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Protein Databases on the Internet

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Abstract

Protein databases have become a crucial part of modern biology. Huge amounts of data for protein structures, functions, and particularly sequences are being generated. Searching databases is often the first step in the study of a new protein. Comparison between proteins or between protein families provides information about the relationship between proteins within a genome or across different species, and hence offers much more information than can be obtained by studying only an isolated protein. In addition, secondary databases derived from experimental databases are also widely available. These databases reorganize and annotate the data or provide predictions. The use of multiple databases often helps researchers understand the structure and function of a protein. Although some protein databases are widely known, they are far from being fully utilized in the protein science community. This unit provides a starting point for readers to explore the potential of protein databases on the Internet.

Keywords

Bioinformatics; Biological Databases; Protein Analysis; Protein Modeling

INTRODUCTION

Protein databases have become a crucial part of modern biology. Huge amounts of data for protein structures, functions, and particularly sequences are being generated. These data cannot be handled without using computer databases. Searching databases is often the first step in the study of a new protein. Without the prior knowledge obtained from such searches, known information about the protein could be missed, or an experiment could be repeated unnecessarily. Comparison between proteins and protein classification provide information about the relationship between proteins within a genome or across different species, and hence offer much more information than can be obtained by studying only an isolated protein. In this sense, protein comparison through databases allows one to view life as a forest instead of individual trees. In addition, secondary databases derived from experimental databases are also widely available. These databases reorganize and annotate the data or provide predictions. The use of multiple databases often helps researchers understand evolution, structure, and function of a protein.

Protein databases are especially powered by the Internet. Unlike traditional media, such as the CD-ROM, the Internet allows databases to be easily maintained and frequently updated with minimum cost. Researchers with limited resources can afford to set up their own databases and disseminate their data quickly. Notably, many small databases on specific types of proteins, such as the EF-Hand Calcium-Binding Proteins Data Library (http://structbio.vanderbilt.edu/cabp_database/), are widely available. Users worldwide can

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easily access the most up-to-date version through a user-friendly interface. Most protein databases have interactive search engines so that users can specify their needs and obtain the related information interactively. Many protein databases also allow submitters to deposit data, and database servers can check the format of the data and provide immediate feedback.

Although some protein databases are widely known, they are far from being fully utilized in the protein science community. This unit provides a starting point for readers to explore the potential of protein databases on the Internet. Databases for different aspects of proteins are discussed with the focus on sequence, structure, and family. The strengths and weaknesses of the databases are addressed. For Web addresses of the databases discussed in this unit, see Internet Resources and Table 19.4.1. From hundreds of on-line protein databases, several major databases are discussed as examples to illustrate their features and how they can be used effectively. Most other protein databases can be explored in a similar way.

PROTEIN SEQUENCE DATABASES

Thanks to the Human Genome Project and other sequencing efforts, new sequences have been generated at a prodigious rate. These sequences provide a rich information source and are the core of the revolutionary movement toward “large-scale biology.” The protein sequences can be computationally annotated from these genomic sequences. Various databases contain protein sequences with different focuses. Among all protein sequence databases, UniProt (UniProt Consortium, 2011) is the most widely used one. It provides more annotations than any other sequence database with a minimal level of redundancy through human input or integration with other databases. UniProtKB has three components: (1) Protein knowledgebase, including Swiss-Prot (manually annotated and reviewed) and TrEMBL (automatically annotated) (Bairoch and Apweiler, 1999); (2) UniRef (sequence clusters for fast sequence similarity searches); and (3) UniParc (sequence archive for keeping track of sequences and their identifiers). In addition to Swiss-Prot and TrEMBL, UniProtKB includes information from Protein Sequence Database (PSD) in the Protein Identification Resource (PIR; Barker et al., 1999), which builds a complete and non-redundant database from a number of protein and nucleic acid sequence databases together with bibliographic and annotated information. The National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov) also provides rich information and a number of useful tools for protein sequences. For example, the nr protein database is used for BLAST search (Altschul et al., 1997), which is described in *UNIT 2.5* of this book. It includes entries from the non-redundant GenBank (Benson et al., 1999) translations, UniProt, PIR, Protein Research Foundation (PRF) in Japan, and the Protein Data Bank (PDB). Only entries with absolutely identical sequences are merged.

Most of the sequence databases have a sequence search tool and cross-references to entries of other protein and gene databases. Many sequence databases, such as UniProt, also provide text searching using, for instance, protein names or key words. To study a new protein, the author recommends first performing a sequence search using BLAST in nr if the protein sequence is available. The search often gives entry names in the protein databases included in nr. Even when the protein is not found in nr, it is likely that a homologous protein will be hit, which can often lead to some useful information, such as the function of the query protein. If the sequence of the query protein is unavailable, doing a text search in UniProt usually identifies the protein. UniProt is probably the place to obtain the most information about a protein if it can be found in UniProt. However, some additional information may be found by checking other sequence databases. For example, the Kyoto Encyclopedia of Genes and Genomes (KEGG; Ogata et al., 1999) annotates some gene entries with information about metabolic and regulatory pathways. One can also study proteins based on gene models (predicted protein sequences) from many species-specific genome resources, such as Mouse Genome Database (MGD, http://www.informatics.jax.org), FlyBase (a resource for *Drosophila* genes, http://flybase.org), WormBase (a resource for *C. elegans*, http://www.wormbase.org), *Saccharomyces* Genome Database (SGD, http://www.yeastgenome.org), *Arabidopsis* Information Resource (TAIR, http://www.arabidopsis.org), and Soybean Knowledge Base (SoyKB, http://soykb.org). Although predicted sequences generated by computational gene-finding tools in these resources may contain errors, a large number of proteins are covered and are often reliable enough to provide useful information. When the protein of interest is from a species that is not covered by any of these databases, it is likely that some information can be retrieved from its homolog of a model organism in one of the databases.

