

Supporting Information for:  
Energy-Screened Many-Body Expansion for Protein–Ligand  
Interactions: Examining Convergence for Metalloenzymes through  
Seven-Body Interactions

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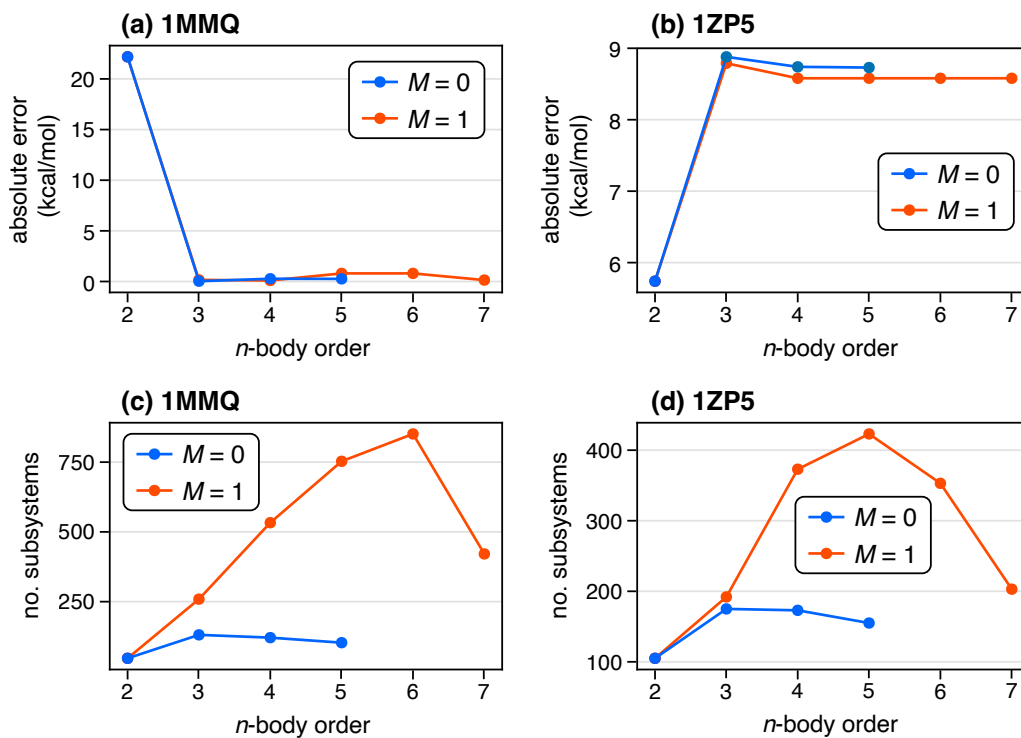


Figure S1: Upper panels: comparison of  $\text{MBE}(n)$  accuracy with  $M > 0$  versus  $M > 1$  as a screening threshold, for (a) 1MMQ and (b) 1ZP5 at the HF-3c level. Lower panels: number of unique subsystems generated for (c) 1MMQ and (d) 1ZP5. Screening thresholds were set to  $\tau_{2B} = 0.25$  kcal/mol and  $\tau_{3B} = 0.05$  kcal/mol for 1MMQ, and to  $\tau_{2B} = 0.05$  kcal/mol and  $\tau_{3B} = 0.05$  kcal/mol for 1ZP5.

Table S1: HF-3c results for 1MMQ as a function of  $n$ -body order.

