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Supplementary Information for

Matching protein surface structural patches for high-resolution blind peptide docking

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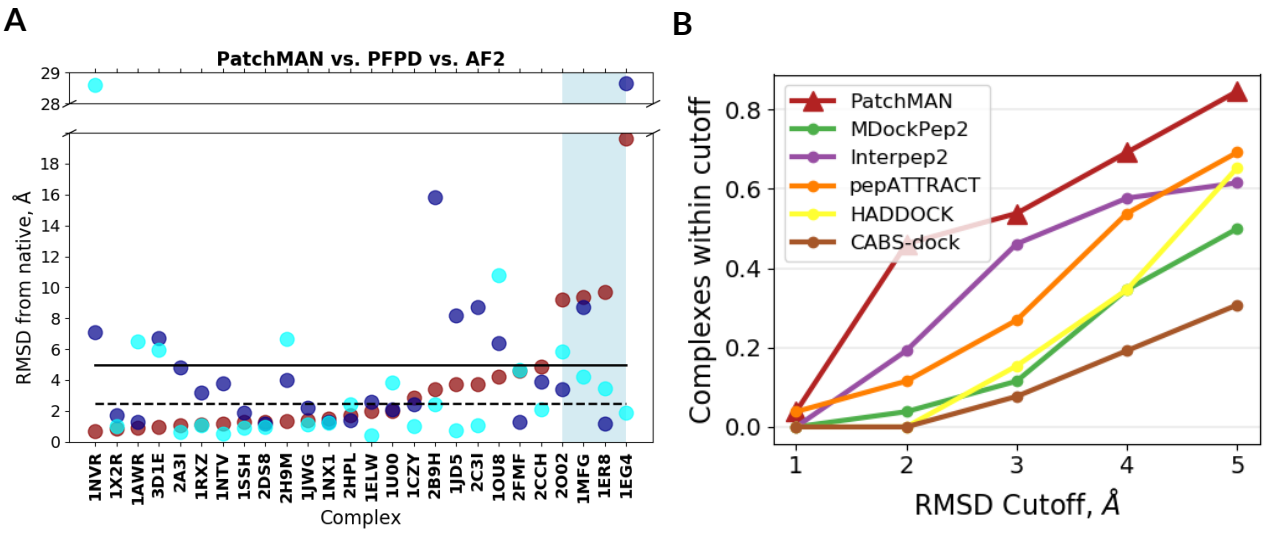

Fig. S1, **PatchMAN performance compared to other approaches**

A. Detailed comparison of PatchMAN (red) PFPD (blue) and AF2 (cyan) performance on the PFPD dataset. Shaded region of the plot indicates complexes for which PatchMAN failed to produce models within 5Å RMSD. **B.** PatchMAN performance on the PFPD data set shows superior performance compared to other global peptide docking approaches.For the CABS-dock and HADDOCK protocols, results are reported for a subset of 23/21 structures out of the 26 in this benchmark, respectively. Note that this plot reports ligand RMSD, L-RMSD, while the rest of the paper reports interface peptide residue backbone RMSD, rmsBB_if.

