Supporting Information

Entropic Effect and Residue Specific Entropic Contribution to the Cooperativity in Streptavidin-biotin Binding

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Table S1. The binding free energy components and the standard errors of the mean under the ff12SB force field.

Energy (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{sol}	ΔH	$-T\Delta S$	ΔG_{cal}	ΔG_{exp}
WT	-81.73±0.65	-30.65±0.14	80.94±0.51	-31.43±0.22	17.77±0.00	-13.66±0.22	-18.1
S45A	-70.11±0.56	-29.11±0.14	73.92±0.46	-25.29±0.23	14.90±0.01	-10.39±0.23	-13.8
D128A	-87.66±0.59	-27.65±0.15	87.20±0.48	-28.11±0.20	15.25±0.00	-12.85±0.20	-13.8
DM	-86.91±0.57	-26.39±0.15	90.30±0.48	-23.00±0.20	11.84±0.00	-11.16±0.20	-8.1
Cooperativity				-1.03	-0.54	-1.58	1.4

Table S2. The binding free energy components and the standard errors of the mean under the ff02 force field.

Energy (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{sol}	ΔH	$-T\Delta S$	ΔG_{cal}	ΔG_{exp}
WT	-61.69±0.45	-29.37±0.14	66.44±0.38	-24.62±0.18	10.63±0.00	-13.99±0.18	-18.1
S45A	-63.24±0.52	-28.80±0.13	72.06±0.45	-20.01±0.20	12.00±0.01	-8.00±0.20	-13.8
D128A	-91.27±0.80	-28.67±0.13	92.11±0.70	-27.82±0.17	20.79±0.03	-7.03±0.18	-13.8
DM	-80.91±0.49	-27.65±0.14	85.29±0.43	-23.26±0.16	10.92±0.00	-12.34±0.16	-8.1
Cooperativity				-0.05	-11.24	-11.30	1.4

Table S3. The binding free energy components and the standard errors of the mean under the ff15ipq force field.

Energy (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{sol}	ΔH	$-T\Delta S$	ΔG_{cal}	ΔG_{exp}
WT	-75.50±0.62	-31.96±0.15	72.63±0.51	-34.82±0.22	17.94±0.01	-16.88±0.22	-18.1
S45A	-63.59±0.71	-29.86±0.15	68.05±0.59	-25.40±0.29	18.41±0.01	-6.98±0.29	-13.8
D128A	-69.48±0.65	-28.14±0.14	72.49±0.53	-25.13±0.19	16.44±0.01	-8.69±0.19	-13.8
DM	-68.25±0.66	-27.30±0.13	73.52±0.57	-22.03±0.15	17.86±0.01	-4.17±0.15	-8.1
Cooperativity				-6.32	0.95	-5.38	1.4

Table S4. The binding free energy components and the standard errors of the mean for the second simulation under the PPC force field.

Energy (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{sol}	ΔH	$-T\Delta S$	ΔG_{cal}	ΔG_{exp}
WT	-132.41±0.70	-26.20±0.20	112.79±0.55	-45.82±0.26	19.31±0.01	-26.50±0.26	-18.1
S45A	-120.28±0.64	-24.90±0.20	102.37±0.46	-42.82±0.25	17.64±0.01	-25.17±0.25	-13.8
D128A	-115.39±0.55	-24.46±0.18	105.38±0.41	-34.46±0.18	15.67±0.01	-18.80±0.18	-13.8
DM	-123.49±0.59	-23.06±0.18	113.92±0.44	-32.62±0.24	16.86±0.01	-15.76±0.01	-8.1
Cooperativity				-1.16	2.86	1.71	1.4

Table S5. The binding free energy components and the standard errors of the mean for the third simulation under the PPC force field.

