AlphaFold reveals commonalities and novelties in protein structure space for 21 model organisms

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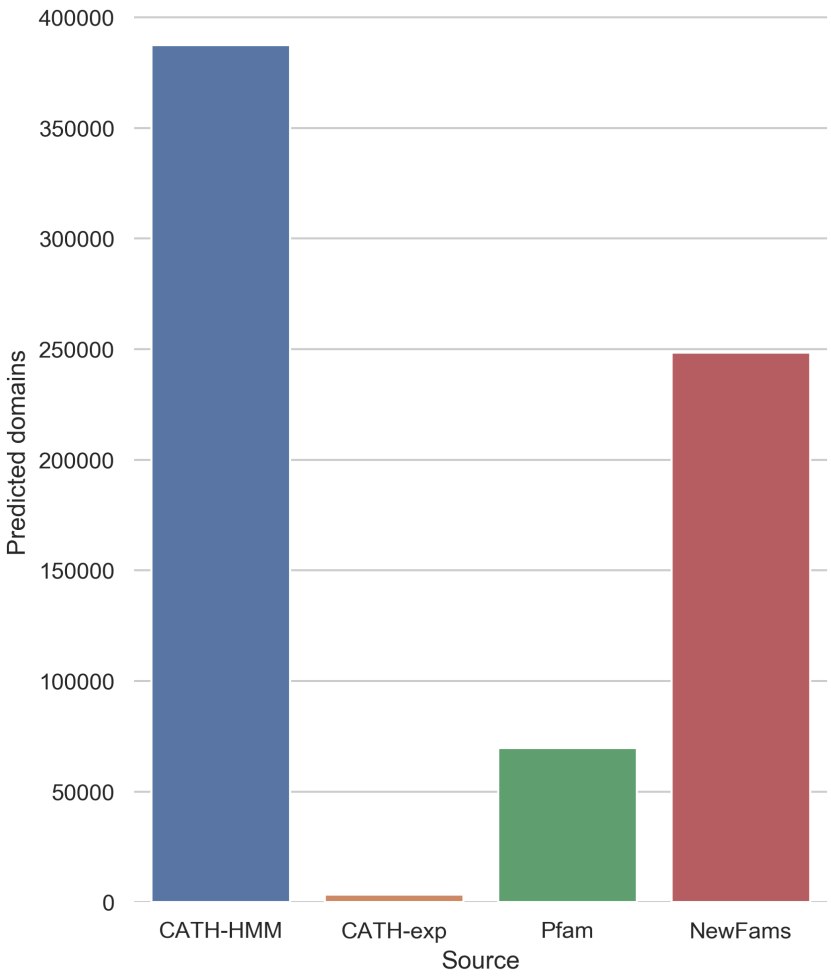
Species	Chopped	Filtered	Structurally validated	Percentage of domains brought into CATH over total
Arabidopsis thaliana	54586	29959	27603	92.1%
Caenorhabditis elegans	34581	19057	17134	89,9%
Candida albicans	8509	6069	5611	92.5%
Danio rerio	66965	33398	31306	93.7%
Dictyostelium discoideum	23647	11916	10455	87.7%
Drosophila melanogaster	27928	14187	12883	90.8%
Escherichia coli	7315	5727	5190	90.6%
Glycine max	107848	56035	51556	92%
Homo sapiens	59314	28029	26484	94.5%
Leishmania infantum	13520	6700	5940	88.7%
Methanocaldococcus jannaschii	2513	2090	1857	88.9%
Mus musculus	55270	27403	25915	94.6%
Mycobacterium tuberculosis	6515	4685	4247	90.7%
Oryza sativa	56618	29116	27431	94.2%
Plasmodium falciparum	7187	3934	3654	92.9%
Rattus norvegicus	52663	26620	25105	94.3%
Saccharomyces cerevisiae	8526	6085	5683	93.4%
Schizosaccharomyces pombe	7618	5627	5350	95.1%
Staphylococcus aureus	4409	3442	3078	89.4%
Trypanosoma cruzi	28392	14650	13056	89.1%
Zea mays	75017	34783	31675	91.1%

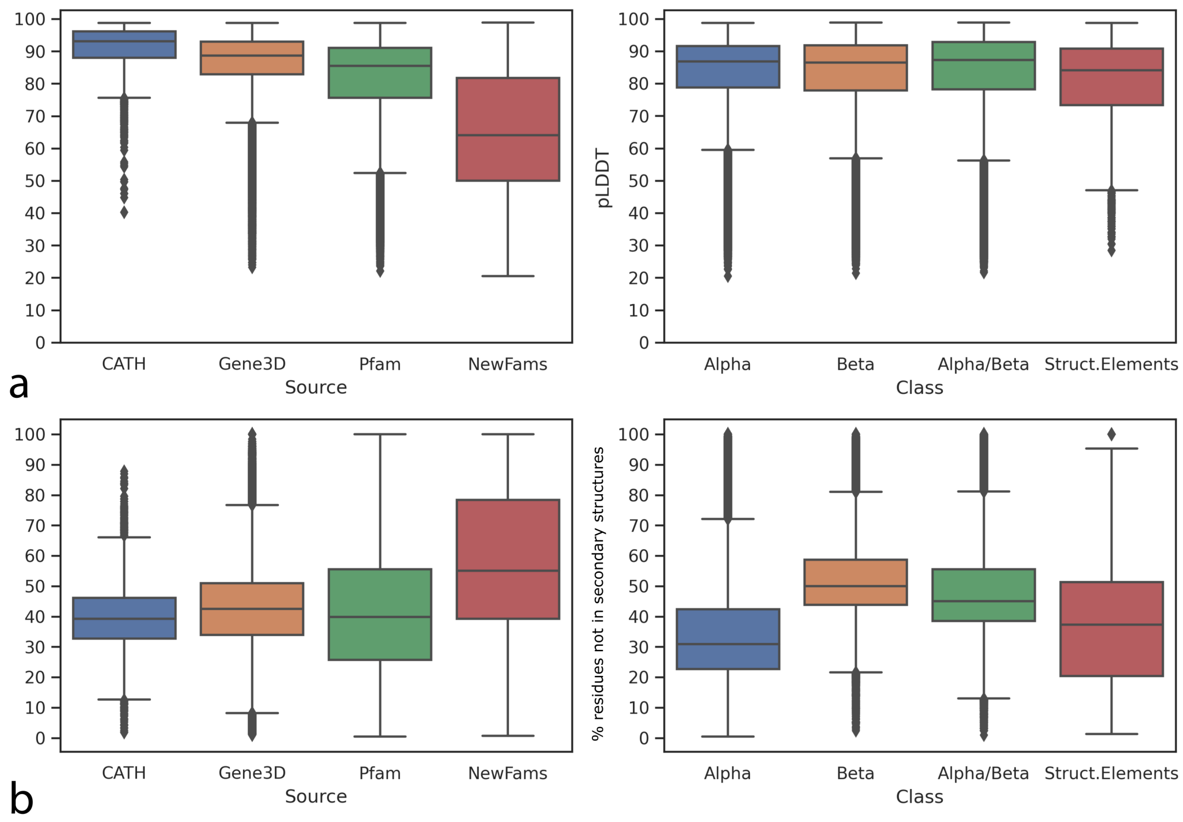
Supplementary Table 1. Number of domains at each step of processing.

