SUPPLEMENTARY TABLES AND FIGURES

Table S1: **HEX docking settings.**

Setting	**Value**
GRID_SIZE	0.6
RECEPTOR_RANGE_ANGLE	180
LIGAND_RANGE_ANGLE	180
TWIST_RANGE_ANGLE	360
DOCKING_R12_RANGE	40
DOCKING_R12_STEP	0.75
DOCKING_R12_SUBSTEPS	2
DOCKING_MAIN_SCAN	18
DOCKING_MAIN_SEARCH	25

Table S2: **List of benchmark complexes subjected to CC-D using ZDOCK.**

1AVX 1AY7 1BVN 1CGI 1CLV 1D6R 1DFJ 1E6E 1EAW 1EWY 1EZU 1F34 1FLE 1GL1 1GXD 1HIA 1JTG 1MAH 1N8O 1OC0 1OPH BOYV 1OYV 1PPE 1R0R 1TMQ 1UDI 1YVB 2ABZ 2B42 2J0T 2MTA 2O8V 2OUL

Table S3: **Lists of the 15 most sociable proteins identified by the docking programs.**

HEX	ZDOCK	MAXDo
1PPE (l)	**1PPE (l)**	**1PPE (l)**
1MAH (l)	**1CGI (l)**	**1BVN (l)**
1UDI (l)	**1MAH (l)**	**1CGI (l)**
1BVN (l)	**1BVN (l)**	1TMQ (l)
1CGI (l)	1D6R (l)	**1MAH (l)**
1EAW (l)	**1EAW (l)**	**1F34 (l)**
1F34 (l)	**2MTA (l)**	**1UDI (l)**
1DFJ (r)	**1AY7 (r)**	**2MTA (l)**
1TMQ (l)	**1EWY (l)**	**1EAW (l)**
1HIA (l)	**1DFJ (r)**	**1HIA (l)**
1AY7 (r)	**1UDI (l)**	**1E6E (l)**
1E6E (l)	**1E6E (l)**	**1DFJ (r)**
1PPE (r)	**1F34 (l)**	**1AY7 (r)**
2MTA (l)	1AY7 (l)	**1EWY (l)**
1EWY (l)	**1HIA (l)**	1AY7 (l)
1D6R (l)	1EZU (l)	1AVX (l)

Only the subset of 34 proteins on which all three programs were applied are considered. Proteins highlighted in bold are common to the three lists.

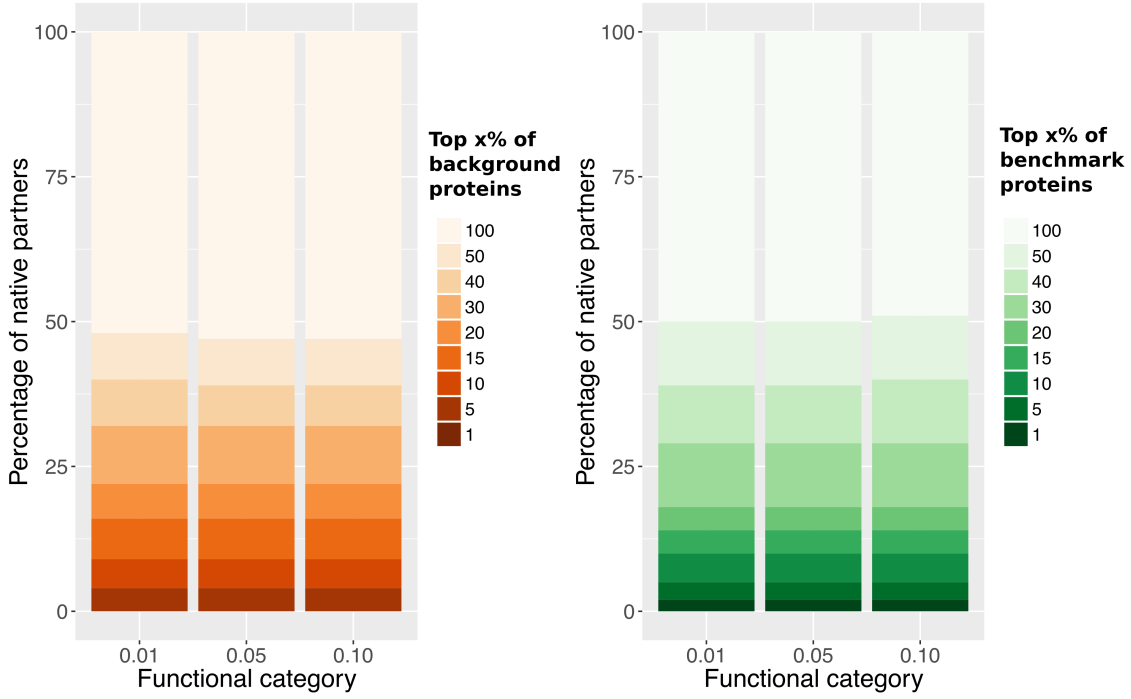

Figure S1: **Influence of the p-value threshold on the discrimination of cognate partners and non-interactors.** In y-axis are reported the percentages of cognate partners whose docking score distribution is indistinguishable from the top x% of non-interactors distributions, where x varies between 1 and 100 (color scales). In total, we seek to identify 372 ($y = 100\%$) native partners from PPDBv4. Each protein from PPDBv4 was docked against its native partner and **(a)** a background of 918 ($x = 100\%$) non-interactors, or **(b)** 371 ($x = 100\%$) non-interactors from PPDBv4. Different p-value thresholds were used for the Wilcoxon rank-sum test: 0.01, 0.05 and 0.10 (in x-axis).

