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PROTEIN INTERACTION DATABASES: A REVIEW

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ABSTRACT: The development of experimental techniques for detecting protein–protein interactions has generated an extensive amount of data. Over the past few years, the number of known protein-protein interactions has increased considerably. To make this information easily available, numerous public databases have been created to store protein-protein interaction data. The role of the bioinformatician is to evaluate this data and to explore biologically relevant interactions and pathways. There is a need for the development of strategies to predict novel protein–protein interaction networks *insilico*. In this paper, an attempt has been made to overview the various protein-protein interactions databases.

KEYWORDS: Protein, Interactions, Databases, Bioinformatics

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1.INTRODUCTION

Numerous techniques have been employed for studying protein interactions by genetic, biochemical and biophysical techniques including protein–protein affinity chromatography, immunoprecipitation, sedimentation and gel-filtration. However, tools of high-throughput detection methods have generated substantial amount of data on protein-protein interactions. Consequently, since last decade the number of known protein-protein interactions has increased considerably. Numerous publicly available databases have been set out to collect and store protein-protein interaction data for the advantage of biological and biomedical research. Creating precise and complete cellular map, equivalent dynamic high dimensional information matrix, require the integration of multifold systematic cellular and molecular biology experimental efforts. This

requires powerful information storage, query capacity and analysis engines to efficaciously manipulate data. Predominantly, bimolecular interactions and pathway data were stored in printed journal articles where the information is difficult to manage and compute upon. Hence, many researchers have attempted to compile databases of protein–protein interaction data. The main aim of these databases is to retrieve and integrate the enormous information about protein– protein interactions accessible in numerous scientific journals and in archives such as MEDLINE (National Library of Medicine, MD, USA). These databases also offer tools to inspect networks of interactions, to map pathways across taxonomic branches, and to generate information for kinetic simulations [1].

Protein-Protein Interaction (PPI) databases: PPI databases can be grouped into two categories, General databases that store interaction networks from a variety of organisms [2]; Specialized databases that contain interaction networks from specific organisms. These databases are employed during prediction of protein-protein interactions. Creating databases require a considerable effort. Thus, creating a database large enough to capture cell map information will require huge community investment and innovation, ranging from the individual researcher (biologists to computer scientists and database developers) to the funding agencies and journals. Till date, most of the protein–protein interactions reported in many databases are for *S. cerevisiae*, for which the most detailed protein–protein interaction datasets are available. The credibility of the data appears to be limited by the excess of false-positive interactions [2], which complicates the identification of biologically important interactions. This led to the development of a mammalian protein–protein interaction (PPI) databases [3]. PPI databases have developed immensely in the last few years, and important aspects like data exchange, are being presently undertaken by some of the databases. A significant step towards enhancing the number and quality of protein interaction data would be to introduce a submission requirement — as, before, already present for sequence and microarray data. These data are to be submitted to public databases before publication in a scientific journal, which ensures data availability and consistent annotation, and enables researchers to utilize the data with maximum efficacy [4]. The aspect of integrating the data from PPI different repositories began with the efforts of the Human Proteome Organization Proteomics Standards Initiative (HUPO-PSI) and International Molecular Exchange (IMEx) consortium and followed by publishing the ‘minimum information about a molecular interaction experiment’ (MIMIX) guidelines. The HUPO-PSI has developed the PSI-MI XML format to establish a single, unified format for PPI data. Additionally, a simplified tabular format, MITAB has been developed. The IMEx is an international collaboration between a group of major public interaction data providers who have agreed to share literature-curation efforts and make a non-redundant set of PPI available in a single search interface on a common website (http://www.imexconsortium.org/) [5]. Numerous databases exist to evaluate binary protein interactions along with higher order interactions in protein complexes. PPI databases

