

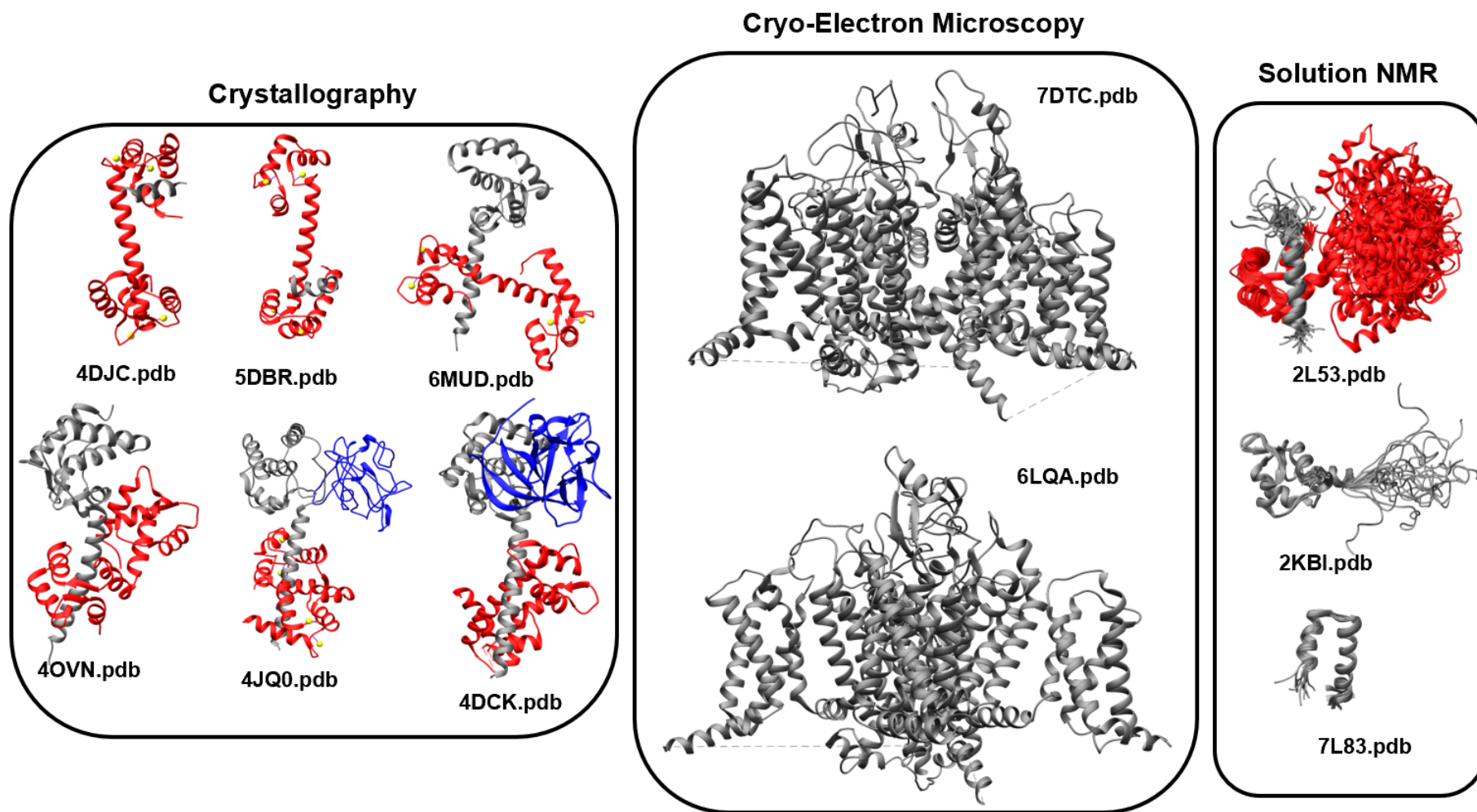
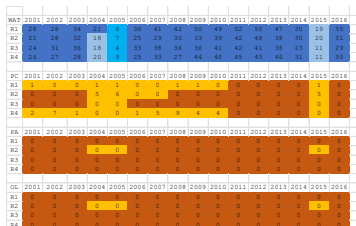


Fig. S1. Empirically determined structures that were used by AlphaFold that to generate a model of Na_v1.5 (UniProt ID: Q14524)

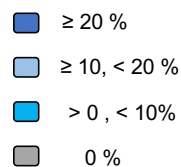
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R2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
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R18	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63																																					

[illegible]

[illegible]



Water



Lipids



Fig. S2. Contacts between each amino acid with with water, PC, PA, and OL molecules. Values are expressed as a percentage of frames where contact was observed. Cells are color coded to facilitate rapid visual scanning for consistency. Images of the table are generated in high resolution to allow for enlargement after downloading SI files.

	Extended beta (parallel beta)										anti-parallel beta										3-10 helix										Alpha helix										Turn										Bend																																																																																																																																																																																																																																																																																																																																																																																																																																										
1	M	A	N	F	L	L	P	R	G	T	S	S	F	R	R	F	T	R	E	S	L	A	A	I	E	K	R	M	A	E	K	A	R	G	S	T	T	L	Q	E	S	R	E	R	E	G	L	F	E	E	E	A	P	R	P	Q	L	D	L	Q	A	S	K	K	L	P	D	L	Y	G	N	F	P	Q	E	L	I	G	E	P	L	E	D	L	D	P	F	Y	S	T	Q	K	T	F	I	V	L	N	K	G	S																																																																																																																																																																																																																																																																																																																																																																																								
101	T	I	F	R	F	S	A	T	T	N	G	L	V	V	S	P	F	H	P	I	R	R	A	A	V	K	I	L	V	H	S	L	F	N	M	L	I	M	C	T	I	G	A	L	T	N	C	V	F	M	A	Q	H	D	P	F	F	W	T	K	Y	V	E	S	T	F	A	I	Y	T	F	E	S	L	V	K	I	L	A	R	G	F	C	L	H	A	F	T	F	L	R	L	E	F	F	N	V	L	N	K	G	S																																																																																																																																																																																																																																																																																																																																																																																							
201	I	I	M	A	Y	T	T	E	F	V	D	L	G	N	V	S	A	L	R	T	F	R	V	L	R	A	L	K	T	I	V	S	V	I	S	G	L	K	T	I	V	G	A	L	I	Q	S	V	K	K	L	I	V	C	A	D	V	M	V	L	T	V	F	C	E	S	T	F	A	L	I	G	L	Q	L	F	M	G	N	L	R	H	K	C	V	R	N	F	T	A	L	N	G	T	L	N	G	S	V	E	A	D	G	L	V	S																																																																																																																																																																																																																																																																																																																																																																																			
301	W	E	S	L	D	L	Y	L	S	D	E	E	N	Y	L	K	N	G	T	S	D	V	L	L	C	G	N	S	S	D	A	G	T	C	P	E	G	Y	R	C	L	K	A	G	E	N	S	P	D	H	G	Y	T	S	F	D	S	F	A	W	A	L	F	L	A	L	F	R	L	M	T	Q	D	C	E	W	E	R	L	Y	Q	Q	T	L	R	S	A	G	E	K	I	Y	M	I	F	F	M	V	L	F	L	S																																																																																																																																																																																																																																																																																																																																																																																							
401	S	F	Y	L	V	N	L	I	L	A	V	N	V	A	M	A	Y	E	E	Q	A	T	I	A	E	T	E	M	K	E	K	R	F	Q	E	A	M	E	M	L	K	K	E	H	E	A	L	T	I	R	G	V	D	T	V	S	R	S	S	L	E	M	S	P	L	A	P	V	N	S	H	E	R	R	S	K	R	R	K	S	R	M	S	S	G	T	E	E	C	G	E	I	D	F	L	P	K	S	D	L	S																																																																																																																																																																																																																																																																																																																																																																																								
501	D	G	P	R	A	M	N	H	L	S	L	T	R	G	L	S	R	T	S	K	M	P	R	S	S	R	G	S	I	F	T	F	R	R	R	D	L	G	S	E	A	D	F	A	D	D	E	N	T	A	G	E	S	E	S	H	H	T	S	L	L	V	F	W	L	R	R	T	S	A	Q	P	G	S	P	G	T	S	A	P	G	H	A	L	H	G	K	N	S	T	V	D	C	N	G	V	S																																																																																																																																																																																																																																																																																																																																																																																												
601	V	S	L	L	G	A	G	D	P	E	A	T	S	P	G	S	H	L	L	P	V	M	L	S	E	H	P	P	D	T	T	P	S	E	P	G	G	A	F	Q	M	L	T	S	Q	A	P	C	V	D	G	F	E	E	P	G	A	R	S	L	V	S	V	L	T	S	A	L	E	E	L	E	S	R	H	K	C	P	P	C	N	L	A	Q	R	Y	L	I	W	E	C	K	S																																																																																																																																																																																																																																																																																																																																																																																																
701	F	L	M	S	M	S	I	K	Q	G	V	K	L	V	W	M	D	P	F	T	L	T	I	T	M	C	I	V	L	N	T	L	F	M	A	L	E	H	Y	N	M	T	S	E	F	E	E	M	L	V	G	N	L	V	T	G	I	F	T	A	E	M	T	F	K	I	A	I	L	D	P	Y	Y	Y	F	Q	Q	G	W	N	I	F	D	S	I	V	I	L	S	L	M	E	L	G	L	S	F	S																																																																																																																																																																																																																																																																																																																																																																																											
801	M	S	N	L	S	V	L	R	S	E	R	L	L	R	V	F	K	L	A	K	S	W	P	T	P	L	N	T	L	I	K	I	I	G	N	S	V	G	A	L	G	N	T	L	L	V	A	I	V	P	I	F	A	V	M	G	M	Q	L	F	A	G	K	N	Y	S	E	L	R	D	S	F	S	G	L	L	F	R	W	H	M	M	D	F	F	H	A	F	L	I	F	R	I	L	C	G	E	W	S																																																																																																																																																																																																																																																																																																																																																																																										
901	E	T	M	W	D	C	M	E	V	S	G	Q	S	L	C	L	L	V	F	L	V	M	V	I	I	G	N	L	V	L	S	L	V	N	L	F	L	A	L	L	S	S	F	S	A	D	N	L	T	A	P	D	E	D	R	E	M	N	L	L	Q	L	A	L	A	R	I	Q	R	G	L	R	F	V	K	R	T	T	W	D	F	C	C	G	L	L	R	Q	R	P	Q	K	P	A	A	L	A	Q	G	K	S																																																																																																																																																																																																																																																																																																																																																																																								
1001	L	P	S	C	I	A	T	P	S	P	P	P	P	T	E	K	V	P	T	R	K	E	T	R	F	C	E	E	G	E	Q	P	G	Q	G	T	P	G	S	T	D	E	P	E	D	C	V	P	I	A	E	L	V	A	E	S	D	T	D	D	Q	D	E	D	E	E	N	S	L	G	T	E	E	S	S	K	Q	C	E	S	Q	P	V	S	G	G	P	E	A	P	P	D	S	R	T	S	Q	V	S	A	S	S																																																																																																																																																																																																																																																																																																																																																																																							
1101	T	A	S	E	A	E	A	S	A	Q	A	D	W	R	Q	Q	W	K	A	E	A	P	Q	A	P	G	C	F	E	E	T	P	E	D	S	C	S	E	G	S	T	P	E	D	A	M	T	N	T	A	L	E	Q	I	P	D	L	G	Q	D	E	W	K	D	P	E	D	C	F	T	E	G	C	V	R	K	C	P	C	A	C	V	D	D	T	Q	A	P	G	K	W	L	R	L	R	K	T	C	Y	F	S																																																																																																																																																																																																																																																																																																																																																																																								
1201	I	V	E	H	S	W	F	E	T	F	I	F	M	L	L	S	G	S	A	L	A	F	E	D	I	Y	L	E	B	R	K	T	I	K	V	L	L	E	Y	A	D	K	M	F	T	Y	V	F	V	E	L	M	L	K	W	V	A	Y	G	F	K	K	Y	F	T	N	A	W	C	W	L	D	F	L	I	V	D	V	S	V	L	S	L	V	A	N	T	L	G	F	A	E	M	G	K	P	I	K																																																																																																																																																																																																																																																																																																																																																																																											
1301	S	L	R	T	L	R	A	L	R	L	P	L	R	A	L	S	R	F	E	G	M	R	V	V	N	A	L	V	A	I	P	S	I	M	N	V	L	L	V	C	L	I	F	I	F	S	I	M	G	V	N	L	F	A	G	K	V	A	G	R	C	I	N	Q	T	E	G	D	L	P	L	N	Y	T	I	V	N	K	S	Q	C	E	S	L	N	L	T	G	E	L	Y	A	E	M	G	K	P	I	K																																																																																																																																																																																																																																																																																																																																																																																										
1401	N	F	D	N	V	G	A	G	Y	L	A	L	L	Q	V	A	T	F	K	G	W	M	D	I	M	Y	A	A	V	D	S	R	G	Y	E	B	L	Q	P	Q	W	E	Y	N	L	Y	M	Y	I	Y	F	V	I	F	I	I	F	G	S	F	F	T	L	N	L	F	I	G	V	I	I	D	N	F	N	Q	Q	K	K	K	L	G	G	Q	D	I	F	M	T	E	E	Q	K	K	Y	N	A	M	K	I	S																																																																																																																																																																																																																																																																																																																																																																																								
1501	L	G	S	K	K	F	Q	K	P	I	P	R	P	L	N	K	Y	Q	G	F	I	F	D	I	V	T	K	Q	A	F	D	T	I	M	F	L	I	C	L	N	M	V	T	M	M	Y	E	T	D	Q	S	P	E	K	I	N	I	L	A	K	I	L	L	F	V	A	I	T	G	T	E	C	E	I	V	K	L	A	I	L	R	H	Y	Y	F	T	N	S	W	N	I	F	D	F	V	Y	S	S																																																																																																																																																																																																																																																																																																																																																																																											
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1901	E	E	V	S	A	M	V	I	Q	R	A	F	R	R	H	L	L	Q	R	S	L	K	H	A	S	F	L	F	R	Q	Q	A	G	S	G	L	S	E	E	D	A	P	E	R	E	G	L	I	A	Y	V	M	S	E	N	F	S	R	P	L	G	P	P	S	S	S	I	S	S	T	S	F	P	P	S	Y	D	S	V	T	R	A	T	S	D	N	L	Q	V	R	G	S	D	Y	S	H	S	E	I	S																																																																																																																																																																																																																																																																																																																																																																																									
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 $\geq 20 \%$
 $\geq 10, < 20 \%$
 $> 0, < 10\%$
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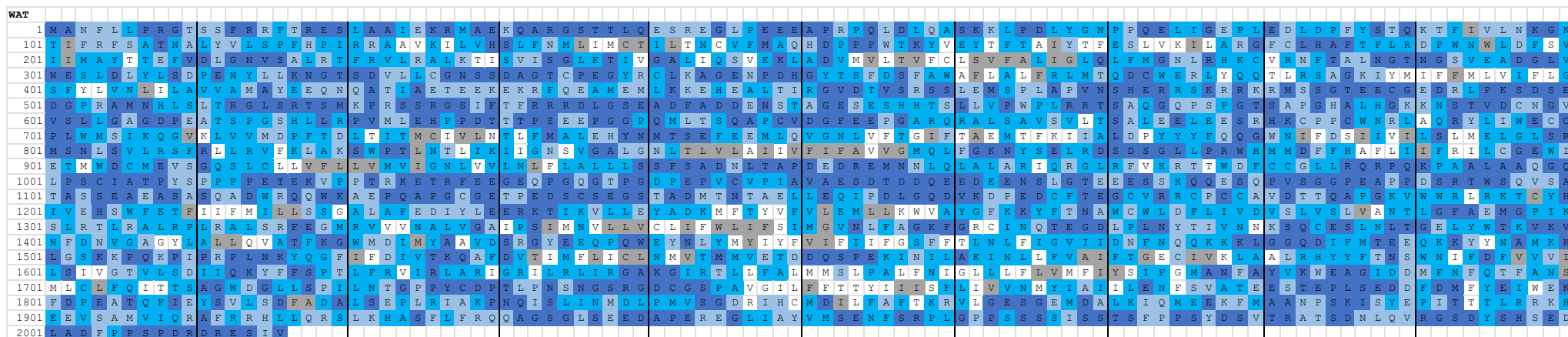


