

ProNet DB: A proteome-wise database for protein surface property representations and RNA-binding profiles

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ABSTRACT

The rapid growth in the number of experimental and predicted protein structures and more complicated protein structures challenge users in computational biology for utilizing the structural information and protein surface property representation. Recently, AlphaFold2 released the comprehensive proteome of various species, and protein surface property representation plays a crucial role in protein-molecule interaction prediction such as protein-protein interaction, protein-nucleic acid interaction, and protein-compound interaction. Here, we proposed the first comprehensive database, namely ProNet DB, which incorporates multiple protein surface representations and RNA-binding landscape for more than 326,175 protein structures covering 16 model organism proteomes from AlphaFold Protein Structure Database (AlphaFold DB) and experimentally validated protein structures deposited in Protein Data Bank (PDB). For each protein, we provided the original protein structure, surface property representation including hydrophobicity, charge distribution, hydrogen bond, interacting face, and RNA-binding landscape such as RNA binding sites and RNA binding preference. To interpret protein surface property representation and RNA binding landscape intuitively, we also integrate Mol* and Online 3D Viewer to visualize the representation on the protein surface. The pre-computed features are available for the users instantaneously and boost computational biology development including molecular mechanism exploration, geometry-based drug discovery and novel therapeutics development. The server is now available on <https://proj.cse.cuhk.edu.hk/aihlab/pronet/>.

Background & Summary

Proteins perform vital functions in a variety of cellular activities, and protein-molecule interactions decipher the complexity of organisms such as gene expression regulation¹, signal transduction² and drug therapy³. However, the dedicated mechanism of most protein-molecule interactions has not been well illustrated and hinders the development of mechanism exploration and drug discovery. During the process of protein interacting with molecules, molecules are intended to recognize the surface of the protein, such as the hydrophobicity, charge distribution, hydrogen/electron donor, and binding steric hindrance. Thus, a comprehensive and efficient representation of the protein surface is essential to elucidate the mechanism of protein-molecule interaction. For example, Rudden et al.⁴ utilize a single volumetric descriptor representing protein surface including electrostatics and local dynamics for protein docking and achieved an average success rate of 54%. Experimental assessments such as NMR-based measurement⁵, hydrophobic interaction chromatography (HIC)⁶ of protein surface property are time-consuming and costly. Besides, with the presence of AlphaFold2 Protein Structure Database⁷, a number of protein structures are determined by computational prediction, indicating that the traditional approaches are unable to handle this series of protein surface property evaluation.

To overcome the limitations of experimental approaches, several *in silico* methods of protein surface property have been

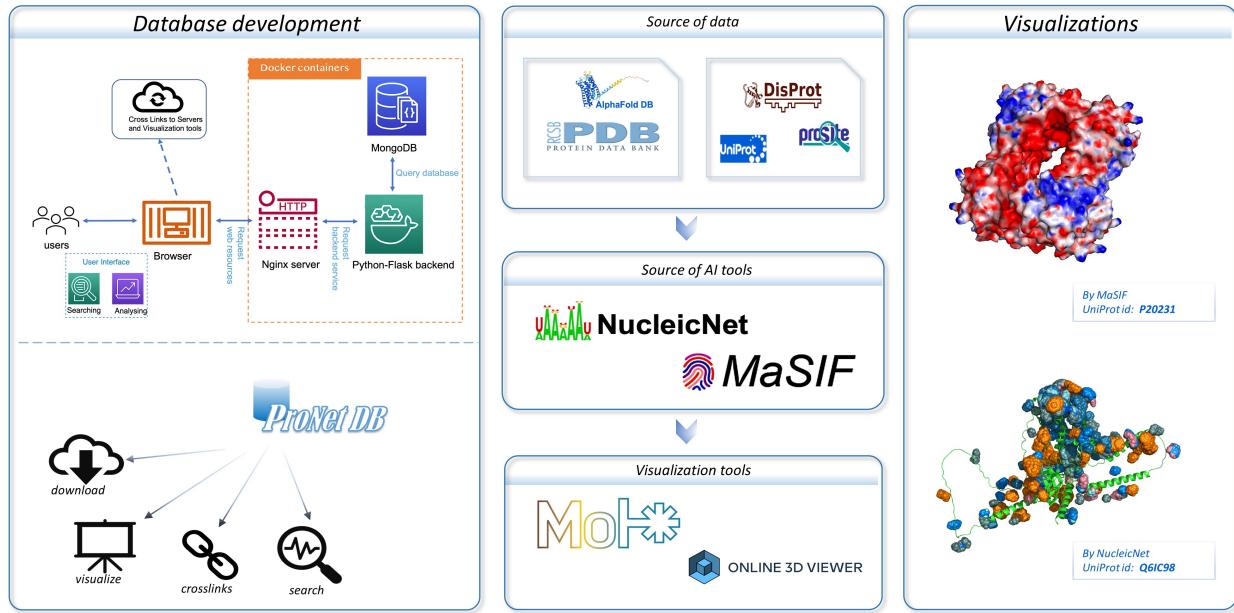


Figure 1. An overview of the ProNet DB and the illustration for two main outputs. The right panel shows the example of the protein surface physicochemical property and RNA binding profiles.

