Table S1. Template information and RMSDs of the homology-modeled monomers obtained from sequence using Robetta. Related to STAR Methods.

PDB ID	Symmetry	Template _Chain	Template symmetry	Identity (%)	Coverage (%)	Best Model RMSD (Å)
1dv7	C2	1dqw_A	C2	25	78	2.09
1muy	C2	2abk_A	C1	31	56	2.78
2nlv	C2	2nwv_A	C2	37	100	1.3
3urr	C2	3lf6_B	C2	29	71	0.43
4zo2	C2	4o98_A	C2	28	98	1.31
1sg4	C3	1ef9_A	C1	24	69	0.18
2vji	C3	2uve_A	C1	24	32	16.92
4co0	C3	3ncq_A	C3	46	100	0.1
4d7y	C3	4dou_A	C1	35	96	0.74
5i6n	C3	1oe1_A	C3	70	99	0.34
1ojr	C4	1dzu_P	C4	18	60	4.42
1p5b	C4	1kbj_A	C4	32	93	0.14
2o6n	C4	1dd5_A	C1	64	57	0.16
3v9o	C4	2cg9_C	A2B2	-	-	0.88
4xti	C4	1nf7_B	C4	59	98	0.94
1xb9	C5	1dyo_A	C1	-	-	0.2
4avs	C5	3pvn_A	C5	51	99	0.36
4mby	C5	1sie_A	I	58	98	0.51
4u62	C5	3iys_A	I	56	99	0.12
5a12	C5	4m05_B	C5	42	99	0.64
1nlf	C6	1mo4_A	C1	21	21	0.19
2pmu	C6	2hqr_A	C2	21	79	1.05
2xf7	C6	2b88_A	C1	-	-	1.54
4ox6	C6	3pac_A	C3	37	71	0.11
4w64	C6	1y12_A	C6	88	31	0.73
1h64	C7	1ljo_A	C6	36	86	0.09
4owk	C7	1abr_B	A1B1	29	70	0.85
3b8o	C8	1jad_A	C2	-	-	9.75
4f87	C8	2o1w_A	C1	-	-	3.19

3p9a	C9	2pbx_A	C2	80	3	12.67
3zqo	C9	3kz3_A	C2	40	55	7.35
1nxq	D2	1gco_A	D2	34	98	1.97
1orr	D2	1gy8_C	C2	23	99	0.71
2bv4	D2	2chh_A	D2	62	100	0.39
2vqr	D2	3ed4_D	C2	25	73	1.99
4oqc	D2	2yzc_A	D2	37	97	0.15
1gxu	D3	2acy_A	C1	40	47	6.05
2cwl	D3	1oq4_A	C2	22	47	3.52
2j5g	D3	1szo_A	C3	48	96	0.16
3qns	D3	2y4d_A	C2	22	64	0.2
3v4f	D3	1gua_A	A1B1	58	99	0.38
1umg	D4	1jkj_B	A2B2	34	12	21.6
2r8e	D4	2o2x_A	C1	31	15	0.35

Legend

- : BLAST did not identify sufficient homology

I : Icosahedral

AnBm: Heteromer stoichiometry

Table S2. Estimated reasons for failure of targets. Related to Figure 4 and Table 3.

PDB ID	Symmetry	Reason for failure
1muy	C2	Input model
3urr	C2	Scoring (C & A)
2vji	C3	Input model
2pmu	C6	Scoring (C & A)
2xf7	C6	Scoring (C & A)
4owk	C7	Scoring (C & A)
3b8o	C8	Input model
4f87	C8	Input model
3p9a	C9	Input model
3zqo	C9	Input model
1orr	D2	Scoring (C & A)
2vqr	D2	Sampling
1gxu	D3	Input model
2cwl	D3	Input model
3qns	D3	Sampling
3v4f	D3	Sampling
1umg	D4	Input model

Legend

Input model: In an input model failure, the $RMSD_{C\alpha}$ from native of the best input monomer is greater than 2.5 Å.

Scoring (C): In a coarse-grained scoring failure, re-docking the native structure fails to produce models with better (lower) motif dock scores than incorrect non-native docking models.

Scoring (A): In an all-atom scoring failure, native structure refinement fails to produce models with better (lower) interface scores than incorrect non-native docking models.

Sampling: In a sampling failure, the input models are adequately close and the native structures are correctly identified during scoring, but no non-native docked model is close enough to the native structure to fall into the binding funnel.