UniProt, as a curated protein sequence database, offers a portal to a wide range of annotations, covering areas such as function, family, domain parsing, post-translational modifications, and variants. UniProt can be accessed at http://www.uniprot.org.

Human vitronectin is used here as an example for searching protein sequence databases. To locate the UniProt entry for this protein, one can search either the entry name (VTNC_HUMAN) or the accession number (P04004) obtained from a BLAST search. Alternatively, one can use the full-text search at the UniProt Web page to search by protein name (human vitronectin) or key words (e.g., serum spreading, as vitronectin is also called serum spreading factor s-protein). A combination of several entries can be used in a search.

The entry name in UniProt has the general format X_Y, where X is a mnemonic code of up to four characters indicating the protein name (in this case, VTNC), and Y is a mnemonic species identification code of up to five characters for the biological source of the protein. Some codes used for Y are full English names, e.g., HORSE, HUMAN, MAIZE, MOUSE, PIG, RAT, SHEEP, YEAST (baker’s yeast, *Saccharomyces cerevisiae*), and WHEAT. Some are abbreviations, including BOVIN (bovine), CHICK (chicken), ECOLI (*Escherichia coli*), PEA (garden pea, *Pisum sativum*), RABIT (rabbit), SOYBN (soybean, *Glycine max*), and TOBAC (common tobacco, *Nicotina tabacum*).

An entry name may have several accession numbers if they have been merged. An accession number is always conserved from release to release and, therefore, allows unambiguous citation.

Each entry contains the following items shown in table format in the NiceProt View layout: (1) name and origin, (2) protein attributes, (3) general annotation (comments), (4) ontologies (gene functions), (5) binary protein-protein interactions, (6) sequence annotation (features), (7) sequence, (8) references (literature citation), (9) web resources, (10) cross-references (links to other databases), (11) entry information, and (12) relevant documents. The text in the general annotation entry provides a function annotation for the protein (e.g., “Vitronectin is a cell adhesion and spreading factor found in serum and tissues. Vitronectins interact with glycosaminoglycans and proteoglycans…”). The “Cross-references” entry lists the annotations of the protein by other databases, such as GeneCards (Rebhan et al., 1998) and InterPro (Apweiler et al., 2001). GeneCards, a database of human genes, shows chromosomal location and the involvement of the protein in certain diseases (if applicable). InterPro contains predictive protein “signatures”, such as functional domains, repeats and important sites. Clicking the link to InterPro from UniProt leads to a nice graphic view for domain parsing, as shown in Figure 19.4.1 for vitronectin.

Various research results are given under sequence annotation (features). Some of the sample features items for VTNC_HUMAN are as follows:

Feature key	Position (s)	Length	Description
Signal peptide	1–19	19	Ref.8 Ref.9
Chain	20–398	379	Vitronentin V65 subunit
Peptide	20–63	44	Somatomedin-B (Ref. 8)
Domain	161–204	44	Hemopexin-like 1
Motif	64–66	3	Cell attachment site
Site	398–399	2	Cleavage.
Modified residue	75	1	Sulfotyrosine (Ref. 22)
Glycosylation	86	1	N-linked (GlcNAc…)
Disulfide bond	24 ← → 40		Alternative (by similarity)
Natural variant	122	1	A→S.[dbSNP:rs2227741]
Sequence conflict	50	50	C → N AA sequence

Here, “peptide” represents an active peptide in the mature protein, “modified residue” indicates a post-translationally modified residue, and “sequence conflict” shows that different papers report differing sequences.

PROTEIN STRUCTURAL DATABASES

Searching structure databases is becoming more and more popular in molecular biology. The three-dimensional structures of proteins not only define their biological functions, but also hold a key in rational drug design. Traditionally, protein structures were solved at a low-throughput mode. However, advances in new technologies, such as synchrotron radiation sources and high-resolution nuclear magnetic resonance (NMR), accelerate the rate of protein structure determination substantially. The only international repository for the processing and distribution of protein structures is the PDB (Bernstein et al., 1977). The structures in the PDB were determined experimentally by X-ray crystallography, NMR, electron microscopy, etc. Theoretical models have been removed from PDB, effective July 2, 2002, based on the new PDB policy. The PDB also contains some structures of chemical ligands and nucleotides. Each PDB entry is represented by a four-character identifier (PDB ID), where the first character is always a number from 0 to 9 (e.g., 1cau, 256b). The PDB can be accessed at http://www.rcsb.org/pdb/or http://www.pdb.org.