proposed, such as MaSIF⁷, FEATURE⁷, and AutoDock⁷. For example, AutoDock⁷ calculates the atom-wise biochemical property, and FEATURE⁷ employs a series of centric shells to represent atoms of the protein with 7.5 Å of a grid point with 80 physicochemical properties. MaSIF⁷ presents a method to encode geometric features (shape index and distance-dependent curvature) and chemical features (hydrophobicity, continuum electrostatics, and free electrons/protons) on the surface with the geodesic radius of 9 Å or 12 Å. Despite the availability of those tools for downstream applications, they are not ready-to-use, with the complex running environment and long running time. Also, it is inefficient for each user to run them locally for the same protein, which leads to repetitive work. Theoretically, for the fixed protein structure, the surface representation of the same tool should be the same. Considering that, we build up the database, running MaSIF to encode protein surface physicochemical properties including hydrophobicity, charge distribution, hydrogen bond, interacting face for the protein structure from the experimentally validated database (PDB) and *in silico* database (AlphaFold DB), so that the user can directly use such features for their downstream applications. The successful *de novo* design of protein with learned surface fingerprints revealed that surface property plays a crucial role in function-oriented protein design, and lay the foundation for the development of synthetic biology⁷.

Similar to the physicochemical property, RNA binding landscape is also an important part of surface property. Direct recognition of RNA motifs on RNA-binding proteins (RBPs) can provide information of protein-nucleic acid interaction⁷. For example, the Pumilio/FBF (PUF) family can govern translations by direct base-protein recognition, such as UGUR motifs on RNA transcripts⁷. Thus, the RNA binding profiles of RBPs are the important part to illustrate protein-molecule interaction. In this study, we employed the state-of-the-art deep-learning framework NucleicNet⁷ to predict the binding preference of RNA constituents and the binding sites on protein surface to provide RNA-binding landscape of the protein structure from the experimentally validated database (PDB) and *in silico* database (AlphaFold DB). Although the dataset is based on prediction, we are the first to provide such a ready-to-use database for downstream applications, such as CRISPR-Cas system optimization⁷, RBP-targeting therapeutics discovery⁷, and aptamer-guided drug delivery system development⁷.

In summary, we proposed a comprehensive database for protein surface feature, ProNet DB, which contains protein surface physicochemical representations and RNA-binding landscape for more than 326,175 protein structures covering the 16 model organism proteomes from AlphaFold DB and PDB. For each protein, we provided the original protein structure, surface property representation including hydrophobicity, charge distribution, hydrogen bond, interacting face, and RNA-binding landscape such as RNA binding site and RNA binding preference. To interpret protein surface property representation and RNA binding landscape intuitively, we also integrate Mol* and Online 3D Viewer to visualize representation on the protein surface. The server now can be assessed at <https://proj.cse.cuhk.edu.hk/aihlab/pronet/> and future releases will expand the species and property coverage.

ProNet DB

Home Page

ProNet DB is a comprehensive database for protein surface features, containing protein surface representation and RNA-binding landscape for more than 30000 protein structures from AlphaFold DB and PDB. For each protein, we provide original protein structure, surface property representation including hydrophilicity, charge distribution and interacting preference and RNA-binding landscape such as RNA binding site and RNA binding preference. In addition, we also integrate [MaSIF](#) and [alphaFold](#) to visualize representation on protein surface.

Please refer to [About](#) for more information, Instructions on database and usage about ProNet DB.

Please refer to [Download](#) for various downloading schemes.

Databases

- NucleicNet DB
- MaSIF DB

Servers

- NucleicNet Server
- DEEPro Server

Visualization tools

- McL Viewer
- Online 3D viewer

NucleicNet Protein Binding Database

Source Data From: AlphaFold PDB

Toggle for different source

Search items of Interest

Examples: A2P2R3 Protein-Kinases YMR084W

Filter by species:

- Yeast
- Human
- Mouse
- Ecoli
- Drosophila
- C. elegans
- C. caspia
- Arath

Current Page: 1 / 24007 Entry: NucleicNet DB Page

(Click to sort Ascending)	Species	Protein	Filename	Filedata	Visualization
A0AOA7EPLO	arath	Enzymes	Download	Details	
A0A178VEK7	arath	Others	Download	Details	
A0A178WF56	arath	Others	Download	Details	
A0A196LMX5	arath	Enzymes	Download	Details	
A0A196LN01	arath	Enzymes	Download	Details	
A0A1P8ASY1	arath	Enzymes	Download	Details	
A0A1P8AU94	arath	Others	Download	Details	
A0A1P8AW69	arath	Repeat-Proteins	Download	Details	
A0A2H1ZEF6	arath	Others	Download	Details	
A0MES8	arath	Others	Download	Details	

Species + Yeast:

- Amidotransferases (23)
- Chitinases (665)
- Chromosomal-Proteins (2)
- Structural-Proteins (13)
- Transmembrane-Proteins (203)
- Zinc-Finger-Proteins (47)
- Receptor-Proteins (34)
- Chaperone-Proteins (86)
- Repeat-Proteins (28)
- Subunit (93)
- Glycosylation-Sites (21)
- Putative-Proteins (73)
- Mitochondrial-Proteins (198)
- Ubiquitin-Proteins (10)
- Glycoside-Proteins (42)
- Uncharacterized-Proteins (604)
- Others (1883)