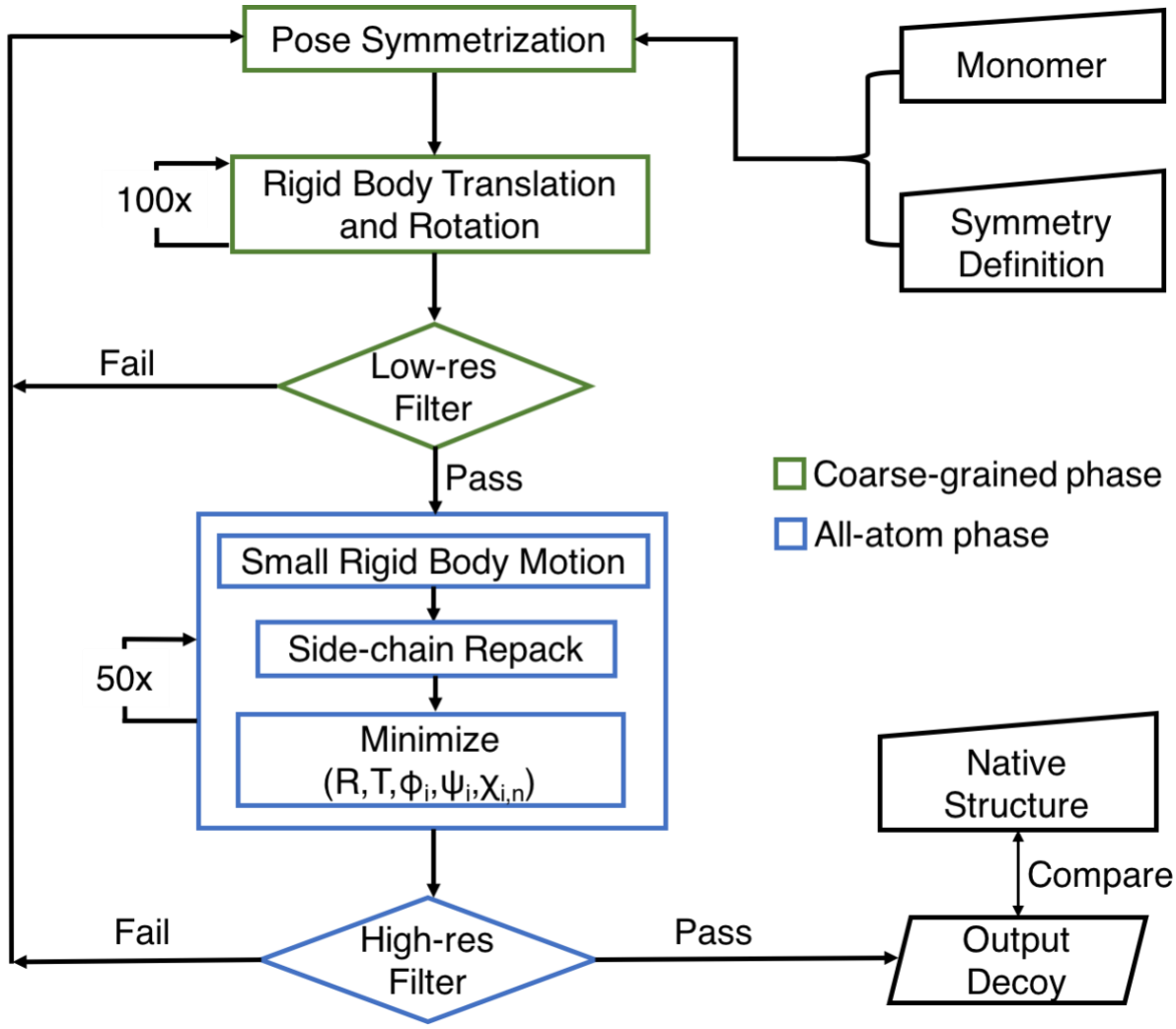

Figure S1. Flowchart describing major steps in Rosetta SymDock protocol. In the all-atom phase the structure is minimized along rotational rigid body coordinates (R), translational rigid body coordinates (T), and the dihedrals of the interface residues ($\{\varphi_i,\psi_i,\chi_{i,n}\}$, where $i \in$ interface). See Methods for filter descriptions. Related to Table 2 and Figure 4.