Species	pLDDT < 70	Domain residues not in secondary structure > 65%	Packing issues	LUR > 30%	SSE < 3
Arabidopsis thaliana	12767	1391	3858	981	5630
Caenorhabditis elegans	8369	509	2557	568	3521
Candida albicans	1109	91	523	107	610
Danio rerio	12976	1496	6869	893	11333
Dictyostelium discoideum	7083	313	1396	404	2535
Drosophila melanogaster	6810	515	2842	475	3099
Escherichia coli	243	43	464	63	775
Glycine max	28300	1685	8323	2041	11464
Homo sapiens	13590	1243	6891	683	8878
Leishmania infantum	4425	150	1155	187	903
Methanocaldococcus jannaschii	84	12	147	12	168
Mus musculus	11641	1170	6242	648	8166
Mycobacterium tuberculosis	482	55	522	83	688
Oryza sativa	19157	617	3397	729	3602
Plasmodium falciparum	2139	61	549	116	388
Rattus norvegicus	11245	1096	5435	673	7594
Saccharomyces cerevisiae	1134	75	516	106	610
Schizosaccharomyces pombe	779	70	486	94	562
Staphylococcus aureus	241	10	213	29	474
Trypanosoma cruzi	9519	341	2089	369	1424
Zea mays	24371	935	6180	1375	7373
AlphaFold	176464	11878	60654	10636	79796

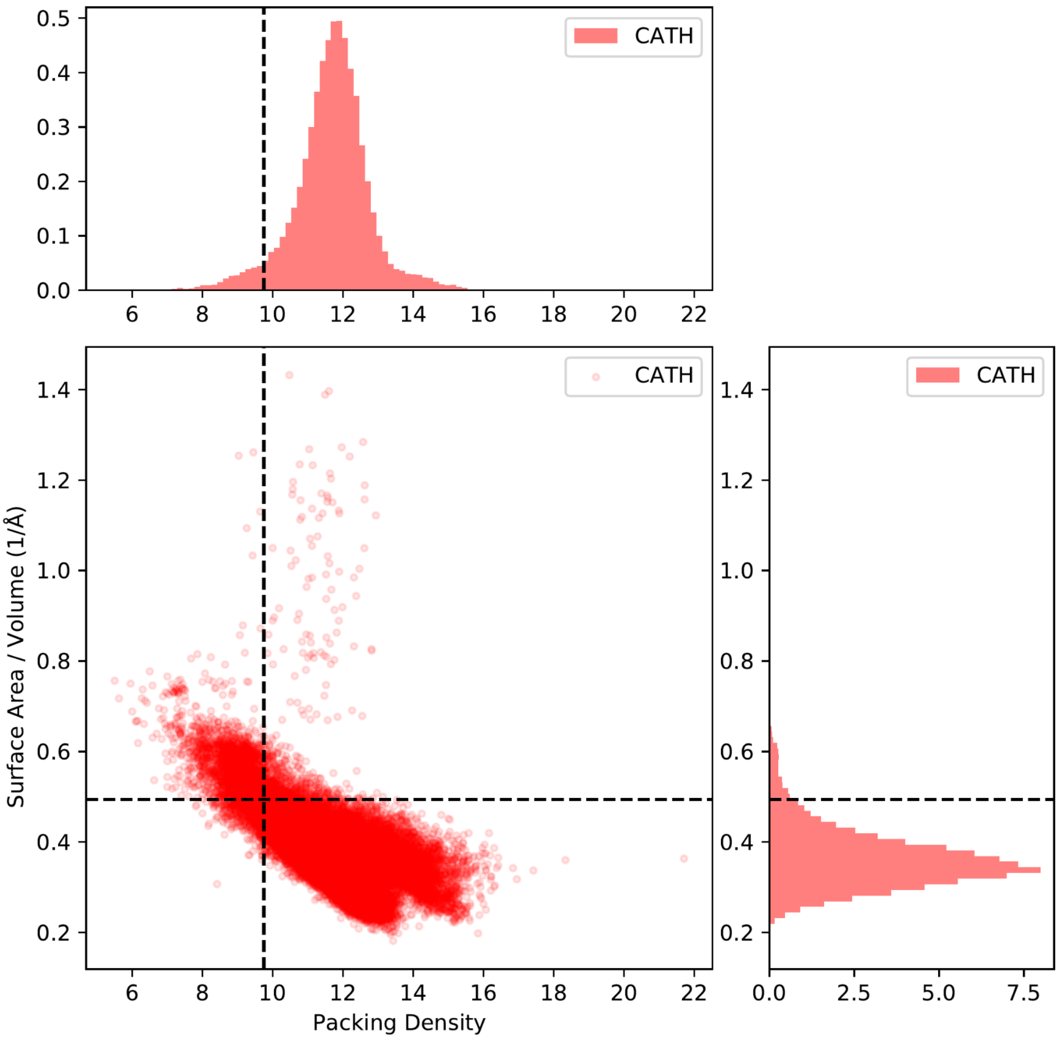
Supplementary Table 2. Number of domains discarded by reason.



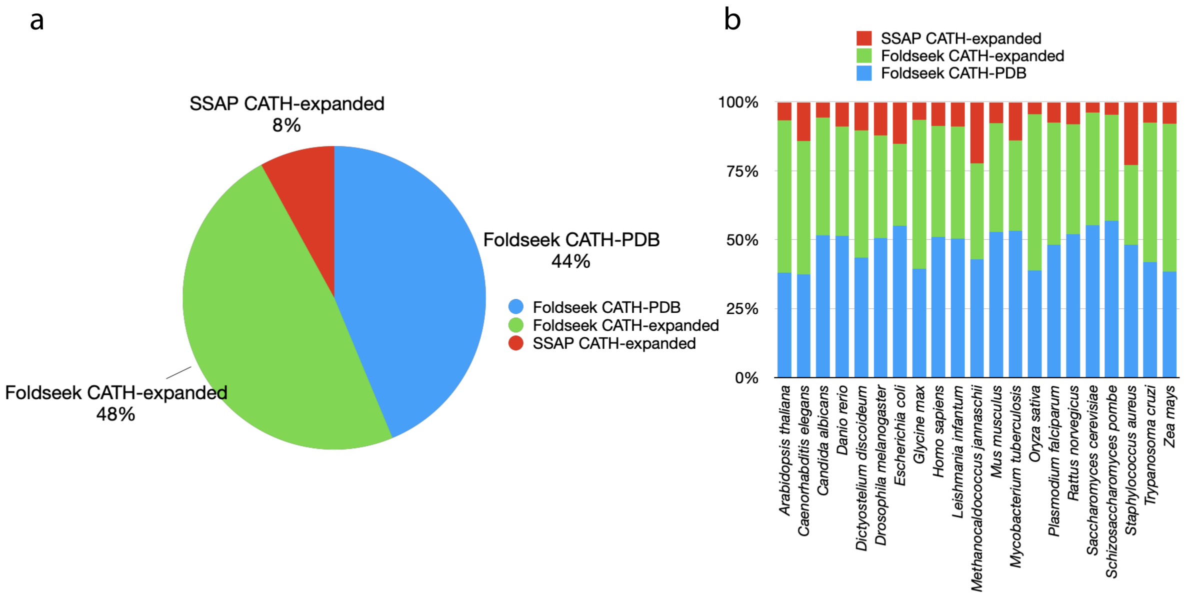
Supplementary Figure 1: Predicted domains in AlphaFold DB by source.



