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Problem Solving Protocol

Structural coverage of the human interactome

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Abstract

Complex biological processes in cells are embedded in the interactome, representing the complete set of protein–protein interactions. Mapping and analyzing the protein structures are essential to fully comprehending these processes' molecular details. Therefore, knowing the structural coverage of the interactome is important to show the current limitations. Structural modeling of protein–protein interactions requires accurate protein structures. In this study, we mapped all experimental structures to the reference human proteome. Later, we found the enrichment in structural coverage when complementary methods such as homology modeling and deep learning (AlphaFold) were included. We then collected the interactions from the literature and databases to form the reference human interactome, resulting in 117 897 non-redundant interactions. When we analyzed the structural coverage of the interactome, we found that the number of experimentally determined protein complex structures is scarce, corresponding to 3.95% of all binary interactions. We also analyzed known and modeled structures to potentially construct the structural interactome with a docking method. Our analysis showed that 12.97% of the interactions from HuRI and 73.62% and 32.94% from the filtered versions of STRING and HIPPIE could potentially be modeled with high structural coverage or accuracy, respectively. Overall, this paper provides an overview of the current state of structural coverage of the human proteome and interactome.

Keywords: human proteome; human interactome; protein complexes; structural coverage; PDB; homology modeling databases; AlphaFold2

INTRODUCTION

Protein interactions (PPIs) are key players in many cellular processes [1, 2]. Constructing a complete and accurate interactome (i.e. the network of protein–protein interactions) is crucial to understand better the fundamental working principles of cells, functions and disease mechanisms and eventually to identify key proteins or pathways for developing new treatment strategies. Several experimental and computational studies aimed to determine interactomes and were released either as resources or software [3–19]. These resources are curated and integrated to eliminate experimental artifacts and false-positive interactions, yielding up to millions of PPIs. Still, the number of studies incorporating the ever-increasing three-dimensional (3D) protein structures to the interactome has been limited, posing an ongoing challenge. Structurally characterized interactomes are essential to find detailed proteome-level functional annotations [20]. Utilizing these interactomes may assist in elucidating interactions that happen simultaneously and that are mutually exclusive [21]. The presence of mutations in protein–protein interfaces [22] and their impact as gain- or loss-of-function can also be revealed with structural information [23]. Drug design and repurposing similarly require structural characterization [24]. Overall, structural annotation of the PPI networks is necessary for molecular-level comprehension of the human interactome.

Understanding the atomic-level interactions between two proteins and the specific amino acids involved is essential for comprehending PPIs at the molecular level. In our previous studies, we developed the PRISM algorithm that uses known protein interfaces to accurately predict structural complexes of protein interactions [25, 26] and a prediction model for hotspots at protein interfaces, which are potential drug targets [27–29]. Other computational methods that are present, but not limited to, are Interactome3D [4] and Interactome INSIDER [3]. Predictions from these studies were further used to elaborate on the impact of mutations [30], structural modeling of signaling pathways [31–35] and analysis of post-translational modifications. The predictive performance of these computational methods highly depends on

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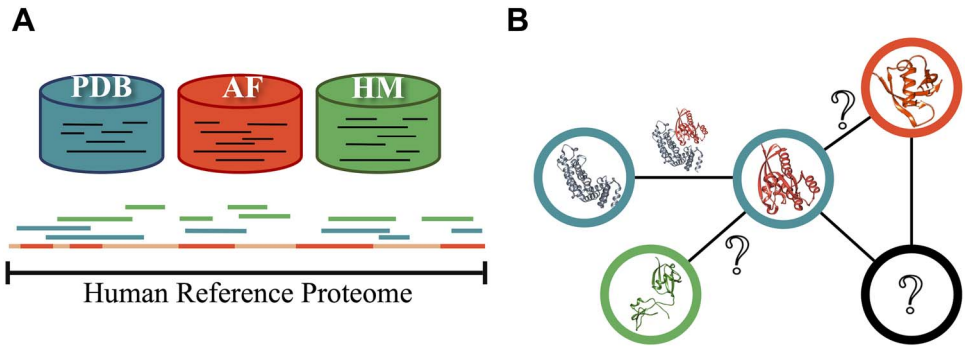


Figure 1. Concept figure. Each database is represented with the same coloring code in both sections. (**A**) for reference human proteome. PDB: Protein Data Bank, HM: homology modeling, AF: AlphaFold. Human reference proteome is shown by a long continuous line. Homology models and PDB structures might have overlapping regions that are represented by discrete lines. While AF provides a model for all of the proteome, we focus on regions that are modeled with high accuracy. (**B**) Sample network representation of the reference interactome. Protein structures are represented by nodes and interactions by edges. Question marks within the nodes show monomers that do not have any known 3D structure in any of the databases. Question marks on the edges show unknown 3D structures of the interactions (complex) between structurally known monomers.

the completeness of the proteome and the availability of protein structures.

Human proteome is now 93.2% complete [36], and structural data are dramatically boosted with the accumulated experimental data (Protein Data Bank (PDB) [37]), homology modeling (ModBase [38], SWISS-MODEL [39]) and models from deep-learning methods such as AlphaFold (AF) [40]. AF is also adapted for modeling protein complex structures (i.e. AF2Complex) [41]. Other methods, such as AF2 followed by FoldDock, report promising results. However, these methods may have varying prediction performances on different organisms and be affected by the size of the protein complexes and post-translational modifications [42, 43]. Despite these advances, AF's contribution to modeling the human structural interactome is still relatively limited, estimated to be less than 5% [44]. Intrinsically disordered proteins (IDPs) or regions (IDRs) are conformationally heterogeneous and do not have a fold under physiological conditions [45]. Their contribution to several biological processes and pathologies [46] makes them important targets that require rigorous structural elaboration. Approximately 22% of the human proteome is likely disordered [47]. These regions often pose challenges in structural modeling, making it difficult to obtain high-quality models [48, 49]. A significant portion of AF predicted very low– and low-confidence regions are found to have overlap with predicted IDRs [50].