are generally grouped according to the interactions they have or the methodology applied to collect & curate information. A comparison of the main databases and repositories including protein interactions is depicted in **Table 1**, exhibiting the sources of the data ("PPI Sources"), the different molecular interactions ("Type of MI") involved and the total number of proteins and interactions (where available).There are three exquisite approaches to collect and present interaction data: (i) primary databases, encompassing only experimentally proven protein interactions coming from either small-scale (Ssc) or large-scale (Lsc) published studies that have been manually curated; (ii) meta-databases, which include only experimentally proven PPIs derived by consistent integration of various primary databases (sometimes including small sets of original PPI data); (iii) prediction databases, including mainly predicted PPIs obtained from diverse approaches, combined with experimentally proven PPIs [6].

Table 1: Comparison of Main Protein – Protein Interaction Databases

Database	**Database Full Name and URL**	**PPI Sources**	**Type of MI**	**Species**	**No. of Proteins**	**No. of Interactions**	**Refer-ence**
Primary Databases: PPI experimental data curated from large- and small-scale (Lsc & Ssc) experimental studies							
BIND	Bimolecular Interaction Network Database http://bond.unleashedinformatics.com/	Ssc & Lsc (literature-curated)	PPIs & others	All	31,972	>3, 00,000	[7,8]
BioGRID	Biological General Repository for Interaction Datasets http://www.thebiogrid.org/	Ssc & Lsc (literature-curated)	PPIs & others	All	28,717	7, 17,604	[10, 11]
DIP	Database of Interacting Proteins, http://dip.doe-mbi.ucla.edu/dip/	Ssc & Lsc (literature-curated)	Only PPIs	All	28868	81731	[12, 13]
HPRD	Human Protein Reference Database, http://www.hprd.org/	Ssc & Lsc (literature-curated)	Only PPIs	Human	30,047	41,327	[14,15, 16]
IntAct	IntAct Molecular Interaction	Ssc & Lsc (literature-curated)	PPIs & others	All	84570	419709	[17]

	Database, http://www.ebi.ac.uk/intact/						
MINT	Molecular INTeraction database, http://mint.bio.uniroma2.it/mint/	Ssc & Lsc (literature-curated)	Only PPIs	All	25,530	12, 5464	[18,19]
MIPS-MPact	MIPS protein interaction resource on yeast, http://mips.gsf.de/genre/proj/mpact/	Derived from CYGD	Only PPIs	Yeast	1,500	4,300	[20]
Meta-Databases: PPI experimental data (integrated and unified from different public repositories)							
APID	Agile Protein Interaction Data Analyzer, http://bioinfow.dep.usal.es/apid/	BIND, BioGRID, DIP, HPRD, Intact, MINT	Only PPIs	All	29,701	3, 22,579	[21]
MPIDB	The Microbial Protein Interaction Database, http://www.jcvi.org/mpidb/	BIND, DIP, IntAct, MINT etc.	Only PPIs	Microbial	7,810	24,295	[22]
PINA	Protein Interaction Network Analysis platform, http://csbi.ltdk.helsinki.fi/pina/	BioGRID, DIP, HPRD, IntAct, MINT, MPact	Only PPIs	All	-	188,823	[23]
Prediction Databases: PPI experimental and predicted data ("functional interactions", i.e., interactions *lato sensu* derived from different types of data)							
MiMI	Michigan Molecular Interactions, http://mimi.ncibi.org/MimiWeb/	BIND, BioGRID, DIP, HPRD, IntAct, & non PPI data	PPIs & others	All	45,452	391,386	[24,25]