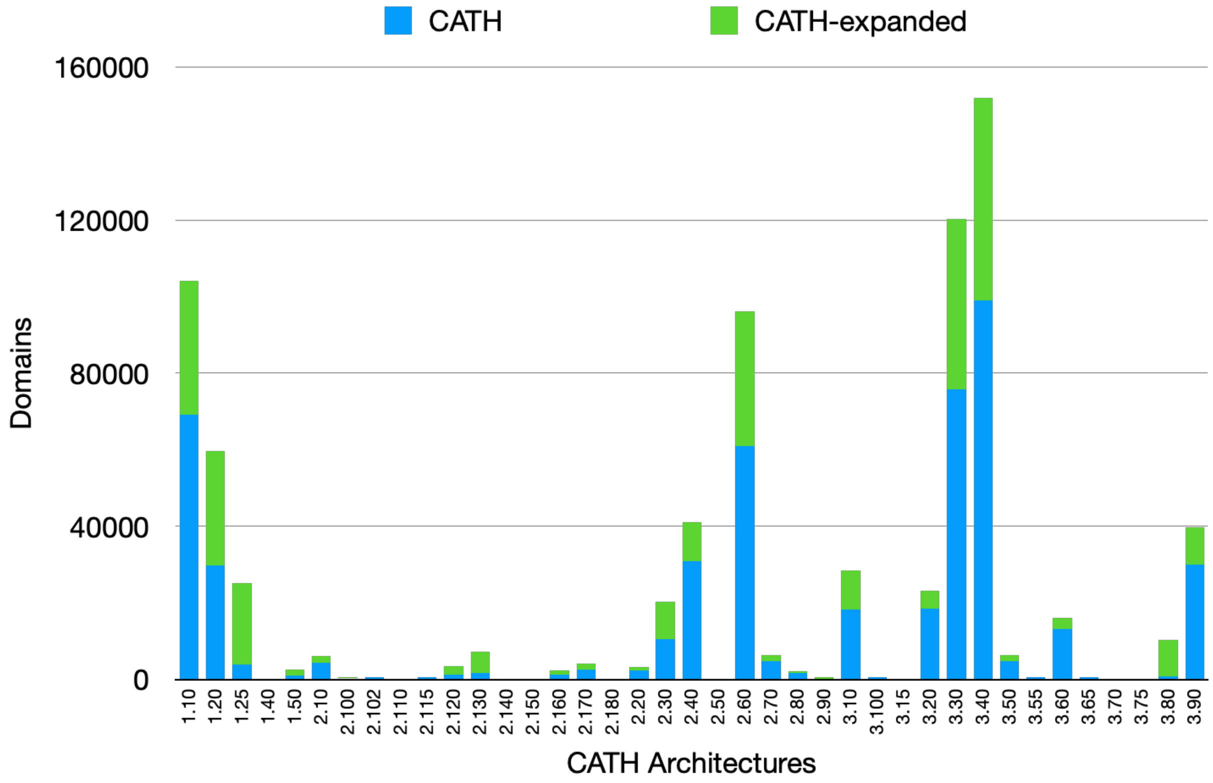
Supplementary Figure 2. a) Distribution of model quality and b) percentage of residues not in secondary structures by domain source and CATH class.



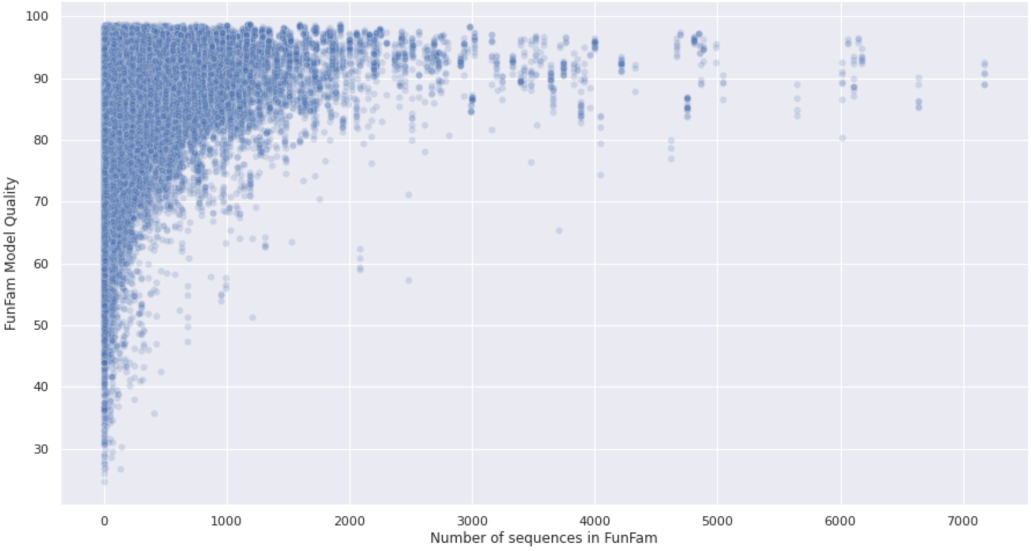
Supplementary Figure 3. Scatter plot of packing density and Surface Area / Volume with marginal distributions for the protein domains in the CATH database. The dashed lines show the 95% cutoff for each metric, which has been used to label the AlphaFold domains as globular or non-globular.



