

Table S1. Classification of water molecules at 224 protein-RNA interfaces

Structure ID	nWat	SWB	DWB	HPHOB	%SWB	%DWB	%HPHOB
1A1T_A_B	121	44	72	5	36.4%	59.5%	4.1%
1A34_A_BC	78	21	45	12	26.9%	57.7%	15.4%
1A4T_B_A	96	43	52	1	44.8%	54.2%	1.0%
1A9N_AB_Q	176	69	95	12	39.2%	54.0%	6.8%
1AQ3_A_R	89	28	61	0	31.5%	68.5%	0.0%
1AUD_A_B	140	56	77	7	40.0%	55.0%	5.0%
1B7F_A_P	198	77	116	5	38.9%	58.6%	2.5%
1BIV_B_A	124	51	64	9	41.1%	51.6%	7.3%
1BMV_2_M	85	32	51	2	37.6%	60.0%	2.4%
1C9S_LtoV_W	618	241	358	19	39.0%	57.9%	3.1%
1CVJ_BE_N	144	56	79	9	38.9%	54.9%	6.3%
1CX0_A_B	148	55	80	13	37.2%	54.1%	8.8%
1DDL_ABC_D	94	36	55	3	38.3%	58.5%	3.2%
1DI2_AB_CD	89	31	54	4	34.8%	60.7%	4.5%
1DI2_AB_E	71	20	49	2	28.2%	69.0%	2.8%
1DZ5_AB_CD	290	85	184	21	29.3%	63.4%	7.2%
1E7K_A_C	101	39	59	3	38.6%	58.4%	3.0%
1E8O_ABCD_E	220	78	138	4	35.5%	62.7%	1.8%
1EC6_A_D	156	55	99	2	35.3%	63.5%	1.3%
1EIY_AB_C	221	63	153	5	28.5%	69.2%	2.3%
1EKZ_A_B	73	17	46	10	23.3%	63.0%	13.7%
1ETF_B_A	159	60	86	13	37.7%	54.1%	8.2%
1EUQ_A_B	400	162	218	20	40.5%	54.5%	5.0%
1EXY_B_A	145	55	75	15	37.9%	51.7%	10.3%
1F8V_ACE_R	105	26	76	3	24.8%	72.4%	2.9%
1G59_A_B	344	101	227	16	29.4%	66.0%	4.7%
1G70_B_A	130	44	81	5	33.8%	62.3%	3.8%
1GAX_A_C	453	137	298	18	30.2%	65.8%	4.0%
1GTF_LtoV_W	616	253	351	12	41.1%	57.0%	1.9%
1H4Q_AB_T	190	68	114	8	35.8%	60.0%	4.2%
1HJI_B_A	99	41	57	1	41.4%	57.6%	1.0%
1HVU_AB_C	154	37	109	8	24.0%	70.8%	5.2%
1I9F_B_A	122	35	80	7	28.7%	65.6%	5.7%
1J1U_A_B	108	22	80	6	20.4%	74.1%	5.6%
1J2B_AB_C	538	194	334	10	36.1%	62.1%	1.9%
1J2B_AB_D	496	181	293	22	36.5%	59.1%	4.4%
1K1G_A_B	133	49	79	5	36.8%	59.4%	3.8%
1KNZ_AB_W	102	50	51	1	49.0%	50.0%	1.0%
1KOG_ABE_J	271	76	182	13	28.0%	67.2%	4.8%
1KOG_AB_I	240	78	153	9	32.5%	63.8%	3.8%
1KQ2_ABHIKM_R	169	67	97	5	39.6%	57.4%	3.0%

Structure ID	nWat	SWB	DWB	HPHOB	%SWB	%DWB	%HPHOB
1L1C_AB_C	140	60	73	7	42.9%	52.1%	5.0%
1L9A_A_B	165	59	96	10	35.8%	58.2%	6.1%
1LNG_A_B	163	63	91	9	38.7%	55.8%	5.5%
1M8V_ALMN_O	100	38	58	4	38.0%	58.0%	4.0%
1M8V_ABL_T	88	27	55	6	30.7%	62.5%	6.8%
1M8W_B_D	139	66	71	2	47.5%	51.1%	1.4%
1M8Y_A_C	160	71	86	3	44.4%	53.8%	1.9%
1MFQ_BC_A	214	69	139	6	32.2%	65.0%	2.8%
1N35_A_BC	280	94	181	5	33.6%	64.6%	1.8%
1N38_A_BC	176	65	103	8	36.9%	58.5%	4.5%
1NYB_A_B	90	37	51	2	41.1%	56.7%	2.2%
1OOA_AB_C	221	70	145	6	31.7%	65.6%	2.7%
1P6V_AC_D	154	53	90	11	34.4%	58.4%	7.1%
1P6V_AC_B	196	75	108	13	38.3%	55.1%	6.6%
1PGL_2_3	75	23	49	3	30.7%	65.3%	4.0%
1QZW_A_B	95	25	66	4	26.3%	69.5%	4.2%
1R9F_A_BC	144	43	93	8	29.9%	64.6%	5.6%
1RC7_A_DE	112	37	71	4	33.0%	63.4%	3.6%
1RC7_A_BC	42	15	24	3	35.7%	57.1%	7.1%
1RKJ_A_B	141	52	83	6	36.9%	58.9%	4.3%
1SI3_A_B	113	49	62	2	43.4%	54.9%	1.8%
1T4L_B_A	123	31	84	8	25.2%	68.3%	6.5%
1TFW_AC_GJ	324	110	204	10	34.0%	63.0%	3.1%
1TFW_B_EH	162	56	101	5	34.6%	62.3%	3.1%
1TFY_AC_GJ	273	94	170	9	34.4%	62.3%	3.3%
1U0B_B_A	353	129	214	10	36.5%	60.6%	2.8%
1ULL_B_A	132	66	65	1	50.0%	49.2%	0.8%
1URN_C_R	115	38	68	9	33.0%	59.1%	7.8%
1UTD_LM_0	76	27	48	1	35.5%	63.2%	1.3%
1VFG_A_C	123	25	90	8	20.3%	73.2%	6.5%
1WMQ_A_C	93	23	60	10	24.7%	64.5%	10.8%
1WNE_A_BC	205	74	125	6	36.1%	61.0%	2.9%
1WSU_A_E	87	29	56	2	33.3%	64.4%	2.3%
1WWD_A_B	73	32	39	2	43.8%	53.4%	2.7%
1WWE_A_B	115	33	76	6	28.7%	66.1%	5.2%
1WWF_A_B	109	43	62	4	39.4%	56.9%	3.7%
1WZ2_A_C	465	132	316	17	28.4%	68.0%	3.7%
1YTU_B_EF	117	50	65	2	42.7%	55.6%	1.7%
1YTY_AB_CD	287	107	171	9	37.3%	59.6%	3.1%
1YVP_B_H	145	60	81	4	41.4%	55.9%	2.8%
1YYK_AB_DEF	111	42	69	0	37.8%	62.2%	0.0%
1YYW_C_KL	88	31	57	0	35.2%	64.8%	0.0%
1YYW_A_GH	94	34	53	7	36.2%	56.4%	7.4%