In this study, we assess the structural coverage of human proteome and interactome by considering available known and predicted protein structures. We first estimated the experimental structural coverage of the reference human proteome. Next, we showed the improvement of structural proteome coverage when complementary methods like homology modeling (SWISS-MODEL, ModBase) and deep learning (AF; v2.0) were utilized (Figure 1A). We further assessed the structural coverage of the reconstructed interactomes (obtained by combining STRING, HuRI and HIPPIE and filtered to produce a comprehensive list of protein–protein interactions). Proteome analysis followed by interactome analysis allowed us to identify the portion of the human interactome that can be predicted using structure-based techniques. This assessment involves determining the proportion of the interactome for which there are complete structural models for both interactors (Figure 1B). This work assesses all existing 3D structural data mapped to human interactome with stringent filtering. These statistics reflect how close we are to reconstructing the complete structural interactome through experimental and computational methods.

RESULTS

Predictive methods improve structural coverage of human proteome

The human reference proteome has 18 401 proteins, of which 7085 are fully or partially covered in PDB (see Methods for coverage calculations). Our results are based on PDB structures containing at least 30 consecutive residues in the corresponding proteins with missing coordinates discarded for each PDB file, and sequence identity with a PDB chain is 100%. At residue resolution, the human reference proteome has 10 789 741 residues, of which 2 125 738 residues have coordinates in PDB that correspond to 19.70% of the proteome (Table 1) consistent with previous studies [47]. Sequence coverage categories at different coverage intervals and corresponding percentages of available structures in human reference proteome are given in Table 2. Calculations showed that 1663 proteins, which correspond to ~9.93% of the reference proteome, are almost fully (at least 90%) structurally covered by PDB. This result indicates that only a small subset of the experimental structures is available for applications that require detailed information, such as molecular simulations, structure-based drug design and structural interactome construction. Additional computational methods, including homology-based and AI-based structural modeling, are required to expand the set of structurally known proteins.

For the proteins in the human reference proteome, we obtained high-quality models with 30 or more residues from the SWISS-MODEL and ModBase databases, resulting in 7886 proteins via SWISS-MODEL and 8618 proteins via ModBase. A total of 11 140 unique proteins were modeled, with 5364 proteins having predicted models in both SWISS-MODEL and ModBase. SWISS-MODEL and ModBase provided 24.99% and 22.18% residue-based coverage of the human proteome, respectively, both higher than the reported 19.70% coverage of PDB. The residue-based proteome coverage of the combination of these databases corresponds to 33.02% of the human reference proteome. These results show that homology modeling can cover approximately one-third of the human proteome without any contribution from PDB. To assess the contribution of homology models to reference proteome coverage, we excluded residues already covered by existing PDB structures and only used residues covered by homology modeling databases. We found 4904 proteins for SWISS-MODEL and 7300 proteins for ModBase. A total of 9096 unique proteins were modeled, with 3108 proteins having predicted models in

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Table 1: Residue-based coverage percentages of whole reference proteome by structure databases

	PDB	SWISS-MODEL (NA in PDB)	SWISS-MODEL	ModBase (NA in PDB)	ModBase	AF[a]
% coverage[b]	19.70	10.09	24.99	11.95	22.18	58.26

NA in PDB: not available in PDB. [a]For AF, structural data are considered available when a residue is predicted with ≥70% pLDDT score. [b]The number of amino acids where structural data are available is divided by the total number of residues in the reference proteome. Overlapping regions are counted only once, and missing residues are not included in the calculation.

Table 2: Protein-based coverage/accuracy percentages of reviewed proteins in reference proteome by structure databases

Protein residue coverage[a] (%)	PDB (%)	SWISS-MODEL (%)	ModBase (%)	AF[b] (%)
≥90	9.93	13.59	17.12	17.04
≥70	19.25	25.99	26.07	52.52
≥50	24.85	32.53	31.10	74.66
<50	13.66	10.33	15.73	23.61

[a]For each protein, available structural data are combined. Coverage percentage is calculated by dividing the number of proteins that are modeled above an arbitrary threshold to the total number of proteins in the reference proteome, which is 18 401. Overlapping regions are counted only once, and missing residues are not included in the calculation. [b]For AF, accuracy was calculated instead of coverage.

both SWISS-MODEL and ModBase. Residue-based coverage of the proteome unavailable in PDB is 10.09% by SWISS-MODEL and 11.95% by ModBase. Residue-based coverage of their combination shows that homology models contribute to PDB structures by increasing human reference proteome coverage by 16.47%.

Next, we utilized the AF database produced by an AI-based method (AF v2.0). The accuracy of the predicted models is provided for each residue with a pLDDT score representing the per-residue estimate of its confidence. Residue positions with pLDDT ≥70% were considered high quality [40]. Residue-based proteome coverage by AF showed that 58.26% of residues have pLDDT ≥70%. For structural coverage, we labeled a protein as 'accurately predicted' if 85% of its residues were predicted with ≥70% pLDDT score. This constraint resulted in the loss of ∼75% of the predicted structures in reference human proteome. Only 4930 (26.79%) of the AF predictions satisfy this condition. Among these, 2425 proteins already have at least a PDB structure, and the remaining 2505 predictions do not have any known structures deposited in any database before. As previously stated, 7085 proteins are fully or partially covered in PDB. All PDB data and accurately predicted AF models combined represent 9590 proteins (52.11%) for the human proteome.

We further assessed if AF's prediction accuracy varies depending on the IDRs and the predicted protein class. Out of 1066 proteins that have IDRs according to the DisProt database [51], we found that AF predicts 797 proteins with low accuracy (LA; disorder percentage: 16.83%) and 256 proteins with high accuracy (HA; disorder percentage: 6.95%). Then, we selected three structural protein classes: mainly alpha, mainly beta and mixed alpha-beta proteins. We found that mainly alpha proteins have the lowest PDB coverage, considering the total protein count within the classes (Table 3). Next, we selected five functional protein classes: enzymes, immunoglobulins, membrane proteins, transcription factors (TFs) and transporter proteins. We discovered that TFs have the lowest count in terms of having a PDB structure and the lowest coverage. Likewise, AF predicts almost all the proteins, 1451 out of 1459, within the TF class, yet only 19 passed our HA thresholds. It is observed that 649 of the proteins from the TF class are zinc finger proteins. We searched for 20 consecutive residues with pLDDT<50 for TFs in order to mimic a disordered region scenario for an AF prediction. Of the 1279 proteins that meet these criteria that we have identified, 628 are zinc finger proteins. Similarly, AF predicts all 74 proteins belonging to immunoglobulins. However, it only predicts 17 of them with HA, showing that the prediction accuracy is positively correlated with structures deposited in the PDB and significantly varies between the classes (Table 4). In summary, despite the high number of predicted proteins by AF, the HA predictions are one-quarter of the total protein counts within the class for almost all protein classes.

