CIS529: Bioinformatics

Protein Interactions and Interfaces

Presented by

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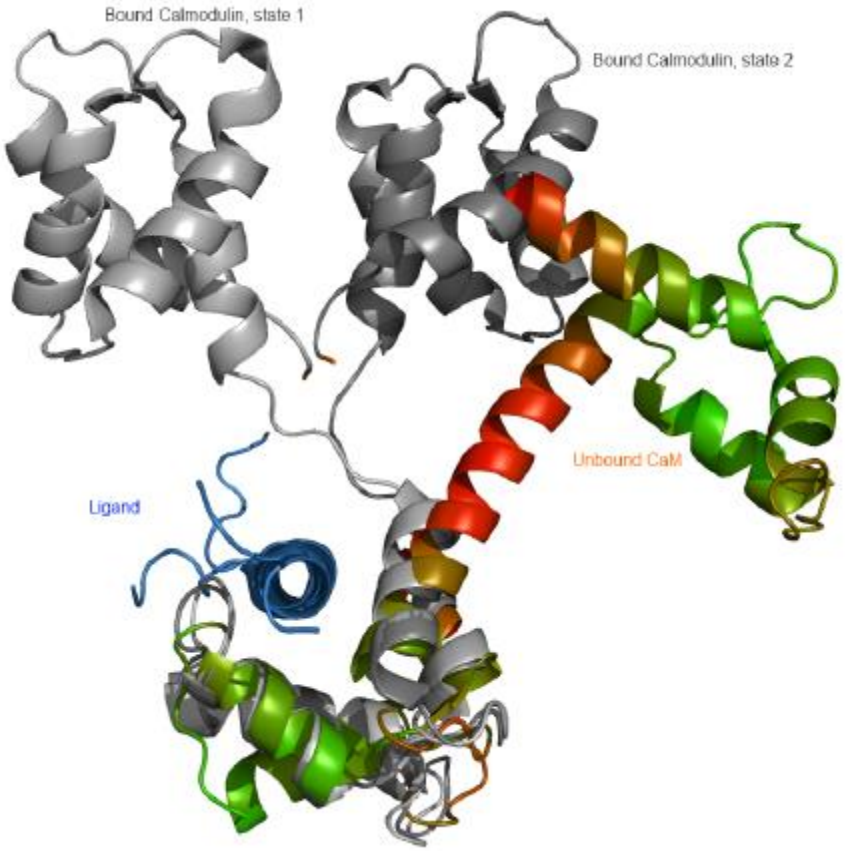
Formation of protein complexes

- Proteins physiochemically interact with eachother
- But why do proteins bind ‘spontaneously’?
- Same energetics and interactions as ones involved in protein folding
- Reduces the free energy of the two proteins separately as a consequence of non-covalent interactions between participating proteins
  - For example: Burial of non-polar residues
    - Decrease in enthalpy
    - Increase in entropy of water molecules

Formation of protein complexes

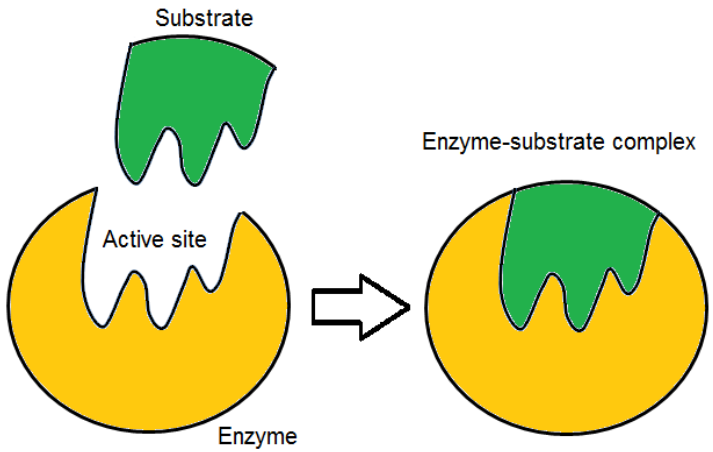


Formation of protein complexes

- Strength of binding
  - Binding affinity
  - Change in free energy of the complex and the sum of free energies of the unbound components
  - Usually very small: - 2.5 to -22 kcal / mol
    - Protein complexes are only marginally stable
    - For comparison: Breaking a single covalent bond requires 65-175kcal/mol

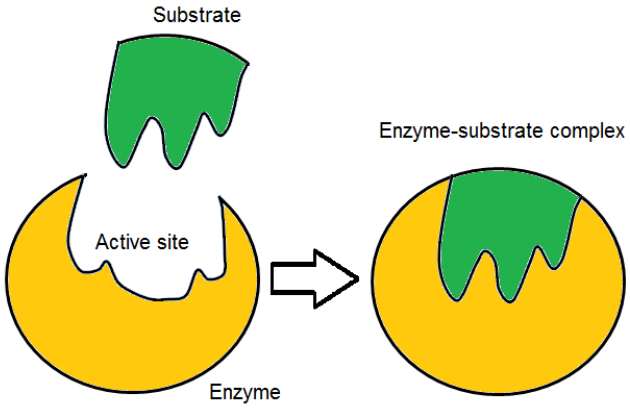
Models for protein interactions

- Lock and Key Model
  - Shape complementarity between the proteins and the binding molecules is essential for binding



