BiHelix: Towards *de novo* Structure Prediction of an Ensemble of G-Protein Coupled Receptor Conformations

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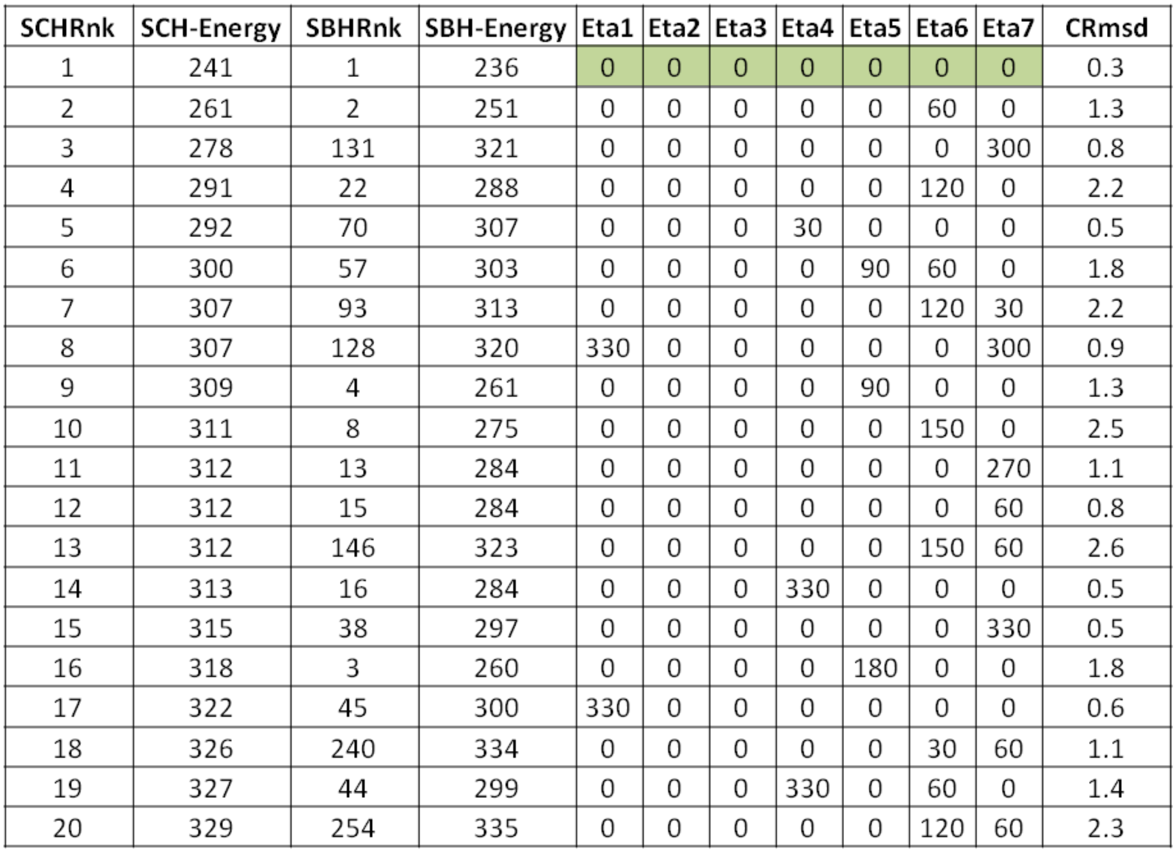
Supplementary Information

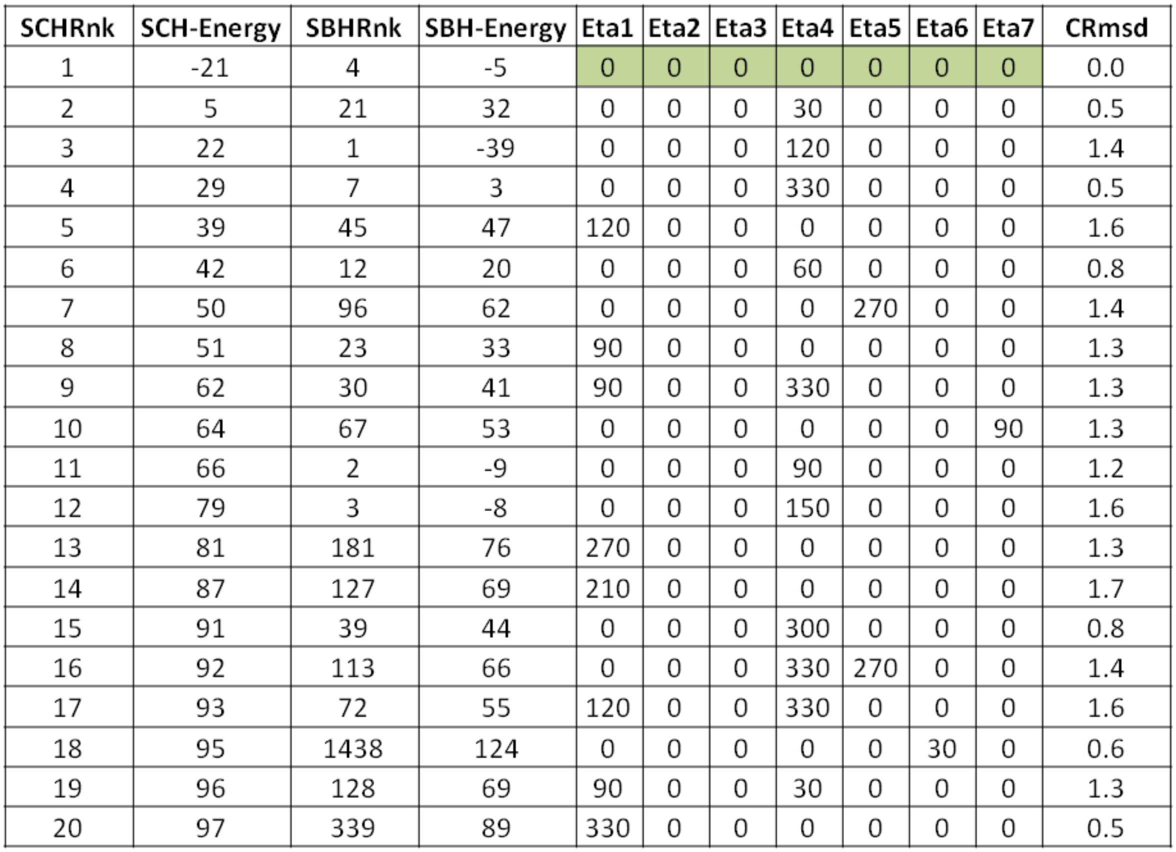
GPCR2-GPCR1	TMH	Δx	Δy	Δh	$\Delta\theta$	$\Delta\varphi$	$\Delta\eta$
Opsin-Rhodopsin	**TMH1**	0.4	0.3	-0.7	-3	6	-5
	TMH2	-0.1	0	0.7	1	5	7
	TMH3	0	0	0.1	1	14	-28
	TMH4	-2.1	-1.4	0.3	0	6	-16
	TMH5	1.1	-3.6	-0.7	1	26	-6
	TMH6	-0.4	-3.7	0.3	-3	-43	-31
	TMH7	0	-0.8	-0.2	-4	10	-2

Table S1: Helix orientation differences between Bovine Opsin and Rhodopsin with biggest changes in rotation angle η highlighted.



