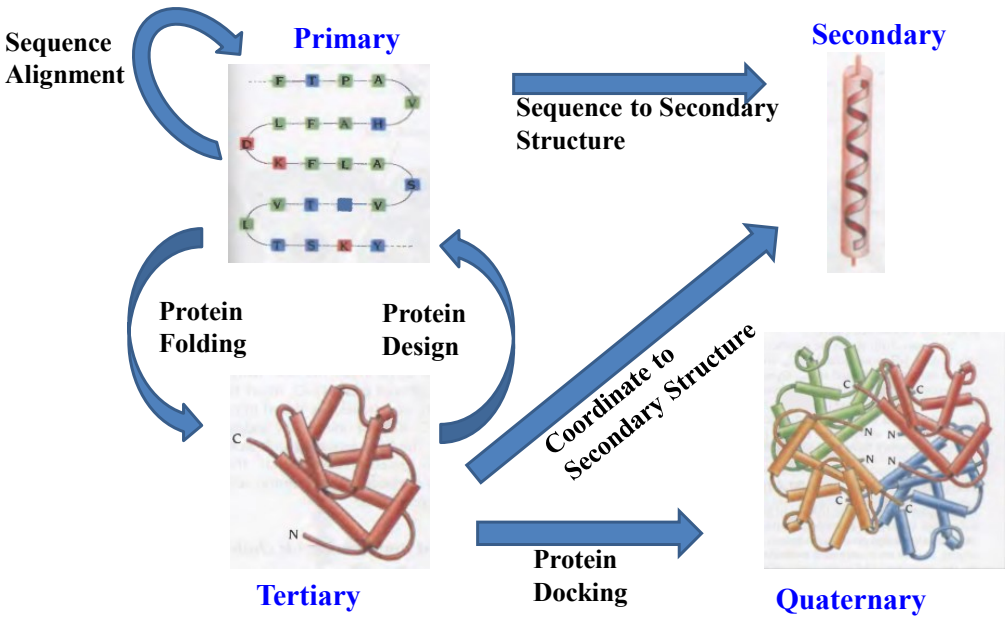
Lecture 23

Protein-protein
Docking

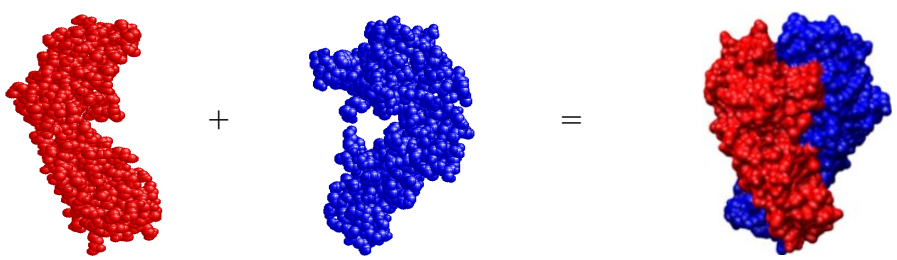
Protein-protein
Docking

Computational Methods in Proteins



Protein-Protein Docking

Ab initio **Protein-protein docking** is the determination of the molecular structure of *complexes* formed by two or more proteins without the need for *experimental* measurement.



