Table 1. Comparison of protein-protein docking programs/methods.

Name Author Publication Web page	**ZDOCK** (in C) Chen & Weng Proteins. 47:281-294 (2002). http://zlab.bu.edu/~rong/dock/	**MolSoft 2000 ICM** Abagyan Protein science (2002), 11:280-291. http://www.scripps.edu/~jfrecio/ICMprotdock/	**MolFit** + **Electrostatics** Heifetz & Eisenstein (Israel) Protein science (2002), 11:571-587.	**BiGGER** Palma & Moura Proteins 39:372-384 (2000)	**GRAMM** Vakser PNAS 96:8477-8482(2000) More papers on http://reco3.ams.sunysb.edu/gramm	**HEX3.0** Ritchie & Kemp Proteins 39:178-194 (2000) http://www.biochem.abdn.ac.uk/hex/
Search algorithm Shape score	Systematic search with FFT grid spacing =1.2Å (100 grids for a typical complex) rotational interval=15°. Shape score = correlation (receptor$^{1, ?i, 0}$, ligand$^{1, ?i, 0}$)	Pseudo-Brownian Monte Carlo sampling. 5 grid probes: two vdw probes H and C atoms. 120 starting orientation by systematically rotating the ligand. Each starting orientation explored by pseudo-Brownian Monte-Carlo sampling. new conformations selected by Metropolis criterion at 300K, 5000K.	Systematic search with FFT. Grid spacing= 1.0-1.2 Å Rotation interval: 12°. Shape score is similar to that in ZDOCK.	Systematic search with FFT. Grid spacing = 1.0 Å. Rotational interval = 15°.	Systematic search with FFT. The first paper introducing FFT to shape correlation in protein-protein docking. PNAS 89:2195-2199 (1992). Basically, it is a shape-based docking program (hydrophobic contacts can also be considered). Resolution can be adjusted.	Systematic search using spherical polar Fourier correlations. No need for grid. The search space is represented by 5 Euler rotation angles and one inter-mol distance. Fast and less memory. Shape and electrostatics are represented using series expansions of orthonormal spherical polar basis functions.

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Energy function (Electr. Vdw. Desolvation)	1. Electr: Coulombic with CHARMM19 charges. 2. Vdw: no 3. Desolvation: Atomic Contact Energy (ACE, emperical, 18 atom types, cutoff = 6Å) Desolvation score = correlation (receptor^{ACE}, ligand^{ACE}) Score=0.01Shape + Desol. +0.06Elect. And other combinations.	1. Electr + desol $E_{ele/solv}$: coulombic with e=4r + atomic solvent accessible surface term. 2. Vdw (E_{Hvw} and E_{Cvw}): smoother 6-12 potential 3. Hbond E_{hb}: spherical Gaussian 4. Hydrophobic E_{hp}: 30 cal/mol.Å2× buried hydrophobic surface area. Score = $E_{Hvw} + E_{cvw} + E_{ele/solv} + E_{hb} + E_{hp}$ optimal scrore = $E_{Hvw} + E_{cvw} + 2.16E_{ele/solv} + 2.53E_{hb} + 0.20E_{hp} + 0.20E_{solv}$	1. Electr: PB by Delphi; grid spacing = 0.5 Å. The potential of Delphi grid is transferred to each MolFit grid by constructing a potential spheres. Delphi potential is calculated only once. But the potential of each MolFit grid will change with the translation/rotation of the molecules during the search. Charges: PARSE partial charges (better) or formal charges on Arg, Lys, Asp, Glu and His. Score = Shape + wElectr. Optimal w = 0.35	1. Electr: coulombic with rij = rij+c. c is the minimal contact distance = 1.5 Å. Amber4.1 force field. 2. solvation: solvent-accessible surface area.	Only shape complementarity is considered in GRAMM. But energy score functions can be used in the post-GRAMM stage to rank the results. See table 2.	1. electr.: Poisson's equations. score = (139.14/K_R) electr. + $K_H$shape. For HyHel-5-lysozyme complex, K_R = 8 K_H= 0.8 KJ/mol/Å^3.

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Flexibility Side chain or backbone	Arg and Lys: side chain collapse allowed.	Biased probability Monte Carlo minimization on side chains torsion angles of surface residues of ligand.	No consideration.	Side chain flex: Arg, Lys, Asp, Glu and Met.	No consideration.	No consideration.
timing	Computer: R10000 origin 2000 10 h: 100 grids (single cpu, typical) 19 h: 128 grids	667MHz Alpha: 2-7h for rigid docking and 7-20 min for refinement. (FTDOCK: 6h on 8 R10000)	R10000 SCI octone: 9h for 128 grids.	2-8 h on 450MHz pII.	Convex C-220: 7.5h with 1100 atoms. If grid=128, orientations = 3×10^7	2h: SCI R5000 for 5.4×10^8 orientations.