Fig. S4a. Sequence of Na_v1.5. with each amino acids color coded by number of frames that it contacts water. Amino acids that varied water contact between simulations shown in white.

Lipids

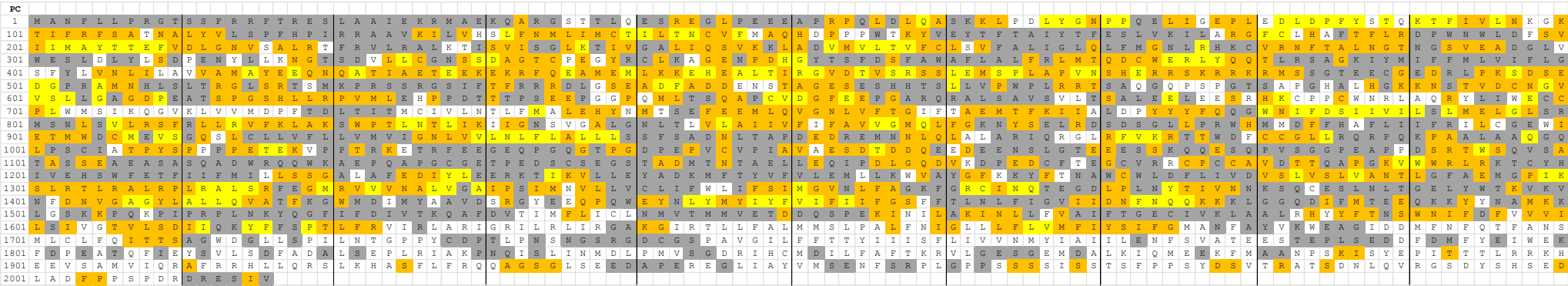


Fig. S4b. Sequence of Na_v1.5. with each amino acids color coded by number of frames that it contacts PC.

Lipids

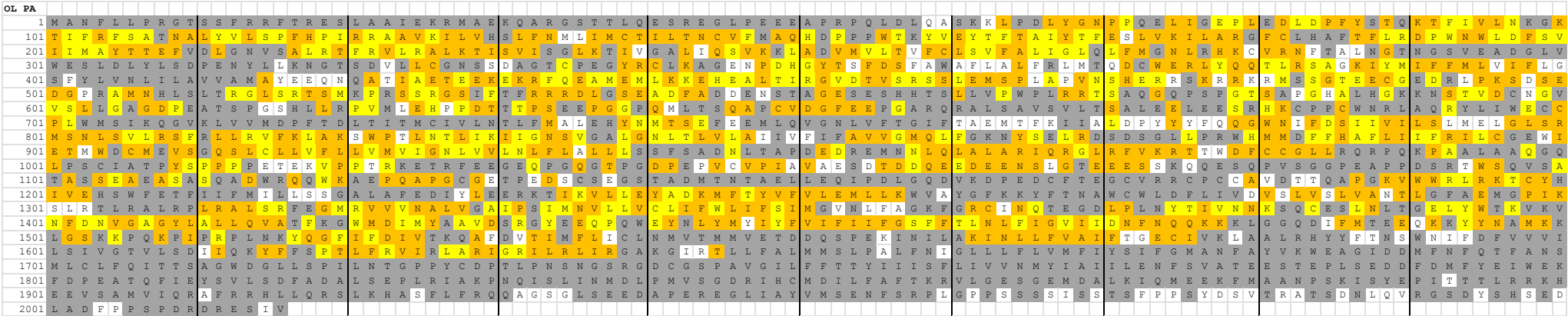
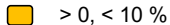
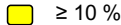


Fig. S4c. Sequence of Na_v1.5. with each amino acids color coded by number of frames that it contacted OL or PA.