Antiviral helicase SKI2

Protein Information Page

Information

Entry: P35207
UniProt: Go to UniProt P35207
AlphaFold: Go to AlphaFold P35207
MaSIF: Go to MaSIF database
Protein: Antibodies
Gene: SKI2 YLR398C L8084.17
Species: **Results of NucleicNet** Saccharomyces cerevisiae (strain ATCC 204508 / S288c) (Baker's yeast)
Details: Antiviral helicase SKI2 (EC 3.6.4.13) (Superkiller protein 2)
download: [.psb](#) [.clif](#) [.pdbs](#) [original](#)

NucleicNet: Go to NucleicNet database
Protein: Antibodies
Gene: SKI2 YLR398C L8084.17
Species: **Results of MaSIF** Saccharomyces cerevisiae (strain ATCC 204508 / S288c) (Baker's yeast)
Details: Antiviral helicase SKI2 (EC 3.6.4.13) (Superkiller protein 2)
download: [.ply](#) [.npy](#) [original](#) [load model](#)

Visualization

NucleicNet Prediction Result

AlphaFold Result

MaSIF Prediction Result

NucleicNet DB Page

(Click to sort Ascending)	Species	Protein	Filename	Filedata	Visualization
Q93HK5	Human	Enzymes	Q93HK5_A.pdb	Download	Details
O96905	Human	Enzymes	O96905_A.pdb	Download	Details
P04439	Human	Antibodies	P04439_A.pdb	Download	Details
Q5T9Z0	Human	Enzymes	Q5T9Z0_A.pdb	Download	Details
P32314	Human	Others	P32314_A.pdb	Download	Details
Q9Y4A0	Human	Others	Q9Y4A0_A.pdb	Download	Details
Q9Y2H6	Human	Domain-Containing-Proteins	Q9Y2H6_A.pdb	Download	Details
Q6ZWK4	Human	Others	Q6ZWK4_A.pdb	Download	Details

Figure 2. User interface of ProNet DB. **Top-left:** Home page contains three subsections: servers, databases, and visualization tools. **Top-right:** NucleicNet DB page. Users can search, filter and view the searched results. On the top-right corner of NucleicNet DB page, a toggle button provides different protein sources. **Bottom:** Protein information page and visualization details for each item.

Methods

Data Source

We first collected 23,391 protein structures on *Homo sapiens* proteome and 6,042 protein structures on *Saccharomyces cerevisiae* proteome from AlphaFold DB⁷. If the corresponding experimentally validated protein structures exist in PDB, we collected the protein structure with the highest resolution from PDB (*Homo sapiens*: 6,030, *Saccharomyces cerevisiae*: 1,160)⁷. For further comprehensive database construction, we collected the other 14 model organism proteomes from AlphaFold DB, including *Arabidopsis thaliana*, *Caenorhabditis elegans*, *Candida albicans*, *Danio rerio*, *Dictyostelium discoideum*, *Drosophila melanogaster*, *Escherichia coli*, *Glycine max*, *Methanocaldococcus jannaschii*, *Mus musculus*, *Oryza sativa*, *Rattus norvegicus*, *Schizosaccharomyces pombe* and *Zea mays*. Finally, the proteomes of these model organisms sufficiently expanded ProNet DB protein structure coverage from 33,000 to 333,365 (Table 1) and led to a more comprehensive and user-friendly database.

Protein Surface Physicochemical Property

MaSIF is a general framework to encode protein surface fingerprints⁷. For each protein, it will generate a discretized molecular surface by assigning calculated physicochemical features on every vertex of the surface. In this way, the properties of the protein surface can be clearly represented. As shown in Figure 1, the user can determine which part of the surface area is

Table 1. The model organism proteomes in ProNet DB.

ID	Species	Name	Reference Proteome	AlphaFold DB	PDB
1	<i>Arabidopsis thaliana</i>	Arabidopsis	UP000006548	27,434	-
2	<i>Caenorhabditis elegans</i>	Nematode worm	UP000001940	19,694	-
3	<i>Candida albicans</i>	<i>C. albicans</i>	UP000000559	5,974	-
4	<i>Danio rerio</i>	Zebrafish	UP000000437	24,664	-
5	<i>Dictyostelium discoideum</i>	Dictyostelium	UP000002195	12,622	-
6	<i>Drosophila melanogaster</i>	Fruit fly	UP000000803	13,458	-
7	<i>Escherichia coli</i>	<i>E. coli</i>	UP000000625	4,363	-
8	<i>Glycine max</i>	Soybean	UP0000008827	55,799	-
9	<i>Homo sapiens</i>	Human	UP000005640	23,391	6,030
10	<i>Methanocaldococcus jannaschii</i>	<i>M. jannaschii</i>	UP000000805	1,773	-
11	<i>Mus musculus</i>	Mouse	UP000000589	21,615	-
12	<i>Oryza sativa</i>	Asian rice	UP000059680	43,649	-
13	<i>Rattus norvegicus</i>	Rat	UP000002494	21,272	-
14	<i>Saccharomyces cerevisiae</i>	Budding yeast	UP000002311	6,040	1,160
15	<i>Schizosaccharomyces pombe</i>	Fission yeast	UP000002485	5,128	-
16	<i>Zea mays</i>	Maize	UP000007305	39,299	-
				326,175	7190

hydrophilic or hydrophobic, and which part is more likely to interact with other molecules (interacting face). We computed the surface properties by the MaSIF tool for the proteins in our database so that users can obtain the physicochemical property profile for every protein efficiently. These computed features can benefit many downstream tasks a lot including binding site prediction⁷, protein-protein interaction prediction⁸ and protein design⁹. The recent study of protein design based on surface fingerprints confirmed that surface property plays a crucial role in function-oriented protein design, and indicated that such geometric features on protein surface boost protein-centric issue development⁹.