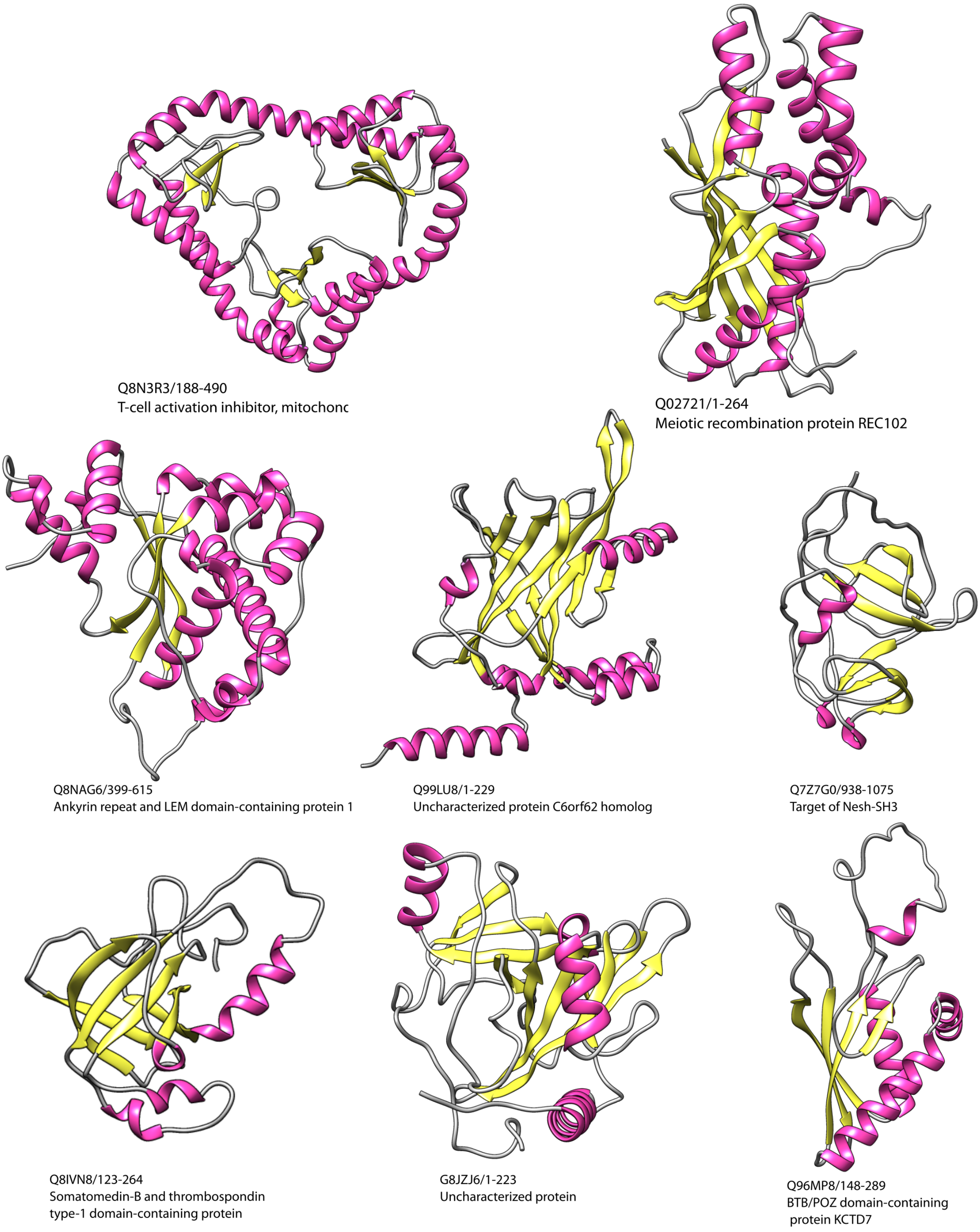
Supplementary Figure 4. a) Total proportion of domains structurally validated using CATH-PDB and CATH-expanded by Foldseek and SSAP, and b) by organism.



Supplementary Figure 5. CATH Architecture expansion by AF2 models. CATH Architectures are displayed on x-axis, with the relative expansion measured by the total domains in them (before – “CATH”, after – “CATH-expanded”) is displayed on the y-axis.



Supplementary Figure 6. AF2 domains model qualities in FunFams versus sequences in each FunFam.



Q8N3R3/188-490
T-cell activation inhibitor, mitochonc

Q02721/1-264
Meiotic recombination protein REC102

Q8NAG6/399-615
Ankyrin repeat and LEM domain-containing protein 1

Q99LU8/1-229
Uncharacterized protein C6orf62 homolog

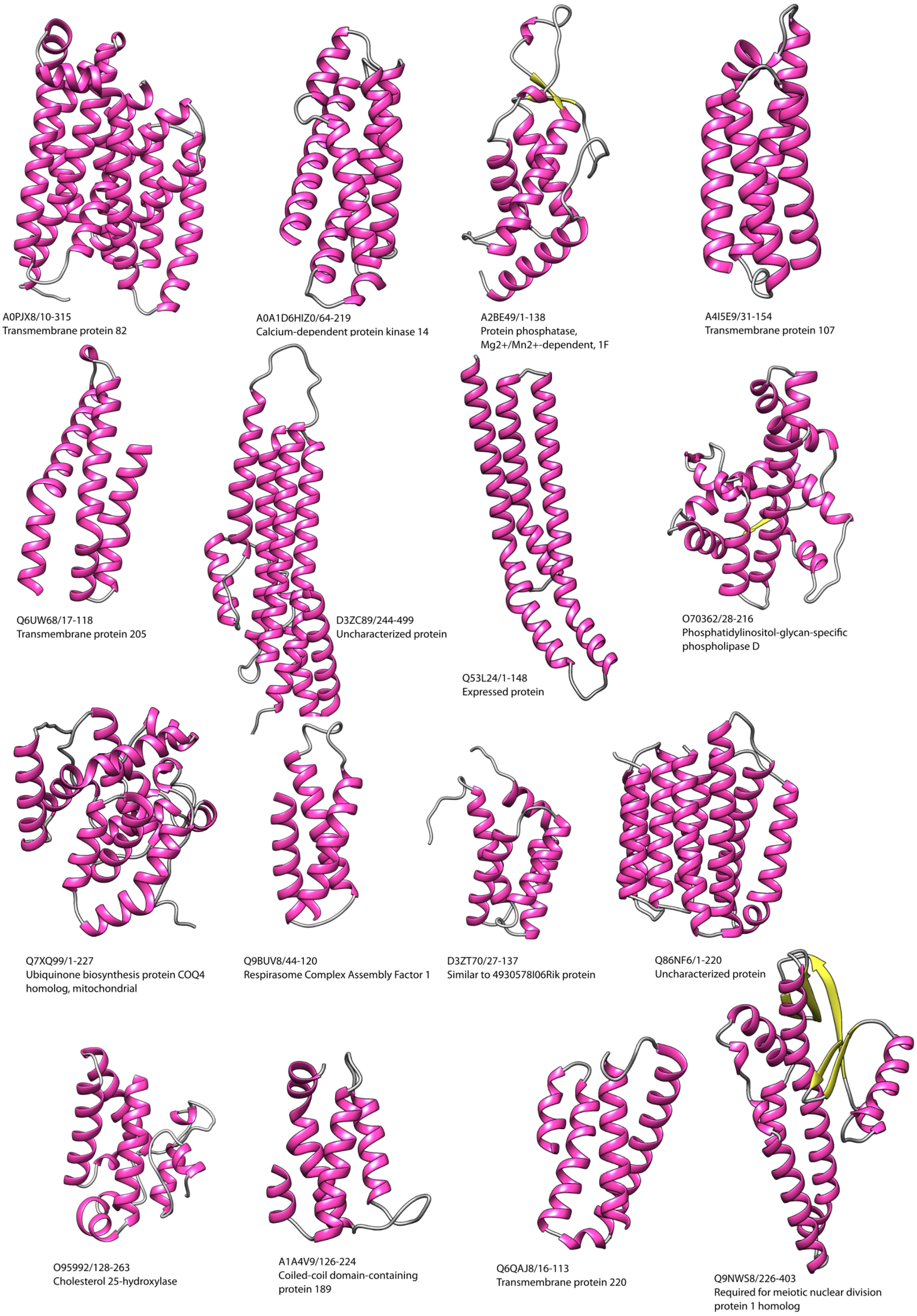
Q7Z7G0/938-1075
Target of Nesh-SH3

Q8IVN8/123-264
Somatomedin-B and thrombospondin
type-1 domain-containing protein

G8JZJ6/1-223
Uncharacterized protein

Q96MP8/148-289
BTB/POZ domain-containing
protein KCTD7

Supplementary Figure 7. All alpha/beta novel folds in AF2.