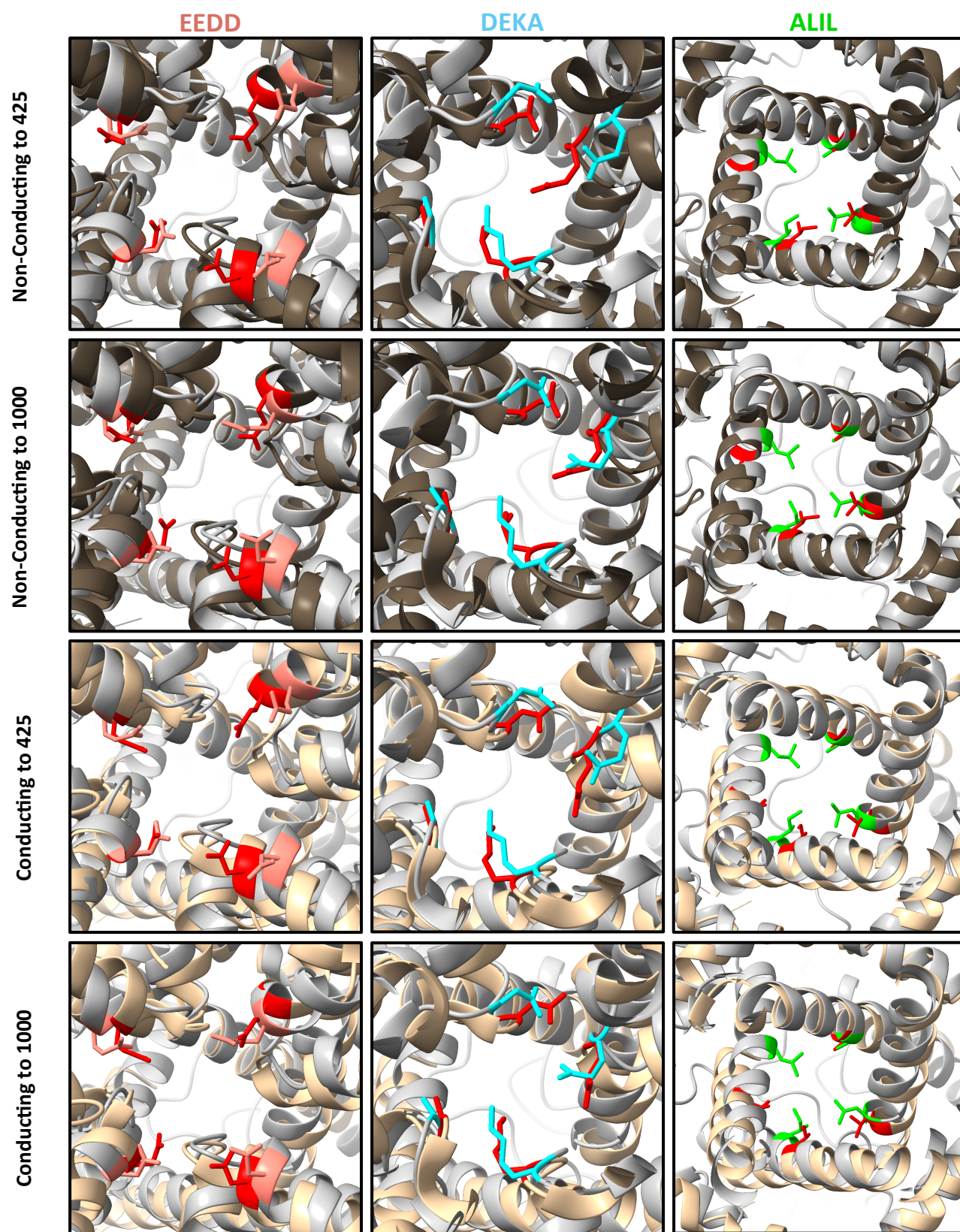
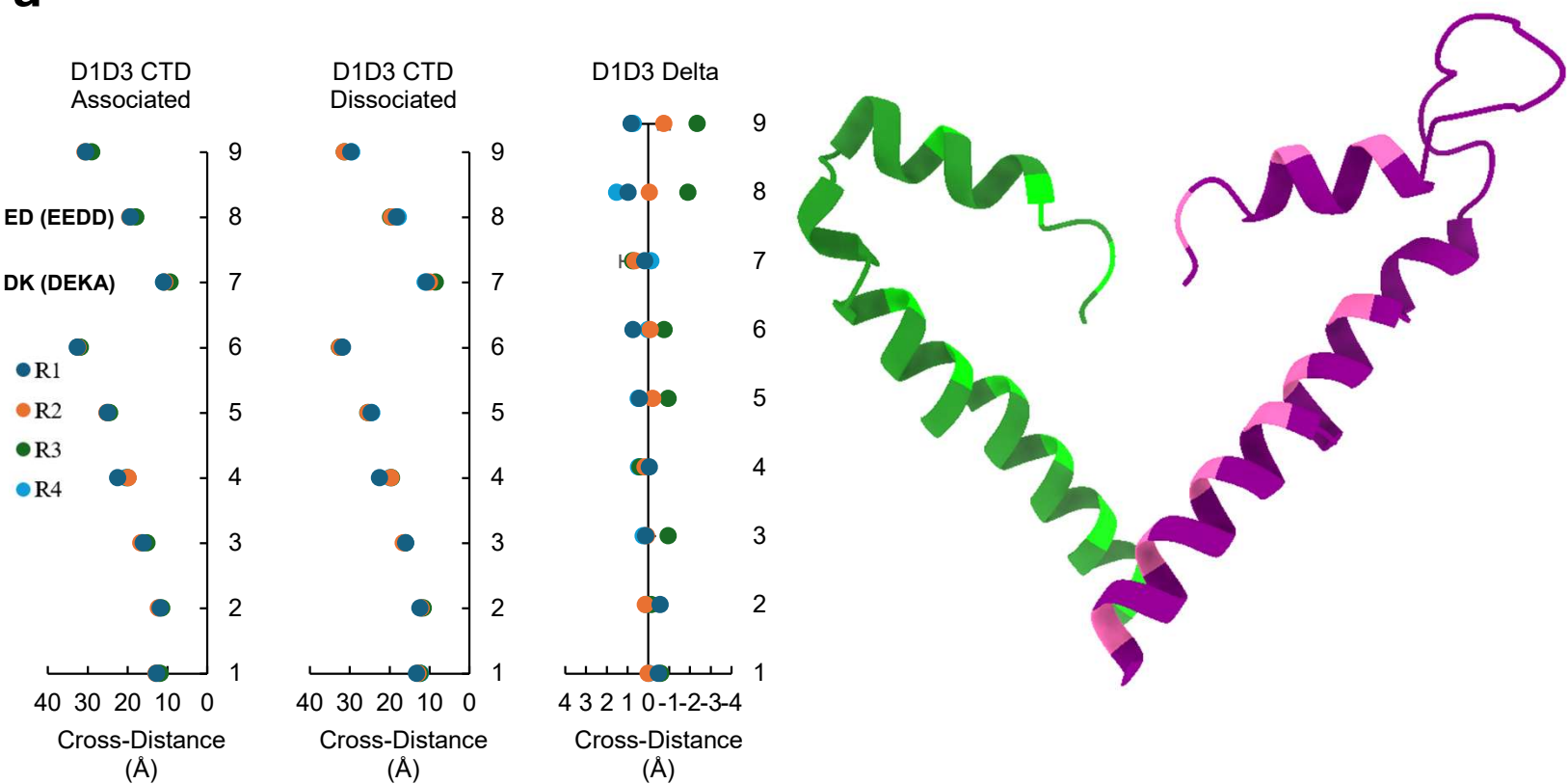
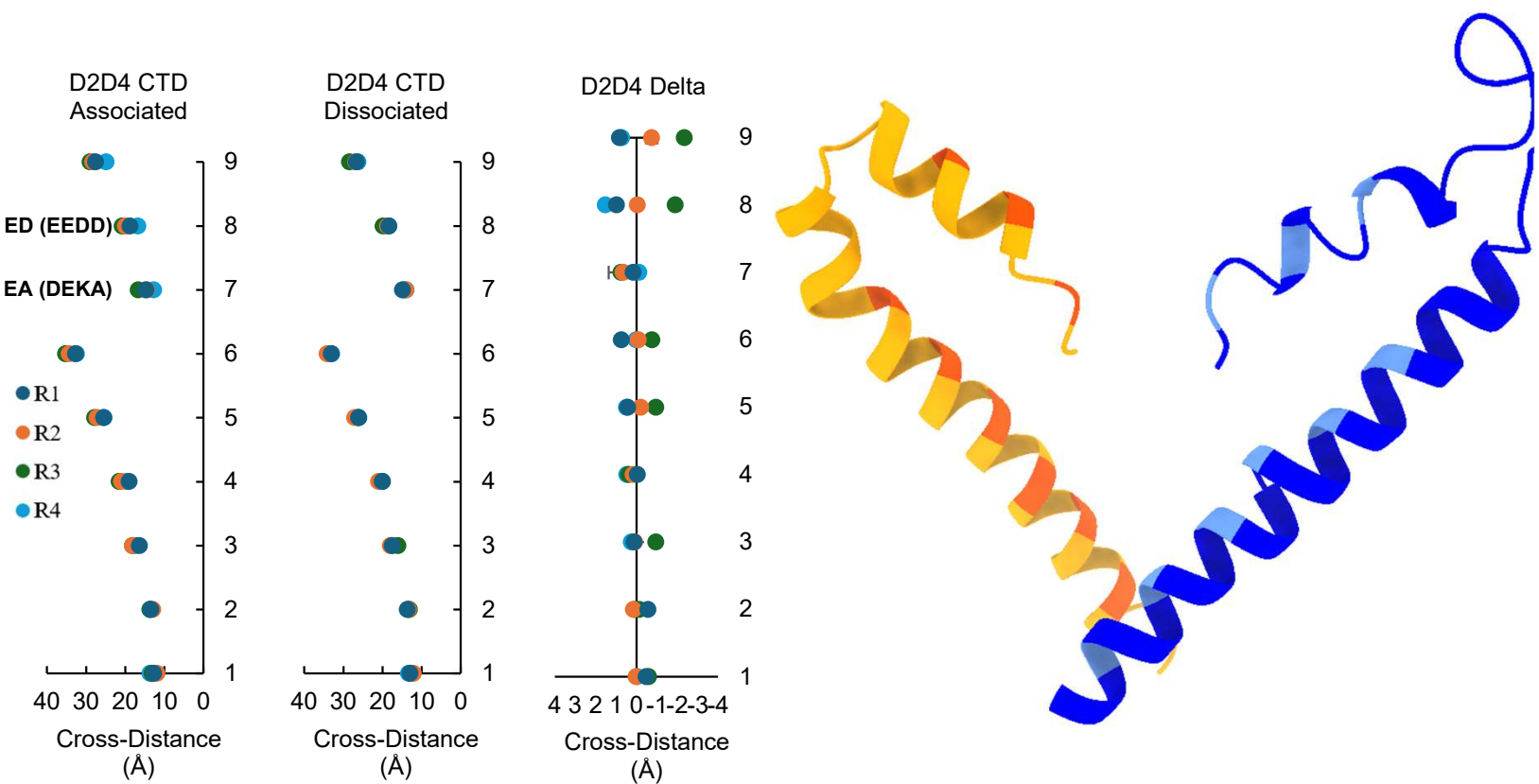


Fig. S6. Overlays of post-MD model (grey) with nonconducting (dark brown, PDB ID 6UZ3) and conducting (tan, PDB ID 7FBS) CryoEM structures.

