FACTS: Fast Analytical Continuum Treatment of Solvation

Supplementary Material

Urs Haberthür and Amedeo Caflisch*

Department of Biochemistry, University of Zurich

Winterthurerstrasse 190, CH-8057 Zurich, Switzerland

E-mail: caflisch@bioc.uzh.ch

Phone: +41 44 635 55 21

Fax: +41 44 635 68 62

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*Corresponding author

1 Dependency of FACTS Parameters on Training Set of Proteins

Two different tests are performed to assess the dependency of the FACTS solvation parameters on the training set. The first test is a one-against-all, the second one is a leave-one-out.

In the one-against-all test two different setups are chosen. In the first setup, training and test sets are identical and consist of all proteins. In the second one, training and test sets are disjoint; the training set consists only of the native state of 1a2p, and the test set of all proteins without the native state of 1a2p. The results are shown in Table 1 and Figures 1 and 2. They demonstrate that the dependency of the FACTS parameters on the training set is marginal - there is no impact on accuracy.

In the leave-one-out test a total of ten different FACTS parameter sets are derived by fitting on all possible combinations of nine structures out of a set of ten structures. Averages and variations are evaluated and given in Table 2. They demonstrate the stability of the FACTS parameters with respect to different training sets.

The FACTS parameters for PARAM19 and PARAM22 for $\varepsilon_m = 1$ and $\varepsilon_m = 2$ are given in Tables 3, 4, 5, 6, 7, and 8.

2 Atomic (or Self) Electrostatic Solvation Energy With Interior Dielectric $\varepsilon_m = 2$

Figure 3 shows atomic solvation energy values calculated by FACTS, GBMV2, and GBMVgrid versus the benchmark fdP values with $\varepsilon_m = 2$. The numerical approach GBMVgrid is the most accurate method, followed by GBMV2 and FACTS. However, the maximal absolute error is largest for GBMV2 because of some significant outliers, yet its statistical spread is between the one of FACTS and GBMVgrid. This is observed for both PARAM19 and PARAM22.

3 Atomic SASA

Figure 4 compares SASA values calculated by FACTS and the Hasel formula [1]. The accuracy of the FACTS SASA suffer from the large R_i^{sphere}, in particular for small molecules. For computational efficiency reasons, the sphere radii were not optimized for the atomic SASA but set equal to those of the electrostatic atomic solvation energy.

4 Pairwise Electrostatic Energies and Their Sums

The results for $\epsilon_m = 1$ and $\epsilon_m = 2$ are given in Figures 5, 6, 7, and 8. For FACTS, if not specified otherwise, $\kappa = 12$. For GBMV2 and GBMVgrid $\kappa = 8$.

5 Electrostatic Solvation Energy of Protein Conformations

Results are shwon in Tables 9, 10, 11, 12, and 13. For FACTS, if not specified otherwise, $\kappa = 12$. For GBMV2 and GBMVgrid $\kappa = 8$.

6 Energy in Solution

The electrostatic free energy of solvation ΔG can be written as the sum of a self-energy term and an interaction energy term

$$\Delta G = \sum_i \Delta G_i + \sum_{i<j} \left(G_{ij}^{sl} - G_{ij}^{vac} \right) \tag{1}$$

where the superscript sl indicates the solvent. The electrostatic free energy in solution G can be formally written as the sum of electrostatic free energy in vacuo G^{vac} and ΔG [2]

$$G = \Delta G + G^{vac} \tag{2}$$

Assuming that the solute (macromolecule) has the same dielectric constant as vacuo (i.e., $\varepsilon_m = 1$), one has a system with homogeneous dielectric response where Born's self energy formula and Coulomb's law apply, so that

$$G^{vac} = \sum_i \frac{q_i^2}{2\varepsilon_m r_i^{vdW}} + \sum_{i<j} \frac{q_i q_j}{\varepsilon_m r_{ij}} \tag{3}$$

Note that ε_m is kept in the above equation because the homogeneous dielectric response is present for a solute in any environment with $\varepsilon_{out} = \varepsilon_m$. The value of $\varepsilon_m = 1$ is usually adopted to be consistent with the assumptions under which the partial charge of common force fields have been derived [3]. Combining Equations (1), (2), and (3), the electrostatic free energy in solution can be written as

$$G = \sum_i \Delta G_i + \sum_i \frac{q_i^2}{2\varepsilon_m r_i^{vdW}} + \sum_{i<j} G_{ij}^{sl} \tag{4}$$

It is important to note that the Born term $\sum_i \frac{q_i^2}{2\varepsilon_m r_i^{vdW}}$ is an additive constant because it does not depend on the solute configuration.

It has been shown previously that a high correlation between approximated and exact solvation energies does not necessarily imply a good correlation between approximated and exact energies in solution [4, 5]. This is because vacuo pair interaction energies can always be calculated exactly and they dominate the correlation between approximated and exact solvation energies. Eliminating vacuo energies from the comparison, i.e., comparing energies in solution instead of solvation energies, is therefore another useful test of the accuracy of a solvation model [4, 5].

For this purpose high temperature unfolding simulations at 450 K for 50 ns using an implicit solvation model [6]

of 29 proteins were performed. Coordinates were saved every 10 ps and all snapshots were sorted according to increasing radius of gyration (RG). A total of 100 conformations were chosen from each trajectory as follows: every 20th conformation from the 500 snapshots with the lowest RG (25 conformations), every 20th conformation from the 500 snapshots with the largest RG (25 conformations), and every 80th conformation from the remaining 4000 snapshots (50 conformations). The 100 conformations of each protein cover a wide range of RMSD and RG. For each structure in every trajectory the quantity G was calculated according to Equations (4), for FACTS, GBMV2, and GBMVgrid, and compared to the fdP values. Note that the Born term $\sum_i \frac{q_i^2}{2\varepsilon_m r^{vdW}}$ in Equation (4) is neglected since it is an additive constant as mentioned above. The results are shown in Figure 9 and Tables 14, 15, and 16.

7 Molecular Dynamics Results with FACTS PARAM19

Table 17 shows the results of 100-ns molecular dynamics runs with FACTS PARAM19 (i.e., polar hydrogen CHARMM force field [3]).

References

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8 Supplementary Figures

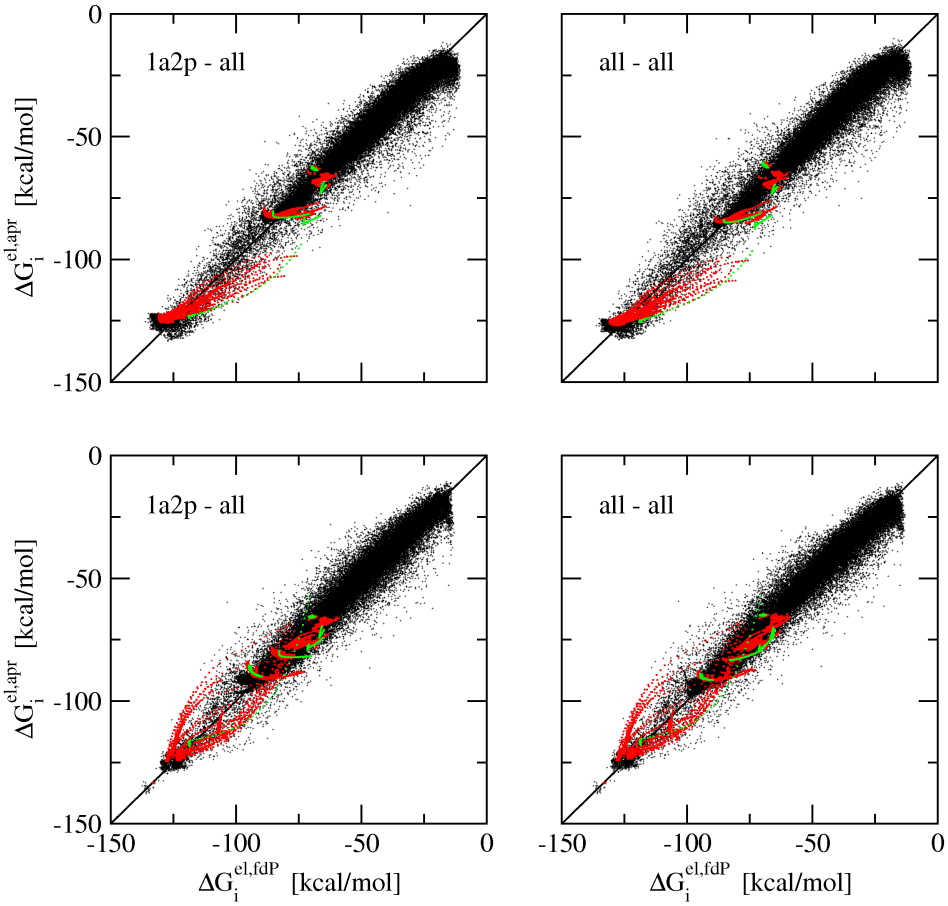

Figure 1: Cross validation of FACTS solvation parameters ($\varepsilon_m = 1$). On the abscissa the exact values are given, and on the ordinate the approximated values. In the left column, training and test set are disjoint. The training set consists only of the native state of 1a2p and the test set of all protein structures but the native state of 1a2p, pairs of ionic side chains, and the conformations of the N-methyl-acetamide dimer. In the right column, the training set consists of all protein structures and the test set of all protein structures, pairs of ionic side chains, and the conformations of the N-methyl-acetamide dimer. Unit charges are used because they allow for a more stringent comparison that is not affected by the charge parameter set. The protein conformations are in black, the pairs of ionic side chains in red, and the conformations of the N-methyl-acetamide dimer in green. There is essentially no difference between the results obtained with the two parameter sets. (Top): Atomic solvation energy values of 77'609 atoms from 1'082 structures from 37 molecular systems calculated with the van der Waals radii from PARAM19. (Bottom) Atomic solvation energy values of 90'747 atoms from 1'073 structures from 32 molecular systems calculated with the van der Waals radii from PARAM22.