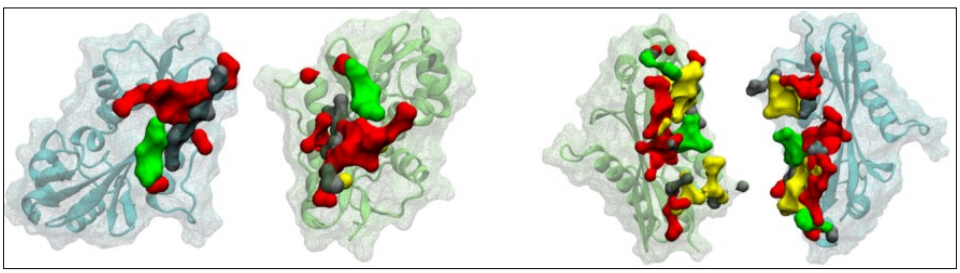
Definition of Protein Surface

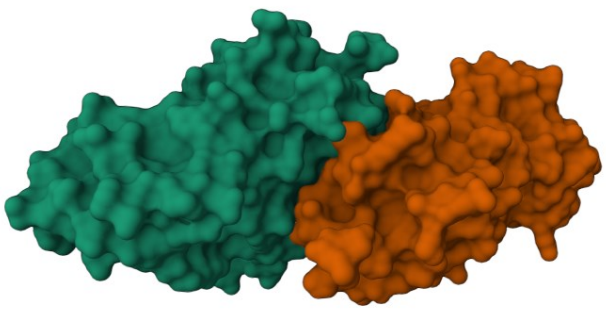
- Roll the probe over the protein molecule using NACCESS program to compute the accessible surface area (ASA) (also called as SASA – surface accessible surface area)
- If an atom's accessible surface area (ASA) is more that 0.1 $Å^2$ then that is define as surface atom.

Definition of Protein Interface Area

- The surface area where two protein molecules interacts during complex formation is called as the interface region.
- If an atom loses its ASA by more than 0.1 $Å^2$ then we call that as an interface atom. The total loss of ASA by all the interface atoms are the interface area.
- Sometimes, we take the average for interface area to call it as interface area per protein molecule.
- How to compute identify interface atoms? How to compute interface area?
  - Run the NACCESS on individual protein molecules
  - Run the NACCESS on the protein complex
  - Identify the atoms that loses its ASA by more than 0.1 $Å^2$

Definition of Protein Interface Area

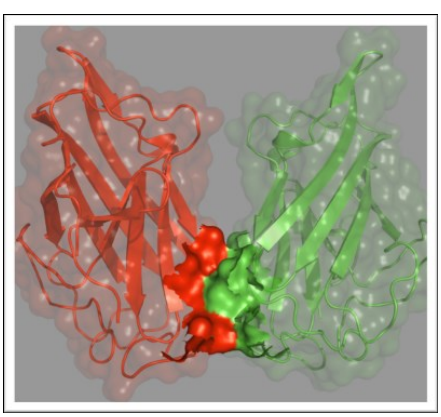




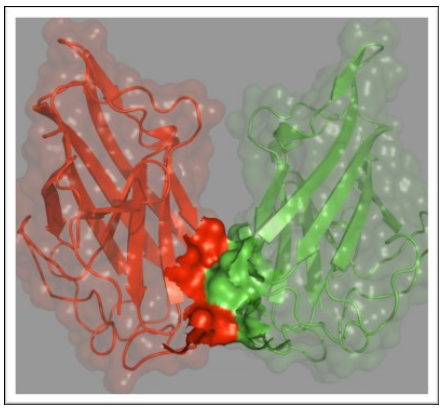
Protein Interaction

➢Identify the interacting surface for two given protein molecules.

- To model the protein complex structure formed out of two protein molecules – protein-protein docking



Measuring the correctness of protein docking



➢Identify the interacting surface for two given protein molecules.

Assume the larger docking unit is receptor and smaller docking unit is ligand.

LRMSD:
RMSD between two ligand molecules after aligning receptor molecules.

