GPCRdb Homology Models - "Less Model & More Crystal"

GPCRdb.org

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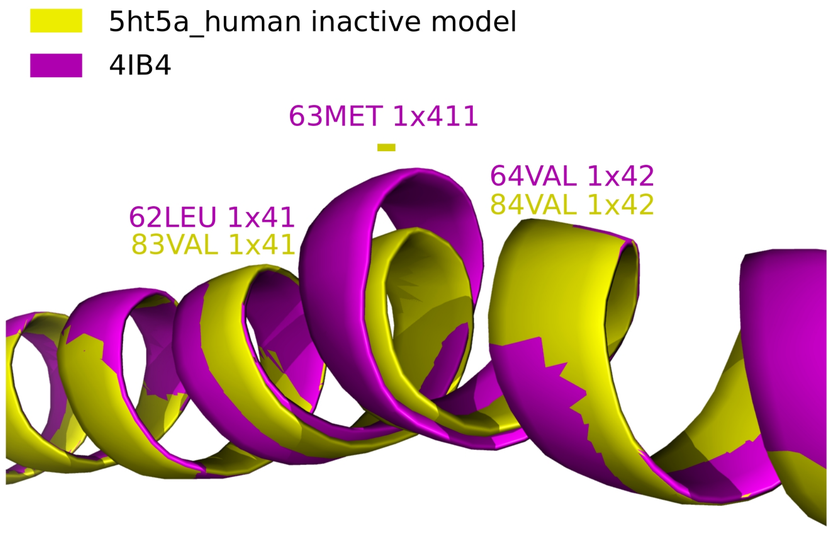
SUMMARY

- **Knowledge-based approach**
- **Multiple backbone templates**
- **Multiple rotamer templates**
- **Alternative loop templates**
- **Modeling structural distortions in the helices**
- **MODELLER [1] for regions without a template**
- **Automated model building pipeline**
- **Models automatically updated with new Xtal data**



Bulge in main template. A normal helix turn is inserted into the initial model.

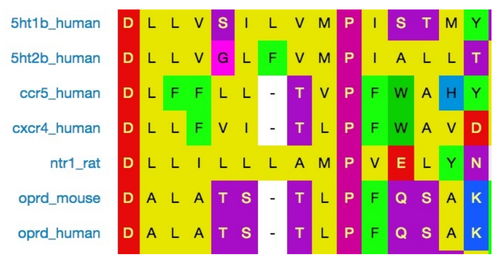
4. Modeling local structural distortions in the helix – bulges and constrictions

- GPCRdb generic numbers can show local structural distortions in the helix
- Bulge – **5 residues** instead of normal 4 in a helix turn
- Constriction – **3 residues** instead of normal 4 in a helix turn
- A bulged or constricted turn can be switched to a normal turn
- Alternative templates are found based on generic numbers

MODEL BUILDING STEPS

1. Main template selection – The frame

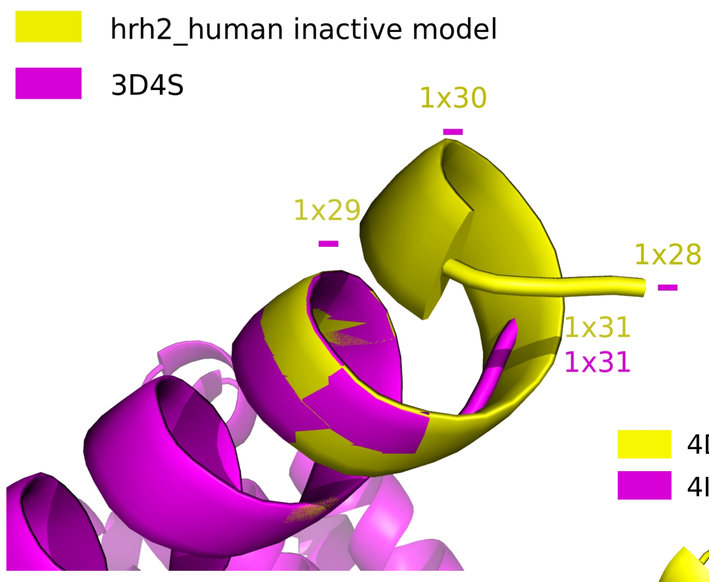
- Same class (A, B, C, F) as target
- Same activation state as target
- Highest overall sequence similarity
- If multiple choices, one with best resolution
- GPCRdb [2] generic numbers [3] are used for the sequence similarity alignment
- Only 7TM and H8 – **Initial model**