Models for protein interactions

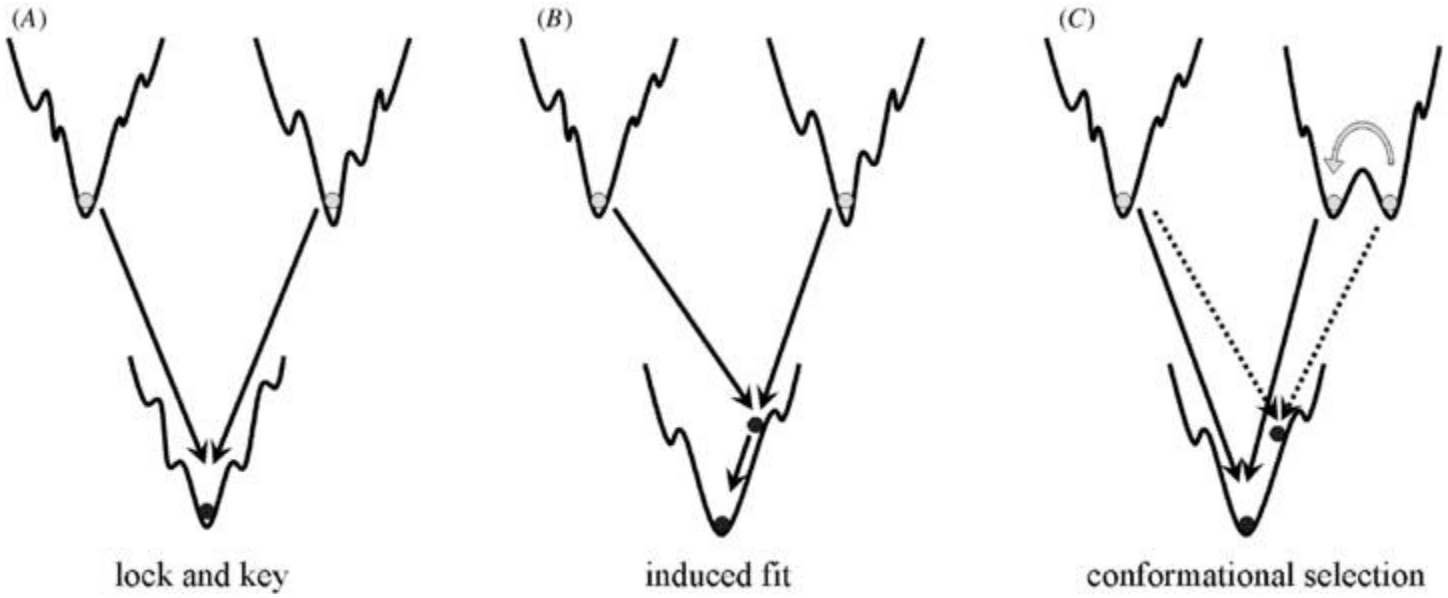
- Induced Fit Model
  - Shape complementarity is important but is not the sole cause of binding
  - The binding process is also driven by non-covalent intermolecular forces such as van der Waals interactions, hydrophobic effects and Hydrogen bonding
  - Binding process can cause conformational changes in the protein leading to an induced fit of the binding partner to the protein



Models for protein interactions

- Conformation Selection Model
  - The protein is dynamically fluctuating
  - The ligand selects the conformation of the protein which is compatible with binding
  - Shifts the conformational ensemble towards this state

Energetics



he three classical models for interactions between globular proteins: (*A*) lock and key model, (*B*) induced fit model and (*C*) conformational selection. The energy of the system is sketched against a single coordinate of the conformational space. The initial and final states of proteins are represented by light and dark dots, respectively. Arrows mark the pathways of binding and dotted arrows show binding pathways with unfavorable energies.

. Mészáros, I. Simon, and Z. Dosztányi, "The expanding view of protein–protein interactions: complexes involving intrinsically disordered proteins," *Phys. Biol.*, vol. 8, no. 3, p. 035003, Jun. 2011.

Types of Protein Interactions

- Homo and Hetero Complexes
- Obligate or Non-obligate
  - If proteins in a complex can exist as independent tertiary structures then such a complex is called non-obligate
  - Non-obligate complexes can be transient or permanent
    - Transient complexes break down after formation in vivo

Types of Protein Interactions

- Based on functional context
  - Enzyme-Substrate
  - Antibody-Antigen
  - Receptor-Hormone

- Task
  - Find at least one example of each of the following in the PDB
    - Homodimer
    - Heterotrimer
    - Obligate Complex
    - Transient Coimplex
    - Permanent Complex
    - Enzyme-Substrate, Antibody-Antigen, Receptor-Hormone

Computational Problems in Protein Interactomics

- Binding prediction
  - Whether two proteins bind or not?
- Prediction of protein complex stability
- Prediction of interfaces / binding sites
- Predicting the bound structure of the protein
- Data mining in protein-protein interaction networks
- Computational Design of protein interfaces
  - Design of protein specificities