a**b**

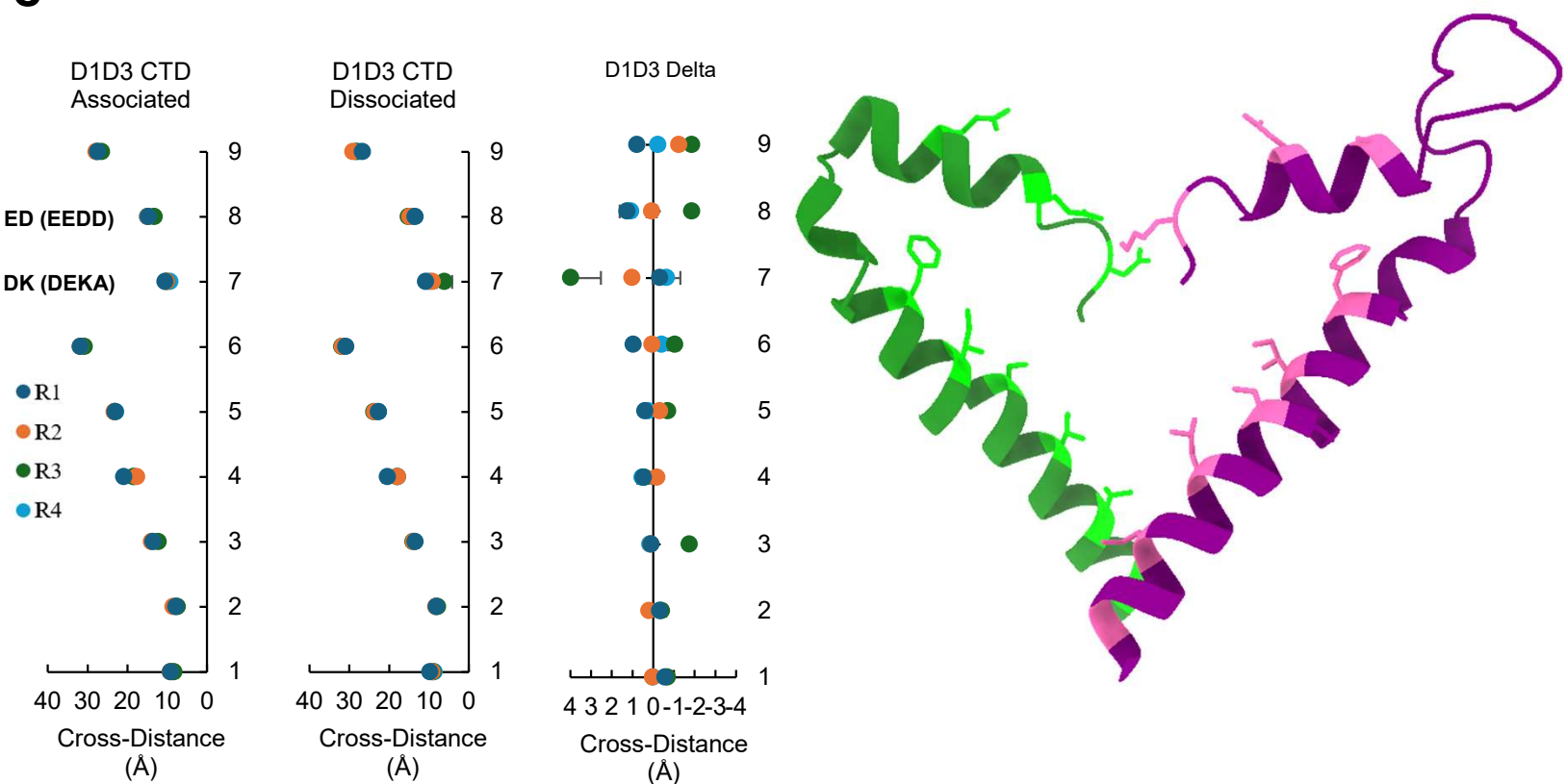
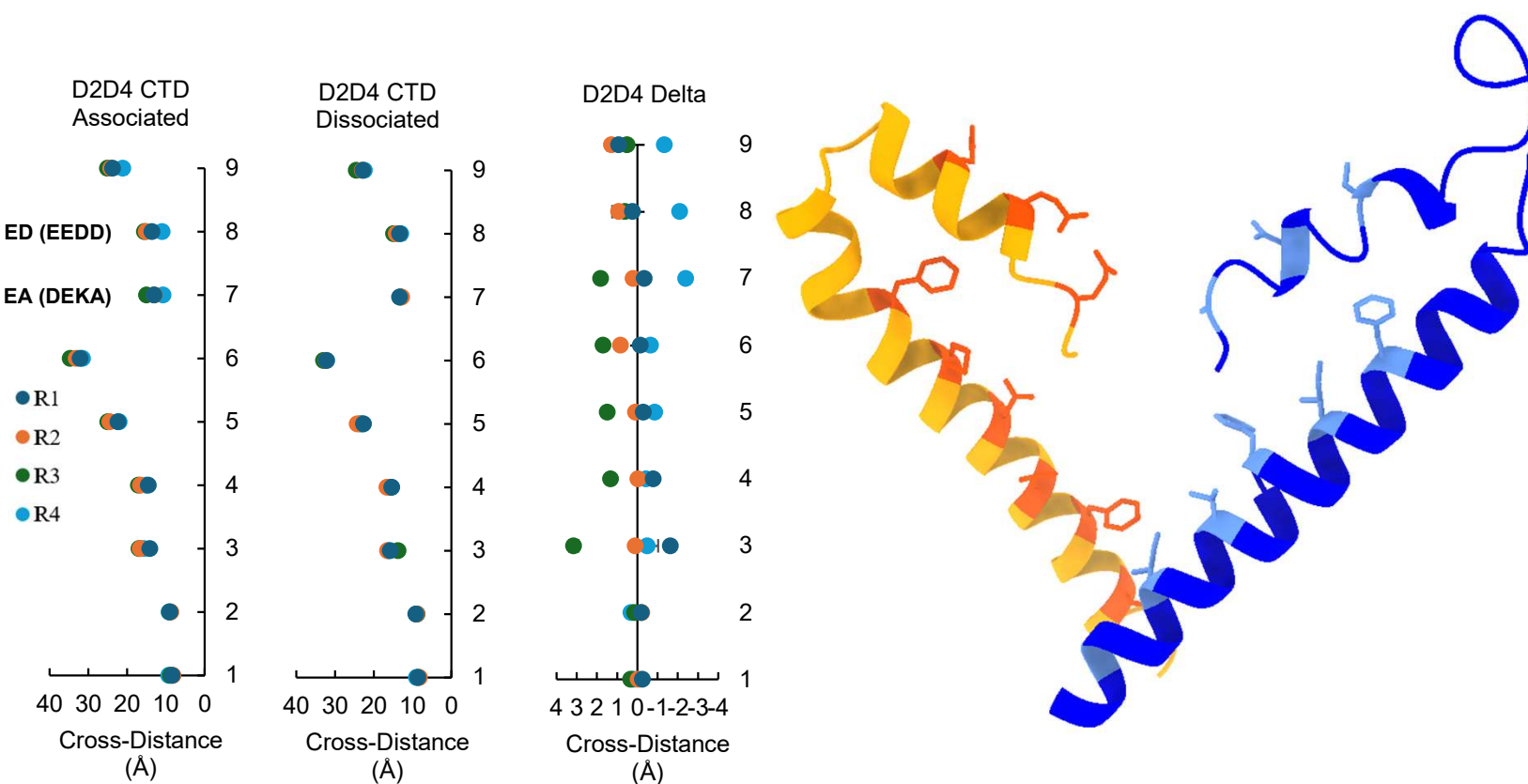
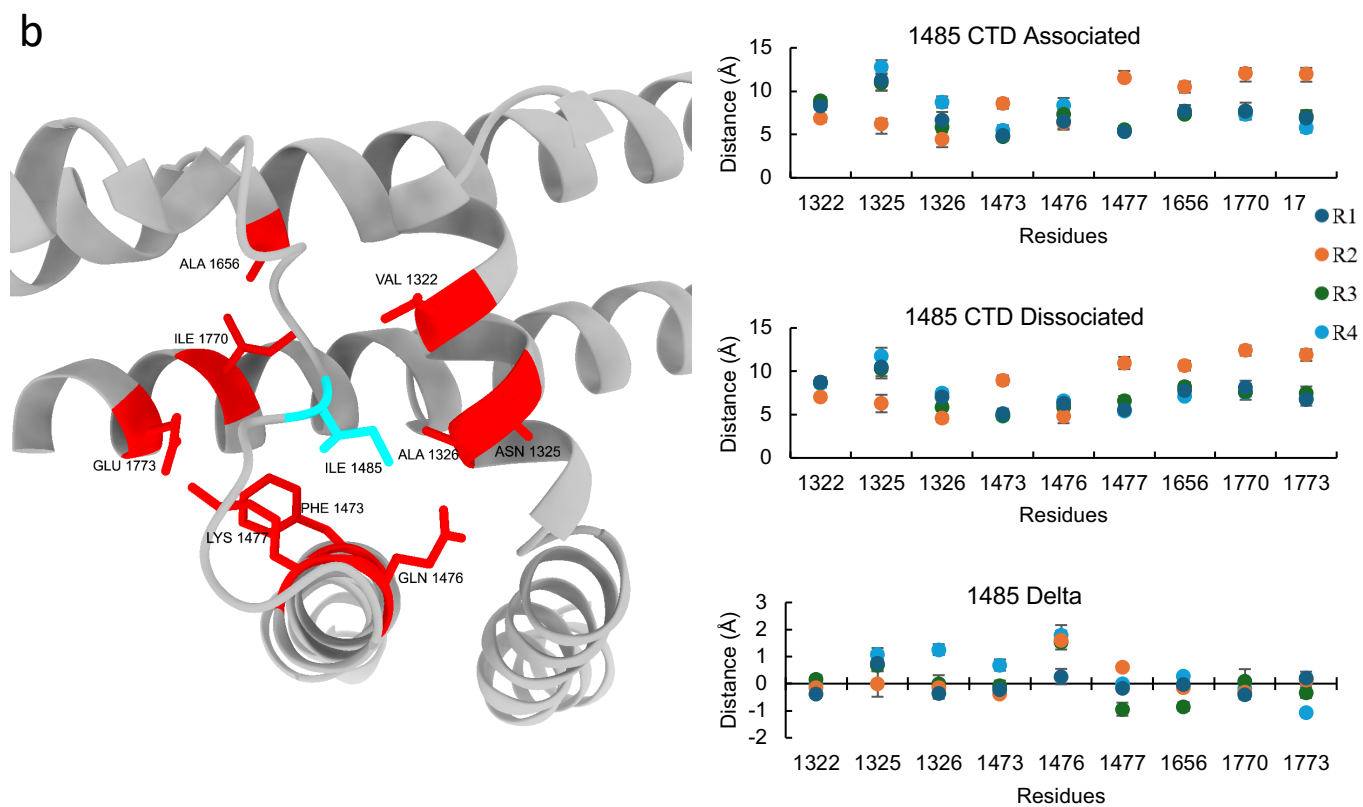
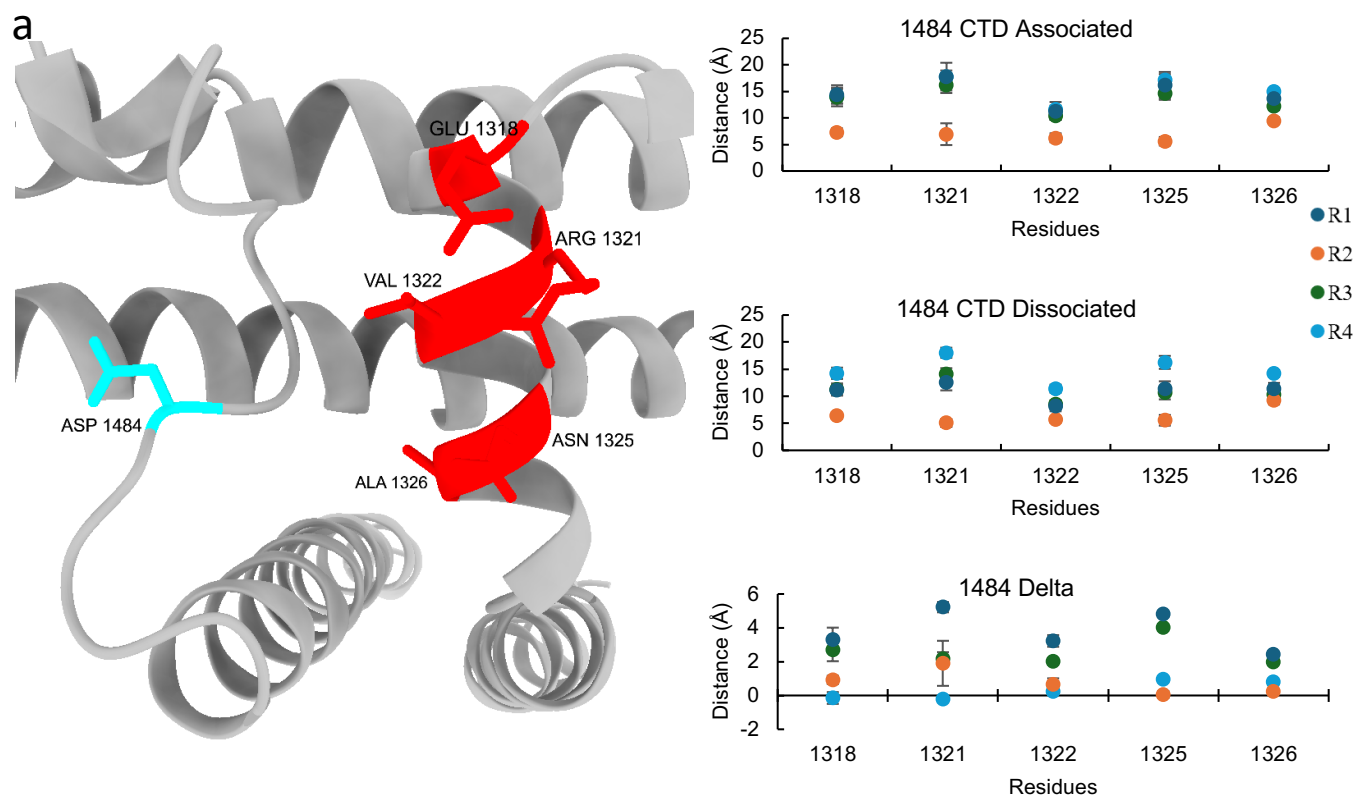
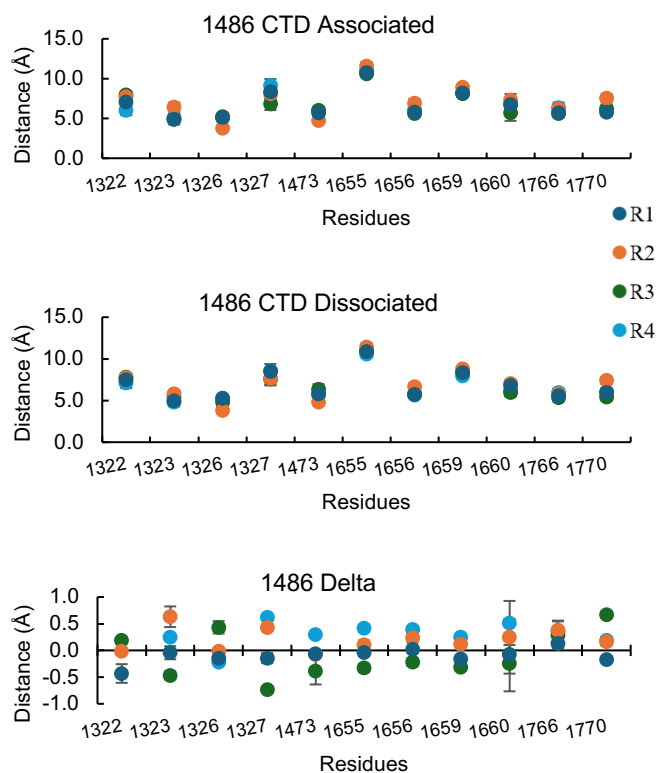
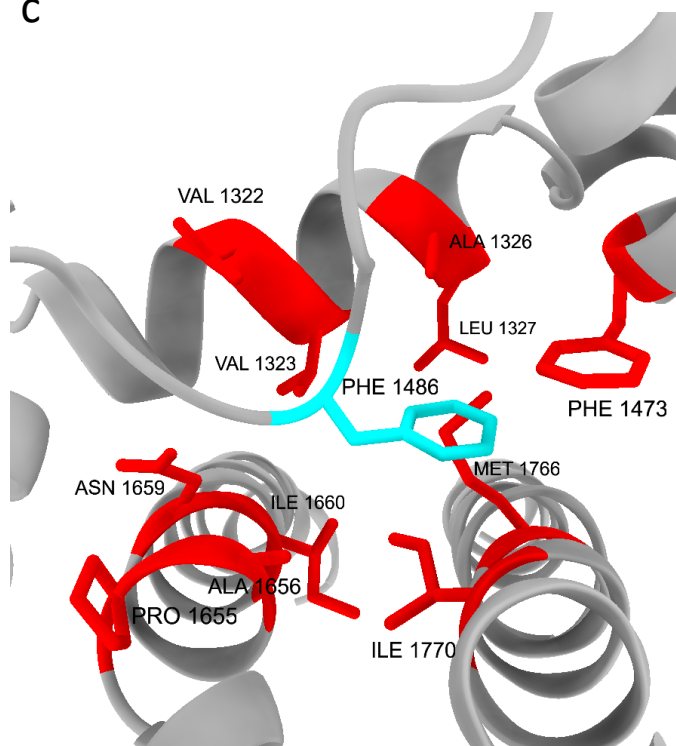
c**d**