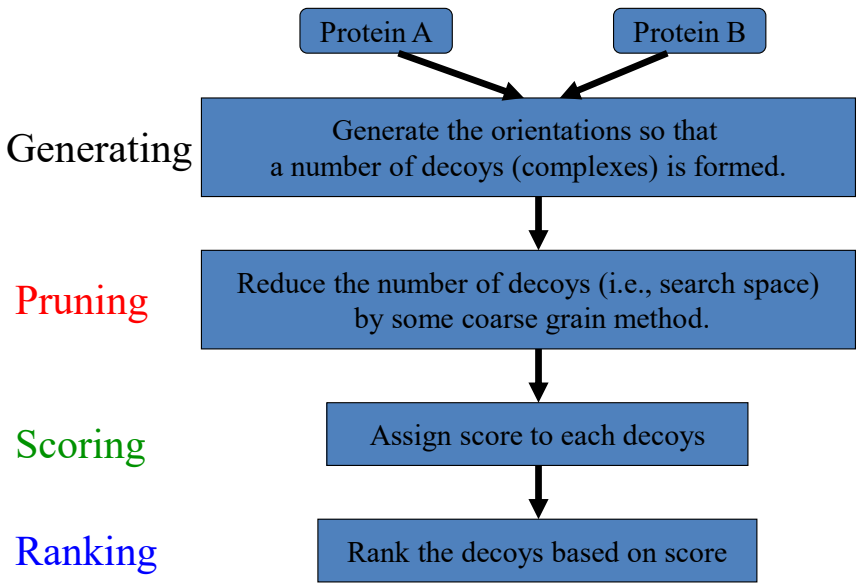
IRMSD:
RMSD between the interface atoms of two ligand molecules after aligning receptor molecules.

Fnat score:
Parentage of interface residues correctly identified as interface residues.

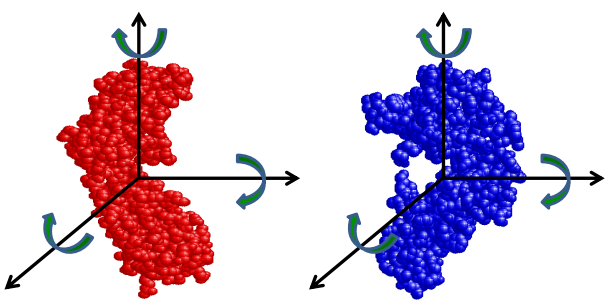
Lecture 24-26

Protein-protein Docking

Docking Strategy

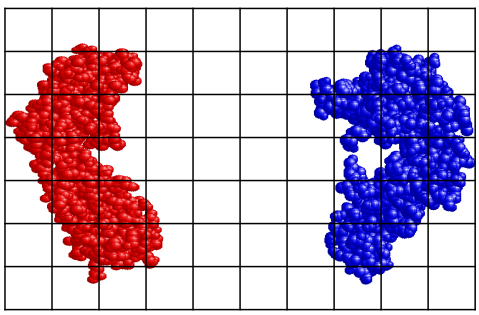


Generation methods



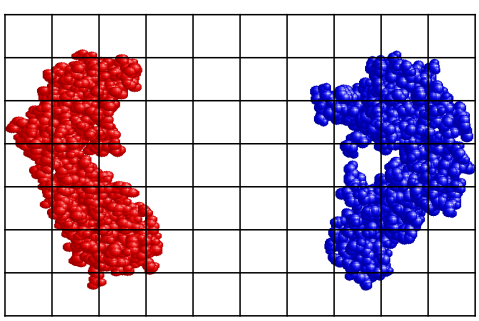
- Tagline – “Higher the decoys; better the possibility of having a hit”
- How many is good?
- Move to discrete space

Generation methods



On an average some brute force method can generate ~10^7 decoys.

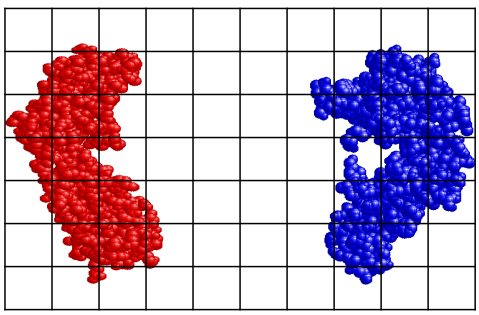
Generation methods



On an average some brute force method can generate ~10^7 decoys.

