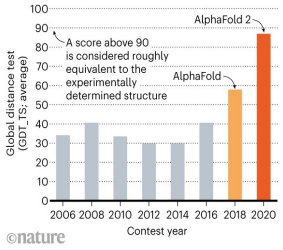
Step 1: protein structure prediction

6 of world's top 20 best-selling drugs target GPCRs (*source: IMS Health MIDAS*). In the table we summarize the performance of our algorithm at predicting the structures of 10 of the most targeted GPCRs by marketed drugs, that include angiotensin receptors for hypertension, histamine receptors for allergy, and dopamine & serotonin receptors for mental disorders.

OUR RESULTS

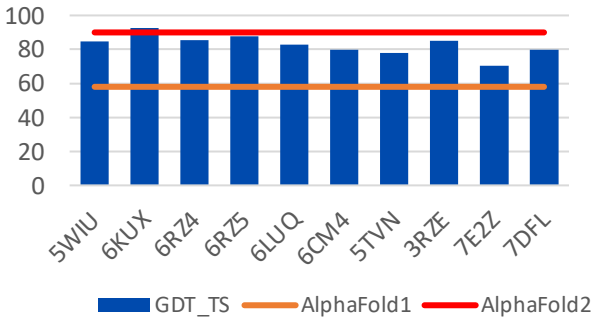
Benchmark

DeepMind's AlphaFold2 algorithm was considered a breakthrough in biology as it represents a considerable advance in terms of generalized protein structure prediction. AlphaFold2 significantly outperformed all other teams by a wide margin at the CASP14 (Critical Assessment of Structure Prediction) protein folding world contest in 2020 and drastically improved the results compared to previous years.



GDT_TS Test

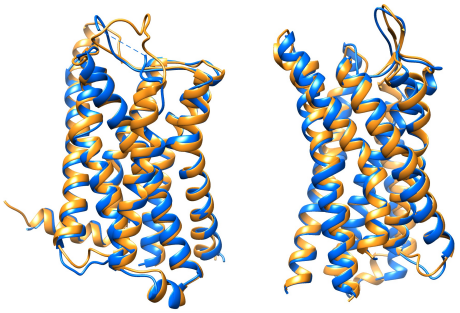
(higher is better)



Our results on 10 GPCRs highly targeted by marketed drugs.

Details of sevenTM's results for both GDT_TS and RMSD tests

GPCR	Class - subclass	Sequence ID	RMSD	GDT_TS	Ligand (drug)	Indication(s)
5WIU	A - dopamine receptor	21.0%	1.45 Å	84.6%	Nemonapride	Schizophrenia
6LUQ	A - dopamine receptor	23.7%	1.47 Å	82.7%	Haloperidol	Schizophrenia
6CM4	A - dopamine receptor	26.0%	1.70 Å	79.9%	Risperidone	Bipolar disorder, schizophrenia
6KUX	A - adrenoceptor	26.2%	0.96 Å	92.5%	E3F	High blood pressure
7E2Z	A - serotonin receptor	23.7%	2.24 Å	70.6%	Aripiprazole	Bipolar disorder, schizophrenia, depression
5TVN	A - serotonin receptor	21.0%	1.88 Å	77.9%	LSD	Mental disorders
7DFL	A - histamine receptor	23.3%	1.73 Å	79.9%	Histamine	Allergy
3RZE	A - histamine receptor	22.7%	1.35 Å	85.1%	Doxepin	Depression, anxiety, chronic hives, sleep disorders
6RZ4	A - leukotriene (opioid)	21.5%	1.60 Å	85.5%	Pranlukast	Asthma
6RZ5	A - leukotriene (opioid)	24.5%	1.18 Å	87.7%	Zafirlukast	Asthma
	Avg	***23.4%***	***1.56 Å***	***82.6%***		



6KUX
92.5 % match

6RZ4
85.6 % match

The GPCR structures characterized experimentally are reported in blue (source: Protein Data Bank), our predicted structures are in orange.

