Analysis and Prediction of Protein Complex

Master-Module Biological Networks
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http://biofold.org/

Biomolecules
Folding and
Disease

Institute for Mathematical Modeling
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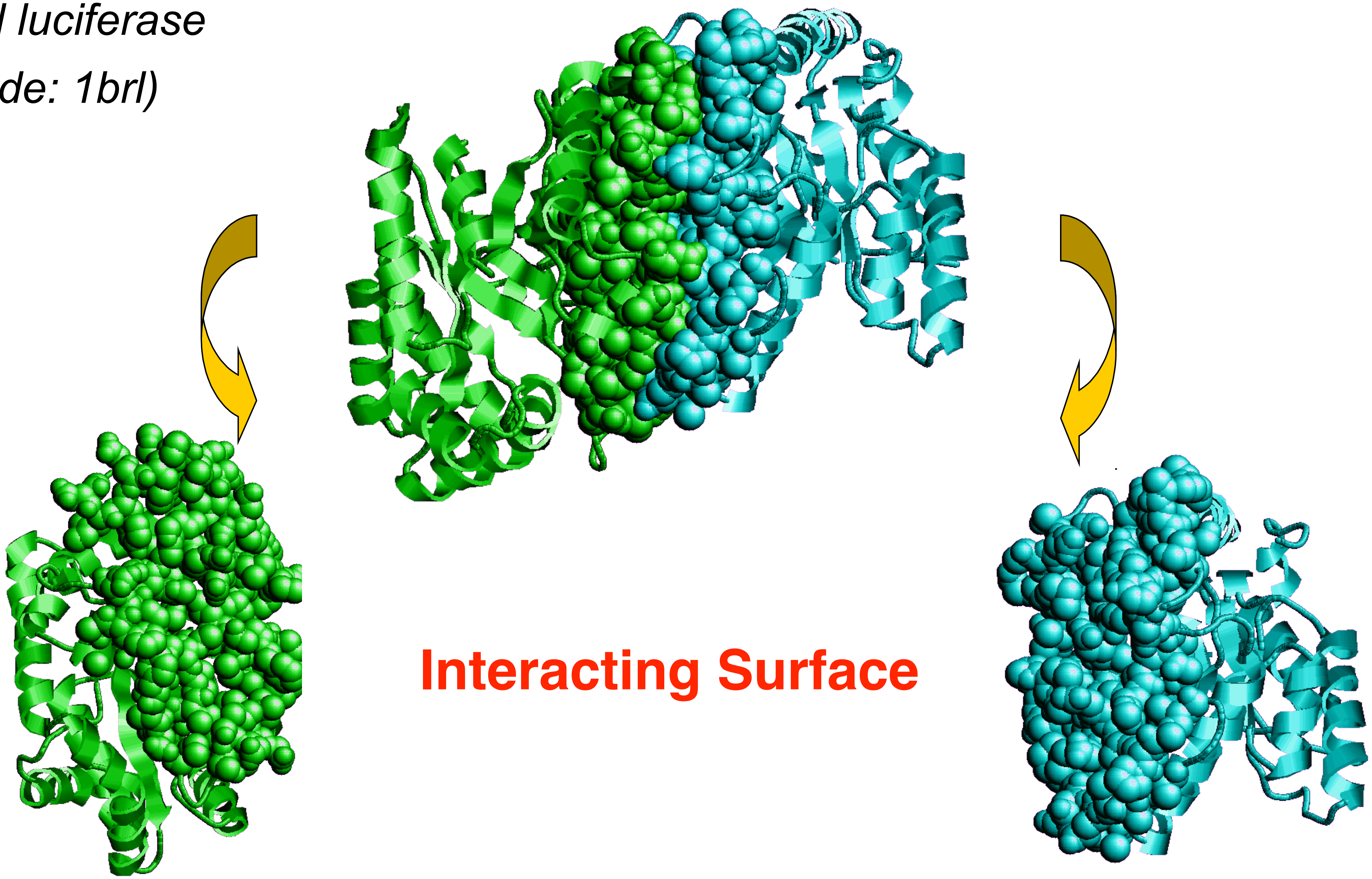
Interacting surface

Difference in Accessible Surface Area (ASA) between monomers and complex

Bacterial luciferase

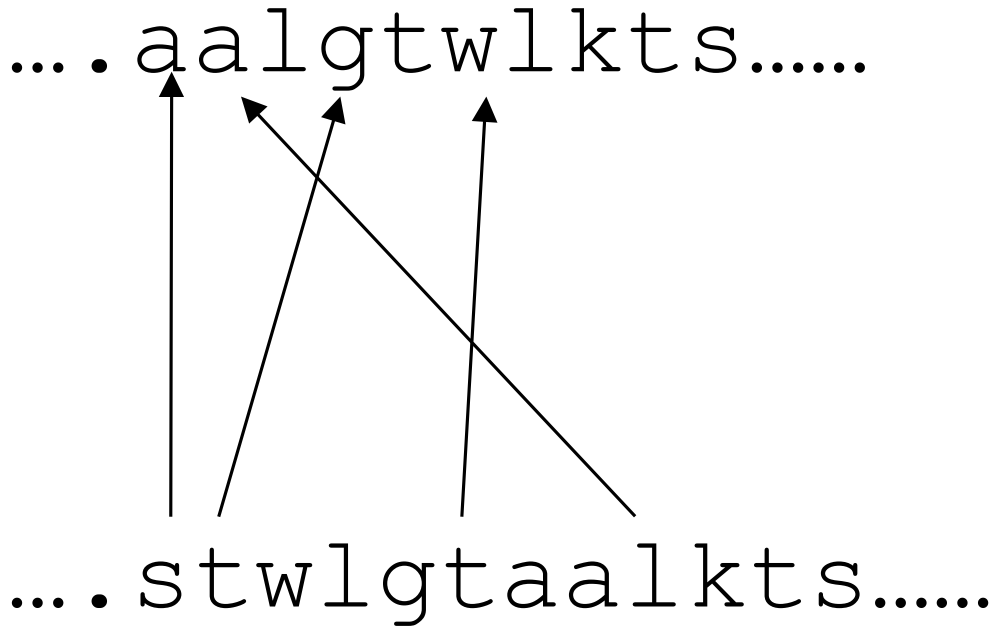
(PDB code: 1brl)



