Table S1. Distance analysis for the 60 highest-ranking DI pairs in exemplary RR structures of ArcA, PhoP, and MicA. Three different types of pairings are evident, which can be broken down into 3 groups. The white color identifies *group A* pairings that represent direct contacts within the monomer. Not all contacts are made in each representative structure suggesting that the majority but not all of the contacts are required to maintain the structural fold of the RR protein. In principle, this group of pairings could aid other methods in the de novo prediction of tertiary structures from sequence alone. Red color highlights *group B* parings, which involve residue positions distant in the monomer but proximal in the dimer. The fact that two of the pairings are among the top three highest DI scores strongly suggests that the dimeric mode captured in the crystal structure of ArcA, MicA and PhoP is representative for most (if not all) OmpR class RR. This has been suggested by Ann Stock *et al.* based on these 3 individual crystal structures and the observed conserved contacts at the dimer interface of OmpR/PhoB class RR proteins.[a] The results presented here give strong, independent support for this notion as they are based on unbiased survey of over 2,000 RR sequences. The determination of the physiological relevance of quaternary structures observed in protein crystals is a general problem, and DI provides a method that can aid in this determination if sufficient sequence homologues of the protein of interest exist. Additionally, this group of pairings could aid in de novo prediction of quaternary structures. Green color highlights *group C* pairings distant in both monomer and dimer structures. Without further information they would have to be considered false positives. The high DI values for these pairings can be rationalized nonetheless. All 9 pairings include at least 1 but often 2 residues on the α1-helix that are strongly correlated with SK residues as demonstrated in the first part of this article. *Group C* pairings therefore identify a heteromeric interaction surface in the absence of knowledge on the interaction partner. This group, although false positive from a distance standpoint still identifies biological function. No true false positives are present within the set of the top 60 scoring pairs (see also Fig. S7).

Rank[b]	*Res.1*[c] (ArcA)	*Res.2*[c] (ArcA)	*MI*	*DI*	d_{intra}/Å (ArcA)[d]	d_{inter}/Å (ArcA)[e]	d_{intra}/Å (PhoP)[d]	d_{inter}/Å (PhoP)[e]	d_{intra}/Å (MicA)[d]	d_{inter}/Å (MicA)[e]
1	86	106	0.611199	0.167732	16.94	3.56	18.59	3.32	18.12	2.62
2	16	32	0.490017	0.161740	2.61	43.05	3.16	42.83	3.58	41.93
3	94	115	0.348604	0.138914	20.00	2.54	19.44	6.12	19.53	5.16
4	22	107	0.561541	0.116803	3.63	28.17	3.37	31.76	3.32	30.46
5	55	63	0.257683	0.106511	3.85	28.05	3.43	27.04	4.13	27.21
6	60	68	0.235060	0.101913	2.92	42.15	2.74	40.61	4.25	40.89
7	16	34	0.286186	0.091815	3.85	42.96	3.38	43.00	3.79	41.98
8	36	60	0.332878	0.085328	5.42	46.53	3.36	43.81	3.12	44.43
9	74	76	0.327425	0.083084	3.55	15.28	3.66	20.98	3.11	14.52
10	21	22	0.440629	0.082273	1.33	36.00	1.33	40.16	1.32	38.71
11	5	29	0.210272	0.080279	3.22	33.68	3.17	32.71	3.38	34.17

