M1 ISDD - BI (Feb 2018)

PROTEIN DOCKING

Lesson 2

Geometry-based docking methods

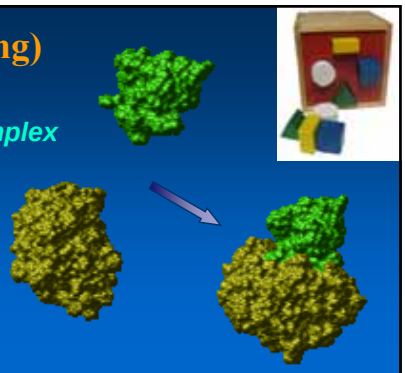
Juan Fernández-Recio

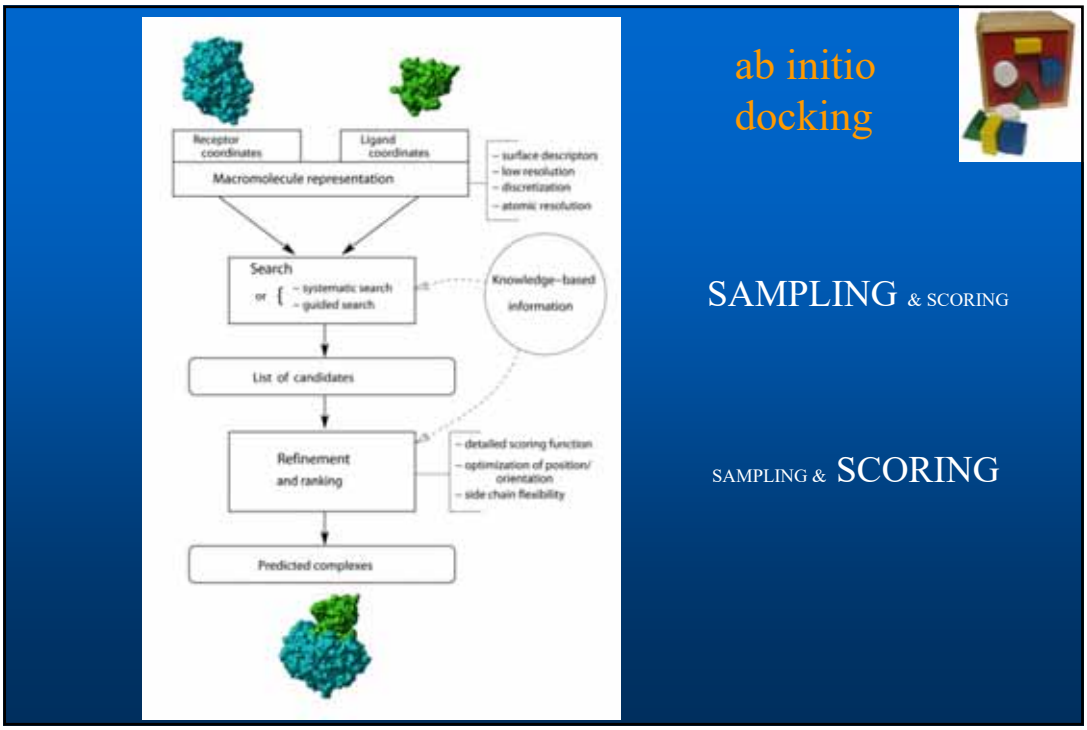
CSIC, BSC

juanf@bsc.es

Complex structure prediction (docking)

Generation of the structure of a protein-protein complex from the individual protein structures




Receptor coordinates
Ligand coordinates
Macromolecule representation
– surface descriptors
– low resolution
– discretization
– atomic resolution
Search
or { – systematic search
– guided search
Knowledge-based information
List of candidates
Refinement and ranking
– detailed scoring function
– optimization of position/ orientation
– side chain flexibility
Predicted complexes
ab initio docking
SAMPLING & SCORING
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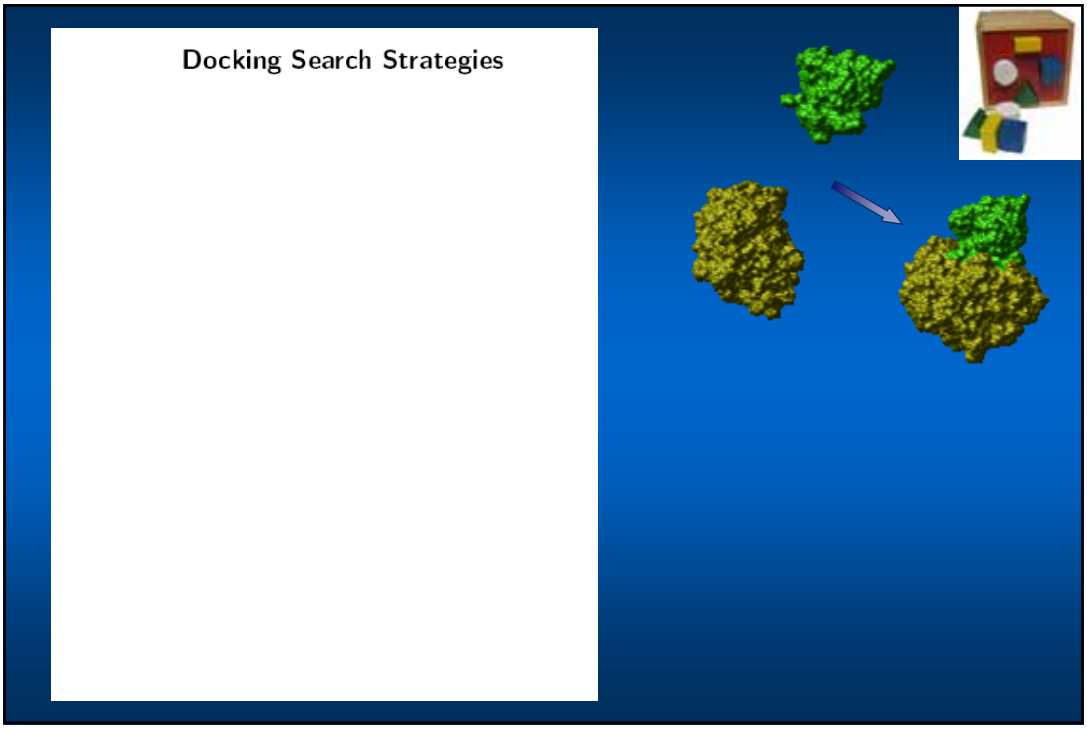
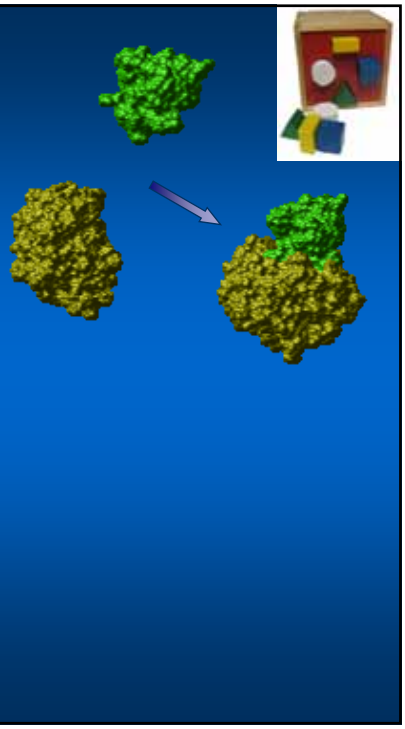
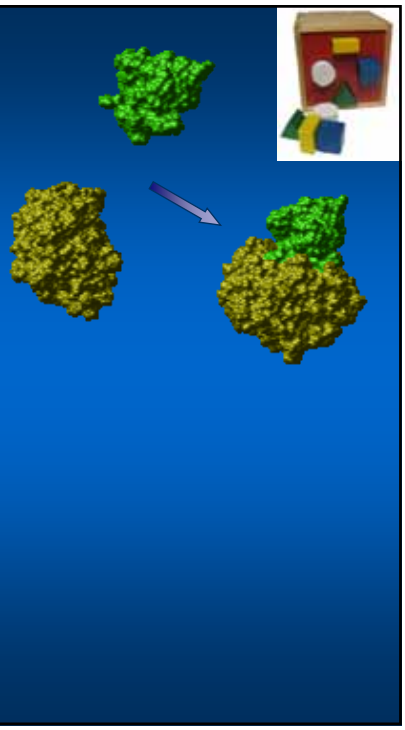

Docking Search Strategies

Docking Search Strategies

- **Pseudo Random**
  - Simulated Annealing / Monte Carlo
  - Genetic Algorithms
- **Directed Search**
  - Geometric Hashing
  - Spherical Harmonic Surface Triangles
- **Brute-Force Search**
  - Explicit Grid Correlations
  - Fast Fourier Transform (FFT) Correlations
  - Spherical Polar Fourier Correlations
- **Refinement Phase**
  - Classical or Soft Potentials (+/- Electrostatics)
  - Desolvation, Solvent Dipoles...
  - Visual Inspection!!