The PDB offers a broad range of search methods, from PDB ID and keywords to structural features and binding ligands. The PDB stores structural information in two formats: the PDB file format (Bernstein et al., 1977) and the macromolecular crystallographic information file (mmCIF) format (Bourne et al., 1997). The PDB file format is still the dominant format used in the protein community. It contains three parts: annotations, coordinates, and connectivities. The connectivity part, which shows chemical connectivities between atoms, is optional. It is listed at the end of the PDB file, beginning the line with the key word CONECT. The coordinate part uses each line for a three-dimensional coordinate of an atom, starting from ATOM (for standard amino acids) or HETATM (for nonstandard groups). The following shows an example of the PDB file format:

```
HEADER   OXIDOREDUCTASE               (OXYGEN(A))   14-JUN-89        1GOX   1GOX   3
COMPND   GLYCOLATE   OXIDASE          (E.C.1.1.3.1)                         1GOX   4
```

```
…
ATOM     232    N     ALA    29    54.035   4.332    19.352      1.00   23.93    1GOX   374
ATOM     233    CA    ALA    29    52.992   65.356   19.569      1.00   24.74    1GOX   375
ATOM     234    C     ALA    29    53.519   66.762   19.309      1.00   25.43    1GOX   376
ATOM     235    O     ALA    29    54.648   67.179   19.655      1.00   25.66    1GOX   377
ATOM     236    C     BALA   29    52.433   65.340   20.993      1.00   24.54    1GOX   378
…
HETATM   3165   O     HOH    658   62.480   62.480   0.000       0.50   65.79N   1GOX   3170
CONECT   2837   2838  2854                                                        1GOX   3171
```

Each line shows the atom serial number, atom type, residue type, chain identifier (in case of multi-chain structure), residue serial number, orthogonal coordinates (three values), occupancy, temperature factor, and segment identifier.

The annotation part of the PDB file format contains dozens of possible record types, including: HEADER (name of protein and release date), COMPND (molecular contents of the entry), SOURCE (biological source), AUTHOR (list of contributors), SSBOND (disulfide bonds), SLTBRG (salt bridges), SITE (groups comprising important sites), HET (nonstandard groups or residues [heterogens]), MODRES (modifications to standard residues), SEQRES (primary sequence of backbone residues), HELIX (helical substructures), SHEET (sheet substructures), and REMARK (other information and comments).

The PDB allows a user to view a molecule structure interactively through Jmol (Hanson, 2010), PDB SimpleViewer, PDB ProteinWorkshop, and RCSB-Kiosk, when the browser is configured to support these free rendering tools. The PDB provides related information about the protein, such as secondary structure assignment and geometry. Each PDB entry also links to a wide range of annotations from secondary databases, including (1) summary and display databases such as Structural Biology Knowledgebase (SBKB, http://sbkb.org), PISA (Protein Interfaces, Surfaces and Assemblies; Krissinel and Henrick, 2007), Molecular Modelling Database (MMDB; Marchler-Bauer et al., 1999) in Entrez, PDBsum (Laskowski et al., 1997), Jena Library of Biological Macromolecules (JenaLib, http://www.fli-leibniz.de/IMAGE.html), PDBWiki (a community annotated knowledge base of biological molecular structures, http://pdbwiki.org), and Proteopedia (a collaborative 3D-encyclopedia of proteins and other molecules; Prilusky et al., 2011); (2) domain annotation from SCOP (Murzin et al., 1995), CATH (Orengo et al., 1997), and Pfam (Finn et al., 2010); (3) structure comparison to other proteins using various methods; (4) the MEDLINE bibliography; (5) protein movements recorded in Database of Macromolecular Movement (MolMovDB; Gerstein and Krebs, 1998); and (6) geometry analyses of the protein, such as CSU Contacts of Structural Units (Sobolev et al., 1999) and castP Identification of Protein Pockets & Cavities (Liang et al., 1998).

In addition to PDB and its linking databases, other structure-related databases can also provide useful information. For example, pdbLight (http://mufold.org/pdblight.php) integrates protein sequence and structure data from multiple sources for protein structure prediction and analysis, together with predicted SCOP classification for the weekly updated PDB structures. BioMagResBank (BMRB; University of Wisconsin, 1999) is a repository for NMR spectroscopy data on proteins, peptides, and nucleic acids. Particularly, it provides partial NMR data (e.g., chemical shifts) before the full structure is solved. Protein Model

Portal (PMP; Arnold et al., 2009) provides predicted structural models and their quality assessments for a large number of proteins.

PROTEIN FAMILY DATABASES

Introduction

Proteins can be classified according to their sequence, evolutionary, structural, or functional relationships. A protein in the context of its family is much more informative than the single protein itself. For example, residues conserved across the family often indicate special functional roles. Two proteins classified in the same functional family may suggest that they share similar structures, even when their sequences do not have significant similarity.

There is no unique way to classify proteins into families. Boundaries between different families may be subjective. The choice of classification system depends in part on the problem; in general, the author suggests looking into classification systems from different databases and comparing them. Three types of classification methods are widely adopted based upon the similarity of sequence, structure, or function. Sequence-based methods are applicable to any proteins whose sequences are known, while structure-based methods are limited to the proteins of known structures, and function-based methods depend on the functions of proteins being annotated. Sequence- and structure-based classifications can be automated and are scalable to high-throughput data, whereas function-based classification is typically carried out manually. Structure- and function-based methods are more reliable, while sequence-based methods may result in a false positive result when sequence similarity is weak (i.e., two proteins are classified into one family by chance rather than by any biological significance). In addition, since protein structure and function are better conserved than sequence, two proteins having similar structures or similar functions may not be identified through sequence-based methods.

Databases for Sequence-Based Protein Families

Sequence-based protein families are classified according to a profile derived from a multiple-sequence alignment. The profile can be shown across a long domain (tens of residues or more) or can be revealed in short sequence motifs. Classification methods based on profiles across long domains tend to be more reliable but less sensitive than those based on short sequence motifs.