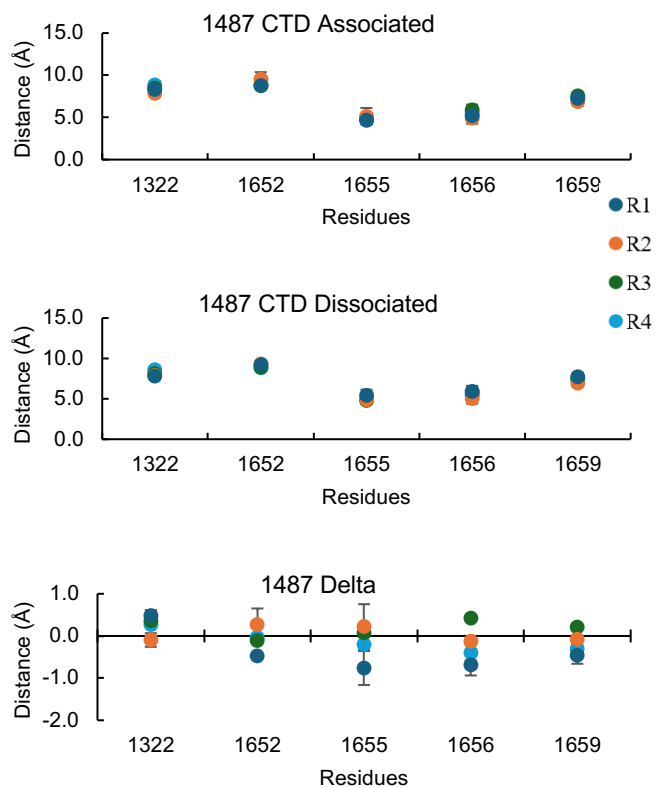
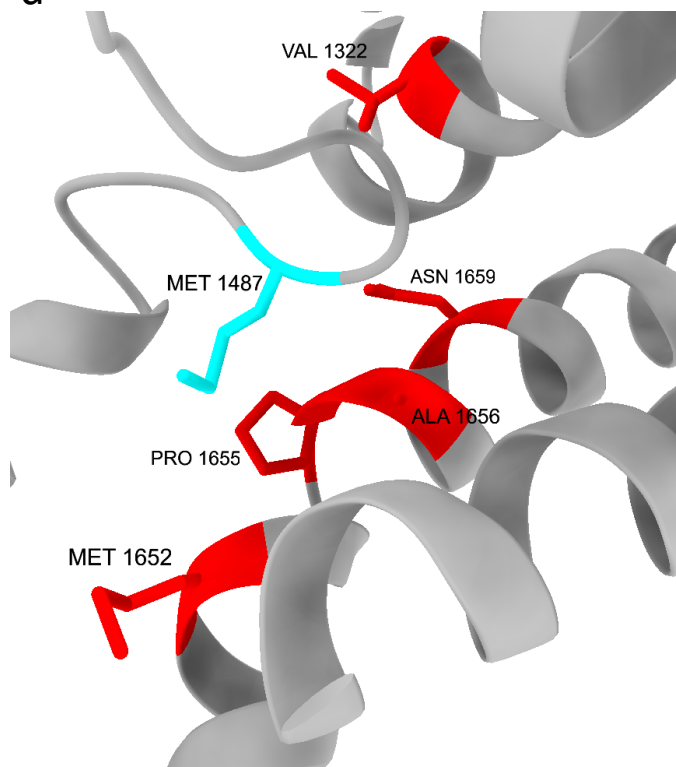
Fig. S7. Each dot corresponds to the average distance calculated for the duration of each simulation (200ns to 1000ns). Error bars depicting the standard deviation are also included, however, for the majority of the data, the size of the dot exceeded the standard deviation. In panels a) and b) distances were measured between alpha carbons to gain insight into the movement of the helices. In panel c) and d) distances were measured using the side chain center of mass to investigate amino acid conformational change. The high degree of structural conservation across the course of our simulation is consistent with other reports that employ standard MD simulations with the latest Amber forcefields (Wang et al., 2021).



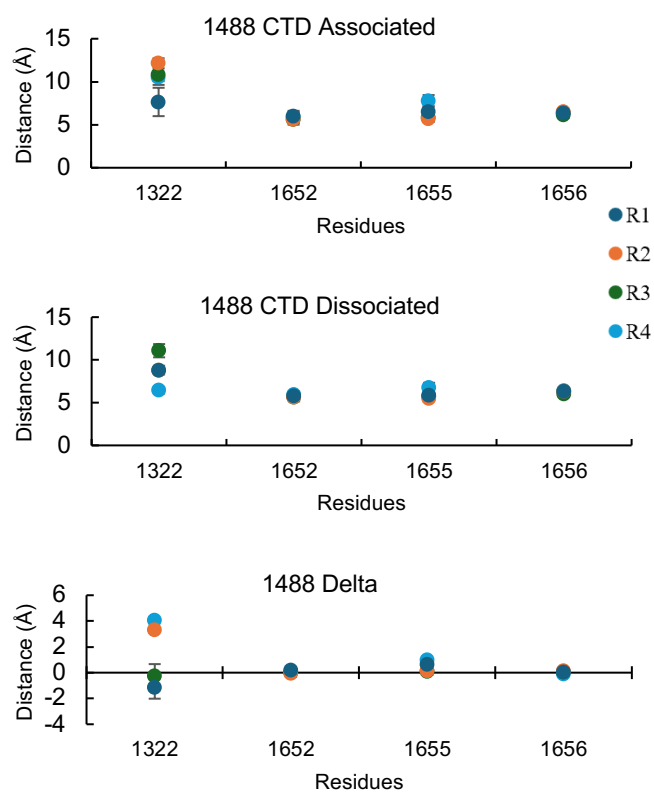
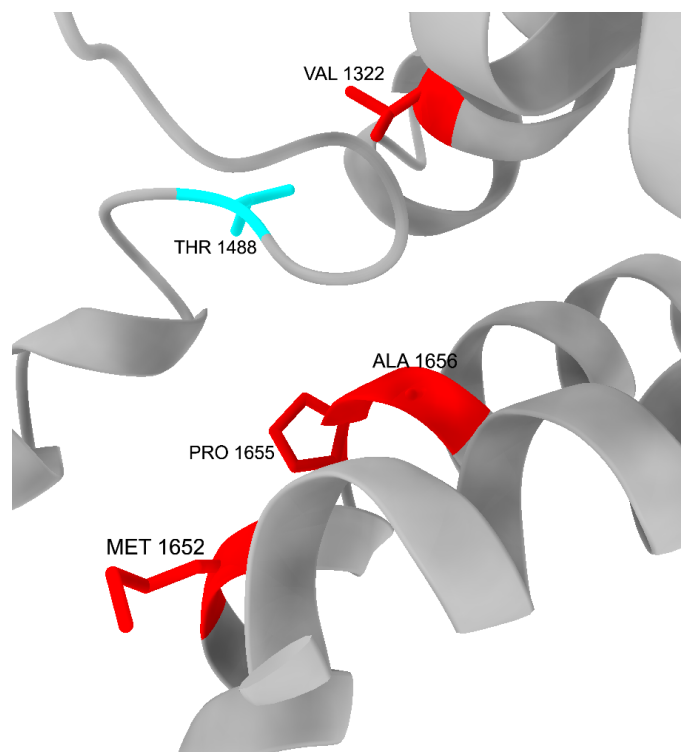
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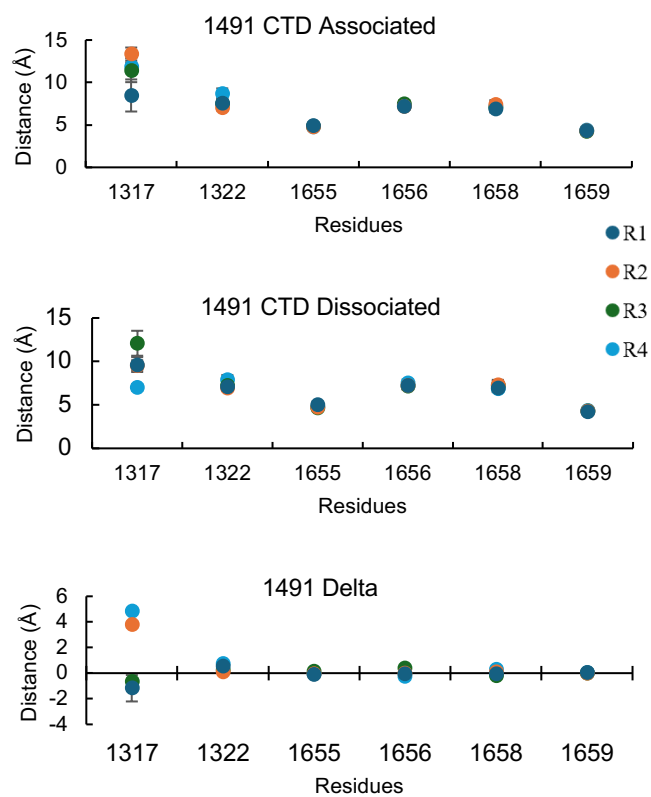
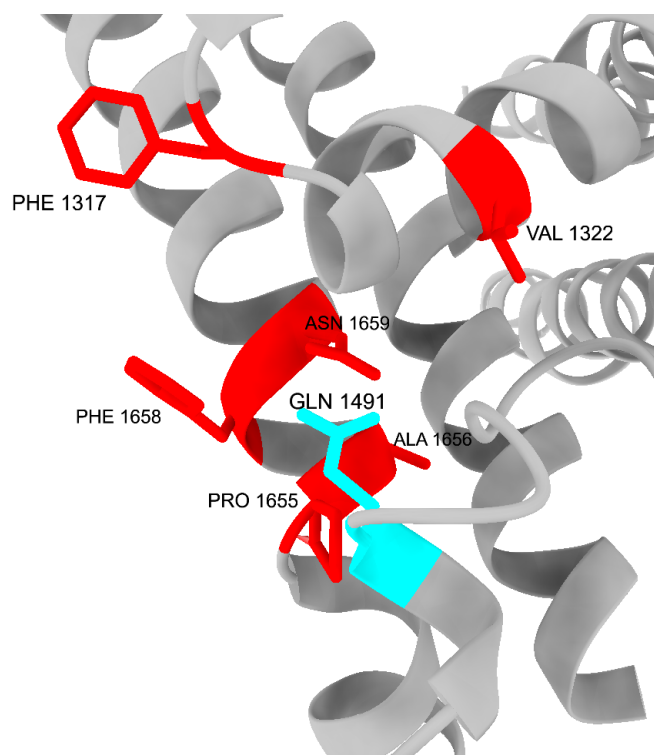
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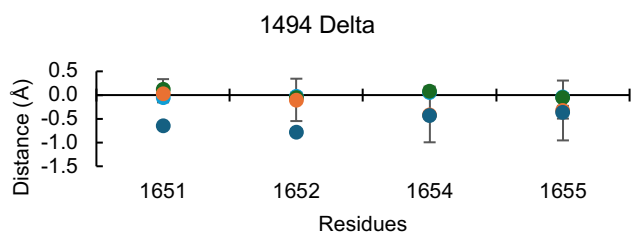
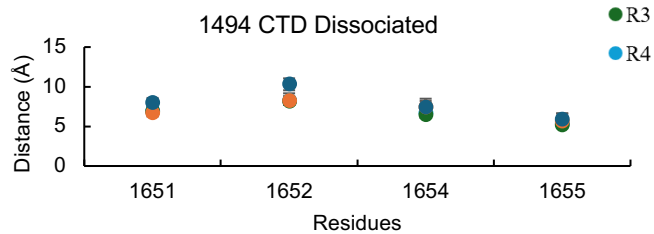
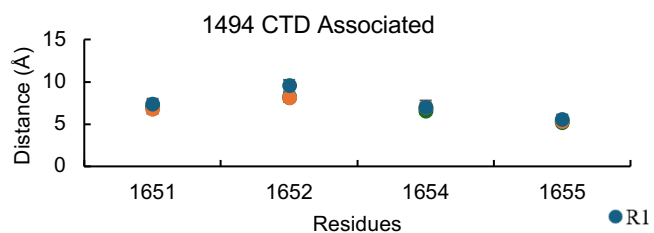
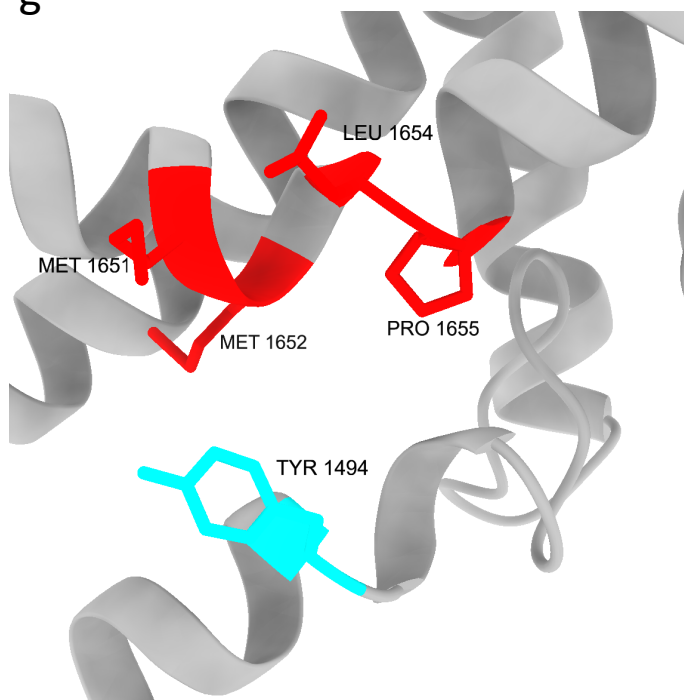
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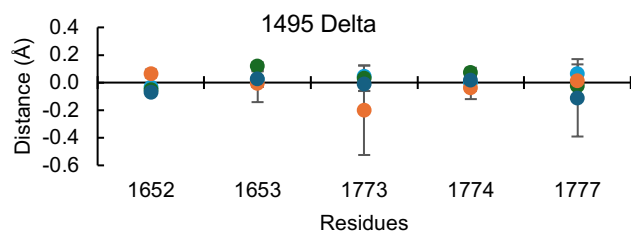
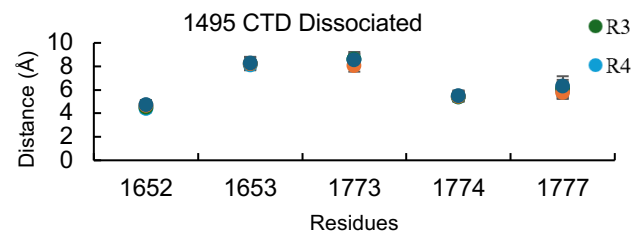
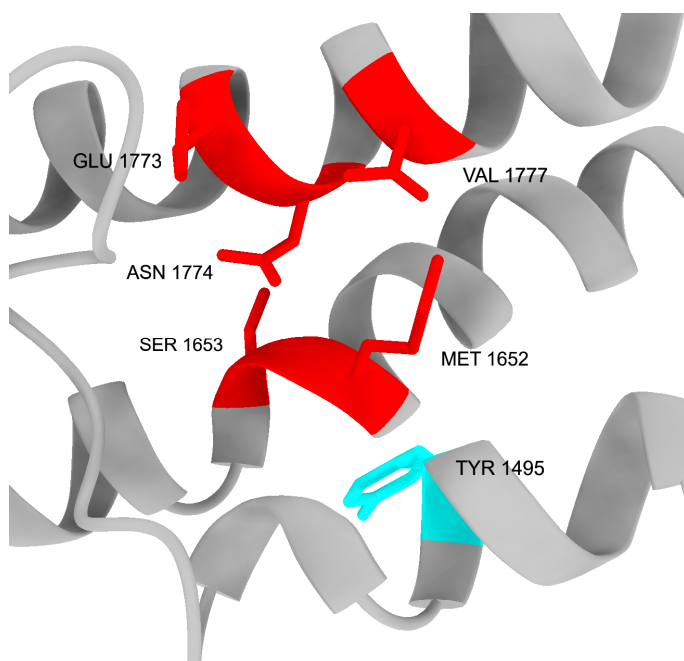
f



