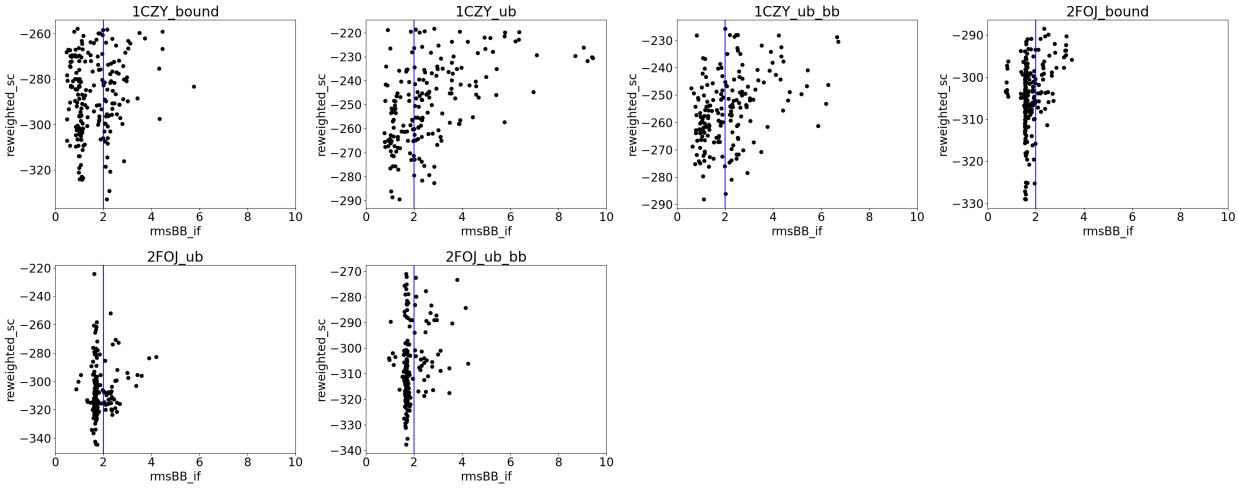
Scientific test: FlexPepDock

FAILURES

None

RESULTS



AUTHOR AND DATE

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PURPOSE OF THE TEST

This test showcases the execution of the FlexPepDock refine protocol on 2 example targets.

Results compare executions starting from different receptor conformations:

(1) the bound (native) receptor conformation,

(2) the unbound (free) receptor conformation,

and (3) the unbound receptor conformation, including receptor backbone minimization.

The same native peptide starting conformation is used for all three simulations.

BENCHMARK DATASET

The dataset includes:

1CZY_bound - the bound (native) conformation. Receptor chain C, peptide E.

1CZY_ub - this is receptor 1CA4 chain C with peptide from 1CZY:E

1CZY_ub_bb - same as above but with backbone minimization protocl.

2FOJ_bound - the bound (native) conformation. Receptor chain A, peptide B.

2FOJ_ub - this is receptor 2FOJ chain A with peptide from 2FOJ:B

2FOJ_ub_bb - same as above but with backbone minimization protocl.

PROTOCOL

Rosetta FlexPepDock is a high-resolution peptide-protein docking protocol that is able to refine a coarse starting structure of a peptide-protein complex, to a near-native model of the interaction. The full degrees of freedom of the peptide are optimized (rigid body orientation, peptide backbone and side chains). Optionally, the receptor backbone can be minimized during optimization.

For more information, read:

1) Raveh, B., London, N. & Schueler-Furman, O.: Sub-angstrom modeling of complexes between flexible peptides and globular proteins. Proteins (2010). https://onlinelibrary.wiley.com/doi/full/10.1002/prot.22716, and

2) Alam, N. & Schueler-Furman, O. Modeling peptide-protein structure and binding using monte carlo sampling approaches: Rosetta flexpepdock and flexpepbind. in Methods in Molecular Biology (2017).

Running this benchmark takes approximately 70 CPU hours.

PERFORMANCE METRICS

A passing test means that at least 5 out of the top10-scoring points are below the interface RMSD cutoff of 2A, the same as in the paper (as per Ora's request). The interface RMSD is represented by the rmsBB_if tag in the score file.

KEY RESULTS

The default implementation of FlexPepDock can reliably refine peptide conformations to near-native resolution for starting structures that are up to 4-5 Angstrom away from the native conformation. An extended range can be obtained by including an ab initio search of the peptide backbone conformation (see Raveh et al. PLoSOne 2011), or by coupling the FlexPepDock refinement step to a low-resolution fast rigid body search using other approaches (e.g. FFT, as implemented in PIPER-FlexPepDock, Alam PlosCB 2017).

DEFINITIONS AND COMMENTS

We use the reweighted_score to rank different models: this score term is the sum of total score, interface score and peptide score, providing more weight to the energy terms contributed by the peptide, compared to the energy of the full complex. Alternatively, interface score (I_Sc) may be used. Both terms will reduce the influence of possible conformational changes far away from the binding site that introduce noise.

LIMITATIONS

The protocol needs an approximate starting conformation of the peptide. This starting structure may be obtained from structures of homologous complexes, or from low-resolution docking protocols.