Several sequence-based methods focus more on profiles across long domains, including Pfam (Finn et al., 2010), ProDom (Corpet et al., 1999), and Clusters of Orthologous Group (COG; Tatusov et al., 1997). These methods differ in the techniques used to construct families. Pfam builds multiple-sequence alignments of many common protein domains using hidden Markov models. The ProDom protein domain database consists of homologous domains based on recursive PSI-BLAST searches (*UNIT 2.5*). COG aims toward finding ancient conserved domains by delineating families of orthologs across a wide phylogenetic range. SMART (Simple Modular Architecture Research Tool; Letunic et al., 2009) collects domain families, which are annotated with respect to phyletic distributions, functional class, three-dimensional structures and functionally important residues. It can be used for identification and annotation of genetically mobile domains and analysis of domain architectures. The iProClass database (Wu et al., 2004) combines multiple sources of information for protein classification. One can use all these databases for a comprehensive analysis or choose one of them based on the purpose of the study. Various sequence-based protein families have different focuses. For example, Pfam focuses on function, ProDom on sequence domain, and COG on evolution.

The following shows an example of Pfam for the GRIP domain (accession number PF01465). Pfam lists some useful functional information for the entry as follows:

> "The GRIP (golgin-97, RanBp2alpha, Imh1p and p230/golgin-245) domain is found in many large coiled-coil proteins. It has been shown to be sufficient for targeting to the Golgi. The GRIP domain contains a completely conserved tyrosine residue. At least some of these domains have been shown to bind to GTPase Arl1, see structures in [4,5]."

In addition, Pfam gives the alignment among the family members.

One can identify some features of the family through this pattern (i.e., from particularly conserved residues at specific alignment positions).

Some methods are based on "fingerprints" of small conserved motifs in sequences, as with PROSITE (Hofmann et al., 1999), PRINTS (Attwood et al., 1999), and BLOCKS (Heniko et al., 1999). In protein sequence families, some regions have been better conserved than others during evolution. These regions are generally important for the function of a protein or for the maintenance of its three-dimensional structure or function. The fingerprints may be used to assign a newly sequenced protein to a specific family. Fingerprints are derived from gapped alignments in PROSITE and PRINTS, but are derived from ungapped alignments (corresponding to the highly conserved regions in proteins) in BLOCKS. A fingerprint in PRINTS may contain several motifs from PROSITE, and thus may be more flexible and powerful than a single PROSITE motif. Therefore, PRINTS can provide a useful adjunct to PROSITE. It should be noted that some functionally unrelated proteins may be classified together due to chance matches in short motifs.

Databases for Structure-Based Protein Families

The hierarchical relationship among proteins can be clearly revealed in structures through structure-structure comparison. Structure families often provide more information on the relationship between proteins than what sequence families can offer, particularly when two proteins share a similar structure but no significant sequence identity. Figure 19.4.2 shows an example of a structure-structure alignment between two proteins. Sometimes, sequence similarity between two proteins exists but is not strong enough to produce an unambiguous alignment. In this case, the alignment between two structures can generate better alignment in terms of biological significance, and thus may pinpoint the evolutionary relationship and active sites more accurately.

Different structure-structure comparison methods yield different structure families. CATH (Class, Architecture, Topology and Homologous superfamily; Orengo et al., 1997) is a hierarchical classification of protein domain structures. CE (Combinatorial Extension of the optimal path; Shindyalov and Bourne, 1998) provides structural neighbors of the PDB entries with structure-structure alignments and three-dimensional superposition. FSSP (Fold classification based on Structure-Structure alignment of Proteins; Holm and Sander, 1996) features a protein family tree and a domain dictionary, in addition to whole-chain-based classification, sequence neighbors, and multiple structure alignments. SCOP (Structural Classification of Proteins; Murzin et al., 1995) uses augmented manual classification, class, fold, superfamily, and family classification. VAST (Vector Alignment Search Tool; Gibrat et al., 1996) contains representative structure alignments and three-dimensional superposition. Among these five databases, SCOP provides more function-related information. However, due to the manual work involved, SCOP is not updated as frequently as the others (as of September 2011, it was last updated for the PDB release on June, 2009), whereas FSSP and CATH follow the PDB updates closely.

SCOP is used here as an example to show the features of structure-based families. SCOP can be accessed through its home server in the UK (http://scop.mrc-lmb.cam.ac.uk/scop/). SCOP describes the hierarchical relationship among proteins through the major levels of (homologous) family, superfamily, and fold. Proteins are clustered together into a (homologous) family if they have significant sequence similarity. Different families that have low sequence similarity but whose structural and functional features suggest a common evolutionary origin are placed together in a superfamily. Different superfamilies are categorized into a fold if they have the same major secondary structures in the same arrangement and with the same topological connections (the peripheral elements of secondary structure and turn regions may differ in size and conformation). Two superfamilies in the same fold may not have a common evolutionary origin. Their structural similarities may arise from the physics and chemistry of proteins favoring certain packing arrangements and chain topologies (Murzin et al., 1995). Figure 19.4.3 shows the SCOP interface using an example of protein 1gox in the PDB.

