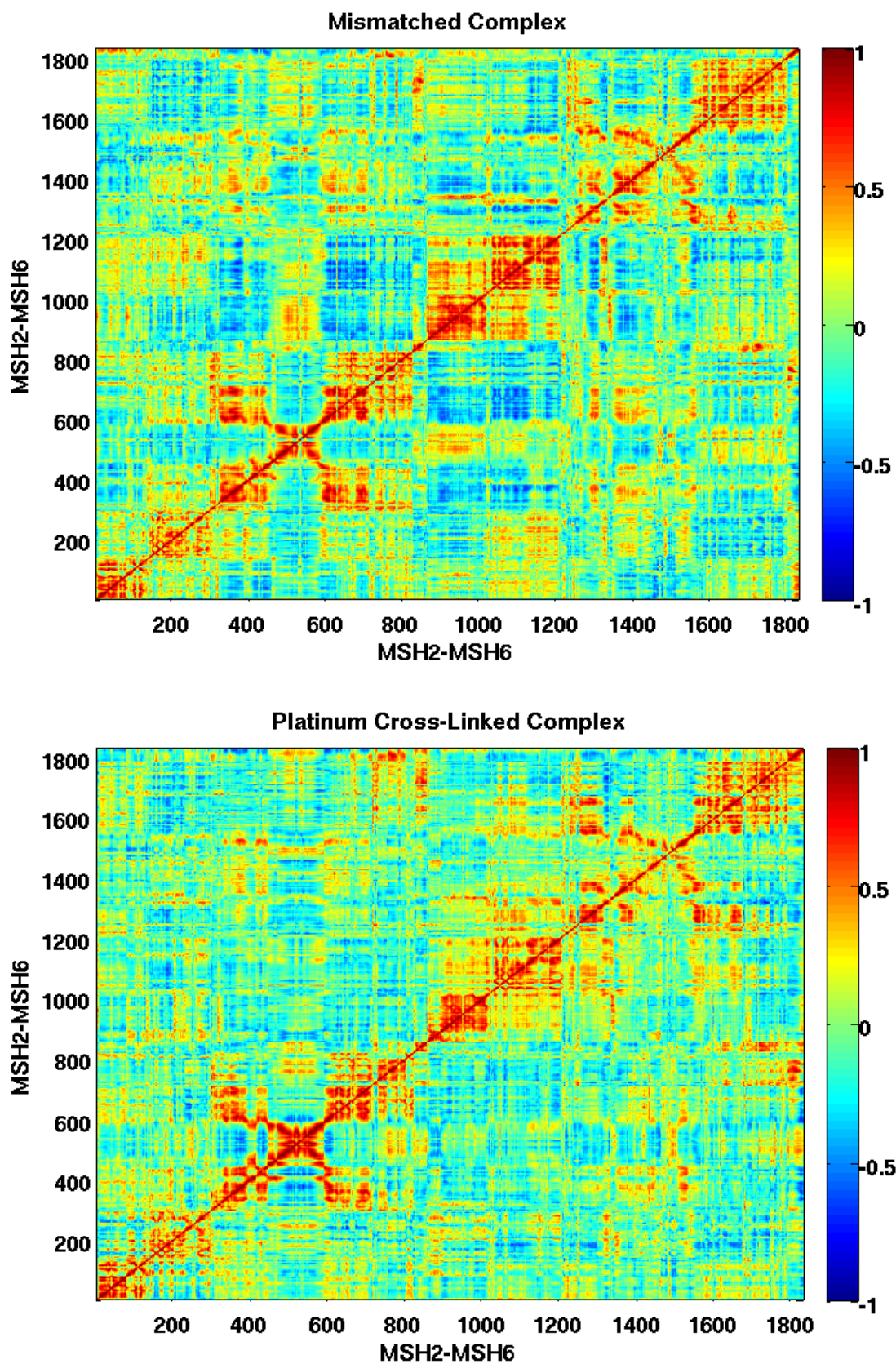


## Supplementary Material

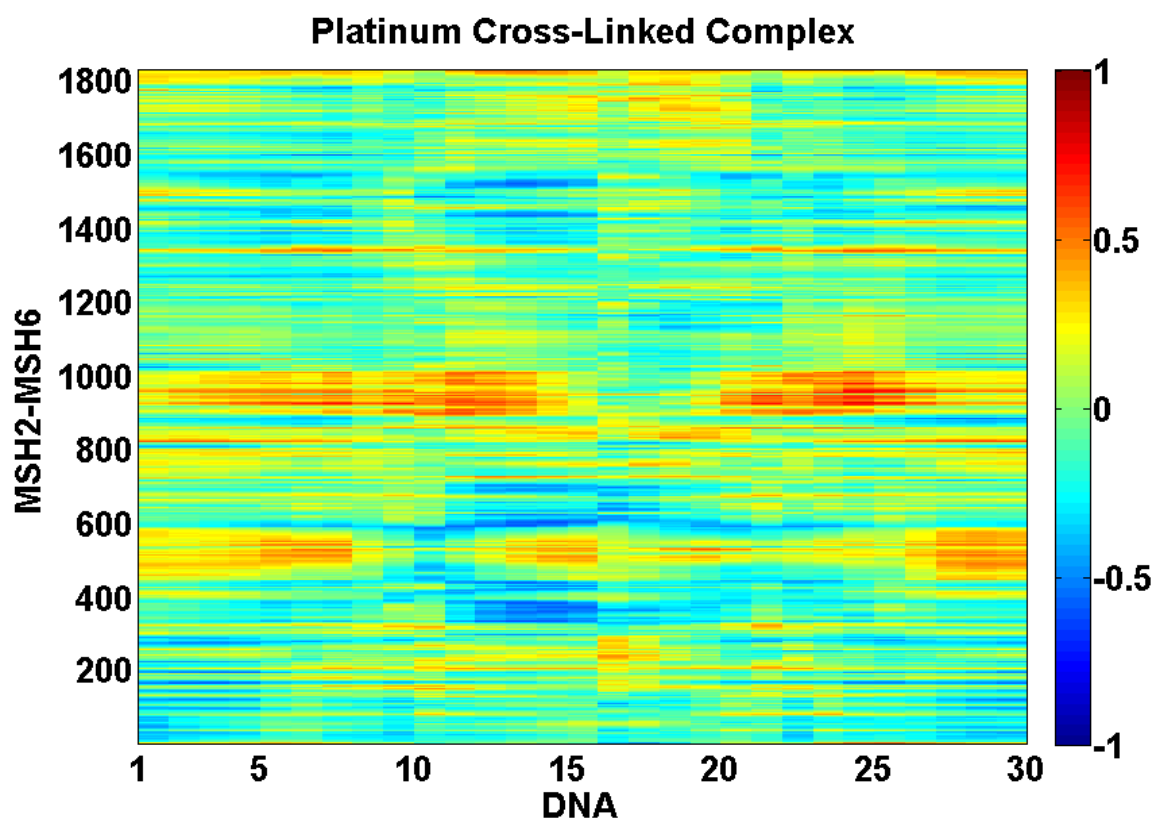
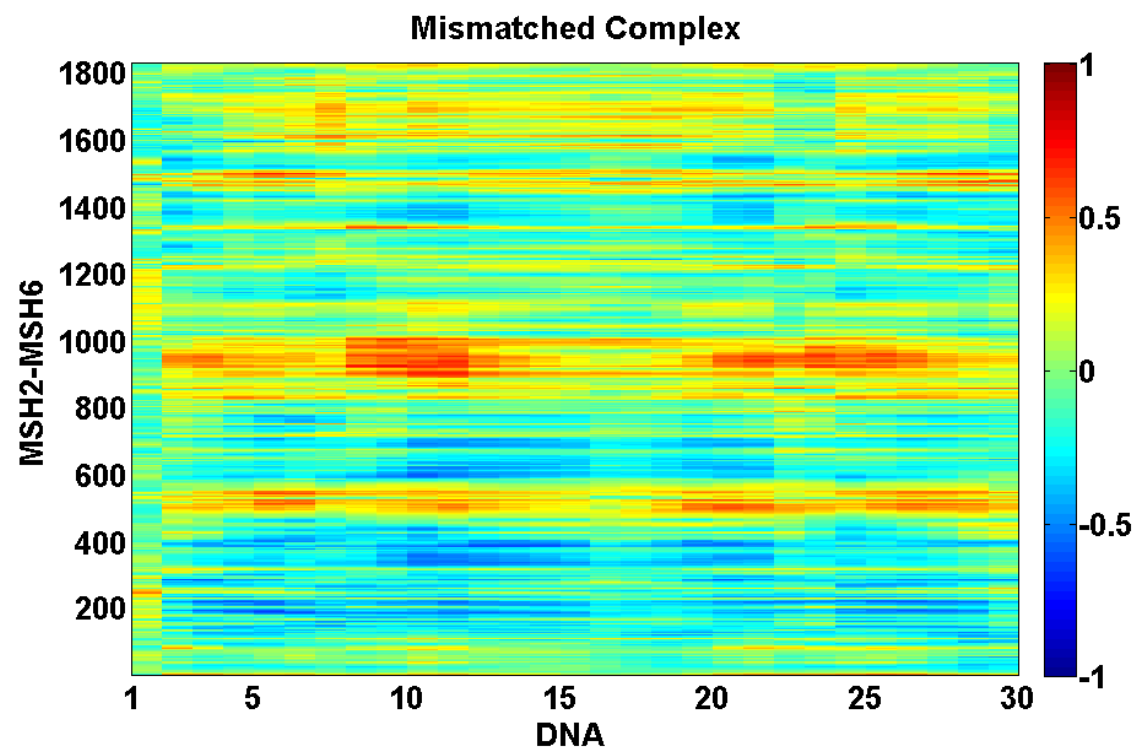
### Protein-DNA Correlations