Structure ID	nWat	SWB	DWB	HPHOB	%SWB	%DWB	%HPHOB
1YYW_A_EF	56	12	43	1	21.4%	76.8%	1.8%
1YZ9_A_CDEF	165	55	107	3	33.3%	64.8%	1.8%
1ZBH_AD_F	136	45	81	10	33.1%	59.6%	7.4%
1ZBH_AD_E	162	54	100	8	33.3%	61.7%	4.9%
1ZDJ_A_R	64	17	47	0	26.6%	73.4%	0.0%
1ZSE_AB_R	114	36	78	0	31.6%	68.4%	0.0%
2A8V_B_E	58	16	40	2	27.6%	69.0%	3.4%
2A9X_1_2	88	29	52	7	33.0%	59.1%	8.0%
2AD9_A_B	94	33	57	4	35.1%	60.6%	4.3%
2ADC_A_C	103	41	58	4	39.8%	56.3%	3.9%
2ADC_A_B	126	50	76	0	39.7%	60.3%	0.0%
2AKE_A_B	109	29	72	8	26.6%	66.1%	7.3%
2AZX_B_D	74	22	44	8	29.7%	59.5%	10.8%
2B2E_AB_R	162	55	105	2	34.0%	64.8%	1.2%
2B6G_A_B	38	10	26	2	26.3%	68.4%	5.3%
2BBV_CF_N	51	15	36	0	29.4%	70.6%	0.0%
2BGG_A_PQ	152	55	94	3	36.2%	61.8%	2.0%
2BTE_AD_B	379	110	253	16	29.0%	66.8%	4.2%
2BX2_L_R	78	21	51	6	26.9%	65.4%	7.7%
2C06_AB_C	97	41	55	1	42.3%	56.7%	1.0%
2C4R_L_R	149	42	100	7	28.2%	67.1%	4.7%
2CSX_A_C	223	64	155	4	28.7%	69.5%	1.8%
2CT8_A_C	196	57	136	3	29.1%	69.4%	1.5%
2D6F_C_E	149	32	111	6	21.5%	74.5%	4.0%
2DEU_AB_D	276	92	172	12	33.3%	62.3%	4.3%
2DR5_A_B	189	78	107	4	41.3%	56.6%	2.1%
2DU3_A_D	144	41	90	13	28.5%	62.5%	9.0%
2DU5_A_D	153	43	103	7	28.1%	67.3%	4.6%
2EC0_A_BC	224	80	141	3	35.7%	62.9%	1.3%
2ERR_A_B	120	49	62	9	40.8%	51.7%	7.5%
2ESE_A_B	88	29	48	11	33.0%	54.5%	12.5%
2EZ6_AB_CD	439	128	295	16	29.2%	67.2%	3.6%
2F8K_A_B	80	26	53	1	32.5%	66.3%	1.3%
2F8S_A_CD	96	34	62	0	35.4%	64.6%	0.0%
2FK6_A_R	158	43	112	3	27.2%	70.9%	1.9%
2FY1_A_B	135	52	77	6	38.5%	57.0%	4.4%
2G4B_A_B	78	30	48	0	38.5%	61.5%	0.0%
2GIC_ABCDE_R	929	310	593	26	33.4%	63.8%	2.8%
2GJE_AD_RS	211	65	143	3	30.8%	67.8%	1.4%
2GTT_LtoV_X	1904	652	1202	50	34.2%	63.1%	2.6%
2GTT_AtoK_W	1923	669	1211	43	34.8%	63.0%	2.2%
2HGH_A_B	175	50	110	15	28.6%	62.9%	8.6%
2HT1_AB_M	122	37	83	2	30.3%	68.0%	1.6%

Structure ID	nWat	SWB	DWB	HPHOB	%SWB	%DWB	%HPHOB
2I91_AB_CD	273	115	150	8	42.1%	54.9%	2.9%
2IHX_A_B	242	81	151	10	33.5%	62.4%	4.1%
2IPY_A_C	213	83	129	1	39.0%	60.6%	0.5%
2IX1_A_B	299	100	186	13	33.4%	62.2%	4.3%
2IY5_AB_T	259	71	167	21	27.4%	64.5%	8.1%
2IZN_C_S	65	22	42	1	33.8%	64.6%	1.5%
2JEA_AB_C	119	41	73	5	34.5%	61.3%	4.2%
2JPP_AB_D	163	55	101	7	33.7%	62.0%	4.3%
2JPP_AB_C	124	43	76	5	34.7%	61.3%	4.0%
2KDQ_A_B	100	37	61	2	37.0%	61.0%	2.0%
2KFY_A_B	75	35	35	5	46.7%	46.7%	6.7%
2KH9_A_B	80	28	47	5	35.0%	58.8%	6.3%
2KM8_BC_A	238	78	142	18	32.8%	59.7%	7.6%
2KX5_B_A	102	30	59	13	29.4%	57.8%	12.7%
2L2K_B_A	137	44	85	8	32.1%	62.0%	5.8%
2L3C_A_B	106	27	68	11	25.5%	64.2%	10.4%
2L3J_A_B	192	63	117	12	32.8%	60.9%	6.3%
2NR0_ACD_G	317	103	199	15	32.5%	62.8%	4.7%
2NR0_ABC_E	233	56	163	14	24.0%	70.0%	6.0%
2NR0_CD_H	186	48	132	6	25.8%	71.0%	3.2%
2NR0_AB_F	272	83	176	13	30.5%	64.7%	4.8%
2NUE_AB_C	163	54	106	3	33.1%	65.0%	1.8%
2NUG_AB_CDEF	429	144	268	17	33.6%	62.5%	4.0%
2OZB_AB_C	193	73	113	7	37.8%	58.5%	3.6%
2PLY_AB_C	195	61	130	4	31.3%	66.7%	2.1%
2PY9_AC_F	184	61	116	7	33.2%	63.0%	3.8%
2QUX_ABDE_C	184	59	122	3	32.1%	66.3%	1.6%
2R7T_A_X	171	55	109	7	32.2%	63.7%	4.1%
2R7V_A_X	113	36	76	1	31.9%	67.3%	0.9%
2R8S_HL_R	202	62	132	8	30.7%	65.3%	4.0%
2R92_AB_PT	333	103	222	8	30.9%	66.7%	2.4%
2R93_AB_R	228	67	161	0	29.4%	70.6%	0.0%
2RKJ_ABEF_CDG	629	160	436	33	25.4%	69.3%	5.2%
2V3C_BCD_N	339	125	198	16	36.9%	58.4%	4.7%
2V3C_AC_M	474	163	292	19	34.4%	61.6%	4.0%
2W2H_AC_R	142	35	97	10	24.6%	68.3%	7.0%
2W2H_BD_S	139	33	102	4	23.7%	73.4%	2.9%
2WYY_ACD FHM_R	980	279	640	61	28.5%	65.3%	6.2%
2XD0_AE_G	330	119	199	12	36.1%	60.3%	3.6%
2XGJ_A_C	114	42	72	0	36.8%	63.2%	0.0%
2XNR_A_C	65	22	40	3	33.8%	61.5%	4.6%
2ZI0_AB_CD	383	146	231	6	38.1%	60.3%	1.6%
2ZKO_AB_CD	176	61	108	7	34.7%	61.4%	4.0%