Databases for Function-Based Protein Families

There are various protein functional families classified from different perspectives. The ENZYME data bank (Bairoch, 1993) contains the following data for each enzyme: EC number, recommended name, alternative names, catalytic activity, cofactors, pointers to the UniProt entry, and pointers to any disease associated with a deficiency of the enzyme. BRENDA (Scheer et al., 2011) collects extensive enzyme functional data. Catalytic Site Atlas (Porter et al., 2004) is a database of three-dimensional enzyme active sites derived from PDB structures. Various gene ontologies, such as Gene Ontology (GO; The Gene Ontology Consortium, 2000) and KEGG, also organize proteins into functional categories. Annotation and analysis by these ontologies for a given list of genes can be carried out using tools and databases such as DAVID (Database for Annotation, Visualization and Integrated Discovery; Huang et al., 2009). In addition, there are a growing number of databases dedicated to special types of proteins, such as G-protein-coupled receptors, transporters, and protein kinases, as shown in Table 19.4.1.

OTHER DATABASES

Protein Modification Databases

There are a number of databases for protein post-translational modifications. O-GlycBase (Gupta et al., 1999) collected, experimentally verified O- or C-glycosylation sites. Plant Protein Phosphorylation Database (P3DB; Gao et al., 2009) condenses phosphoproteomics information (including experimental phosphorylation sites) from various plants. Compendium of protein lysine acetylation (CPLA; Liu et al., 2010) includes manually curated lysine acetylated substrates with their sites.

Protein Localization Databases

A number of databases are available to describe protein subcellular localization and targeting. These databases are for various species, such as eSLDB (eukaryotic Subcellular Localization database) for general eukaryotes (Pierleoni et al., 2007), LOCATE for human and minor (Sprenger et al., 2008), SUBA for Arabidopsis (Heazlewood et al., 2007), and PSORTdb for bacteria and archaea (Yu et al., 2011). Some databases focus on special organelles, such as Organelle DB (Wiwatwattana and Kumar, 2005) and Centrosome:db (Nogales-Cadenas et al., 2009).

Protein Binding Databases

Protein binding includes protein-substrate docking and protein-protein association. ReLiBase (Hendlich, 1998) is a database system for analyzing receptor-ligand complexes in the PDB. BindingDB (Liu et al., 2007) describe many interactions between drug-target proteins and small, drug-like molecules. As protein-protein interactions are measured in large scales, there are many protein interaction databases. An early one is Database of Interacting Proteins (DIP; Xenarios et al., 2000). Some later databases are more comprehensive. For example, Biological General Repository for Interaction Datasets (BioGRID; Stark et al., 2011) includes protein–protein and genetic interactions for all major model organism species; STRING (Search Tool for the Retrieval of Interacting Genes/Proteins; Jensen et al., 2009) covers known and predicted protein interactions for many species, as well as direct (physical) and indirect (functional) associations. Furthermore, some protein interaction databases are based on protein structures, such as 3D Complex (Levy et al., 2006), DOMMINO (http://dommino.org), etc.

Protein Energetics Databases

There are few databases for protein energetics, due to the low-throughput nature of the data source. One useful energetics database can be found in ProTherm (Thermodynamic Database for Proteins and Mutants; Gromiha et al., 1999). It contains thermodynamic data on mutations, including Gibbs free energy, enthalpy, heat capacity, and transition temperature. Another database is 3D-footprint (Contreras-Moreira, 2010), which provides estimates of binding specificity for protein-DNA complexes in PDB.

Bibliographic Databases

Searching for protein information through traditional bibliographic databases, such as MEDLINE or Grateful Med, can be rewarding. In addition, some bibliographic reference databases dedicated to proteins may provide certain information more directly. For example, iProLINK (integrated Protein Literature, INformation and Knowledge; Hu et al., 2004) provides literature information on proteins and their features or properties.

Combined Databases

By integrating different types of protein databases together, a database of databases (or a data warehouse) can be built. Such combined databases not only serve as a “one-stop shop,” but also provide cross-references between entries in different databases. One example of such databases is SRS (Sequence Retrieval System; Etzold et al., 1996), which is a comprehensive database for molecular biology. The home server at http://srs.ebi.ac.uk supports many biological databases, including almost all the major protein/genetic databases. As an indexing system, it provides fast access to different databases through searches by sequence or by key words from various data fields. SRS also builds indices using cross-references between databases. An entry from one database can be linked to other databases that contain the entry. However, it should be noted that the contents of SRS might lag behind the other databases in updating (i.e., some new entries in the original databases may not be included in SRS).

SUMMARY

This unit reviews some of major protein databases on the Internet and shows what kind of information users can expect from protein databases. Although all technical procedures cannot be described here, most of the protein databases are easy to use and provide detailed on-line manuals so that even users with little computer skill can learn them quickly. Readers are encouraged to study additional protein databases that are not covered in this unit. For example, the portals listed in “INTERNET RESOURCES” give links to many other protein databases. Furthermore, the journal “Nucleic Acids Research” has a Database issue every year, which describes many high-quality, well-maintained protein databases.

Protein databases may not always be easily accessible or usable through the Internet. Sometimes a database server may be down or the Internet connection may be interrupted. For a frequent user, it may be worthwhile to install the database on a local machine. On the other hand, it must be kept in mind that a mirror site or a local copy may contain an older version of the database than the one on the home server.