The mean covariance from the absolute covariance values for the mismatched complex (0.19) is 10.5% greater than that for the platinum cross-linked complex (0.17), indicating that there is a slight decrease in the protein-DNA correlated fluctuations upon cisplatin binding. This is in contrast with the increase seen in the within protein correlated fluctuations. The absolute value of the correlation coefficients was taken into account since its negative sign has no meaning on the strength of the correlation; the negative sign only indicates that the fluctuations are correlated in the opposite direction.

In the strong correlations range (Figure S8, middle set of plots), mismatched Gua8 is coupled with residues 46-48, 64-66, 70, 72-74, 78, 88-91, 97-103, 122-132, 143, and 146-153 from the mismatch binding domain, as well as I482, M483, and Y484 from the lever domain of MSH6. In both systems, Gua8's mispaired base is coupled with residues 64-69, 73-74, 79-98, 102-109, 111-112, 122-124, 127, and 150-151 from the mismatch binding domain, as well as I482, M483, and Y484 from the lever domain of MSH6. Additionally, the mispair of the platinum cross-linked guanine strongly correlates with residues 2-4, 45-46, 48-50, and 146-147 from the mismatch binding domain, as well as 165 of the connector domain of MSH6.



**Figure S1.** Dynamic cross-correlation maps of the Ca atom motions for MutS $\alpha$  calculated from molecular dynamics simulations of the mismatched and platinum cross-linked protein-DNA complexes. The size of the correlation coefficient is proportional to the shading indicated by the scale on the right.