$n$	$\tau_{2B}$	$\tau_{3B}$	no distance screening				$d_2 = 8 \text{ \AA}$			
			$N$	error  (kcal/mol)	error /frag. (kcal/mol)	$t_{CPU}$ (h)	$N$	error  (kcal/mol)	error /frag. (kcal/mol)	$t_{CPU}$ (h)
2	none	none	–	–	–	–	83	21.4	0.13	4.1
3	none	none	–	–	–	–	833	1.0	0.01	69.4
2	0.25	0.025	47	22.2	0.13	2.6	41	22.0	0.13	2.4
3	0.25	0.025	425	0.2	0.00	43.5	187	0.7	0.00	20.8
4	0.25	0.025	1301	0.0	0.00	230.5	491	0.6	0.00	93.8
5	0.25	0.025	2243	0.0	0.00	570.3	733	0.5	0.00	190.8
6	0.25	0.025	2503	0.1	0.00	839.5	687	0.5	0.00	225.9
7	0.25	0.025	1941	0.1	0.00	732.5	241	0.5	0.00	94.3
2	0.25	0.050	47	22.2	0.13	1.9	31	23.7	0.14	1.9
3	0.25	0.050	259	0.2	0.00	27.1	147	0.8	0.00	17.3
4	0.25	0.050	533	0.1	0.00	108.7	343	0.8	0.00	72.2
5	0.25	0.050	753	0.8	0.00	230.3	445	0.7	0.00	133.9
6	0.25	0.050	851	0.8	0.00	333.9	371	0.7	0.00	145.8
7	0.25	0.050	421	0.1	0.00	218.0	159	0.7	0.00	65.3
2	0.50	0.050	31	23.7	0.14	1.9	31	23.7	0.14	1.9
3	0.50	0.050	249	0.9	0.01	27.1	141	0.1	0.00	16.9
4	0.50	0.050	513	0.8	0.00	108.7	331	0.2	0.00	71.1
5	0.50	0.050	753	0.8	0.00	230.3	441	0.1	0.00	133.7
6	0.50	0.050	851	0.8	0.00	333.9	367	0.1	0.00	145.6
7	0.50	0.050	403	0.8	0.00	218.0	153	0.1	0.00	65.0
2	0.75	0.050	27	24.8	0.15	1.8	27	24.8	0.15	1.8
3	0.75	0.050	241	1.3	0.01	26.5	139	0.3	0.00	16.6
4	0.75	0.050	475	1.2	0.01	100.7	413	0.3	0.00	67.6
5	0.75	0.050	661	1.2	0.01	201.4	317	0.2	0.00	124.7
6	0.75	0.050	729	1.2	0.01	283.5	361	0.3	0.00	141.8
7	0.75	0.050	309	1.2	0.01	161.8	147	0.3	0.00	61.3
2	0.75	0.075	27	24.8	0.15	1.8	27	24.8	0.15	1.8
3	0.75	0.075	195	1.3	0.01	22.7	119	0.5	0.00	14.7
4	0.75	0.075	351	1.1	0.01	79.2	251	0.3	0.00	57.9
5	0.75	0.075	485	1.2	0.01	153.9	341	0.4	0.00	108.5
6	0.75	0.075	535	1.2	0.01	204.2	263	0.4	0.00	109.6
7	0.75	0.075	183	1.2	0.01	75.6	117	0.4	0.00	56.8
2	1.00	0.050	27	24.8	0.15	1.8	27	24.8	0.15	0.3
3	1.00	0.050	231	1.1	0.01	25.7	131	0.1	0.00	16.1
4	1.00	0.050	461	1.1	0.01	98.5	309	0.1	0.00	66.8
5	1.00	0.050	653	1.1	0.01	198.8	405	0.2	0.00	122.6
6	1.00	0.050	723	1.1	0.01	281.3	357	0.2	0.00	140.5
7	1.00	0.050	297	1.1	0.01	158.0	137	0.2	0.00	58.8

Table S2: HF-3c results for 1ZP5 as a function of  $n$ -body order.