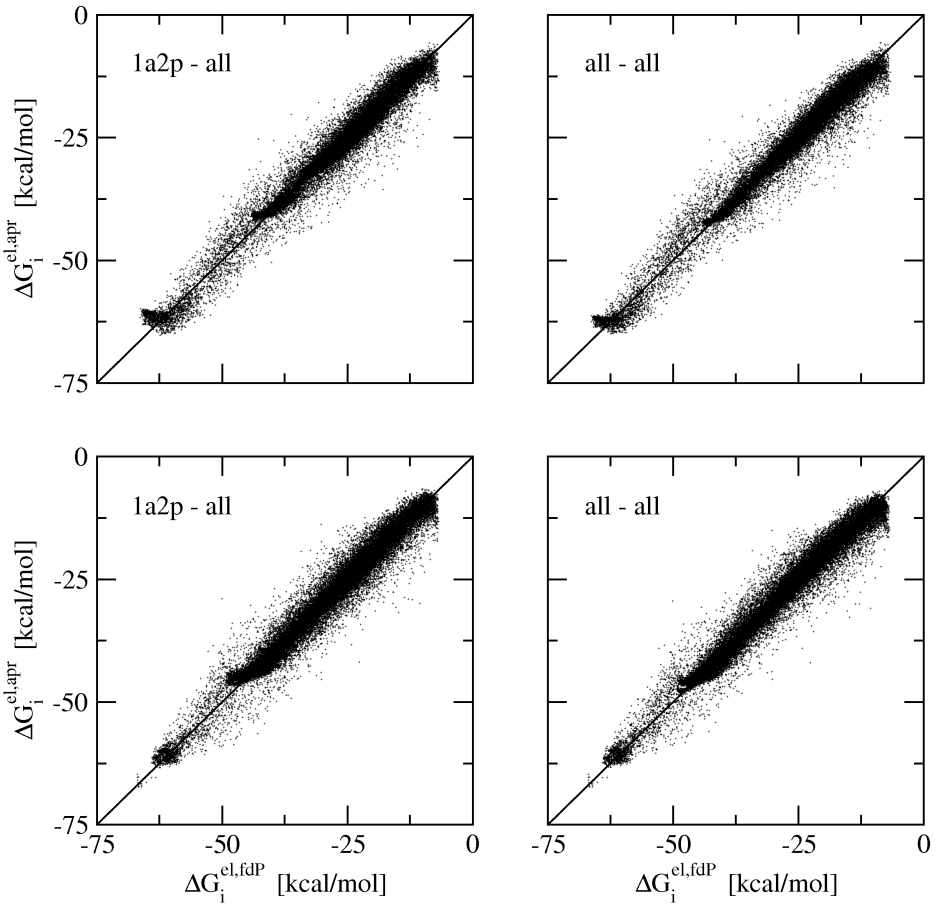

Figure 2: Cross validation of FACTS solvation parameters ($\varepsilon_m = 2$). See legend of Figure 1 for details.

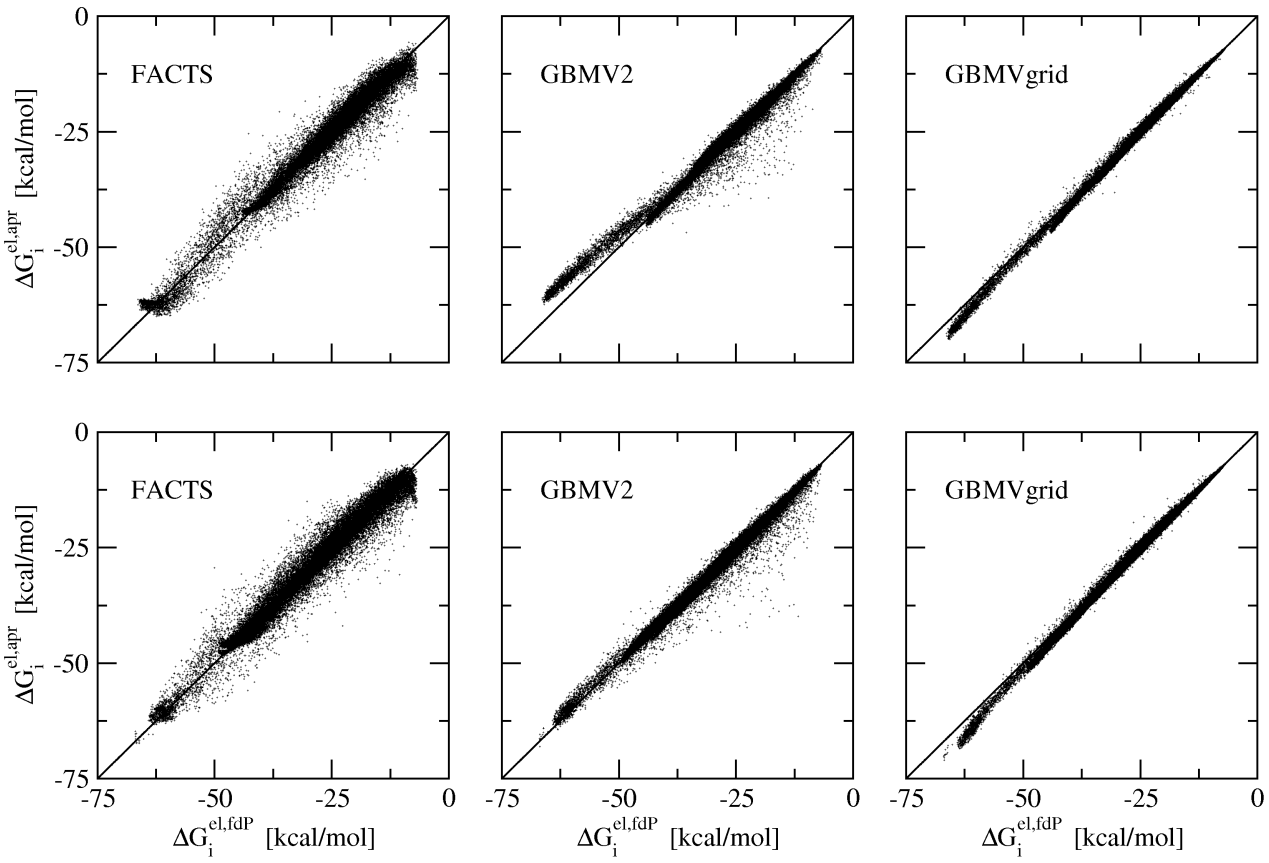

Figure 3: Comparison between FACTS and GBMV. The plot shows the atomic electrostatic solvation energy evaluated with unit charges and $\varepsilon_m = 2$ for PARAM19 (top) and PARAM22 (bottom). Unit charges are used because they allow for a more stringent comparison that is not affected by the charge parameter set. On the abscissa the fdP derived values are given, and on the ordinate the approximated values. (Top) Slope, correlation, and maximal absolute error for the 31'036 atoms from 63 protein structures are 0.969, 0.984, and 17.4 kcal/mol for FACTS; 0.919, 0.991, and 21.3 kcal/mol for GBMV2 [9]; 1.042, 0.998, and 7.8 kcal/mol for GBMVgrid [10]. (Bottom) Slope, correlation, and maximal absolute error for the 38'514 atoms from 57 structures are 0.967, 0.983, and 20.7 kcal/mol for FACTS; 0.977, 0.994, and 28.2 kcal/mol for GBMV2; 1.053, 0.998, and 6.9 kcal/mol for GBMVgrid.