Our results prove that combining PDB structures with homology and AF models increases the structural coverage (Table 2). In Figure 2A, we show the number of proteins in the human reference proteome shared by the structure databases when all accurate structures are considered. ModBase contributes the most by providing structures exclusively for 1599 proteins. Also, in Figure 2B, we show how the partial and complete coverage changes. PDB covers 1828 proteins (9.93%) when only highly covered (90%) structures are considered. The addition of high-coverage (≥90%) homology models and accurately predicted (85% of its residues were predicted with ≥70% pLDDT score) AF models raise this percentage to 33.16%.

A reference human interactome can be constructed by integrating multiple resources

Estimating the exact size of the human interactome still remains challenging [15]. Available interactions in databases, obtained via multiple techniques, are the best resource for reconstructing a complete human interactome. Here, we analyzed eight major human interaction databases, HuRI, STRING, BioPlex, BioGRID, HIPPIE, IID, APID and PICKLE, to evaluate the current status of the interactome coverage with available structural data and decided on which database to use toward the construction of a comprehensive structural human reference interactome. We investigated the number of proteins and interactions available after mapping the interactions to the human reference proteome and removing redundant interactions with the same UniProt identifier. Then, we quantified the number of proteins and interactions in each database with a structure and/or a model available in our structural data sources. These statistics are summarized in Table 5. HuRI is one of the most comprehensive experimental data providing direct physical interactions for 48 763 PPIs. The filtered STRING database, hereinafter referred to as $STRING_F$, resulted in 57 192 physical interactions with high confidence scores (>0.7), considering only experimental and database channels. In addition, there are 53 136 interactions in the BioPlex database. However, these are not restricted to binary physical interactions because the affinity purification–mass spectrometry

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Table 3: Coverage of structural protein classes according to PDB and AF

Structural class	Total protein count	Proteins [have PDB] (average PDB coverage, %)	Protein count [all predictions w/ AF] (average pLDDT score)	Protein count [high acc. predictions w/ AF] (average pLDDT score)
Mainly alpha	6406	2830 (58.5)	6294 (76.5)	1735 (89.3)
Mainly beta	4711	2395 (56.1)	4577 (77.9)	1220 (89.7)
Mixed alpha–beta	6696	3268 (65.3)	6585 (78.7)	2367 (91.0)

Proteins in reference proteome are classified according to the data provided by CATH-Gene3D. Proteins [have PDB] (average PDB coverage, %): The number of UniProt entries that belong to each class and have at least a PDB structure and average PDB coverage of the class calculated by taking the averages of UniProt entry's corresponding PDB coverages (see Methods for coverage calculations). Protein count [all predictions w/ AF] (average pLDDT score, 0–100): The number of UniProt entries that belong to each class and have a predicted 3D structure produced by AF. In an AF prediction file, pLDDT scores of each residue were averaged and referred to as prediction accuracy of this corresponding UniProt entry. Protein count [high acc. predictions w/ AF] (average pLDDT score, 0–100): the number of UniProt entries that belong to each class and have a predicted 3D structure that 85% of the residues predicted with ≥70% pLDDT score. Only the UniProt entries within a class predicted with HA are considered and calculated by taking the averages of the UniProt entry's corresponding AF prediction accuracies.

Table 4: Coverage of functional protein classes according to PDB and AF

Functional class	Total protein count	Proteins [have PDB] (average PDB coverage, %)	Protein count [all predictions w/ AF] (average pLDDT score)	Protein count [high acc. predictions w/ AF] (average pLDDT score)
Enzymes	3618	2114 (72.2)	3574 (83.5)	1831 (91.6)
Immunoglobulins	74	25 (85.6)	74 (89.6)	17 (90.5)
Membrane proteins	5013	1500 (60.5)	4939 (78.1)	1391(88.8)
Transcription factors	1459	372 (30.7)	1451 (63.2)	19 (86.9)
Transporter proteins	1843	721 (67.8)	1823 (78.6)	517 (88.3)
Others	8416	7085 (62.4)	8304 (74.3)	1929 (89.9)

Proteins in reference proteome are classified according to the data provided by the HPA. Proteins [have PDB] (average PDB coverage, %): the number of UniProt entries that belong to each class and have at least a PDB structure and average PDB coverage of the class calculated by taking the averages of UniProt entry's corresponding PDB coverages (see Methods for coverage calculations). Protein count [all predictions w/ AF] (average pLDDT score, 0–100): the number of UniProt entries that belong to each class and have a predicted 3D structure produced by AF. In an AF prediction file, pLDDT scores of each residue were averaged and referred to as prediction accuracy of this corresponding UniProt entry. Protein count [high acc. predictions w/ AF] (average pLDDT score, 0–100): the number of UniProt entries that belong to each class and have a predicted 3D structure that 85% of the residues predicted with ≥70% pLDDT score. Only the UniProt entries within a class predicted with HA are considered and calculated by taking the averages of the UniProt entry's corresponding AF prediction accuracies.