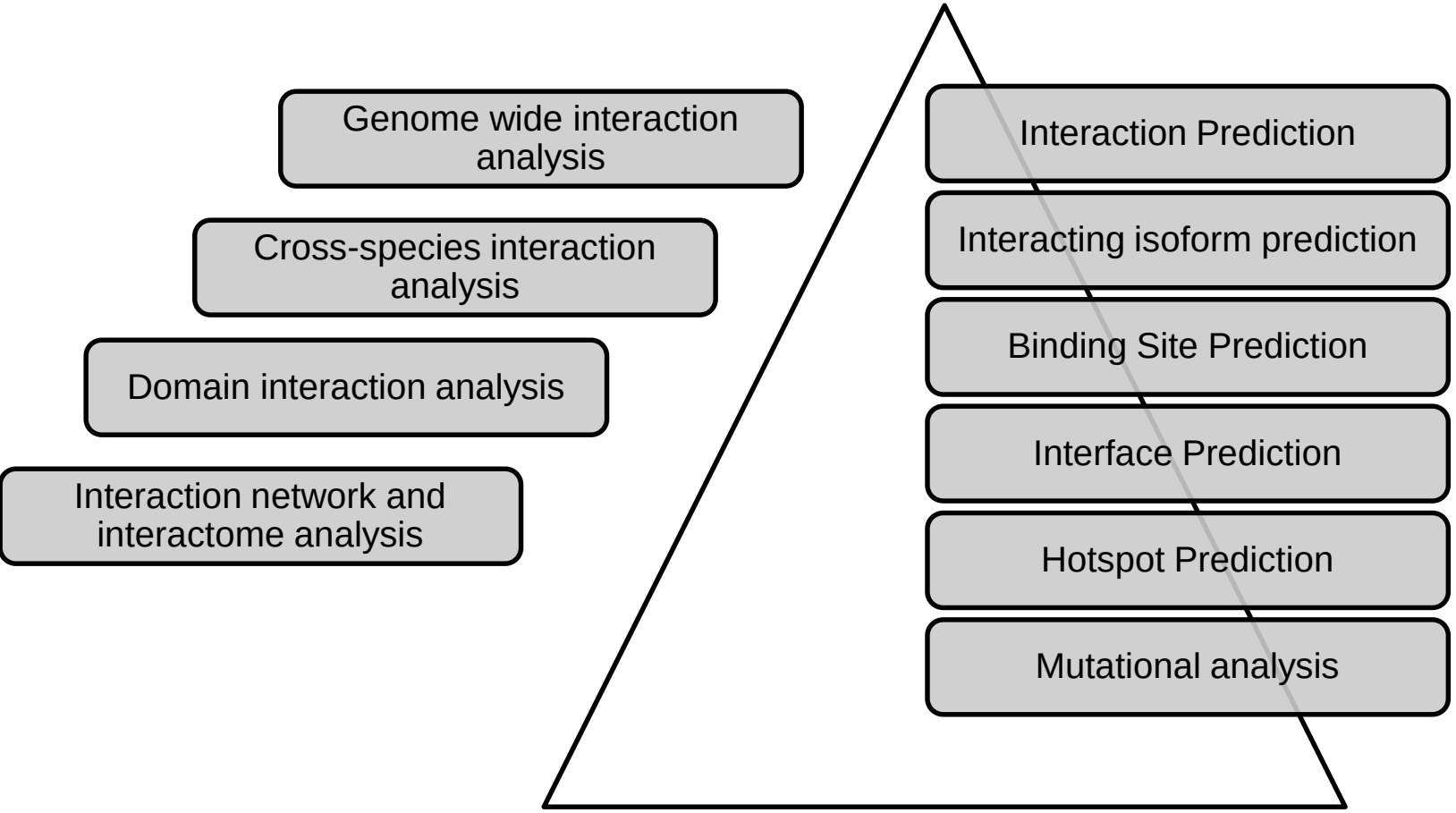
Protein interactions

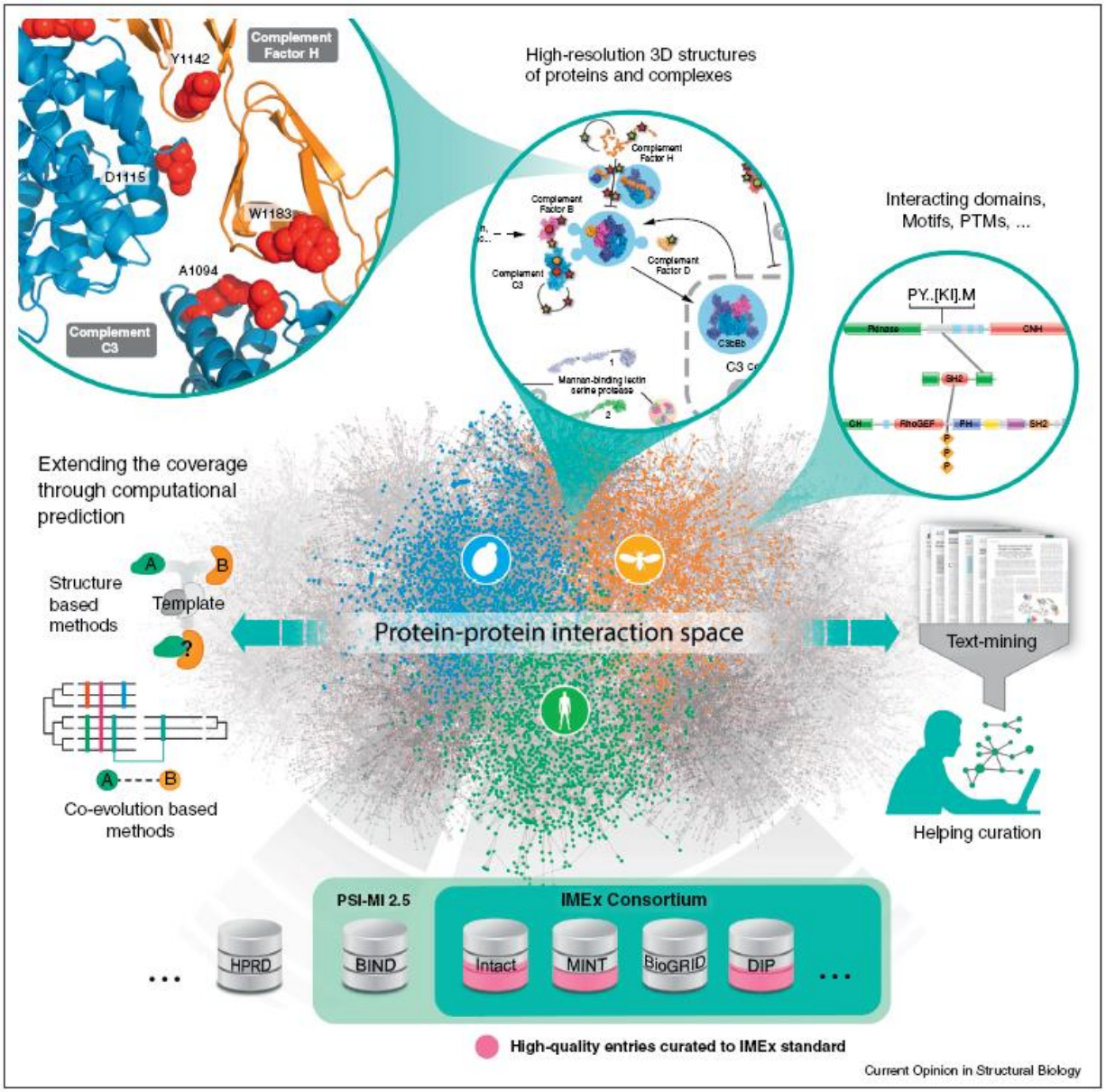
- Methods to investigate protein-protein interactions
  - Yeast two-hybrid screening
  - Affinity Purification coupled to Mass Spectrometrs