Structure ID	nWat	SWB	DWB	HPHOB	%SWB	%DWB	%HPHOB
2ZM5_AB_C	317	112	194	11	35.3%	61.2%	3.5%
2ZNI_AB_D	296	112	173	11	37.8%	58.4%	3.7%
2ZNI_AB_C	290	105	181	4	36.2%	62.4%	1.4%
2ZUE_A_B	384	134	230	20	34.9%	59.9%	5.2%
2ZZM_A_B	376	126	235	15	33.5%	62.5%	4.0%
2ZZN_AB_C	505	164	323	18	32.5%	64.0%	3.6%
2ZZN_AB_D	388	130	247	11	33.5%	63.7%	2.8%
3A2K_AB_C	402	161	233	8	40.0%	58.0%	2.0%
3A2K_AB_D	408	165	230	13	40.4%	56.4%	3.2%
3A6P_FH_IJ	361	102	246	13	28.3%	68.1%	3.6%
3A6P_AC_DE	406	136	260	10	33.5%	64.0%	2.5%
3ADB_A_C	339	86	238	15	25.4%	70.2%	4.4%
3ADC_B_D	247	68	167	12	27.5%	67.6%	4.9%
3ADC_A_C	332	96	221	15	28.9%	66.6%	4.5%
3ADI_AB_DE	53	17	33	3	32.1%	62.3%	5.7%
3AEV_B_C	170	69	91	10	40.6%	53.5%	5.9%
3AKZ_ABC_E	464	151	302	11	32.5%	65.1%	2.4%
3AL0_BC_E	551	189	346	16	34.3%	62.8%	2.9%
3AM1_A_B	200	61	129	10	30.5%	64.5%	5.0%
3BOY_ABC_D	300	88	182	29	29.3%	60.7%	9.7%
3CIY_AB_CD	362	123	227	12	34.0%	62.7%	3.3%
3CZ3_ABCD_EF	401	155	240	6	38.7%	59.9%	1.5%
3CZ3_ABCD_GH	436	168	254	14	38.5%	58.3%	3.2%
3D2S_B_F	33	12	21	0	36.4%	63.6%	0.0%
3D2S_A_E	37	16	21	0	43.2%	56.8%	0.0%
3EPH_A_E	331	130	195	6	39.3%	58.9%	1.8%
3EQT_AB_CD	184	59	112	13	32.1%	60.9%	7.1%
3EX7_CDI_F	123	43	77	3	35.0%	62.6%	2.4%
3FTE_A_CD	108	30	76	2	27.8%	70.4%	1.9%
3GIB_ABC_H	138	46	80	12	33.3%	58.0%	8.7%
3HL2_ABCD_E	417	105	300	12	25.2%	71.9%	2.9%
3HSB_ABCD_X	132	52	69	11	39.4%	52.3%	8.3%
3HTX_A_BC	489	156	314	19	31.9%	64.2%	3.9%
3IAB_AB_R	392	132	251	9	33.7%	64.0%	2.3%
3ICQ_BT_D	337	96	233	8	28.5%	69.1%	2.4%
3IIN_A_BCD	147	49	89	9	33.3%	60.5%	6.1%
3IVK_AB_C	178	63	111	4	35.4%	62.4%	2.2%
3IWN_CD_A	206	70	126	10	34.0%	61.2%	4.9%
3IWN_D_B	148	48	86	14	32.4%	58.1%	9.5%
3KFU_DEF_M	257	81	159	17	31.5%	61.9%	6.6%
3KS8_ABCD_EF	282	92	184	6	32.6%	65.2%	2.1%
3KTV_BD_C	239	75	143	21	31.4%	59.8%	8.8%
3LOB_CF_R	52	12	37	3	23.1%	71.2%	5.8%

Structure ID	nWat	SWB	DWB	HPHOB	%SWB	%DWB	%HPHOB
3M7N_DG_Y	115	47	66	2	40.9%	57.4%	1.7%
3MDG_A_C	94	27	59	8	28.7%	62.8%	8.5%
3NNC_A_B	101	30	67	4	29.7%	66.3%	4.0%
3NNH_AC_E	199	66	127	6	33.2%	63.8%	3.0%
3O3I_X_A	84	28	52	4	33.3%	61.9%	4.8%
3OG8_AB_CD	281	84	192	5	29.9%	68.3%	1.8%
3OK7_A_BC	221	77	131	13	34.8%	59.3%	5.9%
3OL6_AE_BCG	502	151	343	8	30.1%	68.3%	1.6%
3OL6_A_BCD	370	114	249	7	30.8%	67.3%	1.9%
484D_A_B	165	71	91	3	43.0%	55.2%	1.8%
6MSF_A_R	78	22	56	0	28.2%	71.8%	0.0%

Table S2. Parameter estimates from the predictive model (Eq. 1) and the jackknife estimates.