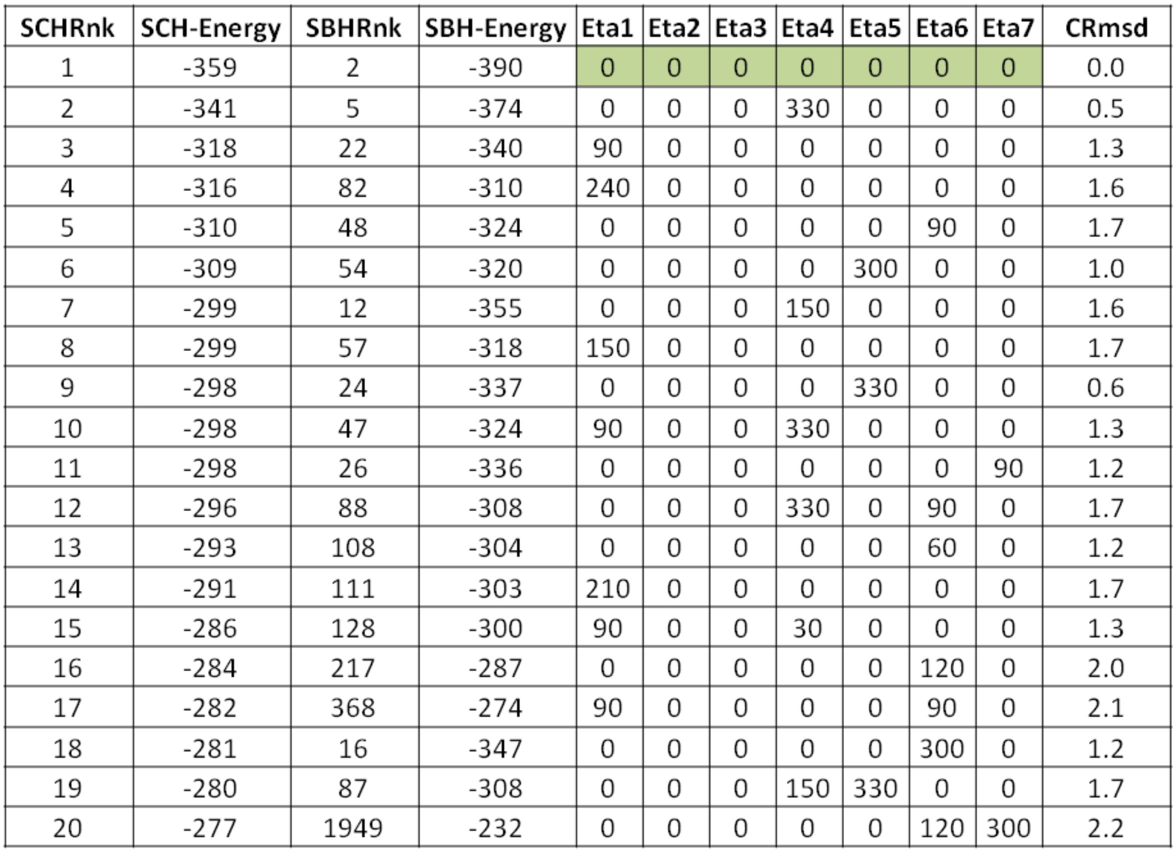
SCHRnk	SCH-Energy	SBHRnk	SBH-Energy	Eta1	Eta2	Eta3	Eta4	Eta5	Eta6	Eta7	CRmsd
1	241	1	236	0	0	0	0	0	0	0	0.3
2	261	2	251	0	0	0	0	0	60	0	1.3
3	278	131	321	0	0	0	0	0	0	300	0.8
4	291	22	288	0	0	0	0	0	120	0	2.2
5	292	70	307	0	0	0	30	0	0	0	0.5
6	300	57	303	0	0	0	0	90	60	0	1.8
7	307	93	313	0	0	0	0	0	120	30	2.2
8	307	128	320	330	0	0	0	0	0	300	0.9
9	309	4	261	0	0	0	0	90	0	0	1.3
10	311	8	275	0	0	0	0	0	150	0	2.5
11	312	13	284	0	0	0	0	0	0	270	1.1
12	312	15	284	0	0	0	0	0	0	60	0.8
13	312	146	323	0	0	0	0	0	150	60	2.6
14	313	16	284	0	0	0	330	0	0	0	0.5
15	315	38	297	0	0	0	0	0	0	330	0.5
16	318	3	260	0	0	0	0	180	0	0	1.8
17	322	45	300	330	0	0	0	0	0	0	0.6
18	326	240	334	0	0	0	0	0	30	60	1.1
19	327	44	299	0	0	0	330	0	60	0	1.4
20	329	254	335	0	0	0	0	0	120	60	2.3

Table S2: Top 20 bovine Opsin conformations after BiHelix/CombiHelix. Conformation observed in the receptor's crystal structure shown in green cells.



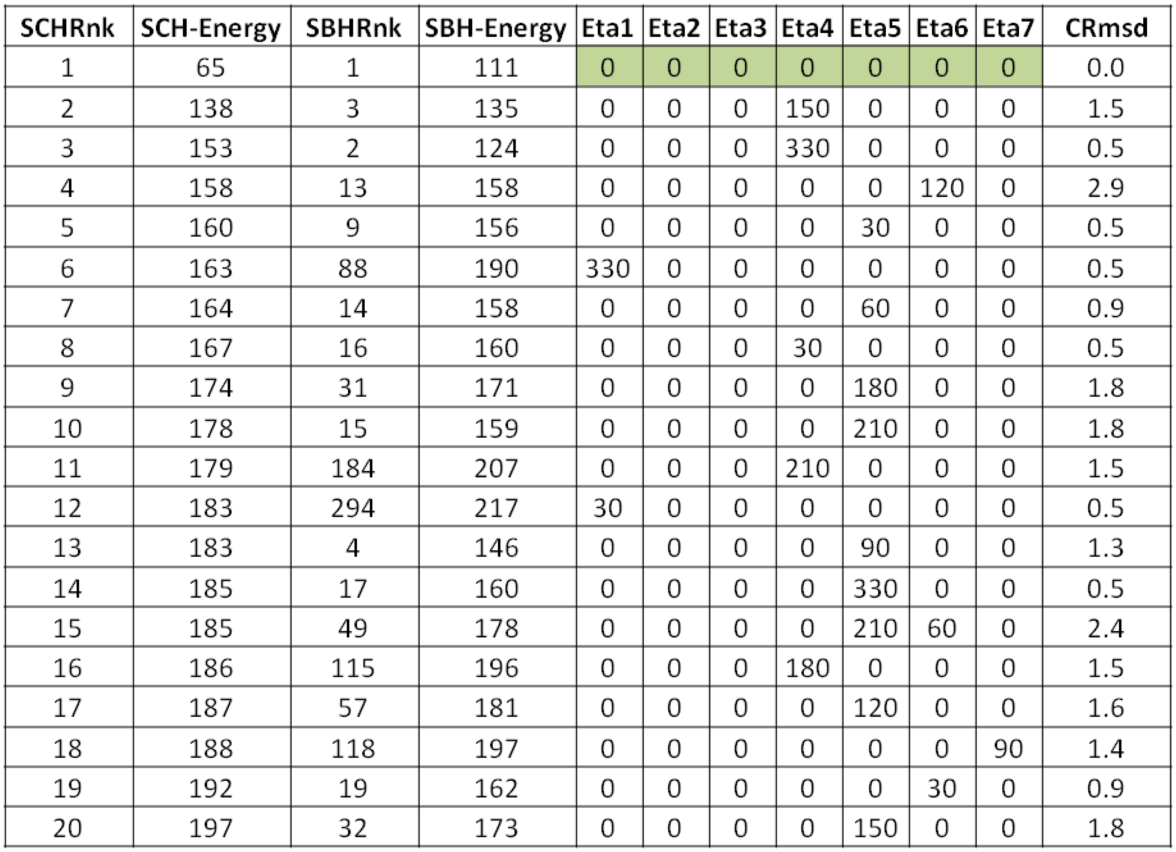
SCHRnk	SCH-Energy	SBHRnk	SBH-Energy	Eta1	Eta2	Eta3	Eta4	Eta5	Eta6	Eta7	CRmsd
1	-21	4	-5	0	0	0	0	0	0	0	0.0
2	5	21	32	0	0	0	30	0	0	0	0.5
3	22	1	-39	0	0	0	120	0	0	0	1.4
4	29	7	3	0	0	0	330	0	0	0	0.5
5	39	45	47	120	0	0	0	0	0	0	1.6
6	42	12	20	0	0	0	60	0	0	0	0.8
7	50	96	62	0	0	0	0	270	0	0	1.4
8	51	23	33	90	0	0	0	0	0	0	1.3
9	62	30	41	90	0	0	330	0	0	0	1.3
10	64	67	53	0	0	0	0	0	0	90	1.3
11	66	2	-9	0	0	0	90	0	0	0	1.2
12	79	3	-8	0	0	0	150	0	0	0	1.6
13	81	181	76	270	0	0	0	0	0	0	1.3
14	87	127	69	210	0	0	0	0	0	0	1.7
15	91	39	44	0	0	0	300	0	0	0	0.8
16	92	113	66	0	0	0	330	270	0	0	1.4
17	93	72	55	120	0	0	330	0	0	0	1.6
18	95	1438	124	0	0	0	0	0	30	0	0.6
19	96	128	69	90	0	0	30	0	0	0	1.3
20	97	339	89	330	0	0	0	0	0	0	0.5

Table S3: Top 20 human Beta2 adrenergic receptor conformations after BiHelix/CombiHelix. Conformation observed in the receptor's crystal structure shown in green cells.



