Data Sources

Getting Protein Data
from the Internet

Introduction

- Structural bioinformatics deals with the representation of molecular structural data along and its subsequent storage, retrieval, analysis and visualization.
- Objectives:
  - Design geometric algorithms for manipulating structural data.
  - Design pattern analysis algorithms for detecting structural patterns in macromolecules.
  - Applying these algorithms to further the understanding of cellular processes and to accomplish therapeutic interventions.

Structural Data

- The study of protein domains and their functionality requires a reliable source of structural data for both macromolecules and ligands.
- We will review the following sources of molecular data:
  - There are many others…
    - PDB
    - PDBsum
    - Relibase
    - SCOP
    - CATH
    - PubChem
    - HIVSDB

PDB: The Protein Data Bank

http://www.rcsb.org/pdb

- The PDB is a large protein public domain repository maintained by the RCSB
  - Research Collaboratory for Structural Bioinformatics
  - "a non-profit consortium dedicated to improving our understanding of the function of biological systems through the study of the 3-D structure of biological macromolecules"
  - Most of the structures have been determined by x-ray crystallography.
    - More recently, NMR data has been added.
  - Currently (Jan. 4, 2015) there are 105,465 entries.
    - This represents less than 10-15% of all known proteins.
    - Only deposited data is available to the public…
      - One year ago: Jan. 08 there were 96,980 entries.

Statistics

Jan. 4, 2015:

Exp.Method	Proteins	Nucleic Acids	Protein/NA Complexes	Other	Total
X-RAY	87785	1596	4322	4	93707
NMR	9456	1104	222	7	10789
ELECTRON MICROSCOPY	518	29	164	0	711
HYBRID	68	3	2	1	74
other	161	4	6	13	184
Total	97988	2736	4716	25	105465

An 8.7% increase in one year.

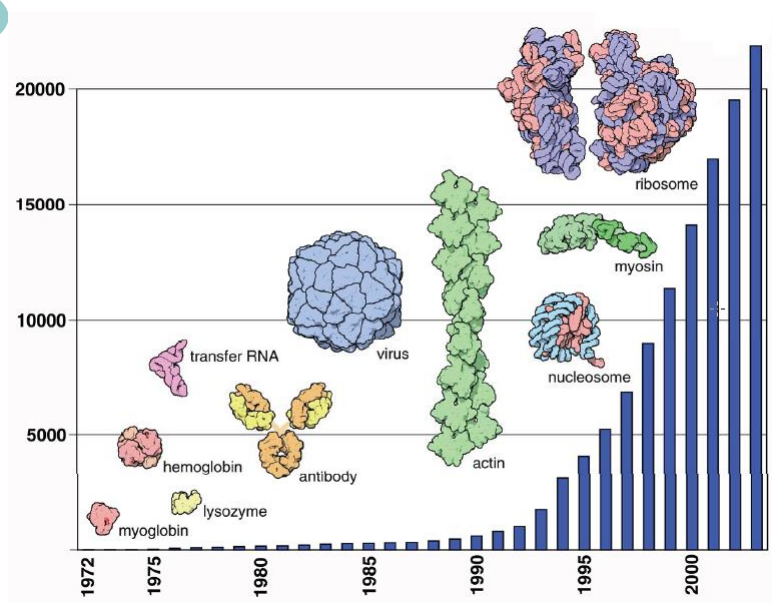
Jan. 2014:

Exp.Method	Proteins	Nucleic Acids	Protein/NA Complexes	Other	Total
X-RAY	80083	1497	4169	4	85753
NMR	9000	1066	197	7	10270
ELECTRON MICROSCOPY	497	51	170	0	718
HYBRID	55	3	2	1	61
other	155	4	6	13	178
Total	89790	2621	4544	25	96980

"Other" is mainly carbohydrates.