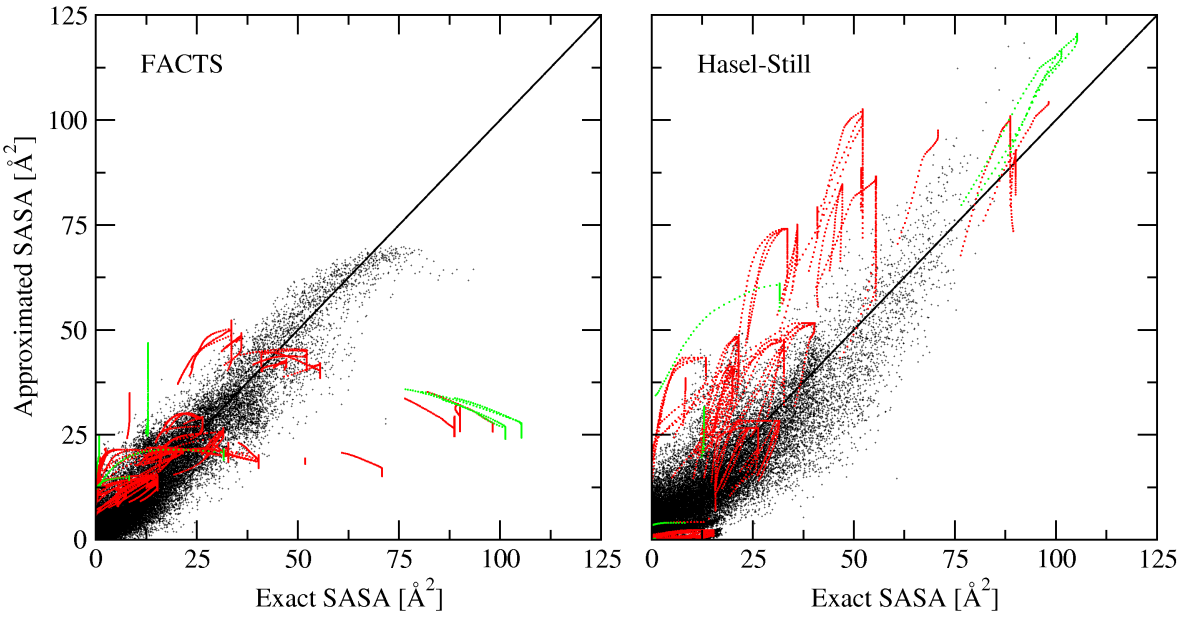

Figure 4: Atomic SASA of 1'082 structures with PARAM19 and $\varepsilon_m = 1$. In the left plot the data are obtained with the FACTS model, and in the right plot with the approximated formula by Hasel et al. [1]. The benchmark are the exact values of atomic SASA [11]. The color coding is the same as in Figure 1.

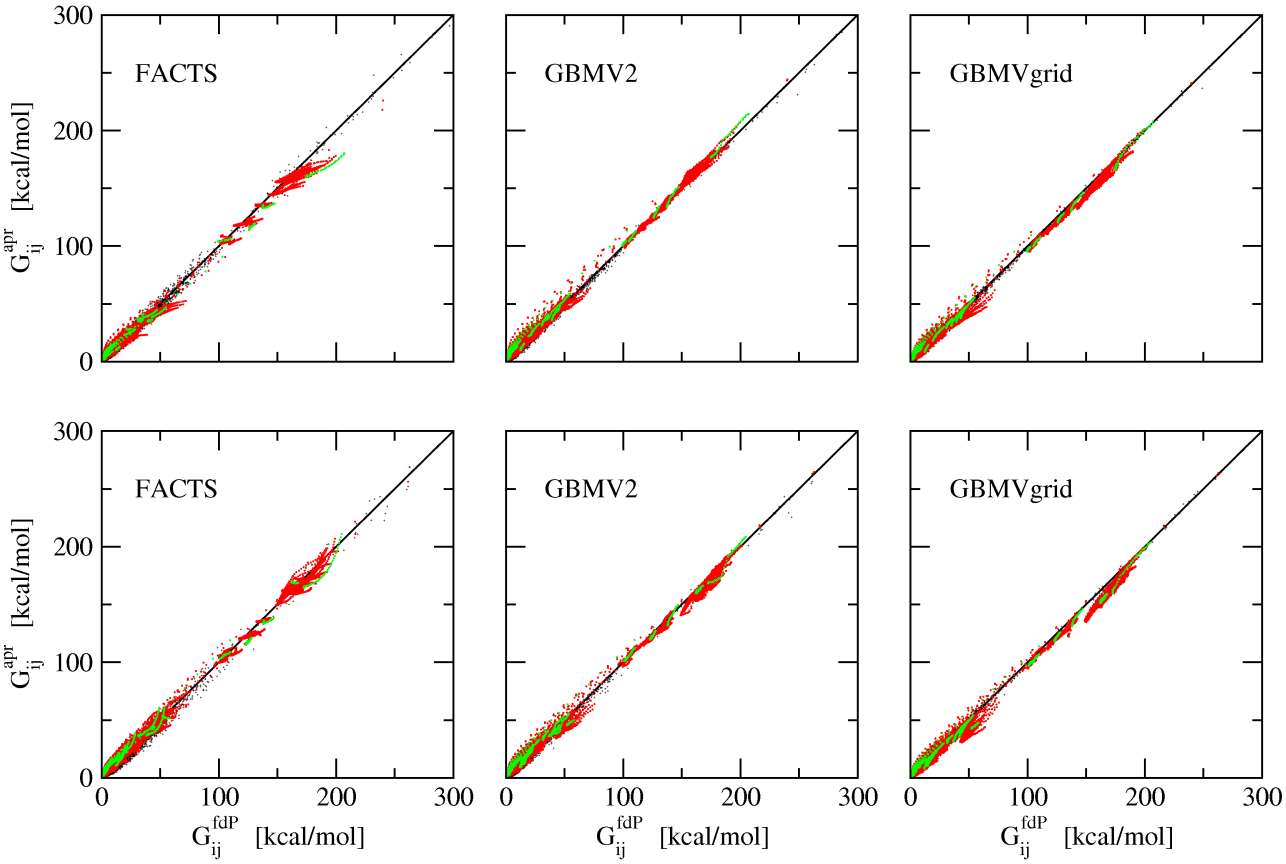

Figure 5: Interaction energy values for PARAM19 (top) and PARAM22 (bottom), $\varepsilon_m = 1$, and unit charges for all atoms. On the abscissa the fdP derived values are given, and on the ordinate the approximated values. The color coding is the same as in Figure 1.

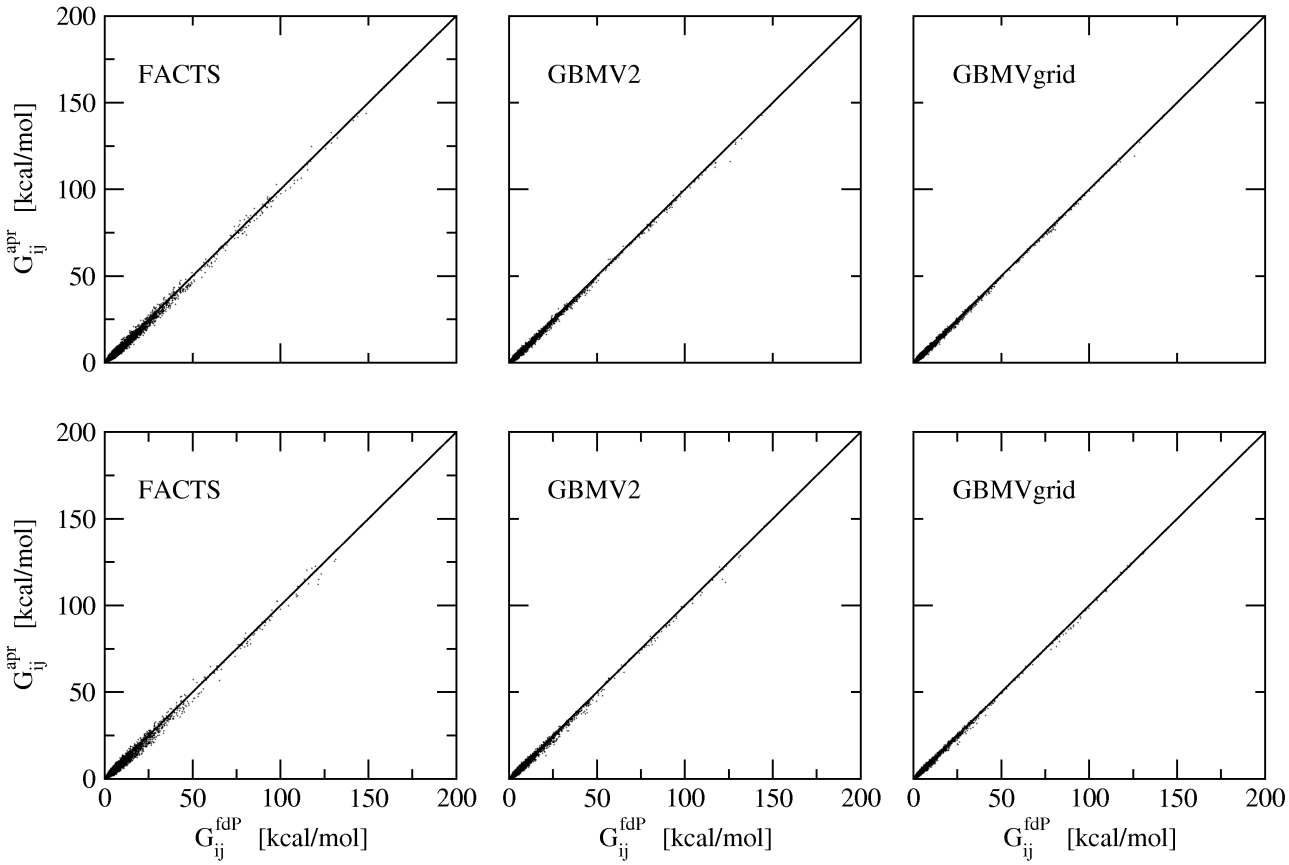

Figure 6: Interaction energy values for PARAM19 (top) and PARAM22 (bottom), $\varepsilon_m = 2$, and unit charges for all atoms. On the abscissa the fdP derived values are given, and on the ordinate the approximated values.