SCHRnk	SCH-Energy	SBHRnk	SBH-Energy	Eta1	Eta2	Eta3	Eta4	Eta5	Eta6	Eta7	CRmsd
1	-359	2	-390	0	0	0	0	0	0	0	0.0
2	-341	5	-374	0	0	0	330	0	0	0	0.5
3	-318	22	-340	90	0	0	0	0	0	0	1.3
4	-316	82	-310	240	0	0	0	0	0	0	1.6
5	-310	48	-324	0	0	0	0	0	90	0	1.7
6	-309	54	-320	0	0	0	0	300	0	0	1.0
7	-299	12	-355	0	0	0	150	0	0	0	1.6
8	-299	57	-318	150	0	0	0	0	0	0	1.7
9	-298	24	-337	0	0	0	0	330	0	0	0.6
10	-298	47	-324	90	0	0	330	0	0	0	1.3
11	-298	26	-336	0	0	0	0	0	0	90	1.2
12	-296	88	-308	0	0	0	330	0	90	0	1.7
13	-293	108	-304	0	0	0	0	0	60	0	1.2
14	-291	111	-303	210	0	0	0	0	0	0	1.7
15	-286	128	-300	90	0	0	30	0	0	0	1.3
16	-284	217	-287	0	0	0	0	0	120	0	2.0
17	-282	368	-274	90	0	0	0	0	90	0	2.1
18	-281	16	-347	0	0	0	0	0	300	0	1.2
19	-280	87	-308	0	0	0	150	330	0	0	1.7
20	-277	1949	-232	0	0	0	0	0	120	300	2.2

Table S4: Top 20 turkey Beta1 adrenergic receptor conformations after BiHelix/CombiHelix. Conformation observed in the receptor's crystal structure shown in green cells.



SCHRnk	SCH-Energy	SBHRnk	SBH-Energy	Eta1	Eta2	Eta3	Eta4	Eta5	Eta6	Eta7	CRmsd
1	65	1	111	0	0	0	0	0	0	0	0.0
2	138	3	135	0	0	0	150	0	0	0	1.5
3	153	2	124	0	0	0	330	0	0	0	0.5
4	158	13	158	0	0	0	0	0	120	0	2.9
5	160	9	156	0	0	0	0	30	0	0	0.5
6	163	88	190	330	0	0	0	0	0	0	0.5
7	164	14	158	0	0	0	0	60	0	0	0.9
8	167	16	160	0	0	0	30	0	0	0	0.5
9	174	31	171	0	0	0	0	180	0	0	1.8
10	178	15	159	0	0	0	0	210	0	0	1.8
11	179	184	207	0	0	0	210	0	0	0	1.5
12	183	294	217	30	0	0	0	0	0	0	0.5
13	183	4	146	0	0	0	0	90	0	0	1.3
14	185	17	160	0	0	0	0	330	0	0	0.5
15	185	49	178	0	0	0	0	210	60	0	2.4
16	186	115	196	0	0	0	180	0	0	0	1.5
17	187	57	181	0	0	0	0	120	0	0	1.6
18	188	118	197	0	0	0	0	0	0	90	1.4
19	192	19	162	0	0	0	0	0	30	0	0.9
20	197	32	173	0	0	0	0	150	0	0	1.8

Table S5: Top 20 human Adenosine A2A conformations after BiHelix/CombiHelix. Conformation observed in the receptor's crystal structure shown in green cells.

SCHRnk	SCH-Energy	SBHRnk	SBH-Energy	Eta1	Eta2	Eta3	Eta4	Eta5	Eta6	Eta7	CRmsd
1	-50	1	-48	0	0	0	0	0	0	0	0.3
2	-9	2	-29	0	0	0	0	0	60	330	1.5
3	5	27	21	0	0	0	0	0	30	0	0.8
4	24	10	0	0	0	0	0	0	60	300	1.7
5	26	13	5	0	0	0	0	0	30	330	0.9
6	32	3	-22	0	0	0	0	0	60	0	1.4
7	34	23	17	0	0	0	0	0	60	30	1.5
8	39	65	46	330	0	0	0	0	60	300	1.7
9	42	20	15	330	0	0	0	0	0	0	0.6
10	43	79	51	0	0	0	0	0	60	120	2.1
11	47	11	4	0	0	0	0	0	120	300	2.5
12	59	22	17	0	0	0	120	0	0	0	1.4
13	64	164	75	0	0	0	0	0	0	330	0.6
14	66	7	-7	0	0	0	0	330	0	0	0.7
15	69	56	41	330	0	0	0	0	60	0	1.5
16	76	6	-11	0	0	0	0	0	90	0	1.9
17	80	50	39	330	0	0	0	0	60	30	1.5
18	83	4	-15	0	0	0	0	0	90	330	2.0
19	83	18	15	0	0	0	0	0	60	90	1.9
20	85	8	-6	0	0	0	0	0	90	300	2.1

Table S6: Top 20 squid Rhodopsin conformations after BiHelix/CombiHelix. Conformation observed in the receptor's crystal structure shown in green cells.

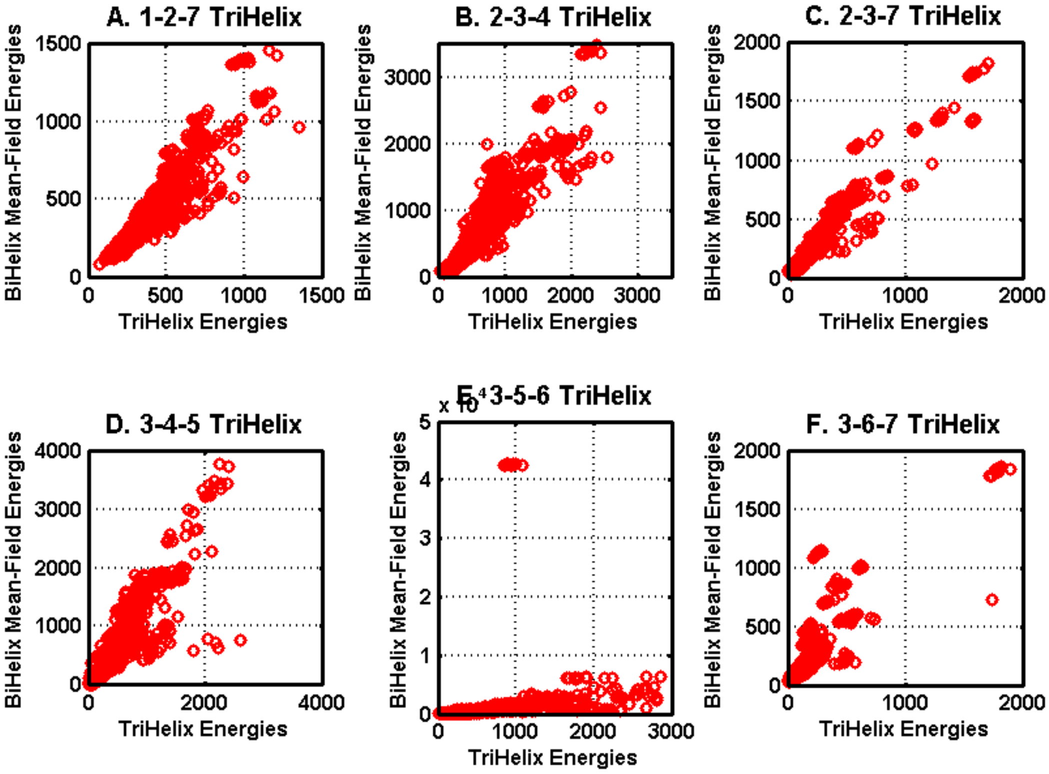


Figure S1: Comparison of the BiHelix Mean-Field energies with exact energies for 6 three-helix bundles for hβ2-AR. **A.** H1-H2-H7; **B.** H2-H3-H4; **C.** H2-H3-H7; **D.** H3-H4-H5; **E.** H3-H5-H6; **F.** H3-H6-H7.