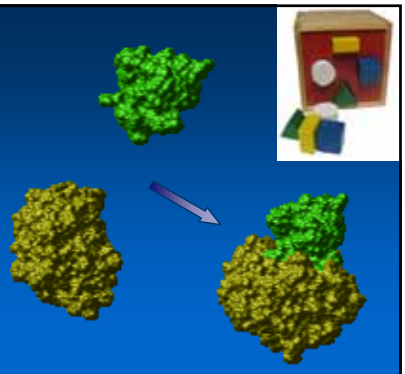


Criteria for Good Docking Orientations



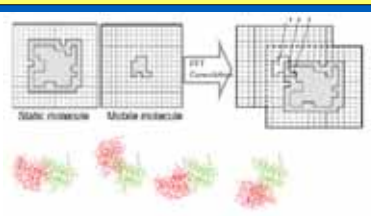
Criteria for Good Docking Orientations

- Low Free Energy (Difficult!)
- Low Pseudo-Energy (Easy) Based On...
- Large Surface Burial: $\sim 1600 \pm 400 Å^2$
- Small van der Waals Overlaps
- No Large Cavities in Interface
- Good H-Bonding: $\sim$ 1 HB/100 $Å^2$
- Good Charge Complementarity
- Polar/Polar Contacts Favoured
- Polar/Non-Polar Contacts Disfavoured



Protein-protein docking methods

Exhaustive search (FFT, surface-based)

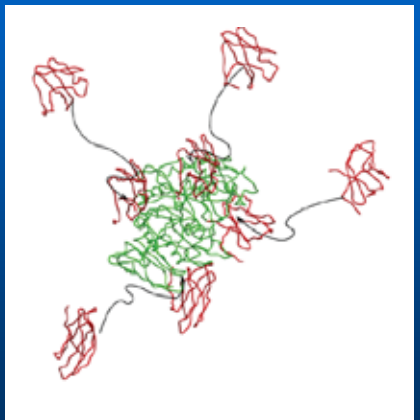


Scoring function

- Energy terms: ES, H-bonds, ...
- Conservation
- Statistical potentials

Geometry-based docking

Stochastic sampling (Monte-Carlo, minimization)



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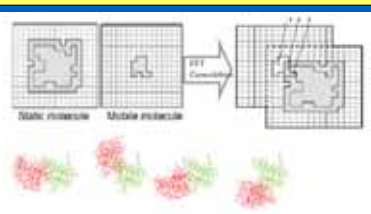

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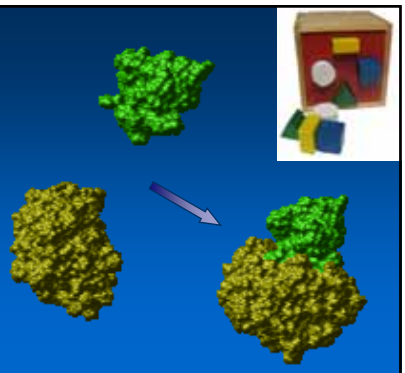

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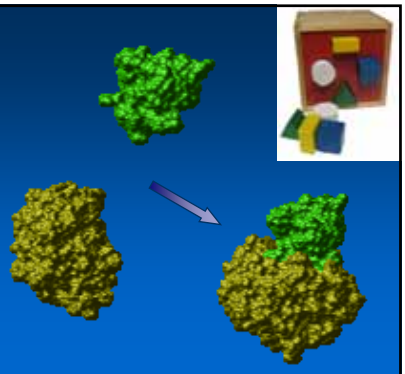
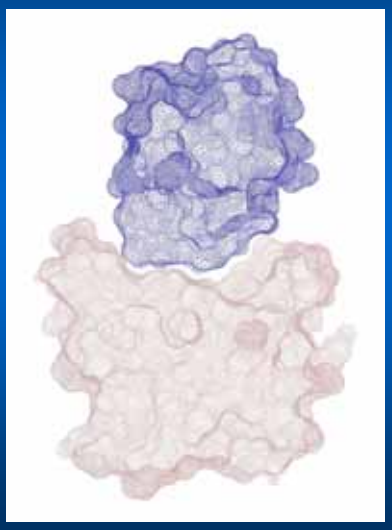


- **FFT-based grid search**
- **Geometric Hashing**
- **Adding distance-, symmetry- constraints**

Rigid-Body Docking: Geometry Approach



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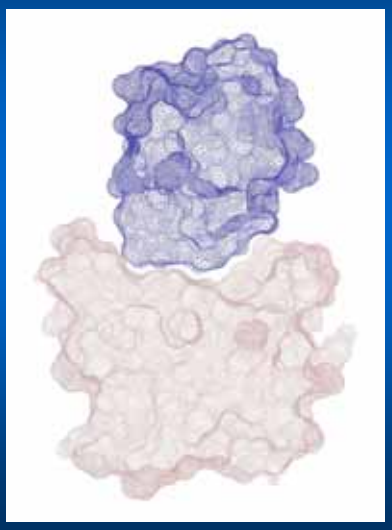
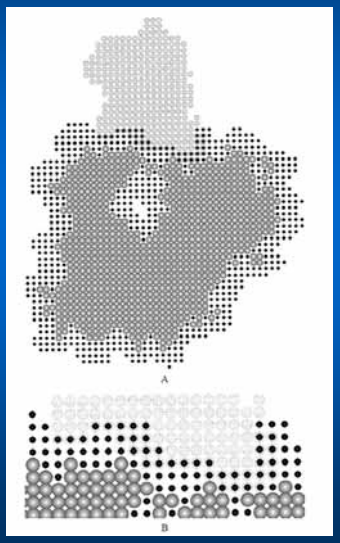
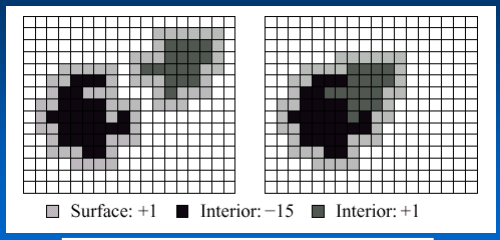




MolFit



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

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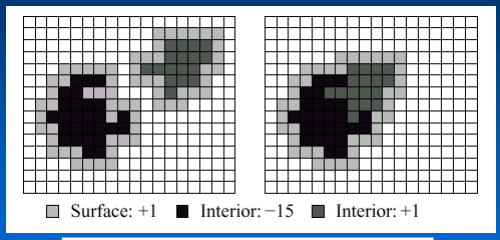

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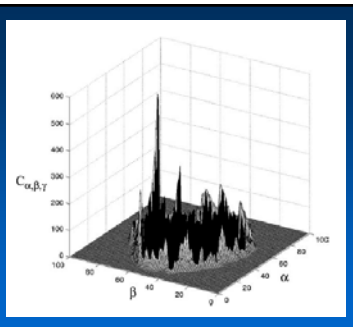

a

b

Corr(a,b)

c

Fourier Transform

It re-express a function in terms of sinusoidal basis functions

Fourier transform equations:

$$F(k) = \int_{-\infty}^{\infty} f(x) e^{-2\pi i k x} dx$$

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$F(k)$ = FT($f(x)$)

$f(x)$ = IFT($F(k)$)

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Correlation function:

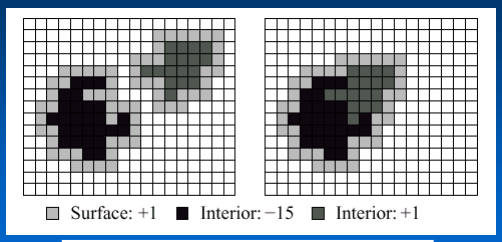
$$c(t) = \mathrm{Corr}(g, h) \equiv \int_{-\infty}^{\infty} g(\tau + t) h(\tau)\, d\tau$$

"Correlation Theorem":

$$FT(c) = \mathrm{FT}(g) \cdot [\mathrm{FT}(h)]^*$$

$$c = \mathrm{IFT}(\ \mathrm{FT}(g) \cdot [\mathrm{FT}(h)]^*\ )$$

MolFit



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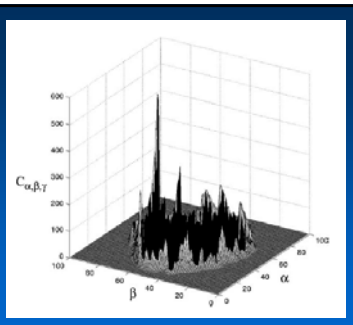
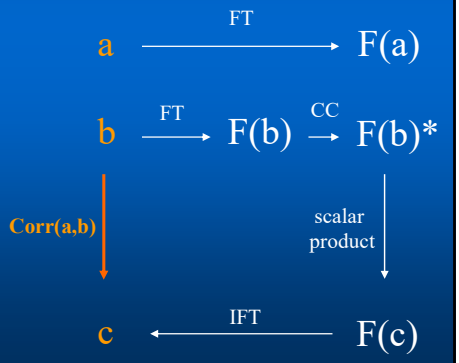




FFT (Fast Fourier Transform)

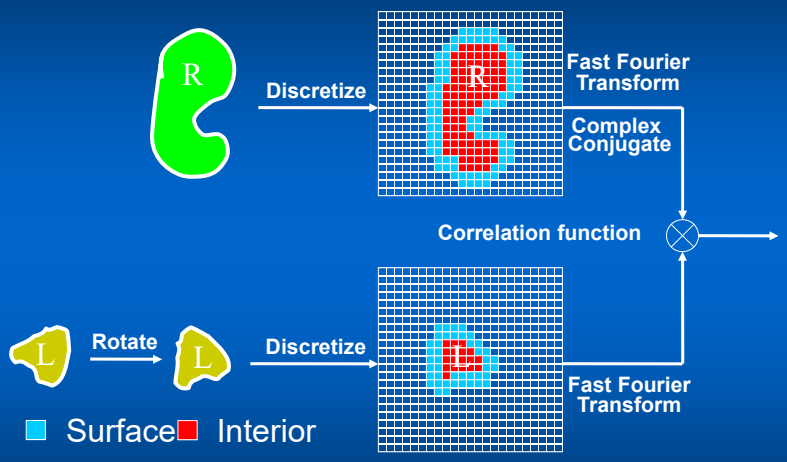
Algorithms for efficient calculation of FT and IFT