Predictor	Proposed predictive model				Jackknife results		
	Coeff. ^a	SE ^b	P-Value	95% CL ^c	Coeff. ^a	SE ^b	P-Value
Intercept	-0.553	2.968	0.8524	(-6.401, 5.296)	-0.553	2.460	0.8225
nIntfaa ^d	2.448	0.037	<0.0001	(2.376, 2.521)	2.448	0.069	<0.0001
nIntfnt ^e	3.315	0.158	<0.0001	(3.003, 3.627)	3.315	0.207	<0.0001

^a Coefficient; ^bStandard Error; ^cConfidence Limits

^d Number of amino acids in the protein-RNA interface

^e Number of nucleotides in the protein-RNA interface

Table S3. Types of water molecules at 224 protein-RNA interfaces

Structure ID	Single-water bridges							Double-water bridges							Hphob	
	0	1	2	3	4	≥5	bur	dir	1	2	3	4	≥5	bur	acc	bur
1A1T_A_B	19	17	2	1	1	1	3	56	7	4	0	0	5	0	5	0
1A34_A_BC	15	3	0	0	0	0	3	42	3	0	0	0	0	0	12	0
1A4T_B_A	20	11	4	3	2	1	2	47	3	0	1	0	1	0	0	1
1A9N_AB_Q	28	26	9	4	0	0	2	79	14	1	1	0	0	0	12	0
1AQ3_A_R	13	10	2	0	1	2	0	52	4	2	1	1	1	0	0	0
1AUD_A_B	23	13	11	3	1	0	5	57	12	2	2	1	1	2	6	1
1B7F_A_P	34	24	9	4	2	0	4	87	8	7	7	3	0	4	4	1
1BIV_B_A	18	13	7	3	1	0	9	53	3	5	3	0	0	0	9	0
1BMV_2_M	12	10	5	4	0	0	1	39	5	5	2	0	0	0	2	0
1C9S_LtoV_W	86	99	37	5	1	0	13	295	37	14	3	0	0	9	18	1
1CVJ_BE_N	30	13	4	5	2	0	2	67	7	2	2	0	0	1	8	1
1CX0_A_B	34	16	4	0	0	0	1	72	5	1	1	0	0	1	13	0
1DDL_ABC_D	21	12	0	0	0	0	3	54	1	0	0	0	0	0	3	0
1DI2_AB_CD	19	9	2	0	0	0	1	47	4	3	0	0	0	0	4	0
1DI2_AB_E	15	5	0	0	0	0	0	42	4	3	0	0	0	0	2	0
1DZ5_AB_CD	26	38	15	3	0	0	3	141	30	6	5	0	0	2	21	0
1E7K_A_C	16	14	5	4	0	0	0	49	5	3	2	0	0	0	1	2
1E8O_ABCD_E	31	27	12	5	1	0	2	101	19	13	3	0	0	2	4	0
1EC6_A_D	22	16	10	2	2	2	1	75	14	5	2	1	1	1	2	0
1EIY_AB_C	24	29	8	1	1	0	0	115	23	10	1	0	1	3	5	0
1EKZ_A_B	9	6	1	0	0	0	1	42	2	2	0	0	0	0	10	0
1ETF_B_A	18	17	7	6	6	3	3	70	6	5	1	1	3	0	13	0
1EUQ_A_B	51	57	30	14	2	0	8	160	19	17	9	5	3	5	19	1
1EXY_B_A	21	14	9	4	1	0	6	64	6	1	1	2	0	1	15	0
1F8V_ACE_R	14	11	1	0	0	0	0	66	8	2	0	0	0	0	3	0
1G59_A_B	40	34	7	6	3	4	7	165	31	11	10	4	3	3	13	3
1G70_B_A	11	15	13	2	0	0	3	65	8	5	3	0	0	0	5	0
1GAX_A_C	58	51	12	5	0	0	11	227	50	18	0	1	0	2	18	0
1GTF_LtoV_W	100	111	28	7	0	0	7	294	37	14	3	3	0	0	10	2
1H4Q_AB_T	35	21	8	1	1	0	2	90	20	2	1	1	0	0	8	0
1HJI_B_A	18	16	4	2	0	0	1	48	6	3	0	0	0	0	1	0
1HVV_AB_C	30	7	0	0	0	0	0	98	11	0	0	0	0	0	8	0
1I9F_B_A	18	12	5	0	0	0	0	65	14	1	0	0	0	0	7	0
1J1U_A_B	12	5	1	0	0	0	4	72	5	2	0	0	0	1	6	0
1J2B_AB_C	52	62	34	14	8	5	19	223	46	19	20	6	9	11	8	2
1J2B_AB_D	48	62	29	8	7	8	19	200	39	19	12	6	8	9	22	0
1K1G_A_B	20	17	8	1	0	0	3	61	8	8	1	0	0	1	5	0
1KNZ_AB_W	12	12	3	2	2	2	17	26	6	2	1	4	1	11	0	1
1KOG_ABE_J	37	27	8	2	0	0	2	148	27	7	0	0	0	0	12	1
1KOG_AB_I	35	18	13	4	0	0	8	124	18	7	0	0	0	4	8	1
1KQ2_ABHIKM_R	22	18	3	4	4	6	10	70	17	7	0	0	0	3	4	1
1L1C_AB_C	25	17	5	4	2	1	6	62	4	6	1	0	0	0	7	0