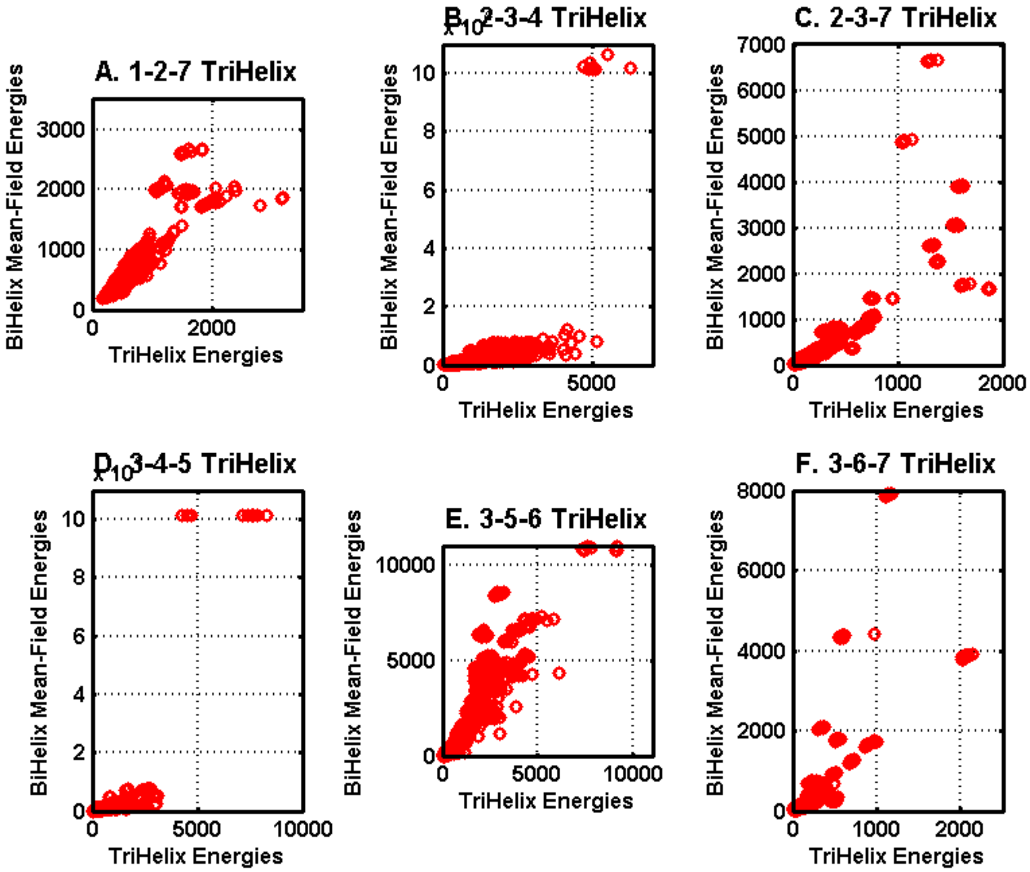


Figure S2: Same comparison as in **Figure S1** for hA2AR.

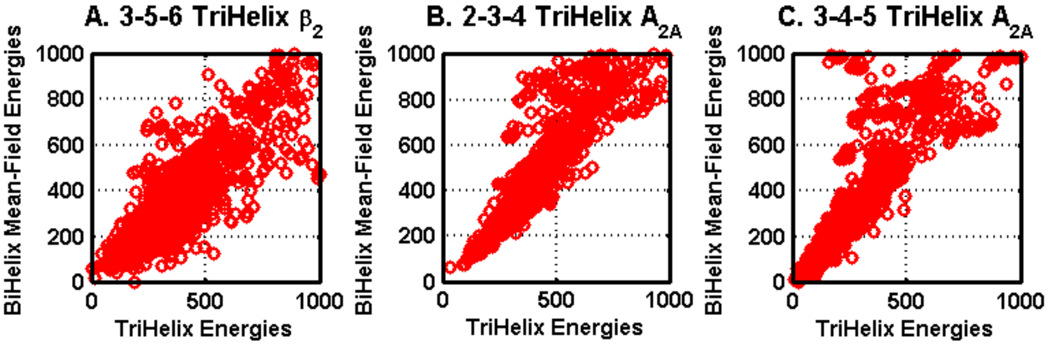


Figure S3: Same comparison as in Figures S1 and S2, but focusing on lowest 1000kcal/mol energy range for three cases. **A.** hb2-AR H3-H5-H6; **B.** hA2AR H2-H3-H4; **C.** hA2AR H3-H4-H5.

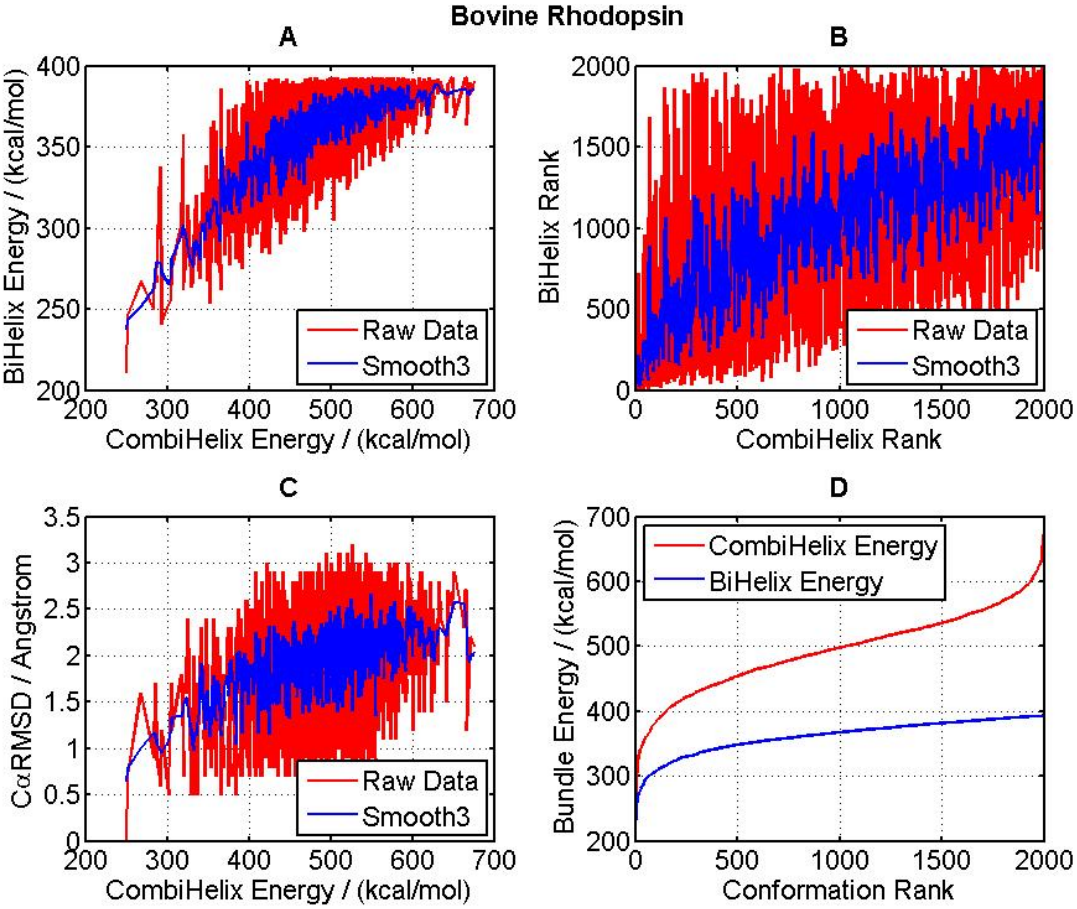


Figure S4: Bovine Rhodopsin. **A.** Correlation between CombiHelix energies and BiHelix energies of the predicted helix bundle conformations, raw data (in red) and smoothed data using ±1 data points (in blue); **B.** Correlation between CombiHelix Rank and BiHelix Rank of the predicted conformations (colors same as in panel A); **C.** Correlation between CombiHelix energies and the corresponding Ca-RMSD of those conformations relative to the conformation observed in the crystal structure (colors same as in panel A); **D.** BiHelix (Blue) and CombiHelix (Red) energies as a function of Conformation Rank.