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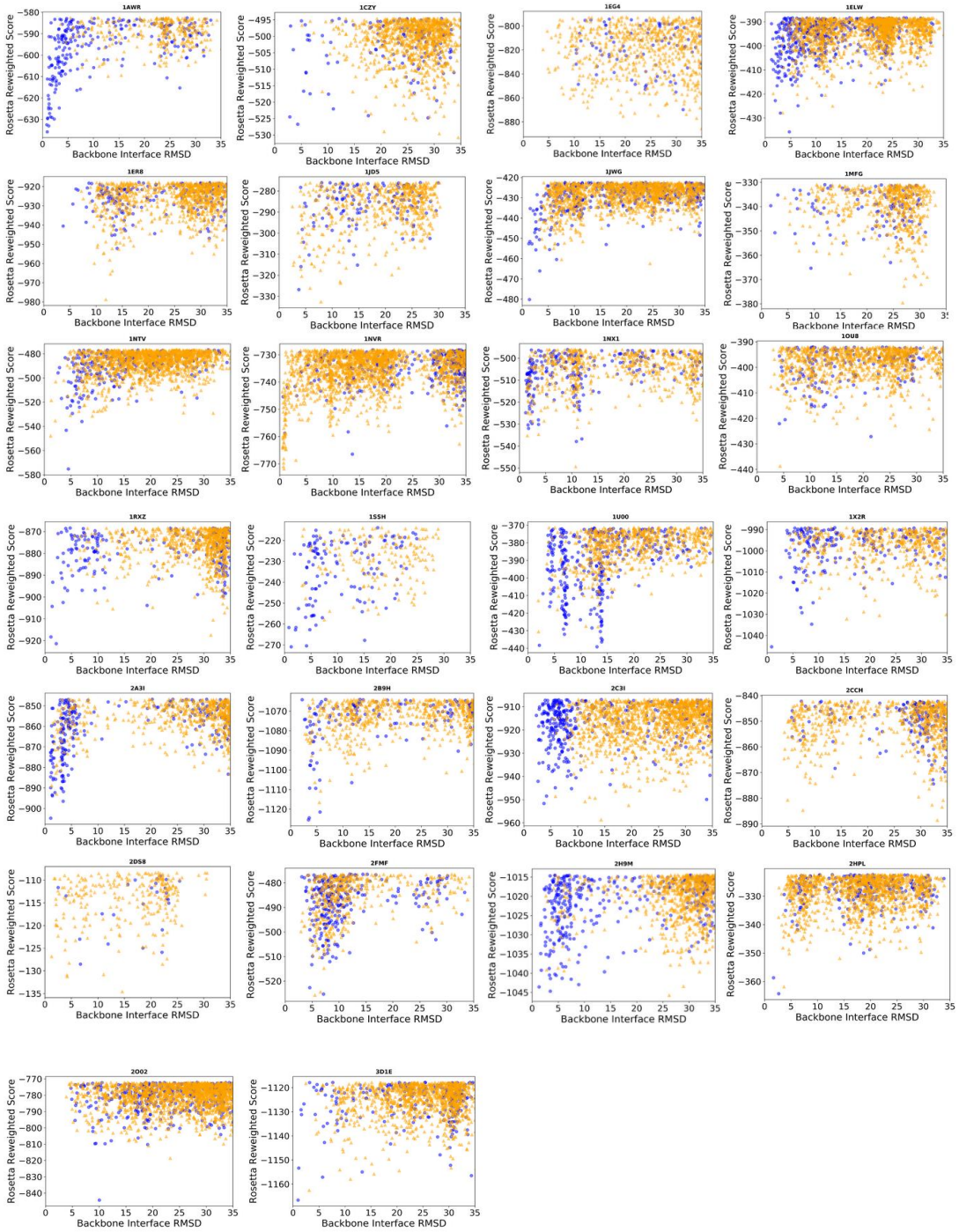

Fig. S2. Energy landscapes

Rosetta reweighted score *vs.* RMSD plots are shown for each of the complexes in the PFPD benchmark. Models generated based on templates originating from monomers are indicated in orange triangles, while those stemming from interfaces are indicated by blue circles.