A0PJX8/10-315
Transmembrane protein 82

A0A1D6HIZ0/64-219
Calcium-dependent protein kinase 14

A2BE49/1-138
Protein phosphatase,
Mg2+/Mn2+-dependent, 1F

A4I5E9/31-154
Transmembrane protein 107

Q6UW68/17-118
Transmembrane protein 205

D3ZC89/244-499
Uncharacterized protein

Q53L24/1-148
Expressed protein

O70362/28-216
Phosphatidylinositol-glycan-specific
phospholipase D

Q7XQ99/1-227
Ubiquinone biosynthesis protein COQ4
homolog, mitochondrial

Q9BUV8/44-120
Respirasome Complex Assembly Factor 1

D3ZT70/27-137
Similar to 4930578I06Rik protein

Q86NF6/1-220
Uncharacterized protein

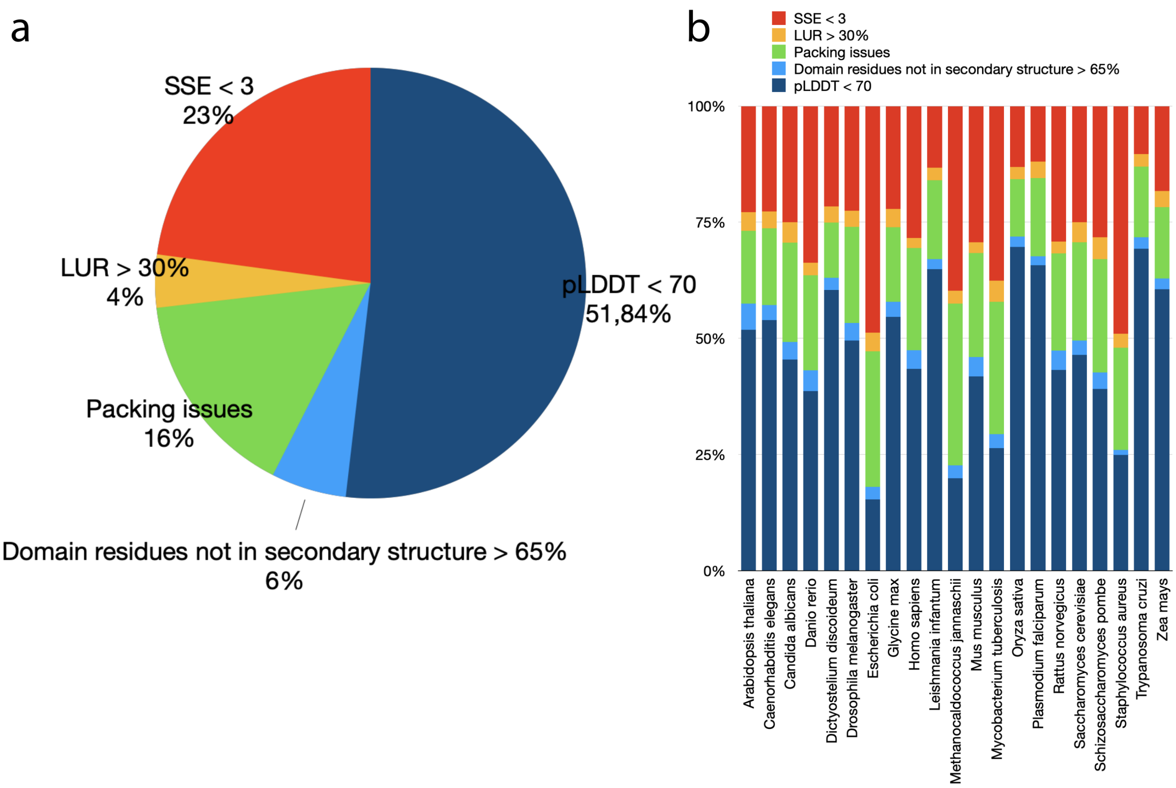
O95992/128-263
Cholesterol 25-hydroxylase

A1A4V9/126-224
Coiled-coil domain-containing
protein 189

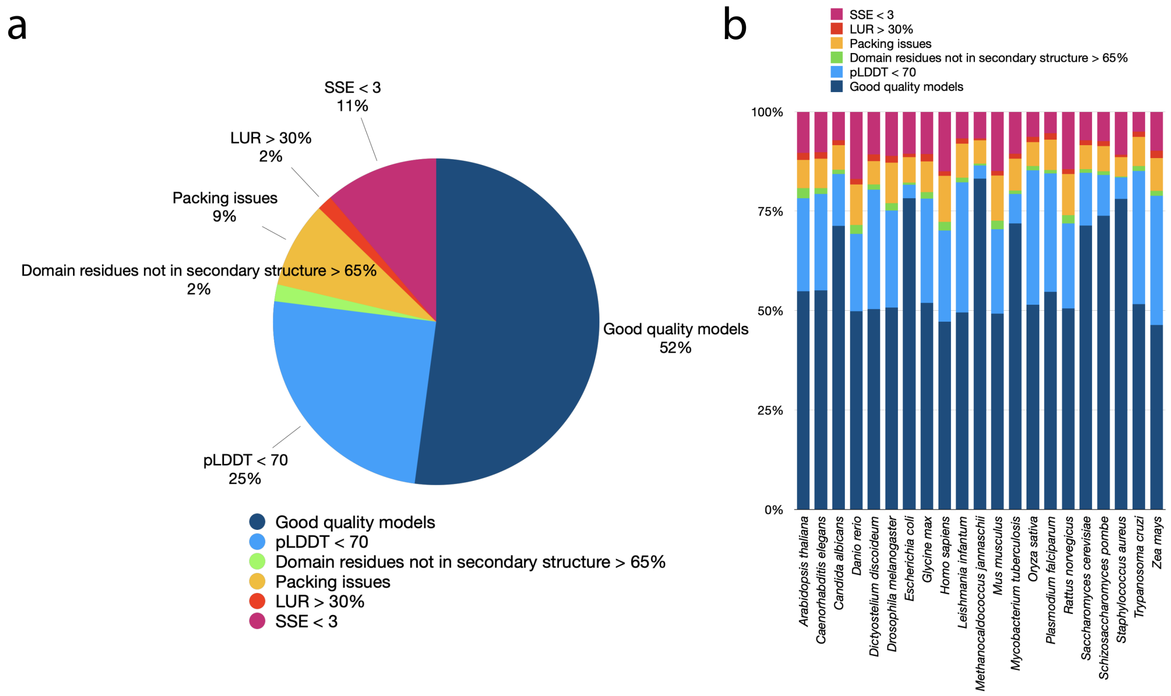
Q6QAJ8/16-113
Transmembrane protein 220

Q9NWS8/226-403
Required for meiotic nuclear division
protein 1 homolog

Supplementary Figure 8. All mainly-alpha novel folds in AF2.



Supplementary Figure 9. a) Distribution of AF2 domains not included in CATH overall and b) by organism.