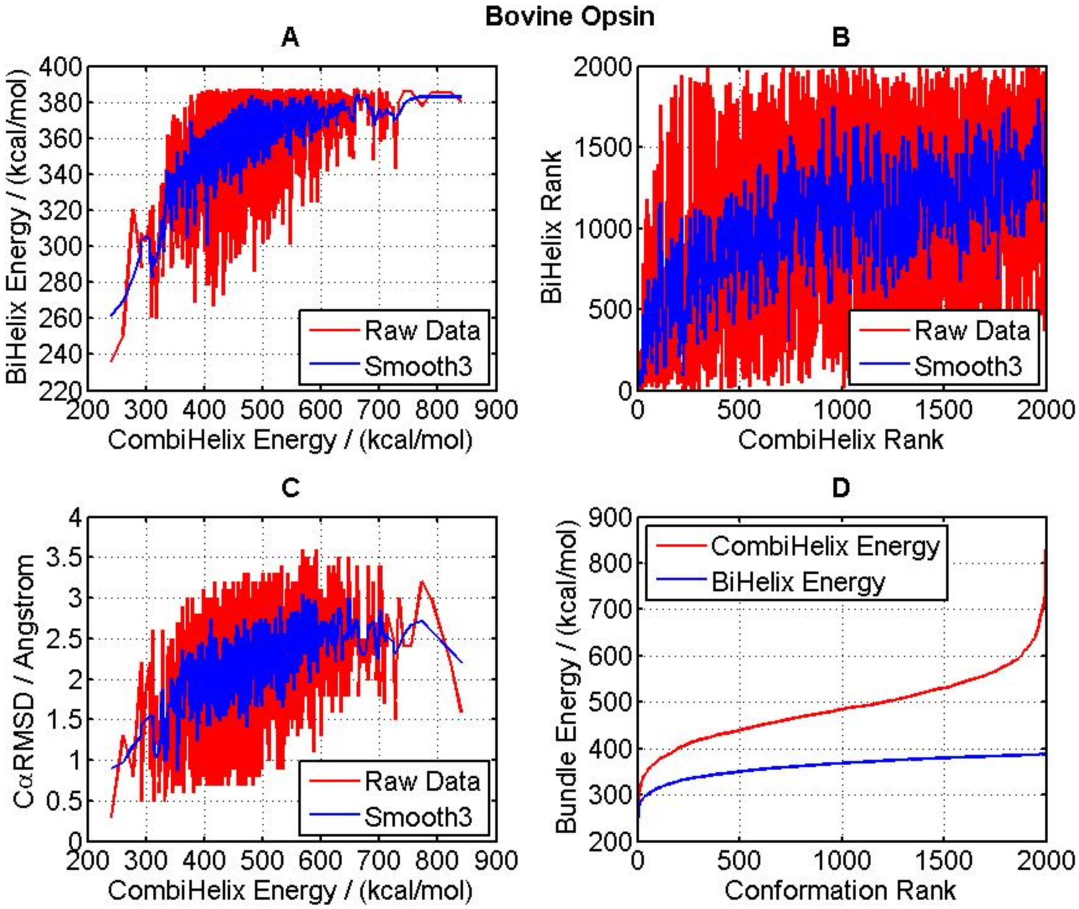


Figure S5: Same as **Figure S4** for Bovine Opsin.

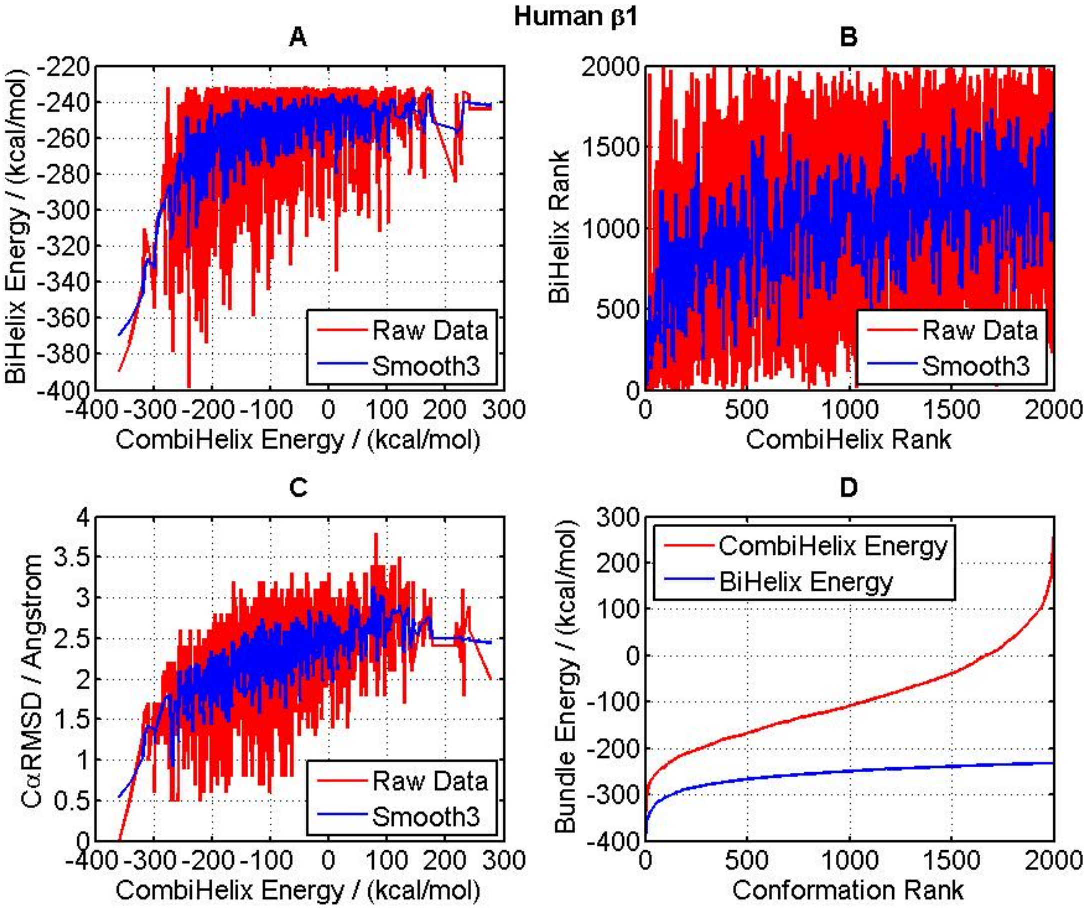


Figure S6: Same as **Figure S4** for human Beta1 adrenergic receptor.

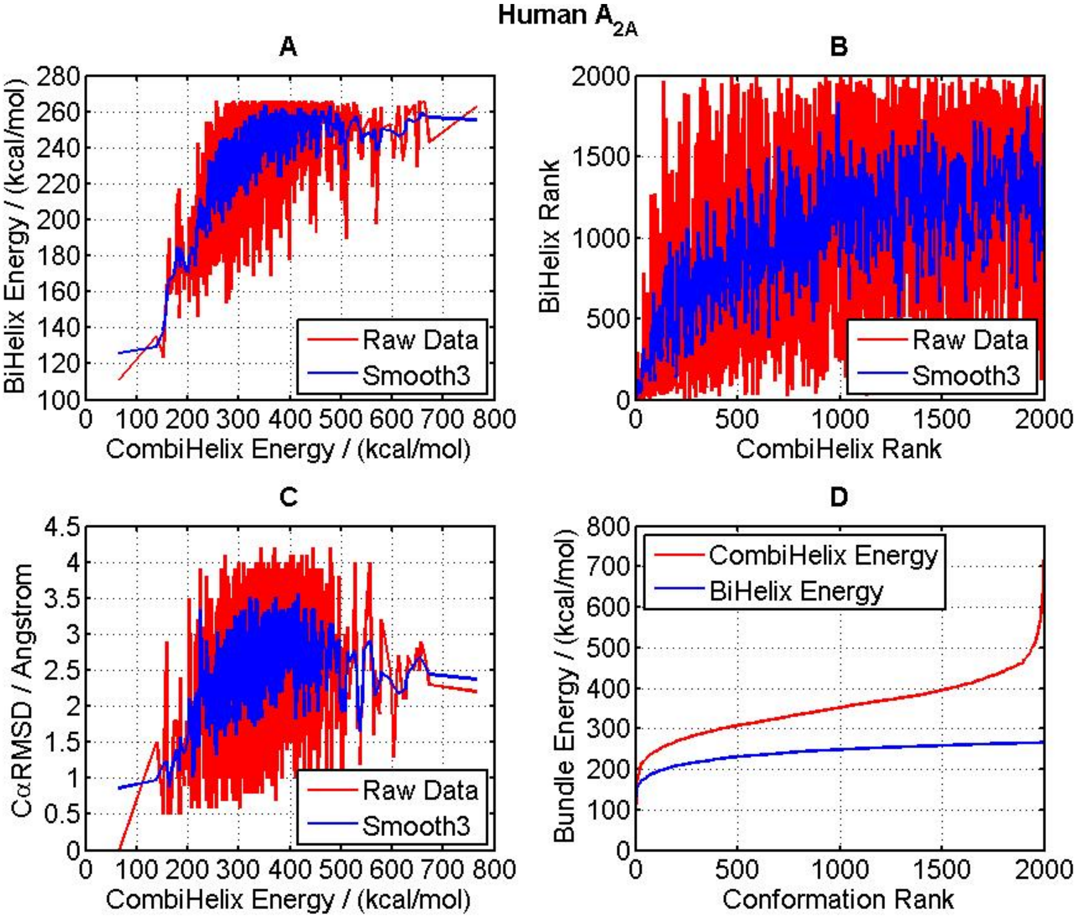


Figure S7: Same as **Figure S4** for human A_{2A} adenosine receptor.