http://en.wikipedia.org/wiki/Tandem_affinity_purification

http://en.wikipedia.org/wiki/Methods_to_investigate_protein%E2%80%93protein_interactions

Binding Prediction





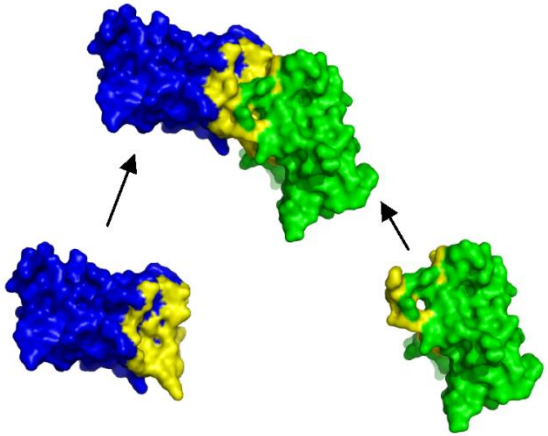
MUST READ

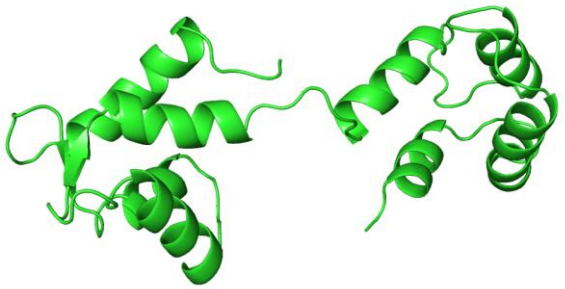
Mosca, Roberto, Tirso Pons, Arnaud Céol, Alfonso Valencia, and Patrick Aloy. "Towards a Detailed Atlas of Protein–protein Interactions." *Current Opinion in Structural Biology*, Catalysis and regulation / Protein-protein interactions, 23, no. 6 (December 2013): 929–40. doi:10.1016/j.sbi.2013.07.005.

Predicting Interactions

- Servers
  - Interologs -- BIPS. Biana Interolog Prediction Server
    - http://www.ncbi.nlm.nih.gov/pubmed/22689642
    - http://sbi.imim.es/web/index.php/research/servers/bips
  - iLoops
    - http://sbi.imim.es/iLoops.php
    - http://www.ncbi.nlm.nih.gov/pubmed/23842807
  - PrePPI
    - http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23193263/
    - http://bhapp.c2b2.columbia.edu/PrePPI
    -

