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FrustraPocket: a method to predict protein–ligand binding sites based on frustration

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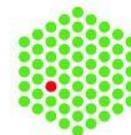
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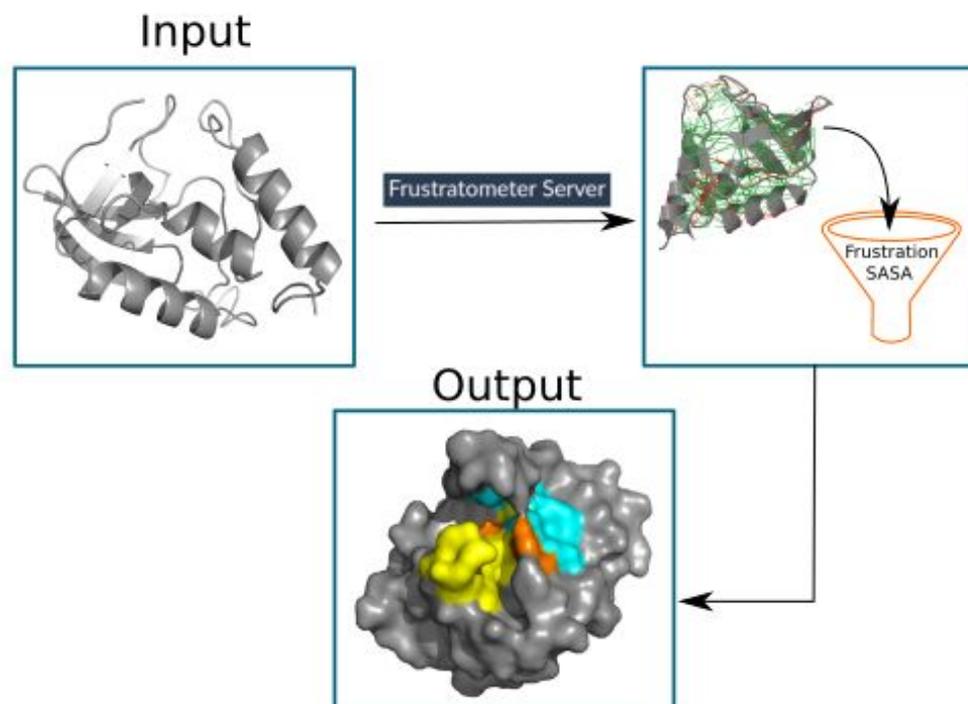
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FrustraPocket: a method to predict protein–ligand binding sites based on frustration

Graphical Abstract



Introduction

- Need to predict protein-ligand interaction pockets for docking.
- It has been shown that frustration is associated with several biological aspects.
- The energetic patterns of the protein-ligand interaction sites were characterized.



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Introduction

Energy Landscapes Theory

Native interactions are more favorable than random interactions.

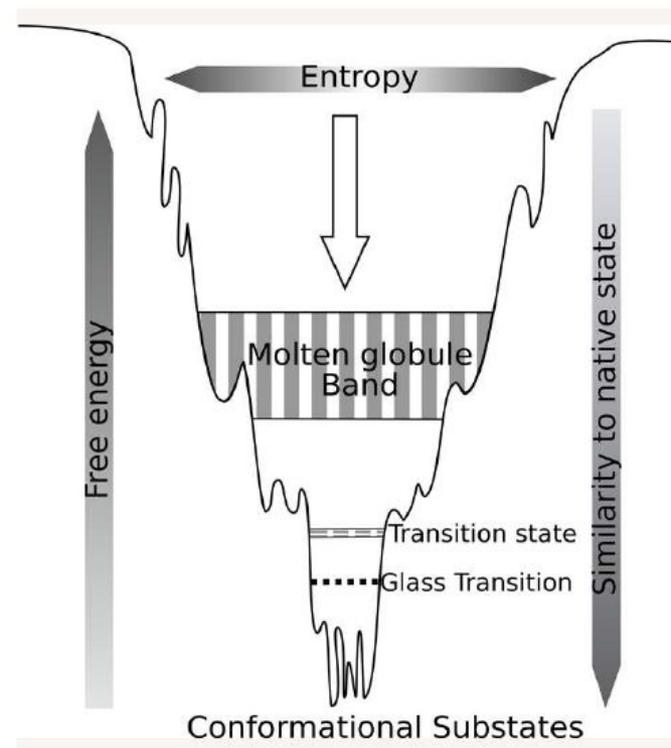
Protein folding is cooperative.