Energy (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{sol}	ΔH	$-T\Delta S$	ΔG_{cal}	ΔG_{exp}
WT	-130.58±0.59	-27.13±0.18	109.94±0.43	-47.77±0.25	19.36±0.01	-28.41±0.25	-18.1
S45A	-120.07±0.68	-24.96±0.19	103.35±0.50	-41.68±0.27	16.77±0.00	-24.91±0.27	-13.8
D128A	-124.48±0.50	-24.88±0.17	114.09±0.39	-35.27±0.20	13.59±0.00	-21.68±0.20	-13.8
DM	-121.25±0.58	-23.33±0.17	112.97±0.45	-31.61±0.19	15.65±0.01	-15.96±0.19	-8.1
Cooperativity				-2.43	4.65	2.22	1.4

Table S6. The occupancy of the hydrogen bonds between the eight residues of the streptavidin and biotin under the four force fields.

Occupancy (%)		N23	S27	Y43	S45	N49	S88	T90	D128
WT	ff12SB	63.22	99.93	99.50	92.75	53.18	38.47	95.45	99.81
	ff02	7.11	99.31	99.81	91.22	97.88	57.39	85.79	35.56
	ff15ipq	92.15	98.89	99.90	94.75	75.47	41.68	85.73	99.70
	PPC	53.33	100.00	100.00	96.32	98.63	94.91	98.10	100.00
S45A	ff12SB	0.00	95.67	98.84	N/A	90.60	60.31	96.67	0.25
	ff02	0.00	5957	79.08	N/A	82.96	25.11	76.69	1.25
	ff15ipq	61.58	85.84	98.69	N/A	55.51	15.16	81.88	67.14
	PPC	32.77	100.00	100.00	N/A	99.97	92.72	98.76	100.00
D128A	ff12SB	0.06	99.91	99.95	97.98	70.93	21.90	94.23	N/A
	ff02	0.00	99.82	99.97	95.94	99.12	72.69	90.99	N/A
	ff15ipq	0.00	98.32	99.91	93.58	51.41	12.99	58.95	N/A
	PPC	0.00	100.00	100.00	99.24	98.44	97.81	97.35	N/A
DM	ff12SB	0.00	98.15	99.92	N/A	66.48	16.62	88.61	N/A
	ff02	0.00	99.34	99.12	N/A	82.14	15.77	72.18	N/A
	ff15ipq	0.00	96.34	99.37	N/A	60.65	2.80	40.25	N/A
	PPC	0.00	99.94	100.00	N/A	97.95	96.50	97.74	N/A

Table S7. The decomposition of the binding free energy of S88 residue under the PPC force field.

S88 (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{pb}	ΔG_{np}	ΔH	$-T\Delta S$	ΔG_{cal}
WT	-16.00±0.87	0.26±0.12	14.88±0.71	-0.12±0.00	-1.00±0.11	7.88±0.00	6.88±0.11
S45A	-23.70±0.59	1.38±0.17	20.62±0.42	-0.12±0.00	-1.82±0.09	6.96±0.00	5.14±0.11
D128A	-20.96±0.32	0.90±0.17	18.88±0.18	-0.18±0.00	-1.34±0.08	8.08±0.00	6.74±0.11
DM	-22.44±0.47	1.20±0.16	19.88±0.31	-0.16±0.00	-1.54±0.09	7.38±0.00	5.84±0.11

Table S8. The decomposition of the binding free energy of T90 residue under the PPC force field.

T90 (kcal/mol)	ΔE_{ele}	ΔE_{vdw}	ΔG_{pb}	ΔG_{np}	ΔH	$-T\Delta S$	ΔG_{cal}
WT	-1.04±0.09	-0.94±0.07	3.06±0.09	-0.10±0.00	0.98±0.08	0.20±0.00	1.18±0.11
S45A	-1.66±0.08	-0.54±0.09	3.58±0.08	-0.10±0.00	1.28±0.10	0.20±0.00	1.48±0.11
D128A	-1.20±0.07	-0.98±0.07	3.24±0.08	-0.08±0.00	0.98±0.09	0.16±0.00	1.14±0.11
DM	-1.80±0.09	-1.00±0.06	3.96±0.10	-0.08±0.00	1.06±0.08	0.19±0.00	1.25±0.11