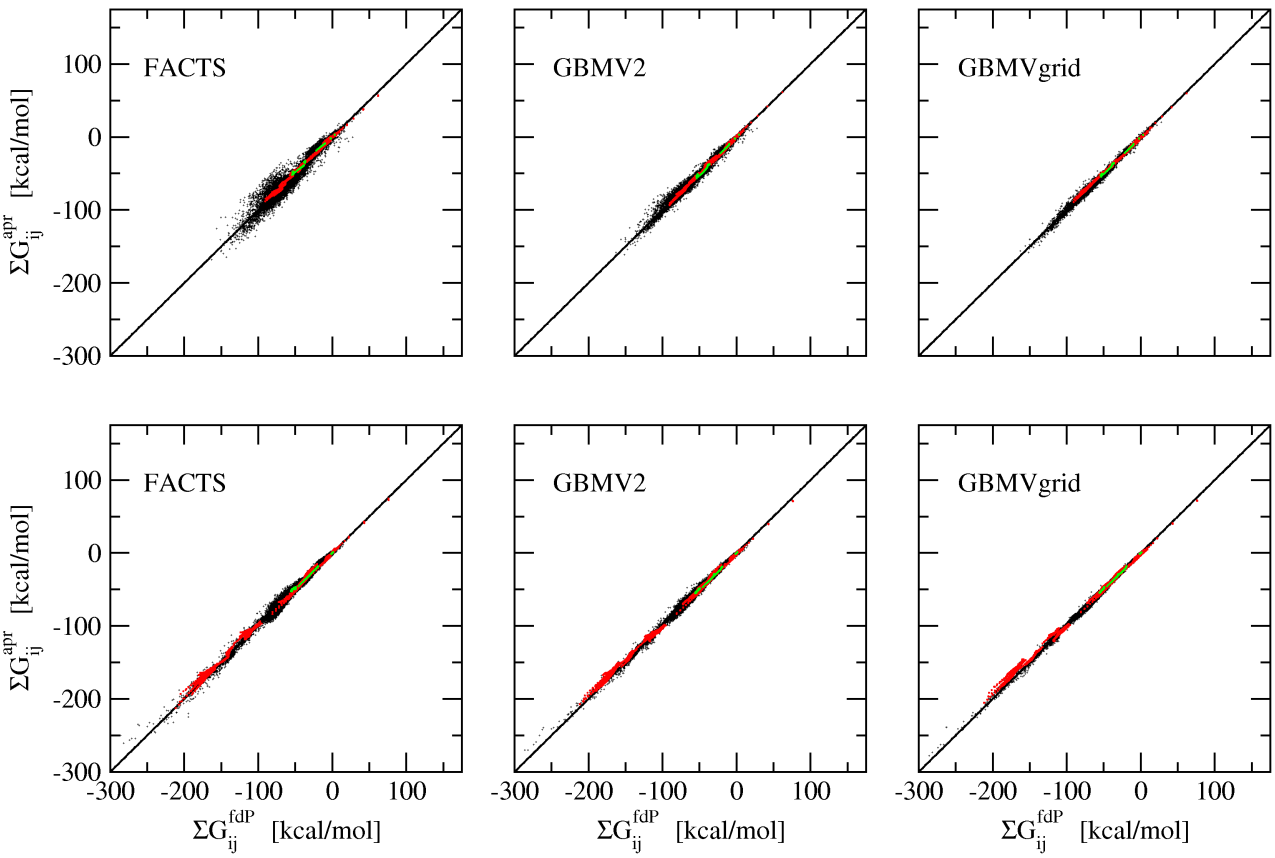

Figure 7: Comparison of sums of interaction energy values between FACTS and GBMV. For each solute atom the sum over all its interaction energies, using partial charges, is calculated with $\varepsilon_m = 1$. On the abscissa the fdP derived values are given, and on the ordinate the approximated values. (Top) PARAM19. (Bottom) PARAM22.

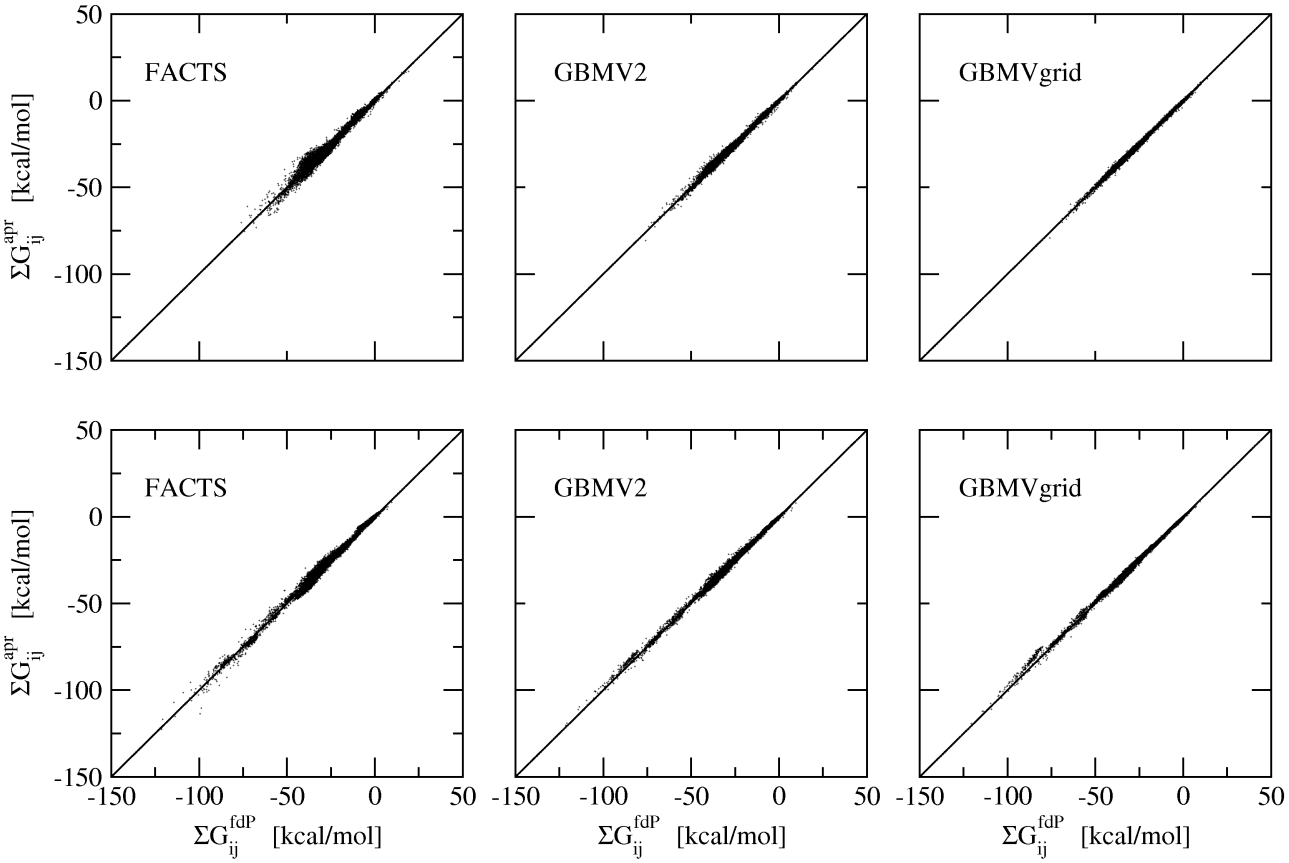

Figure 8: Comparison of sums of interaction energy values between FACTS and GBMV. For each solute atom the sum over all its interaction energies, using partial charges, is calculated with $\varepsilon_m = 2$. On the abscissa the fdP derived values are given, and on the ordinate the approximated values. (Top) PARAM19. (Bottom) PARAM22.