- Most common: Cooley-Tukey FFT (divide and conquer)
- Other: Prime-factor, Bruun's, Rader's, Bluestein's

Fourier transform timing: N^2 **(if** $N = 10^6$ **1MHz CPU time ~2 weeks)**
Fast Fourier transform: $N\log_2 N$ **(if** $N = 10^6$ **1MHz CPU time ~ 30 sec)**

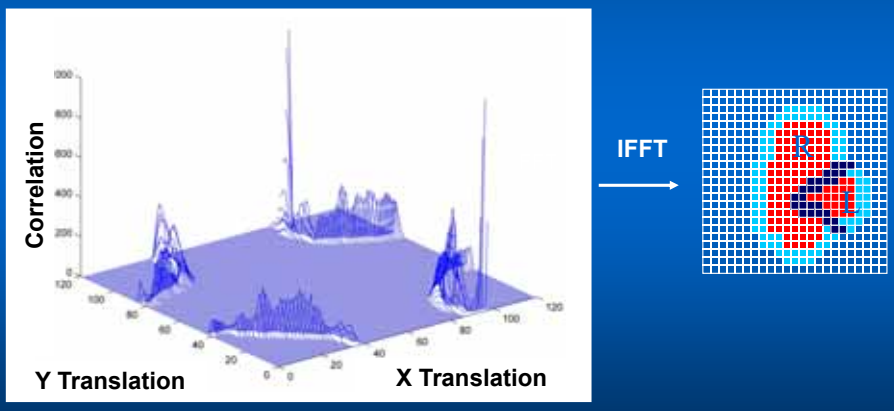
http://www.fftw.org/

Protein Docking Using FFT



Protein Docking Using FFT

Comp. cost can decrease by >10^4 (from N^6 to $N^3 \ln N^3$)



FTDOCK

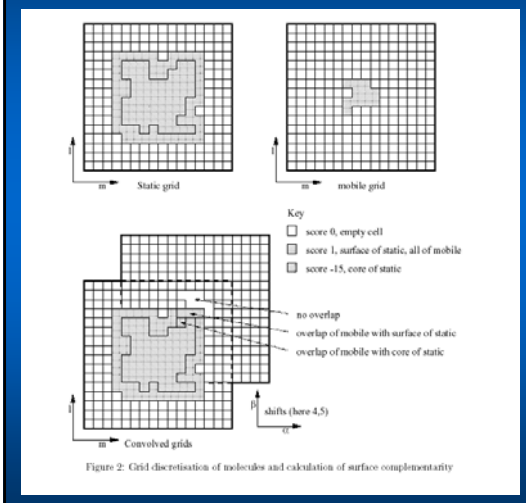
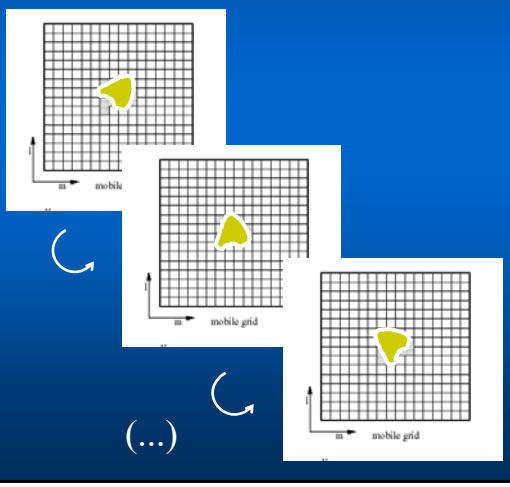


Figure 2: Grid discretisation of molecules and calculation of surface complementarity



FTDOCK

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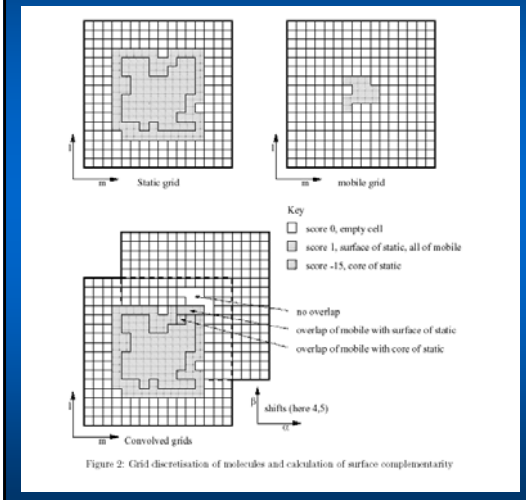

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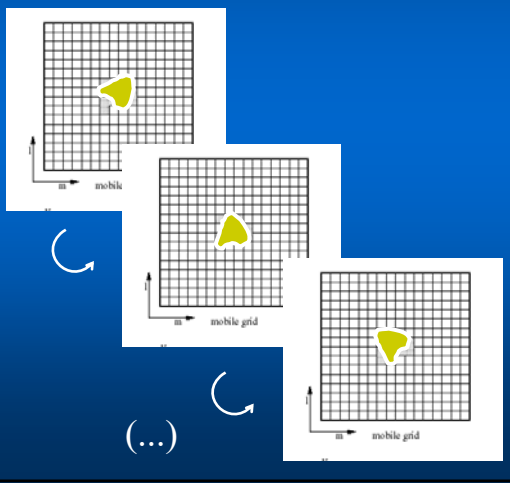

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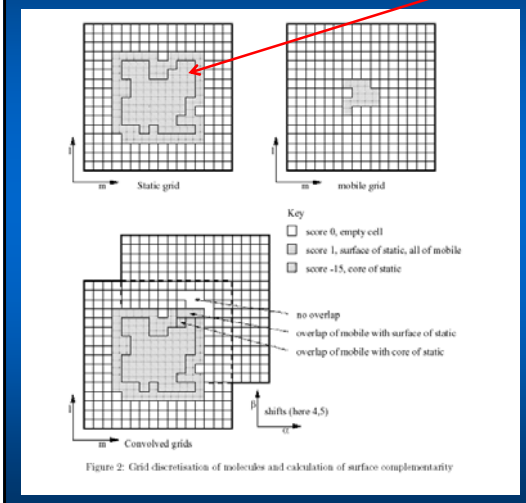

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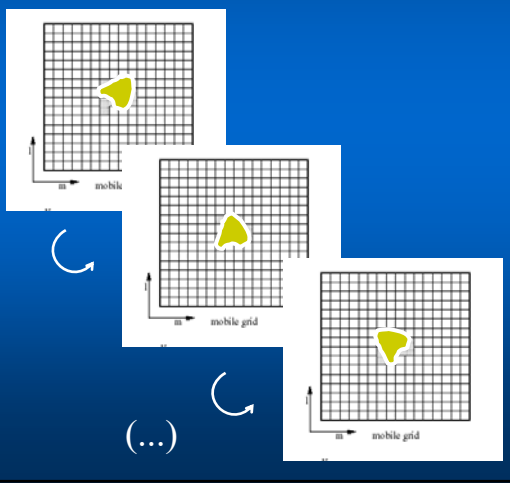

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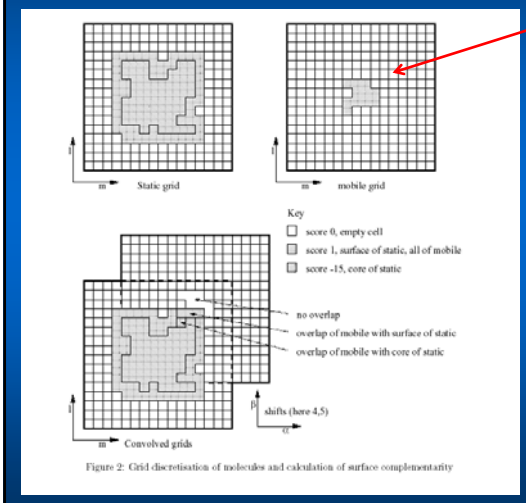

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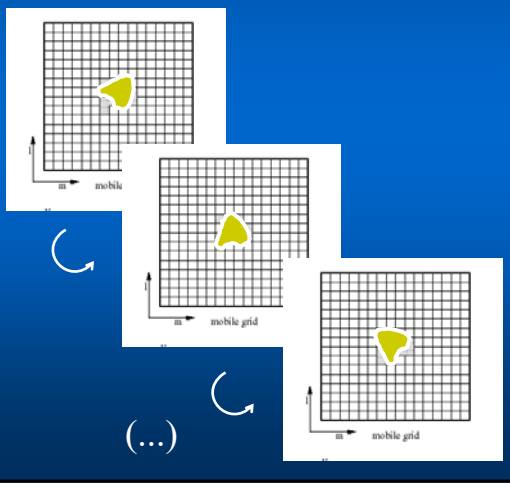

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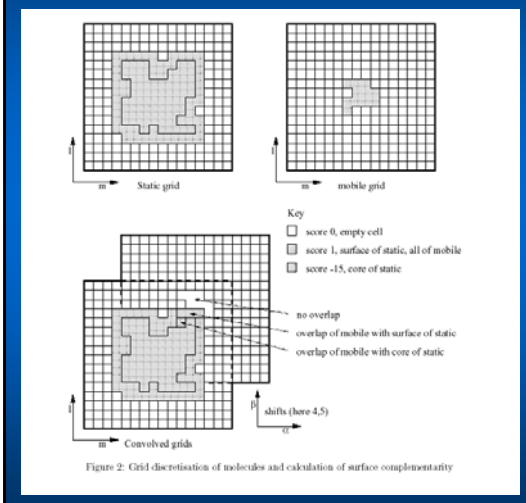