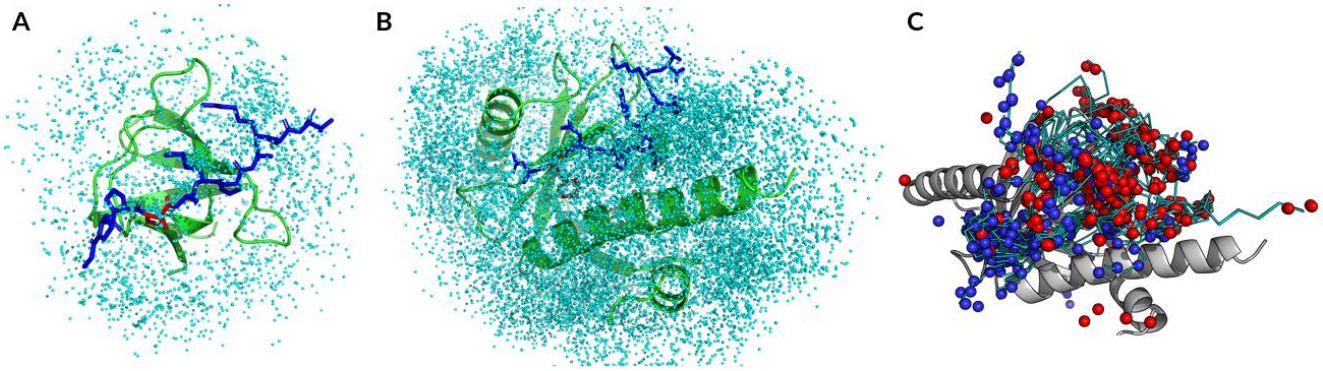

Fig. S3. Local motif matches map the whole receptor surface

A-B. Two examples showing the coverage of the receptor surface with fragments, prior to filtering: (A) 1SSH (1) and (B) 1NTV (2). The receptor and peptide are shown in green cartoon and blue stick representation, respectively. The Cα atoms of one specified peptide residue (highlighted in red in the crystal structure) are shown in cyan spheres. **C.** Sampling at the binding site of 1NTV: Here we show the fragments sampled for a specific surface patch at the binding site. Fragments are represented by ribbons, with their N and C-termini highlighted with blue and red spheres, respectively.

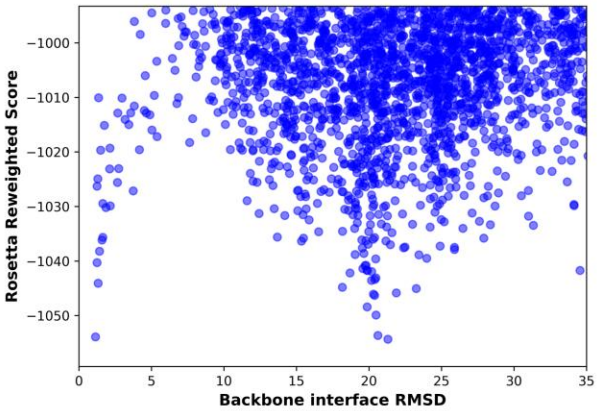

Fig. S4. A strict template match cutoff still allows to accurately model interactions with receptor conformational changes

Setting the matching cutoff to 0.5 Å still generates accurate models of the Moesin FERM domain-peptide interaction, despite considerable movement of the receptor upon binding, as shown by the near-native energy funnel in the energy landscape (compare to **Fig. 4B**).

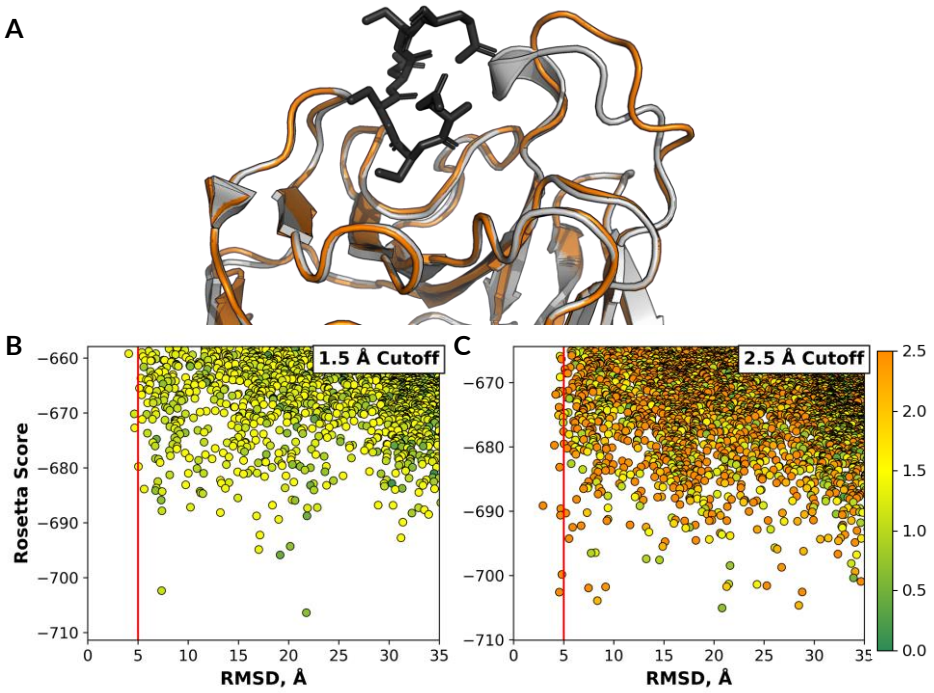

Fig. S5. Increasing patch matching cutoff to 2.5Å can improve the performance on a challenging target.