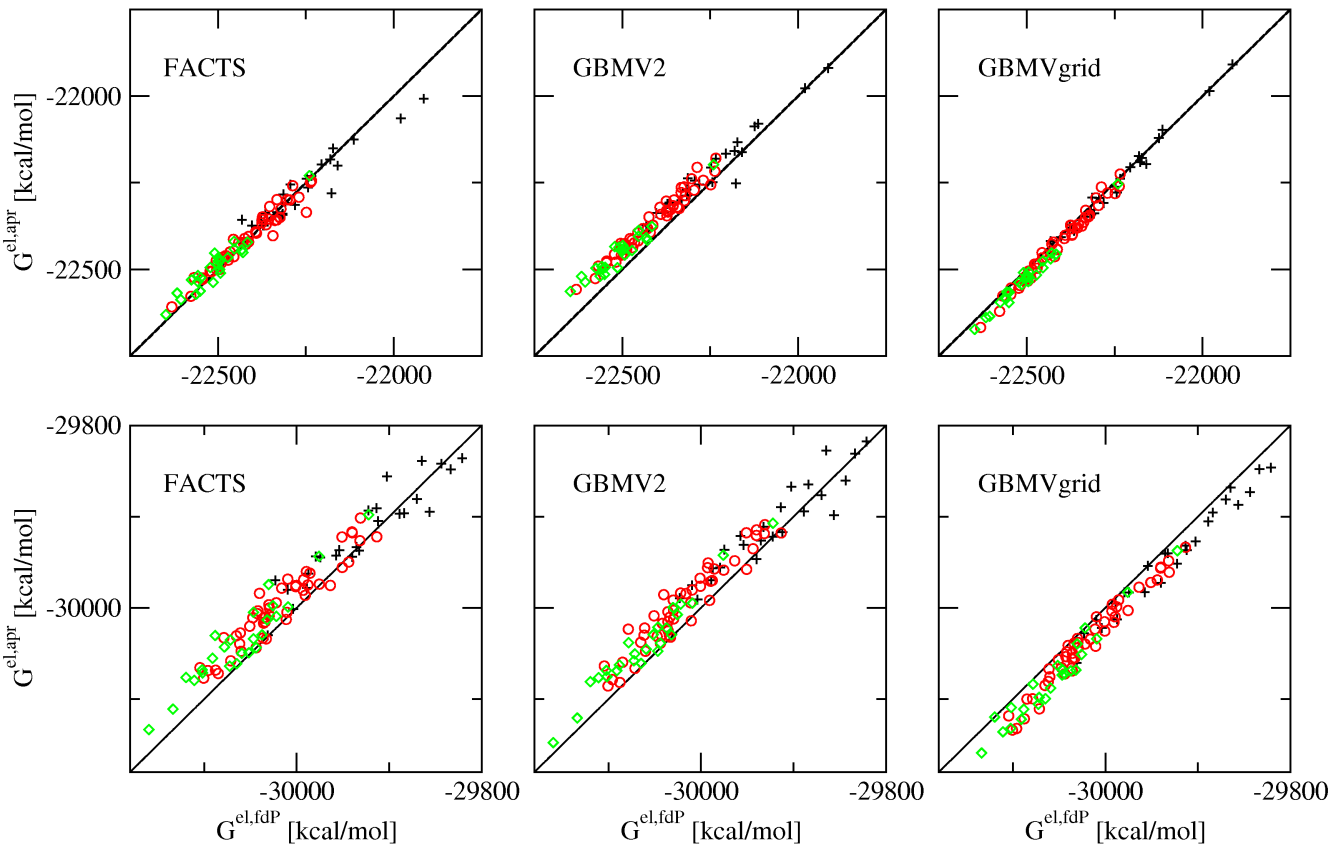

Figure 9: Comparison of energy in solution values between FACTS and GBMV. (The energy in solution of a conformation is its solvation energy plus the vacuo pair interaction energies.) The values for 100 conformations of 1a2p are shown for PARAM19 (top) and PARAM22 (bottom) with $\varepsilon_m = 1$. The structures are chosen along a high temperature unfolding trajectory. Different symbols discriminate between different ranges of the radius of gyration. Pluses and diamonds represent the 25 conformations with small and large radius of gyration, respectively, and circles the 50 intermediate ones. On the abscissa the fdP derived values are given, and on the ordinate the approximated values.

9 Supplementary Tables

	$\varepsilon_m = 1$		$\varepsilon_m = 2$	
Training set	all	native 1a2p	all	native 1a2p
Test set	all	all but 1a2p	all	all but 1a2p
PARAM19				
Average	3.396	3.498	1.462	1.558
SD	3.497	3.539	1.550	1.558
Max	44.719	47.716	17.366	17.620
PARAM22				
Average	3.256	3.448	1.524	1.633
SD	3.383	3.467	1.576	1.616
Max	44.234	43.773	20.656	21.134

Table 1: Cross validation of FACTS solvation parameters. The values are in kcal/mol and represent atomic solvation energy deviations from fdP data calculated with unit charges. In the second and fourth columns, the training set for FACTS parameter optimization is identical to the test set and consists of 81 and 72 protein structures for PARAM19 and PARAM22, respectively. In the third and fifth columns, training and test sets are disjoint; the training set consists of only the native structure of barnase (1a2p) while the test set consists of all the remaining structures.

r_{vdW}	atom type		b_1	b_2	a_2	a_3	R_{sphere}
1.0	H	Average	169	-1.359	0.00327	-146	7.6
		SD	7	0.007	0.00008	57	0.1
		CoV [%]	4	0.5	2.4	39	1.0
1.6	N, O	Average	302	-1.370	0.00193	198	8.9
		SD	16	0.012	0.00004	49	0.1
		CoV [%]	5	0.9	2.0	24	1.1
1.89	S	Average	478	-0.966	0.00229	874	9.5
		SD	51	0.057	0.00056	88	0.4
		CoV [%]	11	5.9	24	10	4.7
2.1	C, CR1E	Average	428	-1.127	0.00179	809	9.6
		SD	32	0.028	0.00004	29	0.1
		CoV [%]	7	2.5	2.4	4	0.9
2.165	CH3E	Average	524	-0.982	0.00245	1147	9.9
		SD	56	0.032	0.00006	57	0.2
		CoV [%]	11	3.3	2.4	5	1.7
2.235	CH2E	Average	584	-1.167	0.00205	1031	9.8
		SD	47	0.027	0.00010	51	0.2
		CoV [%]	8	2.3	4.9	5	2.0
2.365	CH1E	Average	1058	-1.399	0.00192	1164	10.0
		SD	56	0.034	0.00008	18	0.0
		CoV [%]	5	2.4	4.3	2	0.0

Table 2: Stability of FACTS parameters with respect to different training sets. A total of 10 FACTS parameter sets are derived by a leave-one-out procedure over a set of 10 structures. Average, standard deviation, and coefficient of variation are shown for each parameter.

r_{vdW}	atom type	b_1	b_2	a_2	a_3	R_{sphere}
1.0	H	166	-1.370	0.00331	-168	7.5
1.6	N, O	278	-1.347	0.00198	173	8.8
1.89	S	604	-1.202	0.00180	904	10.0
2.1	C, CR1E	497	-1.209	0.00160	841	10.0
2.165	CH3E	542	-0.941	0.00261	1175	10.0
2.235	CH2E	555	-1.201	0.00204	980	9.8
2.365	CH1E	1003	-1.386	0.00193	1146	10.0

Table 3: The 35 FACTS electrostatic solvation parameters for PARAM19 and $\varepsilon_m = 1$.

r_{vdW}	atom type	b_1	b_2	a_2	a_3	R_{sphere}
1.0	H	148	-1.347	0.00306	-466	7.4
1.6	N, O	224	-1.295	0.00186	-96	8.5
1.89	S	470	-1.142	0.00233	732	9.2
2.1	C, CR1E	347	-1.089	0.00154	656	9.6
2.165	CH3E	432	-0.894	0.00230	1128	10.0
2.235	CH2E	421	-1.140	0.00201	831	9.4
2.365	CH1E	811	-1.264	0.00165	1068	10.0

Table 4: The 35 FACTS electrostatic solvation parameters for PARAM19 and $\varepsilon_m = 2$.

r_{vdW}	atom type	d_1	d_2	c_2	c_3
1.0	H	143	-0.863	0.01000	2424
1.6	N, O	281	-1.562	0.00925	1663
1.89	S	454	-1.659	0.00571	2849
2.1	C, CR1E	486	-1.863	0.00750	2828
2.165	CH3E	316	-1.288	0.00374	2394
2.235	CH2E	469	-1.675	0.00511	1613
2.365	CH1E	955	-2.216	0.00540	1570

Table 5: The 28 FACTS surface parameters for PARAM19.