Global energy **minimization**

“Minimum Frustration Principle”

There are residual **conflicts** in the native state.
Important for function

Can we quantify these conflicts? Are they really important for protein function?



(Bryngelson and Wolynes. PNAS 1987)



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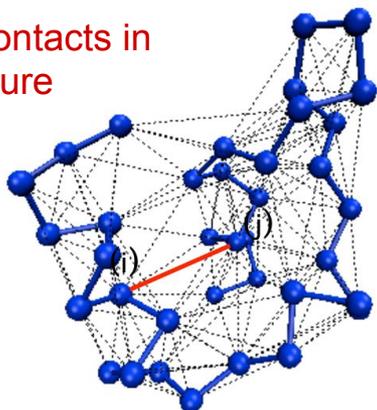


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Introduction

Localize and quantify local frustration

Define Contacts in
the structure



3 different Frustration indexes

Decoys construction (variables i, j, r_{ij})

Contact Level

- Mutational: i and j residues identities randomization.
- Configurational: i and j residues identities and the r_{ij} distance randomization.
- Single Residue Level: i residue identity randomization

Classify Contact:

- **Highly Frustrated** (~10%)
- Neutral (~50%)
- **Minimally Frustrated** (~40%)

(Ferreiro et. al. PNAS 2007)



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Introduction

Data set

- We used the BioLiP database which is a database that has annotations about protein-ligand binding sites.
- We only select enzymatic proteins and their oligomeric state are monomers.
- A total of 1007 proteins were selected



Yang, J. et al. (*Nucleic acids research*, 2012).



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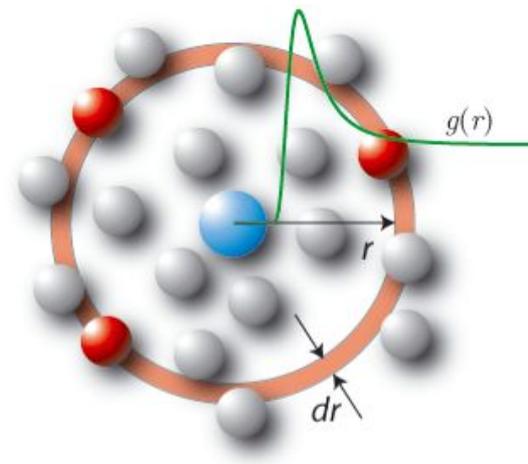