PIPs	Human PPI Prediction database, http://www.compbio.dundee.ac.uk/www-pips/	BIND, BioGRID, HPRD, IntAct, MINT, MPact, & non PPI data	PPIs & others	Human	37 606	69 965	[26]
OPHID	Online Predicted Human Interaction Database, http://ophid.utoronto.ca/	BIND, BioGRID, HPRD, IntAct, MINT, MPact, & non PPI data	PPIs & others	Human	4552	1,279,157	[27]
STRING	Known and Predicted Protein-Protein Interactions, http://string.embl.de/	BIND, BioGRID, DIP, HPRD, IntAct, MINT, & non PPI data	PPIs & others	All	9,643,763	932,.553897	[28,30]
UniHI	Unified Human Interactome, http://www.mdc-berlin.de/unihi/	BIND, BioGRID, DIP, HPRD, IntAct, MINT, & non PPI data	PPIs & others	Human	36,023	~374833	[31,32]

This paper is an attempt to review some of the important databases that dwell data on PPIs. Some of the important databases containing data about PPIs are discussed henceforth.

1. BIND (Bimolecular Interaction Network Database): Peer-reviewed BIND carrying published interactions and complexes encompasses high-throughput experimental datasets and protein complexes from PDB [7]. It contains diverse curated experimental data. A generalized data specification includes not only different types of protein interaction data, but also protein–small molecule interactions and protein-nucleic acid interactions [8]. An interaction viewer is provided to browse the interaction space. BIND also can distinguish several functional types of interactions [9]. Although BIND curation stopped in 2005, BIND still remains a highly cited publicly available interaction database.

2. **BioGRID (The biological general repository for interaction datasets):** (BioGRID) is a database that holds protein and genetic interactions from thirteen different species [10]. It is amongst the most detailed databases of experimentally derived protein-protein interactions. It has repeatedly been updated for the source of protein and genetic interactions from major model organisms and humans (http://www.thebiogrid.org [11]. Its latest update of May 2016 (BioGRID Version 3.4.137) carries non-redundant interactions to 1,066,335, raw interactions to 832,222 and interaction data is freely available for download in different standardized formats. This repository provides information about the experimental methods employed for interaction detection. But this database lacks information about multi-protein complexes larger than dimers and cites any interaction as pairwise interactions.

3. DIP (Database of Interacting Proteins): The DIP (http://dip. doe-mbi.ucla.edu/) database [12, 13] established by the University of California, Los Angeles has amalgamated data from different sources to generate a single, consistent set of PPI. It contains experimentally derived PPIs. Due to numerous experiments and their authenticity, DIP applies some quality assessment methods to choose subsets of most dependable interactions. Beyond sorting details of protein–protein interactions, the DIP is beneficial for understanding protein function and protein–protein relationships, analyzing the properties of networks of interacting proteins, benchmarking predictions of protein–protein interactions, and studying the development of protein–protein interactions The DIP is mainly examined as an important benchmark or confirms the performance of any new method for prediction of PPIs. In addition to the primary sources, DIP drives its data from many databases such as Yeast Protein Database (YPD), EcoCyc and FlyNet, Kyoto Encyclopaedia of Genes and Genomes (KEGG).

4. **HPRD (The Human Protein Reference Database):** HPRD was developed as a collaborative effort between Johns Hopkins University and the Institute of Bioinformatics, this resource provides a collection of human protein-protein interaction that also encompasses the information significant to the function of human proteins in health and disease [14]. Data are manually extracted from the literature, and each record is linked to a detailed piece of information along with the post-

translational modifications, disease associations via OMIM for each protein in the human proteome, sub cellular localizations, enzyme–substrate relationships, protein isoforms and domain architectures. This database currently contains more than 30,047 proteins and about 41,327 protein-protein interactions. Human Protein Reference Database is regularly updated and data can be downloaded from site (HPRD; http: //www. hprd.org/) [15, 16].