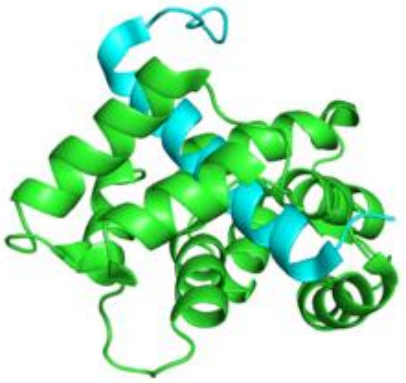
Predicting Interfaces: Difficulties





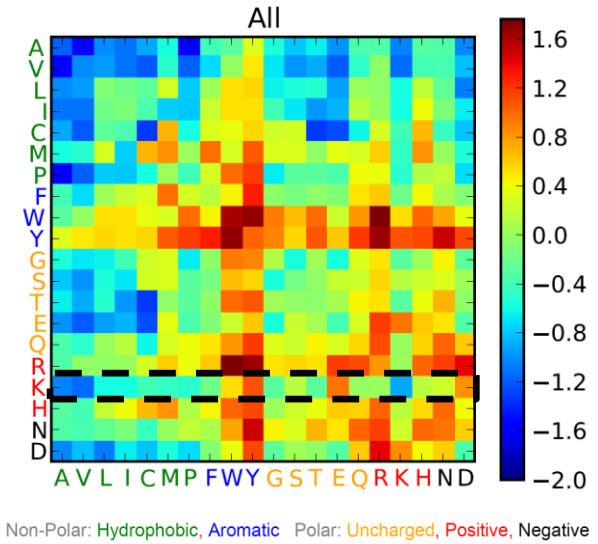
- Conformational change

- Protein flexibility & Motion

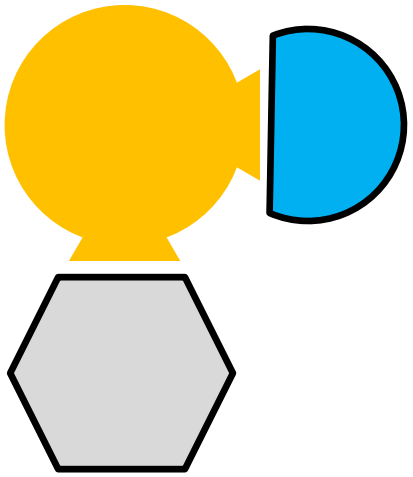


Difficulties in making predictions

- **Dependence of binding propensity on the binding partner**

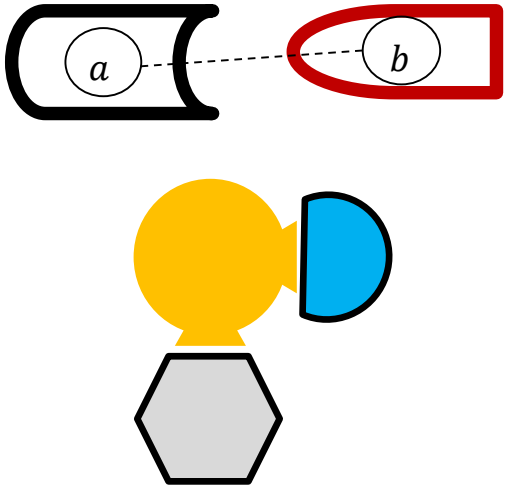


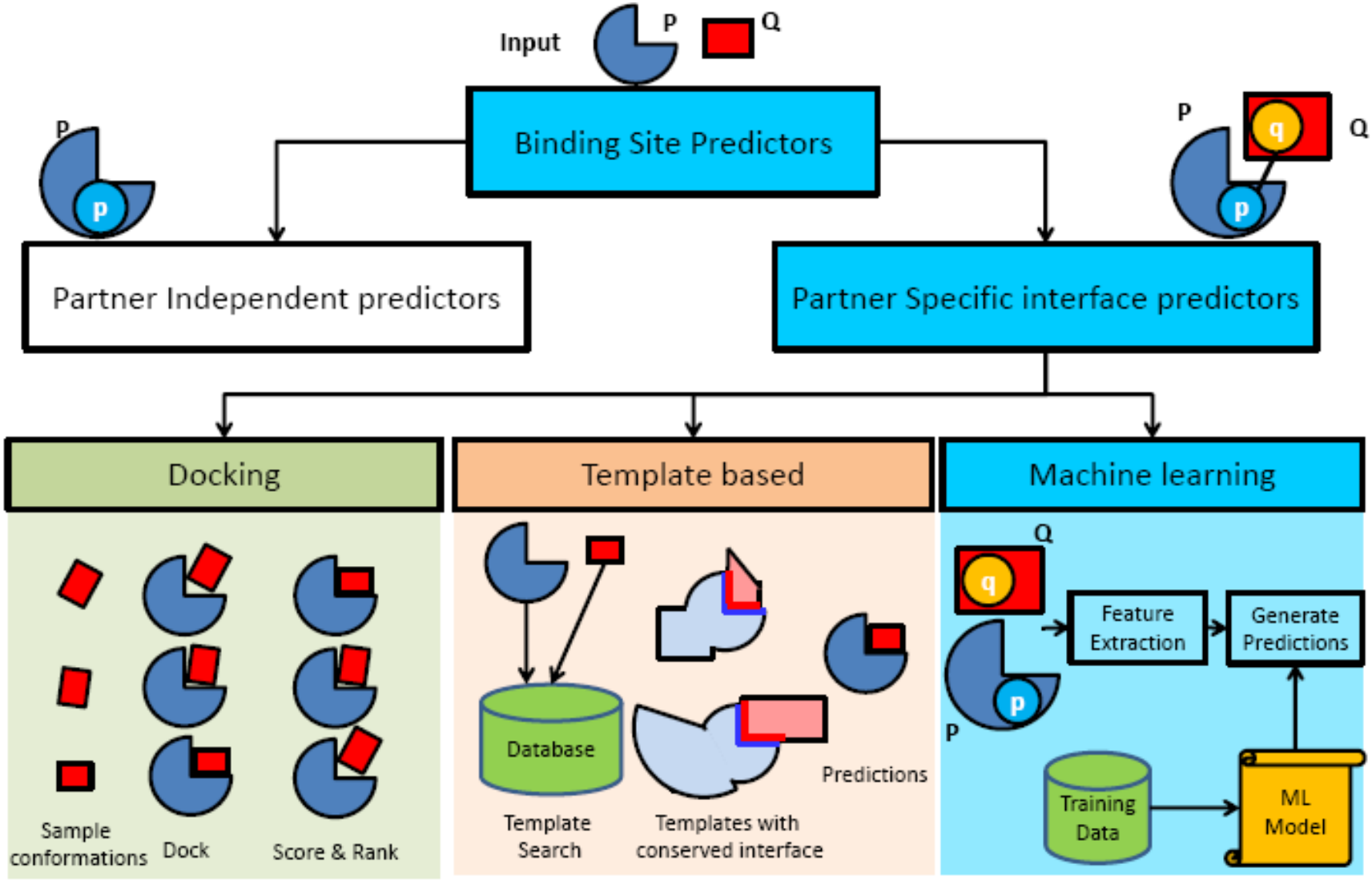
- **Alternative binding modes**



Advantages of partner-specific predictions

- Pairwise interaction prediction
- Enumeration of distinct binding modes
- Simultaneous binding to other proteins possible or not?
- Modeling of the partner-specific nature of binding propensity




Input
P
Q
Binding Site Predictors
P
p
Partner Independent predictors
P
q
Q
p
Partner Specific interface predictors
Docking
Template based
Machine learning
Sample conformations
Dock
Score & Rank
Database
Template Search
Templates with conserved interface
Predictions
Q
q
Feature Extraction
Generate Predictions
p
P
Training Data
ML Model