Structure ID	Single-water bridges							Double-water bridges							Hphob	
	0	1	2	3	4	≥5	bur	dir	1	2	3	4	≥5	bur	acc	bur
1L9A_A_B	21	18	7	6	2	0	5	73	9	11	3	0	0	0	10	0
1LNG_A_B	29	16	5	4	3	1	5	68	6	10	4	1	1	1	9	0
1M8V_ALMN_O	19	10	3	3	0	0	3	51	5	0	0	2	0	0	4	0
1M8V_ABL_T	19	6	1	1	0	0	0	51	3	1	0	0	0	0	5	1
1M8W_B_D	28	20	10	6	2	0	0	56	9	1	2	2	1	0	2	0
1M8Y_A_C	31	17	5	5	4	4	5	64	12	1	1	2	3	3	3	0
1MFQ_BC_A	30	18	8	2	1	3	7	108	17	9	2	1	2	0	5	1
1N35_A_BC	17	38	20	4	3	1	11	98	42	21	10	2	1	7	5	0
1N38_A_BC	20	27	8	4	0	0	6	74	15	8	2	2	0	2	8	0
1NYB_A_B	21	8	3	1	0	0	4	45	2	1	1	1	0	1	2	0
1OOA_AB_C	31	22	9	3	2	1	2	100	25	9	4	1	4	2	6	0
1P6V_AC_D	27	14	2	2	2	1	5	69	5	9	4	0	0	3	9	2
1P6V_AC_B	37	21	9	3	2	0	3	91	7	2	2	1	0	5	12	1
1PGL_2_3	5	13	4	1	0	0	0	36	7	5	1	0	0	0	3	0
1QZW_A_B	15	5	2	0	1	0	2	54	10	1	1	0	0	0	4	0
1R9F_A_BC	19	14	3	3	3	0	1	77	8	3	4	1	0	0	8	0
1RC7_A_DE	24	6	1	4	2	0	0	62	4	3	0	1	1	0	4	0
1RC7_A_BC	10	3	1	0	0	0	1	24	0	0	0	0	0	0	3	0
1RKJ_A_B	17	21	9	2	0	0	3	71	9	2	1	0	0	0	6	0
1SI3_A_B	22	15	7	2	0	2	1	47	5	5	4	1	0	0	1	1
1T4L_B_A	9	14	6	1	0	0	1	70	9	4	1	0	0	0	8	0
1TFW_AC_GJ	43	41	13	5	1	0	7	162	22	11	9	0	0	0	9	1
1TFW_B_EH	20	26	3	3	1	0	3	78	11	6	4	2	0	0	3	2
1TFY_AC_GJ	43	28	9	1	0	0	13	137	18	8	5	0	0	2	9	0
1U0B_B_A	36	45	19	10	4	7	8	149	26	19	4	4	9	3	8	2
1ULL_B_A	27	14	9	2	1	6	7	53	4	4	2	0	1	1	0	1
1URN_C_R	27	7	1	0	0	0	3	61	6	0	0	0	0	1	9	0
1UTD_LM_0	14	9	4	0	0	0	0	40	5	1	2	0	0	0	1	0
1VFG_A_C	10	10	5	0	0	0	0	72	14	3	1	0	0	0	8	0
1WMQ_A_C	9	9	2	0	0	0	3	51	8	1	0	0	0	0	10	0
1WNE_A_BC	23	26	11	4	1	2	7	86	19	11	5	0	2	2	6	0
1WSU_A_E	10	13	5	1	0	0	0	49	3	3	1	0	0	0	2	0
1WWD_A_B	19	8	2	0	0	0	3	34	3	0	0	0	0	2	2	0
1WWE_A_B	19	11	2	0	0	0	1	66	5	5	0	0	0	0	5	1
1WWF_A_B	23	13	3	2	0	0	2	53	3	4	1	0	0	1	4	0
1WZ2_A_C	44	52	22	10	0	0	4	235	45	28	5	0	0	3	17	0
1YTU_B_EF	14	14	6	4	2	1	9	42	11	3	2	1	0	6	1	1
1YTY_AB_CD	34	36	16	7	2	4	8	122	27	11	4	0	7	0	9	0
1YVP_B_H	22	18	14	4	2	0	0	51	14	10	4	2	0	0	4	0
1YYK_AB_DEF	27	11	2	0	0	0	2	62	7	0	0	0	0	0	0	0
1YYW_C_KL	16	7	3	3	1	1	0	45	9	2	0	1	0	0	0	0
1YYW_A_GH	14	7	8	4	1	0	0	46	4	2	1	0	0	0	7	0
1YYW_A_EF	7	4	1	0	0	0	0	32	9	2	0	0	0	0	1	0
1YZ9_A_CDEF	23	16	8	3	1	0	4	82	13	7	4	0	0	1	3	0

Structure ID	Single-water bridges							Double-water bridges							Hphob	
	0	1	2	3	4	≥5	bur	dir	1	2	3	4	≥5	bur	acc	bur
1ZBH_AD_F	20	14	7	0	0	0	4	59	14	6	2	0	0	0	10	0
1ZBH_AD_E	20	21	13	0	0	0	0	75	13	6	6	0	0	0	7	1
1ZDJ_A_R	7	7	2	0	0	0	1	42	3	1	1	0	0	0	0	0
1ZSE_AB_R	11	14	8	2	0	0	1	56	10	7	4	1	0	0	0	0
2A8V_B_E	9	5	0	0	0	0	2	33	4	1	0	0	0	2	2	0
2A9X_1_2	17	8	3	0	0	0	1	46	6	0	0	0	0	0	6	1
2AD9_A_B	18	9	3	1	1	0	1	50	1	2	3	0	1	0	4	0
2ADC_A_C	21	12	2	0	0	0	6	53	2	0	0	0	0	3	3	1
2ADC_A_B	24	14	8	1	0	0	3	57	9	9	1	0	0	0	0	0
2AKE_A_B	12	13	1	0	0	0	3	65	3	1	3	0	0	0	8	0
2AZX_B_D	8	8	1	1	0	0	4	39	3	0	0	0	0	2	8	0
2B2E_AB_R	12	18	9	9	2	1	4	70	12	10	9	4	0	0	1	1
2B6G_A_B	5	3	0	0	0	0	2	22	2	0	0	0	0	2	2	0
2BBV_CF_N	8	7	0	0	0	0	0	33	2	1	0	0	0	0	0	0
2BGG_A_PQ	21	18	3	5	1	1	6	66	13	7	5	2	0	1	3	0
2BTE_AD_B	58	29	14	3	0	0	6	199	37	8	6	1	0	2	16	0
2BX2_L_R	6	11	2	0	2	0	0	36	11	1	2	1	0	0	6	0
2C06_AB_C	21	13	4	1	0	0	2	48	3	2	1	1	0	0	1	0
2C4R_L_R	13	21	8	0	0	0	0	79	15	3	2	1	0	0	7	0
2CSX_A_C	25	20	5	3	3	1	7	116	21	7	2	2	1	6	2	2
2CT8_A_C	21	19	8	1	0	0	8	108	17	5	3	0	0	3	2	1
2D6F_C_E	13	10	3	2	1	0	3	93	15	0	0	1	1	1	6	0
2DEU_AB_D	34	32	12	5	4	1	4	124	26	12	4	4	1	1	10	2
2DR5_A_B	41	20	7	2	0	0	8	92	7	4	2	0	0	2	4	0
2DU3_A_D	24	8	4	0	0	0	5	75	13	1	0	0	0	1	13	0
2DU5_A_D	25	13	2	2	0	0	1	90	12	0	1	0	0	0	7	0
2EC0_A_BC	25	15	11	3	2	8	16	84	29	13	5	5	2	3	3	0
2ERR_A_B	32	11	1	2	1	0	2	53	4	3	0	2	0	0	8	1
2ESE_A_B	15	8	2	1	1	0	2	40	5	2	0	0	0	1	11	0
2EZ6_AB_CD	59	47	14	4	0	0	4	240	36	13	5	1	0	0	16	0
2F8K_A_B	14	6	2	2	0	0	2	43	3	4	3	0	0	0	1	0
2F8S_A_CD	16	14	4	0	0	0	0	42	14	5	1	0	0	0	0	0
2FK6_A_R	25	15	2	0	0	0	1	92	16	2	1	0	0	1	3	0
2FY1_A_B	27	15	5	2	0	0	3	67	4	3	1	0	0	2	5	1
2G4B_A_B	19	5	0	0	0	0	6	44	1	1	0	0	0	2	0	0
2GIC_ABCDE_R	106	111	54	11	6	7	15	415	101	41	20	7	5	4	23	3
2GJE_AD_RS	27	24	6	3	2	2	1	122	13	4	4	0	0	0	3	0
2GTT_LtoV_X	204	232	115	41	15	3	42	852	227	84	21	10	3	5	47	3
2GTT_AtoK_W	213	240	131	40	6	0	39	847	247	77	27	5	1	7	41	2
2HGH_A_B	25	17	6	1	0	0	1	93	16	1	0	0	0	0	11	4
2HT1_AB_M	13	14	7	1	0	0	2	68	10	1	3	1	0	0	2	0
2I91_AB_CD	33	30	14	10	5	20	3	77	23	18	8	9	13	2	8	0
2IHX_A_B	31	30	14	4	2	0	0	118	21	7	5	0	0	0	10	0
2IPY_A_C	35	18	9	8	3	2	8	98	12	3	4	3	3	6	1	0

