Supplementary Material

FoldGPCR: structure prediction protocol for the transmembrane domain of G protein-coupled receptors from class A

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Predicted models for GPCRs from β-, Y-, and δ-groups of class A

We applied the foldGPCR protocol to predict the structures of several GPCRs for which the experimental structure is not known. Since all known GPCR structures are from the α-group of class A, we chose to generate predicted models for receptors belonging to the β-, γ-, and δ-groups that are phylogenetically more distant and perhaps also structurally more divergent from the templates than any receptors in the α-group:[3] human vasopressin V1a receptor (Swiss-Prot ID: P37288), human κ-type opioid receptor (Swiss-Prot ID: P41145), and human proton-sensing receptor GPR4 (Swiss-Prot ID: P46093). Of the available GPCR crystal structures, the closest sequence homolog to the target receptor was selected as the template structure for obtaining the interhelical contact restraints and the topological restraints; the bovine rhodopsin structure (PDB ID: 1U19) was used for the proton-sensing receptor (47 predicted conserved contacts), and the human β_2AR (PDB ID: 2RH1) was used for the vasopressin (55 predicted conserved contacts) and opioid (60 predicted conserved contacts) receptors. The receptors are modeled without bound ligands, but the predicted models are expected to be in the antagonist-bound conformations.

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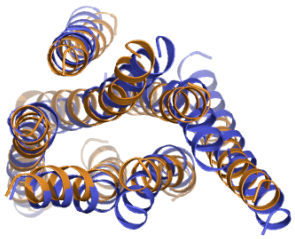
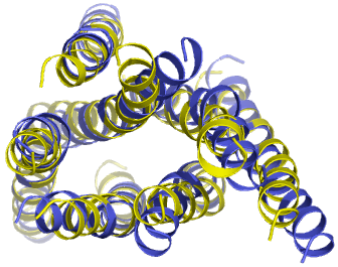
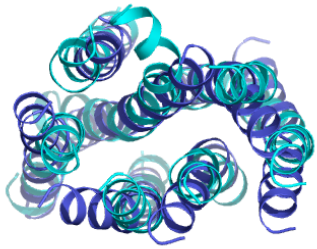
A. vasopressin V1a	B. κ-type opioid	C. proton-sensing GPR4
		

Supplementary Figure 1. Superposition of the predicted models of human vasopressin V1a (orange), κ-type opioid (yellow), and proton-sensing GPR4 (cyan) receptors to their respective templates (blue). The models shown are the average structures of the entire refined ensembles. The vasopressin V1a and κ-type opioid receptor models are 3.4 and 2.6 Å Cα RMSD from the β_2AR template, respectively; the proton-sensing GPR4 receptor model is 3.6 Å Cα RMSD from the rhodopsin template.

Supplementary Table I. List of predicted conserved contacts used to generate the β_2AR models. Residue pair (i,j) predicted to form a contact in β_2AR aligns with contact-forming residue pair (i',j') in rhodopsin.

i	j	i'	j'
51	76	55	80
51	79	55	83
51	80	55	84
51	323	55	303
67	130	71	134
69	326	73	306
71	127	75	131
71	154	75	157
72	322	76	302
72	326	76	306
74	123	78	127
74	154	78	157
74	157	78	160
74	158	78	161
75	123	79	127
75	278	79	257
79	319	83	299
79	323	83	303
121	211	125	215
121	282	125	261
122	211	126	215
124	215	128	219
124	282	128	261
125	211	129	215
125	214	129	218
125	215	129	219
126	153	130	156
126	156	130	159
128	215	132	219
128	218	132	222
129	214	133	218
132	218	136	222
132	221	136	225
163	207	166	211
204	290	208	269
208	287	212	266
212	283	216	262
216	283	220	262
281	321	260	301
281	325	260	305
282	321	261	301
285	317	264	297
285	318	264	298
285	321	264	301
286	318	265	298

Supplementary Table II. List of predicted conserved contacts used to generate the A_{2A} models. Residue pair (i,j) predicted to form a contact in A_{2A} aligns with contact-forming residue pair (i',j') in β_2AR.

i	j	i'	j'
24	49	51	76
24	52	51	79
24	285	51	323
27	45	54	72
27	49	54	76
27	285	54	323
40	101	67	130
41	101	68	130
41	102	68	131
41	235	68	275
43	118	70	147
43	122	70	151
43	125	70	154
44	94	71	123
44	97	71	126
44	98	71	127
44	101	71	130
44	125	71	154
47	94	74	123
47	125	74	154
47	129	74	158
48	95	75	124
48	238	75	278
48	284	75	322
48	288	75	326
52	284	79	322
92	242	121	282
95	193	124	215
95	239	124	279
95	242	124	282
96	193	125	215
98	239	127	279
99	193	128	215
99	239	128	279
100	196	129	218
102	197	131	219
103	196	132	218
103	199	132	221
103	200	132	222
186	242	208	282
187	247	209	287
190	243	212	283
190	247	212	287
193	239	215	279
193	243	215	283
197	239	219	279
241	280	281	318
241	283	281	321

241	287	281	325
242	280	282	318
245	280	285	318
245	283	285	321

Supplementary Table III. Distance measurements (Å) for the topological distance restraints obtained from the rhodopsin, β_2AR, and A_{2A} structures (PDB ID codes 1U19 for rhodopsin; 2RH1 for β_2AR; 3EML for A_{2A}).