Interacting Surface

Prediction features

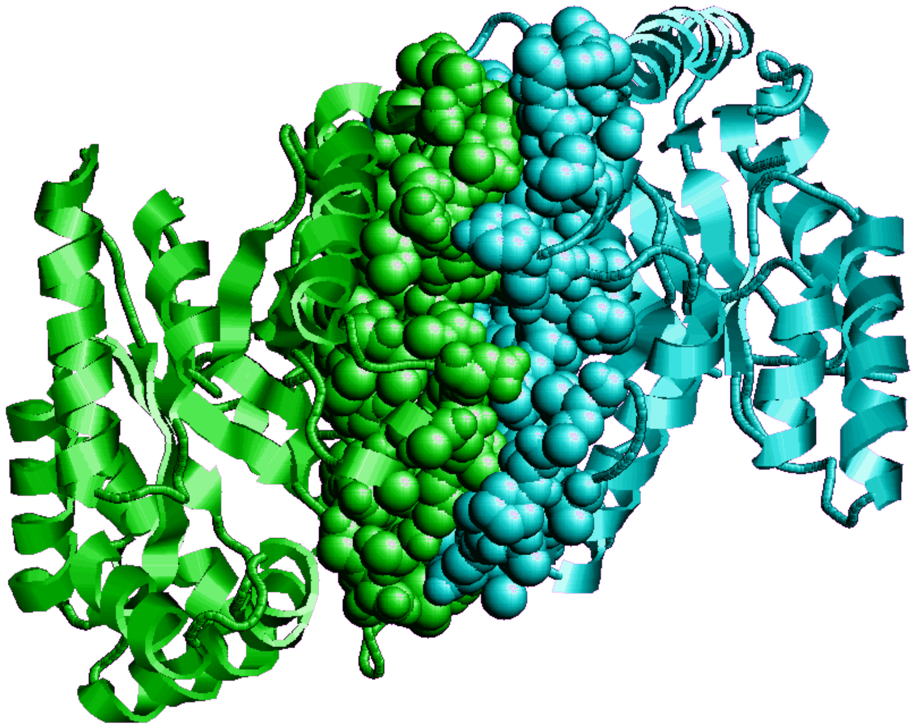
Protein Sequence



….aalgtwlkts……

….stwlgtaalkts……

Protein Structure



+ Whole genome computation

- No exact location, No atomic description

+ Exact location Atomic description

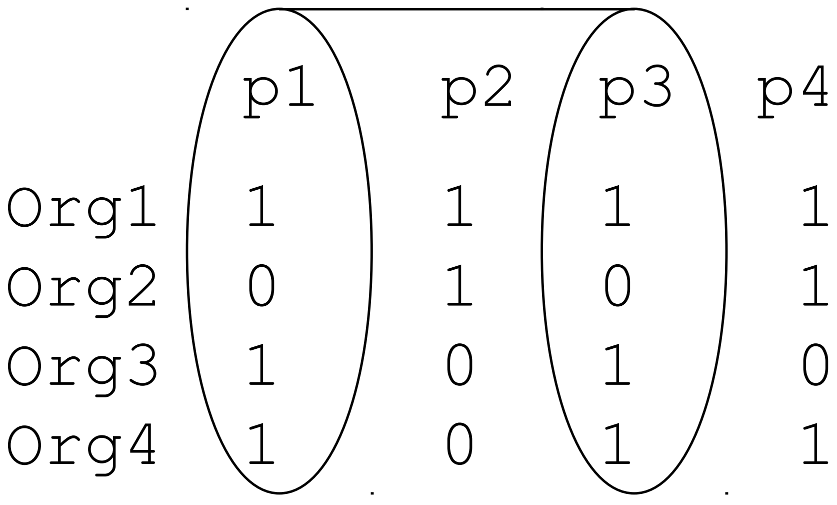
- Availability of the 3D coordinates

Three major problems

- Protein-Protein interaction networks: given a set of proteins, predict the possible partners
- Docking: given a pairs of proteins, known to interact, predict the geometry of the complex
- Protein-interaction sites: given a single protein, predict possible interacting regions

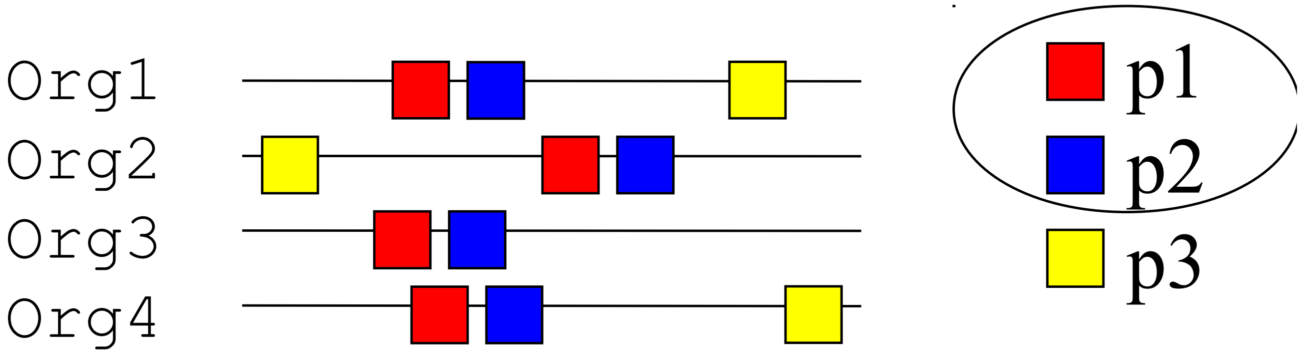
Sequence-based methods

Phylogenetic Profiling: interacting proteins should co-evolve and should have orthologs in closely related species.