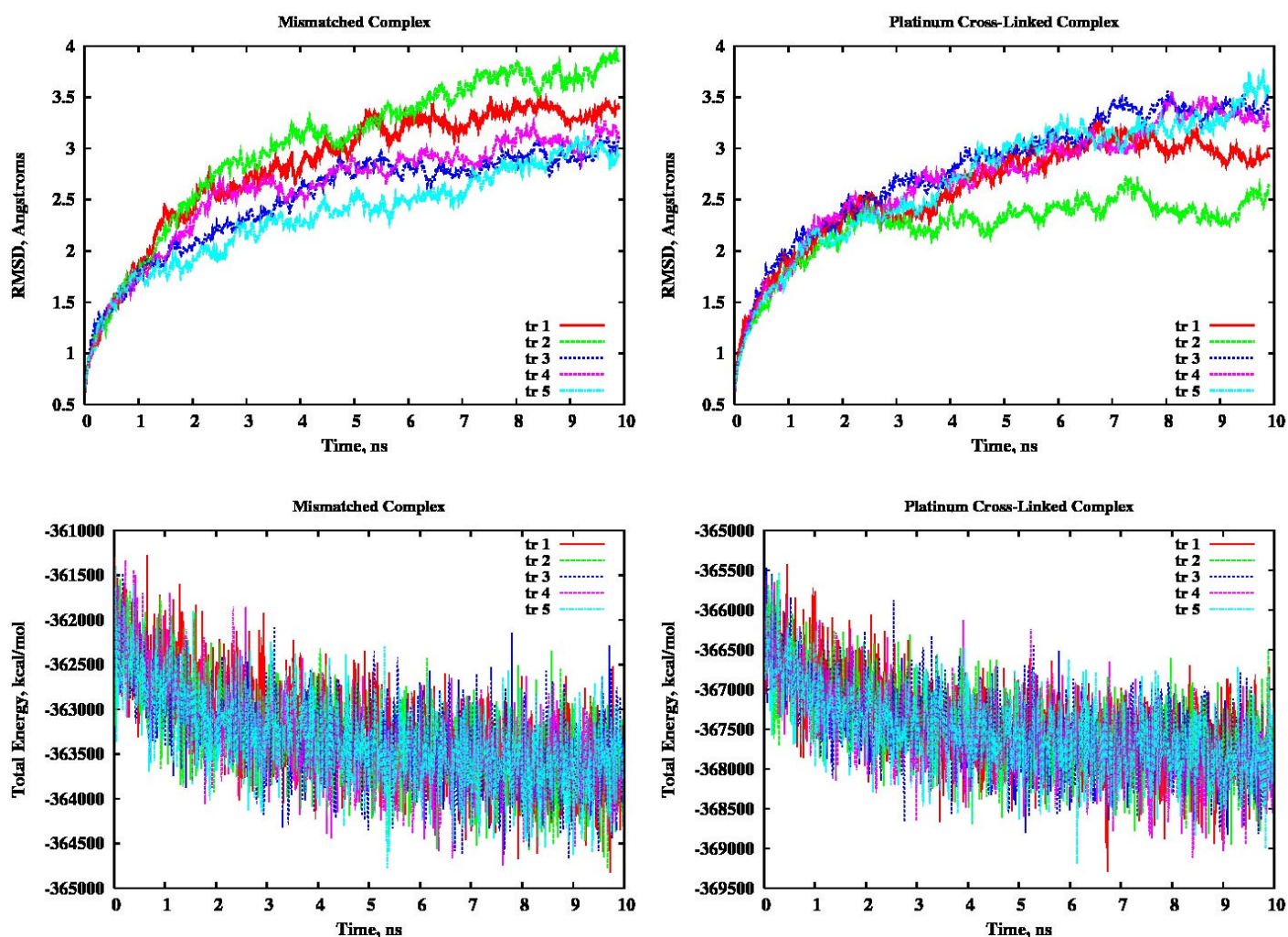


**Figure S2.** MutS $\alpha$ -DNA dynamic cross-correlation maps: correlated motions between  $C\alpha$  atoms of the protein and the heavy-atom residue averaged fluctuations of the 15 base mismatched and platinum cross-linked DNA fragments calculated from their molecular dynamics simulations. The size of the correlation coefficient is proportional to the shading indicated by the scale on the right.

1 M	78 V	151 K	225 T	298 Q	371 E	444 R	517 A	590 E	663 M	736 L	809 E
2 A	79 V	152 M	226 E	299 Y	372 L	445 S	518 Q	591 P	664 F	737 R	810 T
3 V	80 L	153 S	227 R	300 M	373 R	446 D	519 F	592 M	665 H	738 S	811 L
4 Q	81 S	154 A	228 K	301 K	374 Q	447 F	520 G	593 Q	666 I	739 A	812 T
5 P	82 K	155 V	229 K	302 L	375 T	448 S	521 Y	594 T	667 I	740 T	813 M
6 K	83 M	156 D	230 A	303 D	376 L	449 K	522 Y	595 L	668 T	741 K	814 L
7 E	84 N	157 G	231 D	304 I	377 Q	450 F	523 F	596 N	669 G	742 D	815 Y
8 T	85 F	158 Q	232 F	305 A	378 E	451 Q	524 R	597 D	670 P	743 S	816 Q
9 L	86 E	159 R	233 S	306 A	379 D	452 E	525 V	598 V	671 N	744 L	817 V
10 Q	87 S	160 Q	234 T	307 V	380 L	453 M	526 T	599 L	672 M	745 I	818 K
11 L	88 F	161 V	235 K	308 R	381 L	454 I	527 C	600 A	673 G	746 I	819 K
12 E	89 V	162 G	236 D	309 A	382 R	455 E	528 K	601 Q	674 G	747 I	820 G
13 S	90 K	163 V	237 I	310 L	383 R	456 T	529 E	602 L	675 K	748 D	821 V
14 A	91 D	164 G	238 Y	311 N	384 F	457 T	530 E	603 D	676 S	749 E	822 C
15 A	92 L	165 Y	239 Q	312 L	385 P	458 L	531 K	604 A	677 T	750 L	823 D
16 E	93 L	166 V	240 D	313 F	386 D	459 D	532 V	605 V	678 Y	751 G	824 Q
17 V	94 L	167 D	241 L	314 Q	387 L	460 M	533 L	606 V	679 I	752 R	825 S
18 G	95 V	168 S	242 N	315 G	388 N	461 D	534 R	607 S	680 R	753 G	826 F
19 F	96 R	169 I	243 R	316 S	389 R	462 Q	535 N	608 F	681 Q	754 T	827 G
20 V	97 Q	170 Q	244 L	317 V	390 L	463 V	536 N	609 A	682 T	755 S	828 I
21 R	98 Y	171 R	245 L	318 E	391 A	464 E	537 K	610 H	683 G	756 T	829 H
22 F	99 R	172 K	246 K	319 D	392 K	465 N	538 N	611 V	684 V	757 Y	830 V
23 F	100 V	173 L	247 G	320 T	393 K	466 H	539 F	612 S	685 I	758 D	831 A
24 Q	101 E	174 G	248 K	321 T	394 F	467 E	540 S	613 N	686 V	759 G	832 E
25 G	102 V	175 L	249 K	322 G	395 Q	468 F	541 T	614 G	687 L	760 F	833 L
26 M	103 Y	176 C	250 G	323 S	396 R	469 L	542 V	615 A	688 M	761 G	834 A
27 P	104 K	177 E	251 E	324 Q	397 Q	470 V	543 D	616 P	689 A	762 L	835 N
28 E	105 N	178 F	252 Q	325 S	398 A	471 K	544 I	617 V	690 Q	763 A	836 F
29 K	106 R	179 P	253 M	326 L	399 A	472 P	545 Q	618 P	691 I	764 W	837 P
30 P	107 A	180 D	254 N	327 A	400 N	473 S	546 K	619 Y	692 G	765 A	838 K
31 T	108 G	181 N	255 S	328 A	401 L	474 F	547 N	620 V	693 C	766 I	839 H
32 T	109 N	182 D	256 A	329 L	402 Q	475 D	548 G	621 R	694 F	767 S	840 V
33 T	110 K	183 Q	257 V	330 L	403 D	476 P	549 V	622 P	695 V	768 E	841 I
34 V	111 A	185 S	258 L	331 N	404 C	477 N	550 K	623 A	696 P	769 Y	842 E
35 R	112 S	186 N	259 P	332 K	405 Y	478 L	551 F	624 I	697 C	770 I	843 C
36 L	113 K	187 L	260 E	333 C	406 R	479 S	552 T	625 L	698 E	771 A	844 A
37 F	114 E	188 E	261 M	334 K	407 L	480 E	553 N	626 E	699 S	772 T	845 K
38 D	115 N	189 A	262 E	335 T	408 Y	481 L	554 S	627 K	700 A	773 K	846 Q
39 R	116 D	190 L	263 N	336 P	409 Q	482 R	555 K	628 G	701 E	774 I	847 K
40 G	117 W	191 L	264 Q	337 Q	410 G	483 E	556 L	629 Q	702 V	775 G	848 A
41 D	118 Y	192 I	265 V	338 G	411 I	484 I	557 T	630 G	703 S	776 A	849 L
42 F	119 L	193 Q	266 A	339 Q	412 N	485 M	558 S	631 R	704 I	777 F	850 E
43 Y	120 A	194 I	267 V	340 R	413 Q	486 N	559 L	632 I	705 V	778 C	851 L
44 T	121 Y	195 G	268 S	341 L	414 L	487 D	560 N	633 I	706 D	779 M	852 E
45 A	122 K	196 P	269 S	342 V	415 P	488 L	561 E	634 L	707 C	780 F	853 E
46 H	123 A	197 K	270 L	343 N	416 N	489 E	562 E	635 K	708 I	781 A	854 F
47 G	124 S	198 E	271 S	344 Q	417 V	490 K	563 Y	636 A	709 L	782 T	855 Q
48 E	125 P	199 C	272 A	345 W	418 I	491 K	564 T	637 S	710 A	783 H	
49 D	126 G	200 V	273 V	346 I	419 Q	492 M	565 K	638 R	711 R	784 F	
50 A	127 N	201 L	274 I	347 K	420 A	493 Q	566 N	639 H	712 V	785 H	
51 L	128 L	202 P	275 K	348 Q	421 L	494 S	567 K	640 A	713 G	786 E	
52 L	129 S	203 G	276 F	349 P	422 E	495 T	568 T	641 C	714 A	787 L	
53 A	130 Q	204 G	277 L	350 L	423 K	496 L	569 E	642 V	715 G	788 T	
54 A	131 F	205 E	278 E	351 M	424 H	497 I	570 Y	643 E	716 D	789 A	
55 R	132 E	206 T	279 L	352 D	425 E	498 S	571 E	644 V	717 S	790 L	
56 E	133 D	207 A	280 L	353 K	426 G	499 A	572 E	645 Q	718 Q	791 A	
57 V	134 I	208 G	281 S	354 N	427 K	500 A	573 A	646 D	719 L	792 N	
58 F	135 L	209 D	282 D	355 R	428 H	501 R	574 Q	647 E	720 K	793 Q	
59 K	136 F	210 M	283 D	356 I	429 Q	502 D	575 D	648 I	721 G	794 I	
60 T	137 G	211 G	284 S	357 E	430 K	503 L	576 A	649 A	722 V	795 P	
61 Q	138 N	212 K	285 N	358 E	431 L	504 G	577 I	650 F	723 S	796 T	
62 G	139 N	213 L	286 F	359 R	432 L	505 L	578 V	651 I	724 T	797 V	
63 V	140 D	214 R	287 G	360 L	433 L	506 D	579 K	652 P	725 F	798 N	
64 I	141 M	215 Q	288 Q	361 N	434 A	507 P	580 E	653 N	726 M	799 N	
65 K	142 S	216 I	289 F	362 L	435 V	508 G	581 I	654 D	727 A	800 L	
66 Y	143 A	217 I	290 E	363 V	436 F	509 K	582 V	655 V	728 E	801 H	
67 M	144 S	218 Q	291 L	364 E	437 V	510 Q	583 N	656 Y	729 M	802 V	
68 G	145 I	219 R	292 T	365 A	438 T	511 I	584 I	657 F	730 L	803 T	
69 P	146 G	220 G	293 T	366 F	439 P	512 K	585 S	658 E	731 E	804 A	
70 A	147 V	221 G	294 F	367 V	440 L	513 L	586 S	659 K	732 T	805 L	
71 G	148 V	222 I	295 D	368 E	441 T	514 D	587 G	660 D	733 A	806 T	
72 A	149 G	223 L	296 F	369 D	442 D	515 S	588 Y	661 K	734 S	807 T	
73 K	150 V	224 I	297 S	370 A	443 L	516 S	589 V	662 Q	735 I	808 E	