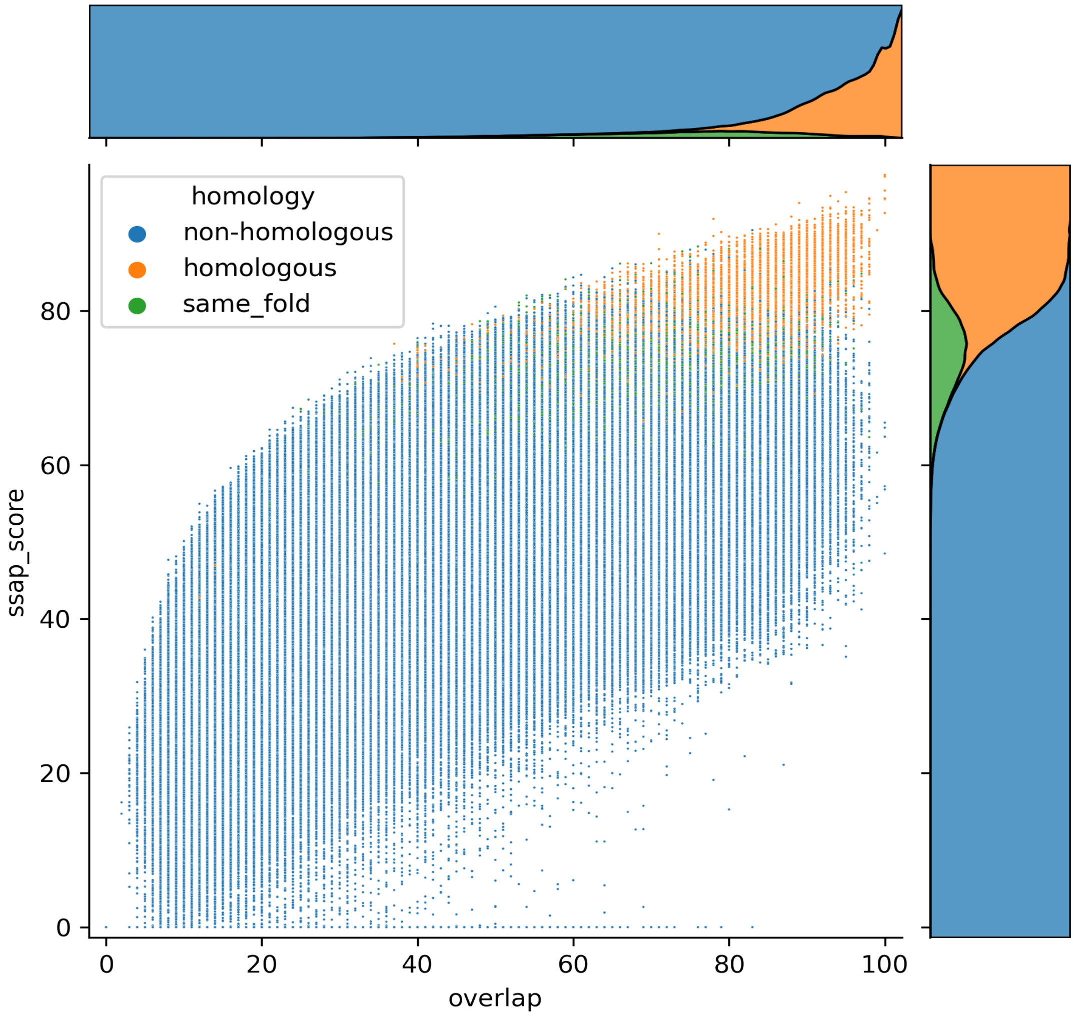
Supplementary Figure 10. a) Distribution of AF2 domains with good model quality and discarded overall and b) by organism.

Benchmarking SSAP, TM-align and Foldseek for homologs detection

To assess the score thresholds for homologs detection using SSAP, TM-align and Foldseek, we created a dataset of 3,186 curated domains that are S30 representatives of CATH that are equivalent in the SCOP classification. As the relationship of each pair of domains is known, we created an all-vs-all half-matrix of structural comparisons to be run using Foldseek, TM-align and SSAP. The half matrix of pairwise comparisons consists of 13,443 homologous pairs, 67,917 pairs that share the same fold and 4,992,345 non-homologous pairs.

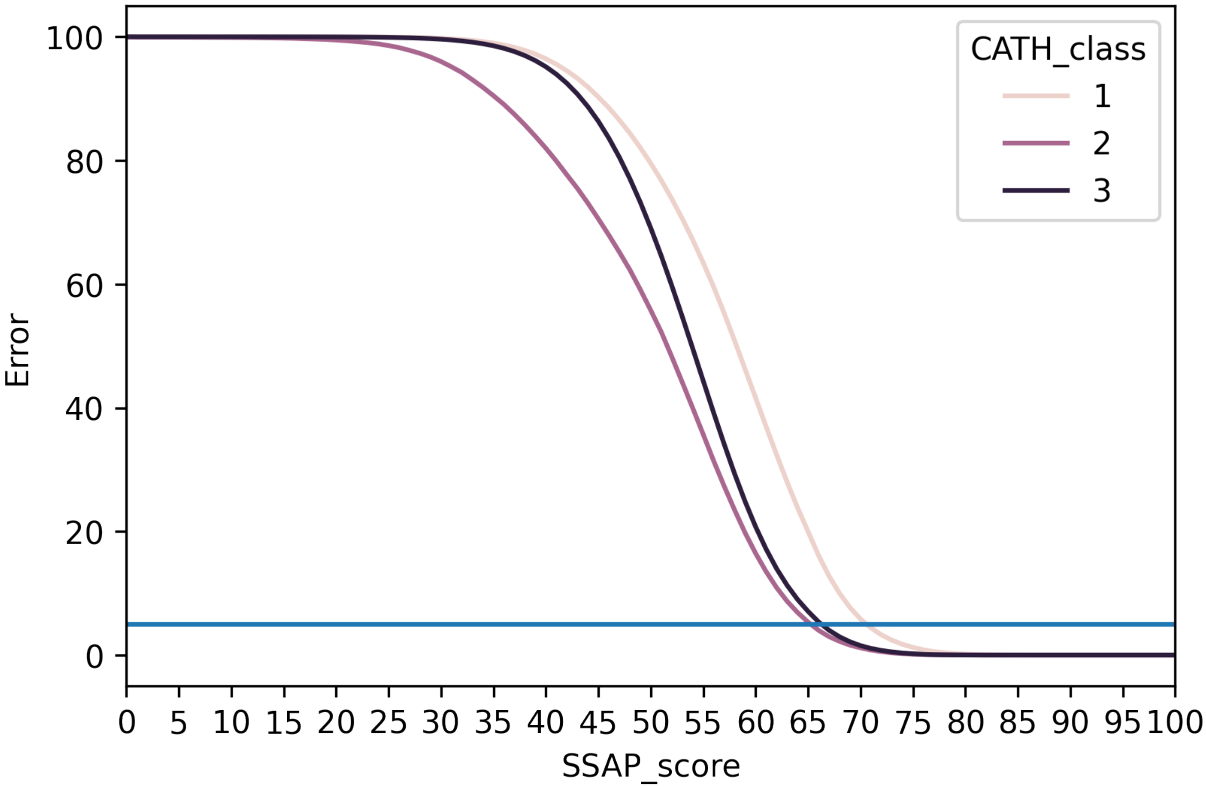
SSAP Benchmark

All domains in the S30 dataset were scanned in an all-vs-all fashion using SSAP. Since SSAP performs pairwise comparisons, one for each run, the half-matrix was generated directly without requiring additional missing pairs in the output.