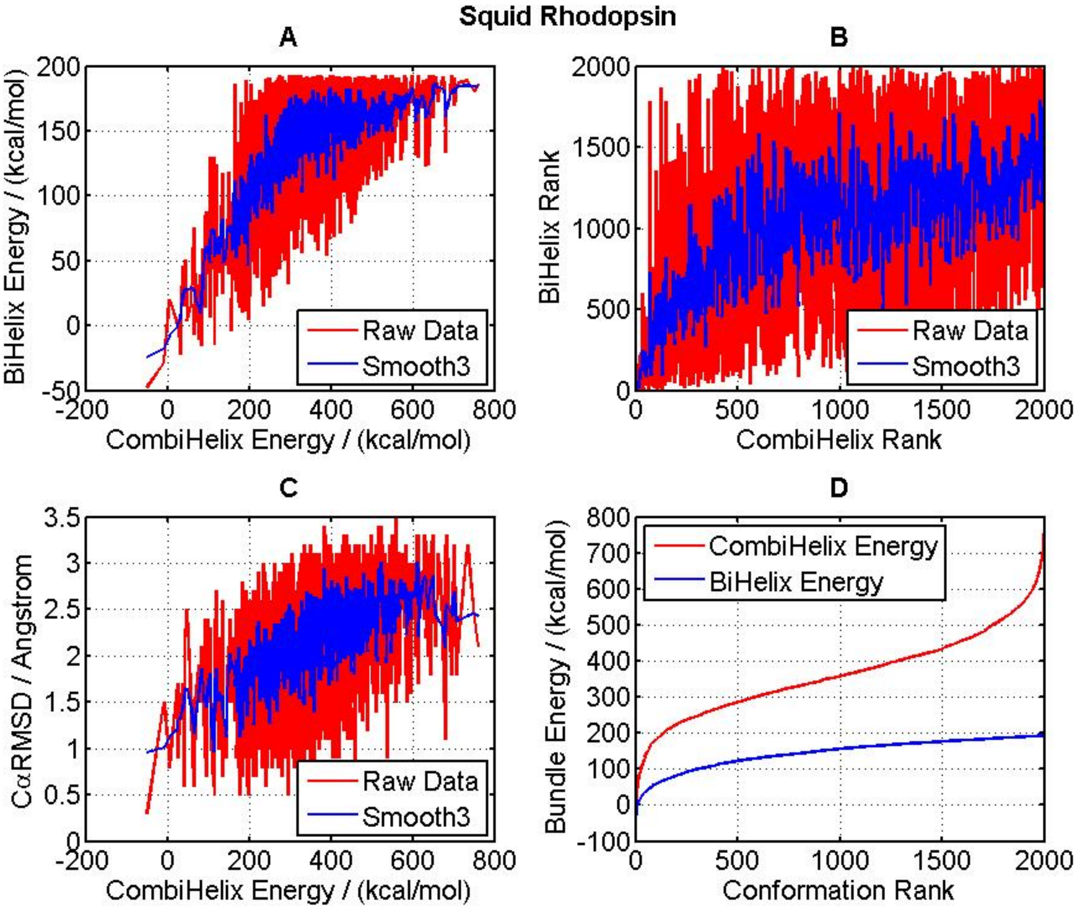


Figure S8: Same as **Figure S4** for squid Rhodopsin.

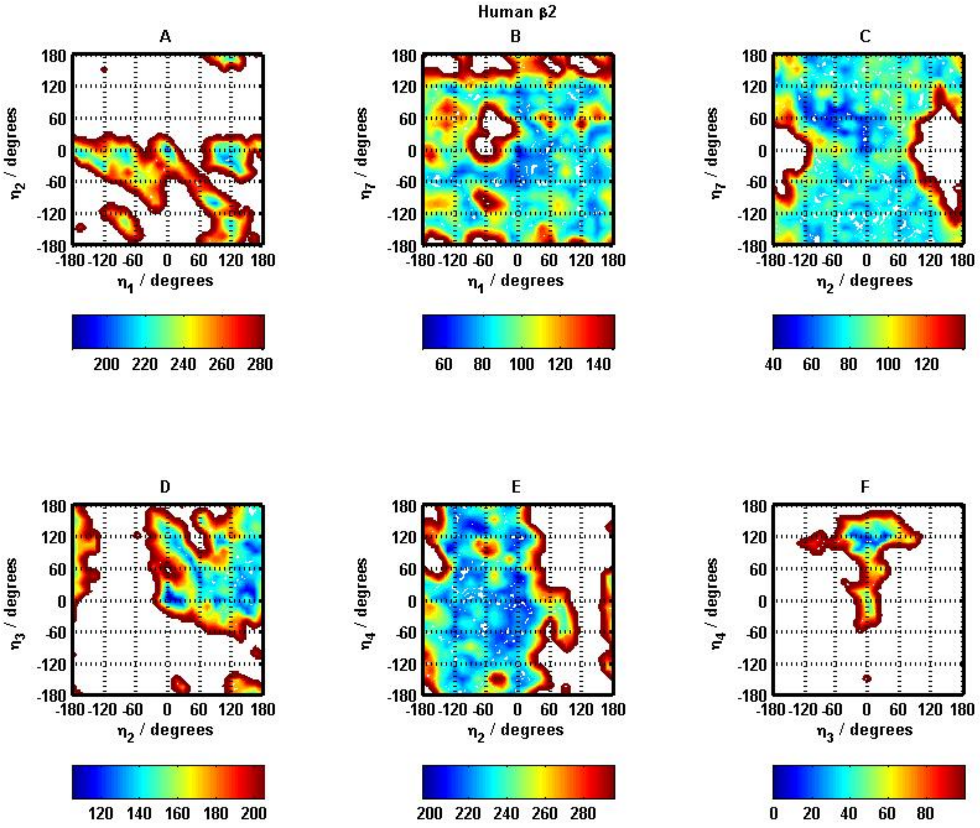


Figure S9: Beta2 adrenergic receptor potential energy surfaces for helix pairs TM1-TM2 (**A**), TM1-TM7 (**B**), TM2-TM7 (**C**), TM2-TM3 (**D**), TM2-TM4 (**E**), and TM3-TM4 (**F**) as a function of helix rotation angles for corresponding helices. The energies are in kcal/mol, where the colorbar under each panel shows the lowest 100 kcal/mol energy range.

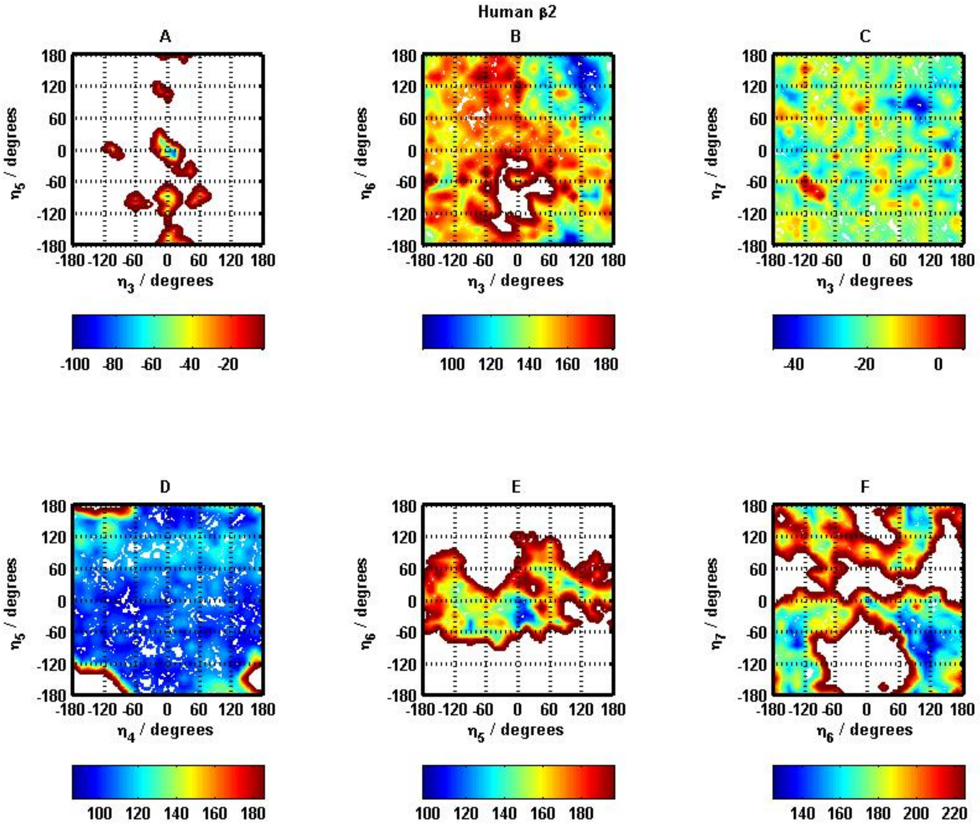


Figure S10: Same as Figure S6 for helix pairs TM3-TM5 (**A**), TM3-TM6 (**B**), TM3-TM7 (**C**), TM4-TM5 (**D**), TM5-TM6 (**E**), and TM6-TM7 (**F**).