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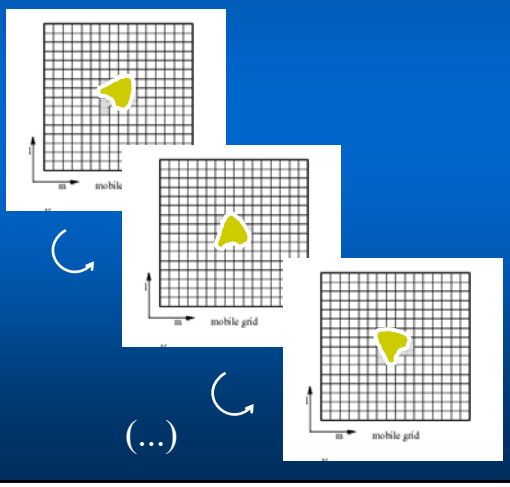

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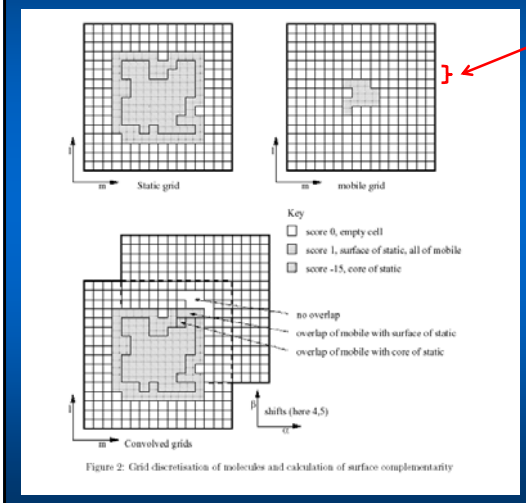

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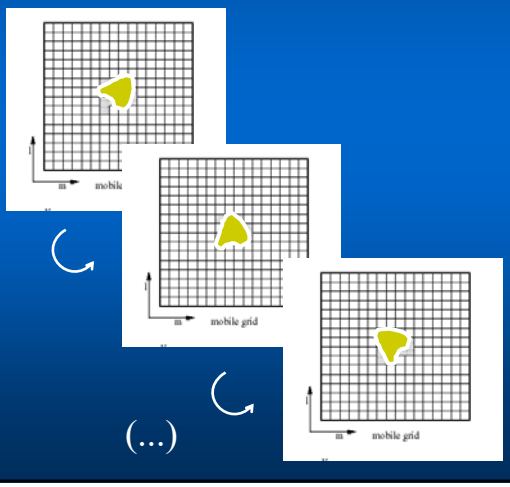

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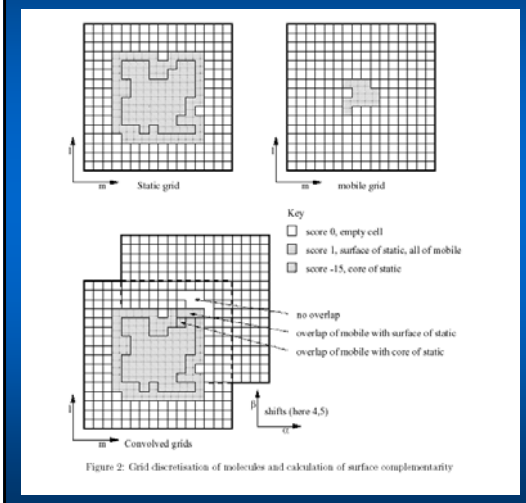

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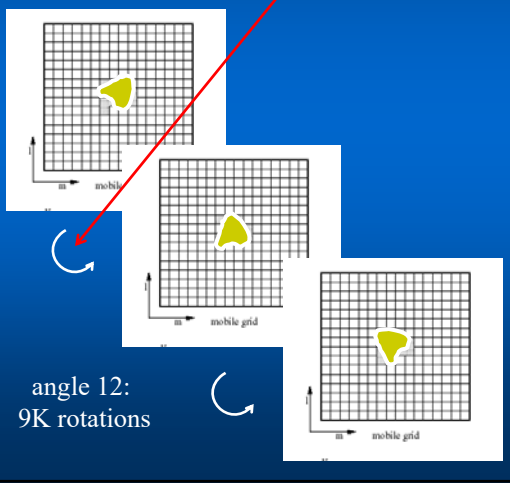
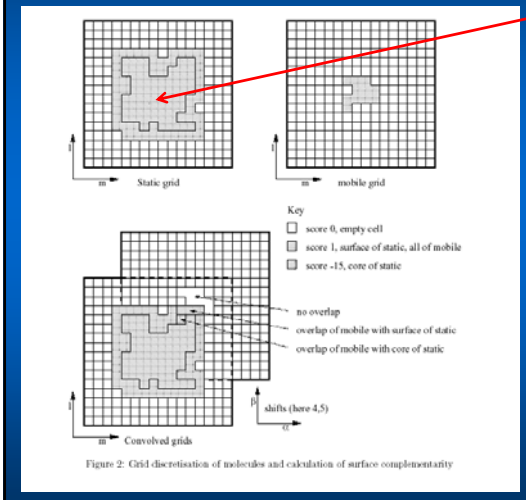


angle 12:
9K rotations



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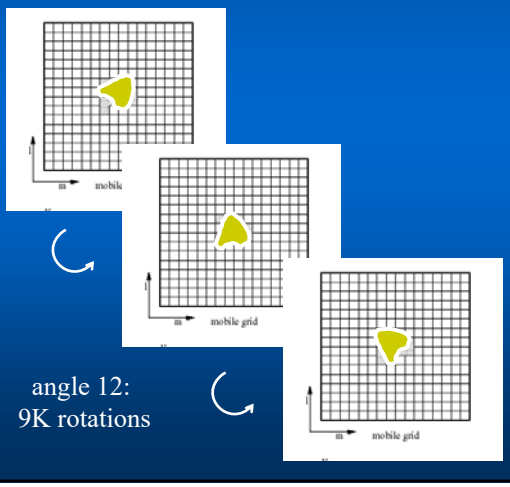

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-internal -15 -surface 1.3 -keep 3
-out 1BRS.ftdock > 1BRS.ftdock.log

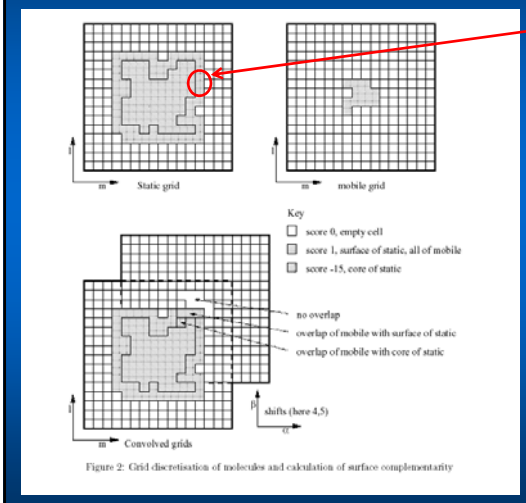
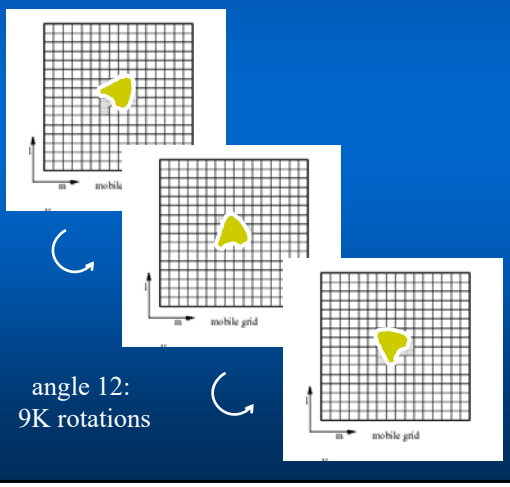


Figure 2: Grid discretisation of molecules and calculation of surface complementarity



angle 12:
9K rotations

FTDOCK

ftdock -static 1A2P_A.pdb -mobile 1A19_A.pdb
-noelec -calculate_grid 1.2 -angle_step 12
-internal -15 -surface 1.3 -keep 3
-out 1BRS.ftdock > 1BRS.ftdock.log