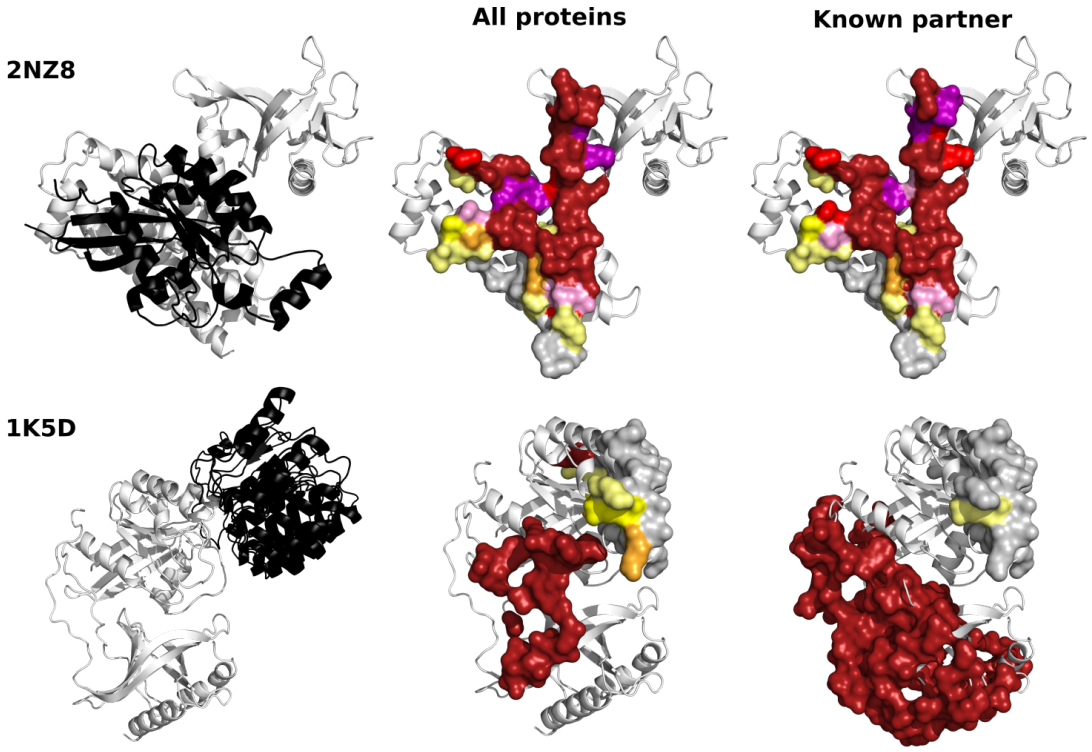

Figure S2: **Mapping of NIP profiles on the proteins three-dimensional structures.** Rac GTPase (2NZ8:R) and Ran GTPase (1K5D:R) are displayed as white cartoons. On the left, their partners DH/PH domain of TRIO and Ran GAP are displayed as black cartoons. In the middle and on the right, the experimental binding site is shown as an opaque surface colored according to NIP values obtained either from all docking calculations involving the protein (in the middle) or from docking the protein with its known partner only (on the right). The color code is the same as that used in Figure S6. For Ran GTPase (1K5D:R), the residues having NIP values above 0.65 (in firebrick) are also displayed as opaque surface.