r_{vdW}	atom type	b_1	b_2	a_2	a_3	R_{sphere}
0.2245	H	386	-1.168	0.00559	-2500	6.9
0.9	H	197	-1.363	0.00499	130	7.2
1.32	H	328	-1.432	0.00264	104	8.1
1.3582	H	323	-1.443	0.00258	247	8.3
1.468	H	208	-0.762	0.00397	597	8.0
1.7	O	272	-1.210	0.00222	500	8.5
1.77	O	219	-1.023	0.00244	584	8.4
1.8	C	227	-1.300	0.00163	-105	8.3
1.85	N	184	-1.089	0.00170	327	8.5
1.975	S	410	-0.973	0.00236	874	8.9
1.9924	C	511	-1.412	0.00170	634	9.1
2.0	C	470	-1.112	0.00172	652	8.8
2.06	C	667	-1.235	0.00184	1149	9.8
2.175	C	500	-1.323	0.00203	813	8.9
2.275	C	1068	-1.568	0.00162	1039	9.5

Table 6: The 75 FACTS electrostatic solvation parameters for PARAM22 and $\varepsilon_m = 1$.

r_{vdW}	atom type	b_1	b_2	a_2	a_3	R_{sphere}
0.2245	H	354	-1.148	0.00605	-2500	6.6
0.9	H	192	-1.382	0.00793	184	6.8
1.32	H	324	-1.421	0.00253	52	8.1
1.3582	H	297	-1.382	0.00262	232	8.2
1.468	H	184	-1.014	0.00385	413	7.5
1.7	O	255	-1.193	0.00217	441	8.4
1.77	O	188	-0.989	0.00219	499	8.4
1.8	C	199	-1.232	0.00149	-341	8.3
1.85	N	168	-1.045	0.00166	264	8.5
1.975	S	614	-1.250	0.00206	901	9.3
1.9924	C	492	-1.410	0.00156	552	9.2
2.0	C	451	-1.075	0.00168	608	8.8
2.06	C	640	-1.224	0.00167	1136	10.0
2.175	C	469	-1.281	0.00196	789	8.9
2.275	C	1027	-1.523	0.00155	1014	9.6

Table 7: The 75 FACTS electrostatic solvation parameters for PARAM22 and $\varepsilon_m = 2$.

r_{vdW}	atom type	d_1	d_2	c_2	c_3
0.2245	H	2000	0.000	0.01000	1624
0.9	H	194	-0.913	0.01000	2353
1.32	H	259	-1.341	0.01000	2173
1.3582	H	259	-1.429	0.00898	1789
1.468	H	187	-1.363	0.00909	2416
1.7	O	232	-1.344	0.00625	2767
1.77	O	165	-1.124	0.00582	2366
1.8	C	257	-1.503	0.01000	2308
1.85	N	170	-1.318	0.00747	2612
1.975	S	651	-2.077	0.00634	2315
1.9924	C	642	-1.812	0.00661	1047
2.0	C	481	-1.851	0.01000	2889
2.06	C	627	-1.656	0.00468	2811
2.175	C	575	-2.011	0.00725	776
2.275	C	1045	-2.446	0.00651	2671

Table 8: The 60 FACTS surface parameters for PARAM22.

		PARAM19					PARAM22				
		FCT	FCT	FCT	GB2	GBg	FCT	FCT	FCT	GB2	GBg
PDB	residues	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$
1cb3	11	1.750	1.880	1.929	1.380	4.589	1.678	2.070	2.320	2.694	5.476
bet1	14	0.885	1.056	1.307	0.641	4.039	1.883	0.860	0.946	1.383	3.767
hlx1	17	0.857	0.858	0.920	1.192	4.370	1.276	1.097	1.179	2.708	5.544
1l2y	20	1.652	0.923	0.930	2.726	3.686	2.763	1.286	1.152	1.448	4.500
Beta3s[a]	20	1.633	1.054	1.482	3.267	3.641	3.454	1.280	1.230	0.906	3.829
1f8a	33	1.780	1.126	0.998	3.247	1.975	2.802	1.130	0.818	0.651	2.523
1abz	38	1.258	1.048	1.012	1.951	3.043	2.115	1.186	1.036	0.886	3.556
1crn	46	3.837	1.312	1.281	3.645	1.762	6.107	2.005	1.209	1.384	1.966
ins2	51	2.861	1.408	1.141	1.939	2.095	4.615	2.406	1.830	0.910	1.919
1enh	54	1.213	1.012	1.012	2.936	1.489	1.873	0.746	0.588	0.595	2.136
1pgb	56	1.340	1.022	0.981	1.197	2.011	2.297	1.388	1.199	0.743	2.019
1shg	57	1.359	1.186	1.167	2.501	2.041	2.994	1.860	1.599	0.723	2.942
1bpi	58	1.544	1.214	1.171	3.033	1.124	2.168	1.069	0.861	0.720	1.810
1fmk	59	2.600	1.300	1.213	1.924	2.015	4.573	2.217	1.631	1.628	1.397
2ptl	61	1.644	1.160	1.135	2.074	2.189	3.337	1.811	1.473	0.872	2.692
2ci2	65	1.431	1.090	1.020	2.123	2.101	3.602	2.312	1.972	0.815	2.453
2a3d	73	1.579	1.273	1.223	2.230	1.894	2.967	1.695	1.437	0.875	2.376
1ubq	76	1.564	1.186	1.109	2.377	1.785	3.588	2.091	1.728	0.998	2.320
1pht	83	1.471	1.092	1.042	1.322	1.591	3.008	1.945	1.726	1.200	1.129
1hdn	85	1.612	0.956	0.879	2.078	1.430	3.713	2.058	1.630	0.819	1.909
1dvd	98	1.423	1.077	1.016	1.952	1.433	3.409	2.121	1.776	0.931	1.967
prph	104	2.780	1.633	1.482	2.594	1.209	5.033	2.554	1.903	2.686	0.768
1a2p	108	2.369	1.460	1.342	2.875	1.216	4.678	2.258	1.690	1.646	1.417
1hel	129	1.938	1.446	1.355	2.856	0.708	2.193	1.119	1.194	1.029	1.529
1lz1	130	2.040	1.503	1.392	3.003	0.878	2.196	1.014	1.072	0.917	1.450
anki	156	2.294	2.586	2.777	1.390	1.486	2.245	1.389	1.239	1.452	0.696
1cus	197	2.778	1.552	1.391	3.480	0.822	5.757	2.775	2.004	2.121	0.711
1inc	240	5.582	3.053	2.354	5.053	1.605	6.597	2.630	1.757	2.058	0.721
1kvd	280	1.835	1.866	1.834	1.775	0.815	3.674	1.507	1.038	1.456	0.803

Table 9: Average percentage error of the solvation energy values of 100 conformations for each protein ($\varepsilon_m = 1$). [a]Beta3s is a three-stranded antiparallel β-sheet peptide [7, 8]. FCT, GB2, and GBg are shortcuts for FACTS, GBMV2, and GBMVgrid, respectively.

		PARAM19					PARAM22				
		FCT	FCT	FCT	GB2	GBg	FCT	FCT	FCT	GB2	GBg
PDB	residues	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$
1cb3	11	4.1	3.8	3.7	2.6	2.6	5.4	4.7	4.5	2.5	2.6
bet1	14	4.9	4.5	4.5	3.5	3.6	5.1	4.3	4.3	3.7	3.9
hlx1	17	5.8	5.3	5.2	4.1	4.4	6.5	6.0	5.8	4.5	4.7
1l2y	20	6.4	5.5	5.3	4.4	3.9	7.0	6.0	5.6	4.0	3.8
Beta3s[a]	20	6.0	5.5	5.5	5.3	4.2	6.9	6.0	5.8	4.2	3.7
1f8a	33	11.4	10.4	10.2	8.2	6.5	10.3	8.9	8.5	7.2	5.3
1abz	38	14.6	13.8	13.8	8.3	10.0	11.5	10.9	11.0	8.9	8.9
1crn	46	9.3	8.5	8.3	8.0	6.7	8.1	6.8	6.7	7.2	4.8
ins2	51	12.8	12.2	12.2	9.1	8.3	10.1	9.7	9.9	8.0	6.3
1enh	54	20.9	18.3	17.9	16.1	13.1	15.9	13.2	12.7	13.0	9.5
1pgb	56	23.0	21.4	20.9	13.5	9.7	16.2	14.7	14.3	12.2	10.1
1shg	57	19.0	18.3	18.6	16.0	12.0	12.5	12.3	12.6	9.4	8.9
1bpi	58	19.8	18.7	18.5	15.3	9.6	14.8	14.0	14.0	12.4	6.9
1fmk	59	18.8	17.4	17.0	14.5	7.7	13.7	11.8	11.5	10.4	9.0
2ptl	61	19.9	18.4	18.0	14.3	12.5	14.1	13.1	13.3	10.6	9.3
2ci2	65	20.1	18.9	18.7	12.0	15.1	14.0	14.1	14.7	11.8	12.6
2a3d	73	25.4	24.3	24.2	18.6	13.8	17.9	17.0	17.1	14.9	12.2
1ubq	76	24.4	23.5	23.3	15.9	14.7	17.0	16.4	16.7	15.0	12.6
1pht	83	30.4	28.8	28.4	23.5	14.7	17.7	17.2	17.6	14.5	11.5
1hdn	85	19.7	18.8	19.0	16.3	14.5	17.0	15.1	14.9	13.5	13.6
1dvd	98	27.4	25.8	25.7	22.8	18.9	19.7	18.8	19.0	16.4	13.7
prph	104	38.9	36.1	35.3	28.3	13.5	18.1	16.6	16.6	15.5	11.6
1a2p	108	32.8	31.3	31.1	26.4	17.5	22.1	20.1	20.1	17.6	11.8
1hel	129	42.0	39.6	39.1	39.2	21.6	32.2	30.3	29.8	27.6	14.7
1lz1	130	48.0	44.5	43.5	39.2	29.2	30.9	29.0	28.7	26.8	15.8
anki	156	96.1	92.2	90.6	59.1	37.3	34.6	30.1	28.8	31.3	21.8
1cus	197	45.3	44.3	44.3	37.9	26.7	30.7	29.0	29.1	24.8	14.9
1inc	240	45.5	44.1	44.1	40.3	28.1	36.8	34.6	34.5	29.5	17.0
1kvd	280	87.5	83.9	83.2	58.6	38.1	34.4	30.2	29.4	27.0	19.8