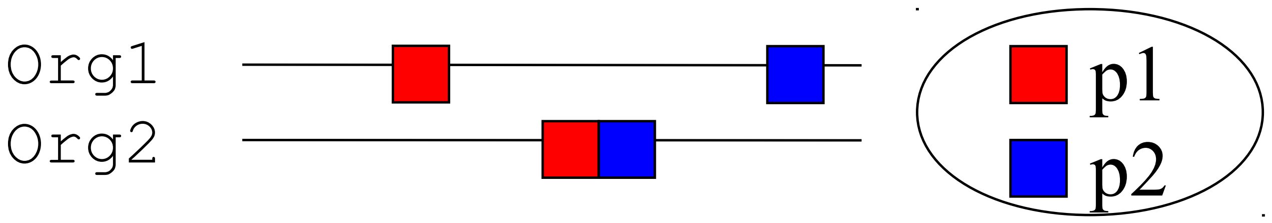


	p1	p2	p3	p4
Org1	1	1	1	1
Org2	0	1	0	1
Org3	1	0	1	0
Org4	1	0	1	1

Gene Neighborhood: interacting proteins and co-evolvig homologs tend to have close genomic locations.



Gene Fusion: two proteins that interact tend to have homologs in other genomes that are fused into a unique protein

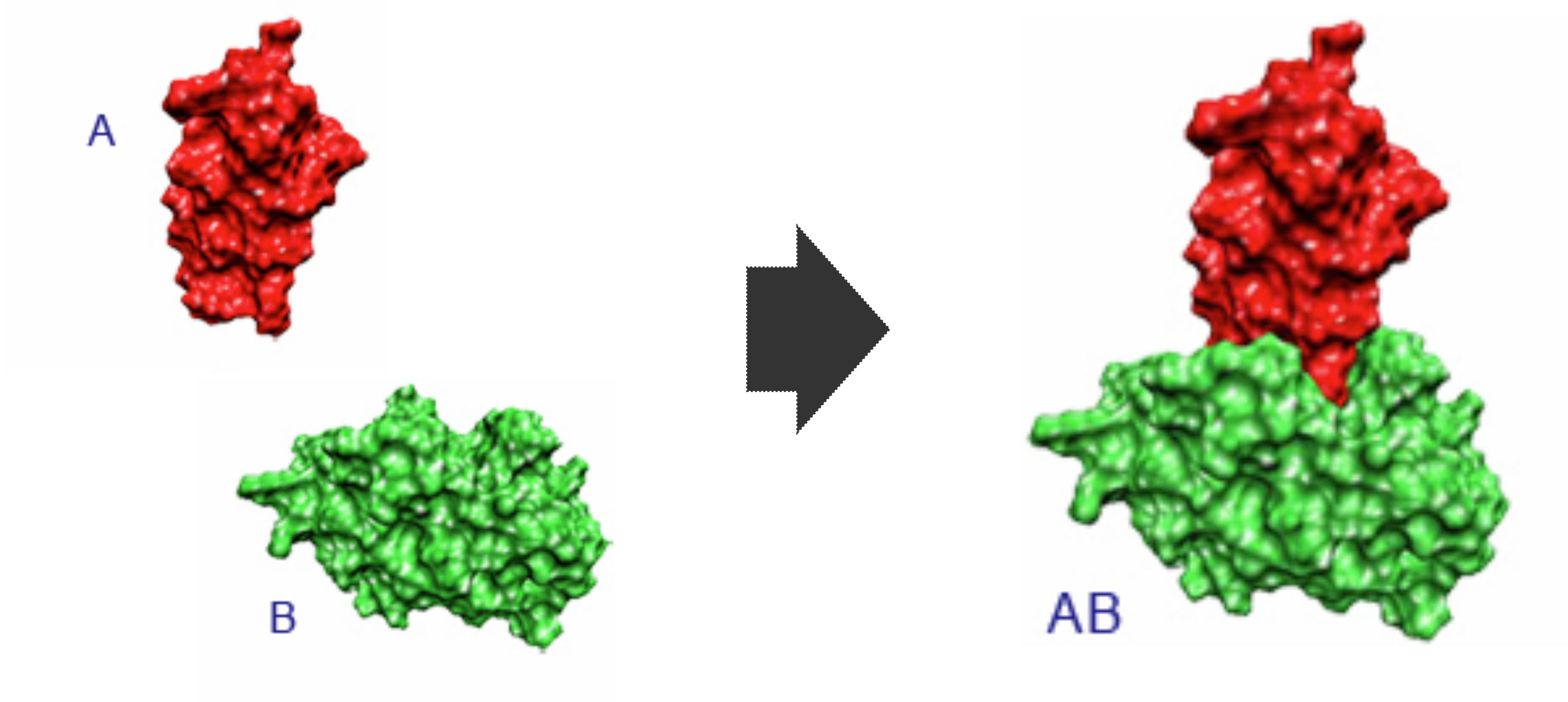


From wikipedia

Protein Docking

- Computational schemes that aims to **find the "best" matching between two molecules**, a **receptor** and a **ligand**

- The molecular docking problem can be defined as follows: **given the atomic coordinates of two molecules, predict their "correct" bound association**



Halperin et al. Proteins, 2002

Protein-Protein docking

- Used to model the quaternary structure of complexes formed by two or more interacting proteins
- It is the “gold standard” for prediction of PPIs
- It used to predict if two proteins interact and also how the interaction takes place ("mode" of binding)
- It is computationally very challenging and thus very unlikely to be applied for high throughput purposes.

Ngounou Wetie et al. Proteomics, 2013

What we can learn?

- Do proteins A (receptor) and B (ligand) bind *in vivo*?