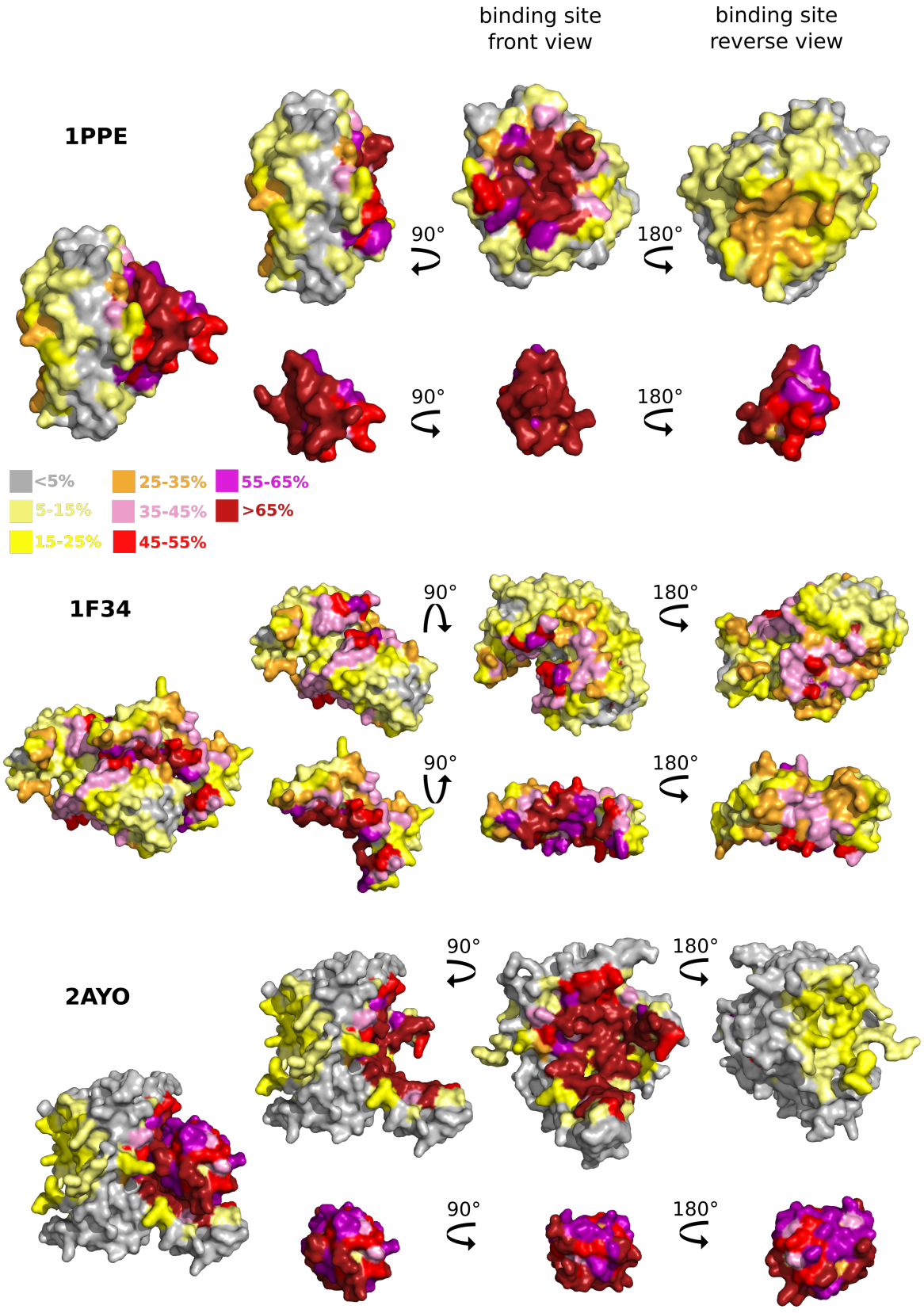

Figure S3: **Interaction propensity (IP^{native}) indexes computed from docking known partners.** The colors indicate how often each residue is found at the interface in the docking poses generated and selected by HEX for Bovine trypsin/CMTI-1 squash inhibitor (1PPE), Porcine pepsin/Ascaris inhibitor 3 (1F34) and Ubiquitin carboxyl-terminal hydrolase 14/Ubiquitin (2AYO).