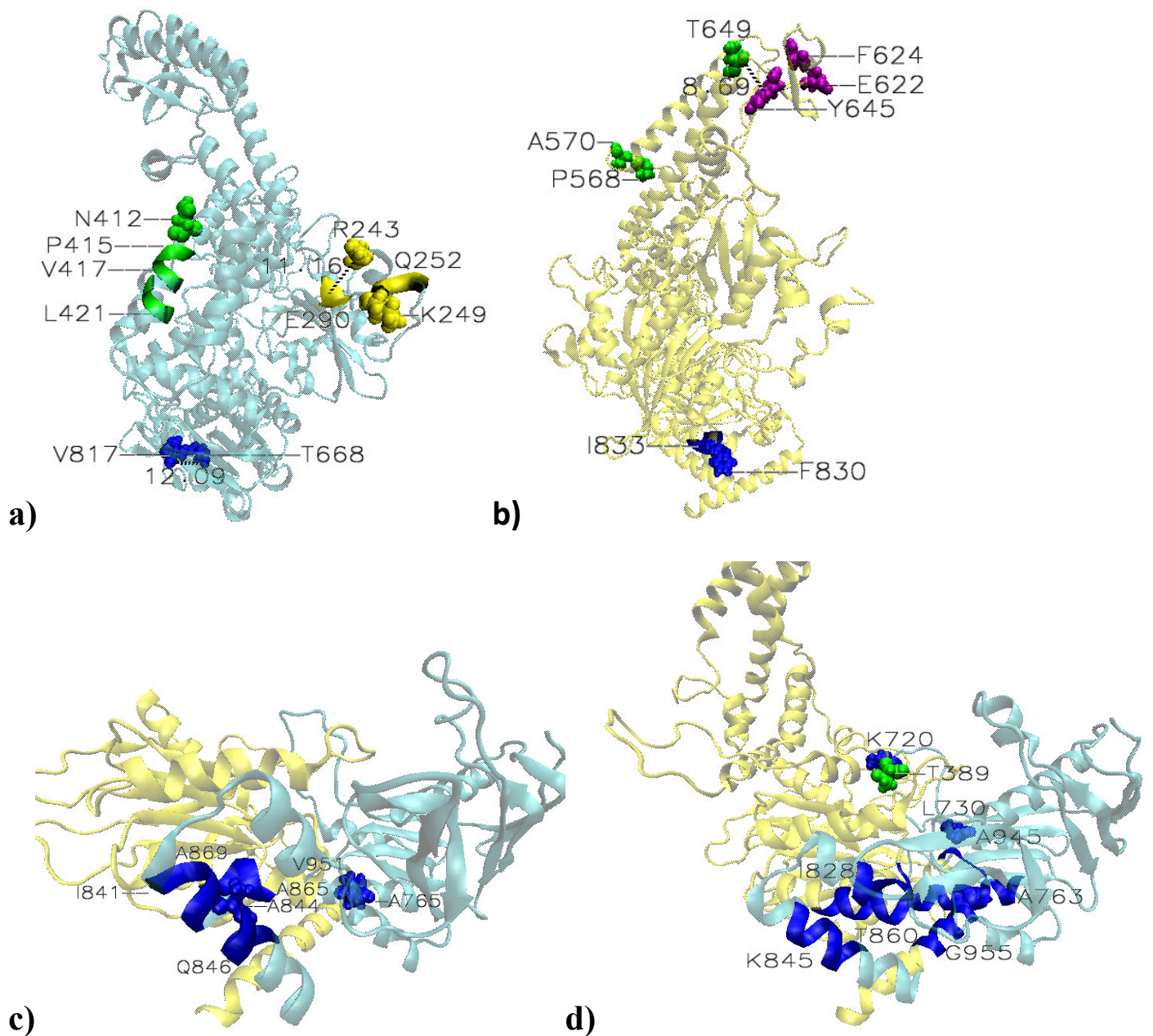
**Figure S3.** Residues sequence and numbering for MSH2 subunit: mismatched binding domain, 1 -124; connector domain,125-297; leveler domain, 300-456 and 554-619; clamp domain, 457-553; ATP-ase domain, 620-855.

