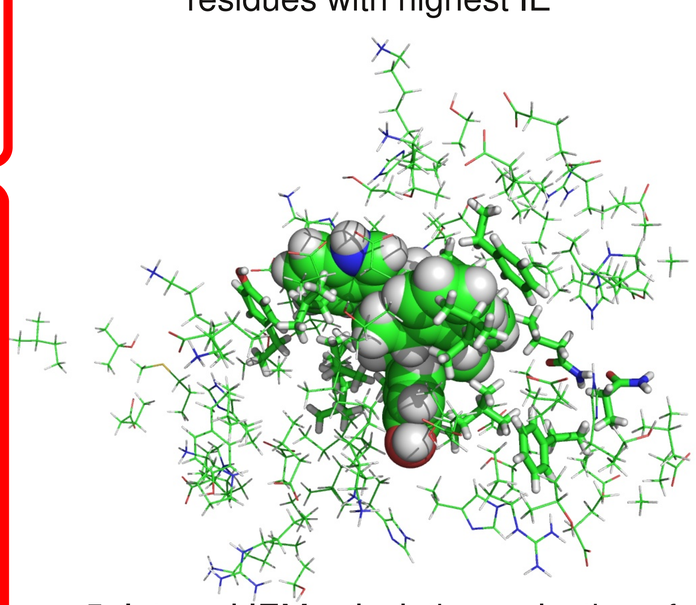
2. A03 C alpha force field, IEM calculation



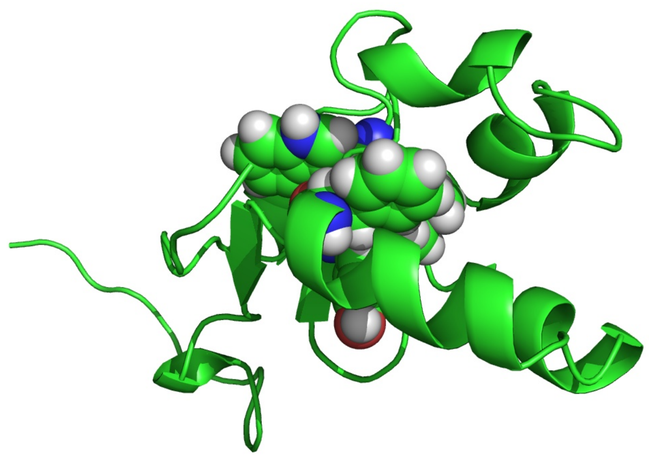
3. Selection of considerable number of residues with highest IE



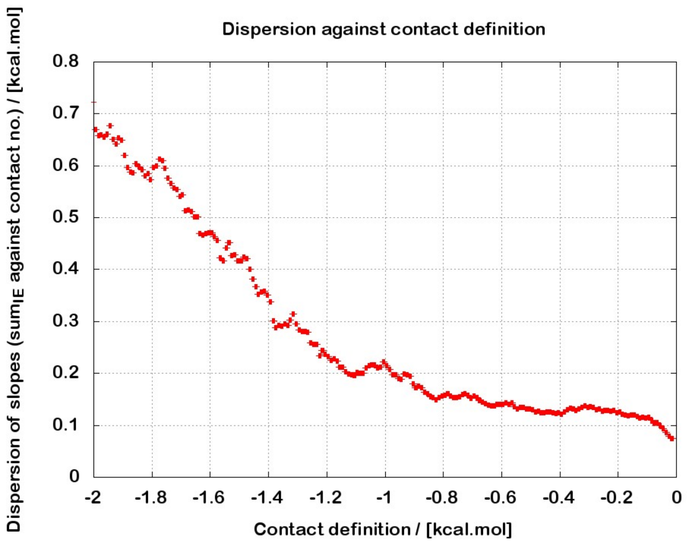
4. Elimination of surface residues

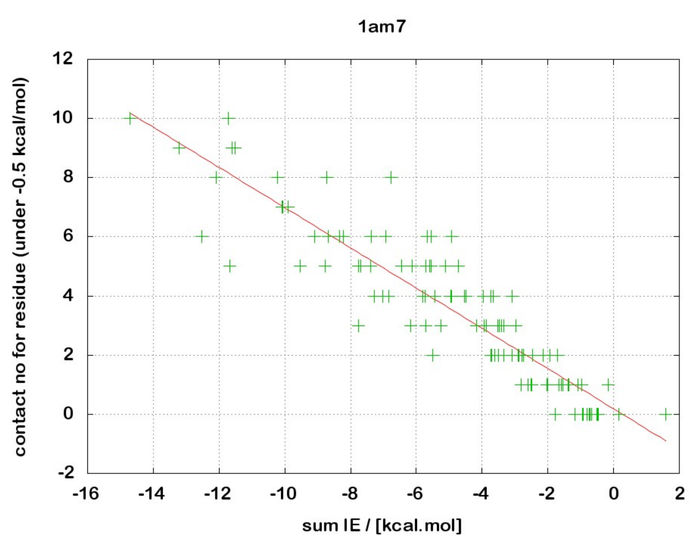


5. Internal IEM calculation, selection of considerable number of residues with highest IE



6. Output of program can be used for latter investigation





Removing surface residues:

- To exclude solvent exposed residues that have high interaction energy but do not contribute to intramolecular stabilization significantly we perform solvent accessible surface analysis using Gromacs computational package to identify these residues and exclude them from the set.
- This step is quite sensitive to parameters.

The HC amino acid final selection:

- The number of residues considered for HC composition is tied to a structural determinant of protein recurrent procedure of amino acid importance according to IEM

RESULTS:

- We offer automatic procedure that returns set of proposed hydrophobic core residues in given globular protein structure with reasonable level of reliability

- We plan to offer this method together with IEM calculation tool as a web application at Center's site.

References:

[1] Identifying stabilizing key residues in proteins using interresidue interaction energy matrix, Bendová-Biedermannová et al., Proteins: Struct., Funct. & Bioinf, 2008
[2] Unexpectedly Strong Energy Stabilization Inside the Hydrophobic Core of Small Protein Rubredoxin Mediated by Aromatic Residues: Correlated Ab Initio Quantum Chemical Calculations, Vondrášek et al., JACS, 2005
[3] Analysis of Energy Stabilization inside the Hydrophobic Core of Rubredoxin, Berka et al., ChemPhysChem, 2009

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