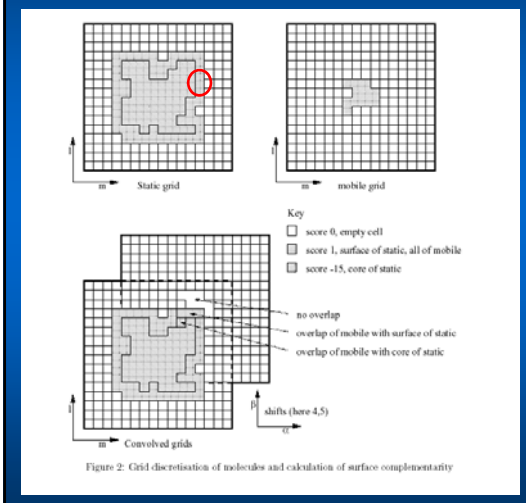
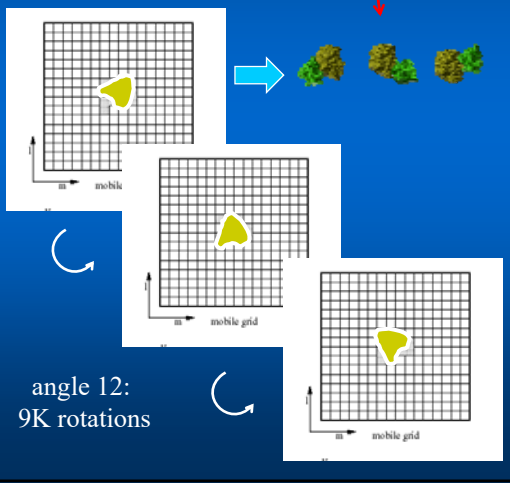
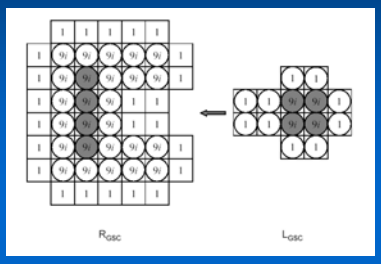


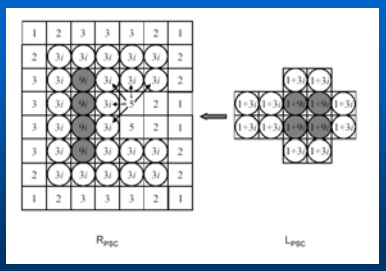
Figure 2: Grid discretisation of molecules and calculation of surface complementarity



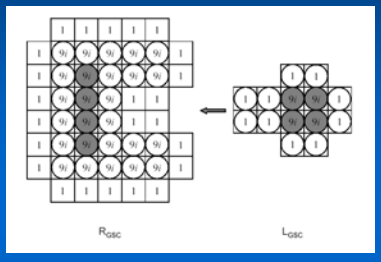
angle 12:
9K rotations

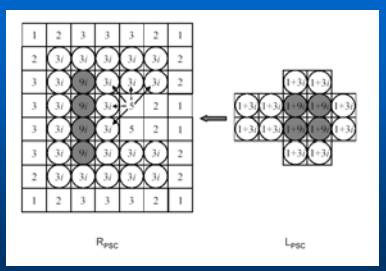
ZDOCK





ZDOCK

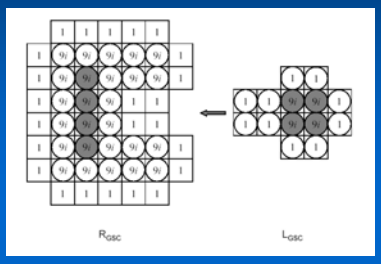




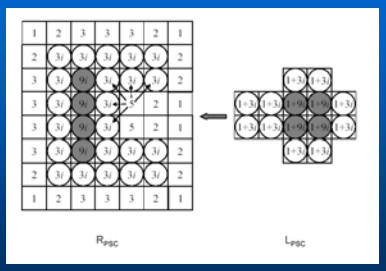
mark_sur 1A2P_A.pdb 1BRS_r.pdb
mark_sur 1A19_A.pdb 1BRS_l.pdb

```
ATOMS LIST
ATOM      1  N   VAL A   3      16.875  37.901  43.478  1     1 1.63    -0.15
ATOM      2  CA  VAL A   3      17.997  38.577  42.795  2     1 2.03     0.10
ATOM      3  C   VAL A   3      18.147  39.997  43.309  3     1 1.67     0.60
ATOM      4  O   VAL A   3      17.180  40.763  43.281  4     1 1.38    -0.55
ATOM      5  CB  VAL A   3      17.786  38.593  41.279  6     1 2.03     0.00
ATOM      6  CG1 VAL A   3      18.621  39.606  40.573 17     1 1.94     0.00
ATOM      7  CG2 VAL A   3      18.024  37.190  40.696 17     1 1.94     0.00
ATOM      8  N   ILE A   4      19.355  40.377  43.690  1     0 1.63    -0.15
ATOM      9  CA  ILE A   4      19.568  41.805  44.109  2     1 2.03     0.10
ATOM     10  C   ILE A   4      20.355  42.488  42.992  3     0 1.67     0.60
ATOM     11  O   ILE A   4      21.489  42.115  42.701  4     0 1.38    -0.55
ATOM     12  CB  ILE A   4      20.430  41.800  45.396  6     0 2.03     0.00
ATOM     13  CG1 ILE A   4      19.774  40.976  46.525 16     1 1.99     0.00
ATOM     14  CG2 ILE A   4      20.779  43.192  45.823 17     1 1.94     0.00
ATOM     15  CD1 ILE A   4      20.598  40.921  47.787 17     1 1.94     0.00
```

ZDOCK

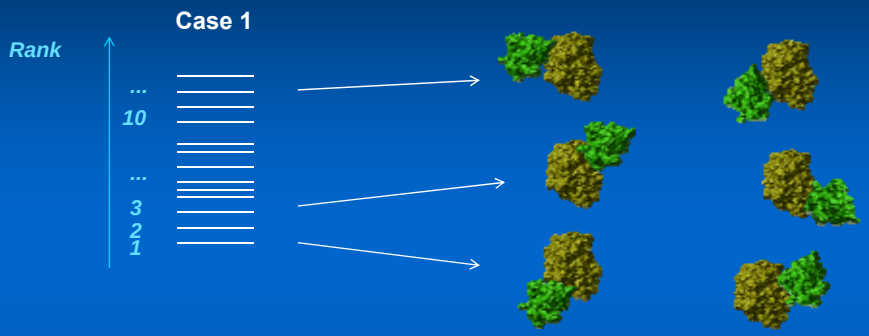


mark_sur 1A2P_A.pdb 1BRS_r.pdb
mark_sur 1A19_A.pdb 1BRS_l.pdb

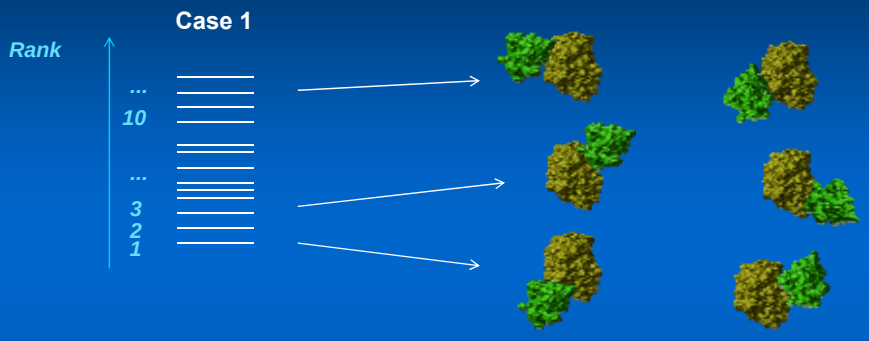


zdock -R 1BRS_r.pdb -L 1BRS_l.pdb -o 1BRS_zdock.out

Assessment of docking performance

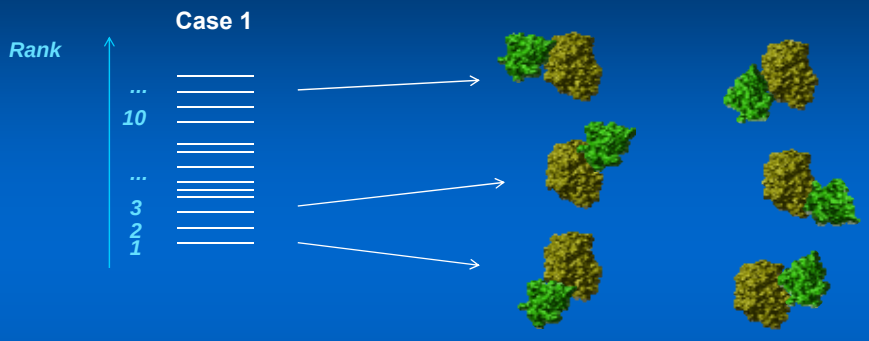


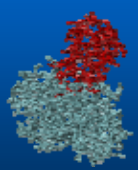
Assessment of docking performance



good solution ??

Assessment of docking performance





reference complex

good solution ??