It is important to assess the quality of the data. There are three types of data in protein databases. (1) Experimental data are generally very reliable. However, some entries may contain errors (e.g., some protein sequences) or may be based on low-resolution data (e.g., some protein structures determined by NMR). (2) Annotation data uses computational techniques on experimental data, for example, secondary structure assignment and domain partition in structure. These data depend on the quality of the experimental data and the computational methods used. Different methods may yield different results. (3) Prediction data includes, for example, sequence domain parsing and three-dimensional structure prediction. No matter how good the method, the results are still predictions and should be subjected to experimental verification. In addition, different methods typically give different predictions.

While protein databases on the Internet become indispensable resources for studying proteins, caution is needed when using the data from databases to draw a conclusion. The qualities of databases vary significantly. Some databases are not well maintained and contain obsolete information. It is not rare to see some protein databases disappear after a few years. In addition, the data in some databases are not carefully validated and may not be reliable. It is worthwhile to check the same type of data from different databases and compare them. It is sometimes necessary to use additional computational tools (e.g., tools to assess the quality of a structure) for further analysis.

INTERNET RESOURCES

The Web addresses of the databases mentioned in this unit are listed in Table 19.4.1. Readers can find more protein databases and related bioinformatics tools in the following Web pages, which collect a large number of useful links:

- http://bioinformatics.ca/links_directory/ (Bioinformatics Links Directory)
- http://www.biophys.uni-duesseldorf.de/BioNet/Pedro/research_tools.html *(Pedro’s biomolecular research tools)*
- http://www.expasy.org (SIB Bioinformatics Resource Portal)
- http://www.123genomics.com (Genomics, Proteomics and Bioinformatics Knowledge Base)
- http://bioinformatics.ws/index.php/Bioinformatics_tools_and_algorithms (Bioinformatics tools and algorithms)

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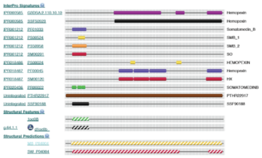


InterPro Signatures

IPR000585	G3DSA:2.110.10.10	Hemopexin
IPR000585	SSF50923	Hemopexin
IPR001212	PF01033	Somatomedin_B
IPR001212	PS00524	SMB_1
IPR001212	PS50958	SMB_2
IPR001212	SM00201	SO
IPR018486	PS00024	HEMOPEXIN
IPR018487	PF00045	Hemopexin
IPR018487	SM00120	HX
IPR020436	PR00022	SOMATOMEDINB
Unintegrated	PTHR22917	PTHR22917
Unintegrated	SSF90188	SSF90188

Structural Features

	1oc0B
g.64.1.1	d1oc0b_

Structural Predictions

MB_P04004

SW_P04004

Figure 19.4.1.

Annotation of human vitronectin by InterPro.

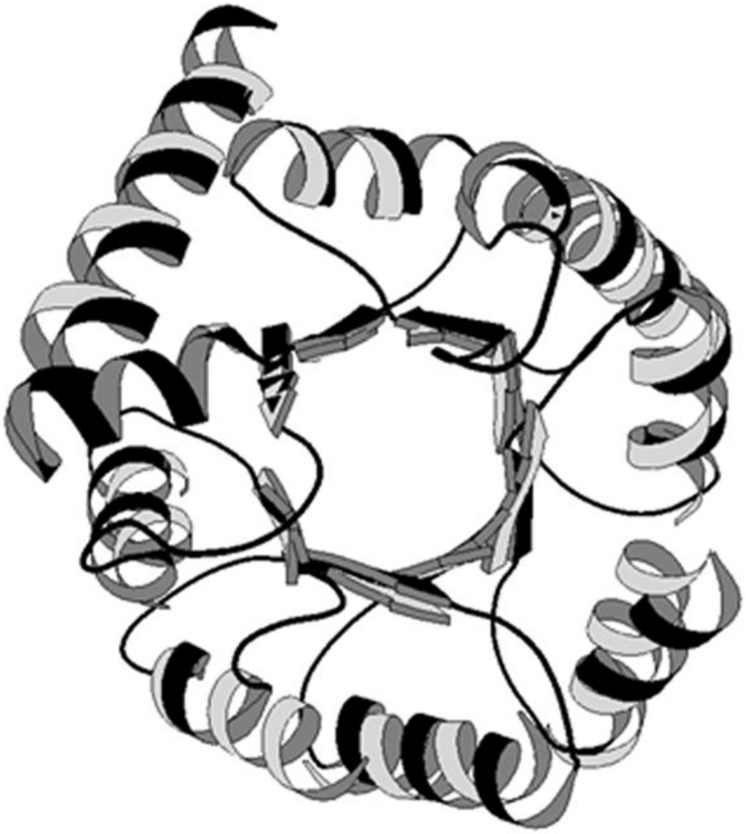
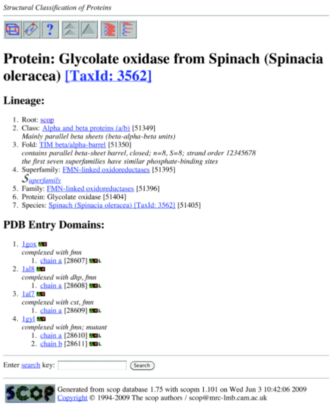


Figure 19.4.2.
Structure superposition between glycolate oxidase(1gox, in black) and inosine monophosphate dehydrogenase (1ak5, in gray). This figure was made using MOLSCRIPT (Kraulis, 1991).