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Results and discussion

Pair distribution function

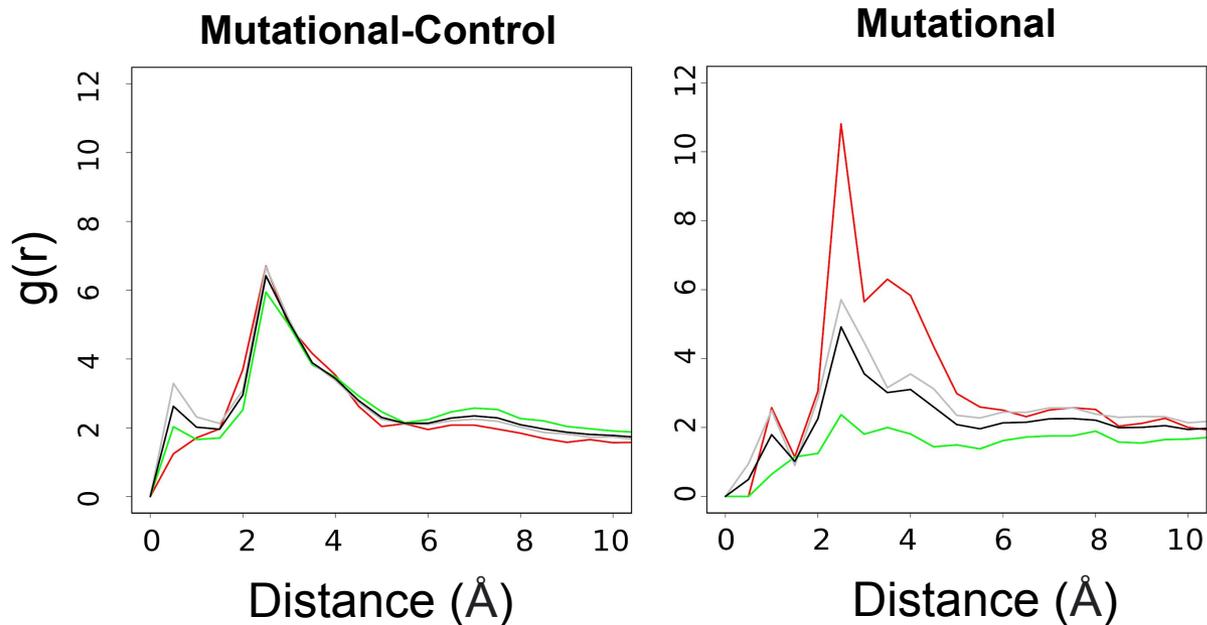
- $g(r)$ between the Ca of the protein and those of residues that are involved in protein-ligand interactions.
- $g(r)$ values were normalized such that $g(20)=1$
- x-axis are represented the distance (\AA)
- y-axis the value of the $g(r)$