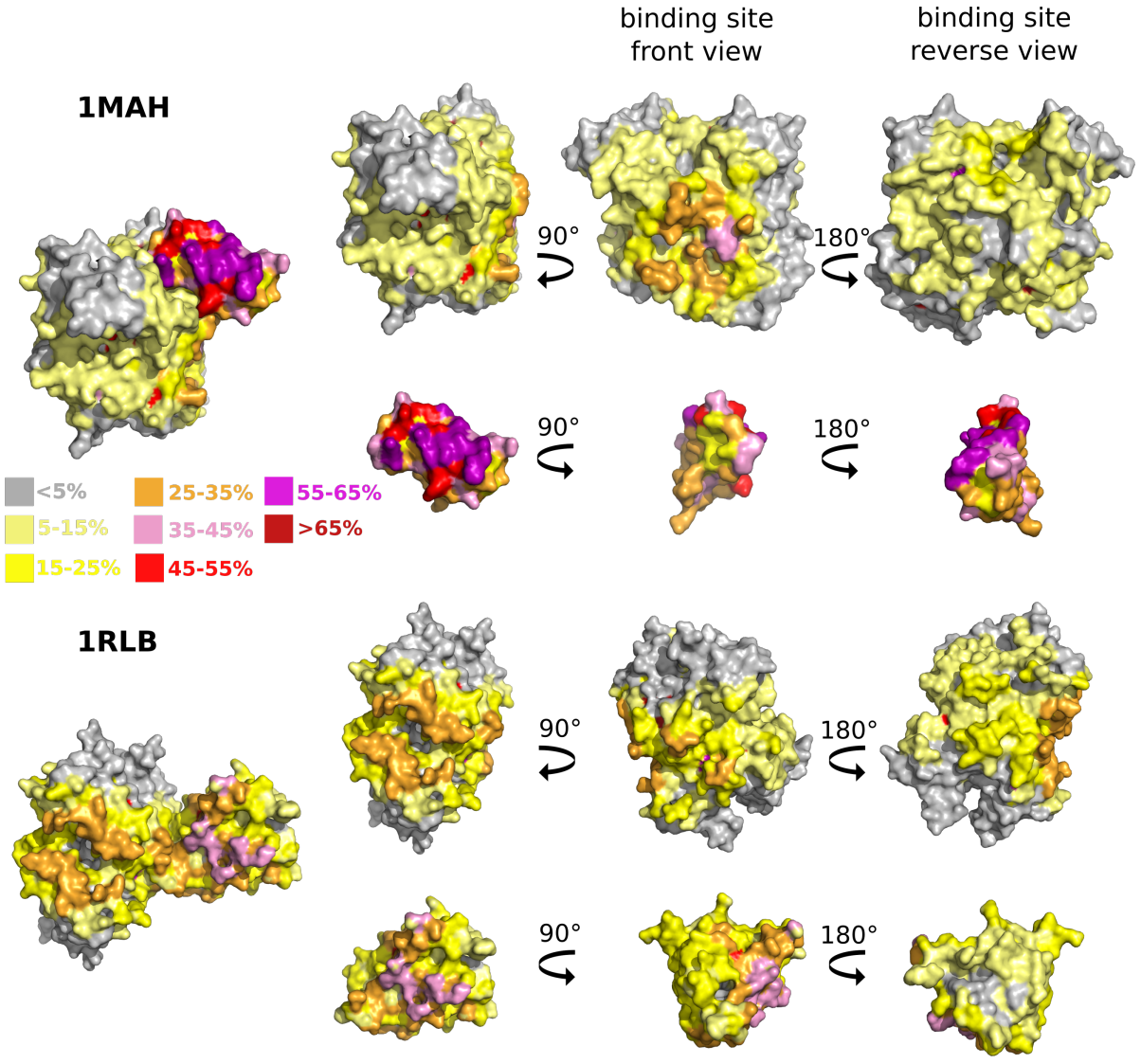

Figure S4: **Interaction propensity (IP^{native}) indexes computed from docking known partners.** The colors indicate how often each residue is found at the interface in the docking poses generated and selected by HEX for Acetylcholinesterase/fasciculin2 (1MAH) and transthyretin/retinol binding protein (1RLB). This figure is directly comparable to Figure 2 in [14].

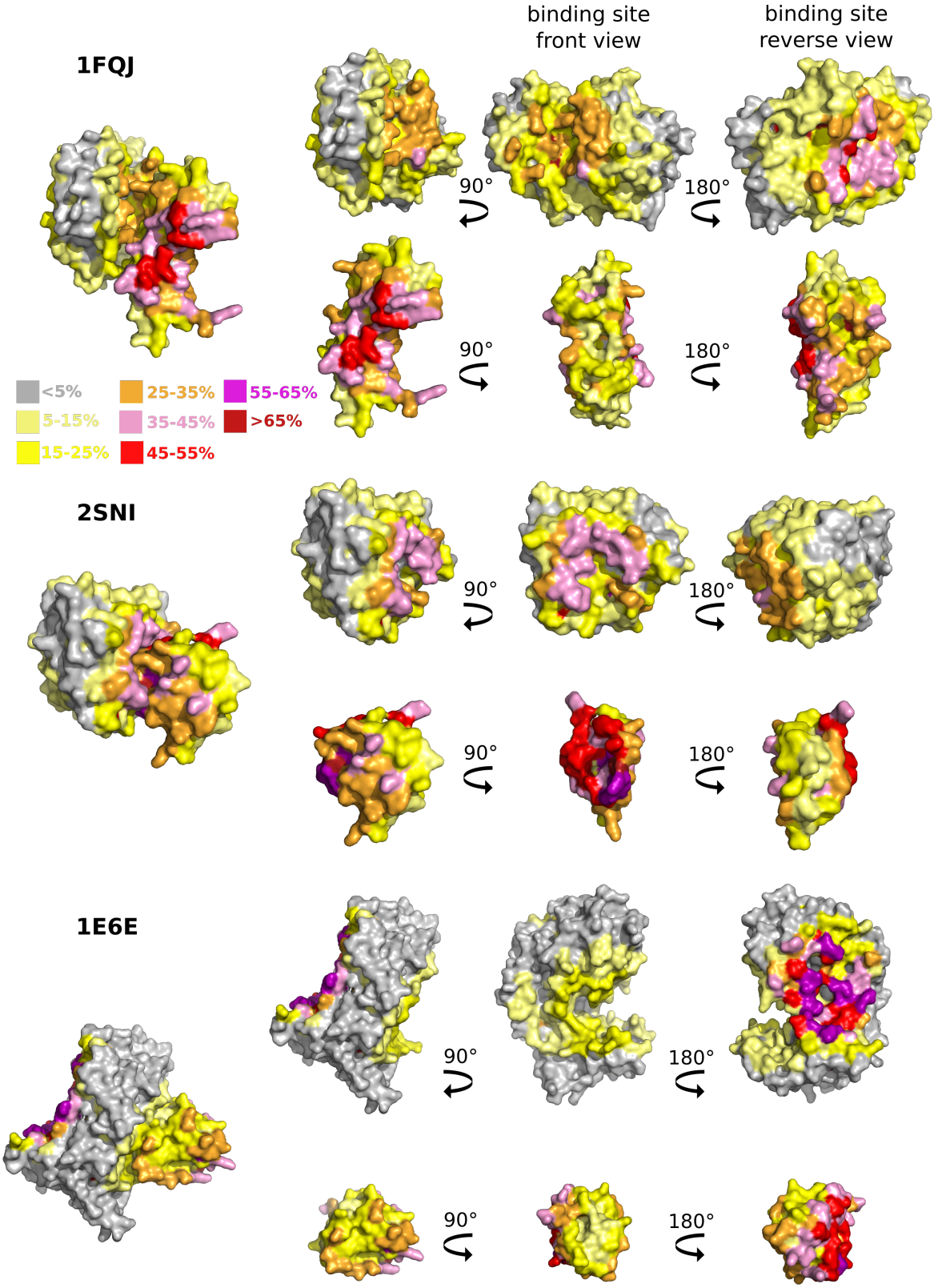

Figure S5: **Interaction propensity (IP^{native}) indexes computed from docking known partners.** The colors indicate how often each residue is found at the interface in the docking poses generated and selected by HEX for Gt-Alpha/RGS9 (1FQJ), Subtilisin/Chymotrypsin inhibitor 2 (2SNI) and Adrenoxin reductase/Adrenoxin (1E6E). This figure is directly comparable to Supplementary Figure S13 in [14].