Partner Independent Predictors

- Meta-PPISP: Combines the outputs of
  - cons-PPISP: ensemble Neural Network with sequence profile and surface accessibility features
  - Promate: Empirical scoring scheme based on physiochemical properties, conservation, B-factors and geometrical features
  - PINUP: Empirical energy function
- PredUS: Conservation based
- PrISEc: Template based

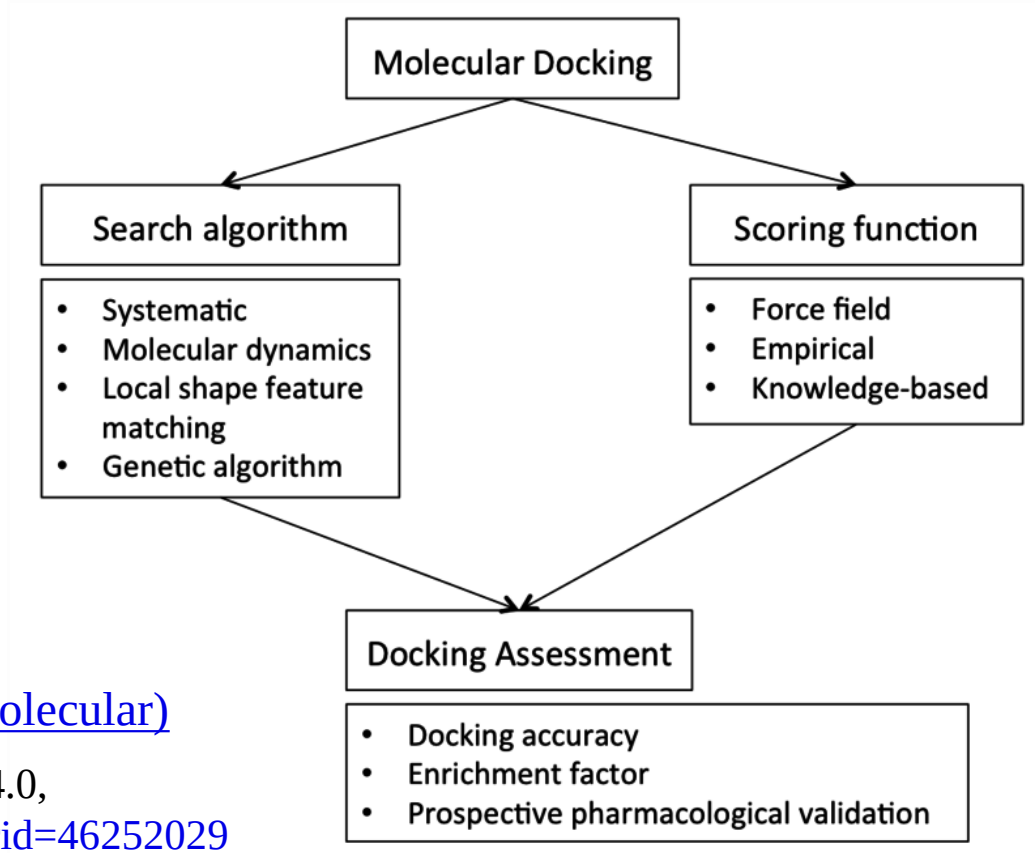
Template Based Methods

- Use known interface templates
  - PIPE-Sites
  - PRISM
  - ISEARCH

- Advantages?
- Disadvantages?

Docking Methods

- Generate the docked or bound structure of the protein with its partner
  - ZDOCK
  - HADDOCK
  - RosettaDock
- Steps
  - Pose Generation
  - Pose Scoring
    - Decoys



https://en.wikipedia.org/wiki/Docking_(molecular)

Machine Learning based Methods

- InSite
  - Indirect information
- PPiPP
- PAIRpred

Hybrid Methods

- Li, Bin, and Daisuke Kihara. 2012. "Protein Docking Prediction Using Predicted Protein-Protein Interface." *BMC Bioinformatics* 13: 7. doi:10.1186/1471-2105-13-7.
- PAIRpred with Template Based Kernels and Docking
- Esmaielbeiki, Reyhaneh, Konrad Krawczyk, Bernhard Knapp, Jean-Christophe Nebel, and Charlotte M. Deane. 2015. "Progress and Challenges in Predicting Protein Interfaces." *Briefings in Bioinformatics*, May, bbv027. doi:10.1093/bib/bbv027.

RaptorX Binding

New Job | Job Status | My Jobs | Inquiry & Bug Report | Docs | About | Xu Group

Model-assisted Protein Binding Site Prediction

For our structure prediciton server please visit RaptorX.

To see the status of a submitted job and download the results, please click here.

You can copy/paste a sample sequence in the "Sequence" box below to submit a new job.

Submit a new job

Fill out the form to submit *up to 20* protein sequences in a batch for prediction. The sequence should be in FASTA format and can be submitted by uploading a text-file or by inputing the sequence into the text-field below. Please SAVE the JobID provided after submission for retrieval of job results, especially when you do not provide an email address in submission.

Job Identification

Jobname: Recommended Email: Recommended

Sequence for Prediction

Sequence:

```
>seq1
ENIEVHMLNKGAEGAMVFEPAYIKANPGDTVTFIPVDKGHNVESIKDMIPEGAEKFKSKINENYVLTVTQPGAYLVK
CTPHYAMGMIALIAVGDSPANLDQIVSAKKPKIVQERLEKVIASAK
```

Sequence file: Choose File No file chosen

Submit

Server Status

979 jobs pending
158 jobs finished in the last 24 hours

http://raptorx.uchicago.edu/BindingSite/

Zhang Lab

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Online Services
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- SPRING
- COTH
- BSpred
- SVMSEQ
- ANGLOR
- BSP-SLIM
- SAXSTER
- ThreaDom
- EvoDesign
- GPCR-I-TASSER
- TM-score
- TM-align
- MMalign
- NWalign

BSpred is a neural network based algorithm for predicting binding site of proteins from amino acid sequences. The algorithm was extensively trained on the sequence-based features ir
secondary structure prediction, and hydrophobicity scales of amino acids. A downloadble package of the BSpred program can be found at the download webpage.