Table 10: Average error in kcal/mol for the difference in electrostatic solvation energy ($\Delta\Delta G$) from *pairs* of protein conformations ($\varepsilon_m = 1$). For each protein, 4950 values of $\Delta\Delta G$ were calculated using 100 conformations. [a]Beta3s is a three-stranded antiparallel β-sheet peptide [7, 8]. FCT, GB2, and GBg are shortcuts for FACTS, GBMV2, and GBMVgrid, respectively.

	FACTS $\kappa = 4$	FACTS $\kappa = 8$	FACTS $\kappa = 12$	GBMV2 $\kappa = 8$	GBMVgrid $\kappa = 8$
PARAM19					
Average [%]	1.96	1.36	1.32	2.37	2.04
SD [%]	1.57	1.25	1.26	1.34	1.31
Max [%]	10.37	11.78	12.21	8.62	8.76
PARAM22					
Average [%]	3.33	1.72	1.42	1.28	2.29
SD [%]	1.88	1.20	1.08	1.03	1.48
Max [%]	11.64	7.40	6.97	6.26	7.21

Table 11: Percentage error of electrostatic solvation energy for PARAM19 (top half) and PARAM22 (bottom half) from 2900 protein conformations (100 conformations from each of 29 trajectories), $\varepsilon_m = 1$.

	FACTS $\kappa = 4$	FACTS $\kappa = 8$	FACTS $\kappa = 12$	GBMV2 $\kappa = 8$	GBMVgrid $\kappa = 8$
PARAM19					
Average	26.91	25.45	25.18	20.04	14.43
SD	36.70	34.99	34.46	26.10	16.70
Max	393	374	367	269	193
PARAM22					
Average	17.28	15.89	15.77	13.94	10.39
SD	17.92	16.46	16.25	14.98	10.20
Max	209	180	169	177	122

Table 12: Error [kcal/mol] of solvation energy values from *pairs* of structures for PARAM19 (top half) and PARAM22 (bottom half) of 2900 conformations (100 conformations from each of 29 trajectories), $\varepsilon_m = 1$.

		PARAM19					PARAM22				
		FCT	FCT	FCT	GB2	GBg	FCT	FCT	FCT	GB2	GBg
PDB	residue	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$
1cb3	11	0.993	0.993	0.994	0.997	0.998	0.989	0.991	0.992	0.998	0.999
bet1	14	0.996	0.996	0.996	0.998	0.998	0.996	0.997	0.997	0.998	0.998
hlx1	17	0.995	0.995	0.996	0.997	0.998	0.994	0.995	0.996	0.998	0.999
1l2y	20	0.991	0.993	0.993	0.996	0.997	0.990	0.993	0.993	0.997	0.998
Beta3s[a]	20	0.991	0.992	0.992	0.992	0.996	0.988	0.991	0.991	0.996	0.998
1f8a	33	0.994	0.995	0.995	0.997	0.999	0.995	0.996	0.997	0.998	0.999
1abz	38	0.993	0.994	0.994	0.998	0.998	0.995	0.996	0.996	0.998	0.999
1crn	46	0.993	0.994	0.995	0.995	0.997	0.995	0.996	0.997	0.996	0.998
ins2	51	0.991	0.991	0.991	0.996	0.997	0.994	0.995	0.995	0.996	0.998
1enh	54	0.992	0.994	0.994	0.995	0.997	0.994	0.996	0.996	0.997	0.999
1pgb	56	0.991	0.992	0.993	0.997	0.999	0.996	0.997	0.997	0.998	0.999
1shg	57	0.993	0.993	0.993	0.996	0.998	0.997	0.997	0.997	0.998	0.999
1bpi	58	0.990	0.991	0.992	0.995	0.998	0.994	0.995	0.995	0.996	0.999
1fmk	59	0.985	0.987	0.988	0.992	0.998	0.991	0.994	0.994	0.995	0.997
2ptl	61	0.990	0.992	0.992	0.995	0.997	0.995	0.995	0.995	0.997	0.999
2ci2	65	0.991	0.991	0.991	0.998	0.998	0.997	0.997	0.996	0.998	0.999
2a3d	73	0.994	0.995	0.995	0.997	0.999	0.997	0.997	0.997	0.998	0.999
1ubq	76	0.992	0.992	0.992	0.996	0.998	0.996	0.996	0.996	0.997	0.999
1pht	83	0.991	0.992	0.992	0.994	0.999	0.997	0.997	0.997	0.998	0.999
1hdn	85	0.996	0.996	0.996	0.997	0.998	0.997	0.998	0.998	0.998	0.999
1dvd	98	0.994	0.995	0.995	0.996	0.997	0.996	0.997	0.996	0.997	0.999
prph	104	0.970	0.973	0.974	0.985	0.997	0.994	0.995	0.995	0.995	0.998
1a2p	108	0.984	0.986	0.986	0.991	0.997	0.992	0.994	0.994	0.995	0.998
1hel	129	0.981	0.983	0.984	0.982	0.994	0.981	0.984	0.984	0.987	0.996
1lz1	130	0.983	0.985	0.986	0.989	0.994	0.991	0.992	0.992	0.993	0.998
anki	156	0.943	0.946	0.947	0.976	0.991	0.989	0.991	0.992	0.991	0.996
1cus	197	0.986	0.987	0.987	0.990	0.995	0.992	0.993	0.993	0.995	0.998
1inc	240	0.981	0.982	0.982	0.986	0.994	0.987	0.988	0.988	0.991	0.997
1kvd	280	0.980	0.982	0.983	0.993	0.997	0.996	0.997	0.997	0.998	0.999

Table 13: Correlation coefficient of electrostatic solvation energy values of 100 conformations for each protein, $\varepsilon_m = 1$. The benchmark are the fdP data. [a]Beta3s is a three-stranded antiparallel β-sheet peptide [7, 8]. FCT, GB2, and GBg are shortcuts for FACTS, GBMV2, and GBMVgrid, respectively.