g



h



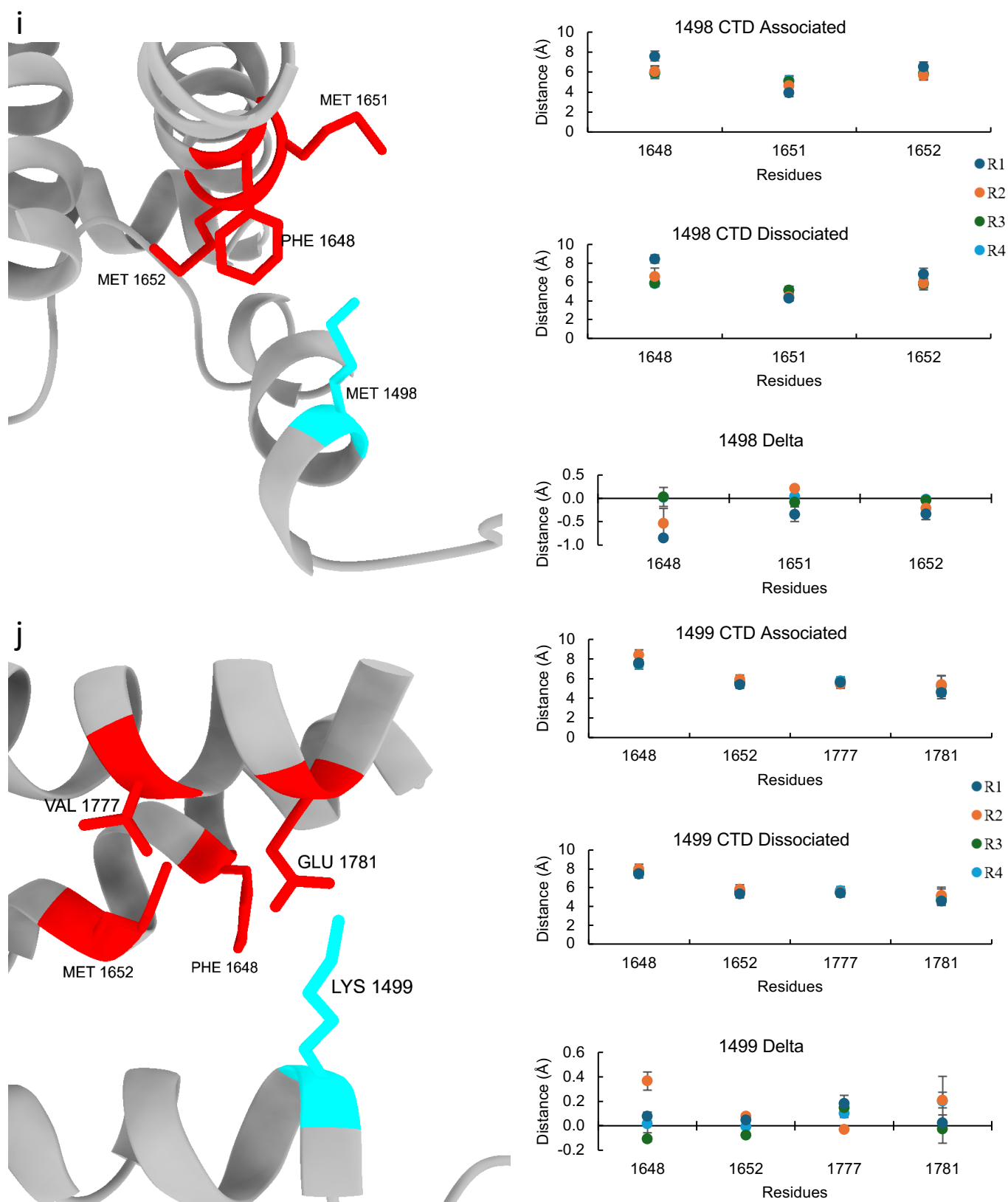
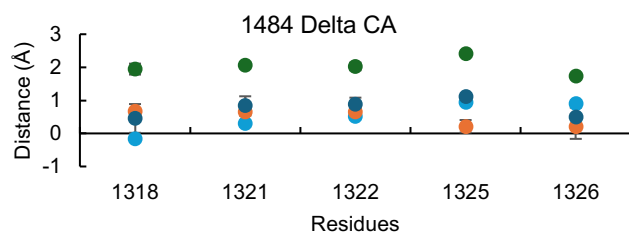
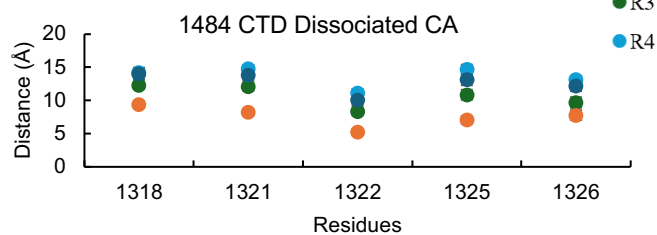
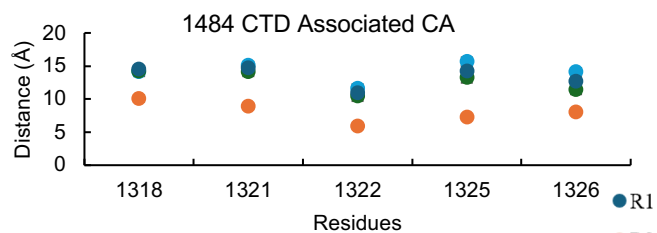
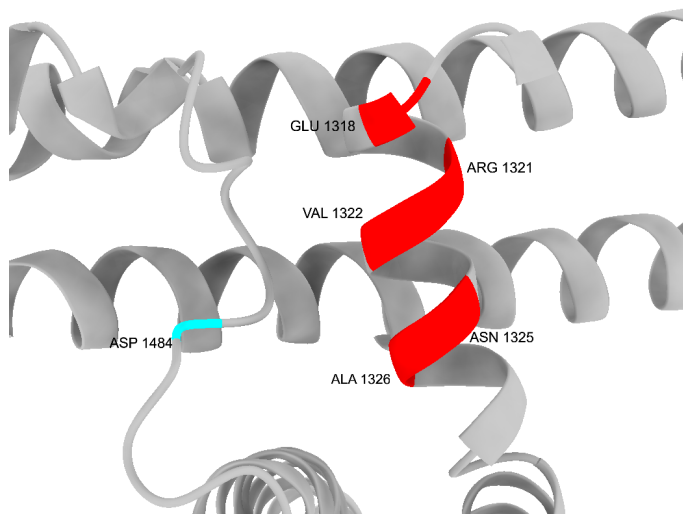
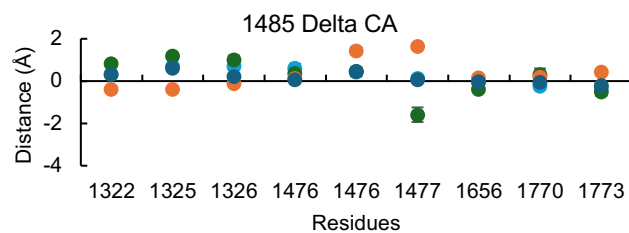
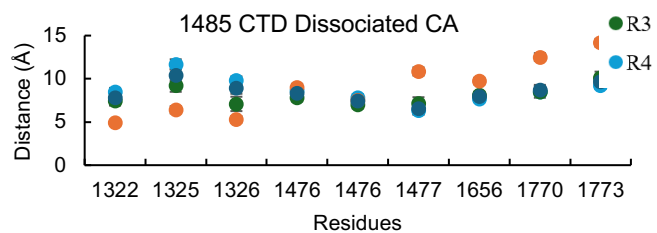
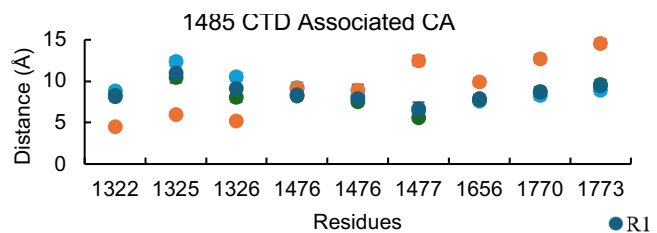
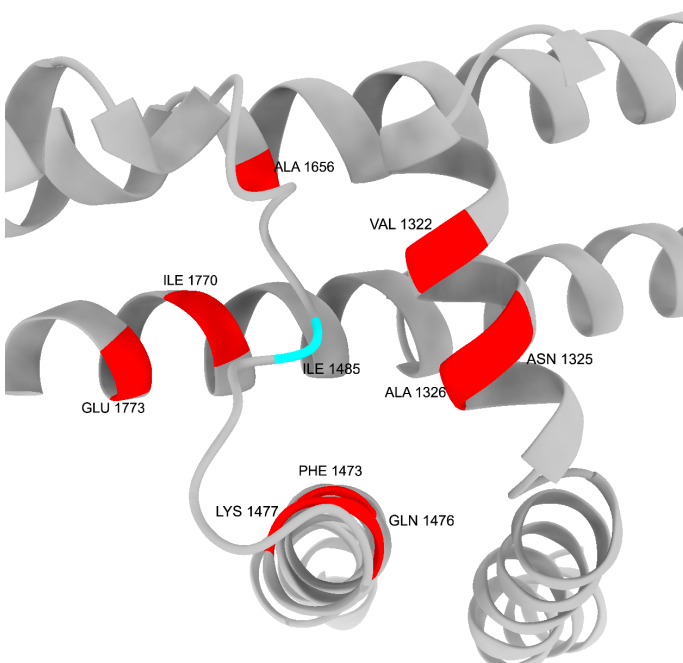