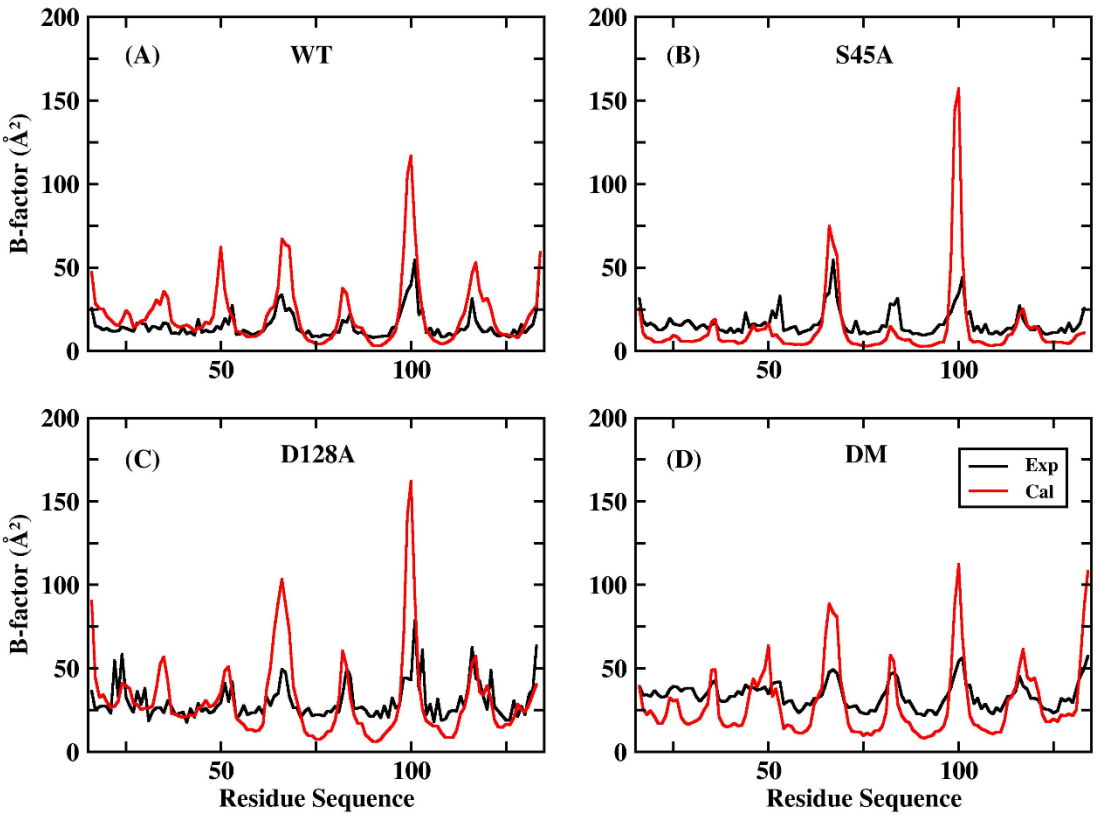

Figure S1. The comparison of B-factors between simulated and experimental values at the four systems under the PPC force field.