The RMSD between the models generated by our algorithm and the corresponding structures determined experimentally are between 1 and 2.2 Å. These values are lower than the resolution of the experimental techniques employed for protein structure characterization. This means that our results are not significantly different from the actual structures. The prediction accuracy of our pipeline appears close to that achieved by the current benchmark in the field AlphaFold2. Our average RMSD obtained is as low as 1.56 vs. AlphaFold2's average of 1.6Å, and our average GDT (83%) is slightly lower than that of AlphaFold2 (90%).

Our predicted GPCR structures are generated using templates with just 20-26% amino acid sequence in common with the target GPCR (3rd column in the table), to mimic our performance in real scenarios, i.e. orphan GPCRs, which have low sequence identity with available templates. Though, our algorithm can match 70-90% of the actual structure (GDT), and the ligand docking zone, in the middle of the protein, appears always the best modeled one.

Currently we progressively lose predictive power (GDT from >90% to 70%) when only inactive configurations are available as structural templates for a target GPCR in its active form.

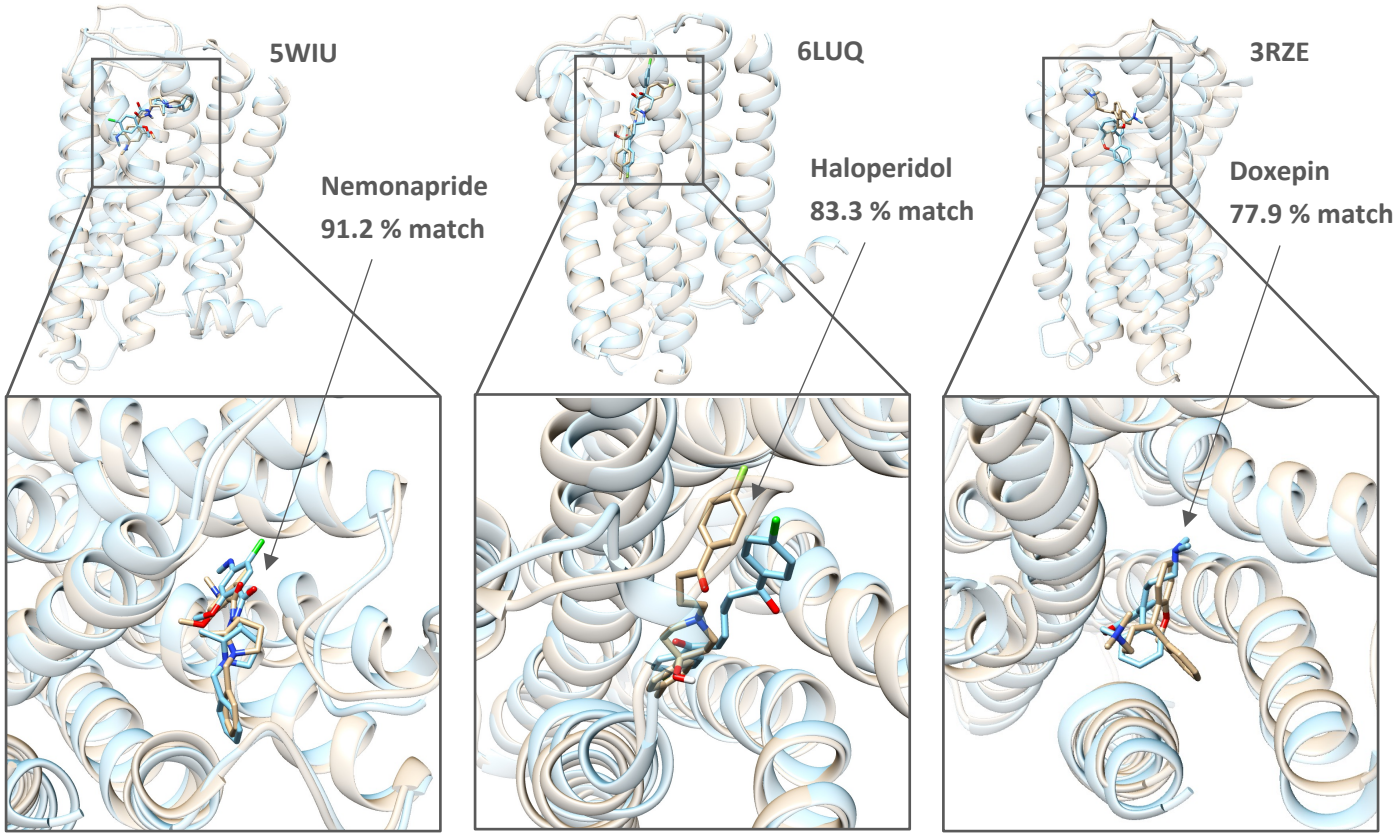
Step 2: ligand (drug) docking

In the table we summarize the performance of our algorithm at predicting the location and pose (docking) of 6 marketed drugs within the active site of GPCRs modelled in Appendix – Step 1. The docking prediction accuracy of our pipeline is given by the overlap % between the volume occupied by the drug (ligand) in its actual pose withing the hosting GPCR, determined experimentally, and that of our predicted pose within our predicted GPCR structure ("Ligand Overlap", 8th column).