If they do bind:

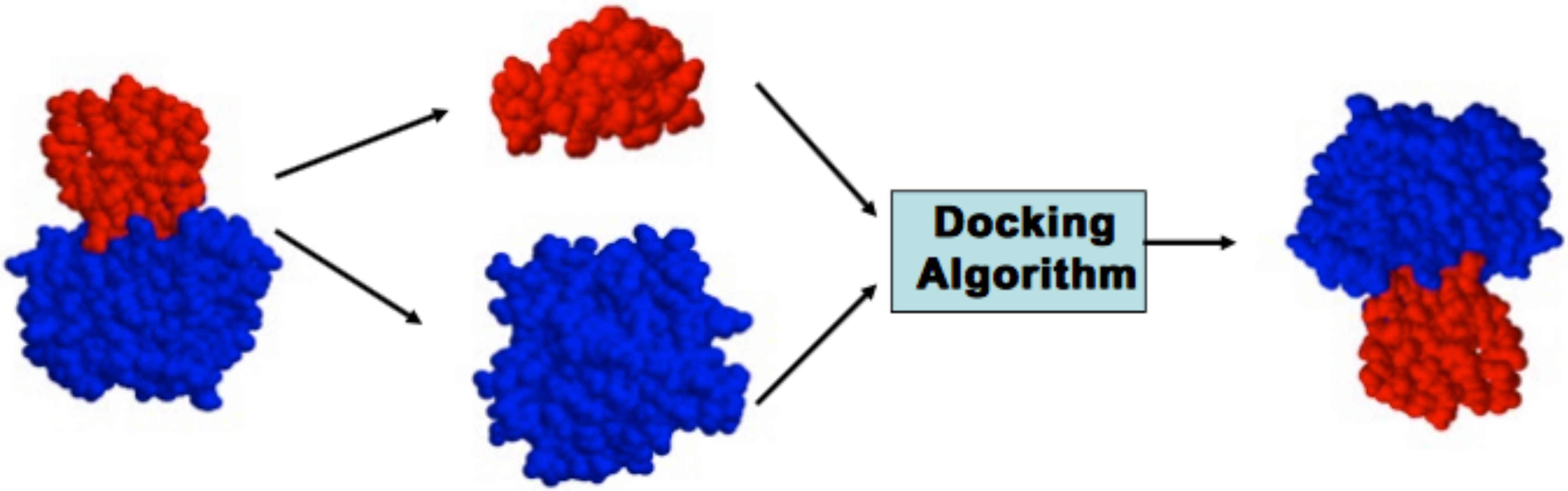
- What is the spatial configuration they adopt in their bound state?
- What is the structure of the protein complex (**near-native structure**) in atomic details ?
- How strong or weak is their interaction (which types of interactions are present)?
- What is the orientation that maximises the interaction, minimizing the energy of the complex?

If they don't bind:

- Would they bind if there was a mutation?

Bound docking

- Reconstruct a complex using the bound structures of the receptor and the ligand.
- After artificial separation of the receptor and the ligand, the goal is to reconstruct the native complex

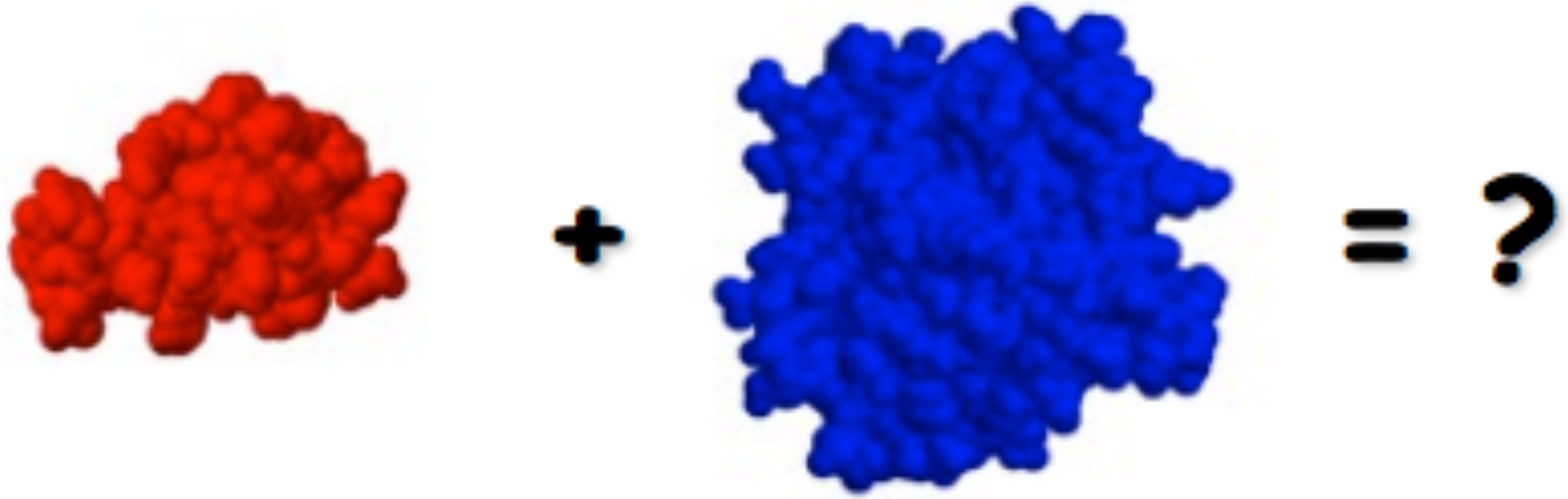


- No conformational changes are involved
- **Used to validate the algorithm**

Allegra Via, Systems Biology Course 2015

Predictive docking

- Schemes that attempt to reconstruct a complex using the unbound structures of the receptor and the ligand
- An "unbound" structure maybe a **native** structure, a **pseudo-native** structure, or a **modelled** structure
- **Native**: free in solution, in its uncomplexed state
- **Pseudo-native**: structure complexed with a molecule different from the one used for the docking