Structure ID	Single-water bridges							Double-water bridges							Hphob	
	0	1	2	3	4	≥5	bur	dir	1	2	3	4	≥5	bur	acc	bur
2IX1_A_B	35	32	16	3	3	3	8	119	44	10	7	1	2	3	13	0
2IY5_AB_T	30	24	6	5	3	0	3	140	15	6	2	1	0	3	20	1
2IZN_C_S	10	7	2	1	1	0	1	36	4	0	1	1	0	0	1	0
2JEA_AB_C	17	12	5	2	1	2	2	52	9	5	2	2	2	1	5	0
2JPP_AB_D	24	16	5	0	0	0	10	80	15	2	2	0	0	2	7	0
2JPP_AB_C	16	12	5	1	0	0	9	69	3	1	1	0	0	2	4	1
2KDQ_A_B	22	5	5	1	1	1	2	52	6	2	0	0	1	0	2	0
2KFY_A_B	19	9	1	0	0	0	6	33	0	1	0	0	0	1	4	1
2KH9_A_B	14	9	2	1	0	0	2	40	3	4	0	0	0	0	5	0
2KM8_BC_A	33	30	4	5	1	0	5	108	14	13	3	2	0	2	16	2
2KX5_B_A	15	9	4	0	1	0	1	52	6	0	1	0	0	0	13	0
2L2K_B_A	16	18	9	1	0	0	0	73	7	3	2	0	0	0	7	1
2L3C_A_B	17	6	1	1	1	0	1	58	5	2	2	0	0	1	11	0
2L3J_A_B	37	16	5	2	2	0	1	99	11	5	2	0	0	0	12	0
2NR0_ACD_G	33	35	18	9	6	1	1	147	24	15	10	2	1	0	15	0
2NR0_ABC_E	25	23	5	2	0	1	0	138	12	9	3	1	0	0	14	0
2NR0_CD_H	19	22	6	0	1	0	0	113	10	7	2	0	0	0	6	0
2NR0_AB_F	33	33	11	3	2	0	1	140	22	6	5	1	2	0	13	0
2NUE_AB_C	33	13	6	1	0	0	1	94	8	1	2	1	0	0	3	0
2NUG_AB_CDEF	67	46	7	5	3	8	8	191	38	18	9	5	5	2	14	3
2OZB_AB_C	30	17	7	4	2	4	9	69	17	11	4	0	6	6	5	2
2PLY_AB_C	28	22	6	2	0	0	3	102	18	6	2	0	0	2	4	0
2PY9_AC_F	24	21	5	4	1	2	4	98	11	4	1	0	0	2	6	1
2QUX_ABDE_C	27	22	4	1	0	2	3	95	19	5	1	1	1	0	2	1
2R7T_A_X	16	24	9	1	1	4	0	73	19	8	3	4	2	0	7	0
2R7V_A_X	11	15	6	2	1	0	1	47	17	6	3	2	1	0	1	0
2R8S_HL_R	19	20	10	3	2	1	7	90	22	11	3	1	1	4	8	0
2R92_AB_PT	27	46	23	3	0	0	4	122	46	30	20	1	0	3	8	0
2R93_AB_R	24	25	12	3	1	0	2	99	28	16	11	1	1	5	0	0
2RKJ_ABEF_CDG	74	63	17	4	0	0	2	342	63	17	7	4	0	3	33	0
2V3C_BCD_N	55	34	14	7	3	1	11	155	24	8	7	2	0	2	14	2
2V3C_AC_M	65	62	13	2	4	1	16	229	42	10	7	1	1	2	18	1
2W2H_AC_R	12	13	4	2	2	0	2	71	14	4	1	2	2	3	10	0
2W2H_BD_S	10	10	3	4	3	3	0	79	14	4	0	2	3	0	3	1
2WYY_ACD FHM_R	74	100	42	11	6	17	29	443	117	28	22	11	13	6	60	1
2XD0_AE_G	40	40	17	13	5	0	4	135	22	23	9	9	1	0	11	1
2XGJ_A_C	14	15	6	1	0	0	6	50	6	9	4	1	0	2	0	0
2XNR_A_C	13	7	2	0	0	0	0	35	1	4	0	0	0	0	3	0
2ZI0_AB_CD	80	40	14	3	1	0	8	172	29	25	4	0	0	1	6	0
2ZKO_AB_CD	22	27	5	1	4	1	1	79	5	3	9	10	1	1	7	0
2ZM5_AB_C	42	37	13	6	1	8	5	129	23	15	9	2	6	10	9	2
2ZNI_AB_D	47	32	11	11	3	0	8	130	29	7	3	2	0	2	11	0
2ZNI_AB_C	37	35	10	3	4	3	13	131	28	12	6	0	0	4	4	0
2ZUE_A_B	41	51	21	6	4	2	9	170	26	15	7	3	3	6	19	1