1	P	74	L	147	V	220	R	293	M	366	T	439	V	512	G	585	E	658	I	731	K	804	C	877	T
2	T	75	Y	148	V	221	F	294	L	367	K	440	V	513	I	586	N	659	N	732	G	805	R	878	I
3	V	76	H	149	R	222	R	295	P	368	A	441	P	514	M	587	E	660	A	733	S	806	L	879	K
4	W	77	M	150	R	223	T	296	Q	369	Y	442	D	515	E	588	Q	661	E	734	R	807	T	880	C
5	Y	78	D	151	E	224	L	297	V	370	Q	443	K	516	E	589	S	662	E	735	H	808	P	881	R
6	H	79	A	152	I	225	V	298	L	371	R	444	I	517	V	590	L	663	R	736	P	809	I	882	T
7	E	80	L	153	C	226	A	299	K	372	M	445	S	518	A	591	L	664	R	737	C	810	D	883	L
8	T	81	I	154	R	227	H	300	G	373	V	446	E	519	D	592	E	665	D	738	I	811	R	884	F
9	L	82	G	155	I	228	Y	301	M	374	L	447	V	520	G	593	Y	666	V	739	T	812	V	885	S
10	E	83	V	156	I	229	P	302	T	375	D	448	V	521	F	594	L	667	S	740	K	813	F	886	T
11	W	84	S	157	T	230	P	303	S	376	A	449	E	522	K	595	E	668	L	741	T	814	T	887	H
12	L	85	E	158	K	231	V	304	E	377	V	450	L	523	S	596	K	669	K	742	F	815	R	888	Y
13	K	86	L	159	G	232	Q	305	S	378	T	451	L	524	K	597	Q	670	D	743	F	816	L	889	H
14	E	87	G	160	T	233	V	306	D	379	L	452	K	525	I	598	R	671	C	744	G	817	G	890	S
15	E	88	L	161	Q	234	L	307	S	380	N	453	K	526	L	599	N	672	M	745	D	818	A	891	L
16	K	89	V	162	T	235	F	308	I	381	N	454	L	527	K	600	R	673	R	746	D	819	S	892	V
17	R	90	F	163	Y	236	E	309	G	382	L	455	P	528	Q	601	I	674	R	747	F	820	D	893	E
18	R	91	M	164	S	237	K	310	L	383	E	456	D	529	V	602	G	675	L	748	I	821	R	894	D
19	D	92	K	165	V	238	G	311	T	384	I	457	L	530	I	603	C	676	F	749	P	822	I	895	Y
20	E	93	G	166	L	239	N	312	P	385	F	458	E	531	S	604	R	677	Y	750	N	823	M	896	S
21	H	94	N	167	E	240	L	313	G	386	L	459	R	532	L	605	T	678	N	751	D	824	S	897	Q
22	R	95	W	168	G	241	S	314	E	387	N	460	L	533	Q	606	I	679	F	752	I	825	G	898	N
23	R	96	A	169	D	242	K	315	K	388	G	461	L	534	T	607	V	680	D	753	L	826	E	899	V
24	R	97	H	170	P	243	E	316	S	389	T	462	S	535	K	608	Y	681	K	754	I	827	S	900	A
25	P	98	S	171	S	244	T	317	E	390	N	463	K	536	N	609	W	682	N	755	G	828	T	901	V
26	D	99	G	172	E	245	K	318	L	391	G	464	I	537	P	610	G	683	Y	756	C	829	F	902	R
27	H	100	F	173	N	246	T	319	A	392	S	465	H	538	E	611	I	684	K	757	E	830	F	903	L
28	P	101	P	174	Y	247	I	320	L	393	T	466	N	539	G	612	G	685	D	758	E	831	V	904	G
29	D	102	E	175	S	248	L	321	S	394	E	467	V	540	R	613	R	686	W	759	E	832	E	905	H
30	F	103	I	176	K	249	K	322	A	395	G	468	G	541	F	614	N	687	Q	760	E	833	L	906	M
31	D	104	A	177	Y	250	S	323	L	396	T	469	S	542	P	615	R	688	S	761	Q	834	S	907	A
32	A	105	F	178	L	251	S	324	G	397	L	470	P	543	D	616	Y	689	A	762	E	835	E	908	C
33	S	106	G	179	L	252	L	325	G	398	L	471	L	544	L	617	Q	690	V	763	N	836	T	909	M
34	T	107	R	180	S	253	S	326	C	399	E	472	K	545	T	618	L	691	E	764	G	837	A	910	V
35	L	108	Y	181	L	254	C	327	V	400	R	473	S	546	V	619	E	692	C	765	K	838	S	911	E
36	Y	109	S	182	K	255	S	328	F	401	V	474	Q	547	E	620	I	693	I	766	A	839	I	912	N
37	V	110	D	183	E	256	L	329	Y	402	D	475	N	548	L	621	P	694	A	767	Y	840	L	913	E
38	P	111	S	184	K	257	Q	330	L	403	T	476	H	549	N	622	E	695	V	768	C	841	M	914	C
39	E	112	L	185	E	258	E	331	K	404	C	477	P	550	R	623	N	696	L	769	V	842	H	915	E
40	D	113	V	186	E	259	G	332	K	405	H	478	D	551	W	624	F	697	D	770	L	843	A	916	D
41	F	114	Q	187	D	260	L	333	C	406	T	479	S	552	D	625	T	698	V	771	V	844	T	917	P
42	L	115	K	188	S	261	I	334	L	407	P	480	R	553	T	626	T	699	L	772	T	845	A	918	S
43	N	116	G	189	S	262	P	335	I	408	F	481	A	554	A	627	R	700	L	773	G	846	H	919	Q
44	S	117	Y	190	G	263	G	336	D	409	G	482	I	555	F	628	N	701	C	774	P	847	S	920	E
45	C	118	K	191	H	264	S	337	Q	410	K	483	M	556	D	629	L	702	L	775	N	848	L	921	T
46	T	119	V	192	T	265	Q	338	E	411	R	484	Y	557	H	630	P	703	A	776	M	849	V	922	I
47	P	120	A	193	R	266	F	339	L	412	L	485	E	558	E	631	E	704	N	777	G	850	L	923	T
48	G	121	R	194	A	267	W	340	L	413	L	486	E	559	K	632	E	705	Y	778	G	851	V	924	F
49	M	122	V	195	Y	268	D	341	S	414	K	487	T	560	A	633	Y	706	S	779	K	852	D	925	L
50	R	123	E	196	G	269	A	342	M	415	Q	488	T	561	R	634	E	707	R	780	S	853	E	926	Y
51	K	124	Q	197	V	270	S	343	A	416	W	489	Y	562	K	635	L	708	G	781	T	854	L	927	K
52	W	125	T	198	C	271	K	344	N	417	L	490	S	563	T	636	K	709	G	782	L	855	G	928	F
53	W	126	E	199	F	272	T	345	F	418	C	491	K	564	G	637	S	710	D	783	M	856	R	929	I
54	Q	127	T	200	V	273	L	346	E	419	A	492	K	565	L	638	T	711	G	784	R	857	G	930	K
55	I	128	P	201	D	274	R	347	E	420	P	493	K	566	I	639	K	712	P	785	Q	858	T	931	G
56	K	129	E	202	T	275	T	348	Y	421	L	494	I	567	T	640	K	713	M	786	A	859	A	932	A
57	S	130	M	203	S	276	L	349	I	422	C	495	I	568	P	641	G	714	C	787	G	860	T	933	C
58	Q	131	M	204	L	277	L	350	P	423	N	496	D	569	K	642	C	715	R	788	L	861	F	934	P
59	N	132	E	205	G	278	E	351	L	424	H	497	F	570	A	643	K	716	P	789	L	862	D	935	K
60	F	133	A	206	K	279	E	352	D	425	Y	498	L	571	G	644	R	717	V	790	A	863	G	936	S
61	D	134	R	207	F	280	E	353	S	426	A	499	S	572	F	645	Y	718	I	791	V	864	T	937	Y
62	L	135	C	208	F	281	Y	354	D	427	I	500	A	573	D	646	W	719	L	792	M	865	A	938	G
63	V	136	R	209	I	282	F	355	T	428	N	501	L	574	S	647	T	720	L	793	A	866	I	939	F
64	I	137	K	210	G	283	R	356	V	429	D	502	E	575	D	648	K	721	P	794	Q	867	A	940	N
65	C	138	M	211	Q	284	E	357	S	430	R	503	G	576	Y	649	T	722	E	795	M	868	N	941	A
66	Y	139	A	212	F	285	K	358	T	431	L	504	F	577	D	650	I	723	D	796	G	869	A	942	A
67	K	140	H	213	S	286	L	359	T	432	D	505	K	578	Q	651	E	724	T	797	C	870	V	943	R
68	V	141	I	214	D	287	S	360	R	433	A	506	V	579	A	652	K	725	P	798	Y	871	V	944	L
69	G	142	S	215	D	288	D	361	S	434	I	507	M	580	L	653	K	726	P	799	V	872	K	945	A
70	K	143	K	216	R	289	G	362	G	435	E	508	C	581	A	654	L	727	F	800	P	873	E	946	N
71	F	144	Y	217	H	290	I	363	A	436	D	509	K	582	D	655	A	728	L	801	A	874	L	947	L
72	Y	145	D																						