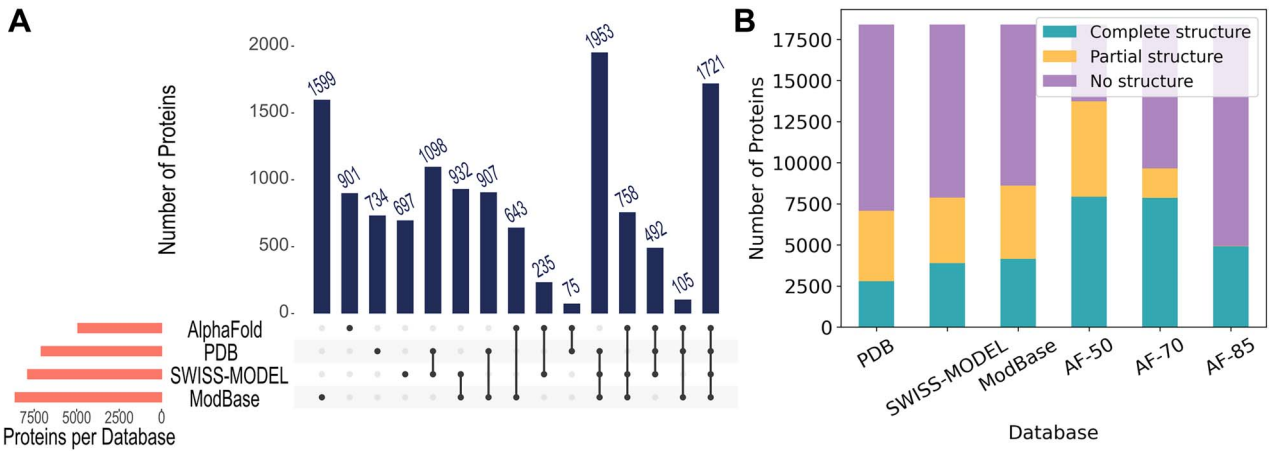


Figure 2. Structural coverage of proteins in the human reference proteome by databases. (**A**) The number of proteins modeled by PDB, SWISS-MODEL, ModBase, AF and their intersections are visualized. AF models with 85% of their residues predicted with ≥70% pLDDT score are used. (**B**) The number of proteins with no structure, partial structure, and complete structure. AF models with 85% (AF-85), 70% (AF-70) and 50% (AF-50) of their residues predicted with ≥70% pLDDT score are used for this demonstration. Partial structure denotes structure coverage <80% for PDB and homology models. For AF, it denotes an average accuracy of <80%. Similarly, complete structure means ≥80% coverage or average accuracy. Although it's not visible, AF-85 has 13 models with partial structures.

(AP-MS) technique finds all physical/non-physical interactions in a complex [52]. Lastly, filtering the HIPPIE dataset, hereafter referred to as $HIPPIE_F$, to binary high-confidence interactions resulted in 22 280 PPIs.

Assessment of human interactomes from HuRI, $HIPPIE_F$ and $STRING_F$: mapping experimental and predicted 3D structures

Figure 3 shows the total number of interactions and the interactions with structures/models listed in Table 5. We chose two databases, HuRI and BioPlex, which output the results of major experimental studies, as well as the well-known databases STRING, which enables filtering the physical interactions by a confidence score, and the HIPPIE, which can be filtered with respect to experiment type and confidence score. We demonstrate that there is little overlap in terms of interactions among these four major databases (Figure 3A). Table 5 shows that the HuRI, $HIPPIE_F$ and $STRING_F$ interaction networks contain 7889, 7640 and 7327 proteins, respectively. While most of the proteins are present in all three databases, a considerable number of proteins

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Table 5: Statistics of the number of proteins and protein–protein interactions in interactome databases that are mapped to human reference proteome

Database	Total number of		Number of proteins with available structures				Number of interactions with structures available for both interacting proteins			
	Interactions	Proteins	PDB	SWISS-MODEL	ModBase	AF[a]	PDB	SWISS-MODEL	ModBase	AF[a]
HuRI	48 763	7889	3317	3414	3729	2026	7046	7014	8938	2737
BioPlex v3.0	53 136	8806	3888	4242	4615	2819	14 036	13 945	15 162	5802
STRING v11.5	57 192	7327	4518	4214	4095	2085	38 005	24 829	21 442	9941
HIPPIE v2.3	22 280	7640	4164	3971	4231	1910	10 193	7795	8412	1586
APID v2021_03	125 722	14 854	6508	6774	7236	3897	39 922	32 453	36 390	8394
PICKLE v3.3	211 943	15 922	6852	4349	7719	4191	88 408	68 328	71 761	14 794
BioGRID v4.4.216	719 566	17 100	6914	7499	8174	4587	292 081	233 361	239 226	70 455
IID v2021_05	542 157	17 331	7015	7636	8250	4600	235 632	181 337	185 030	53 251

Additional filtering was applied to STRING and HIPPIE datasets. [a]AF, 85% of the residues predicted with ≥70% pLDDT score.

Table 6: Classification and observance percentages of domain types of the interacting protein pairs found in reference interactomes

		Single–single	Multi–multi	Single–multi
Reference interactomes	HuRI (41 705)	19 210	5403	17 092
	STRING (54 631)	19 754	12 541	22 336
	HIPPIE (20 601)	5445	6248	8908

Additional filtering was applied to STRING and HIPPIE datasets.

are exclusively present in one (Figure 4). We also found the number of interactions where both partners had PDB structures. The results show that $STRING_F$ has the highest PDB coverage among interactome databases, while HuRI and $HIPPIE_F$ have poor PDB coverage (Figure 3B). The striking disparity might be due to ribosomal and mitochondrial proteins being significantly less represented in HuRI (protein count: 125; interaction count: 1348) and $HIPPIE_F$ (protein count: 186; interaction count: 2175) compared to $STRING_F$ (protein count: 1801; interaction count: 16 453), taking part in so many interactions. Given that the Y2H technique detects the bulk of $HIPPIE_F$ interactions and all HuRI data, the missing proteins may be due to Y2H's technical limitations.

Figure 3C and D show the number of interactions with homology and AF models for both interacting proteins, respectively. Homology models have better interaction coverage compared to AF. $STRING_F$ has the most coverage in both scenarios, while $HIPPIE_F$ has the least. In general, the overlap between databases is minimal, reinforcing the notion that integrating these databases is critical since relying on a single database may result in incomplete interactomes.

Since many human proteins are multi-domain, and interactions may occur between single-domain and multi-domain proteins, we analyzed the differences across various interactome databases. The domain count distribution of interacting proteins, as depicted in Table 6, reveals an interesting trend. Most interactions occur between single-domain proteins, as evidenced by the significantly high number of interactions in the HuRI interactome, where 19 210 out of 41 705 interactions fall into this category. This observation suggests that single-domain–single-domain protein pairs predominantly mediating interactions in the HuRI dataset may be attributed to potential limitations in correctly expressing lengthy multi-domain proteins in yeast [53], which could result in an underrepresentation of interactions involving these proteins in the dataset.

These results have led us to select the HuRI, $STRING_F$ and $HIPPIE_F$ databases as our reference interactome sources. When these three interactomes are combined, 12 748 non-redundant proteins participate in 117 897 interactions. Mapping these interactions to experimental 596 919 binary protein–protein complexes (https://github.com/ku-cosbi/interactome-structural-coverage/blob/main/data/PDB_interface_data.tsv) from PDB (as of December 2022) showed that very few experimentally resolved protein interactions are available and they account for only 3.95% of all non-redundant binary interactions. Next, we concentrated on the interactions and displayed the structural coverage of protein–protein interactions in interactome databases (Figure 5). As can be seen from the percentages, the $STRING_F$ database outnumbers the rest (exp-exp, exp-model and model-model in the inset plot). Experimental and modeled structures of both interactors in HuRI are available for only ∼40% of the whole interactome. In comparison, this figure rises to ∼85% in $STRING_F$. Here, we did not distinguish between high- or low-coverage/accuracy structures.