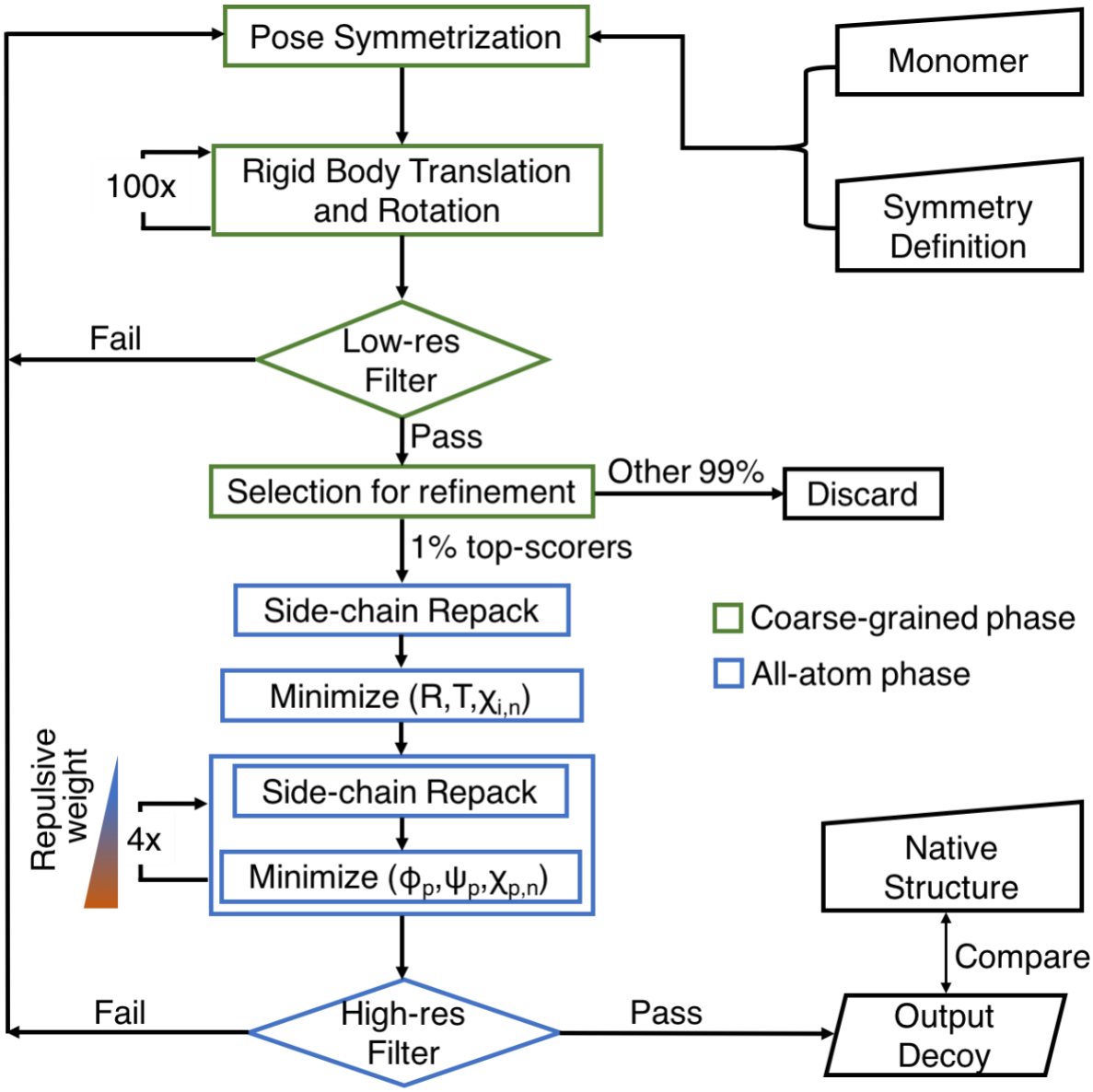

Figure S2. Flowchart describing major steps in Rosetta SymDock 2 protocol. In the all-atom phase the structure is initially minimized along rotational rigid body coordinates (R), translational rigid body coordinates (T), and the dihedrals of the interface residue side chains ($\chi_{i,n}$, where $i \in$ interface). This is followed by four cycles of side-chain repacking and minimization along the dihedrals of all residues ($\{\varphi_p,\psi_p,\chi_{p,n}\}$, where $p \in$ protein). Each cycle is carried out at a different weight of the van der Waals repulsive term starting from 2% of the original weight and ramping up to 100%. See Methods for filter descriptions. Related to Table 2 and Figure 4.