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Test proteins. (cases showing conformational changes)	27 in total. 5 homodimers, 11enzyme/inhibitor, 9 antibody/antigen, 2 others. 13 unbound-unbound, including 1brs (Barnase has conformational change) and 1fss (Fasciculin II has conformational change) interface = 10Å near-native = interface Ca < 2.5 Å. Shape helped 1fss, Electr helped 1brs, desol did not help 1fss or 1brs. 24/27 complexes found near native	24 in total. 20 enzyme/inhibitor (motion: 1fss/FasII, 1bgs/bn, 1ay7/Sa, 1acb/ eglin C), 2 electron transfer, 2 antibody/antigen. Bound-bound redocking and unbound-unbound docking. Docked: ligand interface Ca < 4Å. Rank is <20 in 85% complexes with no major backbone motion. 1fss:1.7Å; 1bgs: 4.2Å; 1ay7: 6.2Å; 1acb:eglin C deformed (interface bone rmsd>1.8Å 2)	17 in total. 11 enzyme/inhibitor (8 unbound-unbound docking), 6 antibody/antigen (2 unbound-unbound docking). Rmsd: all interface Ca< 3Å. Electrostatics helped 1brs: 1.82 Å rank 1 (0.77 crystal), 1fss: 0.88 Å rank 3 (0.91 crystal) , 1bth: 3.87 Å rank 559 (2.52 crsytal)	25 in total. Near native: all Ca rmsd < 4Å. Near native were found for 20 pairs, 14 of which were in top 20 ranks. 1acb: Bound-bound docking rmsd = 0.61 Å. 1fss: unbound-unbound docking rmsd = 3.2 Å. 1brs: unbound-unbound docking rmsd = 1.89 Å.	475 complexes: low resolution docking (7 Å) 52% showed low resolution recognition.	30 complexes: 20 antibody-antigen, 8 enzyme-inhibitor, 2 dimers. 1bgs: 0.88 Å Ca rmsd. Correct conformation frequently identified for re-docking. Unbound docking: 11 out of 18 within top 20.

	in top 2000. On the web page more test cases are shown, including 1bth (unbound thrombin/ unbound BPTI, thrombin has large conformational change) best rmsd=3.67	bone rmsd>1.8Å ?) Side chain refinement helped 1fss, not 1bgs or 1ay7.				

Table 2. Two ranking methods and **Treedock**

Author Publication Web page	**Ranking** after Shape-based docking Camacho & Vajda Protein 40:525-537 (2000) http://reco3.musc.edu/ http://engpub1.bu.edu/bioinfo/MERL	**Ranking** after shape-based docking Camacho & Vajda PNAS 98:10636-10641 (2001)	**Treedock** (in C) Fahmy & Wagner JACS On web 01/25/2002
Score functions	Encounter complexes from GRAMM and DOT. Score = electr. (CHARMM19+4r+polar H) + desol. (ACE) + VDW This is the first time to combine the empirical energy functions for protein-protein docking ranking.	Encounter complexes from DOT: 7-14 Å RMSD (not clear which atoms). Princeple: vdw becomes sensitive only when two proteins get close. Multi-steps: 1. rank by ?G_S : electr. (charmm19+4r +polar H) + desol (ACE). 2. construct new pair from two highly ranked. 3. minimize the new and better pairs (fixed backbone) until vdw converges. Here it is not clear if vdw is calculated in the minimization. 4. rank by ?G_S + ? vdw. ?<= 1.	Systematic search over contact points on molecular surfaces. No need grid. Search space: drastically reduced by using anchor atoms specified by users. (a pair of anchor atom are two atoms on each molecular surface, which are supposed to be in contact upon binding.) Search steps: 1. specify anchor atoms. If both binding sites are known, only one pair anchor atoms is used. Therefore, the docking accuracy depends on the select of anchor atoms. 3. generate a number of contact points (tangent contact) on each anchor atom. 3. Try each contact point pair by moving the ligand under 5 degrees: 2 translational degrees to cover the receptor solvent accessible surface; 2 rotational degrees to cover the ligand solvent accessible surface; 1 rotational degree about the axis through the centers of the anchors. Score: only Lennard-Jones potential.

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Test cases	Correlation R (score, rmsd): 5 complexes. 0.25-0.69.	8 complexes, including 1brs and 1fss. All backbone: < 2 Å in 4 complexes (1brs =2.52Å, 1fss = 1.59Å). Interface Ca (within 10 Å) < 2 Å in 6 complexes (1brs=2.58Å, 1fss = 1.78Å).	3 complexes of immunoglobulin superfamily domains. 1 phosphatase-small inhibitor More efficient for small molecules to dock to a binding site of a protein.
timing	No data	24 h on RISC 10000 SGI	1-30 min on R10000SGI for one pair of anchor atoms. 10 h for 18×13 anchor atoms. Faster if anchor atoms are less solvent accessible.

Comments: In terms of search algorithms, the spherical polar Fourier method in HEX3.0 is faster than the commonly used FFT method. In terms of accuracy, MOLFIT and HEX3.0 are good because they use PB for electrostatics (good results for 1brs and 1fss). Treedock is efficient only when at least a pair of anchor atoms are known.

Questions: is the grid spaceing equal to the translation step size in FFT? The search space = translation steps × rotation steps. If the molecules is large, the search space will be very large. In spherical polar Fourier, the search space is represented by 5 Euler rotation angles and one inter-mol distance.