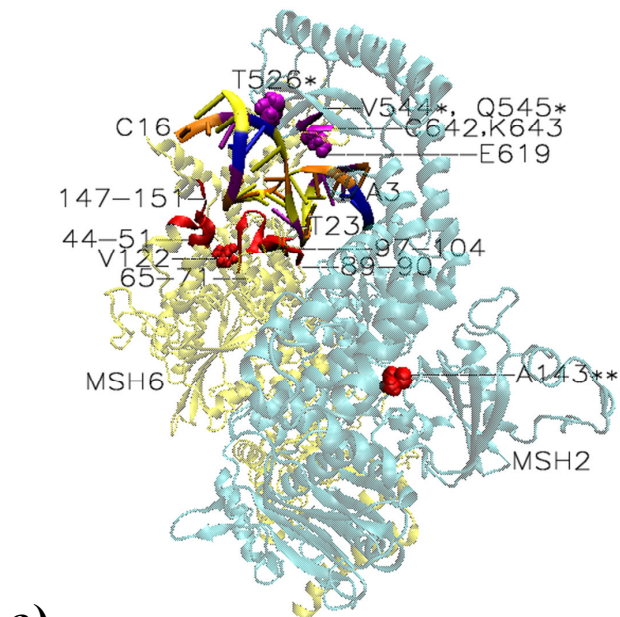


**Figure S5.**  $C\alpha$  root mean square deviations calculated from the initial structure for every 50th snapshot, plotted as a function of time. There are five simulations for each of the mismatched and platinum cross-linked MutS $\alpha$ -DNA complexes. They show that the simulations are equilibrated, with RMSD approximately leveling off by 5 ns.

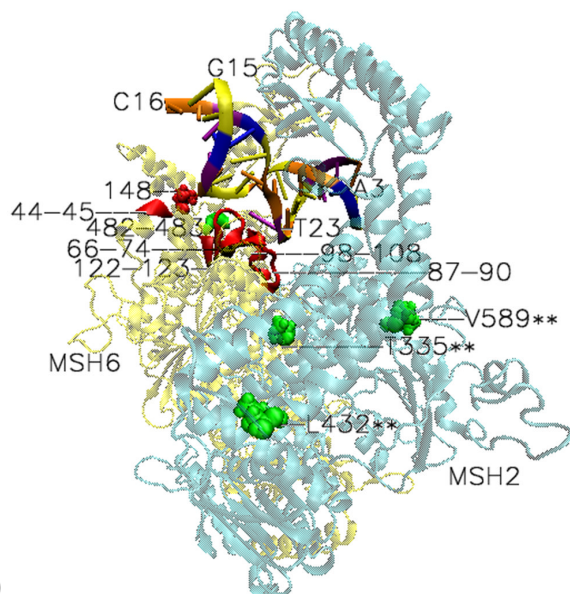
Total energies, presented for every 50th snapshot, for the five simulations of the mismatched and platinum cross-linked MutS $\alpha$ -DNA complexes also show that the systems equilibrate by 5 ns.



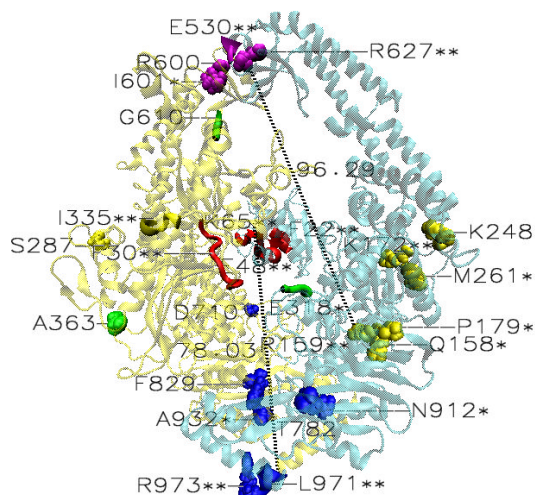
**Figure S6.** Highly significant correlations in the mismatched complex that became weak in the platinum cross-linked complex. **a) MSH2: Correlations within the connector domain** : R243 is paired with E290 and L291, 11.16 Å apart, and K249 is paired with Q252 and M253. **Correlations within the lever domain** involve adjacent residues suggesting either a switch or a very distinctive mechanism in the flow of information in the two systems: N412 is paired with V417 and I418; P415 is coupled with V417 and region 420-421, labeled by L421; N416, not labeled, is coupled with E422. **Correlation within the ATPase domain** between T668 and V817, residues which are 12.09 Å apart. **b) MSH6 : Correlation within the lever domain** involving adjacent residues at the end of the first section of it: P568 and A570. **Correlation within the clamp domain** between E622 and F624. **Correlation at the edge of the lever and the clamp domains connection** between Y645 from the later and T649 from the former, residues which are about 9Å apart. **Correlations within the ATPase domain** between F830 and its nearby region 832-834 labeled by I833. **Highly significant inter-subunits correlations. a) Mismatched DNA complex.** Communications only between the ATPase domains of the MutSa subunits: A765 and A844 from MSH2 are paired with V951 and region A865-A869 from MSH6. Also from MSH2, regions 840-843, labeled by I841, and 845-848, labeled by Q846, are paired with A869 and A865, respectively, from MSH6. **b) Platinum cross-linked DNA complex.** Communication between lever domain of MSH6 by T389 and ATPase domain of MSH2 by K720. Communication between the ATPase domains: from MSH2 subunit, L730 and regions 757-770, labeled by A763, 827-830, labeled by I828, and 842-848, labeled by K845, are paired with A945 and regions 948-963, labeled by G955, 859-862, labeled by T860, and 862-869, (see T860 for reference) from MSH6 subunit.