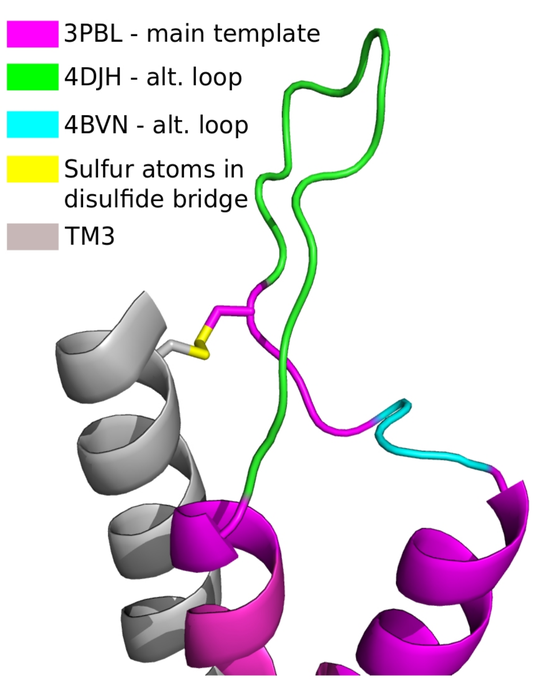
Alignment for receptors

2. Helix start and end adjustments

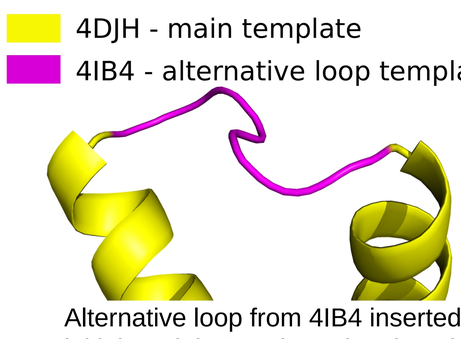
- Distortions in the crystal packing or fused proteins can cause too short or too long TM1-7 and H8 starts and ends.
- GPCRdb has manually annotated segment ends for all structure templates
- When helix start or end is too long → residues are removed from the initial model
- When too short → an alternative template is used to model the missing residues



TM1 of 3D4S was too short at the start for the hrh2_human inactive model. Residues with generic numbers 1x28, 1x29, 1x30 were extracted from 4BVN and superimposed onto 3D4S.



3-part modeling of ECL2 in ada2c_human inactive model.



Alternative loop from 4IB4 inserted in initial model 4DJH based on length.

3. Loop backbone modeling

- Trying loops from main template first
- If not suitable, an alternative template is found
- Selection: 1. length, 2. overall sequence similarity and 3. resolution
- ECL2 – **3-part modeling** – ECL2_1, ECL2_mid (CYS 45x50, X 45x51, X 45x52), ECL2_2

5. Modeling the backbone of N- and C-termini

- N-term – last five residues modeled with TM1 template
- C-term – first five residues modeled with H8 (if not present, TM7) template
- The rest is modeled freely with MODELLER

6. Modeling the rotamers – in-house rotamer library

- When residue mismatch between target and main template → alternative rotamer template based on GPCRdb generic number
- In-house rotamer library
- Selection: 1. overall sequence similarity, 2. same activation state, 3. highest resolution