Structure ID	Single-water bridges								Double-water bridges								Hphob	
	0	1	2	3	4	≥5	bur	dir	1	2	3	4	≥5	bur	acc	bur		
2ZZM_A_B	41	40	19	10	6	8	2	166	28	18	12	2	5	4	15	0		
2ZZN_AB_C	66	55	26	10	3	2	2	238	36	24	11	7	3	4	18	0		
2ZZN_AB_D	46	47	18	6	2	1	10	178	31	12	14	4	3	5	10	1		
3A2K_AB_C	65	50	23	14	0	1	8	159	31	22	9	5	4	3	8	0		
3A2K_AB_D	58	53	22	21	2	3	6	149	26	31	8	8	6	2	13	0		
3A6P_FH_IJ	36	39	16	6	3	0	2	179	36	18	11	1	1	0	12	1		
3A6P_AC_DE	53	56	14	9	2	1	1	198	33	22	4	2	1	0	10	0		
3ADB_A_C	29	39	10	7	0	0	1	185	36	12	5	0	0	0	14	1		
3ADC_B_D	35	17	4	5	1	1	5	130	16	13	3	1	1	3	8	4		
3ADC_A_C	39	34	8	7	5	1	2	165	32	17	3	1	3	0	15	0		
3ADI_AB_DE	12	4	1	0	0	0	0	32	1	0	0	0	0	0	3	0		
3AEV_B_C	36	18	8	1	0	3	3	77	7	4	2	1	0	0	10	0		
3AKZ_ABC_E	59	43	14	10	11	6	8	229	28	13	11	7	7	7	11	0		
3AL0_BC_E	58	74	25	16	6	3	7	249	34	22	20	8	7	6	14	2		
3AM1_A_B	34	10	5	4	0	3	5	99	19	2	1	1	1	6	8	2		
3BOY_ABC_D	31	31	8	0	0	0	18	146	30	3	1	0	0	2	29	0		
3CIY_AB_CD	52	39	17	2	3	3	7	189	26	10	1	1	0	0	12	0		
3CZ3_ABCD_EF	73	44	25	6	4	0	3	181	44	8	7	0	0	0	5	1		
3CZ3_ABCD_GH	66	57	33	8	0	0	4	196	33	19	4	0	0	2	14	0		
3D2S_B_F	9	2	0	0	0	0	1	20	1	0	0	0	0	0	0	0		
3D2S_A_E	10	4	1	1	0	0	0	19	1	1	0	0	0	0	0	0		
3EPH_A_E	38	35	17	11	8	12	9	117	30	11	6	8	18	5	6	0		
3EQT_AB_CD	29	20	2	0	0	0	8	84	19	4	0	0	0	5	10	3		
3EX7_CDI_F	17	14	2	2	1	1	6	59	11	3	0	1	1	2	2	1		
3FTE_A_CD	14	13	1	1	1	0	0	55	15	4	1	1	0	0	1	1		
3GIB_ABC_H	18	18	4	4	0	0	2	69	6	2	0	0	0	3	8	4		
3HL2_ABCD_E	59	36	8	2	0	0	0	248	41	11	0	0	0	0	12	0		
3HSB_ABCD_X	29	14	2	0	0	0	7	61	4	1	0	0	0	3	9	2		
3HTX_A_BC	80	51	16	5	2	1	1	237	48	21	4	1	3	0	19	0		
3IAB_AB_R	45	41	22	8	3	6	7	172	37	23	10	1	5	3	9	0		
3ICQ_BT_D	47	45	4	0	0	0	0	191	35	7	0	0	0	0	8	0		
3IIN_A_BCD	25	17	4	1	1	0	1	78	9	0	0	0	1	1	9	0		
3IVK_AB_C	28	16	3	0	2	7	7	82	12	5	2	0	8	2	4	0		
3IWN_CD_A	33	21	12	1	0	0	3	105	14	3	3	0	0	1	10	0		
3IWN_D_B	21	16	6	2	1	0	2	67	13	5	0	1	0	0	13	1		
3KFU_DEF_M	36	28	8	6	2	1	0	126	18	8	4	2	1	0	14	3		
3KS8_ABCD_EF	37	28	10	8	5	2	2	138	21	12	9	3	0	1	6	0		
3KTV_BD_C	27	30	7	4	2	1	4	115	18	7	2	0	0	1	21	0		
3LOB_CF_R	6	4	2	0	0	0	0	31	4	2	0	0	0	0	3	0		
3M7N_DG_Y	7	16	11	5	4	1	3	38	10	4	4	4	4	2	2	0		
3MDG_A_C	10	9	5	1	0	0	2	43	13	3	0	0	0	0	8	0		
3NNC_A_B	19	9	2	0	0	0	0	57	7	3	0	0	0	0	1	3		
3NNH_AC_E	34	22	6	3	0	0	1	104	17	3	1	1	0	1	6	0		
3O3I_X_A	13	10	0	0	0	0	5	48	1	0	0	0	0	3	4	0		

Structure ID	Single-water bridges							Double-water bridges							Hphob	
	0	1	2	3	4	≥5	bur	dir	1	2	3	4	≥5	bur	acc	bur
3OG8_AB_CD	26	41	10	4	2	0	1	126	46	17	2	0	0	1	5	0
3OK7_A_BC	27	22	7	6	3	9	3	108	11	4	1	5	2	0	13	0
3OL6_AE_BCG	49	62	15	6	7	11	1	235	69	18	9	6	4	2	8	0
3OL6_A_BCD	30	44	16	7	6	11	0	161	50	18	10	5	3	2	7	0
484D_A_B	28	19	8	4	2	2	8	71	5	7	3	1	2	2	3	0
6MSF_A_R	14	3	2	2	0	0	1	49	4	1	1	1	0	0	0	0