		PARAM19					PARAM22				
		FCT	FCT	FCT	GB2	GBg	FCT	FCT	FCT	GB2	GBg
PDB	residue	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$
1cb3	11	0.247	0.262	0.268	0.192	0.647	0.148	0.179	0.199	0.241	0.490
bet1	14	0.116	0.141	0.173	0.086	0.547	0.163	0.076	0.082	0.123	0.337
hlx1	17	0.113	0.113	0.121	0.162	0.590	0.112	0.094	0.100	0.243	0.496
1l2y	20	0.171	0.095	0.096	0.286	0.388	0.188	0.088	0.079	0.100	0.310
Beta3s[a]	20	0.145	0.095	0.132	0.295	0.326	0.223	0.082	0.079	0.058	0.254
1f8a	33	0.216	0.138	0.123	0.398	0.246	0.214	0.086	0.062	0.049	0.195
1abz	38	0.147	0.123	0.119	0.231	0.362	0.135	0.077	0.067	0.057	0.231
1crn	46	0.233	0.078	0.074	0.222	0.108	0.242	0.082	0.049	0.054	0.079
ins2	51	0.227	0.112	0.090	0.156	0.169	0.246	0.130	0.099	0.049	0.103
1enh	54	0.166	0.139	0.139	0.403	0.206	0.145	0.058	0.046	0.047	0.170
1pgb	56	0.167	0.128	0.123	0.153	0.257	0.185	0.112	0.097	0.059	0.168
1shg	57	0.146	0.129	0.127	0.273	0.222	0.182	0.114	0.099	0.043	0.183
1bpi	58	0.186	0.148	0.143	0.369	0.137	0.161	0.080	0.064	0.053	0.135
1fmk	59	0.209	0.103	0.095	0.156	0.162	0.235	0.115	0.085	0.083	0.073
2ptl	61	0.154	0.109	0.106	0.195	0.209	0.196	0.107	0.087	0.051	0.162
2ci2	65	0.150	0.115	0.108	0.227	0.229	0.209	0.135	0.115	0.047	0.149
2a3d	73	0.161	0.130	0.125	0.232	0.197	0.172	0.099	0.084	0.050	0.139
1ubq	76	0.151	0.114	0.106	0.234	0.179	0.203	0.119	0.098	0.055	0.134
1pht	83	0.168	0.124	0.118	0.151	0.185	0.203	0.132	0.117	0.081	0.078
1hdn	85	0.156	0.090	0.081	0.200	0.139	0.227	0.126	0.100	0.049	0.121
1dvd	98	0.137	0.103	0.097	0.189	0.139	0.195	0.123	0.104	0.054	0.115
prph	104	0.198	0.115	0.103	0.185	0.086	0.211	0.108	0.081	0.111	0.033
1a2p	108	0.174	0.107	0.097	0.213	0.089	0.200	0.098	0.073	0.070	0.061
1hel	129	0.164	0.122	0.114	0.243	0.059	0.112	0.057	0.061	0.052	0.079
1lz1	130	0.176	0.131	0.121	0.262	0.076	0.110	0.051	0.054	0.046	0.074
anki	156	0.235	0.265	0.285	0.144	0.155	0.141	0.087	0.078	0.093	0.045
1cus	197	0.169	0.094	0.084	0.211	0.049	0.198	0.096	0.070	0.073	0.024
1inc	240	0.253	0.138	0.107	0.230	0.072	0.191	0.077	0.051	0.060	0.021
1kvd	280	0.122	0.121	0.138	0.119	0.053	0.142	0.059	0.041	0.056	0.031

Table 14: Average percentage error of the energy in solution (i.e., solvation energy plus vacuum energy) values of 100 conformations for each protein ($\varepsilon_m = 1$). [a]Beta3s is a three-stranded antiparallel β-sheet peptide [7, 8]. FCT, GB2, and GBg are shortcuts for FACTS, GBMV2, and GBMVgrid, respectively.

	FACTS $\kappa = 4$	FACTS $\kappa = 8$	FACTS $\kappa = 12$	GBMV2 $\kappa = 8$	GBMVgrid $\kappa = 8$
PARAM19					
Average [%]	0.17	0.13	0.12	0.22	0.22
SD [%]	0.12	0.12	0.12	0.12	0.17
Max [%]	1.16	1.13	1.13	0.74	0.87
PARAM22					
Average [%]	0.18	0.10	0.08	0.08	0.15
SD [%]	0.09	0.07	0.07	0.07	0.13
Max [%]	0.59	0.54	0.57	0.47	0.68

Table 15: Percentage error of energy in solution values for PARAM19 (top half) and PARAM22 (bottom half) of 2900 conformations (100 conformations from each of 29 trajectories), $\varepsilon_m = 1$

		PARAM19					PARAM22				
		FACTS	FACTS	FACTS	GB2	GBgr	FACTS	FACTS	FACTS	GB2	GBgr
PDB	residue	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$	$\kappa = 4$	$\kappa = 8$	$\kappa = 12$	$\kappa = 8$	$\kappa = 8$
1cb3	11	0.968	0.974	0.975	0.988	0.992	0.821	0.855	0.867	0.970	0.975
bet1	14	0.983	0.986	0.986	0.991	0.995	0.940	0.958	0.960	0.975	0.972
hlx1	17	0.978	0.982	0.982	0.988	0.994	0.916	0.929	0.933	0.976	0.980
1l2y	20	0.953	0.966	0.968	0.979	0.988	0.873	0.908	0.916	0.963	0.976
Beta3s[a]	20	0.969	0.974	0.974	0.972	0.987	0.886	0.914	0.921	0.963	0.978
1f8a	33	0.974	0.979	0.980	0.988	0.994	0.942	0.956	0.960	0.971	0.986
1abz	38	0.978	0.981	0.981	0.994	0.994	0.961	0.966	0.967	0.981	0.987
1crn	46	0.976	0.980	0.980	0.982	0.989	0.952	0.965	0.966	0.963	0.985
ins2	51	0.966	0.968	0.968	0.983	0.990	0.950	0.954	0.953	0.973	0.986
1enh	54	0.986	0.988	0.988	0.992	0.995	0.973	0.980	0.981	0.981	0.988
1pgb	56	0.972	0.976	0.977	0.993	0.997	0.957	0.965	0.966	0.979	0.991
1shg	57	0.972	0.975	0.975	0.984	0.992	0.967	0.967	0.965	0.981	0.986
1bpi	58	0.972	0.975	0.975	0.986	0.995	0.951	0.956	0.956	0.967	0.990
1fmk	59	0.977	0.980	0.981	0.988	0.996	0.957	0.969	0.971	0.979	0.989
2ptl	61	0.966	0.971	0.972	0.984	0.990	0.957	0.964	0.965	0.979	0.990
2ci2	65	0.973	0.976	0.976	0.994	0.994	0.974	0.977	0.977	0.986	0.988
2a3d	73	0.976	0.979	0.979	0.987	0.995	0.959	0.961	0.961	0.970	0.984
1ubq	76	0.976	0.978	0.978	0.991	0.993	0.960	0.963	0.962	0.973	0.986
1pht	83	0.966	0.972	0.974	0.980	0.992	0.955	0.959	0.959	0.970	0.984
1hdn	85	0.983	0.984	0.984	0.989	0.993	0.962	0.971	0.972	0.980	0.988
1dvd	98	0.982	0.984	0.984	0.989	0.993	0.961	0.965	0.965	0.976	0.989
prph	104	0.963	0.968	0.969	0.981	0.995	0.972	0.976	0.976	0.980	0.990
1a2p	108	0.978	0.980	0.980	0.987	0.995	0.966	0.971	0.971	0.976	0.990
1hel	129	0.966	0.968	0.968	0.967	0.988	0.928	0.935	0.937	0.946	0.984
1lz1	130	0.955	0.962	0.964	0.974	0.982	0.929	0.938	0.940	0.946	0.982
anki	156	0.919	0.927	0.931	0.969	0.985	0.958	0.965	0.967	0.959	0.979
1cus	197	0.973	0.972	0.972	0.980	0.990	0.949	0.955	0.954	0.966	0.988
1inc	240	0.933	0.936	0.936	0.952	0.977	0.894	0.907	0.907	0.934	0.977
1kvd	280	0.950	0.953	0.954	0.981	0.988	0.960	0.970	0.972	0.977	0.987

Table 16: Correlation coefficient of electrostatic energy in solution (i.e., solvation energy plus vacuum energy) values of 100 conformations for each protein, $\varepsilon_m = 1$. The benchmark are the fdP data. [a]Beta3s is a three-stranded antiparallel β-sheet peptide [7, 8]. FCT, GB2, and GBg are shortcuts for FACTS, GBMV2, and GBMVgrid, respectively.

PDB	residues	$\langle\rangle_{10}$	$\langle\rangle_{20}$	$\langle\rangle_{30}$	$\langle\rangle_{40}$	$\langle\rangle_{50}$	$\langle\rangle_{60}$	$\langle\rangle_{70}$	$\langle\rangle_{80}$	$\langle\rangle_{90}$	$\langle\rangle_{100}$
1cb3	11	3.7	3.7	3.7	3.6	3.8	4.0	3.7	3.8	3.2	3.2
Beta3s[a]	20	2.2	2.1	2.1	2.1	2.1	2.1	2.2	2.1	2.3	2.1
1crn	46	2.1	2.3	2.6	2.1	2.1	2.1	2.1	2.1	2.3	2.8
2ci2	65	2.2	2.3	2.2	2.3	2.3	2.2	2.2	2.4	2.8	2.8
1a2p	108	3.3	3.4	3.8	4.7	4.5	4.8	4.9	4.9	4.9	4.6

Table 17: Deviation from the native structure during molecular dynamics simulations at 300 K. Individual columns contain values of the C_α-RMSD from the native structure averaged over 10 ns intervals, e.g., for the last column $<>_{100}$ the C_α-RMSD was averaged over the 90-100 ns interval. The simulations were performed with FACTS PARAM19, $\kappa = 4$, $\varepsilon_m = 1.0$, and $\gamma = 0.025$ kcal mol^{-1} Å^{-2}. [a]Beta3s is a three-stranded antiparallel β-sheet peptide [7, 8].