Accurate 3D modeling of the interactions in HuRI, $STRING_F$ and $HIPPIE_F$ interactomes requires structurally complete monomer protein structures. In other words, given that two proteins interact, structural knowledge for this protein–protein interaction can be obtained on the availability of the structures of both proteins. To assess the completeness of each interacting pair, proteins in HuRI, $STRING_F$ and $HIPPIE_F$ interactomes were labeled as high coverage (HC) or low coverage (LC) along with the name of the data sources: PDB, SWISS-MODEL or ModBase. On the other hand, AF usually predicts the whole protein structure, yet the prediction quality of each structure, even each residue in a structure, is different. Therefore, rather than using HC and LC metrics, we preferred HA and LA metrics for the AF structures. Figure 6 shows a snapshot of the available structures in different databases. As stated in previous sections, we denoted 50% or higher coverage as HC; the rest as LC; 85% of the structure covered with 70% or

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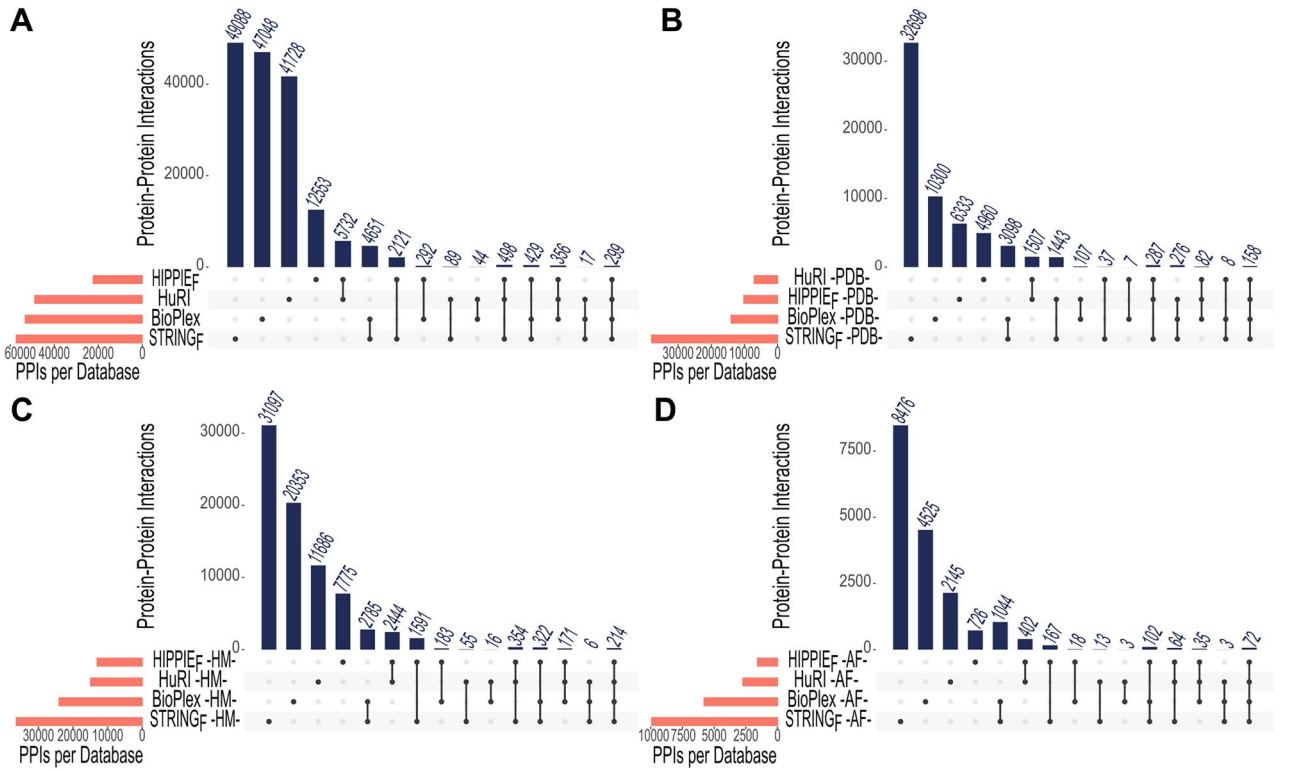


Figure 3. Overview of PPIs found in HuRI, BioPlex, HIPPIE$_F$, and STRING$_F$ databases. (**A**) Interactions are filtered according to the reference proteome. (**B**) Interactions with a PDB structure for both interacting proteins filtered to the reference proteome. (**C**) Interactions with a high-quality homology model for both interacting proteins filtered to the reference proteome. (**D**) Interactions with an AF model that have 85% of their residues predicted with ≥70% pLDDT score for both interacting proteins filtered to the reference proteome. HM: homology modeling, AF: AlphaFold.

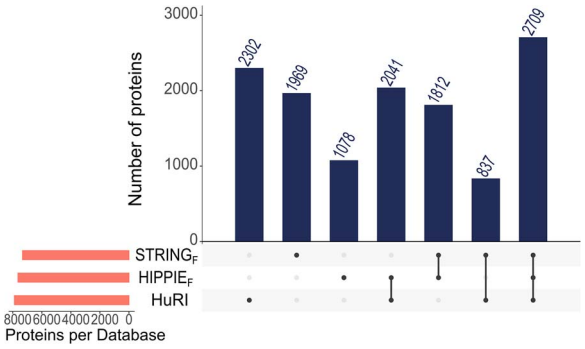


Figure 4. Total number of proteins found in STRING$_F$, HIPPIE$_F$ and HuRI databases.