Results and discussion

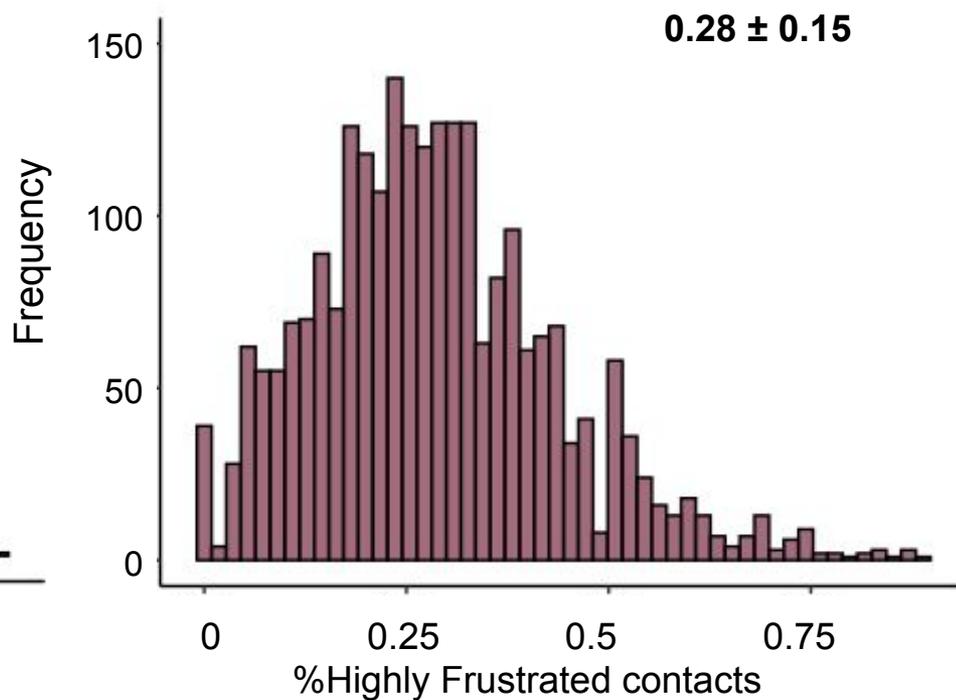
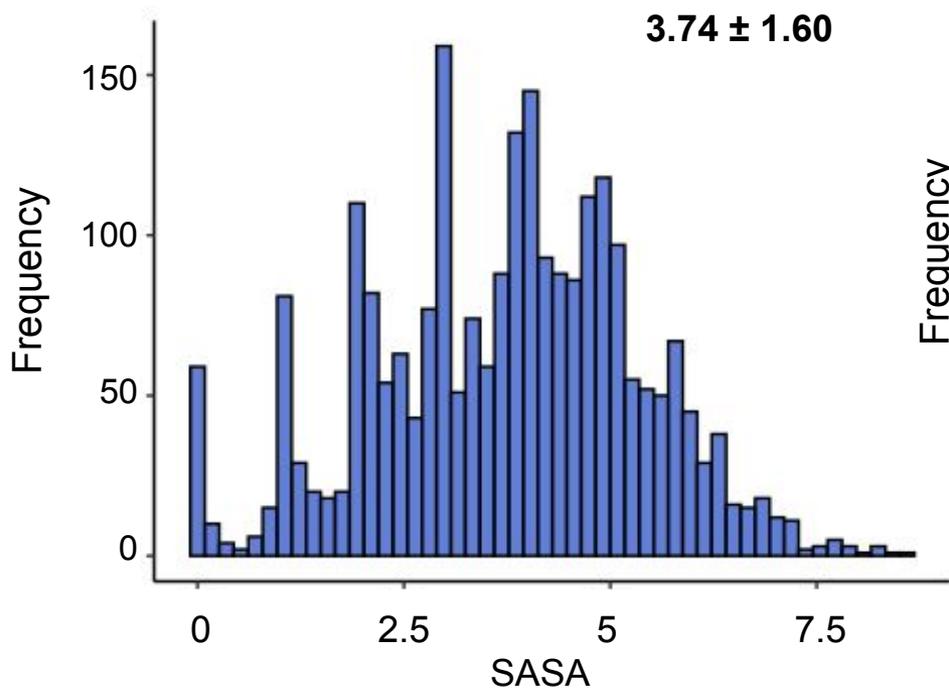
Characterization of residues interacting with ligands

- $g(r)$ between the Ca of the protein and those of residues that are involved in protein-ligand interactions.