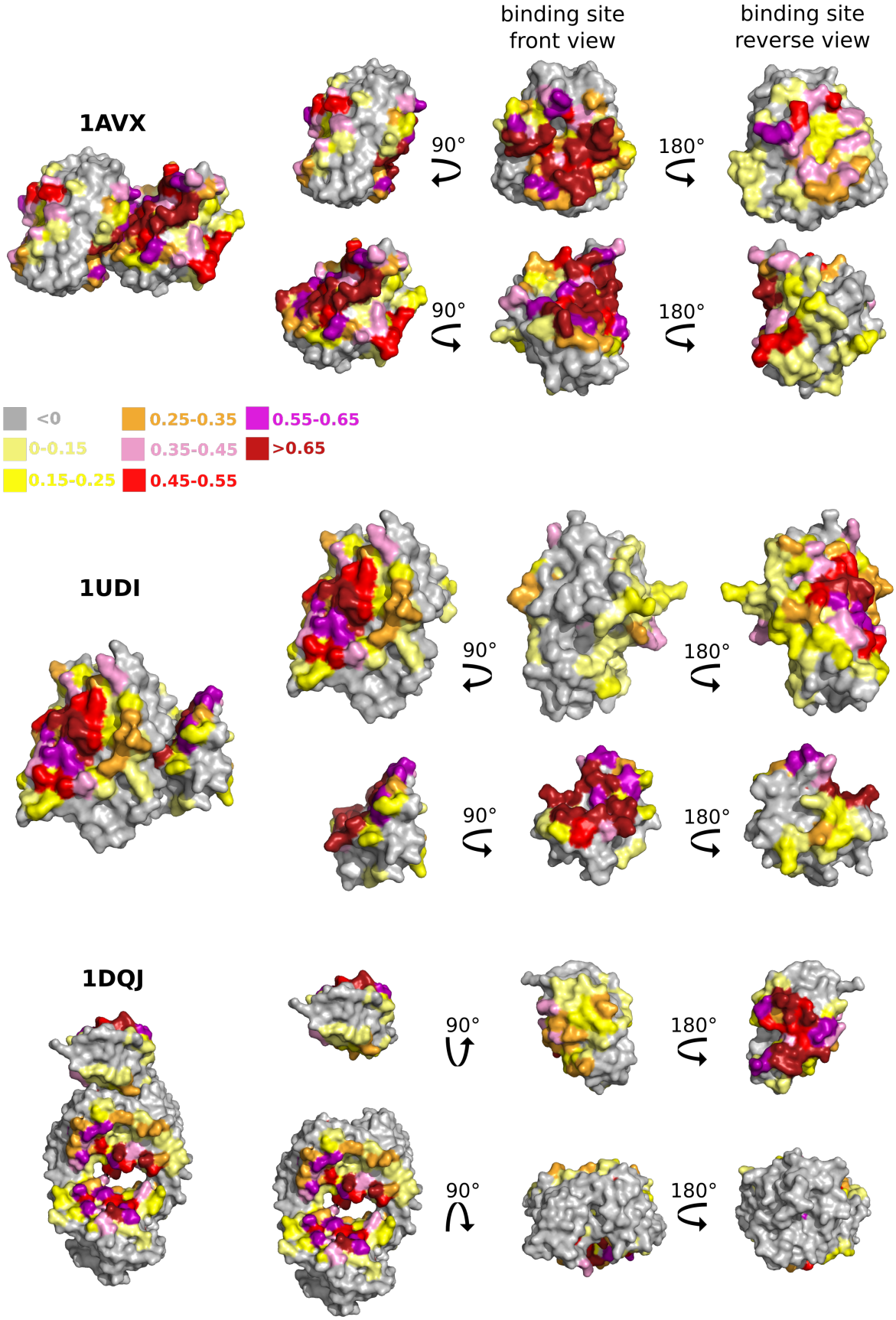

Figure S6: **Normalized interaction propensity (NIP) indexes computed from docking known partners and non-interactors.** The colors indicate the values of the NIP indexes for Porcine trypsin/Soybean trypsin inhibitor (1AVX, $Sens$ = 76% and 60%, PPV =29% and 15%), Uracyl-DNA glycosylase/Glycosylase inhibitor (1UDI, $Sens$ =44% and 67%, PPV =14% and 56%) and Fab Hyhel63/HEW lysozyme (1DQJ, $Sens$ =4% and 62%, PPV =1% and 26%).