Protein RNA-binding Profiles

As RNA-protein interaction is involved in multiple cellular activities, the interaction between RNAs and RBPs plays an important role in understanding cellular activities. The systematic mappings of the RNA-protein interaction for multiple RNA constituents were constructed in ProNet DB. Following the deep-learning framework proposed by NucleicNet⁷, we acquired the binding preference as well as the binding sites for multiple bases for protein structures in Alphafold DB and PDB, such as Ribose (R), Phosphate (P), Adenine (A), Guanine(G), Cytosine (C), and Uracil (U). The protein RNA binding profiles are further classified into multiple sub-classes for each species based on their diverse protein functions. In ProNet DB, users are able to directly address the protein properties such as RNA backbone composition and binding preference of different bases, which intuitively illustrated the protein RNA-binding landscape and partially revealed the protein surface property.

Data Records

All metadata and processed data are now available, and several approaches are provided to access the data. Totally, ProNet DB collected 16 model organism proteomes with 333,365 protein structures, covering various protein surface feature representation including g hydrophobicity, charge distribution, hydrogen bond, interacting face, and RNA-binding landscape such as RNA binding sites and RNA binding preference. A dedicated web page is for downloading archived file <https://proj.cse.cuhk.edu.hk/aihlab/pronet/#/download> and these data are also publicly available from Figshare repository⁷, including the original PDB format files from both PDB and AlphaFold DB, and protein surface representation result files in .PLY, .NPY and .PSE formats through MaSIF and NucleicNet. For each individual protein, a public API linked by UniProt ID is available and provides all meta information details and download links for a separate file. For example, for UniProt ID A2P2R3, its MaSIF information page is <https://proj.cse.cuhk.edu.hk/aihlab/pronet/masifdata.html#/entry/A2P2R3>, and the NucleicNet information page is <https://proj.cse.cuhk.edu.hk/aihlab/pronet/dataview.html#/entry/A2P2R3>.

Technical Validation

Database Statistics

Currently, the database contains over 16 model organism species and 333,365 entries for proteome (Table 1) from AlphaFold DB and PDB (*Homo sapiens*: 23,391 and 6,030; *Saccharomyces cerevisiae*: 6,040 and 1,160, and other 14 model organism