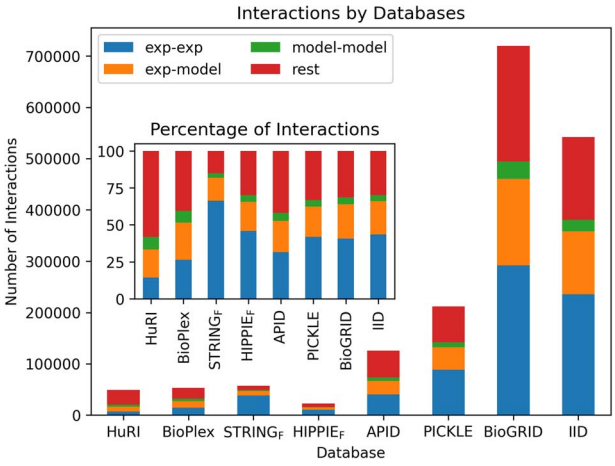


Figure 5. Structural coverage of protein–protein interactions in interactome databases. Exp-exp indicates interactions where both interacting partners have experimental structures from PDB . Exp-model represents interactions where only one interacting partner has an *experimental* structure from PDB, and the other partner has a model from ModBase, SWISS-MODEL or AF. Model-model indicates that both interacting partners do not have experimental structures but have a model. Lastly, rest is for the remaining interactions that have no structural data available. The inset plot shows the same concept in terms of percentages. AF models that have 85% of their residues predicted with ≥70% pLDDT score are considered.

higher accuracy for AF, is designated as HA, with the remaining predictions falling into the LA group. Numerous combinations of databases and coverages are available for an interaction because the 3D structures of each protein can be found across multiple databases with various coverages or accuracies. This is why the sum of the numbers in Figure 6 is greater than the total number of interactions in the reference interactome. AF's LA 3D structures dominate the HuRI, STRING$_F$, and HIPPIE$_F$ interactomes. PDB and homology modeling databases each add roughly equal numbers of structures to model a small number of interactions in HuRI and HIPPIE$_F$. On the other hand, the PDB and homology modeling databases contain many 3D structures with HC that can be used to model the interactions in STRING. Only 12.97% of the HuRI and 32.94% of the HIPPIE$_F$ interactomes contained protein partners with HA or HC structures, while this percentage increased to 73.62% for the STRING$_F$ interactome. Out of 117 897 interactions in total, 47 431 (40.23%) interactions have both protein partners with HA or HC structures.

Some of the proteins are highly studied; these usually correspond to disease-related proteins. Investigation of important

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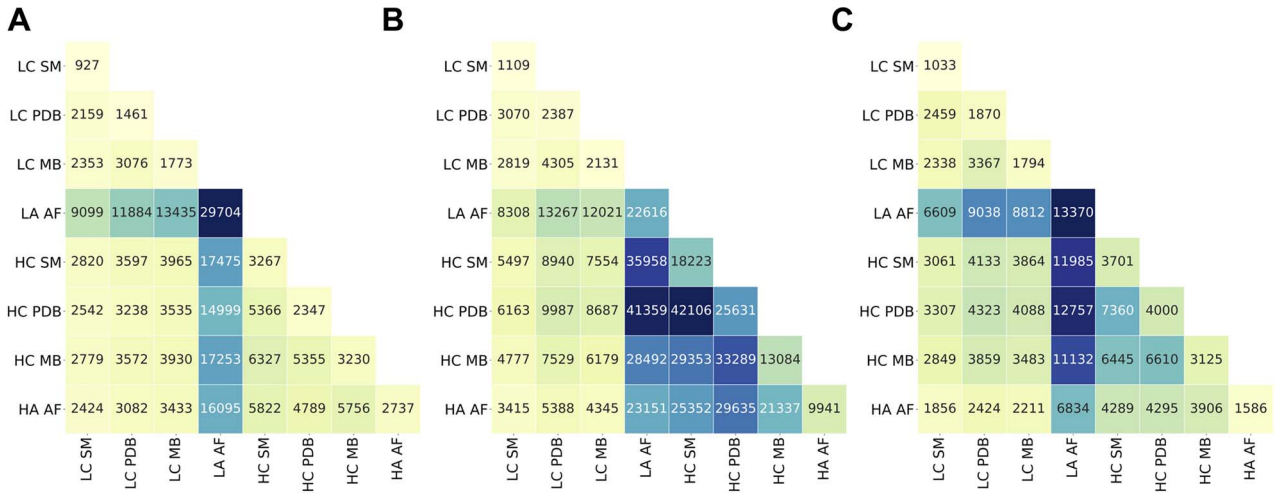


Figure 6. 3D Structure modeling assessment of 'Protein 1-Protein 2' pairs in reference interactomes in (**A**) HuRI, (**B**) $STRING_F$ and (**C**) $HIPPIE_F$. x–y axes labels show the 3D coverage or accuracy label of the databases. LC: low coverage, HC: high coverage, HA: high accuracy, LA: low accuracy, MB: ModBase, SM: SWISS-MODEL, AF: AlphaFold. The number in each cell indicates how many 'Protein 1–Protein 2' pairs of the reference interactome can be potentially constructed by using mentioned sources with given labeled coverage or accuracy.

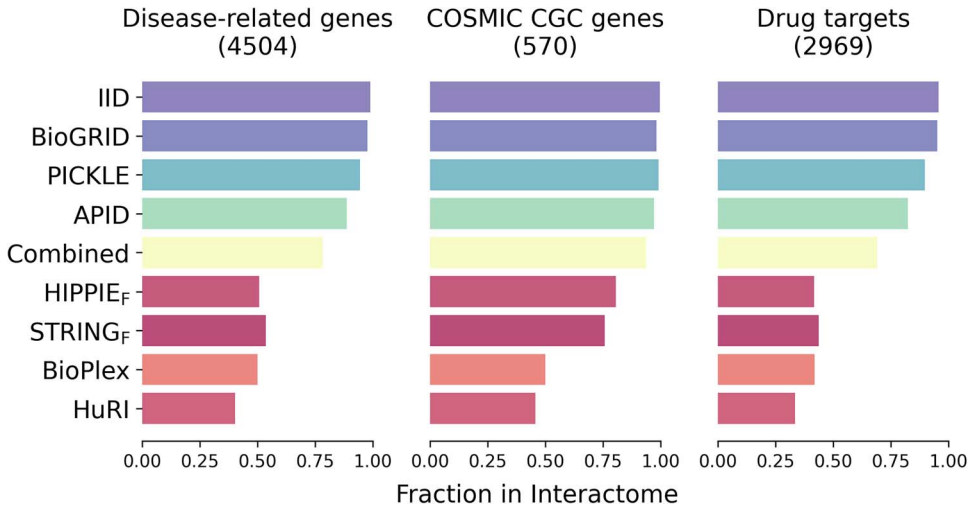


Figure 7. Investigation of important genes in interactome databases. Fraction of disease-related, COSMIC CGC and drug-targeting genes are investigated for all interactome databases. The term 'combined' represents merged interactomes of $HIPPIE_F$, $STRING_F$ and HuRI.

proteins such as disease-related, COSMIC CGC [54], and drug targets in interactome databases shows that except for HuRI, interactomes contain ≥50% of COSMIC CGC and disease-related genes (Figure 7). Even though the number of interactions in the $HIPPIE_F$ dataset is less than HuRI, it is enriched in important genes. The coverage of drug targets, however, is often less extensive across most interactomes. When our selected reference interactomes are combined, drug target coverage increases by up to 69% while others surpass 75%.