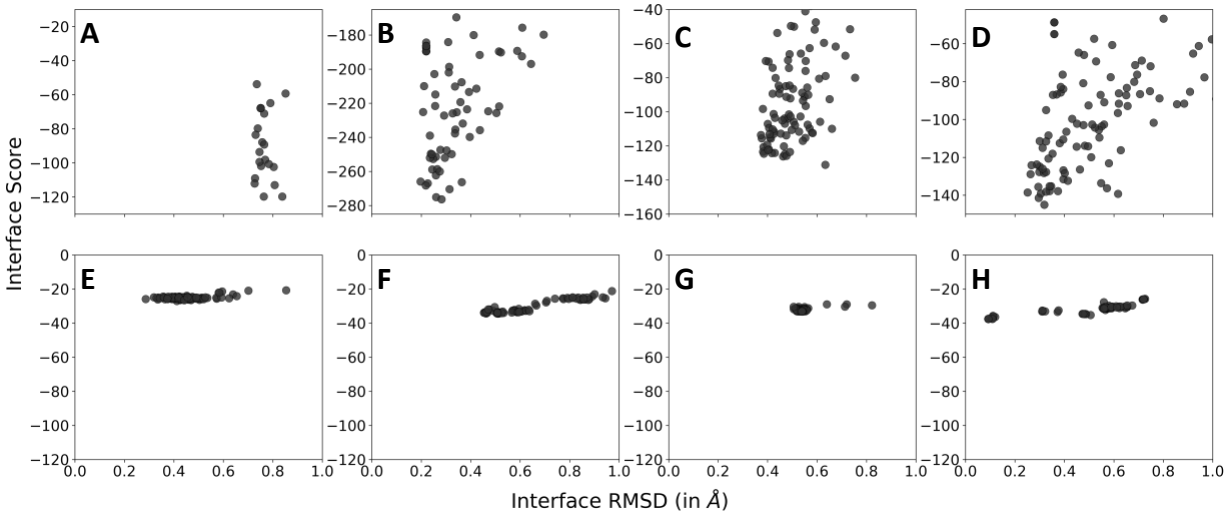

Figure S3. Comparison of interface score versus $RMSD_{C\alpha}$ plots produced by native refinement of homomers and hetero-dimers. The four example homomers are: (A) 3,2-trans-enoyl-CoA isomerase (1SG4, C3), (B) snRNP Sm-like protein (1H64, C7), (C) gp23.1 chaperone (2XF7, C6), and (D) Cytolysin (4OWK, C7). The four example hetero-dimers are: (E) APR-APRin complex (1JIW), (F) *L. casei* HprK/P - *B. subtilis* HPr (1KKL), (G) Glutamyl-tRNA synthetase (2HRK), and (H) IL-13 and C836 FAB (3L5W). In all plots, the y-axis spans 120 energy units. In general, homomer binding funnels are deeper, steeper and narrower. Related to Figure 2.

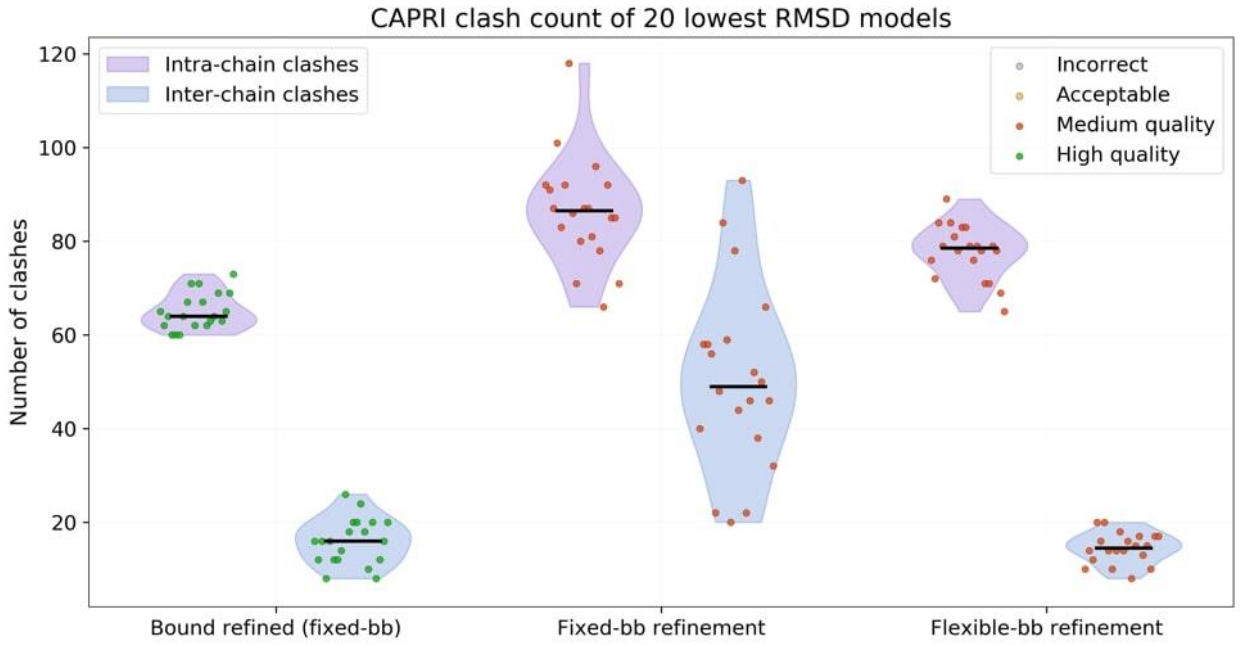

Figure S4. Count of intra-chain and inter-chain clashes for interface residues of *Xenopus* Nucleophosmin as per CAPRI definition. The 20 lowest RMSD models are chosen. Flexible-backbone refinement of complex starting from homology-modeled monomer reduces inter-chain clashes to be close to that observed after fixed-backbone refinement of the native structure. Related to Figure 3.