$n$	$\tau_{2B}$	$\tau_{3B}$	no distance screening				$d_2 = 8 \text{ \AA}$			
			$N$	error  (kcal/mol)	error /frag. (kcal/mol)	$t_{CPU}$ (h)	$N$	error  (kcal/mol)	error /frag. (kcal/mol)	$t_{CPU}$ (h)
2	none	none	–	–	–	–	103	5.3	0.03	2.0
3	none	none	–	–	–	–	6059	10.2	0.06	503.0
2	0.05	0.050	105	5.7	0.04	2.2	75	5.5	0.03	1.8
3	0.05	0.050	192	8.8	0.06	12.9	145	8.7	0.05	9.7
4	0.05	0.050	373	8.6	0.05	53.5	263	8.4	0.05	35.0
5	0.05	0.050	423	8.6	0.05	89.5	255	8.4	0.05	52.7
6	0.05	0.050	353	8.6	0.05	77.9	183	8.4	0.05	38.7
7	0.05	0.050	203	8.6	0.05	42.3	131	8.4	0.05	24.5
2	0.10	0.050	85	6.2	0.04	1.9	75	5.5	0.03	1.8
3	0.10	0.050	175	9.2	0.06	12.6	145	8.7	0.05	9.7
4	0.10	0.050	355	9.0	0.06	53.2	263	8.7	0.05	35.0
5	0.10	0.050	405	9.0	0.06	89.2	255	8.4	0.05	52.7
6	0.10	0.050	335	9.0	0.06	77.6	183	8.4	0.05	38.7
7	0.10	0.050	185	9.0	0.06	42.0	131	8.4	0.05	24.5
2	0.25	0.025	47	7.0	0.04	1.3	45	7.3	0.05	1.3
3	0.25	0.025	269	10.0	0.06	18.4	119	9.9	0.06	9.3
4	0.25	0.025	775	10.0	0.06	105.8	233	9.5	0.06	33.8
5	0.25	0.025	1063	9.9	0.06	227.6	229	9.6	0.06	51.6
6	0.25	0.025	1037	9.9	0.06	267.8	155	9.6	0.06	36.9
7	0.25	0.025	813	9.9	0.06	222.6	103	9.6	0.06	22.7
2	0.25	0.050	47	7.0	0.04	1.3	45	7.3	0.05	1.3
3	0.25	0.050	157	10.1	0.06	12.3	119	9.9	0.06	9.3
4	0.25	0.050	333	9.8	0.06	52.2	233	9.5	0.06	33.8
5	0.25	0.050	387	9.8	0.06	88.2	229	9.6	0.06	51.6
6	0.25	0.050	315	9.8	0.06	75.9	155	9.6	0.06	36.9
7	0.25	0.050	165	9.8	0.06	40.3	103	9.6	0.06	22.7
2	0.50	0.050	35	7.5	0.05	1.0	35	7.5	0.05	1.0
3	0.50	0.050	137	10.4	0.07	11.7	103	10.2	0.06	8.7
4	0.50	0.050	275	10.1	0.06	47.0	183	9.9	0.06	28.9
5	0.50	0.050	335	10.1	0.06	78.7	180	9.9	0.06	41.5
6	0.50	0.050	231	10.1	0.06	57.3	77	9.9	0.06	18.2
7	0.50	0.050	129	10.1	0.06	35.3	77	9.9	0.06	18.2
2	0.75	0.050	29	9.2	0.06	1.0	29	9.2	0.06	1.0
3	0.75	0.050	329	11.0	0.07	19.5	101	10.7	0.07	8.5
4	0.75	0.050	265	10.4	0.07	45.2	175	10.3	0.06	27.5
5	0.75	0.050	319	10.4	0.07	74.9	166	10.3	0.06	38.1
6	0.75	0.050	223	10.4	0.07	54.9	73	10.3	0.06	16.3
7	0.75	0.050	121	10.4	0.07	32.8	73	10.3	0.06	16.3

Table S3: Aggregate  $n$ -body contributions corresponding to the histogram data in Fig. 6 (HF-3c level).