Halperin et al. Proteins, 2002

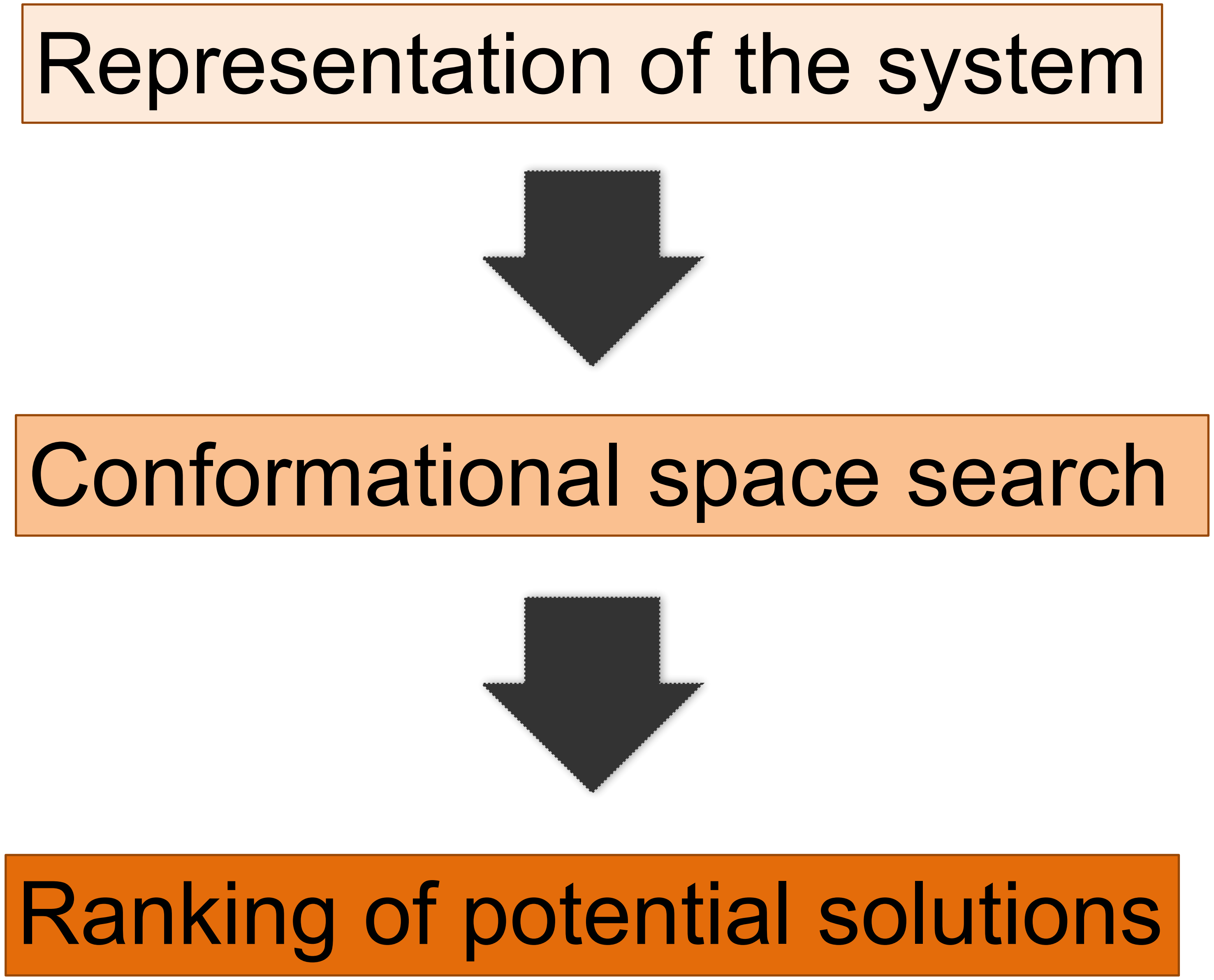
Why it is difficult?

- # of possible conformations are astronomical
  – thousands of degrees of freedom (DOF)

- Free energy changes are small
  – Below the accuracy of our energy functions

- Molecules are flexible
  – alter each other’s structure as they interact

Main docking steps



Representation of the system

Conformational space search

Ranking of potential solutions

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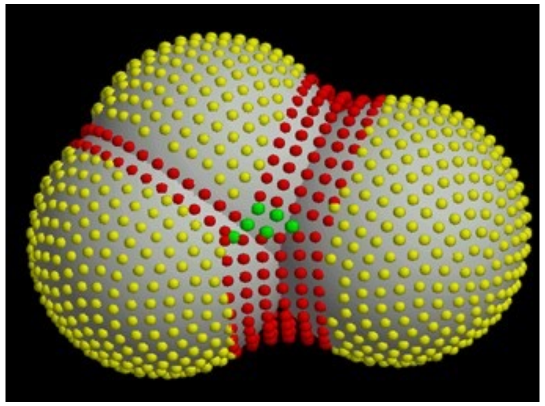
Systems representation

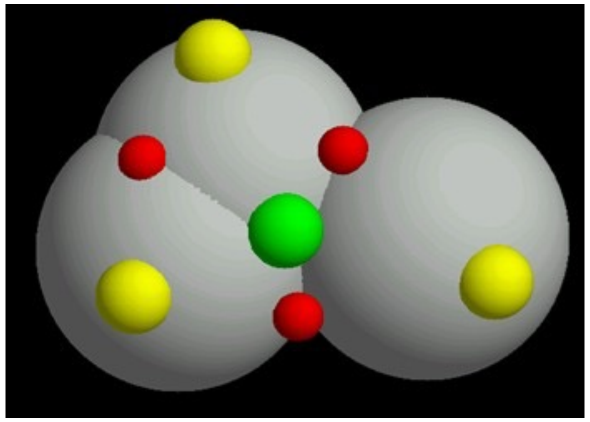
- Docking essentially simulates the interaction of the protein surface

- How do we define a protein surface?
  - Mathematical models (e.g. geometrical shape descriptors, a grid)
  - Static or dynamic treatment of the protein frame (rigid vs flexible)