5 IntAct: IntAct developed at EMBL-EBI, is a free open-source database of molecular interactions that offers a suite of analysis tools. The interactions are derived from literature or from direct data depositions by expert curators furnish an open source database and toolkit for the storage, presentation, and analysis of protein interactions [17]. Its source code and data are directly available for download. Currently this resource encompasses more than 84570 proteins and more than 419709 binary interactions whose evidences have been abstracted from more than 5000 scientific publications. IntAct is an active partner of the IMEx consortium, and most of its protein-protein interaction data is annotated to IMEx standards. The search interface allows the user to iteratively develop complex queries, using the comprehensive annotation with hierarchically controlled vocabularies. This database is updated regularly and contains interaction information from different organisms that includes but specific to *Homo sapiens, Mus musculus, Drosophila melanogaster, Caenorhabditis elegans, Escherichia coli* and *Arabidopsis thaliana* [17]. In addition to protein-protein interaction data, IntAct also contains information on DNA, RNA, and small-molecule interactions.

6. MINT (The Molecular Interaction Database): MINT [18] is a public repository for molecular interactions designed by the University of Rome Tor Vergata. It mainly emphasizes on experimentally confirmed protein-protein interactions. The interaction data and different experimental details are extracted from peer-reviewed published literature by employing a literature-mining program, the MINT assistant, and then expert curators establish the putative interactions. Currently MINT carries more than 12, 5464 interactions and more than 25530 proteins and focused on the model organisms, this database furnishes confidence scores for experimentally detected PPIs, which depict the reliability of the interactions. The resultant score ranges between 0 to 1 (well supported evidence). This database contains interaction networks from *Homo sapiens*, *C. elegans*, bacteria, and 73 different Viruses. MINT is also an active partner of IMEx and shares curation efforts and supports the Protein Standard Initiative (PSI) recommendation. The database has expanded steadily over the years and till September 2011 contained approximately 235,000 binary interactions obtained from over 4750 publications [19] Starting from Sept 2013, MINT employs the IntACT database infrastructure to limit the duplication of efforts and to develop future software.

7. Munich MPact/MIPS database: MPact is a resource to analyze MIPS, carrying manually curated yeast protein interaction dataset [20] collected by curators from the literature. The resource

also includes high-throughput conclusions for yeast, but keeps this data separate. MIPS is generally used as a benchmark of truth database for evaluating the quality of data and the precision of interaction prediction methods.

8. **APID**: Agile Protein Interaction Data Analyzer: APID mines interactions from the six databases BIND, BioGRID, HPRD, DIP, IntAct, and MINT described above, mapping all proteins to UniProt identifiers [21]. Through a web interface, the user can access proteins of interest. APID references the database from which an interaction is obtained and provides the related information available in the original database, like the detection method and the publication identifier. Additionally, APID includes the biological information from different databases, such as the Gene Ontology and Pfam databases. APID is mostly in good agreement with the conclusions of the authors' data integration. APID appears to be a good source of interactome data. It also includes a graphic interactive tool to access selected sub-networks and to navigate on them or along the whole interaction network. The application is available open access at http://bioinfow.dep.usal.es/apid/.

9. MiMI (Michigan Molecular Interactions): Earlier referred to as the Michigan Protein Database (MIPD) allows us to visualize an extensive database of protein interactions, pathways and genes. The data in MiMIis derived from multiple external and internal data sources including DIP, BIND and NCIBI's NLP literature mining efforts. It assists to search through extensive information by including all information from participating data sources through the procedure of deep merging. Consequently, the redundant data are excluded and related data are combined. Furthermore, in doing so, MiMI keeps record of the 'provenance' of segregated information, or from where it was obtained. After receiving an enormous feedback, further progress was made in integrating information [24]. A completely evolved MiMI Release 2 (MiMIr2) was released. MiMI presently has over 3.7 million interactions, along with information about approximately 3.5 million genes, 19.2 million molecules and 1288 pathways [25].

10. The PIPs database: It is a resource for evaluating protein-protein interactions in human. It carries predictions of >37,000 high probability interactions of which >34,000 are unreported in the interaction databases HPRD, BIND, DIP or OPHID. The interactions in PIPs were computed by a Bayesian method that sums up information from expression, orthology, domain co-occurrence, post-translational modifications and sub-cellular location. The predictions also incorporate the topology of the predicted interaction network [26].