Assuming processing of each decoy takes 1 sec; total processing time ~115 days.

Fast Fourier Technique

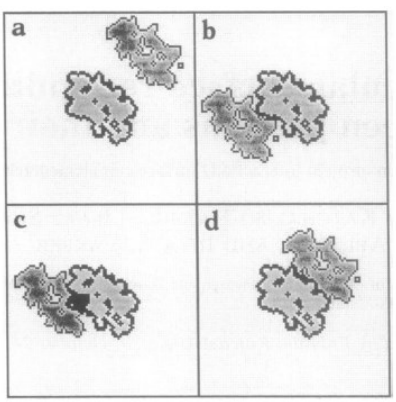


$$\bar{a}_{l,m,n} = \begin{cases} 1 & \text{on the surface of the molecule} \\ \rho & \text{inside the molecule} \\ 0 & \text{outside the molecule,} \end{cases}$$

and

$$\bar{b}_{l,m,n} = \begin{cases} 1 & \text{on the surface of the molecule} \\ \delta & \text{inside the molecule} \\ 0 & \text{outside the molecule,} \end{cases}$$

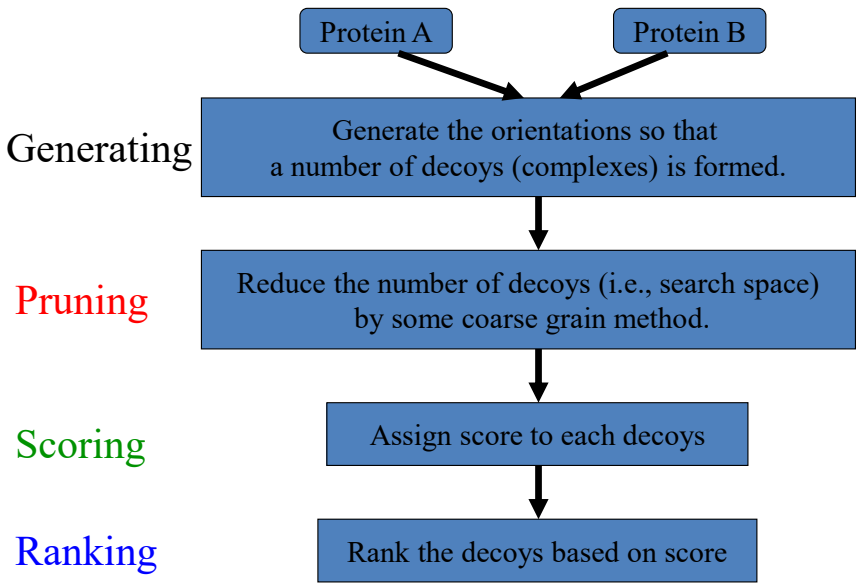
Fast Fourier Technique



$$\bar{c}_{\alpha,\beta,\gamma} = \frac{1}{N^3} \sum_{o=1}^{N} \sum_{p=1}^{N} \sum_{q=1}^{N} \exp[2\pi i(o\alpha + p\beta + q\gamma)/N] \cdot C_{o,p,q}$$

Katchalski-Katzir *et al*, (1992) *PNAS*

Docking Strategy



Scoring methods

Ab initio scoring

- Contact Area
- Contact Packing
- Non-bonded interactions
- Solvation Energy
- Etc.

Template based

Ab initio method

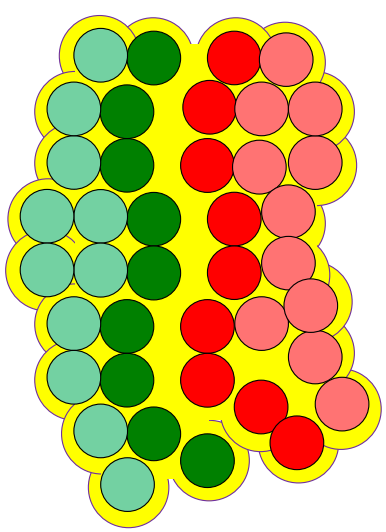
- Interface area (IA)
- Normalized interface packing (NIP)
- Normalized surface complementarity (NSc)
- Non-bonded energy (NE):

$$NE = \sum_{i<j}^{atoms} \left(\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{4\Pi\varepsilon R_{ij}}\right)$$