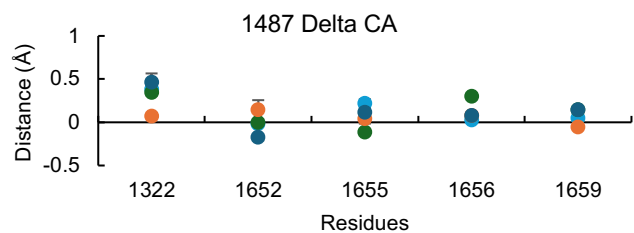
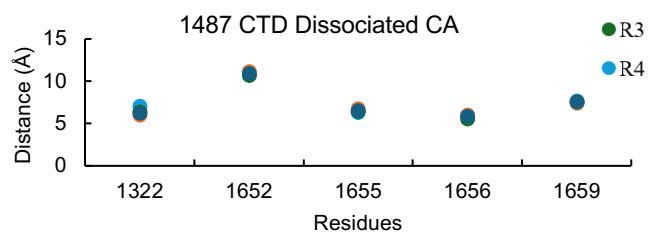
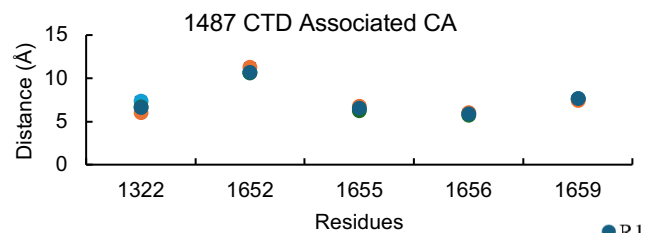
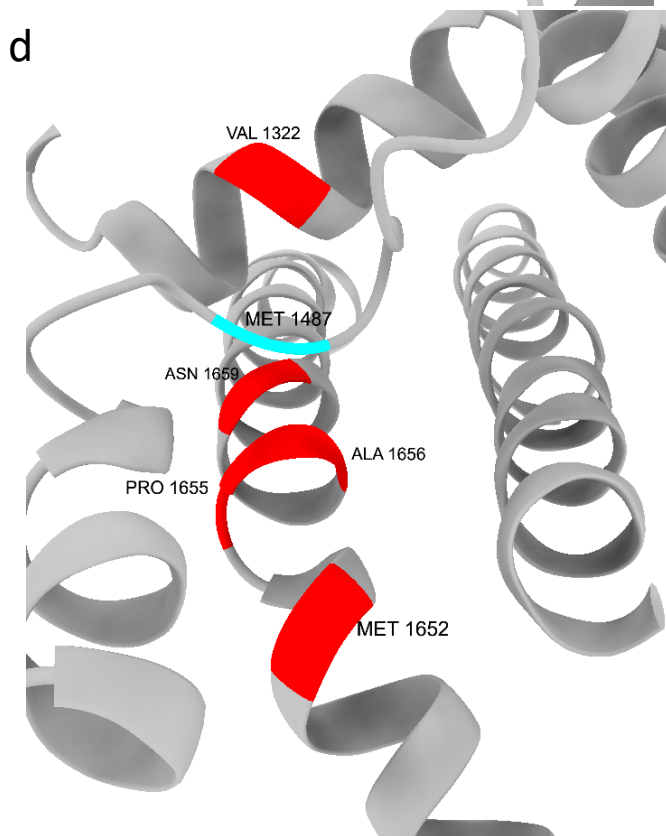
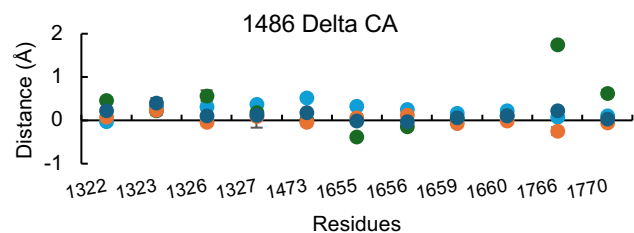
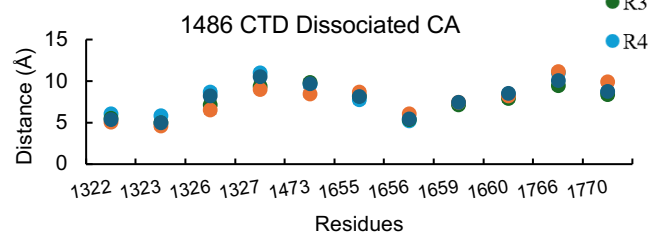
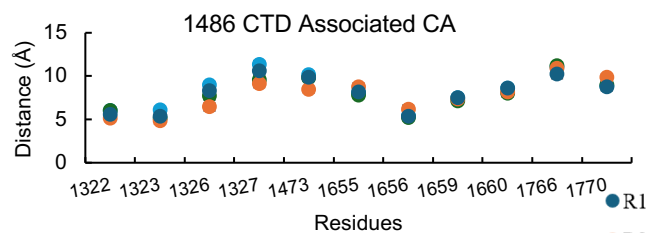
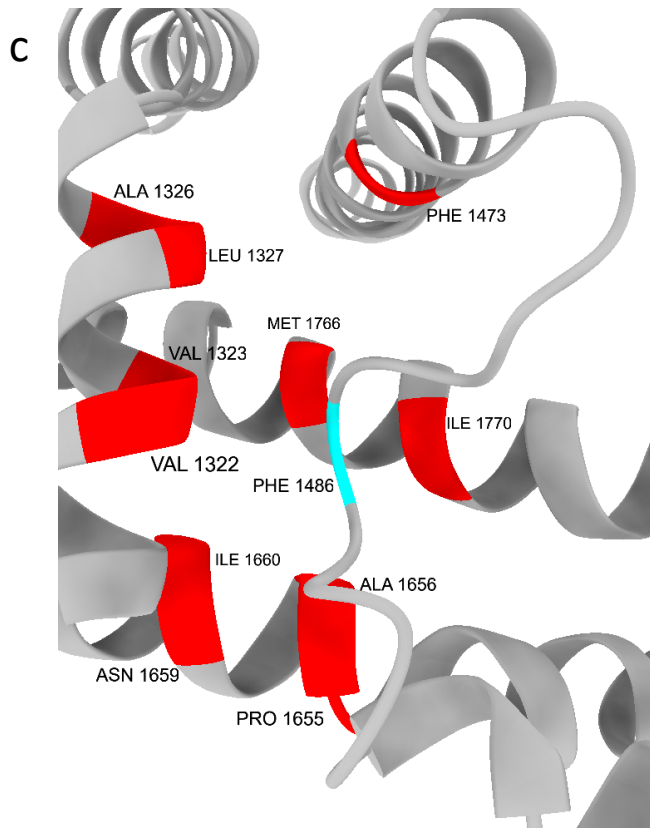
Fig. S8a. Alpha-carbon distance measurements of post-MD model during MD simulation when CTD was associated and dissociated.

a

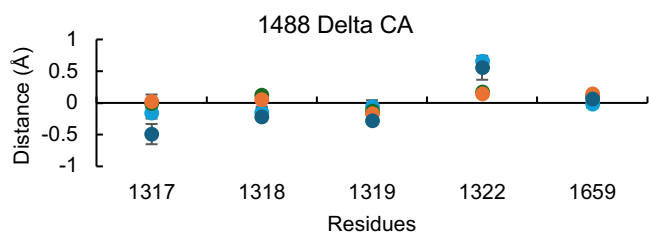
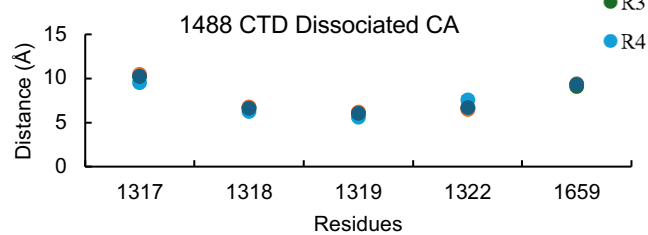
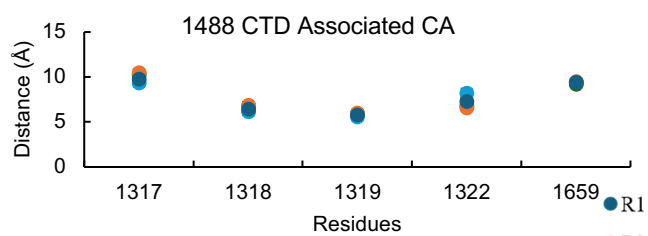
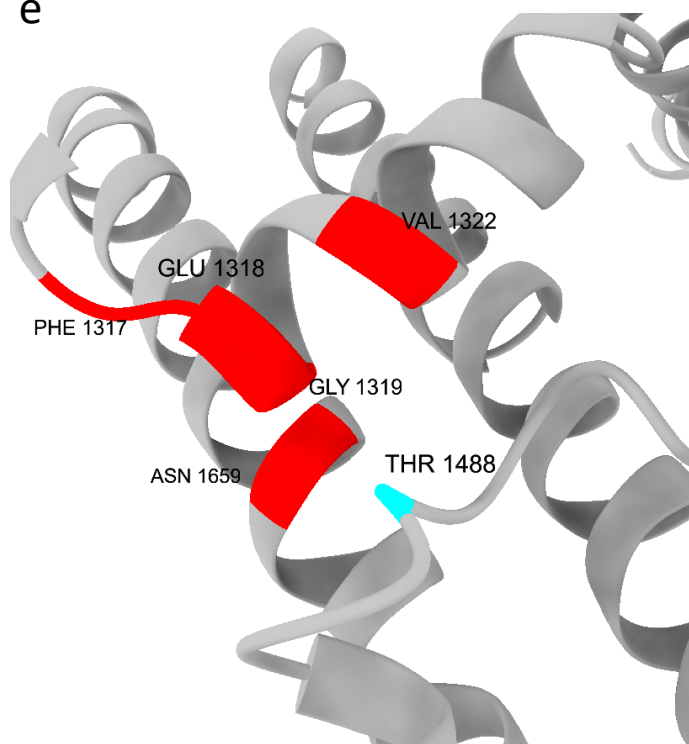