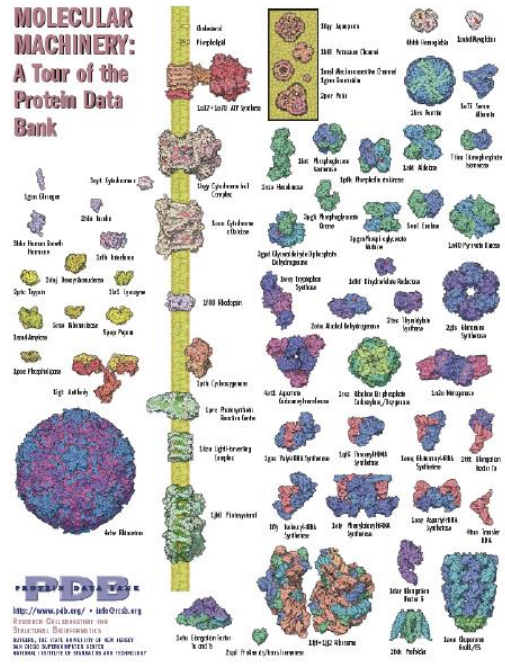
Data Sources

Growth of the PDB

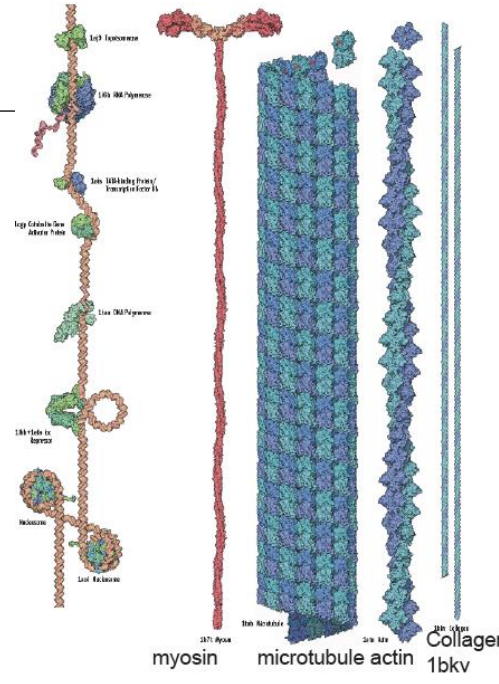


Data Sources

PDB Poster (1)



PDB Poster (2)



Protein Data

- In response to a search the PDB provides information related to a particular protein crystallization study:
  - Title of research paper
  - Authors
  - History
  - Experimental method
  - Parameters and Unit cell specification
  - Molecular description
  - Various classifications (SCOP, CATH, …)
  - The full PDB file is available.

PDB Limitations

- For X-ray structures, the resolution is not high enough to accurately position the hydrogen atoms.
  - So only the "heavy" atoms are given in the file.
- No connection and bond data.
  - There is a CONECT record that for each atom in the chemical component, lists how many and to which other atoms that atom is bonded.
  - Other bonds have to be inferred from the atom name.
- Caution: Some PDB files are inconsistent, informal and not fully checked for errors.

PDBsum: The PDB Summary

- PDBsum:
  - Summaries and analyses of PDB structures.
  - http://www.ebi.ac.uk/thornton-srv/databases/pdbsum/
  - As noted on the site:
    - It provides schematic diagrams of the molecules in each structure and of the interactions between them. Entries are accessed by their PDB code, by simple text search, or through any of the browse options in the left column.
  - There are many links to a variety of other sites dealing any particular protein that you want to specify using PDB ID.

SCOP: Structural Classification Of Proteins

- Introduction
  - Proteins have structural similarities
    - This may be due to common evolutionary origins or possibly convergent evolution.
  - SCOP: (http://scop.mrc-lmb.cam.ac.uk/scop/)
    - has been created by visual inspection
      - but with the help of various software tools
    - hierarchically organizes proteins according to their structure and evolutionary ancestry
    - also provides entry links for coordinates, structure images, literature references, etc.
    - June 2009: 38,221 PDB Entries, 110,800 Domains.
    - Note the arrival of SCOP2:
      - http://scop2.mrc-lmb.cam.ac.uk/

Hierarchical Levels in SCOP

- Classes → Folds → Superfamilies → Families
- The unit of categorization is the protein *domain*.
  - Not the protein itself…
    - Small proteins have a single domain, so in this case categorization is by the protein.
    - Otherwise, large proteins may have more than one domain and these are categorized on an individual basis.
      - More precisely, when a protein is to be placed into the SCOP hierarchy it is first separated into domains.