- Solvation energy (SE):*

$$SE = \sum_{\text{interface atoms}} \Delta\sigma(\text{Atom Type}) \times \Delta\text{ASA}$$

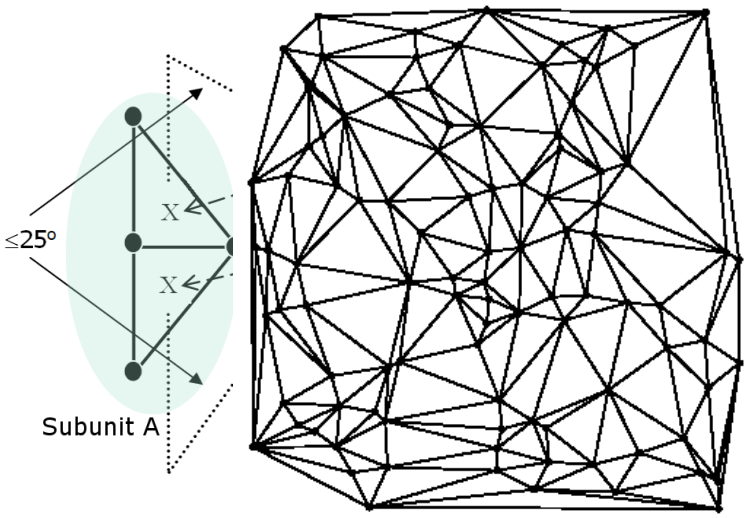
Packing at interfaces



Interface packing =
Actual Volume/Enclosed Volume

Interface packing is divided by interface area to get **Normalized interface packing** (***NIP***)

Surface complementarity

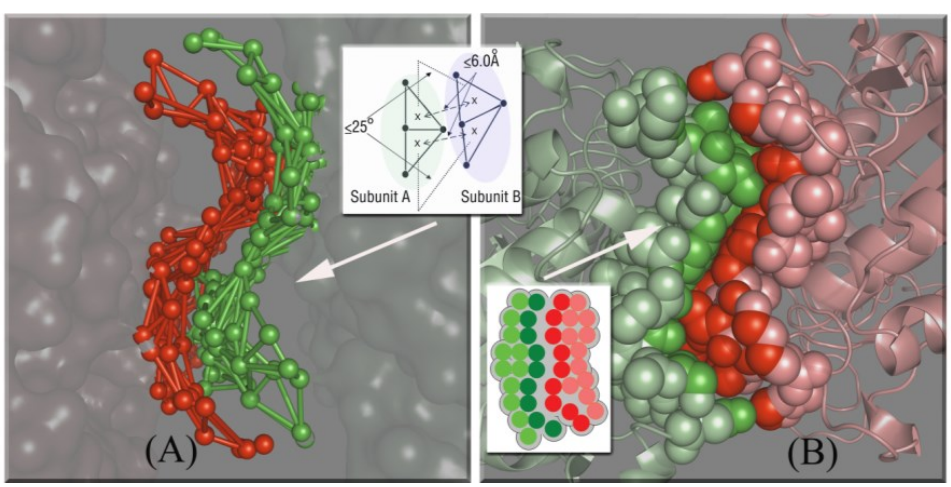


erface atoms
rity between
rmation.
of the different
erface atoms of
by Delaunay

ity =
otal Triangle area

Surface complementarity is divided by interface area to get **Normalized surface complemenarity** (***NSc***)

NSc and NIP at protein interface*



Correlation coefficient of NIP and NSc is **+0.95**