SUPPLEMENTARY FILE

ClusPro2.0 Docking method

Briefly, using the ClusPro docking program:

1. The ligand was subjected to 70,000 rotations and for each rotation, we translated the ligand in x,y,z relative to the receptor on a grid. The translation with the best score from each rotation was chosen and this yielded 1000 rotation/translation combinations.
2. We performed a greedy clustering of these 1000 ligand positions with a 9 angstrom C-alpha rmsd radius. This means we find the ligand position with the most "neighbours" in 9 angstroms, and it becomes a cluster centre, and its neighbours the members of the cluster. These are then removed from the set and we then look for a second cluster centre. This sequence was repeated multiple times.

Note that in step 1, we sampled around 10^9 positions of the ligand relative to the receptor. From this 10^9, we choose 1000 or 10^3 positions. That means these 1000 are in the top millionth of all positions of the ligand relative to the receptor. At this level, the scoring function is too rough to discriminate meaningfully between these 1000. The scoring function's purpose is to pull them out of the 10^9 positions we started from.

$$E=0.40Erep+-0.40Eatt+600Eelec+2.00EDARS$$

Piper is the FFT-based rigid docking program developed in our lab. It provides 1000 low energy results to our clustering program, ClusPro to attempt to find the native site under the assumption that it will have a wide free-energy attractor with the largest number of results. The previous version of ClusPro used a similar clustering algorithm, but obtained 2000 results from other docking programs, not Piper. The scoring function is from: Kozakov *et al*., (2011; 2017).

The protein-protein docking server ClusPro 2.0 performs three computational steps: (i) rigid body docking; (ii) RMSD based clustering of the 1000 lowest energy structures; and (iii) removal of steric clashes by energy minimization. We set up separate docking jobs with both Aβ peptides and Pgp; and these were set up and run as replicates (n = 4) to reveal consistencies or deviations in the docked molecules. For each job we examined the best ten output docking modes. Outputs for the four replicates runs were very similar for both peptides docked to Pgp. We ran the dockings of Pgp to each Aβ peptide four times with virtually identical output modes. No statistical information is given, as the scores are near identical for each docking run. ClusPro only generates binding weighted scores (one such output is given as Suppl Table 1).

ClusPro Method References:

1. Kozakova D, Hallc DR, Xiab B, Porterb KA, Padhornya D, Yuehb C, Beglovb D, and Vajdab S (2017). The ClusPro web server for protein-protein docking. *Nat Protoc* **12**:255-278.

2. Kozakov D, Beglov D, Bohnuud T, Mottarella SE, Xia B, Hall DR, and Vajda S (2013). How Good is Automated Protein Docking? *Proteins* **81**: 2159–2166.

Table S1 ***Representative scores from a ClusPro docking run***

Job Details: AMG12

View Models

Balanced | Electrostatic-favored | Hydrophobic-favored | VdW+Elec

Download Model Scores for this Coefficient

Coefficient Weights

See *Kozakov et. al.* in Papers for a description of these terms

$$E = 0.40E_{rep} + -0.40E_{att} + 600E_{elec} + 1.00E_{DARS}$$

Cluster Scores

We strongly encourage you to read the FAQ related to these scores before using them.

Cluster	Members	Representative	Weighted Score
0	185	Center	-1376.2
		Lowest Energy	-1540.6
1	88	Center	-1238.4
		Lowest Energy	-1326.4
2	71	Center	-1202.1
		Lowest Energy	-1346.7
3	49	Center	-1118.7
		Lowest Energy	-1236.8
4	42	Center	-1068.6
		Lowest Energy	-1143.0
5	39	Center	-1057.3
		Lowest Energy	-1239.5
6	36	Center	-1117.8
		Lowest Energy	-1304.5
7	27	Center	-1114.7
		Lowest Energy	-1163.5
8	26	Center	-1092.5
		Lowest Energy	-1140.6
9	26	Center	-1148.8
		Lowest Energy	-1297.7
10	25	Center	-1193.7
		Lowest Energy	-1193.7
11	22	Center	-1132.8
		Lowest Energy	-1177.9
12	21	Center	-1212.9

Source Link: https://cluspro.org/login.php