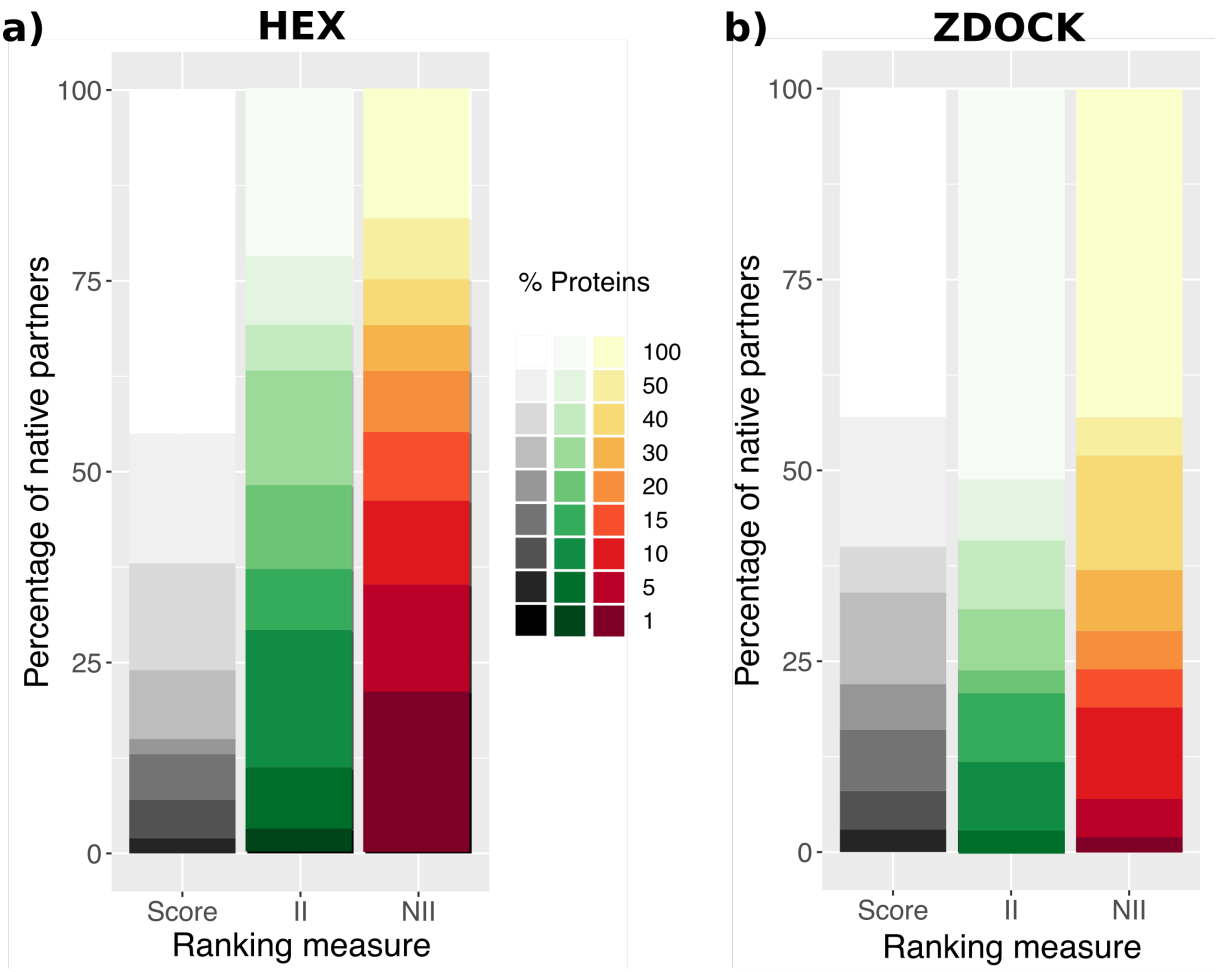

Figure S7: **Comparison of HEX and ZDOCK for partner identification.** In y-axis are reported the proportions of known partners identified within the top x% of proteins, where x varies between 1 and 100 (color scale). Complete cross-docking of a subset of PPDBv4 comprising 33 enzyme-inhibitor complexes was realized using HEX (**a**) and ZDOCK (**b**). The potential partners were ranked using docking score distributions (score), interaction indexes (II) and normalized interaction indexes (NII).