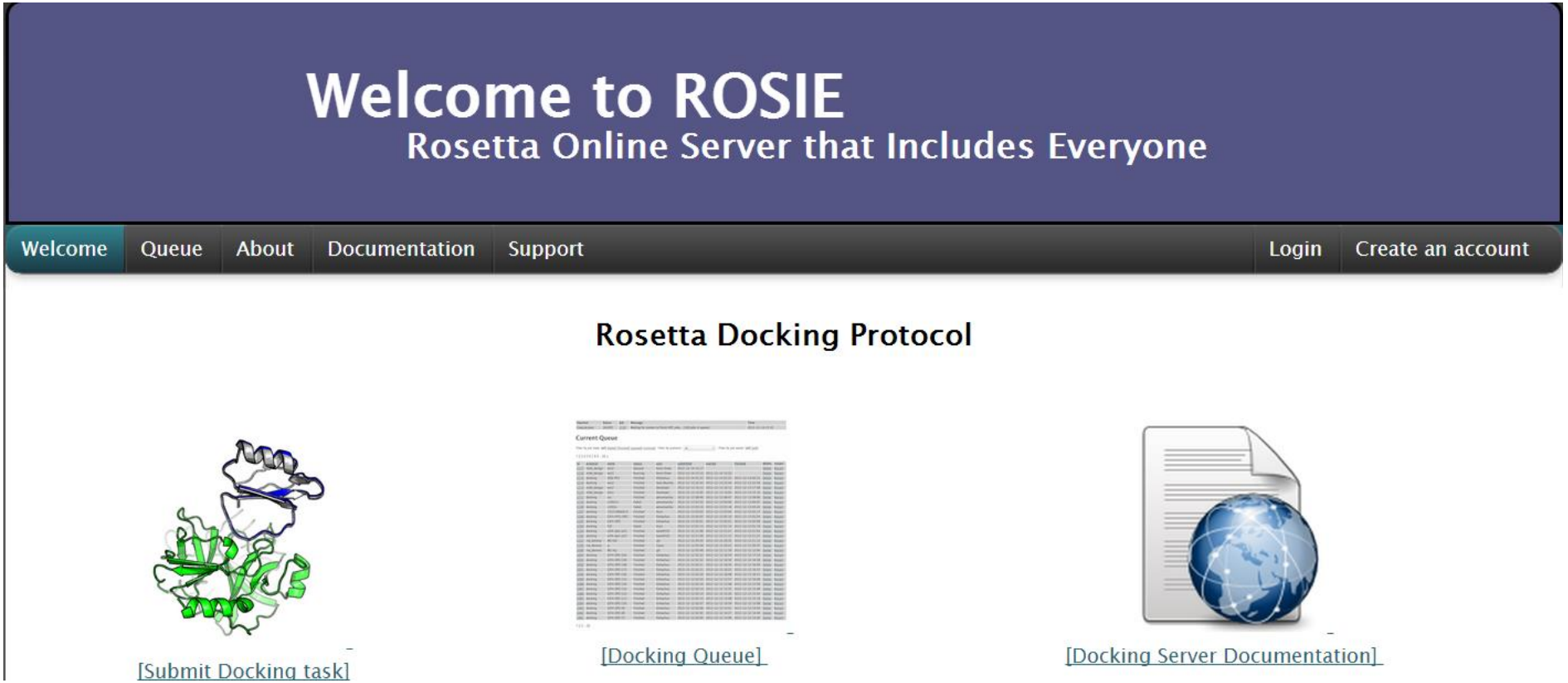
Cut and paste your sequence here (in FASTA format):

Or upload the sequence from your local computer:
Choose File No file chosen
Email: (mandatory, where results will be sent to)
ID: (optional, your given name of the protein)
Run BSpred Clear form

http://zhanglab.ccmb.med.umich.edu/BSpred/

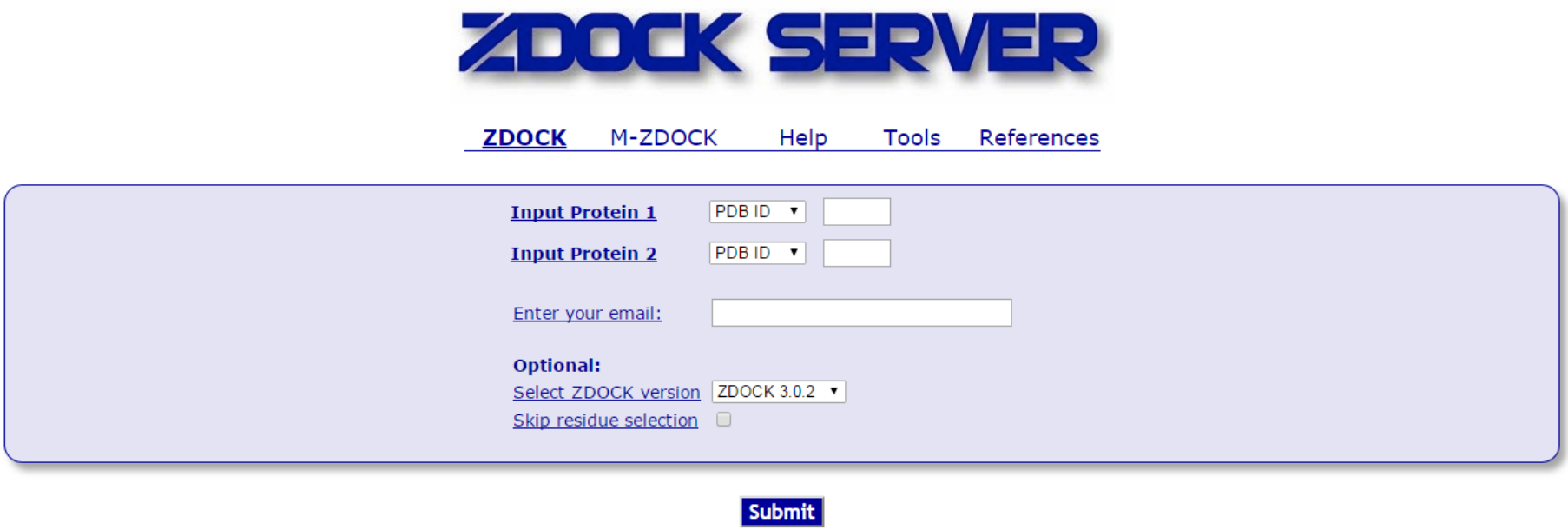
References:
S. Mukherjee, Y. Zhang. *Protein-protein complex structure predictions by multimetic threading and template recombination.* in press (2011).