- The choice of the system (surface) representation decides the types of conformational search algorithms, and the ways to rank potential solutions

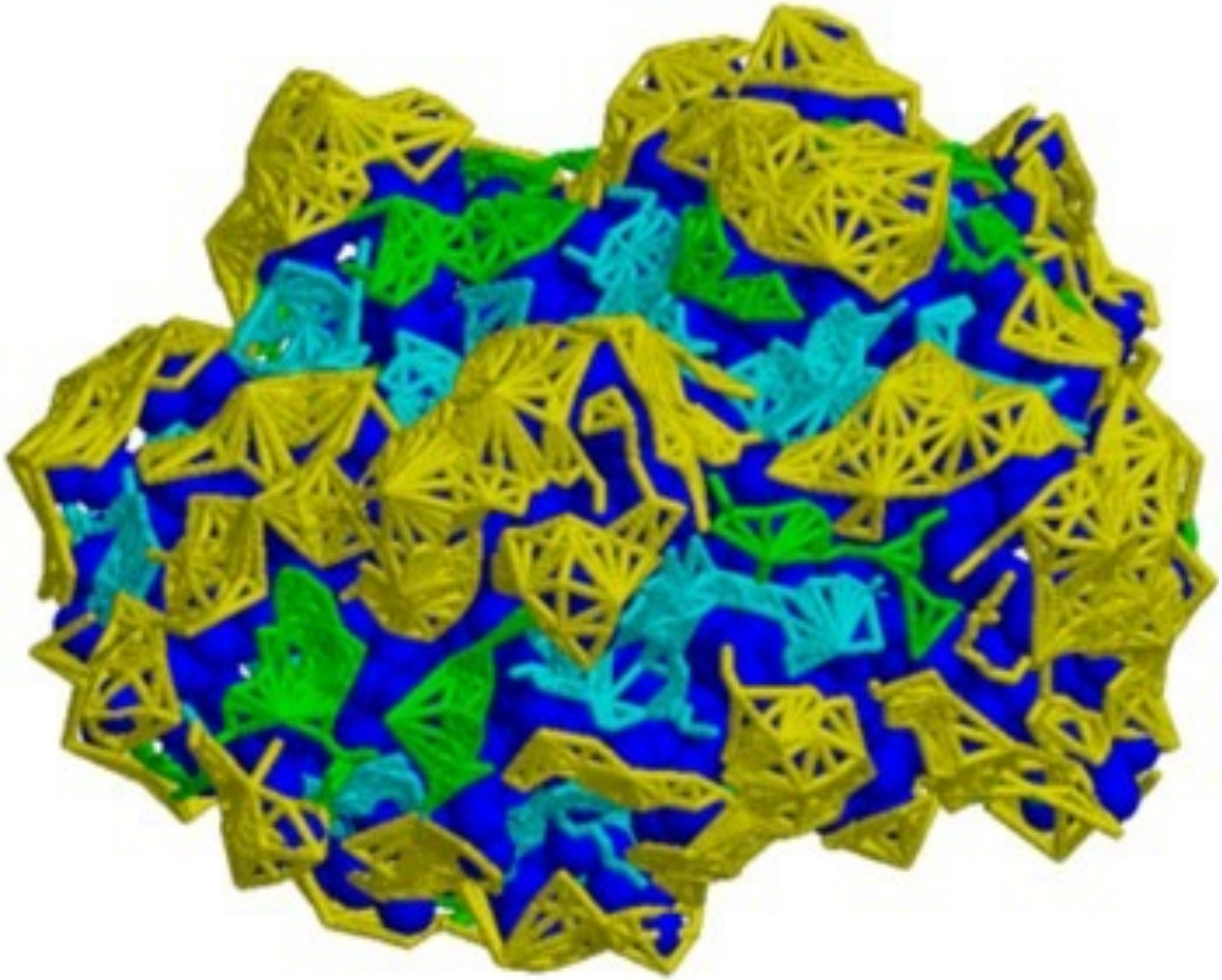
Surface representation





Patch detection

- Divide the surface into connected, non-intersecting, equal sized patches of critical points with similar curvature



Yellow: knob patches
Cyan: hole patches
Green: flat patches
Blue: protein

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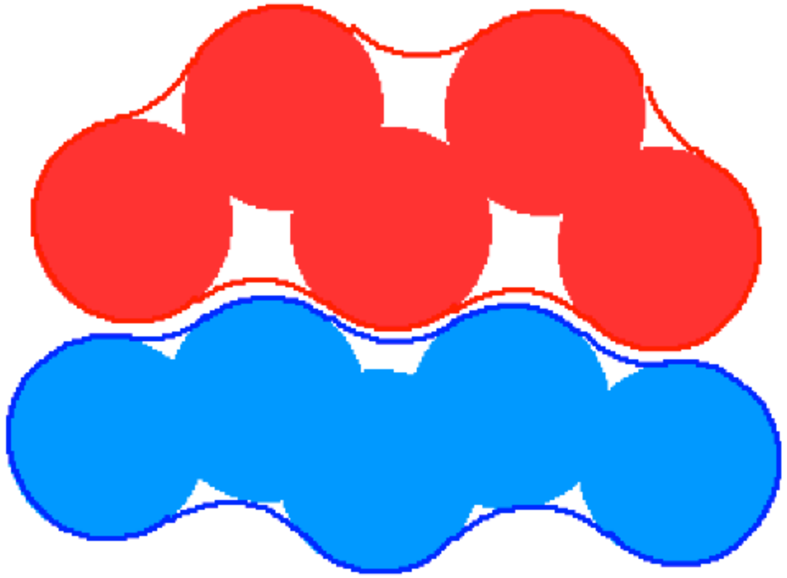
Molecular recognition

- Van der Waals
- Electrostatics
- Hydrophobic contacts
- Hydrogen bonds
- Salt bridges