Results and discussion

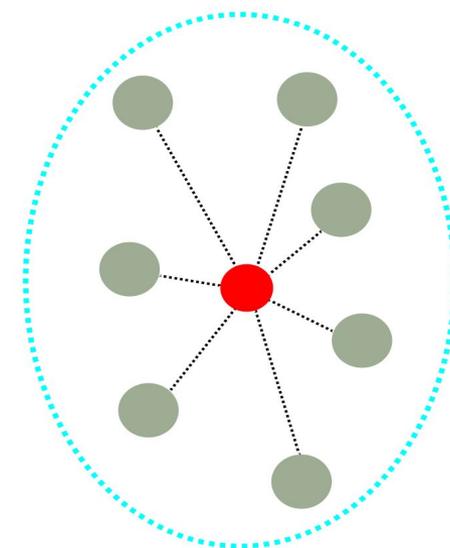
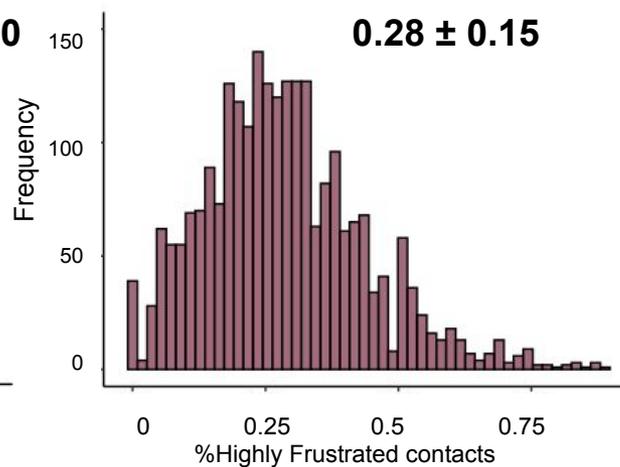
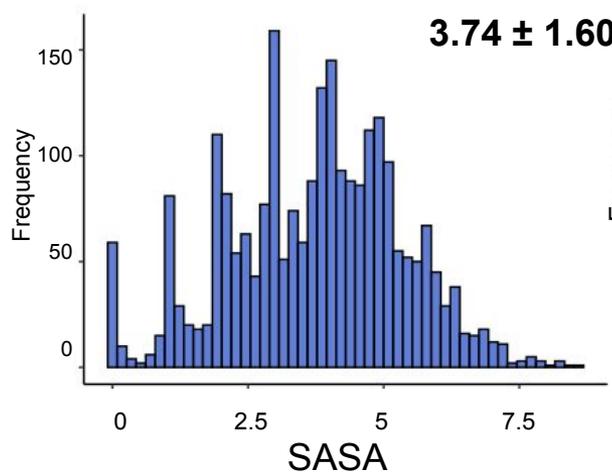
The frustration index and sasa were used as a parameter for prediction.



Results and discussion

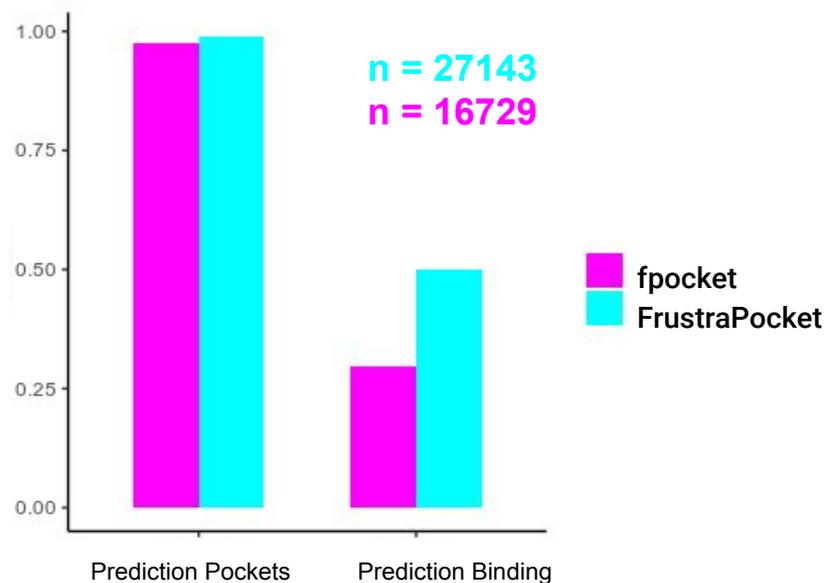
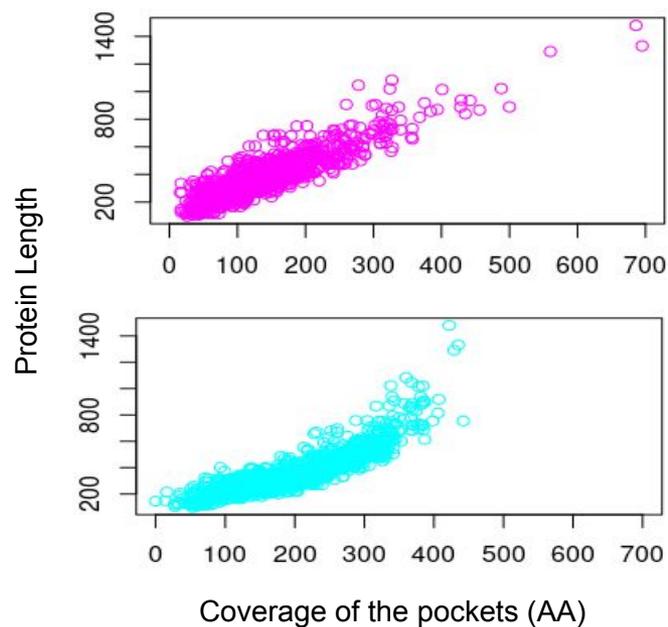
Characterization of residues interacting with ligands