Supplementary Figure 11: SSAP score plotted against the structural alignment overlap calculated as 100% x overlap /length of largest domain.
Each pair of comparisons was coloured according to their homology.

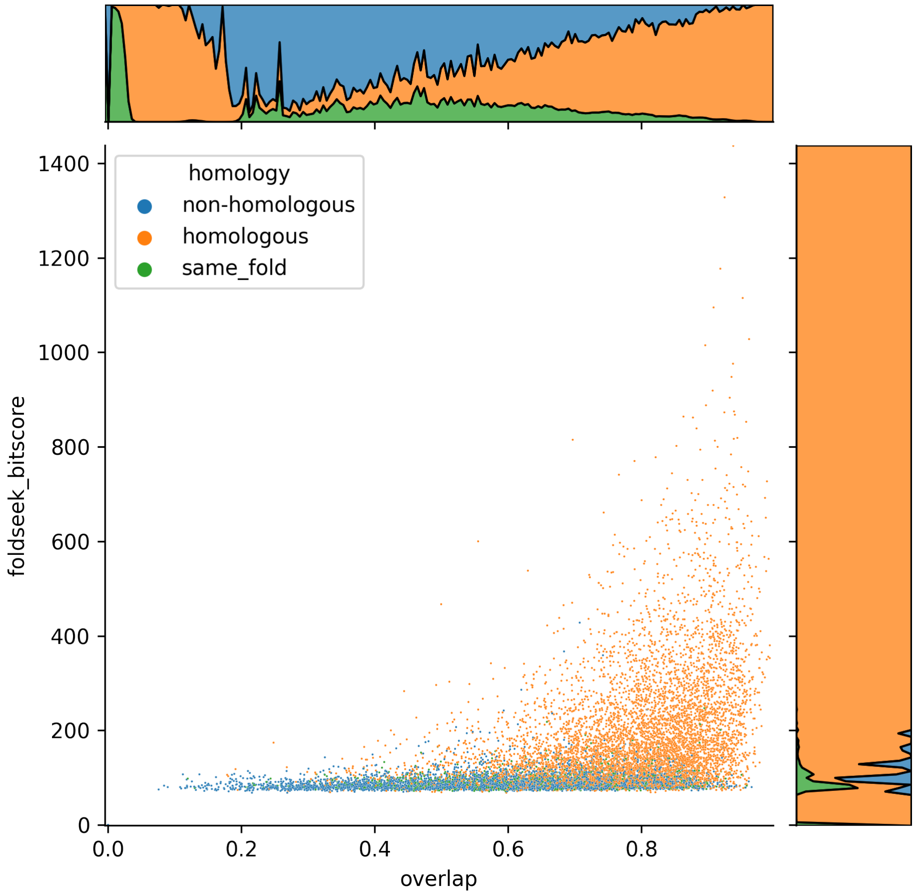
The error rate was calculated in the same fashion as the Foldseek benchmark, resulting in a SSAP score threshold at an overlap of 60% of 71, 66 and 69 for CATH Class 1, 2 and 3 respectively.



Supplementary Figure 12: Error rate by SSAP score for each CATH class. The horizontal blue line represents the 5% error threshold.

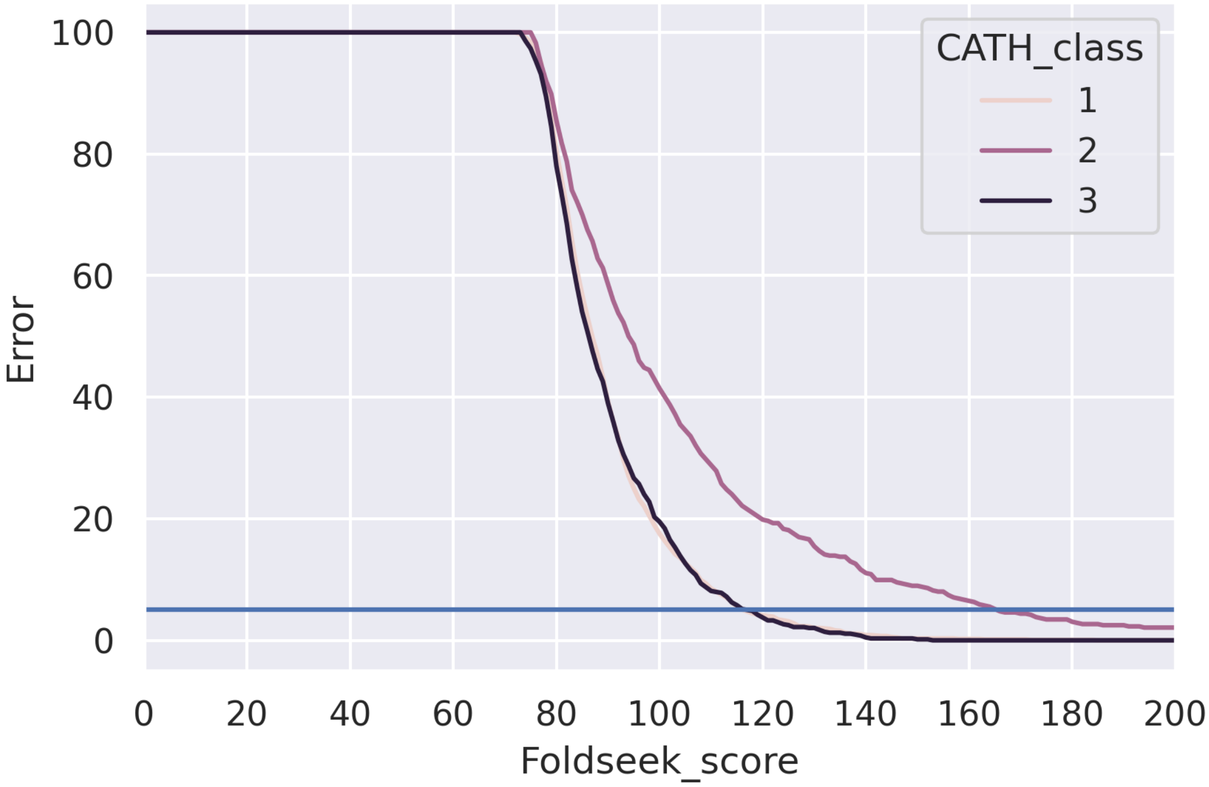
Foldseek Benchmark

We ran Foldseek (version 6315e9b67d08fb7867d6573d38d473a5b01e365d, 06/01/22) using a sensitivity threshold equal to 9 (highest sensitivity, personal communication from Foldseek developers) and retaining as many hits as possible in order to create the half-matrix. Results were parsed and an overlap based over the length of the longest structure was calculated. If a pair was missing from the final output, we included it in the results with bitscore and overlap set to zero.



Supplementary Figure 13: Foldseek bitscore plotted against the structural alignment overlap. Each pair of comparisons was coloured according to their homology.