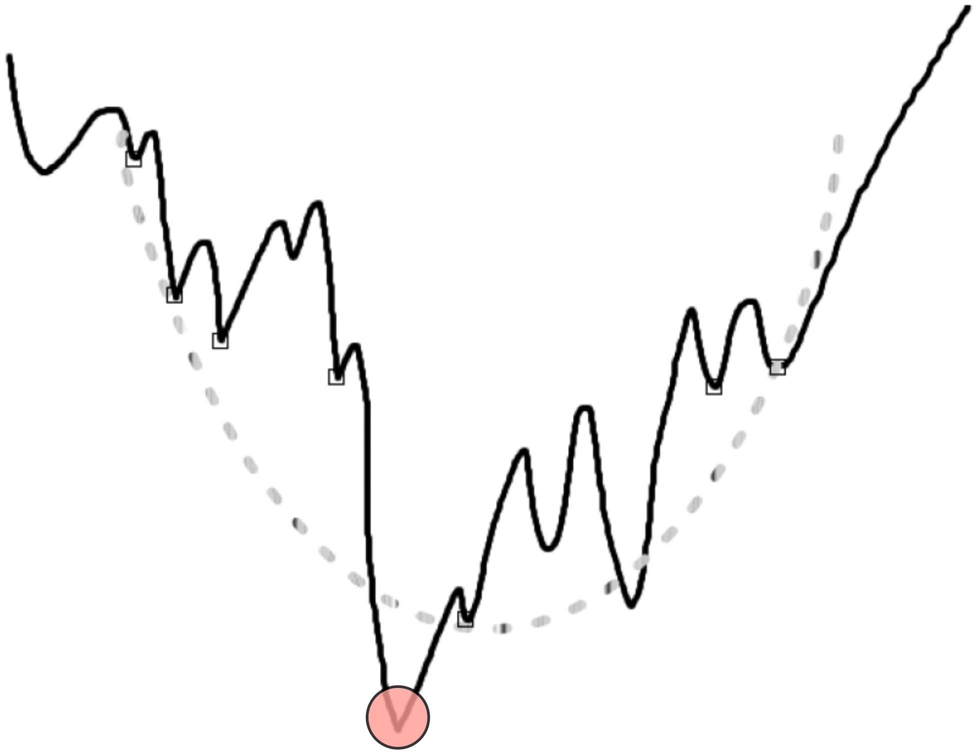
All interactions act at short ranges → surface complementarity is needed for tight binding



Efrat Mashiach, http://bioinfo3d.cs.tau.ac.il/

Conformational space

- Efficient search algorithm
- Speed and effectiveness in covering the relevant conformational space
- Computationally difficult - there are many ways to put two molecules together (3 translational + 3 rotational degrees of freedom)
- Goal: locate the most stable state (global minimum) in the energy landscape



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Docking types

- **Rigid body** is a highly simplistic model that regards the two proteins as two rigid solid bodies
  - fast → can explore the entire receptor and ligand surfaces
  - Less accurate
  - flexibility = "soft" belt into which atoms can penetrate

- The **semi-flexible** model is asymmetric; one of the molecules is considered flexible, while the receptor is regarded as rigid

- **Flexible** docking. Both molecules are considered flexible, though flexibility is limited or simplified
  - Slower
  - More accurate
  - Can model side-chain/backbone flexibility
  - highly reliable but too slow for extensive ligand docking

Minimization protocols

- scan of the entire solution space in a predefined systematic manner

  e.g., complete searches of all orientations between two rigid molecules by systematically rotating and translating one molecule about the other

- a gradual guided progression through solution space. Only part of the solution space is searched, or fitting solutions are generated.

  e.g., Monte Carlo, simulated annealing, molecular dynamics (MD), and evolutionary algorithms.

- Data-driven docking

  it uses the available information about binding site/interface residues .

Scoring the predictions

- A search algorithm may produce a large number of solutions (~10^9)

- Goal: discriminate between "correct" native solutions, i.e., with low RMSD from the crystal structure and others within reasonable computation time

- Good scoring function: fast enough to allow its application to a large number of potential solutions

  effectively discriminates between native and non-native docked conformations

  should include and appropriately weight all the energetic ingredients.

Scoring parameters

- Geometric complementarity - how to score complementarity is strongly coupled with the surface representation.

- Intermolecular overlap – tolerance to slight interface clashes and penalty for protein interior clashes (surface "belt" of nonpenalised penetration area)

- Intra-molecular overlap – when backbone flexibility is taken into account

- Hydrogen bonding

- Contact area: total interactions = hh + pp + hp (h = hydrophobic, p = polar)

- Pairwise aa and atom-atom contacts – empirical term derived form observed statistical frequency of aa contacts in X-ray proteins

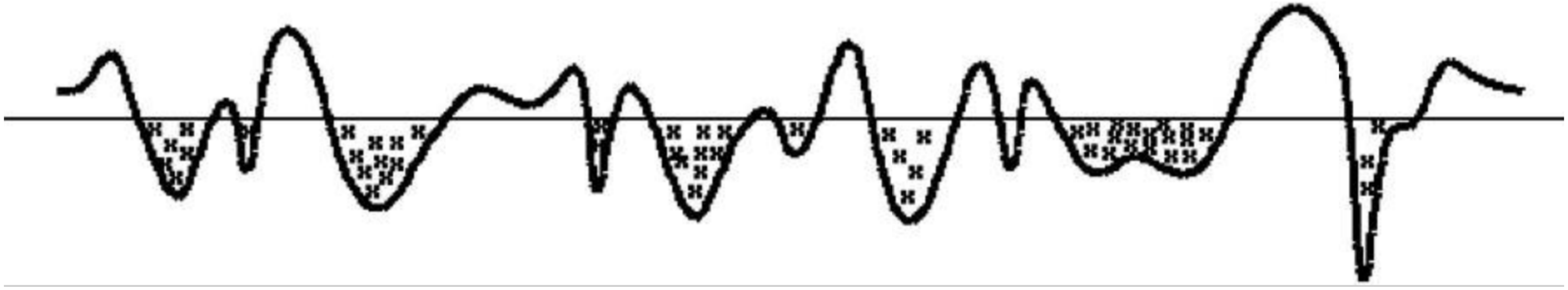
- Electrostatic interactions and solvation energy