SCOP Levels: Classes

There are 11 classes:

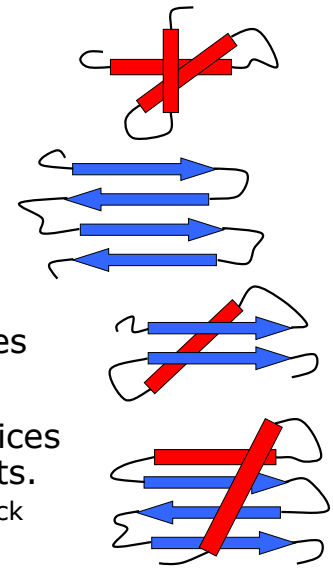
- All alpha proteins
- All beta proteins
- Alpha and beta proteins (α / β)
  Mainly parallel beta sheets (beta-alpha-beta units)
- Alpha and beta proteins (α + β)
  Mainly antiparallel beta sheets (segregated alpha and beta regions)
- Multi-domain proteins (α and β)
  Folds consisting of two or more domains belonging to different classes
- Membrane and cell surface proteins and peptides
  Does not include proteins in the immune system
- Small proteins
  Usually dominated by metal ligand, heme, and/or disulfide bridges
- Coiled coil proteins
  Not a true class
- Low resolution protein structures
  Not a true class
- Peptides
  Peptides and fragments. Not a true class
- Designed proteins
  Experimental structures of proteins with essentially non-natural sequences. Not a true class

SCOP Levels: Classes (cont.)

- A class contains domains with similar global characteristics
  - Not necessarily any evolutionary relation.
  - The next slide gives details for the first four classes.
  - Notes:
    - Membrane proteins are a separate class.
    - *Small* proteins are stabilized by disulfide bridges or by metal ligands in lieu of hydrophobic cores.

SCOP Levels: Classes (cont.)

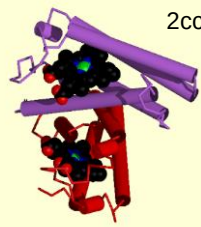
- Class α:
  - A bundle of α helices connected by loops
- Class β
  - Anti-parallel β sheets
- Class α / β
  - Mainly parallel β sheets with intervening α helices
- Class α + β
  - Mainly segregated α helices and anti-parallel β sheets.
    - Note that the helices pack against the sheet.



SCOP Levels: Classes (Some examples)

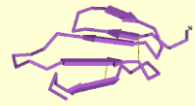
All alpha:

2ccy



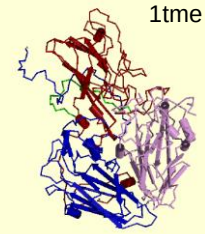
All beta:

1tpm

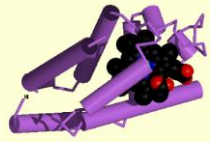


Alpha-beta:

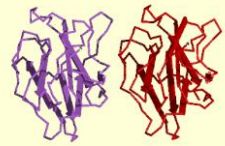
1tme



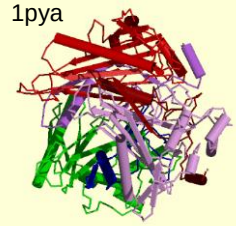
1eca



1vmo



1pya



SCOP Levels: Folds

- Definition:
  - A particular topological arrangement of alpha helices, beta strands, and loops in 3D space is called a fold.
    - There are over 1,195 known folds (Feb. 2009).
    - Many different protein sequences can produce the same fold.
    - A short description of the most significant structural features is used as the name of the fold.

SCOP Levels: Superfamilies

- A superfamily contains a clear *structural* similarity.
  - The stress on *structural* similarity is to emphasize the fact that they might have low sequence identity.
  - Release 1.75 contains 1,962 superfamilies.
  - There is a *probable* common evolutionary origin.
- They share a common fold.
- They usually perform similar functions.

SCOP Levels: Families

- A family contains a clear sequence homology.
  - There is a clear evolutionary relationship.
  - The pair-wise residue identity (sequence similarity) is at least 30%.
    - In some cases, this figure may be lower (say 15%) but the proteins are still put in the same family because they have very similar functions and structures.
    - Release 1.75 contains 3,902 families.
      - An example of this is the family of globins.

Classification Statistics

- **SCOP** release **1.75**
  38,221 PDB Entries (Feb. 2009). 110,800 Domains.