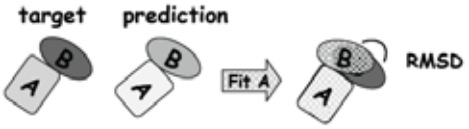
Assessment of docking performance

- F_{nat}: fraction of native contacts (within 5Å)

$$F_{nat} = \frac{\text{Correctly predicted contacts}}{\text{Total number of contacts in the target}}$$

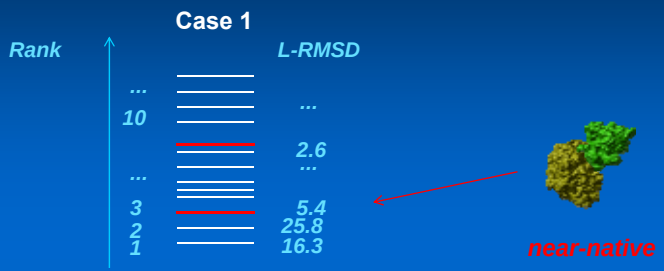
- l-RMSD: RMSD on second protein after superposition on first

near-native: L-RMSD < 10Å

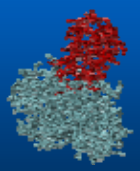


- i-RMSD: RMSD on interface residues (within 10 Å)

Assessment of docking performance

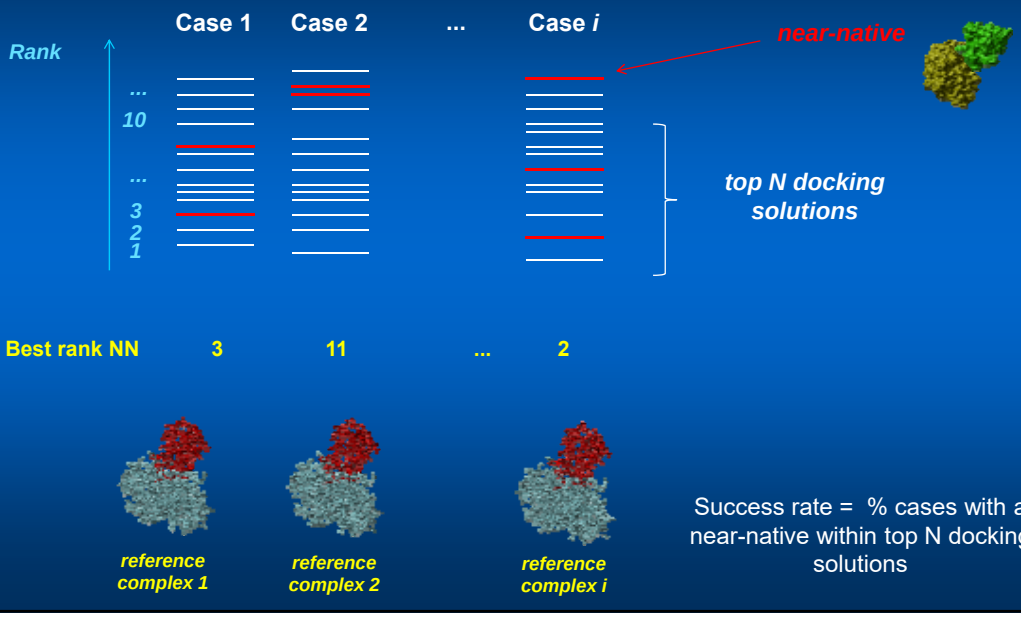


Best rank NN **3**



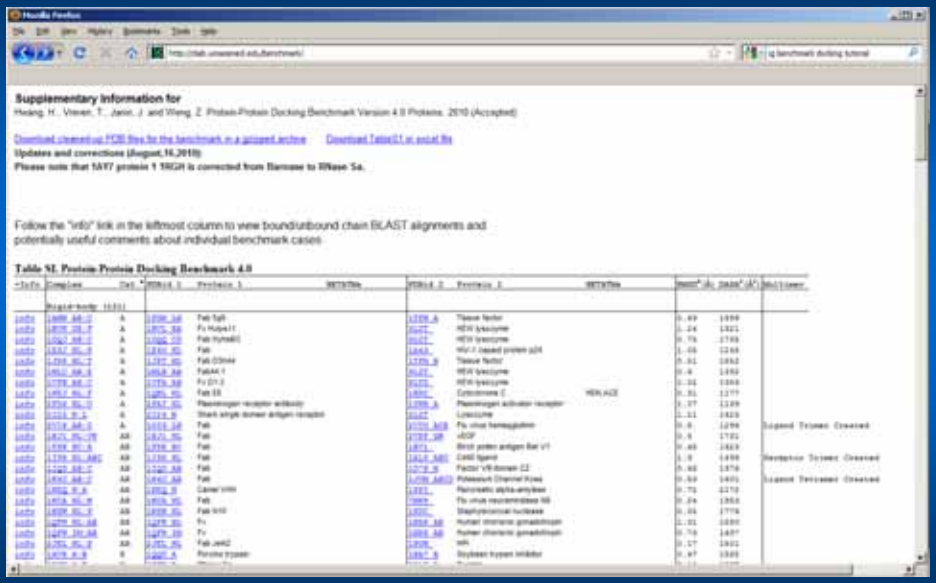
reference complex

Assessment of docking performance



Success rate = % cases with a near-native within top N docking solutions

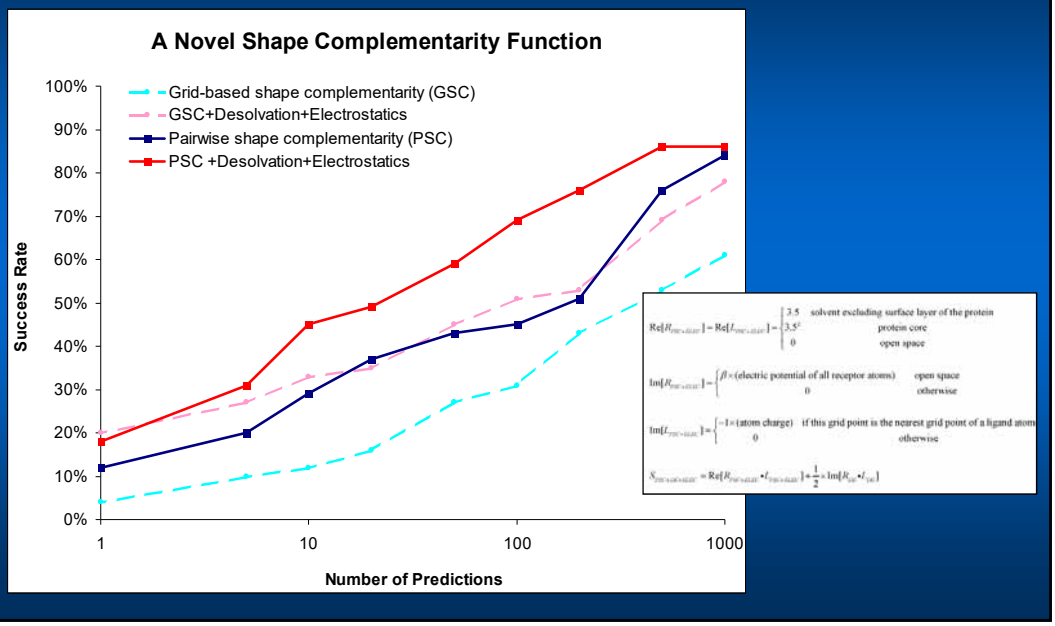
Protein-protein Docking Benchmark 4.0 - Weng



176 cases

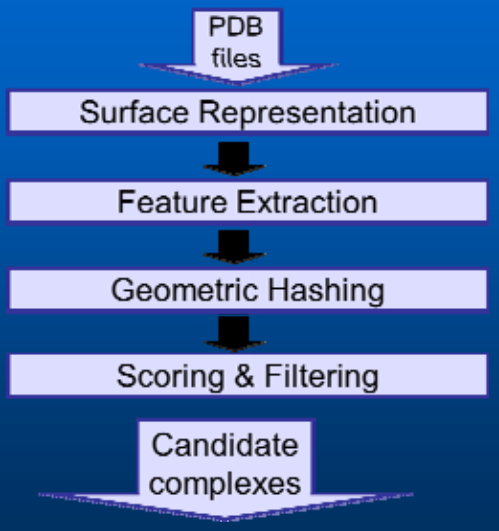
http://zlab.umassmed.edu/benchmark/

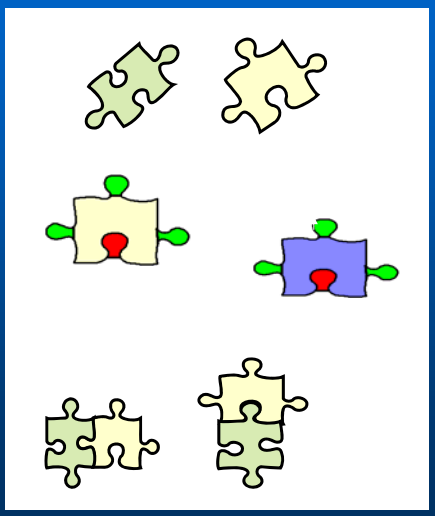
ZDOCK performance



- FFT-based grid search
- **Geometric Hashing**
- Adding distance-, symmetry- constraints

Geometrical hashing - PatchDock



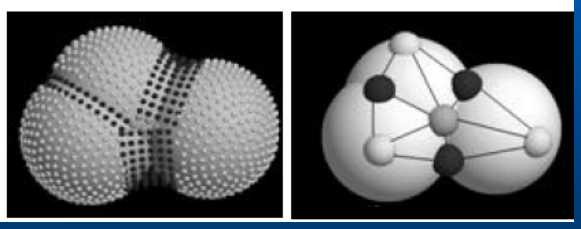


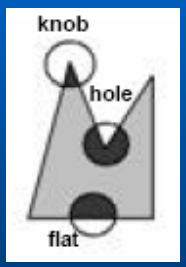
Schneidman-Duhovny et al. Proteins 2003
Duhovny (Schneidman), D., Nussinov, R. Wolfson,HJ. WABI 2002

Surface Representation

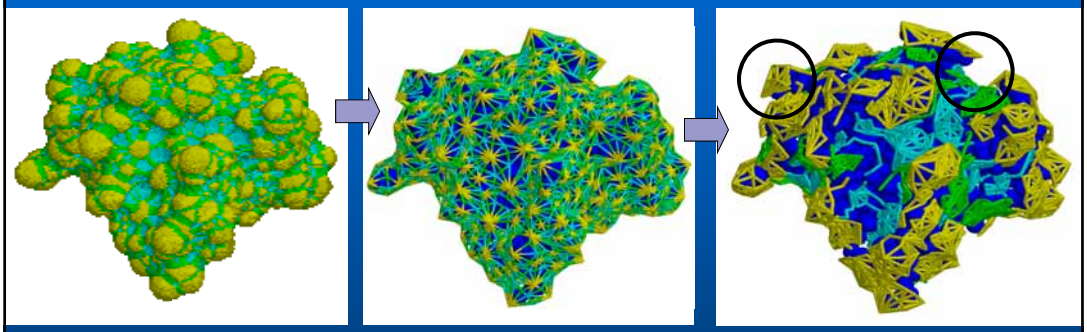
Surface Representation

- Dense MS surface (Connolly)
- Sparse surface (Shuo Lin et al.)