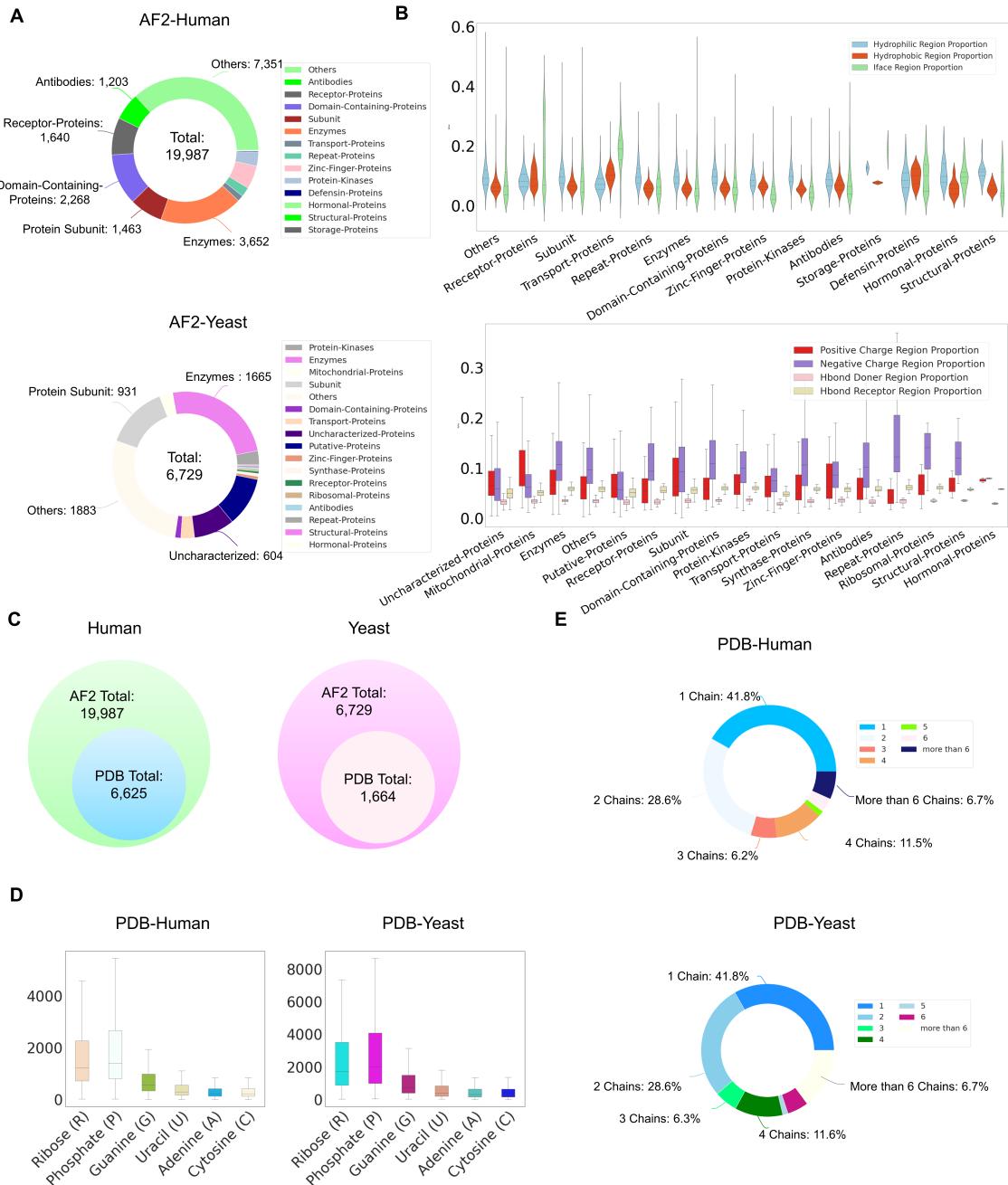


Figure 3. ProNet DB statistics for both Human and Yeast results in AlphaFold DB and PDB. **(A)** The functional classification for protein structures in both AlphaFold DB and PDB. **(B)** The upper panel illustrates the protein surface physicochemical property distribution including hydrophilic, hydrophobic, and interacting face region proportion of Human protein surface in AlphaFold DB. The beneath panel reveals the distribution of the positive/negative charge region and the Hbond Doner/Receptor region proportion of Yeast protein surface in AlphaFold DB. **(C)** Venn diagram shows the number of experimentally validated protein structures from PDB, compared with computationally predicted structures from AlphaFold DB. **(D)** Detailed comparison of the proportion of binding profiles of each RNA constituent in PDB, e.g., 4 bases: Adenine(A)/ Guanine(G)/ Cytosine(C)/ Uracil(U), and 2 backbone constituents: phosphate (P) and ribose (R). **(E)** The proportion of the number of chains in the PDB database in Human and Yeast.

Table 2. An example entry in ProNet DB shows the data content organization of one protein *17-beta-hydroxysteroid dehydrogenase type 1*. An entry has three profiles: **Basic Profile** contains basic information like the protein names, protein types, gene names, as well as the mapping id to other databases; **MaSIF Profile** includes the physicochemical properties computed by MaSIF, describing the protein surface features; **NucleicNet Profile** contains the RNA-binding preference information.

	Description	Example
Basic Profile	Entry ID	P14061
	Protein Name	17-beta-hydroxysteroid dehydrogenase type 1
	PDB ID	1A27
	Uniprot ID	P14061
	Sequence Length	327
	Gene Names	HSD17B1, E17KSR, EDH17B1, EDH17B2, EDHB17, SDR28C1
	Protein Type	Enzymes
	Species	<i>Homo sapiens</i> (Human)
	EC Number	1.1.1.62, 1.1.1.51
MaSIF Profile	Hits for all PROSITE motifs	PS00061
	Disprot ID	DP00023
	Number of total surface vertex	7265
	Number of Interacting face vertex	1061
	Interacting face region proportion	0.146
	Number of hydrophilic vertex	933
	Hydrophilic region proportion	0.128
	Number of hydrophobic vertex	379
	Hydrophobic region proportion	0.052
NucleicNet Profile	Number of Hbond donor vertex	232
	Hbond donor region proportion	0.032
	Number of Hbond receptor vertex	400
	Hbond receptor region proportion	0.055
	Number of positive charge vertex	400
	Positive charge region proportion	0.055
	Number of negative charge vertex	816
	Negative charge region proportion	0.112
	Number of Ribose	882
NucleicNet Profile	Number of Phosphate	925
	Number of Guanine	501
	Number of Uracil	200
	Number of Adenine	175
	Number of Cytosine	188

species.). We further classify these proteins by their function into sub-classes, such as antibodies and enzymes. For *Homo sapiens*, the protein structures are classified into 15 sub-classes: Antibodies, Contractile-Proteins, Enzymes, Hormonal-Proteins, Structural-Proteins, Storage-Proteins, Transport-Proteins, Zinc-Finger Proteins, Receptor Proteins, Domain-Containing-Proteins, Defensin-Proteins, Repeat-Proteins, Subunit, and Protein-Kinases. Those proteins with unknown categories are classified as *Others*. From Figure 3 (A), although the majority of the structures are labeled as unknown (7,351 entries), we see that the majority of the human protein types are clustered in Enzymes (3,652 entries), Domain-Containing-Protein (2,268 entries), and Preceptor-Proteins (1,640 entries). Figure 3 (C) shows that a certain number of protein structures (66.9% in *Homo sapiens*, 75.2% in *Saccharomyces cerevisiae*) have not been validated by experimental approaches. Besides, the Supplementary Figure S2 demonstrates the considerable protein structure prediction performance, since 80.6% of validated proteins in *Homo sapiens* and 74.8% of validated proteins in *Saccharomyces cerevisiae* are accurately predicted ($\text{RMSD} \leq 2.0$). In Figure 3 (B), we integrate the proportion for hydrophobic and hydrophilic vertex over the total number of vertex for AlphaFold2 Human proteins and compare them with the interacting face proportion. A clear pattern is shown in Figure 3 (B) that the Hbond receptor region