Rank	*Res 1*	*Res 2*	*MI*	*DI*	d_{intra}/Å (ArcA)	d_{inter}/Å (ArcA)	d_{intra}/Å (PhoP)	d_{inter}/Å (PhoP)	d_{intra}/Å (MicA)	d_{inter}/Å (MicA)
12	31	48	0.363316	0.080277	3.70	33.55	4.97	32.45	4.94	34.22
13	18	107	0.489920	0.079927	6.28	29.95	3.86	32.95	3.70	29.74
14	75	76	0.432310	0.079010	1.32	16.28	1.33	16.76	1.32	15.97
15	20	32	0.269666	0.076259	2.95	41.45	3.15	41.50	4.27	40.75
16	73	75	0.438267	0.075436	3.42	21.69	3.39	21.88	2.99	20.83
17	14	18	0.439360	0.075339	2.90	38.73	2.86	42.22	3.20	37.75
18	5	31	0.295489	0.075185	3.69	35.14	2.86	34.07	4.24	35.23
19	55	79	0.243911	0.074393	3.52	21.79	3.52	20.92	2.82	20.01
20	66	77	0.204452	0.073625	3.84	22.23	3.82	19.99	4.13	21.28
21	35	59	0.242352	0.072497	6.01	48.53	2.98	47.47	3.50	48.25
22	59	60	0.263583	0.072308	1.33	47.81	1.29	46.36	1.34	47.89
23	40	68	0.216704	0.067064	3.28	40.14	2.68	39.63	3.49	38.52
24	14	21	0.359937	0.065812	7.55	41.28	7.24	43.70	7.82	41.30
25	18	22	0.482512	0.062194	2.81	33.66	2.98	38.44	3.09	35.30
26	21	87	0.251904	0.061940	27.02	21.39	29.90	19.73	28.11	18.30
27	32	34	0.226270	0.061609	4.49	46.03	4.26	44.88	3.48	44.67
28	86	108	0.318099	0.061052	20.70	7.14	21.18	3.61	22.16	3.60
29	106	108	0.324956	0.061042	2.61	22.04	3.03	23.43	3.21	21.78
30	22	25	0.321672	0.060759	3.47	36.01	3.28	40.34	3.38	39.48
31	87	91	0.422243	0.060563	2.85	26.05	2.85	23.78	2.91	25.63
32	40	60	0.295020	0.060015	5.94	45.39	5.15	43.85	3.66	43.05
33	31	42	0.219545	0.059447	3.92	41.23	3.42	40.66	4.28	40.97
34	60	64	0.280812	0.059176	3.39	41.74	3.43	39.93	3.75	40.61
35	21	25	0.297985	0.059068	2.83	40.41	2.71	43.04	2.94	42.22
36	14	22	0.380686	0.056883	8.59	36.39	8.90	39.59	8.54	37.59
37	26	111	0.225573	0.056512	3.63	27.20	--	--	3.21	27.35
38	14	25	0.278020	0.055051	13.42	40.75	12.29	43.16	13.46	41.54
39	33	42	0.243250	0.054726	4.28	44.02	3.75	43.37	4.18	43.50
40	89	109	0.340556	0.053978	8.20	3.07	8.48	3.98	9.12	3.67
41	91	95	0.306397	0.053895	2.77	26.59	2.86	25.77	2.92	26.78
42	63	95	0.211523	0.053654	4.31	27.92	4.16	26.95	3.78	28.40
43	21	107	0.305527	0.053066	7.89	32.68	7.05	35.00	6.79	33.55
44	4	5	0.287063	0.053065	1.32	28.48	--	--	1.32	26.86
45	56	83	0.303691	0.052872	4.66	25.13	5.06	25.51	3.86	25.97
46	18	25	0.312785	0.052791	7.65	38.60	7.18	41.59	7.82	39.61
47	18	21	0.334243	0.051963	2.67	38.55	3.20	41.94	3.50	38.82

Rank	*Res 1*	*Res 2*	*MI*	*DI*	d_{intra}/Å (ArcA)	d_{inter}/Å (ArcA)	d_{intra}/Å (PhoP)	d_{inter}/Å (PhoP)	d_{intra}/Å (MicA)	d_{inter}/Å (MicA)
48	17	21	0.232975	0.051154	2.88	41.52	2.96	43.55	2.88	41.64
49	14	87	0.225235	0.051086	23.58	24.45	26.90	21.08	24.51	21.46
50	73	76	0.437336	0.050892	6.86	19.21	6.13	21.85	6.16	17.93
51	74	75	0.255255	0.050543	1.32	17.22	1.32	20.83	1.33	17.05
52	63	91	0.247030	0.049706	4.16	27.10	3.73	25.31	4.19	27.06
53	14	32	0.245557	0.049546	8.36	44.52	8.46	44.71	9.89	43.36
54	39	43	0.267087	0.049513	2.92	36.25	2.85	37.30	2.84	36.74
55	22	108	0.312342	0.049257	6.03	26.30	5.57	29.96	6.65	28.83
56	25	107	0.294790	0.049179	8.38	33.58	8.87	35.93	9.33	34.94
57	40	65	0.178179	0.048446	4.30	40.03	4.51	39.12	4.06	37.82
58	36	65	0.270694	0.048385	3.86	41.64	3.82	39.79	3.61	39.88
59	22	111	0.213060	0.047837	3.32	26.66	--	--	3.18	28.91
60	73	74	0.258889	0.047544	1.33	20.40	1.33	26.11	1.32	19.59

[a] Toro-Roman A, Mack TR, Stock AM (2005) Structural analysis and solution studies of the activated regulatory domain of the response regulator ArcA: A symmetric dimer mediated by the [alpha]4-[beta]5-[alpha]5 face. *J Mol Biol* 349:11-26.

[b] Rank based on DI values

[c] Res1 and Res2: All residue numbering is based on the ArcA sequence

[d] d_{intra}: residue distance within the monomer of the respective structure in Å

[e] d_{inter}: residue distance between monomers within the dimer of the respective structure in Å