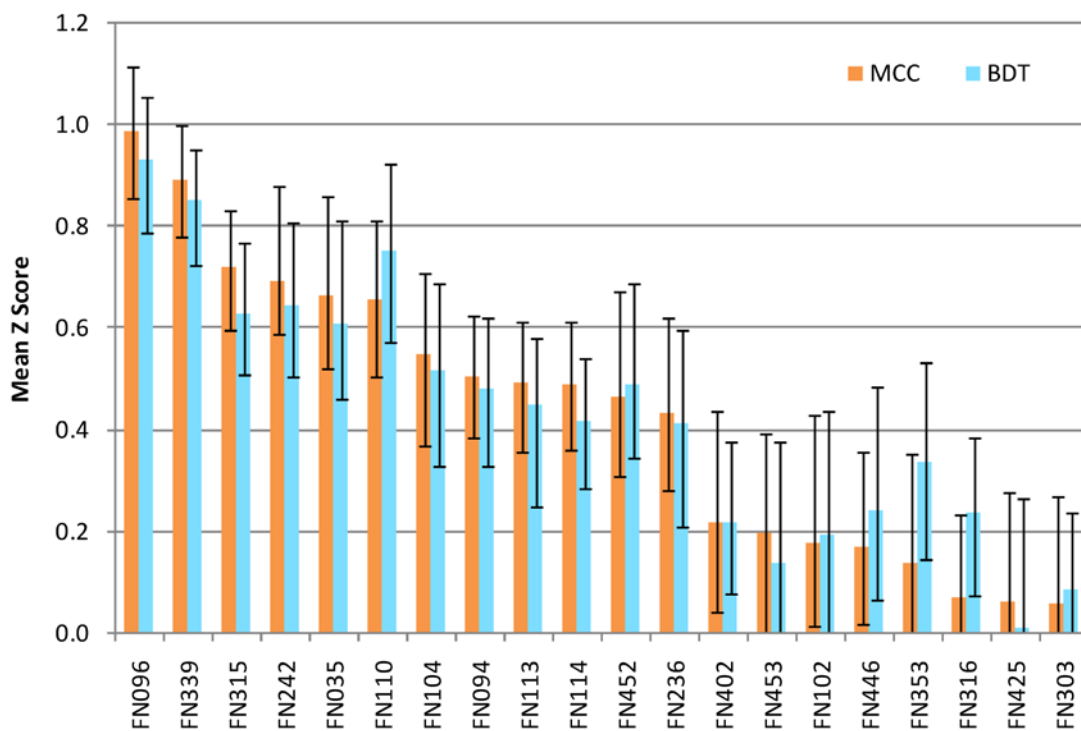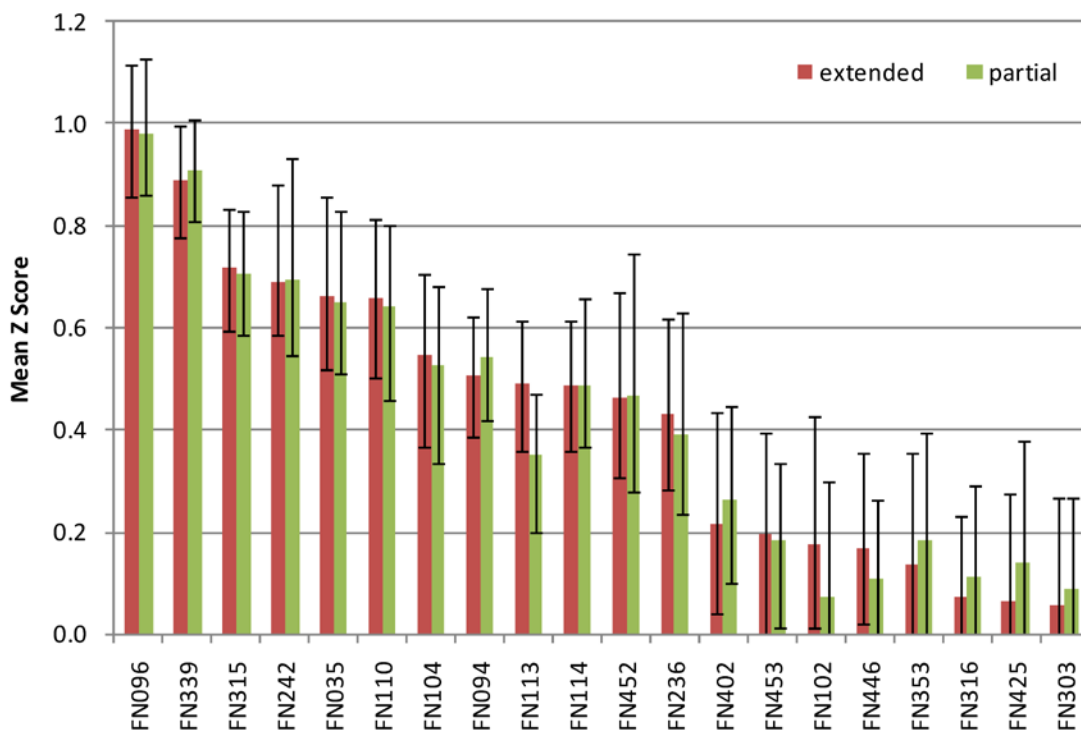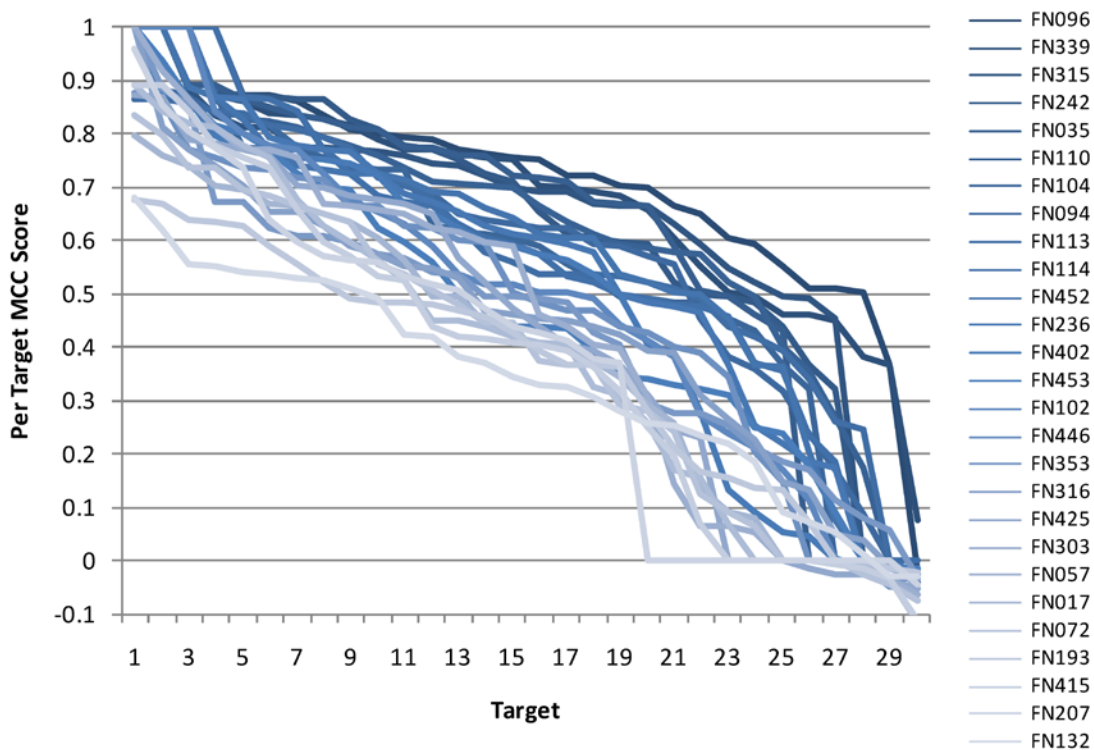**Fig. S1 Influence of different binding site definitions on the prediction performance of the top 12 predictors.** Mean Z score are shown for different tolerance distance used for binding site definition. All residues with a least one atom within the sum of the van der Waals radius plus the tolerance distance were considered to belong to the binding site.

