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CORRELATING ROSETTADOCK BINDING SCORE WITH PROTEIN-PROTEIN BINDING AFFINITY

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Many protein-protein docking algorithms are divided into two steps: the initial global search and subsequent steps of refinements to improve these initial predictions [1]. The global search is a full search of the orientations of the two proteins, typically keeping the larger protein (referred to as the receptor) fixed, while moving the smaller protein (the ligand). This is often a rigid-body search in six dimensions, utilizing a fast Fourier transform (FFT) for efficiency and softness for small overlaps [1]. Subsequently, one or more refinement and scoring steps of a set of preselected rigid docking solutions are added to achieve closer agreement with the native geometry and to recognize near-native docking solutions preferentially either as the best or among the best scoring complexes. The accuracy and speed of flexible refinement and rescoring of preselected docked protein structures are important for the success of the multistage docking protocol. Recently, it has been shown using Principal Component Analysis that the energy landscape of 42 interacting proteins, at least within the 10 Å IRMSD neighborhood of the native state, always includes a permissive subspace (‘tunnel’) along which the conformation of the complex can substantially change without crossing significant energy barriers and that the energy landscape is smooth funnel in a two dimensional permissive subspace [2]. This suggests that methods such as molecular dynamics (MD) or Monte Carlo (MC) simulations that start from productive encounter complexes should fairly quickly converge to native structure (or near-native one because of some inaccuracy of scoring functions) making these strategies as promising tools of the efficient refinement. The Monte Carlo approach is especially attractive as being much less computationally expensive as compared with MD. Several docking protocols including rigid-body

moves and Monte Carlo refinement have been proposed and those including RosettaDock [3] refinements at the second stage have been found to be among the most efficient [4]. In principle, a fairly accurate structure of the complex contains information about binding energy/affinity and a number of structural features have been shown to correlate with affinity [5]. However, precise evaluation of the binding free energy requires highly time-consuming exploration of all the details of the interaction at atomic precision and accurate information on binding affinities is therefore one of the most principal challenges of all current docking methods. We asked whether it is possible to predict affinity by rigid-body approaches followed by one or several RosettaDock refinements if productive encounter complex structure is known. The Version 1 structure-affinity Protein Docking Benchmark of four laboratories [6], which is a nonredundant set of 144 protein–protein complexes that have high-resolution structures available for both the complexes and their unbound components and for which dissociation constants have been measured by biophysical methods, was used to assess the performance of RosettaDock refinements. With the aim of assessment the performance of RosettaDock refinements the unbound structures were superimposed over the bound complex and the resulting superposed structure was used as the starting one for local docking. We first prepared each docking partner in isolation, optimizing their side-chain conformations prior to docking using 'docking_local_refine' option. The same procedure was applied to the structures of complexes. We tested the correlation between the ROSETTADOCK binding score (RDBS), which is the total score difference between the components together and the components pulled far apart from each other after their relaxation (repacking). The convergence of the starting structures to the structure of the bound complex was taken as a measure of RosettaDock refinement performance. To do that we calculated the number of refinement runs resulting in convergence (NRDcnv).

We judged the RosettaDock refinements as convergent if I_rms deviation from the bound state was <0.5Å, and the distinct funnel took place. If such convergence was not reached during 10 refinement runs and the deviation from the bound state remained stable during last five steps the refinement process was judged as nonconvergent. The results of simulations are shown in Table 1. The results show a very good correlation between experimental binding affinity and RDBS with Pearson's coefficients of 0.84/0.81.This suggests that two-step approach including rigid-body global search and local RosettaDock refinements as efficient tool to predict protein-protein binding affinity

Table 1. Performance of RosettaDock refinements on 15 Version 1 Structure-affinity Benchmark [6] complexes.

ref[a]	Complex PDB	Unbound component_1 PDB	Unbound component_1 PDB	Kd (M)	I_rmsd	RDBS bound and funnel (f) pres-ence	nRDcnv (b)	RDBS unbound superimposed on bound after Ncnvb refinement runs and funnel (f) presence
7	1AVX_A:B	1QQU_A	1BA7_B	4.8E-10	0.47	-120.8 (f)	3	-63.4 (f)
8	1AVZ_B:C	1AVV_A	1FYN_A	1.6E-05	0.73	-49.4 (f)	3	-40.1(f)
13	1BUH_A:B	1HCL_A	1DKS_A	7.7E-08	0.75	-92.0(mf)	6	-76.1(f)
15	1BVN_P:T	1PIG_A	1HOE_A	9.2E-12	0.87	-199.6(f)	2	-100.7(f)
26	1EFN_B:A	1AVV_A	1FYN_A	3.8E-08	0.90	-50.3(mf)	5	-39.6(f)
28	1EWY_A:C	1GJR_A	1CZP_A	3.6E-06	0.80	-87.5(mf)	5	-75.2(mf)
30	1F34_A:B	4PEP_A	1F32_A	1.0E-10	0.93	-96.8(f)	3	-79.9(f)
37	1GCQ_B:C	1GRI_B	1GCP_B	1.7E-05	0.92	-26.3(f)	7	-100.4(f)
54	1J2J_A:B	1O3Y_A	1OXZ_A	1.1.E-6	0.63	-36.5(f)	7	-74.3(bf)
58	1JTG_B:A	3GMU_B	1ZG4_A	4.0E-10	0.49	-74.5(f)	4	-69.0(f)
64	1KTZ_A:B	1TGK_A	1M9Z_A	2.0E-07	0.39	-30.6(f)	3	-60.7(bf)
66	1KXQ_H:A	1KXQ_H	1PPI_A	3.5E-09	0.72	-124.0(f)	4	-104.1(f)
100	1Z0K_A:B	2BME_A	1YZM_A	7.7E-06	0.53	-42.3(mf)	7	32.8(f)
101	1ZHI_A:B	1M4Z_A	1Z1A_A	2.0E-07	0.68	-63.8(f)	5	-61.9(f)
132	2TGP_Z:I	1TGB_A	9PTI_A	2.4E-06	0.57	-50.4(f)	5	47.4 (f)

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