11. OPHID (The Online Predicted Human Interaction Database): OPHID) The Online Predicted Human Interaction Database (OPHID) is a web-based database of predicted interactions amongst human proteins. It combines the literature-derived human PPI from BIND, HPRD and MINT, with predictions made from *Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster* and *Mus musculus*. It was basically designed to enhance the human interactome

employing model organism data and to provide a repository for already known, experimentally derived human PPIs. The 619,398 predicted interactions presently listed in OPHID are accessed using protein domains, gene co-expression and Gene Ontology terms. OPHID can be probed using single or multiple IDs and results can be explained using the custom graph visualization program [27].

12. STRING (Search Tool for the Retrieval of Interacting Genes): STRING is an elaborate precomputed database that furnished both experimental and predicted interaction information. The interactions are derivatives of high-throughput experimental data, mining of databases and literature; evaluation of co-expressed genes and also use computational predictions, including those based on genomic context analysis. STRING uses a unique scoring framework based on benchmarks of the different types of associations against a common reference set, to provide a single confidence score per prediction [28]. The graphical user interface is impressive and user-friendly, assisted by an excellent visualization engine. Medusa http://coot.embl.de/ medusa/, a general graph visualization tool, is a front end (interface) to the STRING protein interaction database [29]. It is easily accessible and it is continuously updated. Version 6.0 of STRING is an important source of interactions for any given organism. It has been the source of interaction knowledge from orthologous proteins shown to be interacting in another organism. Since version 9.1, these 'interolog' transfers are based on pre-computed orthology relations imported from the eggNOG database. The latest version 10.0 [30] contains data on about 9.6 millions proteins from more than 2031 organisms ranging from Bacteria, Archaea to *Homo sapiens*.

13. UniHI (Unified Human Interactome): it is a database for retrieval, analysis and accessing of human molecular interaction networks. Its main aim is to furnish a detailed and user friendly platform for network-based assessments to the researchers in biology and medicine. UniHI is aimed at decreasing unnecessary duplication of data, while encompassing the strength of single databases regarding careful curation and annotation of PPIs. In its initial version, UniHI is based on the unification of the following 10 interaction datasets derived by computational and experimental methods, which includes: MDC-Y2H, CCSB, HPRD, DIP, BIND, COCIT, REACTOME, ORTHO, HOMOMINT and OPHID .These maps have been derived from manually curated databases, computational approaches using text-mining, predictions based on orthology, and from large Y2H screenings and includes over 150 000 interactions between more than 17 000 proteins [31]. Later on new updates UniHI 4 [28] and UniHI 7 were released. Its latest version UniHI 7 integrates ~350 000 molecular interactions for more than 30 000 human proteins. It is based on a complete re-implementation of earlier versions of UniHI, with widely extended scope and functionality. Besides protein–protein interactions from 12 different resources, UniHI7 [32] also includes curated transcriptional regulatory interactions from three complementary databases TRANSFAC,

miRTarBase and HTRIdb. Along with these interactions, drug target information from Drug Bank has also been integrated that can be mapped on the interaction network. A specific feature of UniHI 7 is it's easy to use interface designed to be employed in an instinctive manner, allowing researchers to perform network analysis.

2. CONCLUSION

Protein-protein interaction networks helps in understanding biological processes in living cells. There have been various supplementing efforts made to consolidate protein-protein interaction data through the creation of databases from experimental and computational protein-protein interactions networks. Other than the above mentioned databases, there are also some other specific databases for protein–protein interactions. The main focus of these is either on a single organism or integrate different other types of interactions. But in this paper, we have attempted to provide a summary of most widely used protein-protein interactions databases. These databases assist the researchers to collate the data in an organized manner and use it predict the protein function, identify important proteins in diseases and so on.

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4. CONFLICT OF INTEREST

None

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