A. Comparison of the RanBPM protein bound (orange, PDB ID 5JIU) and unbound (gray, PDB ID: 5JI9) conformations show pronounced conformational change at the loop near the binding site of the peptide (black). **B.-C.** Energy landscapes for simulations with matching cutoffs of 1.5 (B) and 2.5Å (C) respectively. The red line indicates the 5Å RMSD cutoff. The structures are colored according to a green-yellow-orange scale reflecting the source-target patch RMSD (in Å).

Table S1. PatchMAN performance for docking only the binding motif (for the PFPD subset of with known motif in Table 1). For all tables, the best model is the top-RMSD model among 10 top-scoring clusters.

Complex PDB ID	Unbound receptor	Best model, motif only [Å]	Best model full peptide [Å]	Best sampled RMSD [Å]	Peptide length
1CZY	1CA4	11.1	2.8	1.5	6
1EG4	1EG3	7.9	19.6	0.9	4
1ELW	1A17	1.5	2.0	0.6	4
1JD5	1JD4	1.1	3.7	0.5	4
1JWG	1JWF	1.4	1.4	1.4	7
1MFG	2H3L	1.1	9.4	1.1	6
1NTV	1P3R	1.0	1.2	1.0	8
1RXZ	1RWZ	0.8	1.1	0.8	6
1SSH	1OOT	7.6	1.3	1.0	6
1X2R	1X2J	1.2	0.9	0.6	6
2A3I	2AA2	0.8	1.1	0.5	7
2CCH	1H1R	3.7	4.9	1.5	5

Table S2. Summary of performance for the LNR subset

Complex PDB ID	Unbound receptor	Best model [Å]	Best sampled RMSD [Å]	Peptide length
1P7W	1EGQ	4.2	1.9	7
1D4T	1D1Z	8.3	5.3	11
1KY7	1QTS	15.0	2.9	9
1T3L	1T3S	1.4	0.8	17
1T5Z	1E3G	1.4	1.2	11
1TJ9	2QU9	4.9	1.5	4
1XQY	1XQX	2.9	2.1	4
2B1N	2B1M	1.4	0.9	5
2FIB	3FIB	2.1	1.7	4
2ORZ	2ORX	4.1	1.7	3
2V8X	5GW6	0.9	0.7	14
2WV5	2J92	6.3	1.2	9
2Z9I	1Y8T	0.8	0.5	4
3AYU	1QIB	2.8	2.5	10
3BRH	2QCJ	8.8	1.8	7
3C3O	2OEW	4.7	1.2	13
3DNJ	3G3P	0.8	0.6	3
3N2D	3RL9	9.6	3.4	6
3N5U	6G0J	2.9	2.0	7
3NIH	3NIL	1.0	0.4	3
3R42	3R3Q	13.9	3.2	8
3R7G	2YLF	10.2	4.7	19
3UFM	2BOO	4.6	1.9	4
4BTA	4BT8	3.6	2.1	9
4FVD	4FVB	1.9	1.3	4
4MVK	6GQZ	2.4	2.1	6
4TJX	4TJV	16.7	4.8	3
4Z2O	4Z27	1.7	1.1	11
5GR9	5JFK	6.3	5.2	12
5JIU	5JI9	7.4	3.6	6
5N85	4IPG	7.7	3.9	12
5ONP	5DLH	21.9	1.6	5
5SGA	2SGA	0.3	0.2	4
5YC2	5YBX	1.1	0.7	14
6CCT	6CCR	4.8	1.8	3
6FC6	6FC5	5.3	1.5	3
6HGT	2GP5	5.3	2.7	5

6N3E	6N3F	1.3	1.0	7
6J0X	6J0V	15.2	5.3	16

Table S3. Increasing the RMSD cutoff for patch alignments does not significantly improve results for complexes that include conformational change upon binding

Complex PDB ID	Best model [Å]	Rerun with matching cutoff 2.5 Å [Å]
2WV5	6.3	16.4
3R7G	10.2	7.2
5JIU	7.4	4.6
5N85	7.7	6.7

SI References

1. P. Kursula, I. Kursula, F. Lehmann, Y. H. Song, M. Wilmanns, Crystal structure of the SH3 domain from a S. cerevisiae hypothetical 40.4 kDa protein in complex with a peptide. *doi: 10.2210/pdb1ssh/pdb* (2005).
2. P. C. Stolt, *et al.,* Origins of peptide selectivity and phosphoinositide binding revealed by structures of disabled-1 PTB domain complexes. *Structure* 11, 569–579 (2003).