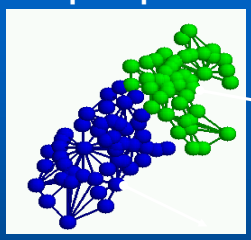
Feature Extraction



- We focus on sparse surface features, preserving the quality of shape representation.
- The sparse features reduce the complexity of the matching step.

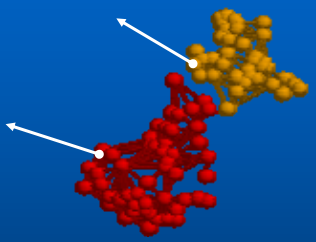
Patch-Pair Matching

Receptor patches



Transformation

Ligand patches

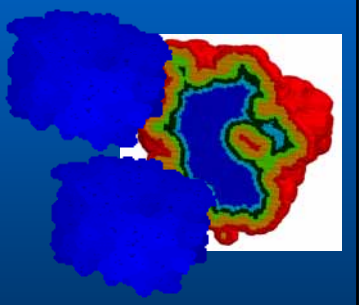


Base: 1 critical point with its normal from one patch and
1 critical point with its normal from a neighboring patch.

- Match every base from the receptor patches with all the bases from complementary ligand patches.
- Compute the transformation for each pair of matched bases.

Geometric Scoring

- The surface of the **receptor** is divided into five shells according to the distance function: **S1-S5**
- The number of **ligand** surface points in every shell is counted.
- The geometric score is a weighted sum of the number of ligand surface points inside every shell.

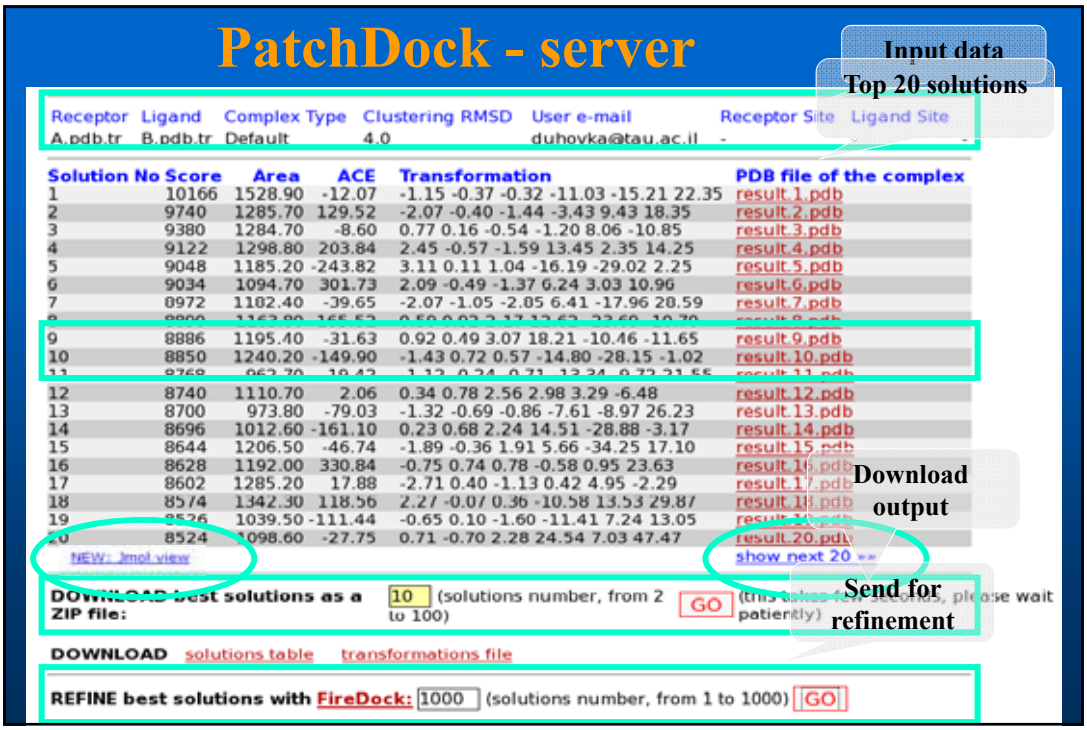


- **Multi-resolution surface** data structure was developed to speed up this stage.

http://bioinfo3d.cs.tau.ac.il/PatchDock

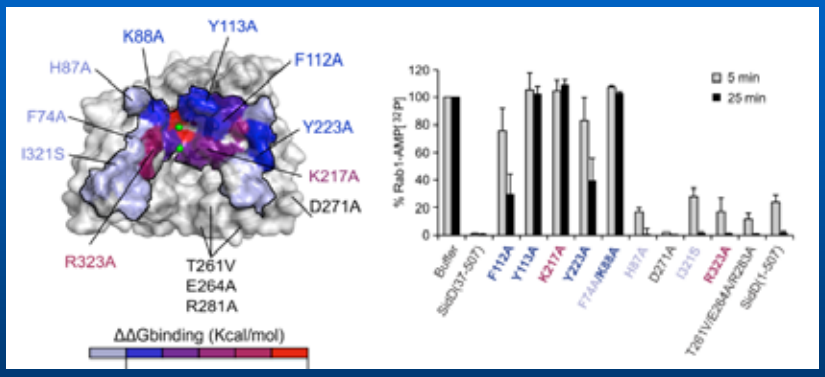
Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ. NAR 2005

PatchDock - server



- FFT-based grid search
- Geometric Hashing
- Adding distance-, symmetry- constraints

Docking with known interface residues



Optional parameters: binding site

Advanced Options:
[Show][Hide]

Receptor Binding Site: Browse... upload receptor binding site file

Ligand Binding Site: Browse... upload ligand binding site file

Distance Constraints: Browse... upload distance constraints file

Submit Form Clear

Optional parameters: binding site

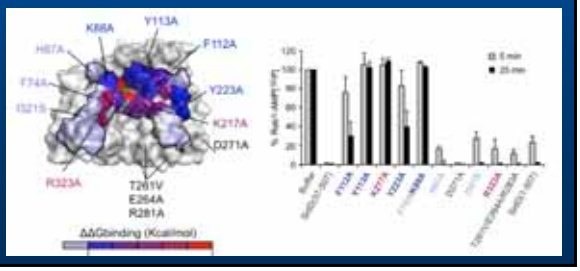
Advanced Options:
[Show][Hide]

Receptor Binding Site: Browse... upload receptor binding site file
Ligand Binding Site: Browse... upload ligand binding site file
Distance Constraints: Browse... upload distance constraints file
Submit Form Clear

Binding Site – list the residues of the receptor potential binding site. Only patches that include these residues will be used for matching.

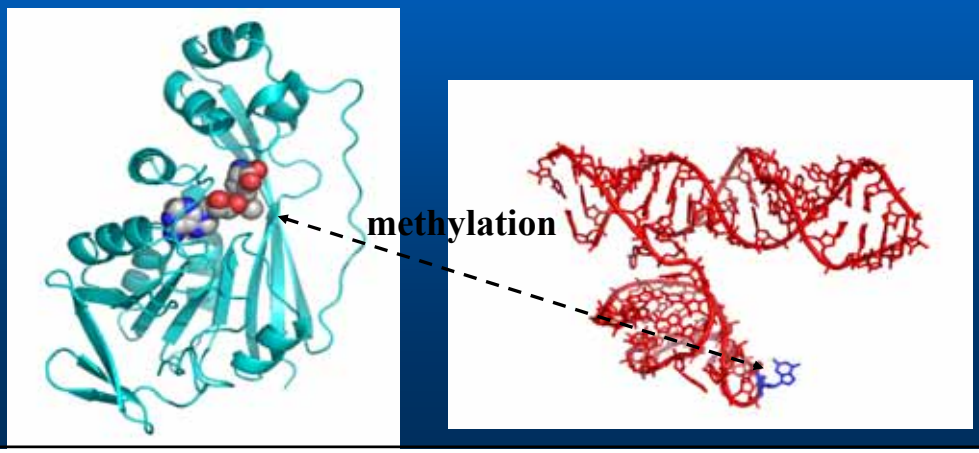
Format: ***[residue index] [chain ID]***
Example:

74 A
88 A
112 A
113 A
217 A
223 A



Docking with Distance Constraints

A complex of RIma2 methyltransferase of S. pneumoniae and a 74 nucleotide RNA transcript



Optional parameters

Advanced Options:
[Show][Hide]

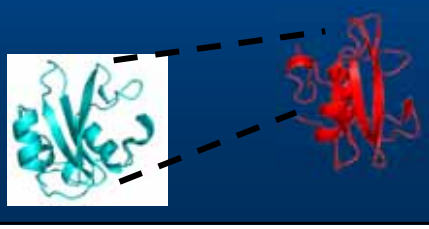
Receptor Binding Site: Browse... upload receptor binding site file
Ligand Binding Site: Browse... upload ligand binding site file
Distance Constraints: Browse... upload distance constraints file
Submit Form Clear

Distance Constraints –between pairs of atoms, one in the receptor and one in the ligand.