Fig. S2 Comparison between the overall prediction performance evaluated using the Mathews Correlation Coefficient (MCC, in orange) and the Binding site Distance Test (BDT, in cyan). Overall prediction performance is shown in mean Z Scores over all targets.

Fig. S3 Comparison of the overall prediction performance observed with the extended (red) and the partial (green) binding site definitions. Overall prediction performance is shown in mean Z Scores over all targets.

Fig. S4 MCC scores for all groups with at least 10 predictions for all targets. Targets were sorted by their respective MCC score, individually for each group.

Table S1 Definition of binding site residues used in the assessment. [a] PDB id for the deposited target structure which was used to define the partial binding site. [b] PDB id of the protein structure related to the target structure, used in addition to define the extended binding site.

Target	Target PDB id [a]	Related PDB id [b]	Partial Binding Site	Extended Binding Site	Neutral Residues
T0515	3MT1	1TWI	198, 199, 232, 233, 324	35, 37, 162, 198, 199, 230, 232, 233, 269, 273, 324, 328	35, 37, 162, 230, 269, 273, 328
T0516	3NO6	2QCX	44, 47, 48, 51, 113, 137, 141, 208, 211	44, 47, 48, 51, 113, 137, 138, 141, 167, 171, 174, 208, 211	138, 167, 171, 174
T0518	3NMB		132, 133, 134, 162, 164, 271, 273	132, 133, 134, 162, 164, 271, 273	
T0521	3MSE		48, 50, 52, 54, 59, 117, 121, 123, 128	48, 50, 52, 54, 59, 117, 121, 123, 128	
T0524	3MWX	1SO0	73, 74, 177, 203, 230, 269, 271, 283	62, 63, 73, 74, 100, 101, 177, 203, 230, 269, 271, 283, 285	62, 63, 100, 101, 285
T0526	3NRE	1NS0	56, 83, 148, 173, 200, 241, 253	43, 56, 77, 83, 148, 173, 200, 241, 253	43, 77
T0529	3MWT		389, 390, 391, 533	389, 390, 391, 533	
T0539	2L0B		33, 36, 51, 53, 56, 59, 70, 73	33, 36, 51, 53, 56, 59, 70, 73	
T0547	3NZP	1TWI	84, 86, 87, 132, 231, 233, 236, 273, 274, 320, 321, 322, 323, 483, 519	84, 86, 87, 132, 231, 233, 236, 273, 274, 320, 321, 322, 323, 452, 483, 484, 519	452, 484
T0548	3NNQ		58, 62, 95, 98	58, 62, 95, 98	
T0565	3NPF	3H41	191, 193, 202, 203, 262, 263	54, 80, 191, 193, 194, 202, 203, 204, 221, 222, 262, 263	54, 80, 194, 204, 221, 222
T0570	3NO3		30, 59, 61, 123, 156, 158, 178, 222	30, 59, 61, 123, 156, 158, 178, 222	
T0582	3O14		58, 60, 64, 94	58, 60, 64, 94	
T0584	3NF2	1RQI	55, 58, 87, 104	55, 58, 87, 90, 91, 94, 103, 104, 155, 183, 184, 221, 248	90, 91, 94, 103, 155, 183, 184, 221, 248
T0585	3NE8		13, 28, 82, 84, 115	13, 28, 82, 84, 115	
T0591	3NRA		109, 110, 111, 135, 185, 189, 217, 219, 251, 252, 260, 283	109, 110, 111, 135, 185, 189, 217, 219, 251, 252, 260, 283	
T0597	3NIE		36, 37, 38, 39, 40, 41, 42, 44, 57, 59, 73, 112, 114, 117, 120, 158, 160, 163, 174	36, 37, 38, 39, 40, 41, 42, 44, 57, 59, 73, 112, 114, 117, 120, 158, 160, 163, 174	