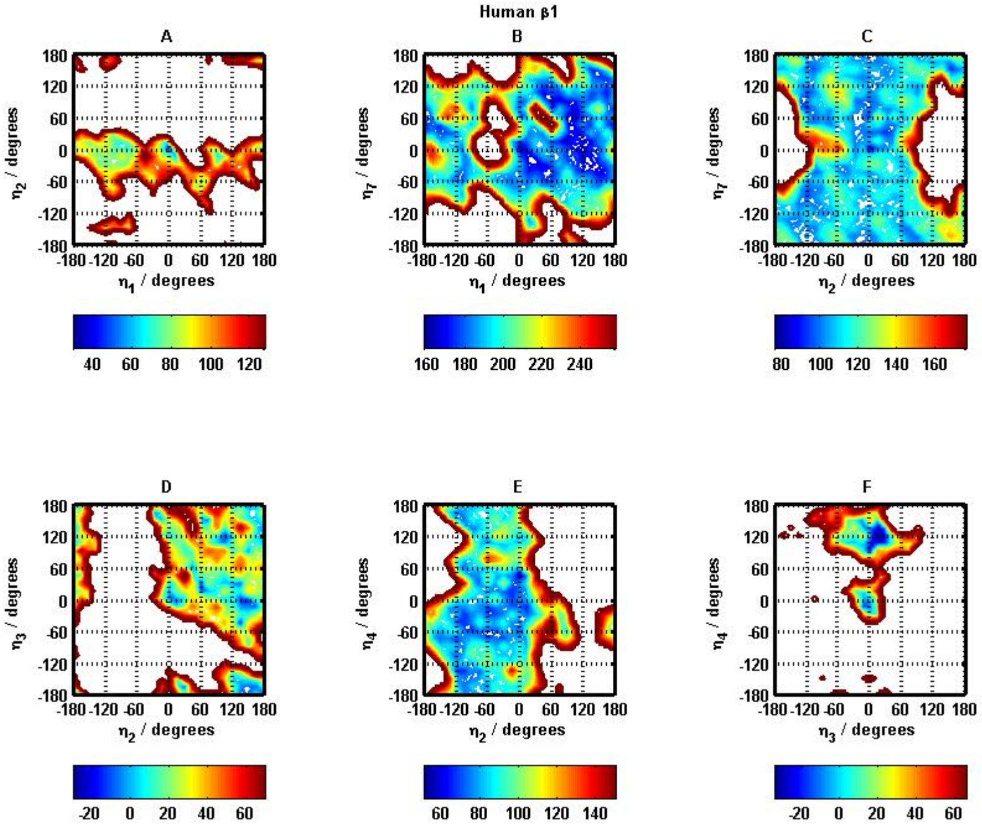


Figure S11: Same as **Figure S9** for Beta1 adrenergic receptor.

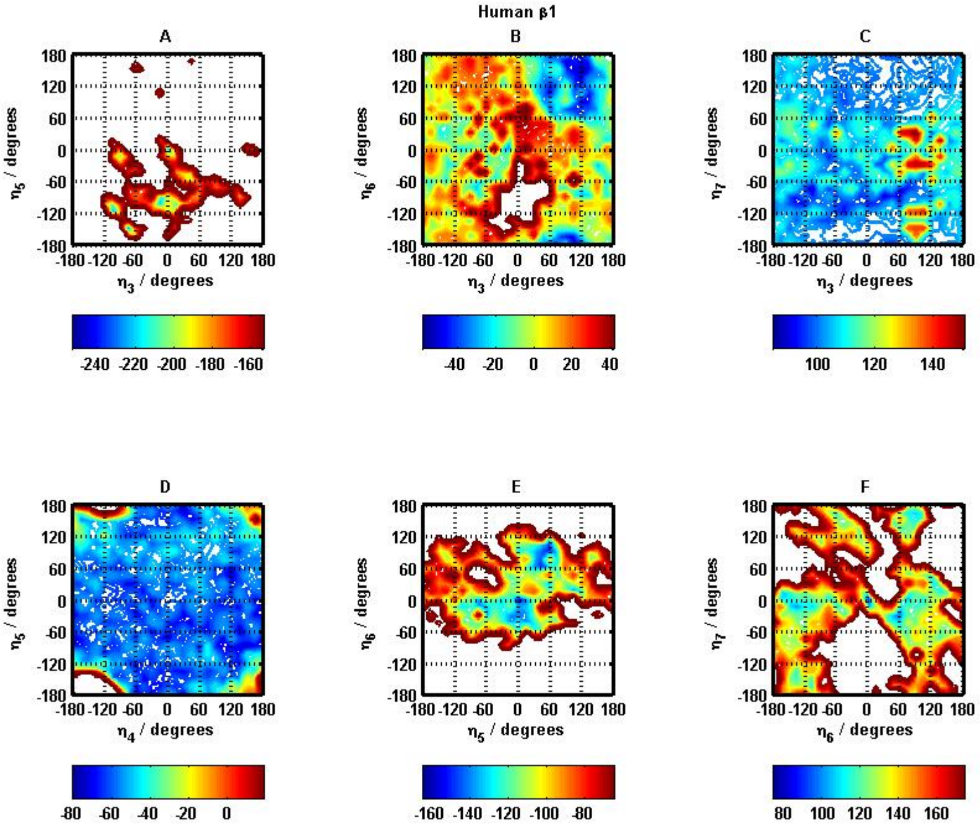


Figure S12: Same as **Figure S10** for Beta1 adrenergic receptor.

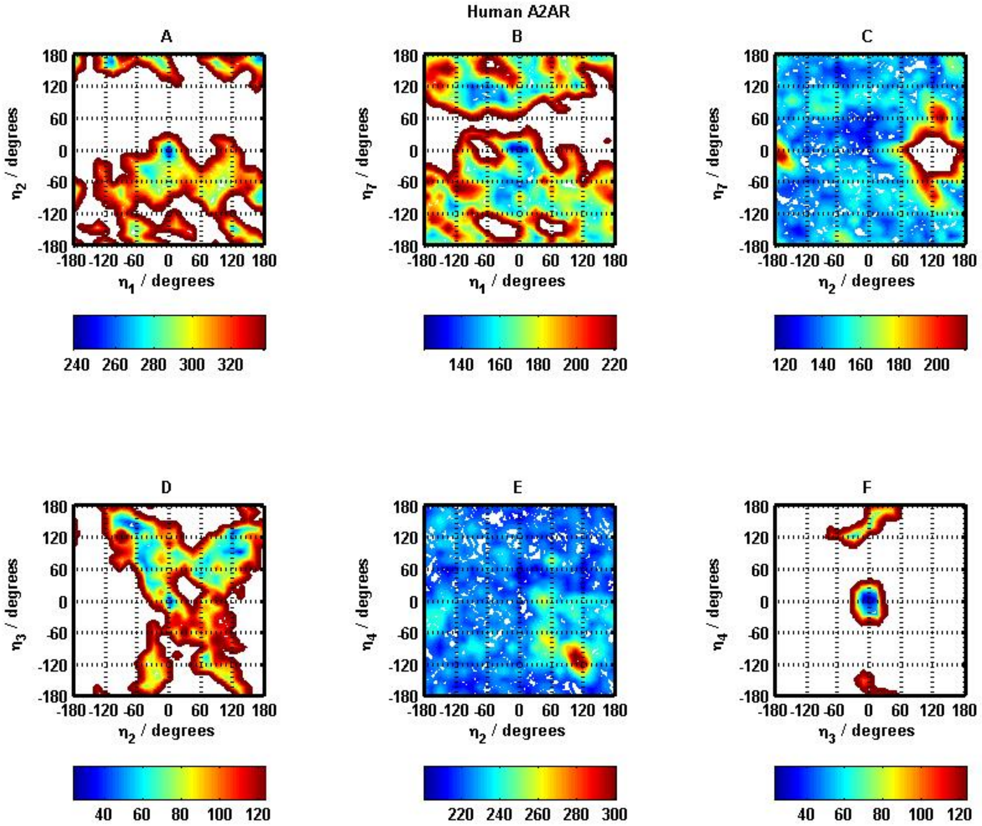


Figure S13: Same as **Figure S9** for adenosine A2A receptor.