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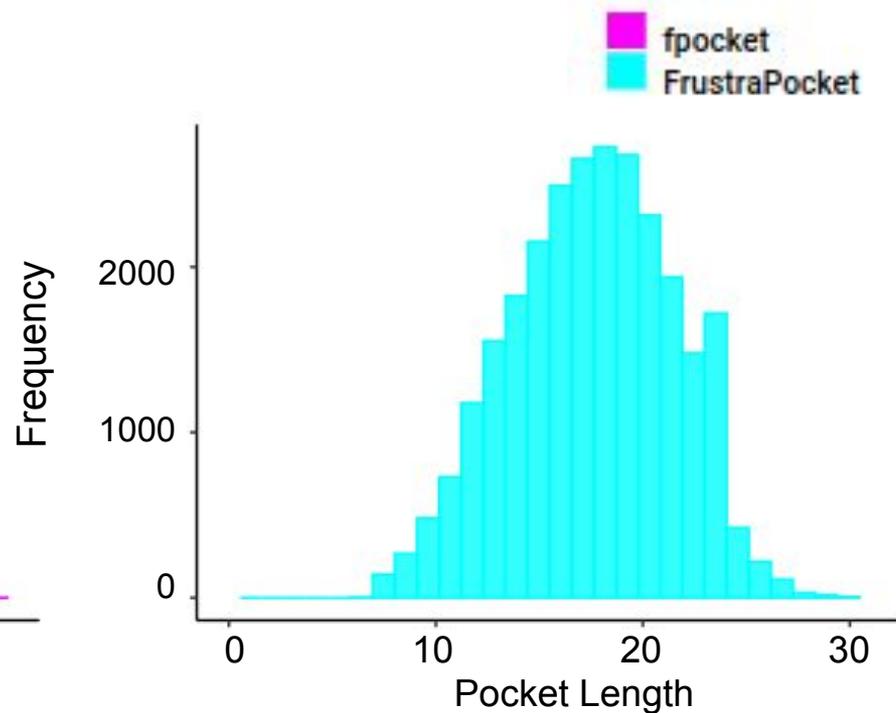
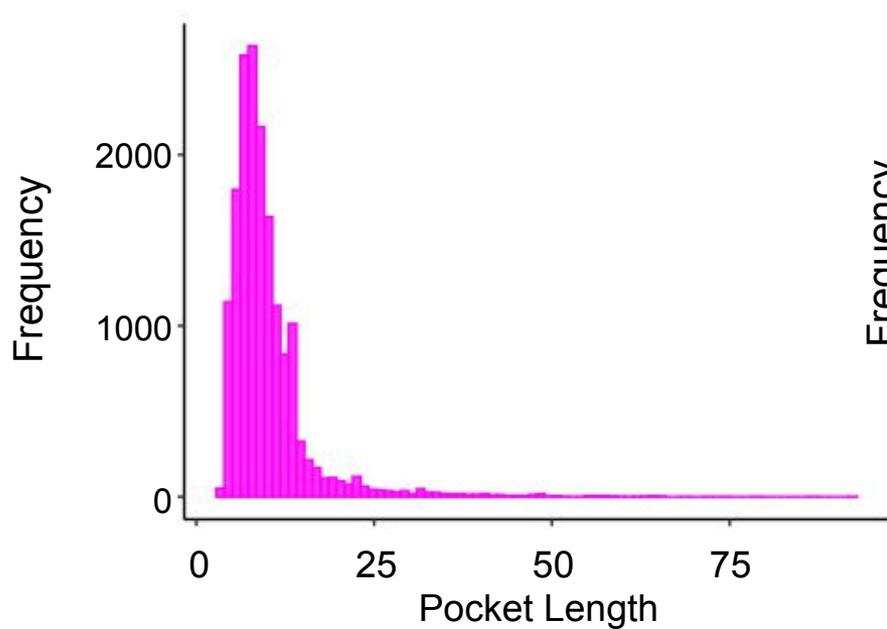
Results and discussion