Class	Number of folds	Number of super families	Number of families
All alpha proteins	284	507	871
All beta proteins	174	354	742
Alpha and beta proteins (a/b)	147	244	803
Alpha and beta proteins (a+b)	376	552	1055
Multi-domain proteins	66	66	89
Membrane and cell surface proteins	58	110	123
Small proteins	90	129	219
Total	1195	1962	3902

Importance of SCOP

- Consider some protein P.
  - Structural bioinformatics query:
    - Is there a protein that is nearby to P in the *structure space*?
  - Molecular biologist query:
    - Is there a another protein with a fold that is similar to the fold of P and so might interact with the same ligand that binds with P?

Entering SCOP at the Top of the Hierarchy

(This hierarchical descent was done with SCOP version 1.63)

Root: scop

- **Classes:**
  1. All alpha proteins (171)
  2. All beta proteins (119)
  3. Alpha and beta proteins (a/b) (117)
     Mainly parallel beta sheets (beta-alpha-beta units)
  4. Alpha and beta proteins (a+b) (224)
     Mainly antiparallel beta sheets (segregated alpha and beta regions)
  5. Multi-domain proteins (alpha and beta) (39)
     Folds consisting of two or more domains belonging to different classes
  6. Membrane and cell surface proteins and peptides (34)
     Does not include proteins in the immune system
  7. Small proteins (61)
     Usually dominated by metal ligand, heme, and/or disulfide bridges
  8. Coiled coil proteins (6)
     Not a true class
  9. Low resolution protein structures (18)
     Not a true class
  10. Peptides (101)
      Peptides and fragments. Not a true class
  11. Designed proteins (37)
      Experimental structures of proteins with essentially non-natural sequences. Not a true class

Clicking on: All alpha proteins

Class: All alpha proteins

Lineage:

1. Root: scop
2. Class: All alpha proteins [46456]

Folds:

1. Globin-like [46457] (2)
   core: 6 helices; folded leaf, partly opened
2. Long alpha-hairpin [46556] (11)
   2 helices; antiparallel hairpin, left-handed twist
3. Type I dockerin domain [63445] (1)
   tandem repeat of two calcium-binding loop-helix motifs, distinct from the EF-hand
4. LEM/SAP HeH motif [63450] (4)
   helix-extended loop-helix; parallel helices
5. Cytochrome c [46625] (1)
   core: 3 helices; folded leaf, opened
6. DNA/RNA-binding 3-helical bundle [46688] (12)
   core: 3-helices; bundle, closed or partly opened, right-handed twist; up-and down
7. Another 3-helical bundle [81602] (2)
   topologically similar to the DNA/RNA-binding bundles; distinct packing
8. RuvA C-terminal domain-like [46928] (6)
   3 helices; bundle, right-handed twist
9. …….

Clicking on: DNA/RNA-binding 3-helical bundle

Fold: DNA/RNA-binding 3-helical bundle

- *core: 3-helices; bundle, closed or partly opened, right-handed twist; up-and down*

Lineage:

1. Root: scop
2. Class: All alpha proteins [46456]
3. Fold: DNA/RNA-binding 3-helical bundle [46688]
   core: 3-helices; bundle, closed or partly opened, right-handed twist; up-and down

Superfamilies:

1. Homeodomain-like [46689] (11)
   consists only of helices
2. Methylated DNA-protein cysteine methyltransferase, C-terminal domain [46767] (1)
3. ARID-like [46774] (1)
   contains extra helices at both N- and C-termini
4. "Winged helix" DNA-binding domain [46785] (36)
   contains a small beta-sheet (wing)
5. C-terminal effector domain of the bipartite response regulators [46894] (3)
   binds to DNA and RNA polymerase; the N-terminal, receiver domain belongs to the CheY family
6. TrpR-like [48295] (2)
   contains an extra shared helix after the HTH motif
7. .....

Clicking on: Homeodomain-like

Superfamily: Homeodomain-like

- *consists only of helices*

Lineage:

1. Root: scop
2. Class: All alpha proteins [46456]
3. Fold: DNA/RNA-binding 3-helical bundle [46688]
   core: 3-helices; bundle, closed or partly opened, right-handed twist; up-and down
4. Superfamily: Homeodomain-like [46689]
   consists only of helices

Families:

1. Homeodomain [46690] (23)
2. Recombinase DNA-binding domain [46728] (5)
3. Myb [46739] (4)
4. GARP response regulators [81683] (1)
   plant myb-related DNA binding motif
5. DNA-binding domain of human telomeric protein, hTRF1 [46745] (1)
6. Paired domain [46748] (3)
   duplication: consists of two domains of this fold
7. .....