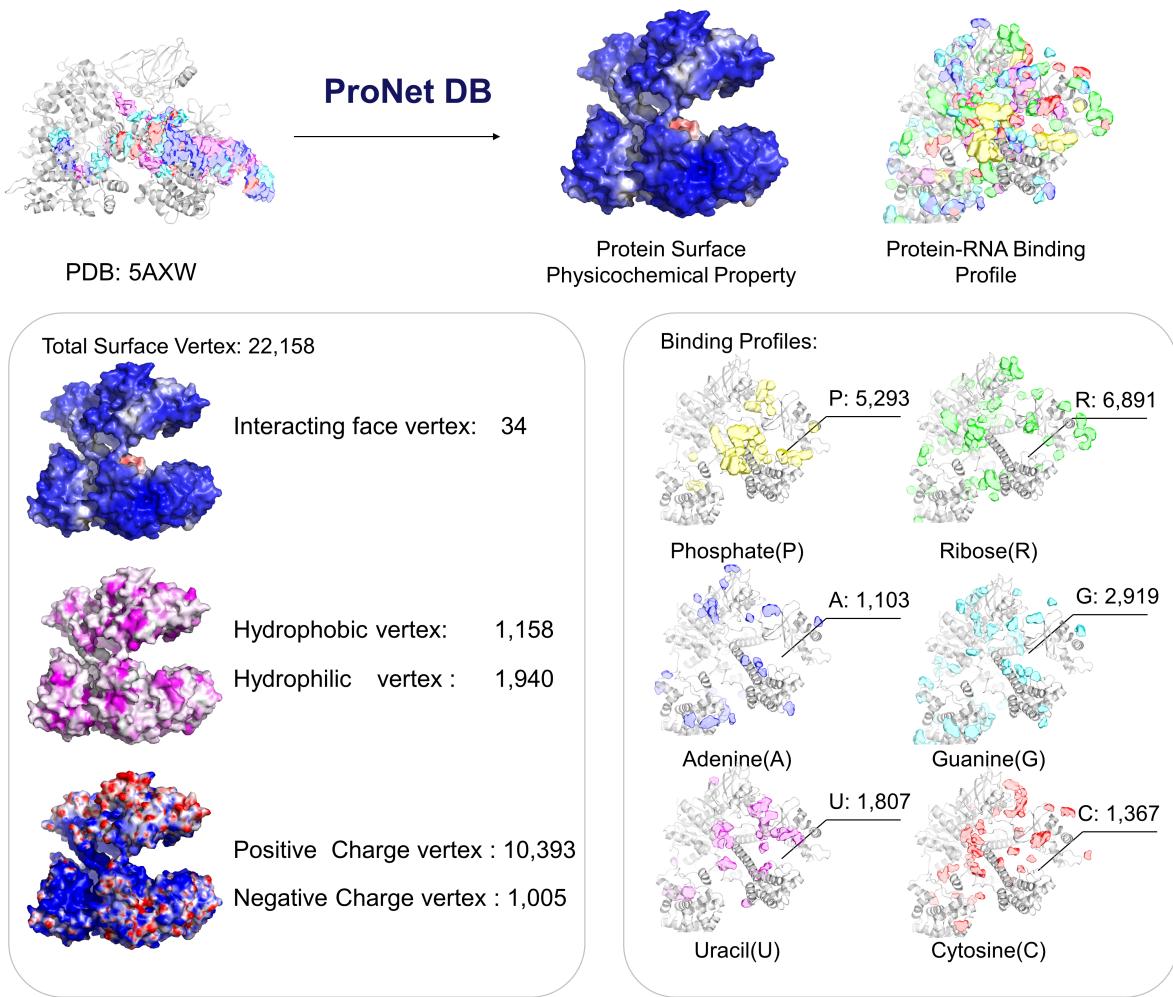


Figure 4. Case study (PDB: 5AXW): ProNet DB shows comprehensive information of the protein structure surface fingerprints as well as the protein RNA binding landscape. On the left panel: Iface region is consistent with the nucleic acid binding sites, and electron donor region is located at non-binding sites. On the right panel: The RNA binding landscape shows the RNA binding sites located at the inner region.

is statistically higher than Hbond donor region in AlphaFold Yeast proteins. In addition, Figure 3 (D) reveals that the overall number of nucleic acids for Yeast is much higher than that of human. The statistical results of the chain numbers from both PDB Human and Yeast data are illustrated in Figure 3 (E). More statistic result of Human and Yeast data can be found in Supplementary Figure S1 and the other model organism proteomes information is in Supplementary Table S1.

Case Study

Here, we employed CRISPR/Cas gene editing system for case study since it is a well-established protein-nucleic acid interaction issue and a variety of structural analysis studies focus on Cas9 protein. Cas9 protein plays an important role in the CRISPR-Cas system, and thus understanding how Cas9 mediates RNA-guided DNA recognition is the essential part to improve the gene editing system. The crystal structure of *Staphylococcus aureus* Cas9 (PDB: 5AXW) was chosen for protein surface physicochemical property and RNA-binding profiles analysis.