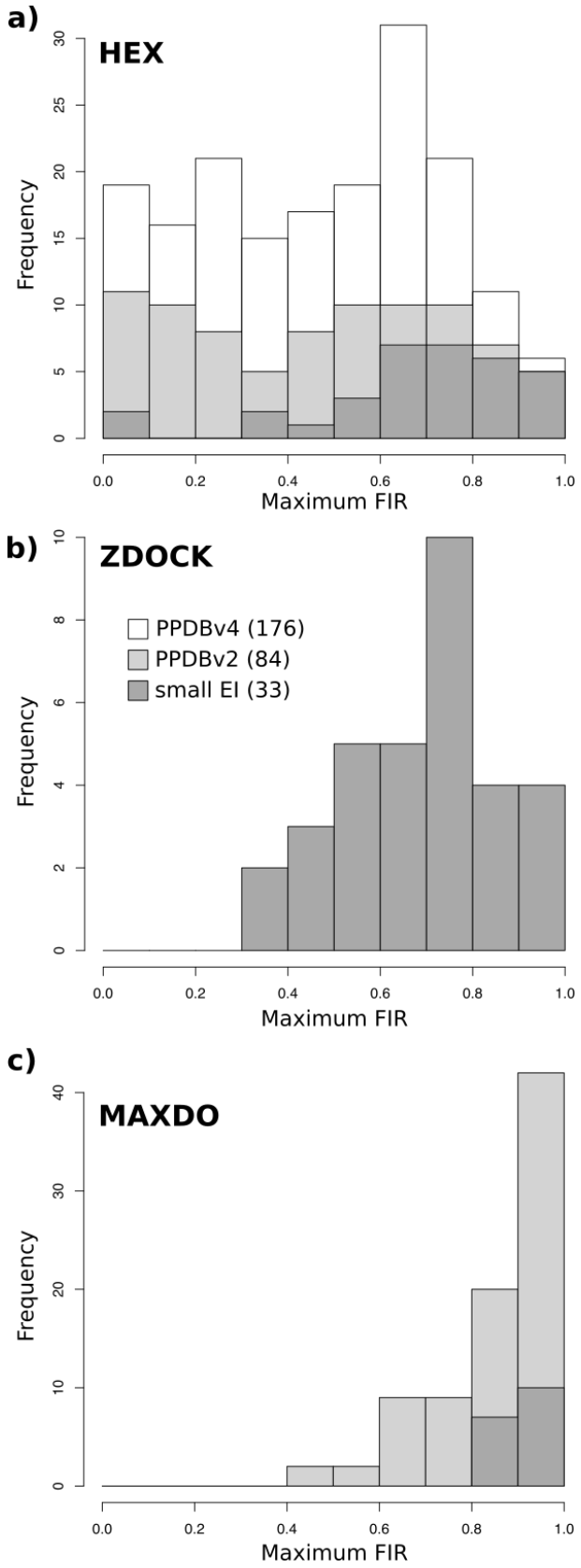

Figure S8: **Quality of the docking conformational ensembles.** Distributions of FIR values corresponding to the docking models that resemble the most the benchmark complexes. The docking ensembles were generated using **(a)** HEX, **(b)** ZDOCK, **(c)** MAXDo. Three inclusive benchmark sets are considered: PPDBv4 (176 complexes), PPDBv2 (84 complexes), small EI (33 enzyme-inhibitor complexes from PPDBv4).

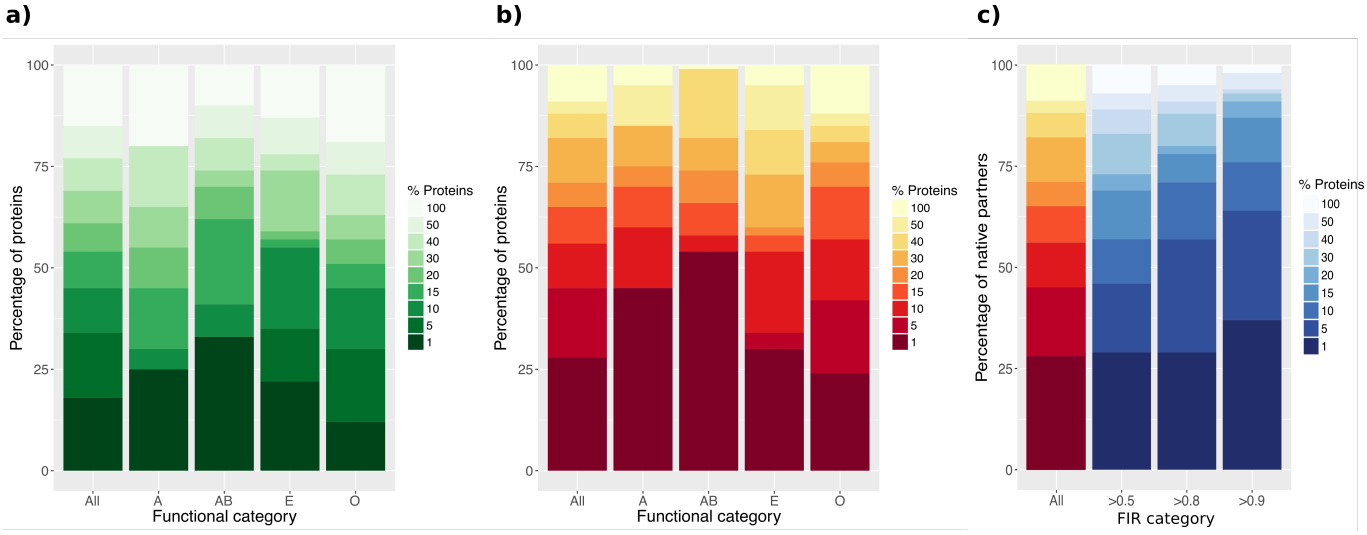

Figure S9: **Discrimination of cognate partners and non-interactors from MAXDo calculations.** In y-axis are reported the proportions of known partners identified within the top x% of proteins, where x varies between 1 and 100 (color scale). Complete cross-docking of PPDBv2 (168 proteins) was performed and the potential partners were ranked using: **(a)** interaction indexes $II^{Ene} = FIR \times Ene$, **(b)** normalized interaction indexes NII^{Ene}. Different subsets are considered based on: **(a-b)** functional categories, **(c)** FIR values.