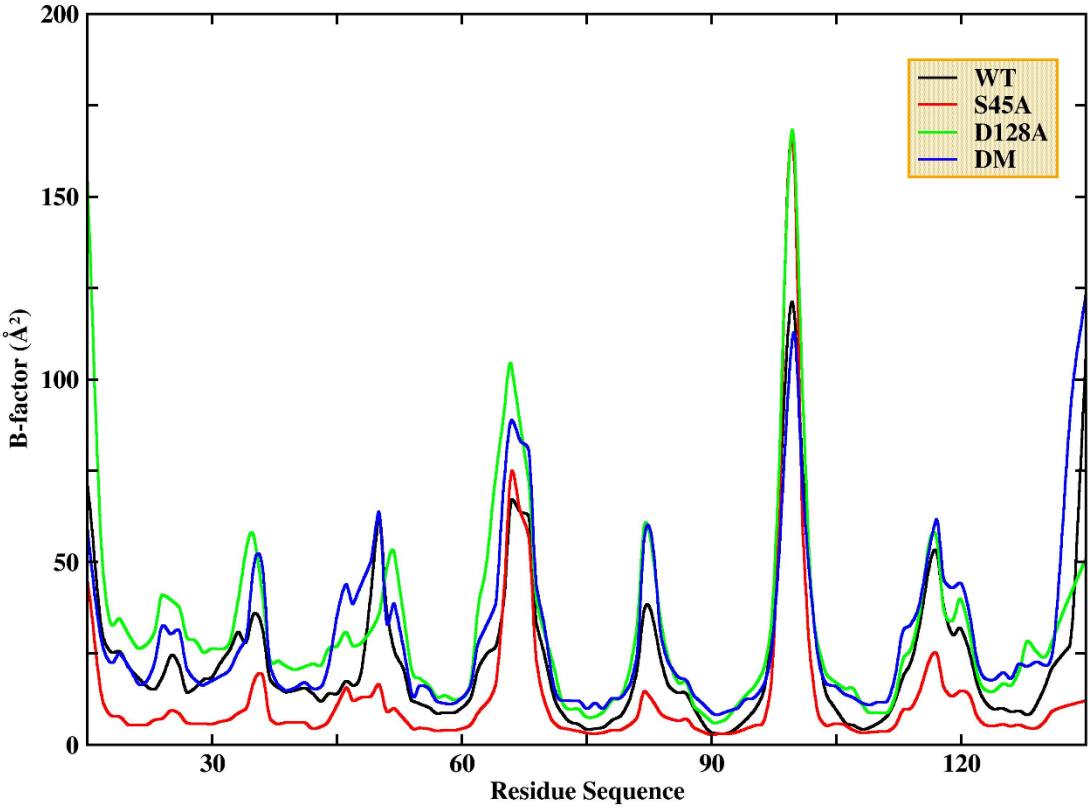

Figure S2. The comparison of simulated B-factors in four system of different

mutation types under the PPC force field.