A. Extracellular side of the helical bundle

Rhodopsin		β_2AR		A_{2A}	
Residues	Distance	Residues	Distance	Residues	Distance
38:41 – 93:96	10.4	34:37 – 89:92	12.4	7:10 - 62:65	12.2
38:41 – 288:291	13.6	34:37 – 308:311	18.2	7:10 - 270:273	12.8
93:96 – 288:291	16.3	89:92 – 308:311	14.1	62:65 - 270:273	14.0
93:96 – 110:113	10.0	89:92 – 106:109	12.5	62:65 - 77:80	10.8
110:113 – 288:291	17.2	106:109 – 308:311	19.3	77:80 - 270:273	19.9
110:113 – 271:274	20.3	106:109 – 292:295	22.5	77:80 - 252:255	21.5
271:274 – 288:291	11.3	292:295 – 308:311	12.3	252:255 - 270:273	12.8
202:205 – 271:274	13.3	198:201 – 292:295	10.4	176:179 - 252:255	10.5
110:113 – 202:205	19.6	106:109 – 198:201	19.3	77:80 - 176:179	17.2
110:113 – 170:173	11.9	106:109 – 167:170	11.0	77:80 - 138:141	10.2
170:173 – 202:205	13.0	167:170 – 198:201	13.5	138:141 - 176:179	13.1
170:173 – 271:274	20.9	167:170 – 292:295	20.8	138:141 - 252:255	21.3

B. Center of the helical bundle

Rhodopsin		β_2AR		A_{2A}	
Residues	Distance	Residues	Distance	Residues	Distance
48:51 – 261:264	19.5	44:47 – 282:285	18.6	17:20 - 242:245	18.0
48:51 – 297:300	9.9	44:47 – 317:320	9.0	17:20 - 279:282	8.8
261:264 – 297:300	10.8	282:285 – 317:320	10.5	242:245 - 279:282	10.1
48:51 – 82:85	11.6	44:47 – 78:81	11.0	17:20 - 51:54	10.0
82:85 – 297:300	9.9	78:81 – 317:320	10.1	51:54 - 279:282	10.1
82:85 – 120:123	9.8	78:81 – 116:119	9.5	51:54 - 87:90	9.9
120:123 – 297:300	10.8	116:119 – 317:320	13.2	87:90 - 279:282	13.5
120:123 – 261-264	12.6	116:119 – 282:285	13.5	87:90 - 242:245	13.8
82:85 – 161:164	14.4	78:81 – 158:161	14.7	51:54 - 129:132	14.9
120:123 – 161:164	9.1	116:119 – 158:161	9.3	87:90 - 129:132	8.9
161:164 – 213:216	14.8	158:161 – 209:212	15.2	129:132 - 187:190	17.0
120:123 – 213:216	14.1	116:119 – 209:212	12.3	87:90 - 187:190	13.5
213:216 – 261:264	14.1	209:212 – 282:285	12.7	187:190 - 242:245	12.3
161:164 – 261:264	19.7	158:161 – 282:285	21.2	129:132 - 242:245	21.3

C. Cytoplasmic side of the helical bundle

Rhodopsin		β_2AR		A_{2A}	
Residues	Distance	Residues	Distance	Residues	Distance
57:60 – 303:306	12.0	53:56 – 323:326	11.5	26:29 - 285:288	11.4
57:60 – 154:157	19.0	53:56 – 151:154	19.1	26:29 - 122:125	19.7
57:60 – 74:77	10.9	53:56 – 70:73	10.7	26:29 - 43:46	10.8
74:77 – 154:157	9.9	70:73 – 151:154	10.5	43:46 - 122:125	10.9
74:77 – 303:306	11.9	70:73 – 323:326	13.7	43:46 - 285:288	14.0
254:257 – 303:306	10.7	275:278 – 323:326	10.4	235:238 - 285:288	10.8

74:77 – 254:257	14.4	70:73 – 275:278	13.9	43:46 - 235:238	14.1
74:77 – 130:133	12.6	70:73 – 126:129	11.7	43:46 - 97:100	11.1
130:133 – 154:157	11.4	126:129 – 151:154	12.9	97:100 - 122:125	13.1
130:133 – 254:257	11.3	126:129 – 275:278	11.9	97:100 - 235:238	11.4
154:157 – 221:224	21.4	151:154 – 217:220	21.7	122:125 - 195:198	22.8
130:133 – 221:224	10.9	126:129 – 217:220	9.7	97:100 - 195:198	10.7
221:224 – 254:257	13.2	217:220 – 275:278	12.2	195:198 - 235:238	11.9
154:157 – 254:257	19.2	151:154 – 275:278	21.1	122:125 - 235:238	21.5