a)



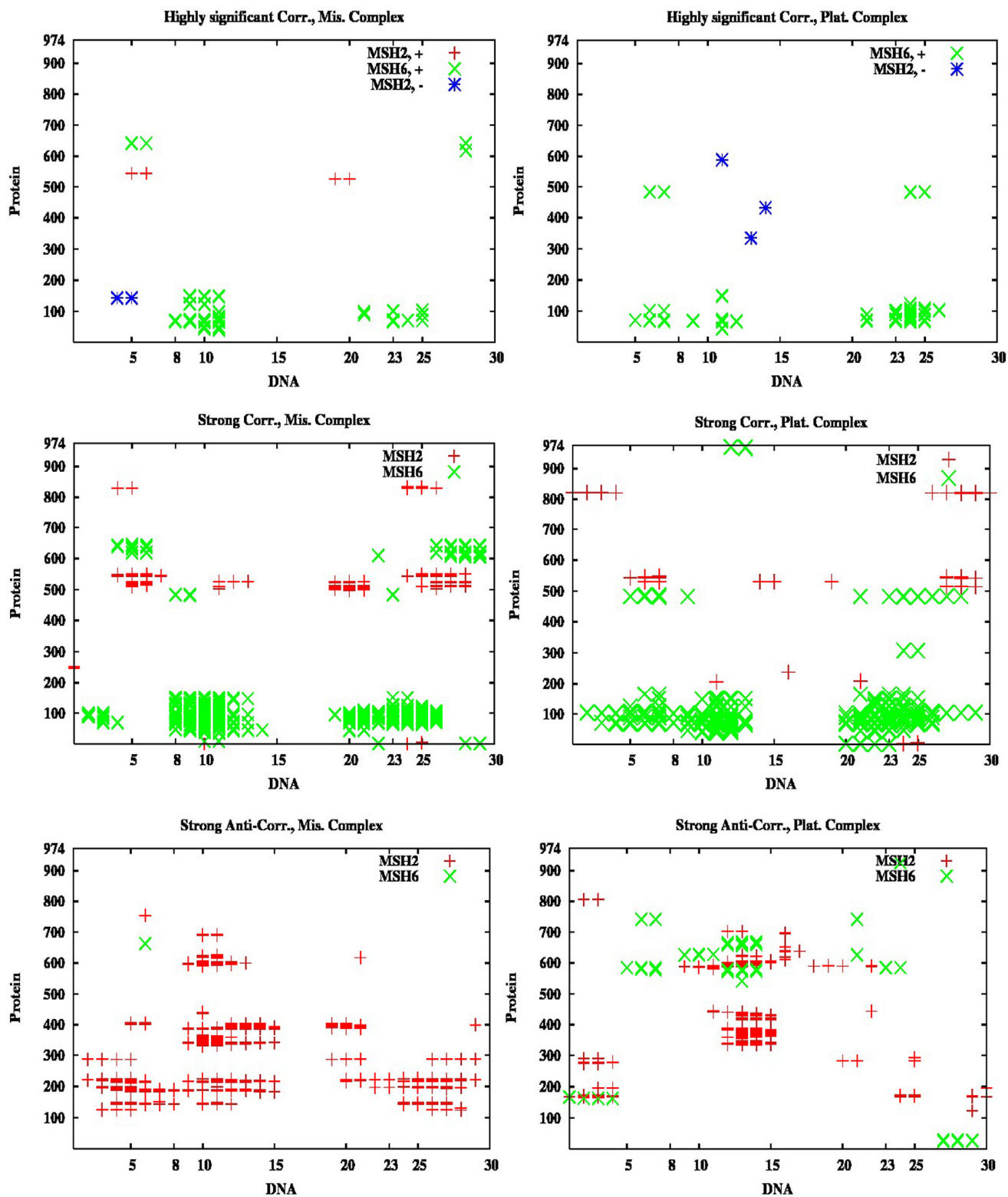
b)



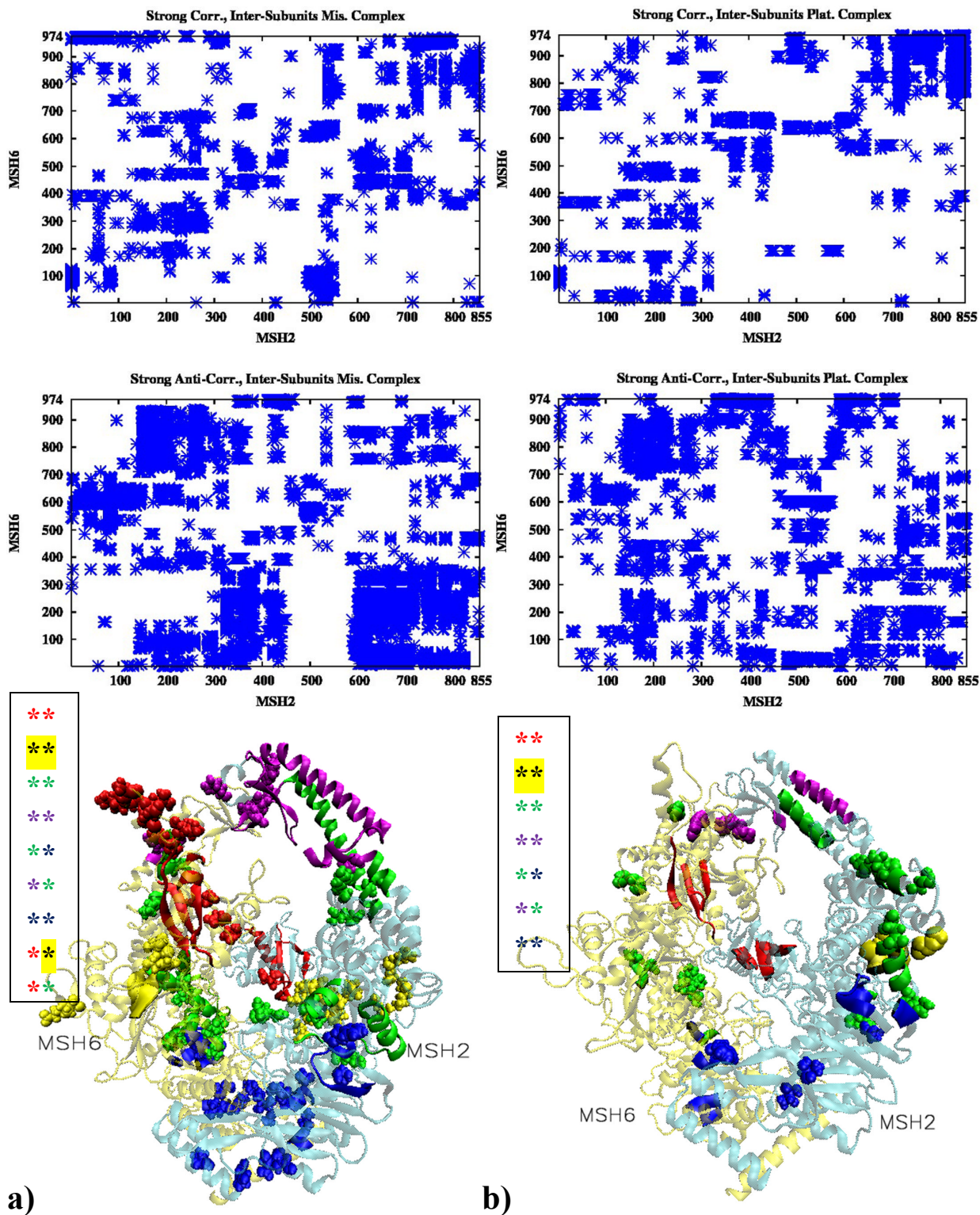
c)