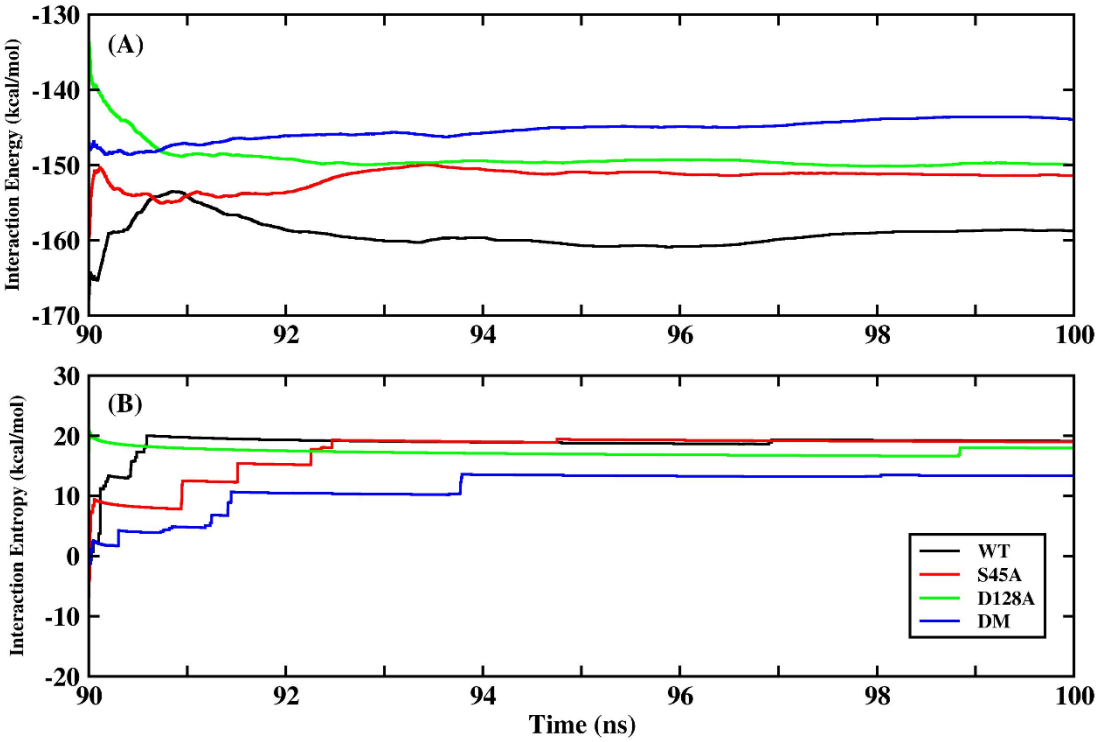

Figure S3. The interaction energy and interaction entropy as function of time during the last 10 ns MD simulation under the PPC force field. (A) is interaction energy; (B) is interaction entropy.

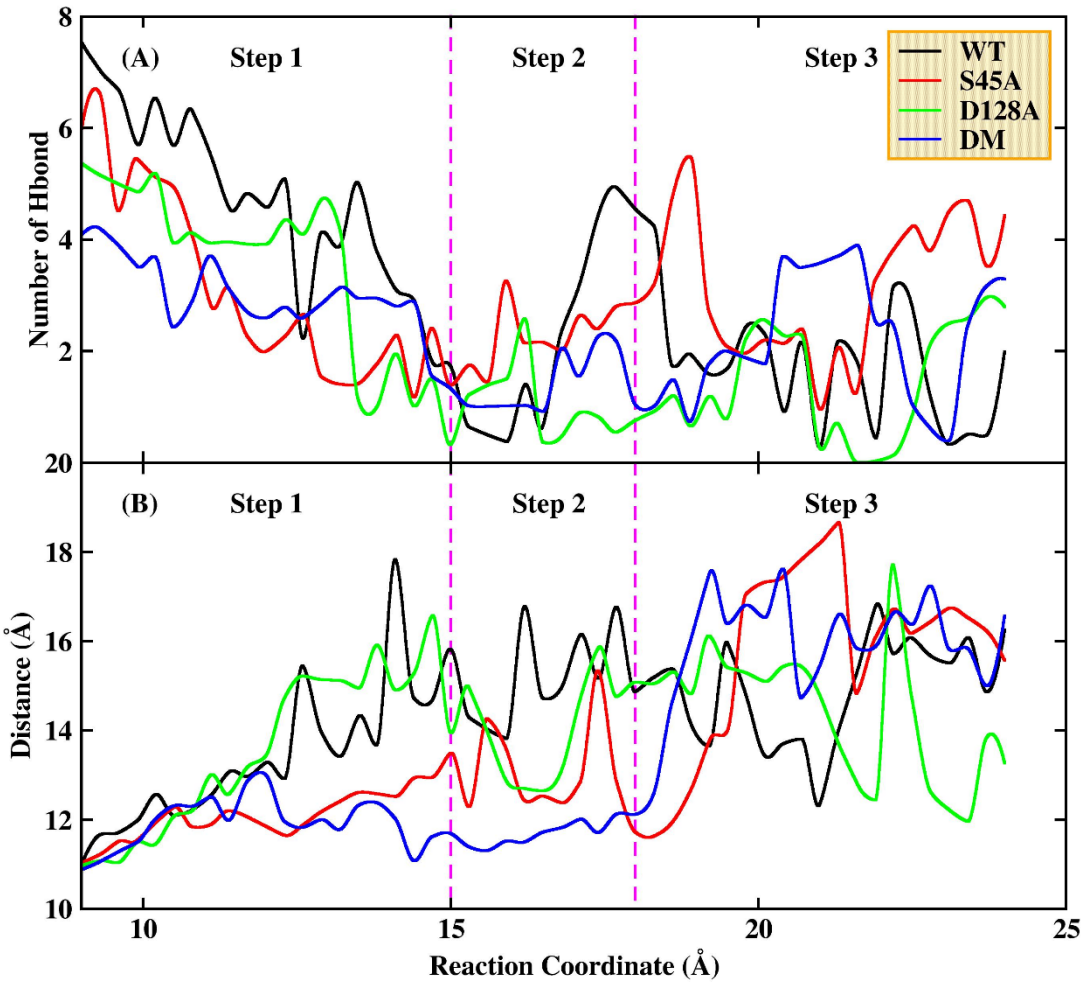

Figure S4. The hydrogen bonds and distance as a function of the reaction coordinates during the unbinding process of streptavidin and biotin. (A): The average number of hydrogen bonds between biotin and streptavidin. (B): The distance between CA atoms of Asn49 and Ala112.