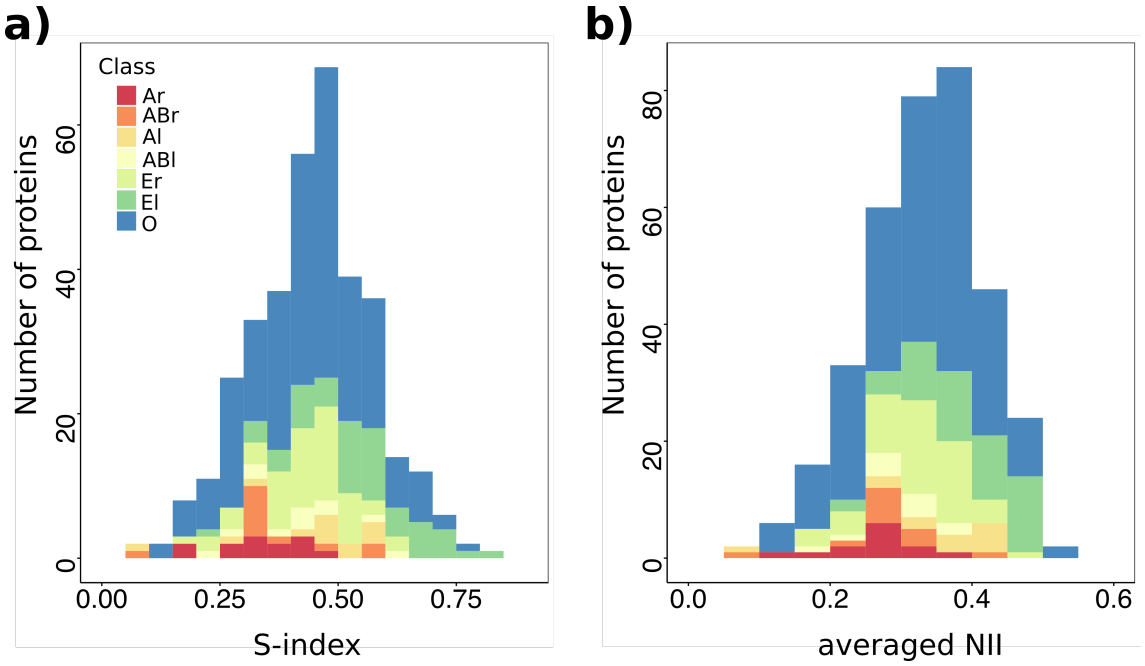

Figure S10: **Protein sociability within and across functional classes.** **(a-b)** Distributions of S-index values (**a**) and by-protein averaged NII values (**b**). The colors indicate the functional classes: antibodies (Ar), bound antibodies (ABr), antigens (Al), bound antigens (ABl), enzymes (Er), inhibitors (El), proteins with other function (O).

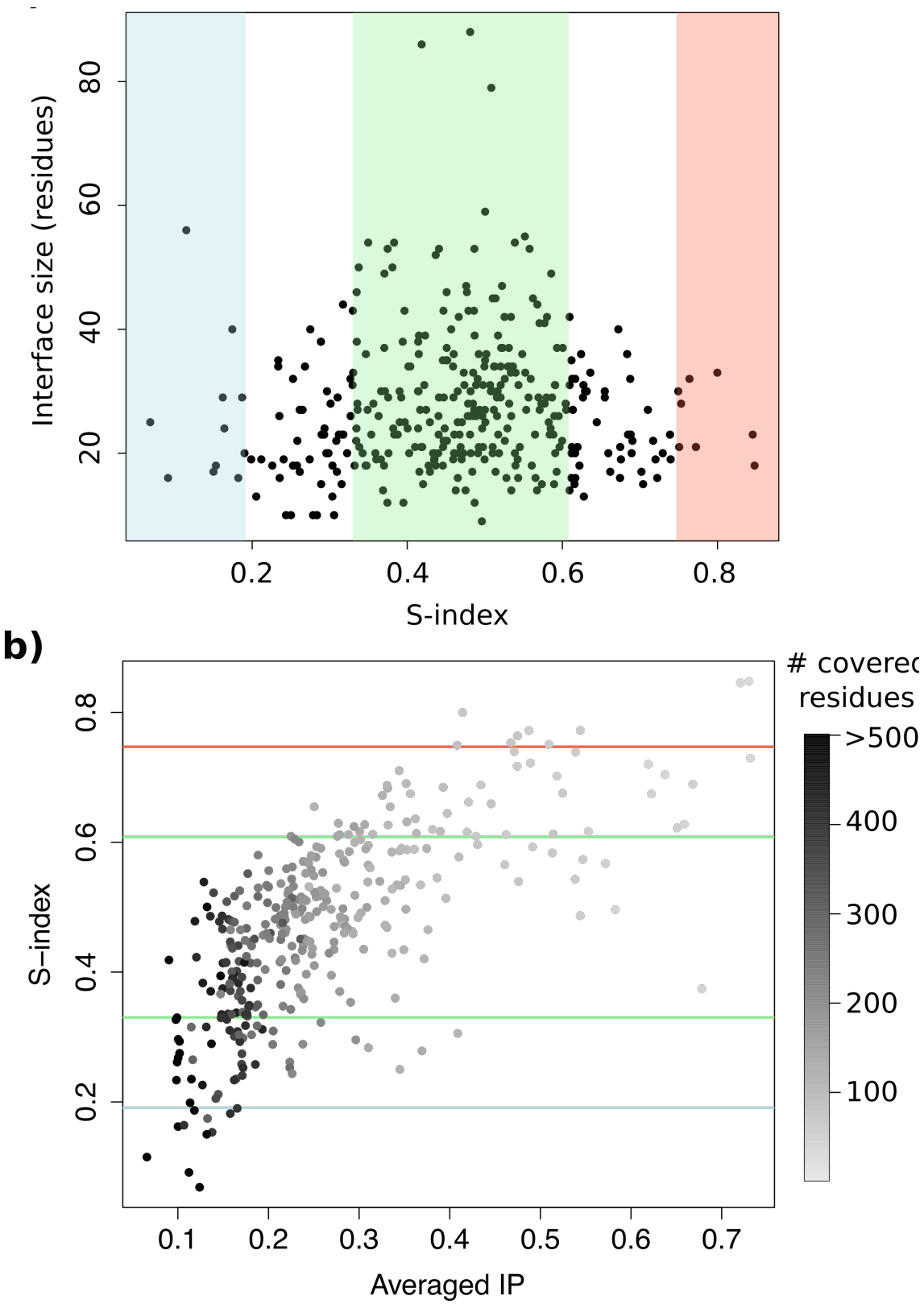

Figure S11: **Link between sociability and other properties. (a)** Interface size (in residues) as a function of sociability (S-index). Blue, green and red rectangles highlight poorly, medium and highly sociable proteins, respectively (compare to **Fig. 4**). **(b)** S-index as a function of IP averaged over the whole protein. Dots are colored from light gray to black with the increasing number of residues covered in the docked interfaces.