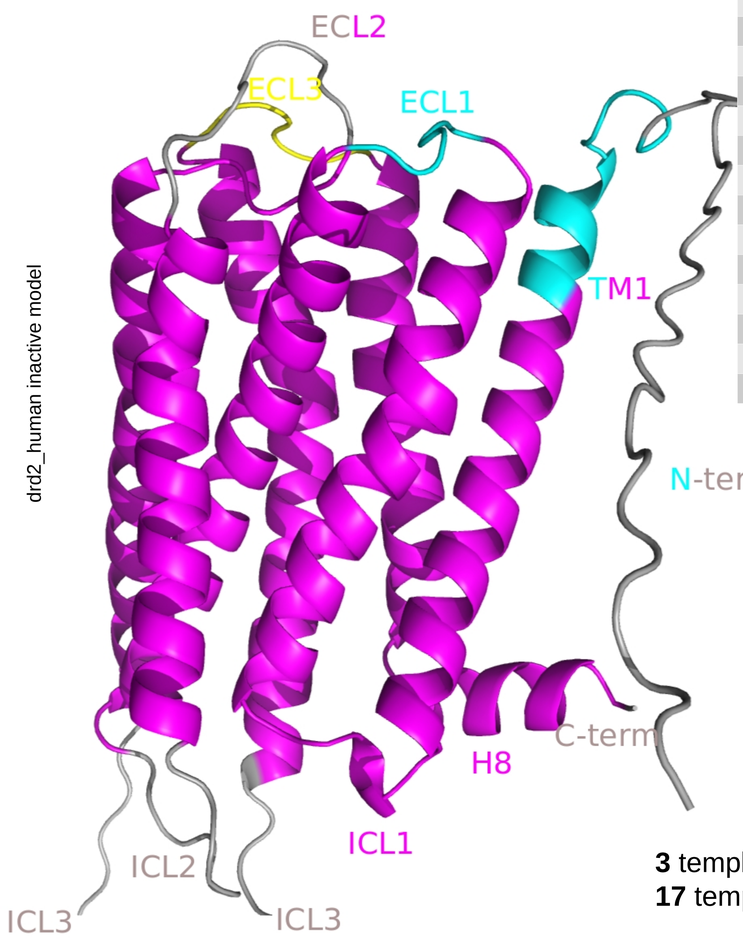
7. Remaining parts - MODELLER

- When no suitable template – free modeling
- Residues are mutated to ALA

Segment	Start num	End num	Backbone Template
N-term	1	25	None
N-term	26	30	4IAR
TM1	31	38	4IAR
TM1	39	62	3PBL
ICL1	63	67	3PBL
TM2	68	97	3PBL
ECL1	98	98	None
ECL1	99	102	4IAR
ECL1	103	103	None
TM3	104	138	3PBL
ICL2	139	148	None
TM4	149	172	3PBL
ECL2	173	181	None
ECL2	182	186	3PBL
TM5	187	218	3PBL
ICL3	219	365	None
TM6	366	398	3PBL
ECL3	399	399	None
ECL3	400	403	3RZE
ECL3	404	404	None
TM7	405	430	3PBL
H8	431	442	3PBL
C-term	443	443	None

Backbone templates for different sections in the drd2_human inactive model

THE FINAL MODELS



3 templates used for backbone modeling
17 templates used for rotamer modeling

3PBL 4IAR 3RZE no template

REFERENCES

[1] B. Webb, A. Sali.: Comparative Protein Structure Modeling Using Modeller. Current Protocols in Bioinformatics, John Wiley & Sons, Inc., 5.6.1-5.6.32, 2014.

[2] Isberg V, Mordalski S, Munk C, Rataj K, Harpsøe K, Hauser AS, Vroling B, Bojarski AJ, Vriend G, Gloriam DE. GPCRdb: an information system for G protein-coupled receptors. Nucleic Acids Res. 2016 Jan 4;44(D1):D356-64.

[3] Isberg V, et al.; Generic GPCR Residue Numbers - Aligning Topology Map Minding The Gaps; *Trends Pharmacol Sci, (2015) 36:22-31*

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