GPCR	Receptor family	GDT_TS	Ligand (drug)	Indication(s)	Status	Company	Ligand Overlap
5WIU	Dopamine	84.6%	Nemonapride	Schizophrenia	Approved	Astellas Pharma	91.2%
6LUQ	Dopamine	82.7%	Haloperidol	Psychosis, schizophrenia, Tourette's disorder	Approved	Janssen (J&J)	83.3%
6CM4	Dopamine	79.9%	Risperidone	Schizophrenia, bipolar disorder	Approved	Janssen (J&J)	85.9%
7CMU	Dopamine	76.9%	Pramipexole	Parkinson's disease	Approved	Boehringer Ingelheim	83.6%
3RZE	Histamine	85.1%	Doxepin	Anxiety, depression, insomnia	Approved	Pfizer	77.9%
6RZ4	Leukotriene	85.5%	Pranlukast	Asthma	Approved	Schering-Plough (Merck)	81.3%

Our results on 6 GPCRs highly targeted by marketed drugs.

Our pipeline autonomously finds the correct active site (pocket) across the whole GPCR and docks the selected ligand (drug) inside it. In most cases it will predict the right spatial conformation of the ligand within the active site, achieving an overlap with the actual pose between 78% and 91%. The high prediction accuracy accomplished enables to implement drug discovery tools in our pipeline to automatically design from scratch new chemical structures (potential drugs) that exhibit high affinity for the active site of a modelled GPCR.



The GPCR & drug structures characterized experimentally are reported in light blue (source: Protein Data Bank), our predicted structures in pink.