T0599	3OS6	3HWO	213, 214, 215, 364, 377, 381	212, 213, 214, 215, 276, 304, 328, 347, 348, 362, 364, 377, 381	212, 276, 304, 328, 347, 348, 362
T0604	3NLC		113, 114, 116, 117, 118, 137, 138, 166, 167, 170, 171, 172, 174, 175, 177, 178, 180, 241, 242, 243, 272, 273, 274, 277, 280, 352, 364, 365, 515, 516, 523, 524, 527	113, 114, 116, 117, 118, 137, 138, 166, 167, 170, 171, 172, 174, 175, 177, 178, 180, 241, 242, 243, 272, 273, 274, 277, 280, 352, 364, 365, 515, 516, 523, 524, 527	
T0607	3PFE	2ZOF	96, 129, 163, 190, 442	96, 129, 162, 163, 165, 190, 191, 205, 340, 410, 412, 413, 414, 442	162, 165, 191, 205, 340, 410, 412, 413, 414
T0609	3OS7	1Z45	67, 69, 108, 184, 288	67, 69, 80, 81, 108, 184, 245, 286, 288, 300	80, 81, 245, 286, 300
T0613	3OBI	1C2T	177, 178, 225, 229, 230	173, 174, 175, 176, 177, 178, 183, 192, 193, 194, 223, 225, 226, 229, 230	173, 174, 175, 176, 183, 192, 193, 194, 223, 226
T0615	3NQW	1VJ7	33, 36, 62, 63, 98, 102, 123, 127, 139, 147	26, 33, 36, 62, 63, 98, 102, 123, 127, 128, 130, 131, 139, 143, 147	26, 128, 130, 131, 143
T0622	3NKL	2VT2	10, 11, 12, 72	7, 9, 10, 11, 12, 33, 34, 35, 38, 69, 70, 71, 72, 77, 81	7, 9, 33, 34, 35, 38, 69, 70, 71, 77, 81
T0625	3ORU		126, 143, 207	126, 143, 207	
T0629	2XGF		73, 75, 105, 107, 119, 121, 156, 158, 170, 172, 179, 181, 188, 190	73, 75, 105, 107, 119, 121, 156, 158, 170, 172, 179, 181, 188, 190	
T0632	3NWZ		76, 83, 109, 110, 117, 118, 119, 120, 134, 136, 137, 138, 139, 164, 166, 167	76, 83, 109, 110, 117, 118, 119, 120, 134, 136, 137, 138, 139, 164, 166, 167	
T0635	3N1U		25, 27, 118	25, 27, 118	
T0636	3P1T	1GEX	22, 47, 145, 172, 197, 301, 306, 313	22, 47, 75, 76, 145, 169, 171, 172, 194, 196, 197, 205, 206, 225, 301, 306, 313	75, 76, 169, 171, 194, 196, 205, 206, 225
T0641	3NYI		30, 65, 66, 67, 96, 97, 127, 128, 129, 164, 166, 179, 204, 241, 272, 275, 279, 286	30, 65, 66, 67, 96, 97, 127, 128, 129, 164, 166, 179, 204, 241, 272, 275, 279, 286	

Table SII P-values computed by Wilcoxon Signed-Rank Test of all against all predictors. Significant differences between two groups are indicated by cells with white background. For clarity, only the 12 top performing predictors are shown, sorted by their overall performance.

	FN096	FN339	FN315	FN242	FN035	FN110	FN104	FN094	FN113	FN114	FN452	FN236
FN096	-	0.11	0.01	0.16	0.14	0.00	0.01	0.00	0.00	0.01	0.00	0.00
FN339	0.11	-	0.26	0.27	0.49	0.12	0.06	0.04	0.02	0.06	0.01	0.02
FN315	0.01	0.26	-	0.76	0.23	0.79	0.39	0.10	0.05	0.18	0.16	0.09
FN242	0.16	0.27	0.76	-	0.91	0.46	0.23	0.12	0.21	0.21	0.05	0.08
FN035	0.14	0.49	0.23	0.91	-	0.92	0.39	0.10	0.10	0.18	0.18	0.17
FN110	0.00	0.12	0.79	0.46	0.92	-	0.52	0.24	0.13	0.50	0.41	0.29
FN104	0.01	0.06	0.39	0.23	0.39	0.52	-	0.78	0.71	0.37	0.73	0.50
FN094	0.00	0.04	0.10	0.12	0.10	0.24	0.78	-	0.68	0.94	0.67	0.72
FN113	0.00	0.02	0.05	0.21	0.10	0.13	0.71	0.68	-	0.87	0.95	0.64
FN114	0.01	0.06	0.18	0.21	0.18	0.50	0.37	0.94	0.87	-	0.83	0.49
FN452	0.00	0.01	0.16	0.05	0.18	0.41	0.73	0.67	0.95	0.83	-	0.87
FN236	0.00	0.02	0.09	0.08	0.17	0.29	0.50	0.72	0.64	0.49	0.87	-