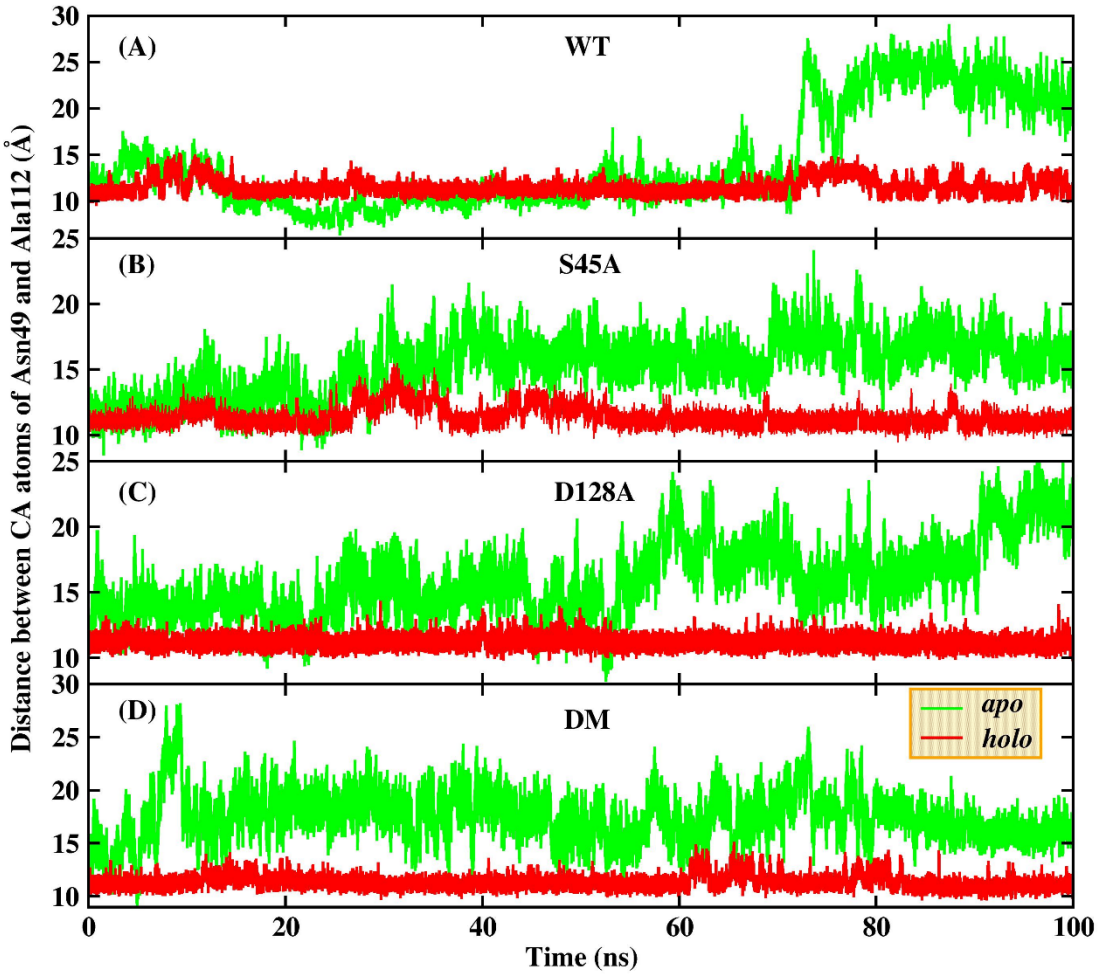

Figure S5. The distances between CA atoms of Asn49 and Ala112 in the *apo* and *holo* structure.