Prediction and pocket coverage



Results and discussion

Pocket size



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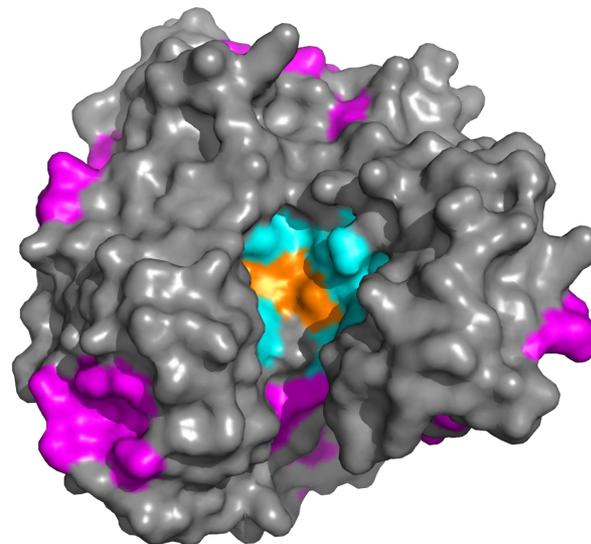
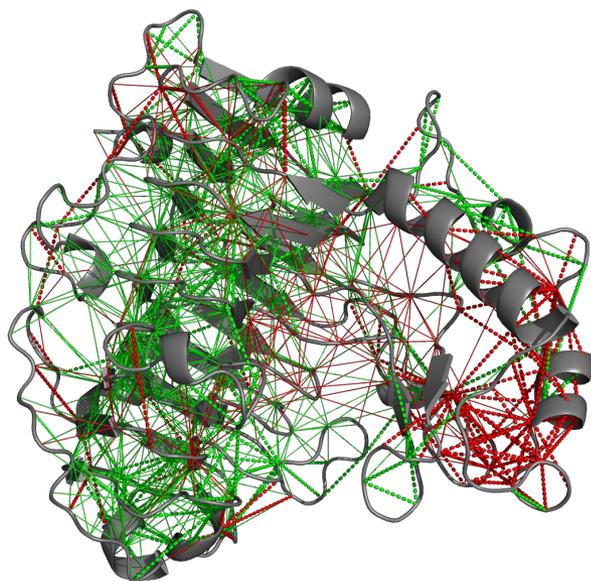
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Results and discussion

Prediction of pockets



PdbId: 1bn8

In orange, the residues of FrustraPocket that match with the protein-ligand interaction residues of the protein, FrustraPocket (blue), fpocket (pink)



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Conclusions

- We have found that the residues that are implicated in **protein - ligand interactions** are enrichment in **highly frustrated interactions**.
- The frustration and SASA were used to predict protein-ligand interaction pockets.
- The prediction of FrustraPocket was compared to the prediction of fpocket tool. It was found that not only does FrustraPocket **predict pockets in more proteins**, but also the **percentage of success of the pocket binding was higher**.



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