$n$	1MMQ <sup>a</sup>		1ZP5 <sup>b</sup>	
	$N$	$\Delta E_{\text{int},n}^c$ (kcal/mol)	$N$	$\Delta E_{\text{int},n}^c$ (kcal/mol)
2	36	-156.724	61	-70.896
3	102	-21.532	136	3.180
4	164	-0.031	98	-40.040
5	75	0.027	41	-0.057
6	23	0.012	4	0.003

<sup>a</sup>Using  $\tau_{2\text{B}} = 0.25$  kcal/mol,  $\tau_{3\text{B}} = 0.05$  kcal/mol, and  $M = 1$ . <sup>b</sup>Using  $\tau_{2\text{B}} = 0.05$  kcal/mol,  $\tau_{3\text{B}} = 0.05$  kcal/mol, and  $M = 1$ .  
<sup>c</sup>Net  $n$ -body contribution to  $\Delta E_{\text{int}}$ .

Table S4:  $\omega\text{B97X-V}$  results for 1MMQ in various basis sets.

Basis Set	$n$	Energy Screening <sup>a</sup>			Energy + Distance Screening <sup>b</sup>		
		$N$	$\Delta E_{\text{int}}$ (kcal/mol)	$t_{\text{CPU}}$ (h)	$N$	$\Delta E_{\text{int}}$ (kcal/mol)	$t_{\text{CPU}}$ (h)
def2-ma-SVP	2	31	-129.5	40	31	-129.5	40
	3	249	-147.7	509	141	-149.0	326
	4	513	-148.0	1876	331	-149.3	1240
	5	753	-148.4	4220	441	-149.5	2497
	6	851	-148.3	6236	367	-149.5	2806
	7	403	-148.3	4124	153	-149.5	1225
def2-ma-TZVP	2	31	-116.2	182	31	-116.2	182
	3	249	-135.8	2250	141	-137.2	1489
	4	513	-135.5	8528	331	-136.9	5715
	5	753	-135.8	18878	441	-137.0	11363
	6	851	-135.7	27142	367	-136.9	12550
	7	403	-135.7	15935	153	-136.9	5279
def2-ma-QZVP	2	31	-115.7	1992	31	-115.7	1992
	3	249	-135.9	24095	141	-137.4	15904

<sup>a</sup>Using  $\tau_{2\text{B}} = 0.5$  kcal/mol and  $\tau_{3\text{B}} = 0.05$  kcal/mol. <sup>b</sup>Using  $\tau_{2\text{B}} = 0.5$  kcal/mol,  $\tau_{3\text{B}} = 0.05$  kcal/mol, and  $d_2 = 8$  Å.

Table S5:  $\omega$ B97X-V results for 1ZP5 in various basis sets.

Basis Set	$n$	Energy Screening <sup>a</sup>			Energy + Distance Screening <sup>b</sup>		
		$N$	$\Delta E_{\text{int}}$ (kcal/mol)	$t_{\text{CPU}}$ (h)	$N$	$\Delta E_{\text{int}}$ (kcal/mol)	$t_{\text{CPU}}$ (h)
def2-ma-SVP	2	35	-74.5	28	35	-74.5	28
	3	137	-75.1	265	103	-75.0	205
	4	275	-76.5	1093	183	-76.4	691
	5	335	-77.0	1836	180	-76.9	995
	6	231	-77.0	1340	77	-76.8	433
	7	129	-77.0	822	77	-76.8	433
def2-ma-TZVP	2	35	-60.7	135	35	-60.7	135
	3	137	-59.9	1315	103	-59.8	156
	4	275	-61.0	5588	183	-60.8	3541
	5	335	-61.2	9609	180	-61.0	798
	6	231	-61.1	7146	77	-61.0	2342
	7	129	-61.1	4397	77	-61.0	2342
def2-ma-QZVP	2	35	-58.6	1421	35	-58.6	1421
	3	137	-58.1	13611	103	-58.0	10640

<sup>a</sup>Using  $\tau_{2\text{B}} = 0.5$  kcal/mol and  $\tau_{3\text{B}} = 0.05$  kcal/mol. <sup>b</sup>Using  $\tau_{2\text{B}} = 0.5$  kcal/mol,  $\tau_{3\text{B}} = 0.05$  kcal/mol, and  $d_2 = 8$  Å.