Oncology

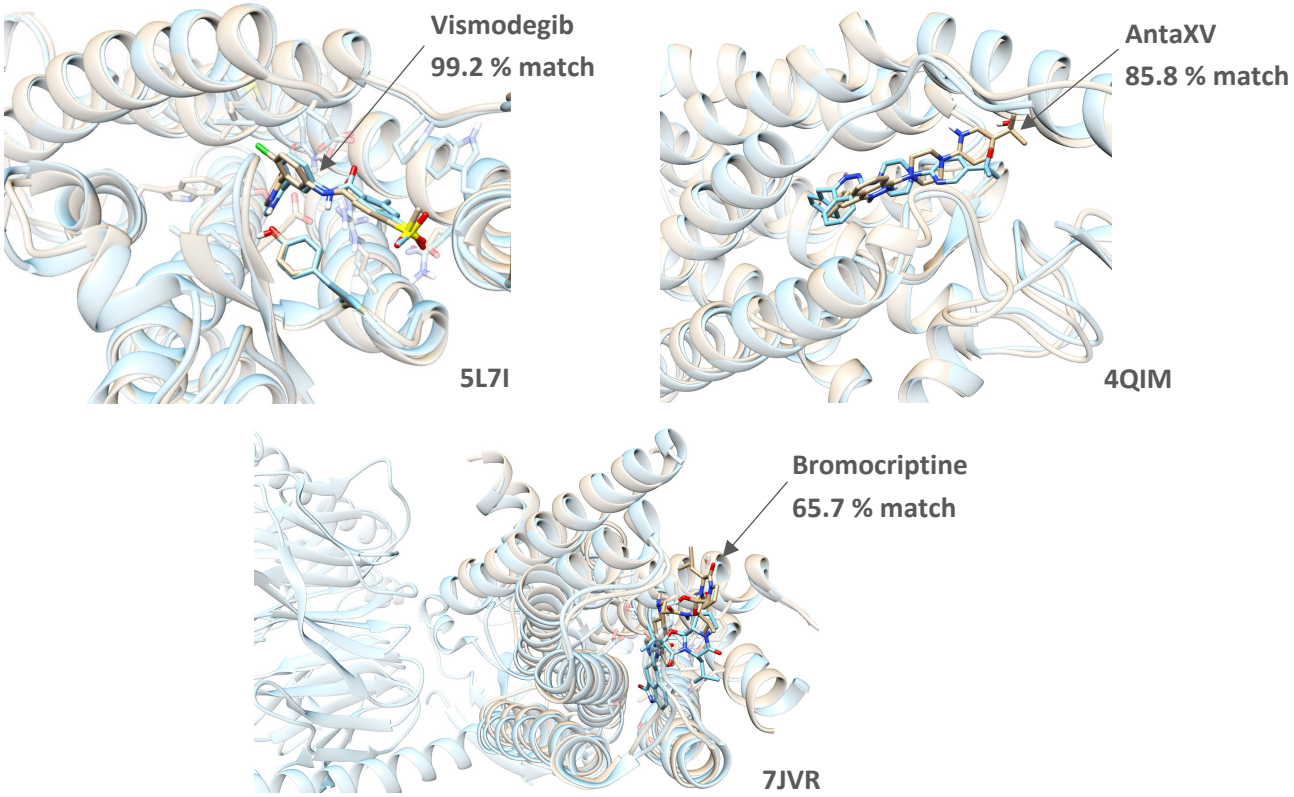
GPCRs regulate a broad range of cellular processes that are critical for cancer such as proliferation (through EGFR/Ras signaling), self-renewal, stress signaling (ATF4/CHOP), immune evasion, angiogenesis, apoptosis (p53 signaling), and metastasis (chemokine signaling). About 20% of all cancers show genetic mutations in their GPCRs. GPCRs have recently become therapeutic targets for oncology and anti-cancer drugs targeting GPCRs (8 approved by FDA for advanced solid tumors and ~20 under clinical trials) exhibited their effect without creating toxicity for normal cells.

In the table we summarize the performance of our algorithm at predicting the structures of 3 GPCRs targeted by anti-cancer drugs (3rd column) and the location & pose chosen by these drugs within the GPCR active sites (docking, 8th column).

GPCR	Receptor family	GDT_TS	Ligand (drug)	Indication(s)	Status	Company	Ligand Overlap
5L7I	Frizzled	94.7%	Vismodegib	Basal cell carcinoma	Approved	Genentech (Roche)	99.2%
4QIM	Frizzled	88.5%	AntaXV	Basal cell carcinomas, medulloblastomas	Preclinical	Novartis	85.8%
7JVR	Dopamine	84.1%	Bromocriptine	Pituitary tumors	Approved	Sandoz (Novartis)	65.7%

Our results on 3 GPCRs targeted by anti-cancer drugs.

The models generated by our algorithm match 84-95% of the corresponding GPCR structures determined experimentally (GDT_TS), showing the same accuracy of AlphaFold2 (90%). Also, our pipeline automatically docks two of the selected anti-cancer drugs inside the corresponding GPCR active sites, in the right conformation and with high spatial precision (85-99%). In the case of the GPCR *7JVR*, our docking predictive power is lower (66%) because all the templates available for its 3D structure modeling are inactive configurations and the drug structure (Bromocriptine) is larger and more complex.



The GPCR & drug structures characterized experimentally are reported in light blue (source: Protein Data Bank), our predicted structures in pink.

These promising results encourage us to focus our drug discovery innovation on the pharmacological engagement of GPCRs in oncology, which is currently underexploited and will yield a new wave of cancer therapies with novel and selective mechanisms of action and exceptional safety profiles.