Structural Classification of Proteins

Protein: Glycolate oxidase from Spinach (Spinacia oleracea) [TaxId: 3562]

Lineage:

1. Root: scop
2. Class: Alpha and beta proteins (a/b) [51349]
   Mainly parallel beta sheets (beta-alpha-beta units)
3. Fold: TIM beta/alpha-barrel [51350]
   contains parallel beta-sheet barrel, closed; n=8, S=8; strand order 12345678
   the first seven superfamilies have similar phosphate-binding sites
4. Superfamily: FMN-linked oxidoreductases [51395]
   Superfamily
5. Family: FMN-linked oxidoreductases [51396]
6. Protein: Glycolate oxidase [51404]
7. Species: Spinach (Spinacia oleracea) [TaxId: 3562] [51405]

PDB Entry Domains:

1. 1gox
   complexed with fmn
   1. chain a [28607]
2. 1al8
   complexed with dhp, fmn
   1. chain a [28608]
3. 1al7
   complexed with cst, fmn
   1. chain a [28609]
4. 1gyl
   complexed with fmn; mutant
   1. chain a [28610]
   2. chain b [28611]

Enter search key: [ ] Search

Generated from scop database 1.75 with scopm 1.101 on Wed Jun 3 10:42:06 2009
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Figure 19.4.3.

An example of the SCOP interface when searching the structure of 1gox in the PDB.

Table 19.4.1

Web Addresses and Sizes of Selected Protein Databases

Database	Web site	Size[a]
Sequence:		
DDBJ	http://www.ddbj.nig.ac.jp	138,030,308 entries
GeneCards	http://bioinfo.weizmann.ac.il/cards/	67,217 genes
InterPro	http://www.ebi.ac.uk/interpro/	14,633 families
NCBI	http://www.ncbi.nlm.nih.gov	NA
nr	http://www.ncbi.nlm.nih.gov/BLAST/	NA
OWL	http://www.bioinf.man.ac.uk/dbbrowser/OWL	279,796 entries
PIR	http://pir.georgetown.edu	NA
PRF	http://www.genome.ad.jp/htbin/www_bfind?prf	1,365,912 entries
UniProt	http://www.uniprot.org	531,473 proteins
SYSTERS	http://systers.molgen.mpg.de	NA
Structure:		
3Dee	http://www.compbio.dundee.ac.uk/3Dee/	NA
ArchDB	http://sbi.imim.es/cgi-bin/archdb//loops.pl	41,294 classified loops
ASTRAL	http://astral.berkeley.edu	NA
BioMagResBank	http://www.bmrb.wisc.edu	6339 entries
CDDB	http://www.cdyn.org	NA
EMDataBank	http://EMDataBank.org	1138 EMDB maps
Enzyme Structures	http://www.biochem.ucl.ac.uk/bsm/enzymes/	10,208 structures
fPOP	http://pocket.uchicago.edu/fpop/	>40,000 structures
JenaLib	http://www.imb-jena.de/IMAGE.html	NA
PMP	http://www.proteinmodelportal.org	3,754,388 proteins
Proteopedia	http://proteopedia.org	>75,000 entries
MolMovDB	http://bioinfo.mbb.yale.edu/MolMovDB/	NA
PDB	http://www.pdb.org	75,594 structures
PDBLight	http://mufold.org/pdblight.php	72,023 structures
PDBsum	http://www.ebi.ac.uk/pdbsum/	78,559 structures
PDBTM	http://pdbtm.enzim.hu	1489 transmembrane structures
PDBWiki	http://pdbwiki.org	74,296 structures
PISA	http://pdbe.org/pisa	NA
PMP	http://www.proteinmodelportal.org	3,754,388 proteins
SBKB	http://sbkb.org	5490 structures
TOPSAN	http://www.topsan.org	NA
Sequence family:		
COG	http://www.ncbi.nlm.nih.gov/COG/	66 genomes
Pfam	http://pfam.sanger.ac.uk	12,273 families
PRINTS	http://www.bioinf.man.ac.uk/dbbrowser/PRINTS/	12,121 sites
iProClass	http://pir.georgetown.edu/iproclass/	18,492,417 entries
ProDom	http://prodom.prabi.fr/prodom/current/html/home.php	2,001,128 sequences