DISCUSSION

We comprehensively analyzed the current structural knowledge of the human proteome and interactomes (HuRI, $STRING_F$ and $HIPPIE_F$) by integrating experimental protein structures from PDB and predicted structures from ModBase, SWISS-MODEL, and AF. Our results showed that combining several resources improved the structural coverage of the human proteome and interactomes. Predicted protein structures bring an orthogonal layer of information toward having a more comprehensive structural proteome with varying degrees of accuracy. The availability of an experimental model significantly impacts the computational accuracy of the structure prediction. Moreover, we implicitly touched on the IDPs/IDRs in our analysis where we diligently separated out low-quality models. This quality control process has helped ensure the reliability of the structural data we have used for our analyses. Besides having a low number of available experimental structures from PDB, the functional class coverage for TFs was also impacted by the presence of IDRs [55] (Table 4). It is also mentioned that TFs with zinc finger domains are not accurately predicted by AF. Given that experimental structure determination is more difficult for the immunoglobulin class of proteins due to their long loop regions [56], our data demonstrate that the prediction ability is indeed restricted for these proteins. Proteome-level analysis shows we are still halfway to a structurally complete human proteome.

Integrating the structural data mapped to reference interactome databases at the interactome level reveals that $STRING_F$ has the highest PDB coverage while HuRI has the lowest. This suggests that STRING may be a valuable resource for researchers

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seeking information about interactions involving experimental structures. While the number of proteins with PDB structures is similar between interactome databases, the number of interactions differs significantly, which might be attributed to the limited sensitivity of Y2H. Therefore, additional computational prediction methods, such as template-based or template-free docking and deep-learning-based methods, complement experimental methods as they capture interactions that Y2H or other experimental techniques may miss.

We also highlight that homology models show better interaction coverage than AF's accurately predicted models. This implies that homology models may continue to be a useful tool for predicting PPIs when experimental data are lacking and may complement the capabilities of AF. Furthermore, we emphasize that there is minimal overlap between interactome databases. Consequently, depending solely on a single database may result in incomplete or biased results, as each database may have its strengths and limitations regarding coverage. Thus, integrating data from multiple databases can provide a more comprehensive and reliable picture of PPIs.

It has also been shown that protein pairs with HA or HC structures constitute a small portion of interactions in HuRI, a larger portion in $HIPPIE_F$ and the majority of interactions in $STRING_F$. HuRI is reported as a less-biased interactome containing genes that belonged to uncharted regions previously [15]. Such a characteristic might be the reason behind its lower coverage of interacting proteins than other interactomes. Considering this, bias toward well-studied proteins may impact the structural coverage of the interactome because less-studied proteins may have fewer interactions reported in the interactome. Despite the increased coverage provided by computational methods, the number of HA/HC interactions remains low compared to all existing interactions. We should note that there are valuable thermodynamic and kinetic data accessible for the stability of human proteins and binding affinity of protein–protein interactions in databases such as ProThermDB, SKEMPI and PROXiMATE [57–59]; however, these data are not exhaustive to cover the entire proteome or interactome. This altogether highlights the need for continued efforts in both experimental and computational methods to improve our understanding of protein–protein interactions and the structural coverage of the human interactome.

METHODS

Reference proteome analysis

A recent version of the UP000005640 was obtained from the UniProtKB proteome database (UniProt release 2022_04). This text-based data contain information for 20 360 reviewed human proteins. First, protein names, including keywords such as 'putative' or 'uncharacterized', are eliminated from the initial proteome dataset. Second, only the proteins with proven existence belonging to experimental evidence at the protein level and experimental evidence at transcript level classes is kept in the dataset. Last, proteins with less than 30 amino acids are removed from the dataset. After the three-step filtering, the final reference proteome dataset contained 18 401 proteins. Domain information was incorporated into this dataset from the PFAM database cross-referenced in UniProt. We considered a protein 'multi-domain' if multiple PFAM IDs are assigned to its UniProt ID.

PDB coverage

We retrieved all PDB structures cross-referenced in UniProt to obtain the structural proteome and its coverage (as of 1 June 2022). We parsed all mm/CIF files by using Biopython's Bio.PDB package [60] to find the protein chains that match UniProt identifiers in the reference proteome. In total, we parsed 128 696 protein chains for 7376 unique human proteins. Calculations run on Koc University High-Performance Computing (KUACC HPC) cluster. In the end, we have an exact begin–end residue range for each PDB chain corresponding to the original UniProt sequence and missing residues that fall into that region. The corresponding PDB file is not considered for further analysis if the resulting region does not contain at least 30 consecutive amino acids. To eliminate redundancies, we removed duplications representing identical residues and excluded missing coordinates only once if there were any repeats in another coordinate file. For all PDB coverage calculations, Equation 1 is used.

$$\text{Coverage}\,(\%) = \frac{\text{UniProtres.end} - \text{UniProtres.begin} - \text{Missingres.\#withintheinterval}}{\text{Totallengthoftheprotein}} \times 100 \quad (1)$$

AF coverage

The DeepMind team released structures predicted by AF v2.0 [61] in October 2022. Predictions for UP000005640 proteome downloaded from the AF Protein Structure Database (https://ftp.ebi.ac.uk/pub/databases/alphafold). There were 23 391 predictions deposited for the reference proteome. After eliminating the predictions previously labeled as unreviewed by UniProt, we ended up with 20 315 reviewed/canonical protein predictions. AF predicts the proteins as fractions whose amino acid count exceeds 2700. Those predictions for 207 unique protein entries are also eliminated. Confidence in the AF predictions is measured by pLDDT, a per-residue accuracy estimate on a scale from 0 to 100. A pLDDT score ≥70% is declared as an indicator of a good backbone prediction [40]. Therefore, in our analysis, we applied a structural constraint. We only assume 'accurately predicted' if a protein's 85% of the residues predicted with ≥70% pLDDT score.