Docking



http://rosie.rosettacommons.org/docking/

Docking



http://zdock.umassmed.edu/

PAIRPred - Partner Aware Interacting Residue PREDictor

by Fayyaz ul Amir Afsar Minhas and Asa Ben-Hur

Department of Computer Science, Colorado State University, Fort Collins, CO USA.

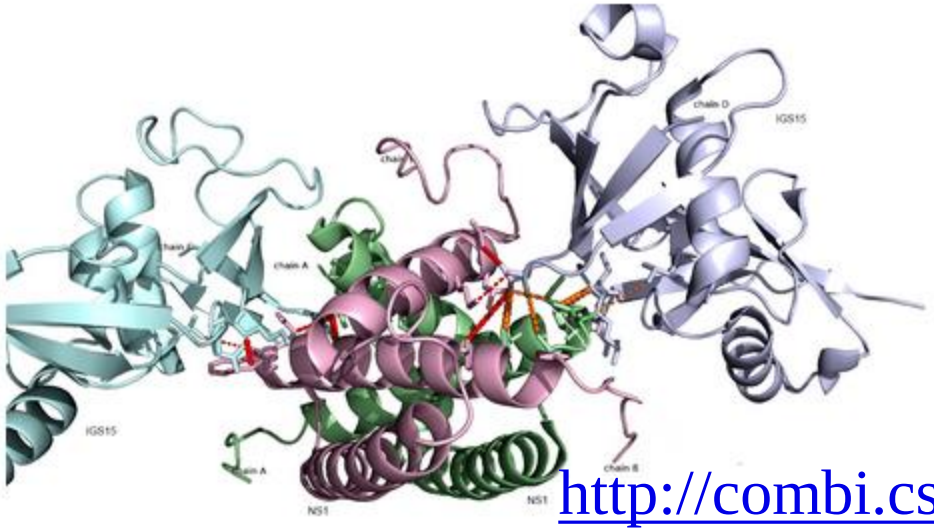
Release Version 1.0 (March 1, 2013)

What is PAIRPred?

PAIRPred is a partner specific protein-protein interaction site predictor that can make accurate predictions of whether a pair of residues from two different proteins interact or not. It differs from most existing interaction site predictors in that it considers the information about the interaction partner of a protein in making its predictions whereas most other methods produce partner-independent predictions. It employs a Support Vector Machine (SVM) with pairwise kernels to generate interaction propensity scores for a pair of residues from sequence information alone or in conjunction with structure based features. PAIRPred offers state of the art prediction accuracy. More details about how PAIRPred works and its performance evaluation are available in this paper.

A test case prediction

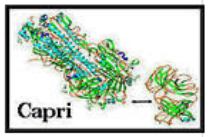
Below is an example prediction from PAIRPred for the interaction between the Influenze Virus NS1 protein (1XEQ) and Human ISG15 (1Z2M). The true complex structure is available as 3SDL. The AUC score for this test case (not a part of PAIRPred's training data) was ~0.90. The true positives are shown in red and orange dotted lines (for different chain contacts) with the width of the dotted line proportional to the prediction score for an interaction between two residues.



http://combi.cs.colostate.edu/supplements/pairpred/

Download Code

CAPRI: Critical Assessment of PRediction of Interactions



- Call For Targets
- Exp. Description
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- ROUND 27
- ROUND 26
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- ROUND 24
- ROUND 23
- ROUND 22
- ROUND 21
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- ROUND 19
- ROUND 18
- ROUND 17
- ROUND 16
- ROUND 15
- ROUND 14
- ROUND 13
- ROUND 12
- ROUND 11
- ROUND 10
- ROUND 9

Databases › PDBe › Services › Capri-Home › Round 27 » contact PDBe

Community wide experiment on the comparative evaluation of protein-protein docking for structure prediction

Hosted By EMBL/EBI-PDBe Group

Round 27
Round 27 ID mapping from group number to Accessor Number for Target 57
Round 27 ID mapping from group number to Accessor Number for Target 58
NOTE The Coordinates are not yet available for download

T57 result summary
T58 result summary

Target 57

Results T57 - click here to see the results

Full results (regular assessment):

Clash threshold	64.12
average	17.20
std dev	23.46

	Predictor
Nr groups	31
High Accuracy (***)	0 (0)
Medium (**)	5 (4)
Acceptable (*)	26 (14)
Incorrect	217 (26)
Clashes	8 (1)
Low Id	0 (0)
Total	256 (26)

http://www.ebi.ac.uk/msd-srv/capri/round27/round27.html

https://en.wikipedia.org/wiki/Critical_Assessment_of_Prediction_of_Interactions