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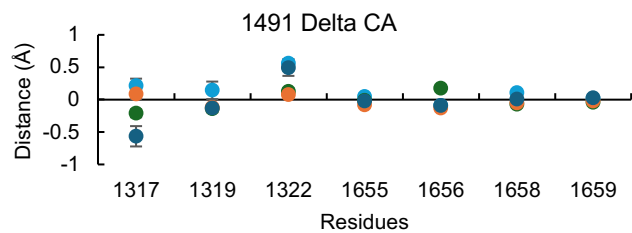
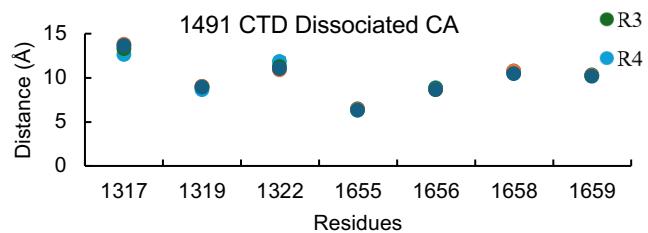
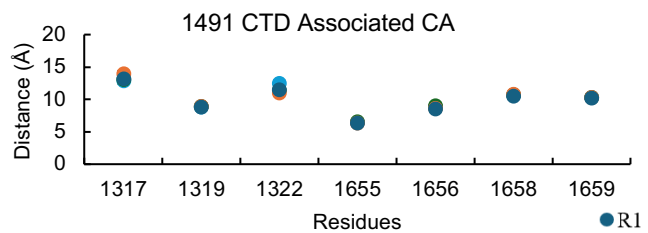
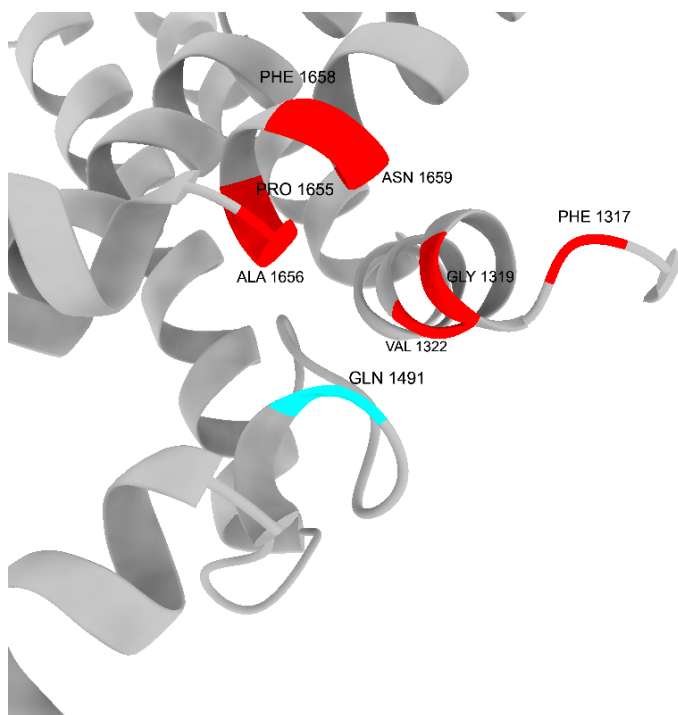




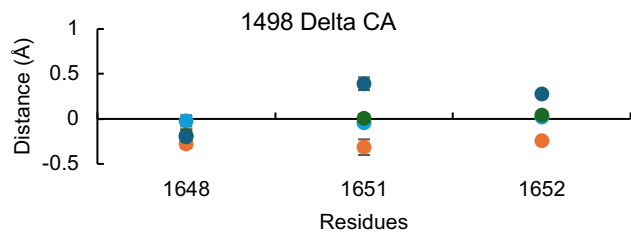
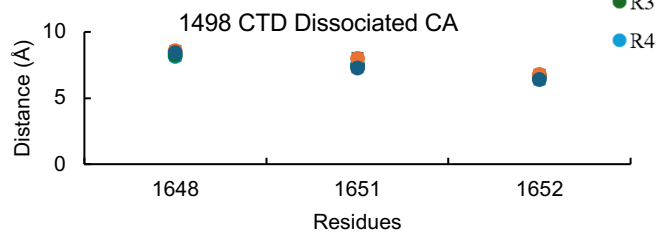
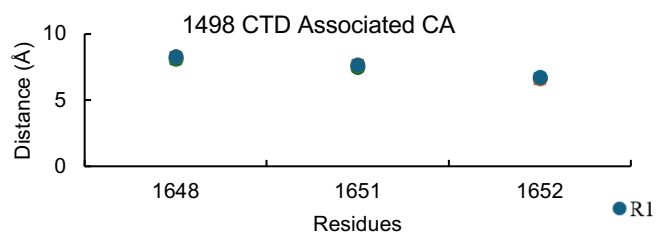
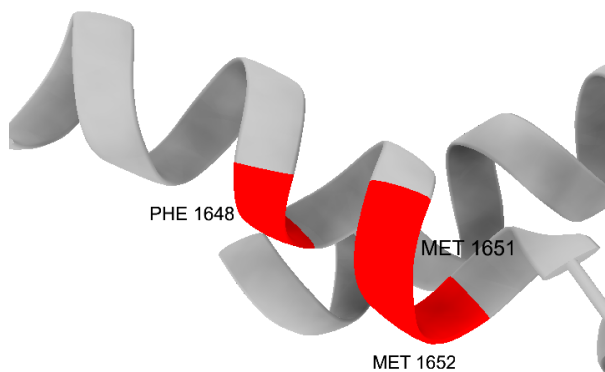
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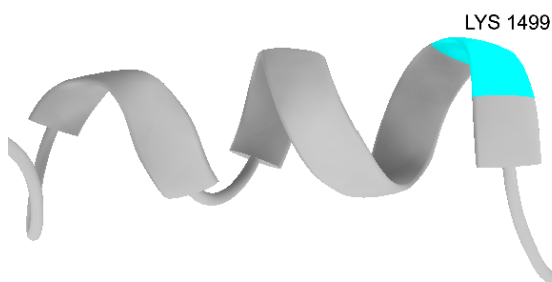
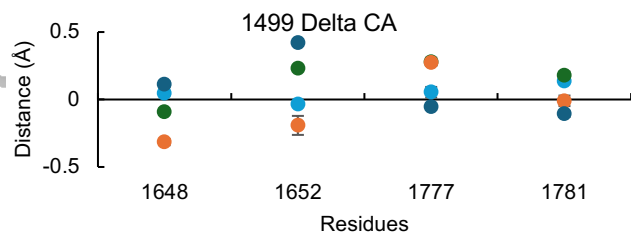
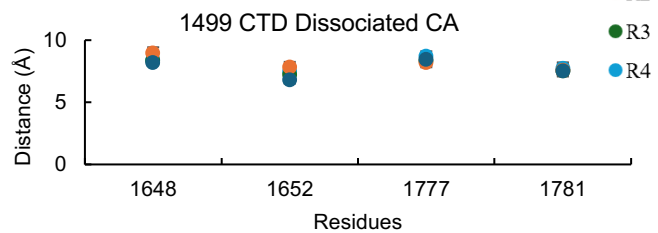
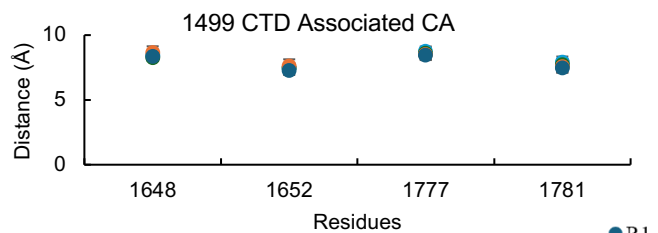
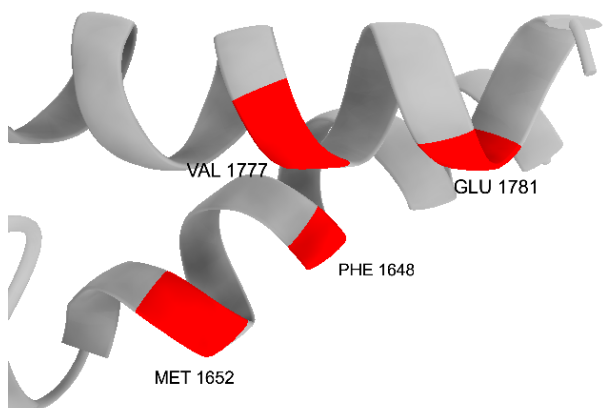
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i



j



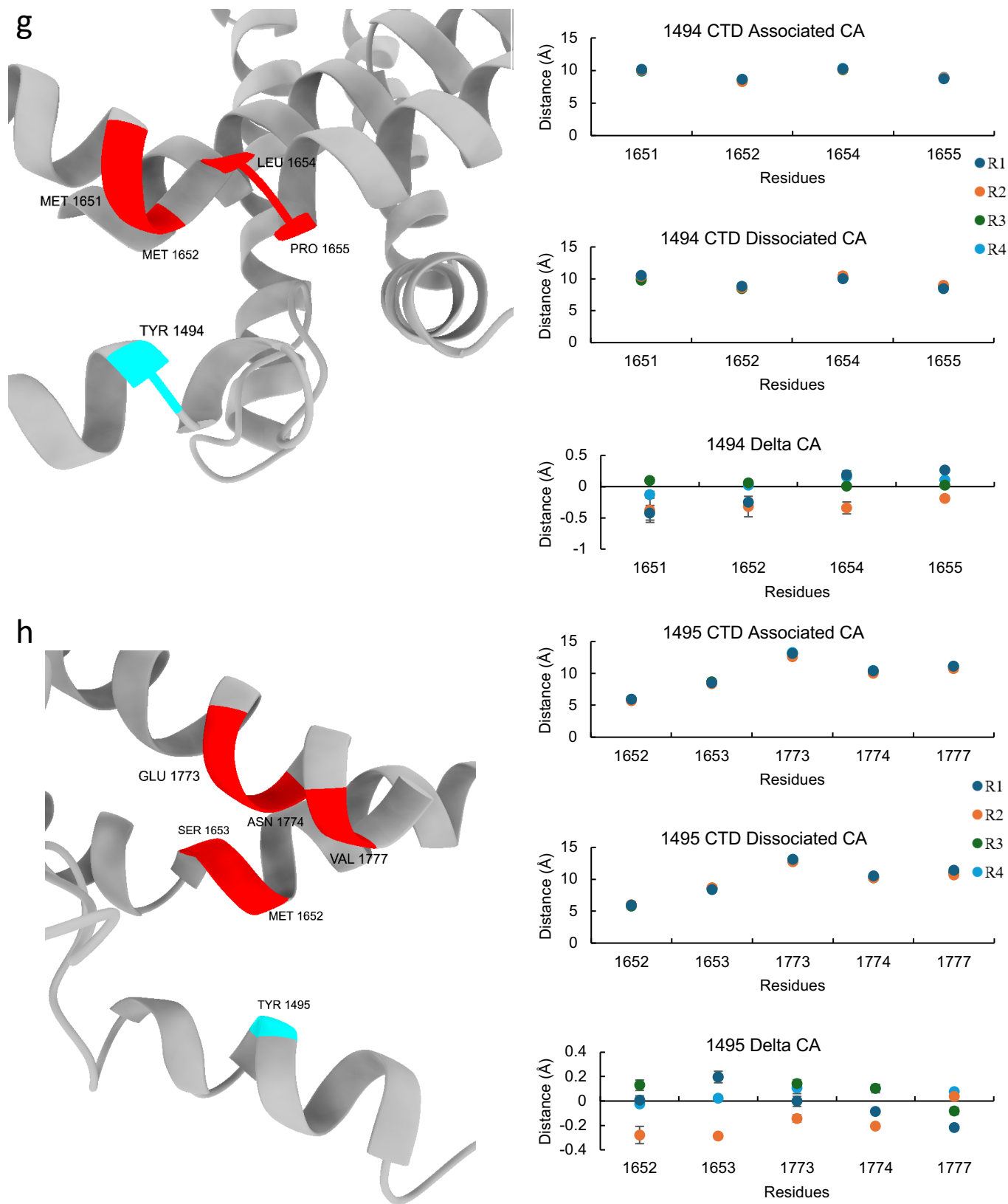


Fig. S8b. Side chain distance measurements of post-MD model during MD simulation when CTD was associated and dissociated.