As shown in Figure 4, we have highlighted the SaCas9-sgRNA chimeric complex structure with its binding guide RNA, in which a central channel was formed in the middle of the structure. From the protein surface fingerprint results of Iface region, ProNet DB reveals that the original nucleic acid binding site is located at the interacting face region, compared to the non-binding site. Besides, the electron donor region shows the inner region is positive-charged, indicating the interaction between protein surface and nucleic acids in the central channel between the recognition and nuclease lobes^{7,8}. In Figure 4, the predicted protein-RNA binding profiles with specific RNA binding site and binding preference indicate that the corresponding

RNA molecule is located in the inner region of protein structure, which is consistent with the ground truth. These results show that such *in silico* approach can efficiently capture the protein physicochemical surface property as well as RNA binding landscape and lay the foundation for downstream tasks such as sgRNA design⁷ and CRISPR system optimization².

Usage Notes

Multi-scale data analyses for 333,365 protein structures and 16 model organism species were processed under diverse protein functional categories. The homepage (Figure 2) integrates all the server tools and is divided into three major components: prediction tools, database queries, and visualization tools. An overview and interactive table present information ranging from protein name, PDB ID, UniProt ID, protein type, interacting face proportion, Hbond region proportion, positive/negative charge region proportion, and protein-RNA-binding profiles (see Table 2). The web interface was established to search for the property profiles of a user-specified protein type in multiple species and the search browser is shown in the top-right part of Figure 2. The protein information page provides detailed information, download link of processed protein surface feature and visualization and more information can be found on <https://proj.cse.cuhk.edu.hk/aihlab/pronet/#/services>.

Code availability

The process code is available at <https://github.com/jxmelody/ProNetProcess>.

The ProNet DB link is <https://proj.cse.cuhk.edu.hk/aihlab/pronet/#/Home>.

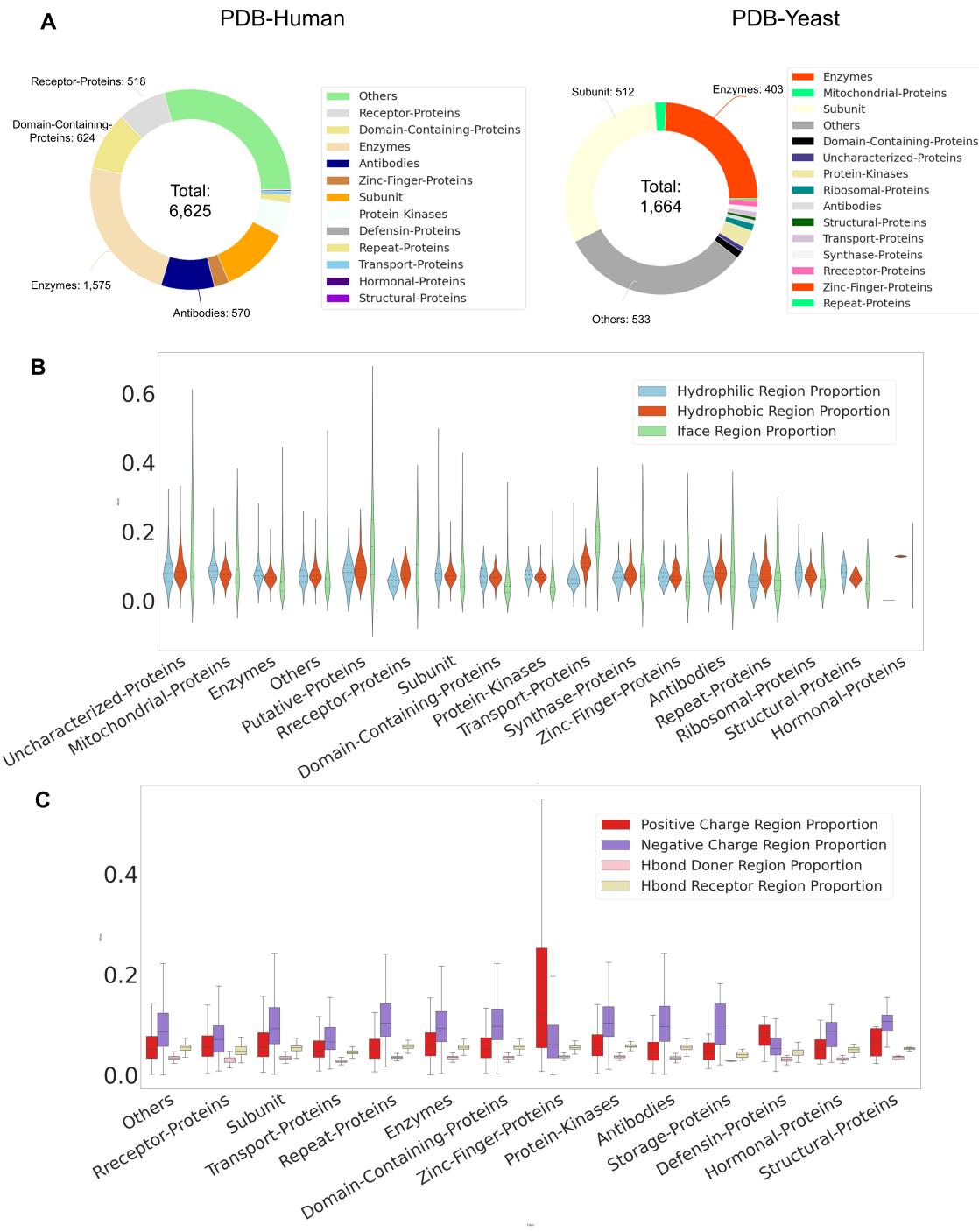
All primary data is uploaded to Figshare <https://figshare.com/s/83bc43fac5aec6d1e0e6>.