Homology modeling coverage

We have utilized two widely known homology modeling databases: SWISS-MODEL and ModBase. We downloaded homology models for reference proteome based on the UniProtKB release 2022_04 from the SWISS-MODEL Repository. Then, we filtered the models based on their QMeanDisCo Global score, a composite scoring function that estimates model quality [62]. We selected models with a QMeanDisCo Global score greater than 0.7 as they are considered confident models by the providers. For ModBase, we downloaded the file named *modbase_models_all-latest.xz* with a last modified date of 28 February 2014 from the downloads section. We eliminated models that are not present in the filtered human reference proteome and have less than 30 amino acids for both databases. We selected models with a ModPipe Quality Score (MPQS) ≥1.1 if available, or if MPQS is not available, sequence identity ≥30% and a model score (GA341) ≥0.7 were selected as good-quality models. MPQS is a composite quality score that includes e-value, z-Dope, GA341, coverage and sequence identity to the template [63]. Also, we selected the model with a higher-quality score for both databases if there were models with precisely the same amino acid start and end positions. We have reported residue-based and protein-based coverage results for these models. For residue-based coverage calculations, a simplified version of Equation (1) is used where the missing residues are not considered because of the nature of homology models. To understand the contribution of homology modeling

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to experimentally determined protein structures, we further eliminated the models that cover the identical residues with available PDB structures. We have utilized the former case where we do not eliminate models concerning PDB data for the analysis of interactome coverage.

Coverage of IDRs, structural and functional protein classes

In this study, we used IDR data from DisProt [51], structural protein classes from CATH-Gene3D [64, 65] and functional classification data of the proteins from the Human Protein Atlas (HPA) [66]. We examined the accuracy of IDRs predicted with AF and computed the disorder percentage of predicted proteins by subtracting the end and start positions of the residues and dividing by the total length of the protein. Three main structural protein classes: mainly alpha, mainly beta and mixed alpha–beta together with five main functional protein classes: membrane proteins, TFs, immunoglobulins and transporter proteins, are investigated in terms of their structural coverage either experimentally (PDB) or computationally (AF). From these datasets, we only include the proteins that are part of our reference proteome. As AF produces whole-protein predictions, its coverage is evaluated in terms of prediction accuracy rather than the count of the protein residues predicted. In this manner, average counts of the proteins in any class are calculated by dividing the number of proteins with a 3D structure by the protein count within the class.

Analysis of interactome databases

We reviewed interactome databases currently available online, including HuRI [15], STRING [9], BioPlex [5], BioGRID [14], HIPPIE [10], Interactome INSIDER [3], Interactome3D [4] hu.MAP [16], IID [7], APID [6] and PICKLE [12]. An overview of these databases can be found in Supplementary Table 1 available online at http://bib.oxfordjournals.org/.. We downloaded the protein–protein interactions from HuRI, STRING, BioPlex, BioGRID, HIPPIE, IID, APID, and PICKLE databases to investigate the number of PPIs available (as of 5 December 2022). Three interactomes were investigated in detail. We downloaded the HuRI.tsv file of the 2020 publication from http://www.interactome-atlas.org/download. ASTRING physical interaction dataset named '9606.protein.physical.links.detailed.v11.5.txt' was downloaded from the Downloads tab at https://string-db.org, and rescoring has been performed using the Python script from https://stringdb-static.org/download/combine_subscores.py, which STRING creators provide. We selected models with a combined score of experimental and database channels greater than 0.7. For HIPPIE, we downloaded the current release (v2.3) from http://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/download.php. We filtered this dataset and have only the binary PPI detection methods that are two-hybrid, atomic force microscopy and fluorescent resonance energy transfer [1]. Then, we set the quality threshold at 0.73 (high quality) and removed interactions smaller than this cutoff value. We converted any different protein identifiers to UniProt identifiers for standardization and removed redundant protein–protein interactions. We filtered the datasets for the proteins present in our reference proteome. Then, we found the number of unique proteins and unique interactions in each interactome database; the number of unique proteins with at least one available structure in PDB; and the number of unique proteins with at least one model in SWISS-MODEL, ModBase and AF databases. Furthermore, we found a number of unique interactions in which both interacting pairs had a structure and/or a model.

Gene Ontology: cellular component analysis and investigation of important genes in interactome databases

For cellular component analysis, we focused only on the proteins available in STRING to reveal the reason behind the difference in the interaction counts between interactome databases. We collected the PFAM IDs of these proteins and found UniProt entries in the reference proteome containing at least one PFAM domain. A common pattern in terms of frequent GO cellular component annotations [67], ribosome (GO:0005739) and/or mitochondrion (GO:0005840) is detected for this protein subset. Then, we checked the existence of such proteins with these annotations in $STRING_F$, HuRI and $HIPPIE_F$. Later, we investigated the coverage of disease-related, COSMIC CGC and drug-targeting genes in interactome databases. For disease-related genes, we downloaded variant summary data from ClinVar [68] (last modified date: 21 January 2023) and filtered them to take genes in assembly GRCh38 and have 'pathogenic' clinical significance. For COSMIC CGC genes, we downloaded cancer gene census data from COSMIC (version 97) and restricted them to Tier 1 genes [54]. Lastly, for drug targets, we utilized the complete target data from IUPHAR/BPS Guide to Pharmacology (2022.4 version) [69].We filtered all datasets for the proteins present in our reference proteome. Then, we calculated the fraction of these important genes in interactome databases to find their coverage.

Key Points

- We employed a large scale computational analysis of protein structures (known or predicted) in human proteome and interactomes to understand how close we are to potentially construct the complete structural interactome with experimental or computational methods.
- We showed that 33.16% of the human proteome can be represented with high accuracy and high coverage protein structures obtained with experimental (PDB) or predicted (homology modeling and AlphaFold) structures.
- In turn, although AlphaFold significantly enriches the structural human proteome (up to 52.11%), we are still halfway in obtaining the high accuracy complete structures.
- The structural representation of interactomes is even more limited than the proteome. However, there is a huge opportunity for 3D modeling techniques to predict the rest where we showed that 40.23% of the interactome is predictable.

SUPPLEMENTARY DATA

Supplementary data are available online at https://academic.oup.com/bib.

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DATA AND SOFTWARE AVAILABILITY

All source code and datasets are freely available at https://github.com/ku-cosbi/interactome-structural-coverage.

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