Database	Web site	Size[a]
PROSITE	http://prosite.expasy.org	1620 entries
SMART	http://smart.embl-heidelberg.de	> 500 domain families
Structure family:		
AutoPSI	http://services.bio.ifi.lmu.de:1046/AutoPSIDB/	NA
CATH	http://www.cathdb.info	152,920 domains
CDD	http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml	NA
CE	http://cl.sdsc.edu/ce.html	NA
CL	http://cl.sdsc.edu/cl1.html	NA
FSSP	http://srs.ebi.ac.uk/srsbin/cgi-bin/wgetz?-page+LibInfo+-id+5Ti2u1RffMj+-lib+FSSP	2860 folds
HOMSTRAD	http://tardis.nibio.go.jp/homstrad/	1032 families
MODBASE	http://modbase.compbio.ucsf.edu	3,497,441 proteins
PartsList	http://bioinfo.mbb.yale.edu/align/	NA
PDBe	http://www.ebi.ac.uk/pdbe/	75,694 entries
SCOP	http://scop.mrc-lmb.cam.ac.uk/scop/	110,800 domains
VAST	http://www.ncbi.nlm.nih.gov/Structure/	NA
Function family:		
AARSDB	http://www.man.poznan.pl/aars/	NA
ASD	http://mdl.shsmu.edu.cn/ASD/	336 allosteric proteins
ASPD	http://wwwmgs.bionet.nsc.ru/mgs/gnw/aspd/	NA
BRENDA	http://www.brenda-enzymes.org	5373 enzymes
Catalytic Site Atlas	http://www.ebi.ac.uk/thornton-srv/databases/CSA/	26,846 entries
DAVID	http://david.abcc.ncifcrf.gov	NA
EF-hand CaBP	http://structbio.vanderbilt.edu/cabp_database/	NA
EcoCyc	http://ecocyc.org	NA
ENZYME	http://enzyme.expasy.org	4579 entries
Gene Ontology (GO)	http://geneontology.org	NA
GPCRDB	http://www.gpcr.org/7tm/	42,110 proteins
Homeobox Page	http://www.biosci.ki.se/groups/tbu/homeo.html	NA
KEGG	http://www.genome.ad.jp/kegg/	NA
Laminin Database	http://www.lm.lncc.br	NA
MatrixDB	http://matrixdb.ibcp.fr	NA
MEROPS (peptidase)	http://merops.sanger.ac.uk	NA
MetaCyc	http://metacyc.org	1747 pathways
P2CS	http://www.p2cs.org	81,988 proteins
PREX	http://www.csb.wfu.edu/prex/	NA
Protein Kinase Resource (PKR)	http://pkr.genomics.purdue.edu	NA
Protein Ontology	http://pir.georgetown.edu/pro/	NA
RNase P	http://www.mbio.ncsu.edu/RNaseP/home.html	NA
SuperCYP	http://bioinformatics.charite.de/supercyp/	2,785 Cytochrome-Drug interactions
TransportDB	http://www.membranetransport.org	365 species
Wnt gene Homepage	http://www.stanford.edu/group/nusselab/cgi-bin/wnt/	NA

Database	Web site	Size[a]
Modifications:		
CPLA	http://cpla.biocuckoo.org	7,151 lysine acetylation sites
O-GlycBase	http://www.cbs.dtu.dk/databases/OGLYCBASE/	2413 O-glycosylation sites
P3DB	http://p3db.org	31,019 phosphosites
Phospho3D	http://www.phospho3d.org	NA
Phospho.ELM	http://phospho.elm.eu.org	>42,500 phosphosites
PHOSIDA	http://www.phosida.com	80,062 sites
Localization:		
Centrosome:db	http://centrosome.dacya.ucm.es	NA
eSLDB	http://gpcr.biocomp.unibo.it/esldb	NA
LOCATE	http://locate.imb.uq.edu.au	>100,000 proteins
MiCroKit	http://microkit.biocuckoo.org	1,489 proteins
NPD	http://npd.hgu.mrc.ac.uk	>1000 proteins
NURSA	http://www.nursa.org	NA
Organelle DB	http://organelledb.lsi.umich.edu	50 organelles
ORGe	http://drake.mcmaster.ca/ogre/	1244 metazoan organisms
PSORTdb	http://db.psort.org	NA
SUBA	http://suba.plantenergy.uwa.edu.au	14,258 entries
PeroxisomeDB	http://www.peroxisomedb.org	2819 proteins
Binding and Interaction:		
3D Complex	http://supfam.mrc-lmb.cam.ac.uk/elevy/3dcomplex/Home.cgi	>30,000 structures
3DID	http://3did.irbbarcelona.org	174,006 proteins
BindingDB	http://www.bindingdb.org	781,982 binding data
BioGRID	http://thebiogrid.org	409,299 interactions
BISC	http://bisc.cse.ucsc.edu	NA
DIMA	http://webclu.bio.wzw.tum.de/dima/	NA
DIP	http://dip.doe-mbi.ucla.edu	71,276 interactions
DOMINE	http://domine.utdallas.edu	26,219 domain-domain interactions
DOMMINO	http://dommino.org	55,650 interactions
IBIS	http://www.ncbi.nlm.nih.gov/Structure/ibis/ibis.cgi	192,213 protein-protein interactions
MIPS	http://www.helmholtz-muenchen.de/en/ibis	NA
PIBASE	http://modbase.compbio.ucsf.edu/pibase	755,998 interfaces
Protein3D Home	http://protein3d.ncifcrf.gov/tsai/	NA
ReLiBase	http://relibase.rutgers.edu	NA
SCOPPI	http://www.scoppi.org	15,058 interfaces
String	http://string-db.org	5,214,234 proteins
Energetics:		
3D-footprint	http://floresta.eead.csic.es/3dfootprint/	2864 complexes
eF-site	http://ef-site.protein.osaka-u.ac.jp/eF-site/	427,984 entries
KineticDB	http://KineticDB.protres.ru/db/index.pl	NA
ProTherm	http://gibk26.bio.kyutech.ac.jp/jouhou/Protherm/protherm.html	14,500 entries
References:		

Database	**Web site**	**Size**[a]
MEDLINE	http://www.ncbi.nlm.nih.gov/PubMed/	>21,000,000 citations
iProLINK	http://pir.georgetown.edu/pirwww/iprolink/	NA
Combined:		
BioSystems	http://www.ncbi.nlm.nih.gov/biosystems	NA
Entrez	http://www.ncbi.nlm.nih.gov/Entrez/	NA
SRS	http://srs.ebi.ac.uk	NA

[a] NA, size not available at time of printing. The data are as of September 2011.