Knowledge-based scores

- Knowledge of the location of the binding site on one or both proteins drastically reduces the number of possible solutions
- Knowledge of the specific binding site residues reduces the search space even further
- Info about active site residues: site directed mutagenesis, chemical cross-linking, phylogenetic data
- Sometimes the binding site can be predicted
- For some families the major binding sites are known in advance (e.g. serine proteases and immunoglobulins)

Prediction clustering

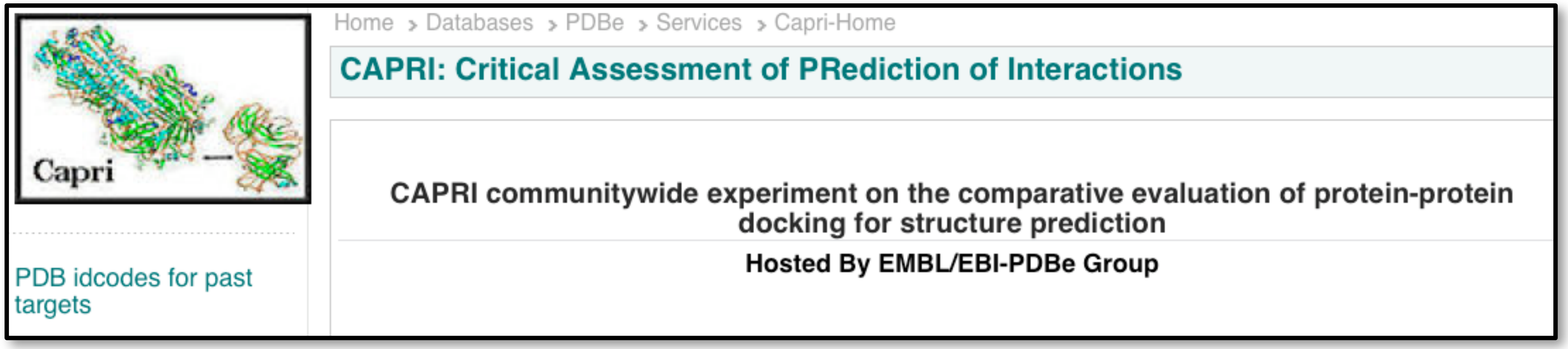
- **Events that occur in clusters are probably not random**
- The cluster with the largest number of low-energy structures is typically the native fold, the center of the most populated cluster being a structure near the native binding site
- Looking for large clusters is a major tool of finding near-native conformations



Kozakov et al, Biophys J, 2005

CAPRI Experiments

- CAPRI is a community-wide experiment in modelling the molecular structure of protein complexes
- CAPRI is a **blind prediction experiment** aimed at testing the performance of protein docking methods
- Rounds take place about every six months
- Each round contains between one and six target protein–protein complexes whose structures have been recently determined experimentally
- Targets are unpublished crystal or NMR structures of complexes, whose coordinates are held privately by the assessors, with the co-operation of the structural biologists who determined them
- The atomic coordinates of the two proteins are given to groups for prediction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CAPRI: Critical Assessment of PRediction of Interactions

CAPRI communitywide experiment on the comparative evaluation of protein-protein docking for structure prediction

Hosted By EMBL/EBI-PDBe Group

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

Conclusions (-)

- The *molecular docking problem* is far from being solved
- It is difficult to find very specific properties of protein-protein interfaces
- Results are generally poor with weakily interacting proteins
- Proteins are flexible and may undergo even large conformational changes upon binding
- Exhaustive space searches provide too many conformations
- Accurate interaction energies are too complicated to compute
- For most complexes the highest ranked structures are still false positives (high RMSD from the complex)
- No efficient method for reliable discrimination between correct solutions and FPs is currently available, in particular if the binding site is unknown
- Many FPs displaying good surface complementarity are far from the native complex

Conclusions (+)

- If the conformational change is limited to surface side-chain atoms, rigid body algorithms have been remarkably successful, even in absence of knowledge of the binding site
- Side-chain flexibility can be handled via a "soft" tolerance belt”
- Docking in steps" is a promising strategy: Initial rigid-body, entire surface algorithm followed by a dynamic method overcoming energy barriers
- Integration of experimental information produces reliable docking results
- Relatively easy for enzyme-inhibitor complexes
- Sometimes good results with antigen-antibody pairs

Some methods

- **HADDOCK** (software/web server).
  http://haddock.chem.uu.nl

- **CLUSPRO** (software/web server)
  http://cluspro.bu.edu

- **ICM-pro** (desktop-modeling environment)
  http://www.molsoft.com/protein_protein_docking.html

- **ROSETTADOCK** (software/web server)
  http://graylab.jhu.edu/docking/rosetta/
- http://rosettadock.graylab.jhu.edu/submit

- **GRAMM-X** (web server)
  http://vakser.bioinformatics.ku.edu/resources/gramm/grammx

- **PATCHDOCK/FIREDOCK** (software/web server)
  http://bioinfo3d.cs.tau.ac.il/PatchDock/

- **HEX** (software/web server)
  http://hexserver.loria.fr

Exercise

Download the DSSP file of the Bacterial luciferase (Vibrio harveyi) from the PDB (code: 1BRL)

- Generate the DSSP file for the protein complex and the isolated chains A and B
- Calculate the total solvent accessible area of the complex and isolated chains and calculate the surface of interaction for both chains.
- Given the size of the binding surface what kind of protein interaction it is expected?
- Find the residue at the interface and calculate the variation of relative solvent accessible area. Which residue are buried in the interacting surface?

Chain = col 12, AA = col 14, SS = col 17, Acc: cols 36-38, Phi: cols 104-109, Psi: cols 110-115