Competing interests

None declared

Author Contributions

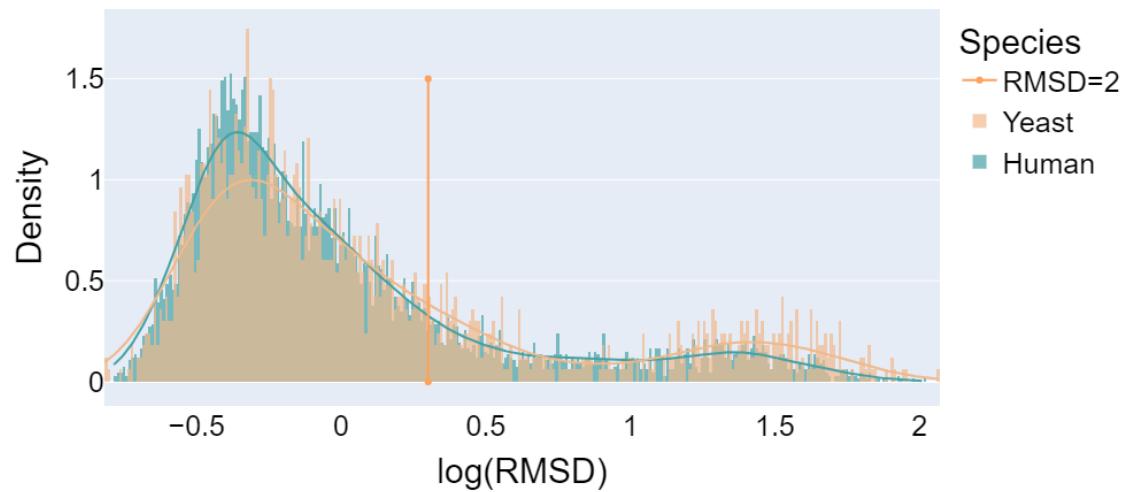
J.W. conducted structure collection and MaSIF analysis; J.X. set up web server and structure visualization; S.C. implemented NucleicNet analysis and statistical analysis; L.Z. performed protein information collection. X.G. and Y.L conceived the study; All authors wrote the manuscript.



Supplementary Figure S1. Supplementary statistical results for ProNet DB. **(A)** The functional classification for protein structures in PDB Human and Yeast. **(B)** Protein surface physicochemical property distribution including hydrophilic, hydrophobic, and interacting face region proportion of Human protein surface in PDB. **(C)** The distribution of the positive/negative charge region and the Hbond Doner/Receptor region proportion of Yeast protein surface in PDB.

Supplementary Table S1. Detailed data statistics for ProNetDB

Species	Protein Types (Top 10 categories)									
	Domain-Containing Proteins	Enzymes	Subunit	Protein Kinases	Mitochondrial Proteins	Ribosomal Proteins	Transport Proteins	Putative Proteins	Membrane Proteins	Others
Candida albicans 5,974	1,093 (18.3%)	961(16.08%)	612(10.3%)	164(2.7%)	159(2.6%)	99(1.7%)	94(1.6%)	71(1.2%)	60(1.0%)	2,304(38.6%)
Arabidopsis thaliana 27,427	Enzymes	Domain-Containing Proteins	Repeat Proteins	Subunit	Putative Proteins	Protein Kinases	Zinc-Finger Proteins	Receptor Proteins	Membrane Proteins	Others
	5,858 (21.3%)	2,348(8.56%)	1,272(4.6%)	1,231(4.5%)	921(3.4%)	841(3.06%)	724(2.6%)	699(2.5%)	675(2.4%)	8,077(29.6%)
Escherichia coli 4,289	Enzymes	Subunit	Transport Proteins	Membrane Proteins	Putative Proteins	Protein Kinases	Antibodies	Synthase Proteins	Zinc-Finger Proteins	Others
	1,528 (35.2%)	337(7.8%)	247(5.7%)	164(3.8%)	129(3%)	117(2.7%)	65(1.5%)	37(0.8%)	21(0.4%)	1,019(23.7%)
Danio rerio 24,664	Enzymes	Domain-Containing Proteins	Receptor Proteins	Subunit	Protein Kinases	Zinc-Finger Proteins	Membrane Proteins	Repeat Proteins	Transport Proteins	Others
	3,348 (13.57%)	2,728(11.1%)	1,673(6.7%)	1,154(4.6%)	881(3.57%)	746(3.0%)	420(1.7%)	371(0.8%)	289(1.1%)	12,128(49.1%)



Supplementary Figure S2. RMSD statistics with $\log 2$ as the threshold. The majority of the RMSD values calculated from protein structures in PDB Human(5,325/6,600) and Yeast(1,242/1,660) falls under the threshold $\log 2 \approx 0.30102$.