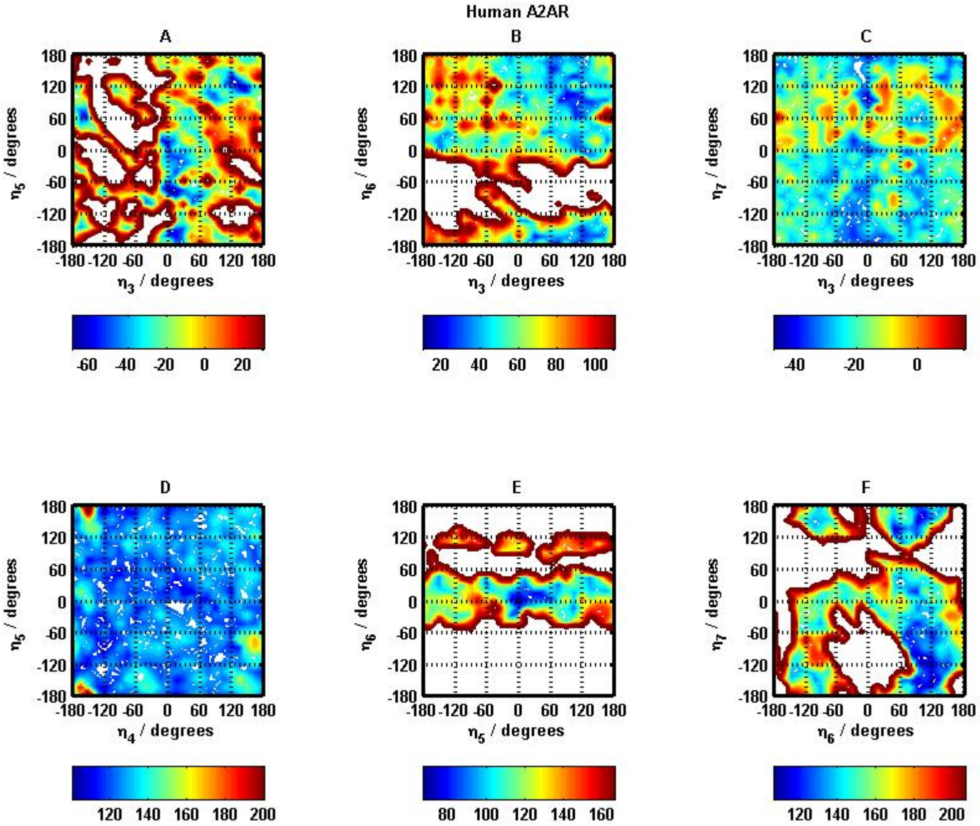


Figure S14: Same as **Figure S10** for adenosine A2A receptor.

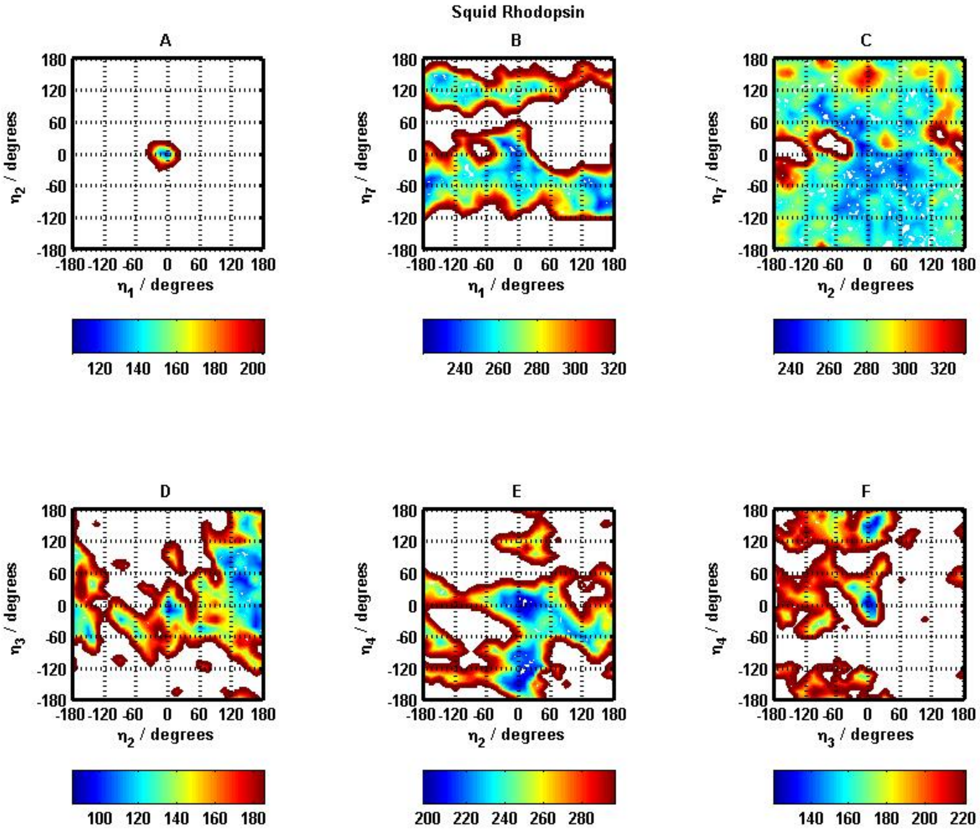


Figure S15: Same as **Figure S9** for squid rhodopsin.

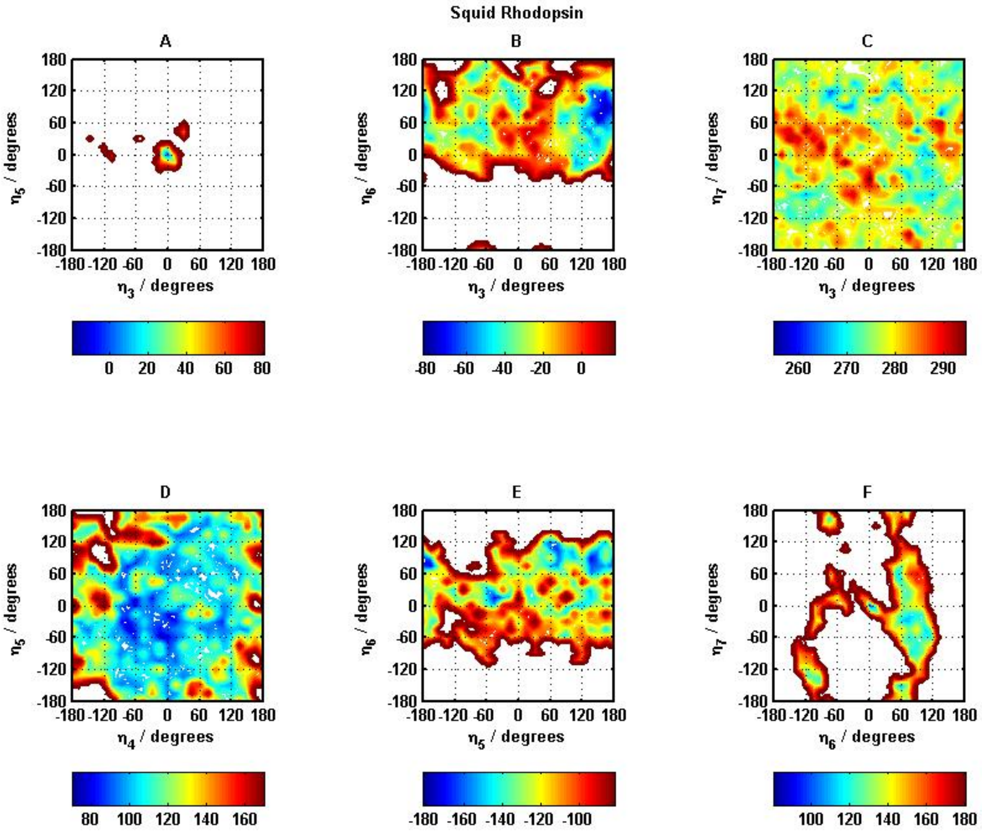


Figure S16: Same as **Figure S10** for squid rhodopsin.