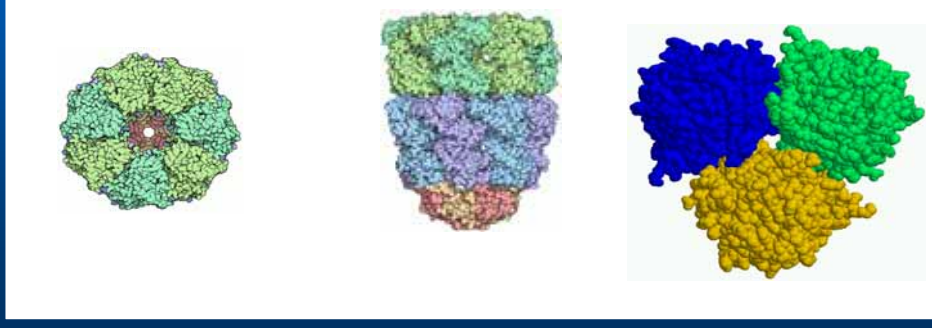
Format: ***[receptor_atom_index] [ligand_atom_index] [max_dist]***

For example:

25 377 5.0
340 5603 10.0



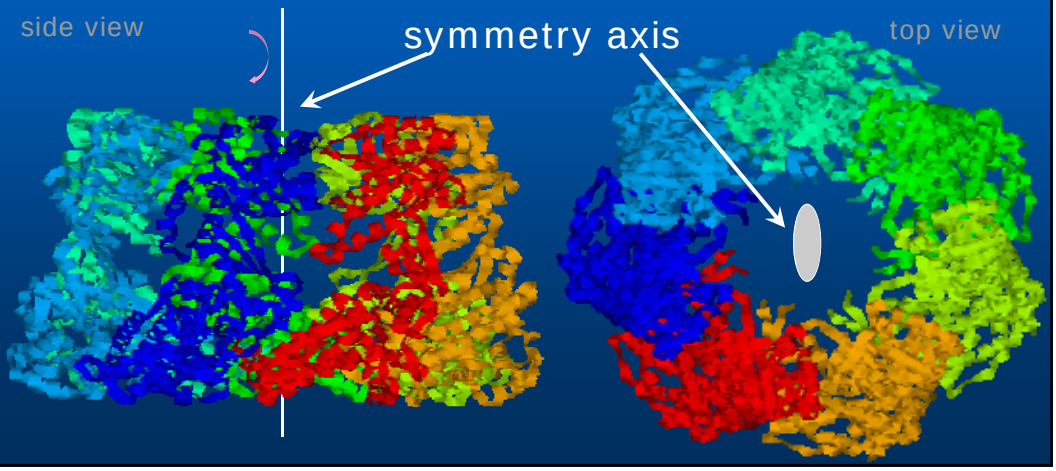
Symmetric Docking



Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ Proteins 05

Cyclic Symmetry

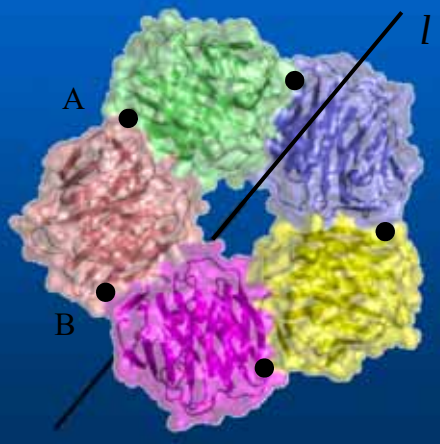
- Cyclic symmetry is defined by rotation of a single unit around an **axis**.
- The angle is determined by a number of units **n**.



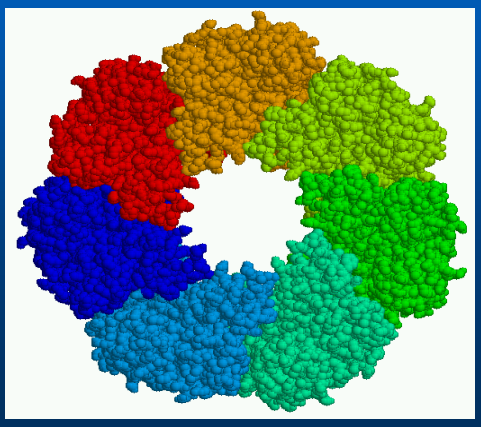
Geometrical view

$T(A) = B$

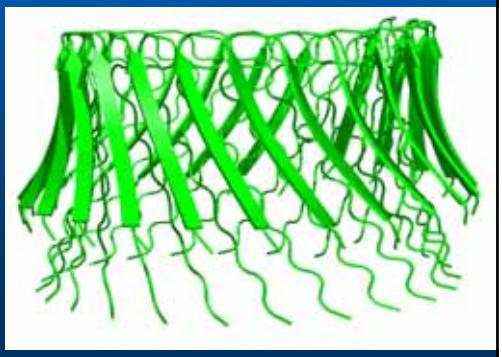
$l \cdot \overrightarrow{AB} = 0$



Chaperon: 2.5 Å RMSD prediction for the homo-heptamer.



Alzheimer's disease amyloid protein. Prediction of the membrane channel



N=24

WWW server: http://bioinfo3d.cs.tau.ac.il/SymmDock

SymmDock

3 mandatory fields

Unit Molecule: the asymmetric unit of the multimer complex (PDB format)

Type the PDB code [ ] (PDB-code:chain Id, e.g. 1f23:A)

or upload a file [ ] Browse...

Symmetry Order: [ ] (any number from 2 to 20: 3 for trimer, 4 for tetramer etc.)

e-mail address [ ] (the results are sent to this address)

Binding Site: [ ] Browse... binding site file (optional)

Submit Form Clear

Option to specify interface residues
(file format as in PatchDock)

Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ. NAR 2005

SymmDock Output Page

Top 20 solutions

Solution No	Score	Area	ACE	Transformation	PDB file of the complex
1	11858	1635.30	370.62	1.41 1.39 0.37 54.14 103.65 17.77	result.1.pdb
2	10512	1545.10	292.99	2.13 0.50 -1.39 42.10 38.18 -0.03	result.2.pdb
3	10468	1347.40	359.91	1.69 1.36 0.06 52.63 102.43 19.92	result.3.pdb
4	10284	1731.50	118.78	0.33 1.04 1.71 67.49 68.41 -23.84	result.4.pdb
5	9994	1808.40	228.47	1.59 1.28 0.26 45.22 104.90 15.19	result.5.pdb
6	9748	1420.40	641.49	2.17 -0.52 0.70 -54.29 101.23 -6.25	result.6.pdb
7	9478	1411.20	561.82	2.18 -0.53 0.68 -53.30 101.31 -2.72	result.7.pdb
9	9212	1528.30	761.87	2.03 0.43 0.17 9.12 119.03 -11.22	result.9.pdb
10	9186	1312.60	36.15	0.58 0.96 1.60 57.31 63.89 -28.67	result.10.pdb
12	9130	1290.40	221.23	1.40 1.13 0.66 24.37 95.76 8.39	result.12.pdb
13	9084	1105.10	319.00	2.41 0.83 -1.82 45.17 23.56 20.96	result.13.pdb
14	8922	1070.60	306.21	2.11 0.43 -1.24 40.73 44.84 -2.10	result.14.pdb
15	8888	1137.10	166.91	2.07 -0.14 0.72 -21.26 50.08 0.49	result.15.pdb
16	8818	1190.60	101.84	-1.01 -1.29 -2.49 -27.92 40.88 20.18	result.16.pdb
17	8798	1347.60	476.51	1.11 0.42 1.60 -1.25 53.16 -18.73	result.17.pdb
18	8784	1452.70	375.98	-0.53 0.79 2.18 86.39 90.79 21.56	result.18.pdb
19	8452	1410.70	499.66	2.08 -0.35 1.17 -52.48 58.60 19.25	result.19.pdb
20	8452	1134.10	342.38	0.31 0.04 2.07 81.88 66.44 -18.55	result.20.pdb

show next 20 »»

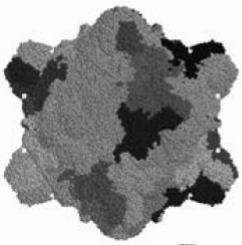
how many solutions to zip? 10 (any number from 2 to 100)

GO (this takes few seconds, please wait patiently)

Download output

Rigid-body docking: symmetry constraints

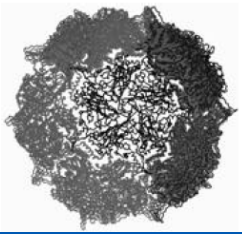
Virus structure prediction



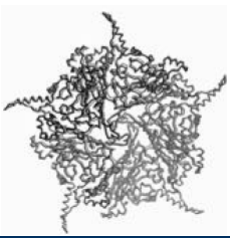
Icosahedron:
12 nodes,
20 faces,
30 edges
60 monomeric units

5-fold, 3-fold, 2-fold cyclic symmetry

Cyclic symmetry n=3



Cyclic symmetry n=5



Geometry-based docking: conclusions

- *Many available methods*
- *Very fast!*
- *In most of the cases, reasonable success rates*
- *Unbound much worse than bound*
- *Some times, missing native (even with bound subunits)*
- *Good as first docking step before refinement*