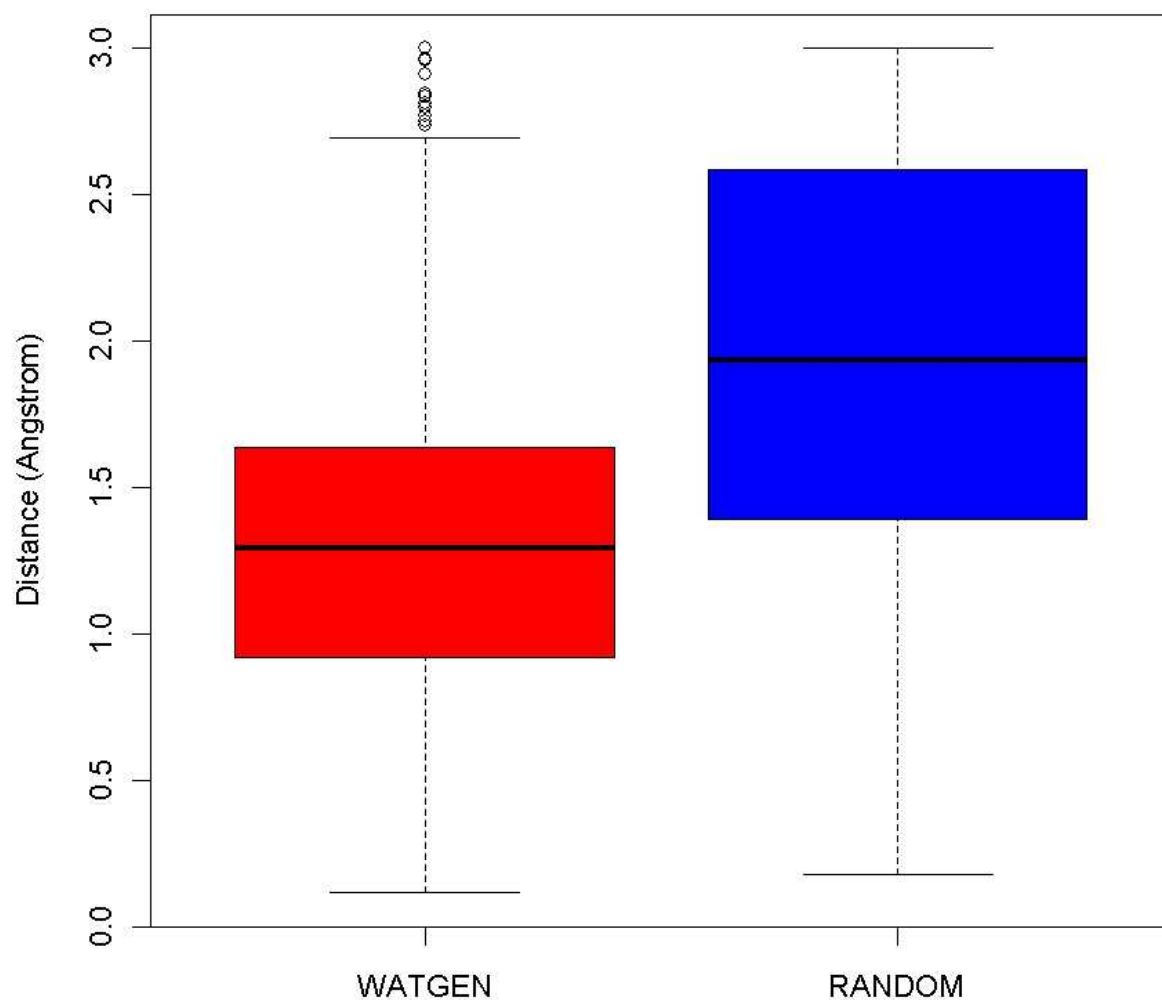


Figure S1. Boxplots of O-O distances between experimental water molecule sites and those in a WATGEN-predicted (red) or a random (blue) network. The quartiles are defined by the edges of the rectangles, which contain 50% of the data. Black horizontal lines within the boxes show medians, circles represent outliers, and dotted lines show the standard deviation. The median values are significantly different ($P < 0.001$ by Wilcoxon rank-sum test).

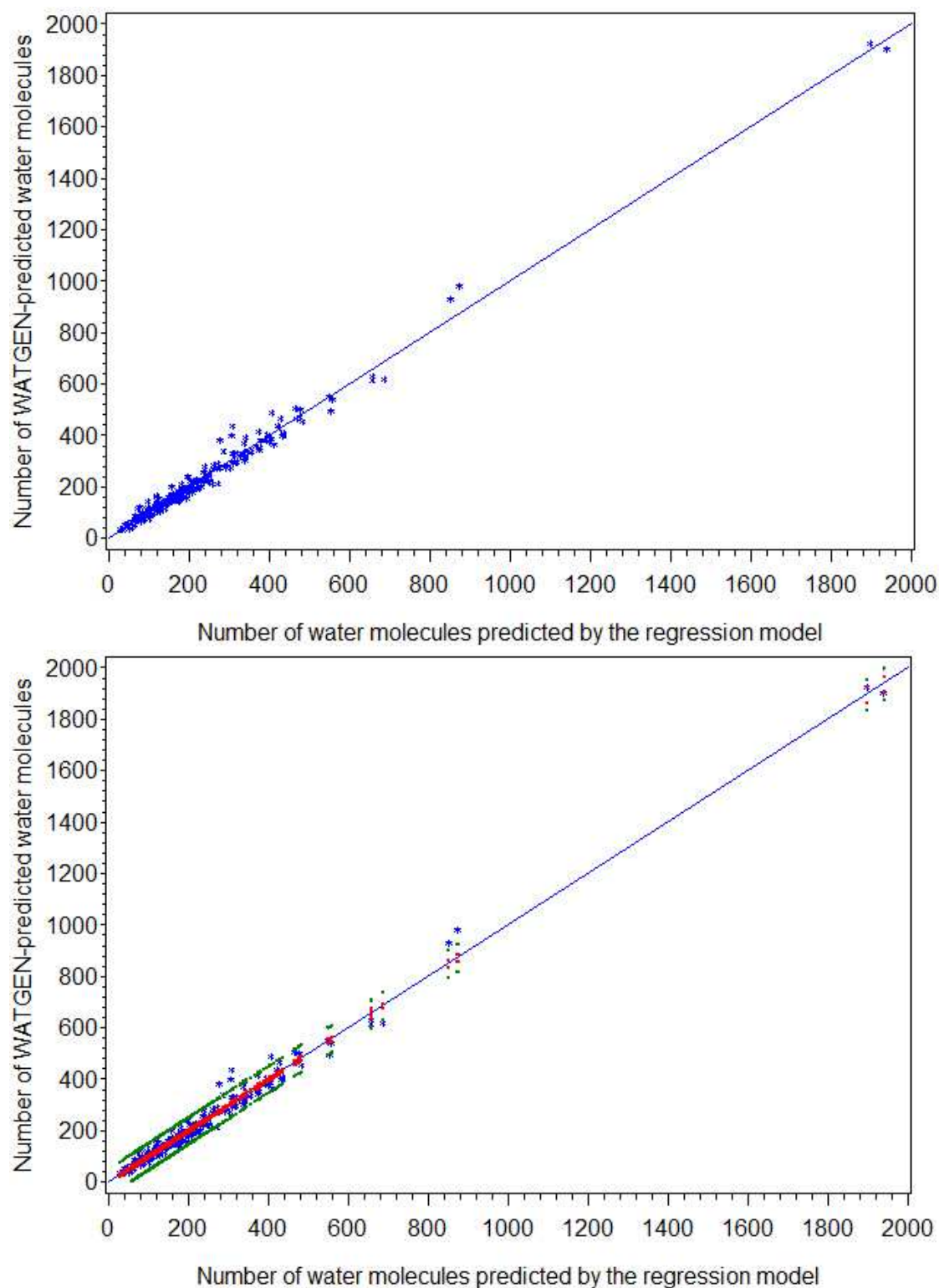


Figure S2. Upper panel. Plot of the number of WATGEN-predicted water molecules vs. the predicted value using the regression model for interface size (Eq. 1). The blue line shows the regression line. Lower panel. Identical plot, with red dots showing the 95% confidence level (CL) of the mean values and green dots showing the 95% CL of the predicted values.