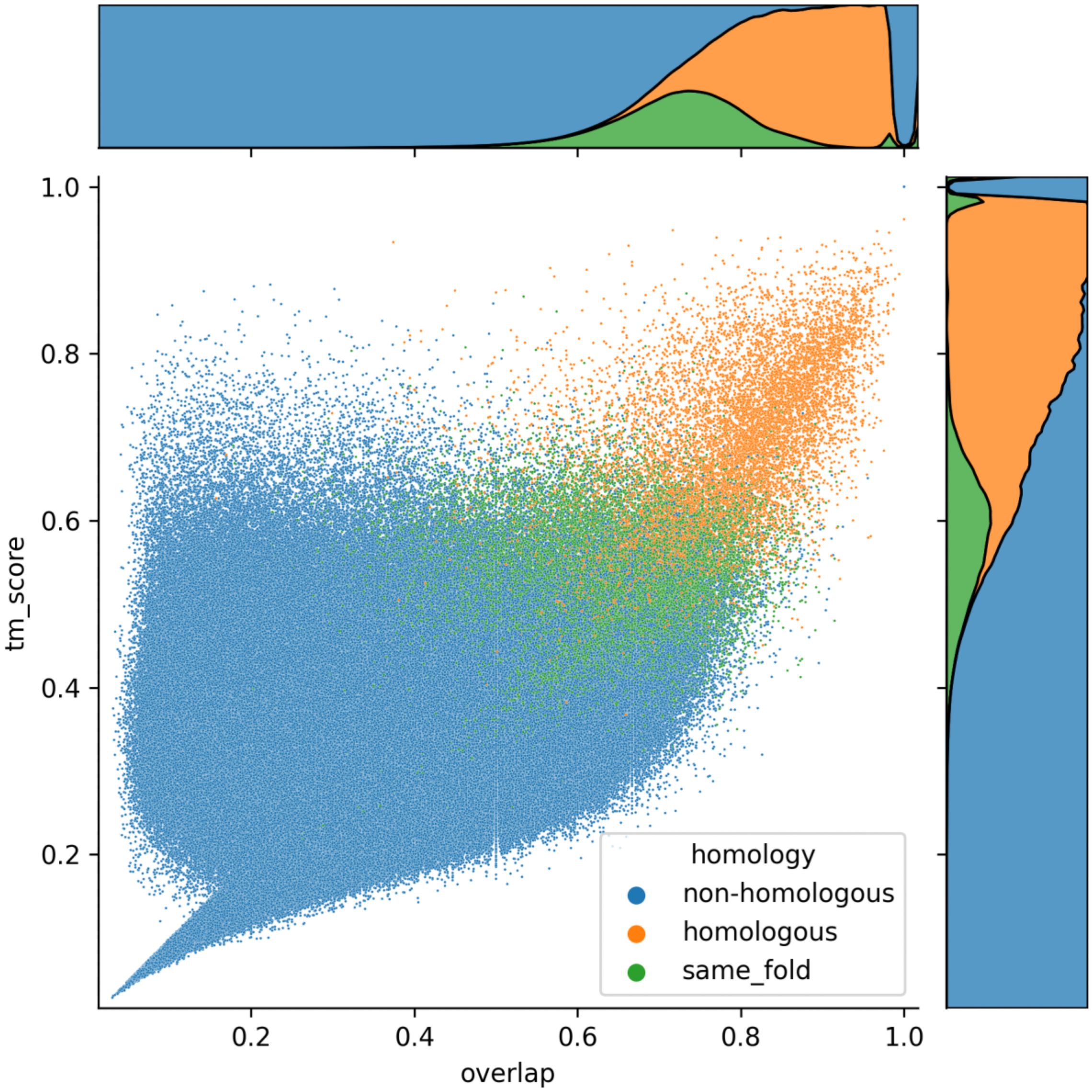
In order to calculate a homology threshold for each CATH class, we divided the dataset into pairs where both query and target belonged to the same CATH class, and calculated the percentage of non-homologous pairs over the total number of non-homologous pairs at a threshold of 60% overlap for all bitscores in the dataset. We identified bitscore cut-offs for homology at 5% error rate at 116, 165 and 117 for Class 1, 2 and 3 respectively.



Supplementary Figure 14: Error rate by Foldseek bitscore for each CATH class. The horizontal blue line represents the 5% error threshold.

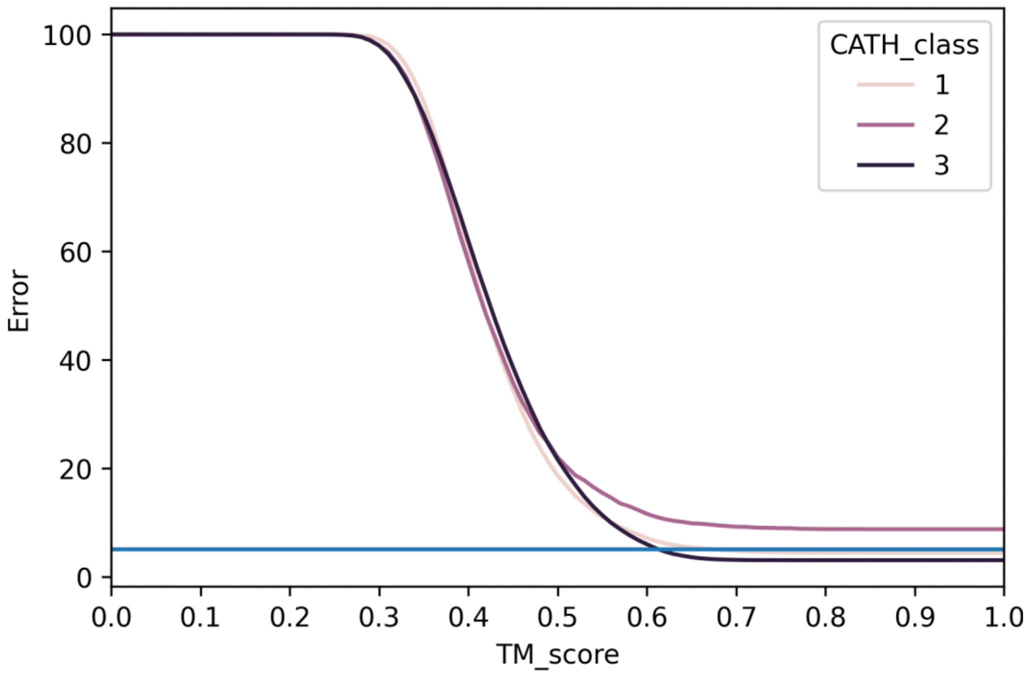
TM-align Benchmark

All domains in the S30 dataset were scanned in an all-vs-all fashion using TM-align. Since TM-align performs pairwise comparisons when provided with lists of domains, the half-matrix was generated directly without requiring additional missing pairs in the output.



Supplementary Figure 15: TMscore plotted against the structural alignment overlap. Each pair of comparisons was coloured according to their homology.

In order to calculate a homology threshold for each CATH class, we divided the dataset into pairs where both query and target belonged to the same CATH class, and calculated the percentage of non-homologous pairs over the total number of non-homologous pairs at a threshold of 60% overlap for all bitscores in the dataset. We identified a TMscore cut-off for homology at 5% error rate at TMscore=0.7 for Class 1 and 3, while for Class 2 the 5% error rate is never reached.



Supplementary Figure 16: Error rate by TM-align TMscore for each CATH class. The horizontal blue line represents the 5% error threshold.