**Figure S7. Protein-DNA highly significant Communications. Mismatch DNA Complex (a) MSH2:** marked with \* are correlations of nucleotides 5, 6, 19, and 20 with T526, V544 and Q545 of the clamp domain; marked with \*\* are anti correlations made by nucleotides 4 and 5 with A143 of the mismatch binding domain. **MSH6:** correlations of nucleotides 5, 6, and 28 with E619, C642 and K643 from the clamp domain; damaged T8 is correlated with mismatch binding residues 67-69 and 71 of the protein's probing loop; nucleotides 9-11 and 21-24 are correlated with residues 44-51, 65-74, 89-90, 97-104, 122, 124 and 147-151 of the mismatch binding domain. **Platinum cross-linked DNA Complex (b): MSH2:** highly significant anti-correlations made by the 11 and 13-14 with three residues from the lever domain T335, L432 and V589. **MSH6:** Unlike in the mismatch complex, the platinum cross-linked G8 makes no highly significant correlations, but its mispair, T23, makes such correlations with residues 67, 71-73, 89, and 98-101 of the mismatch binding domain of MSH6. Unlike in the mismatch complex, correlations with the lever domain, 482-483, by pairs adjacent to the mismatched pair, 6-25 and 7-24; base pairs adjacent to the mismatched base, 9, 11, 12 and 21, are correlated with several regions of the mismatch binding domain: 44-45, 66-74, 79, 83, 87-90, 98-108, 122-123, 148, 150. **c) Change of directionality in long range intra and inter subunits correlations. 1.** Strongly correlated atom displacements in platinum cross-linked complex that change directionality in the mismatched complex, denoted by \*. **Couplings between connector domain of MSH2 (Q158 and P179; M261 ) and ATPase domain of MSH6 (A932; N912).** **Couplings between lever domain of MSH2 (316-319) and clamp domain of MSH6 (I601) ,** about 76 Å apart. **2.** Strongly correlated atom displacements in the mismatched complex that change directionality in the platinum cross-linked complex , denoted by \*\*. **Correlations between mismatch binding domain of MSH2 (20-25, 46-51, 64-67, 72-73, and 75-76 ) and ATPase domain of MSH6 (969-973) . Couplings between connector domain of MSH2 (R159; K172) with both clamp (R627 ) and ATPase domain of MSH6 (R973).** **Couplings between clamp domain of MSH2 (529-531) and mismatch binding (28-34) and connector domains of MSH6 (334-338).** **3. Intra-subunits strong correlations in the platinum cross-linked complex become strong anti-correlations in the mismatched complex.** In MSH2: K531 from the clamp domain and T782 from the ATPase domain. In MSH6: A363 from the lever domain R600 from the clamp domain, as well as S287 from the connector domain and D710 from the lever domain. **Strong correlations in mismatched complex become negative in platinum cross-linked complex.** In MSH2: K248 from the connector domain and E318 from the lever domain. In MSH6: G610 from the lever domain and F829 from the ATPase domain.





**Figure S8. Protein-DNA Correlations.** Highly significant correlations are comparative in number in both systems: six from MSH2 and 88 from MSH6 in the mismatched, and none from MSH2 and 90 from MSH6 in the platinum cross-linked complex. Major difference: while mismatched DNA displays highly significant and strong correlations with the clamp domain of MSH6, residues 619, and 642-643, the damaged DNA displays similar correlations with the lever domain of MSH6, residues 482-483. Limited number of highly significant anti-correlations: two with the mismatch binding domain of MSH2 in the mismatched complex, and three with the lever domain of MSH2 in the platinum cross-linked complex. In each complex, the clamp domain of MSH2 and the mismatch binding domain of MSH6 are responsible for most of the strong protein-DNA correlations. There are 39% more strong anti-correlations in the MSH2 of the mismatched complex than in the platinum cross-linked complex. In the mismatched complex, residues from all but clamp domain of MSH2 are strongly anti-correlated with most of the DNA bases. Gua8-Thy23 is the mismatched pair.



**Figure S9. Inter-subunits correlations.** The C-terminal of MSH6 is strongly correlated with the mismatch binding and connector domains of MSH2 in the mismatched complex, and with ATPase domain in the platinum cross-linked complex. There are 58% more strong inter-subunits anti-correlations in the mismatched than in the damaged complex. Notice the extended anti-correlations between the connector domain of MSH2 and the ATPase of MSH6, and between lever and ATPase domains of MSH2 and the mismatch binding and connector domains of MSH6. In the mismatched complex it is noticeable the lack of strong anti-correlations between clamp domain of MSH2 and the mismatch binding and connector domains of MSH6, seen in the platinum cross-linked complex.

**Summary of highly significant correlations in platinum cross-linked (a) and mismatched (b) MutSa –DNA complexes.** In the platinum cross-linked complex they are about 53% more such correlations than in the mismatched complex. Accounts for the meaningful difference reside in the highly correlated motions between extended regions of the lever domain and the clamp domain of the non-binding subunit, as well as within the connector domain and the lever domain of both subunits. Unique for the platinum cross-linked system, as marked in the legend, are correlations between mismatch binding domain and connector domain in both subunits as well as between the mismatch binding domain and the lever domain in the binding subunit. It is noteworthy the manifold highly correlated residues at the mismatch binding site in the platinum cross-linked system, as well as the lack of highly significant correlations within the connector domain of the binding subunit in the mismatched complex. The latter subunit also exhibits limited highly significant correlations within the lever domain and the ATPase domain.