Clicking on: Paired domain

Family: Paired domain

- *duplication: consists of two domains of this fold*

Lineage:

1. Root: scop
2. Class: All alpha proteins [46456]
3. Fold: DNA/RNA-binding 3-helical bundle [46688]
   core: 3-helices; bundle, closed or partly opened, right-handed twist; up-and down
4. Superfamily: Homeodomain-like [46689]
   consists only of helices
5. Family: Paired domain [46748]
   duplication: consists of two domains of this fold

Protein Domains:

1. Pax-5 [68962]
   1. Human (*Homo sapiens*) [68963] (2)
2. Pax-6 [68936]
   1. Human (*Homo sapiens*) [46750] (1)
3. Paired protein (prd) [46751]
   1. Fruit fly (*Drosophila melanogaster*) [46752] (1)

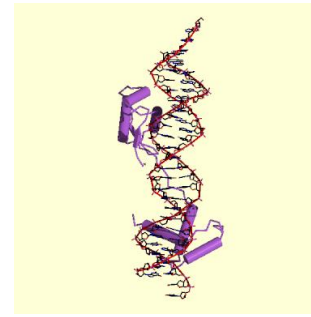
Clicking on: Pax-6 [68936]

Human (*Homo sapiens*) [46750] (1)

Protein: Pax-6 from Human (*Homo sapiens*)

Lineage:

1. Root: scop
2. Class: All alpha proteins [46456]
3. Fold: DNA/RNA-binding 3-helical bundle [46688]
   core: 3-helices; bundle, closed or partly opened, right-handed twist; up-and down
4. Superfamily: Homeodomain-like [46689]
   consists only of helices
5. Family: Paired domain [46748]
   duplication: consists of two domains of this fold
6. Protein: Pax-6 [68936]
7. Species: Human (*Homo sapiens*) [46750]



PDB Entry Domains:

1. 6pax
   1. region a:1-68 [64758]
   2. region a:69-133 [64759]

CATH: The CATH Hierarchy

- CATH is another protein structure classification hierarchy:
  - **C**lass
  - **A**rchitecture
  - **T**opology
  - **H**omologous superfamily
  - **S**equence families

  - http://www.cathdb.info/
  - As with SCOP classification is for protein domains.

CATH: Statistics

- Currently, v4.0:

Class	Architecture	Topology	Homologous Superfamily	S35 Family	S60 Family	S95 Family	S100 Family	Domains
Class 1	5	397	907	3879	5118	6737	13368	48121
Class 2	20	241	547	3650	5221	8373	14526	58944
Class 3	14	626	1158	9171	13415	17047	35313	125772
Class 4	1	111	126	233	293	410	651	3021
TOTAL	**40**	**1375**	**2738**	**16933**	**24047**	**32567**	**63858**	**235858**

CATH Levels: **C**lass

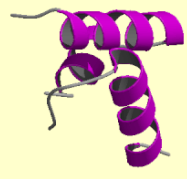
- There are three major classes plus an extra minor class:
  - Mainly α
  - Mainly β
  - Mixed α & β
  - Low secondary structure

  - Most classification (90%) can be done automatically.
    - When this is in doubt, classification is done by visual inspection.

Class Examples

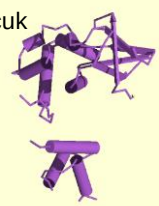
Mainly Alpha

1cuk03



The full protein has two chains:

1cuk



Mainly Beta

1pdc00

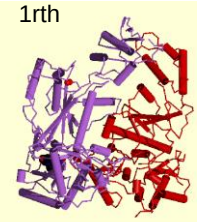
1pdc has only one domain

Mixed Alpha-Beta

1rthA1

Several domains in two chains of the full protein:

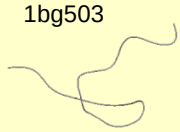
1rth



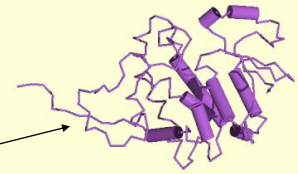
Class Examples (cont.)

Few secondary structures:

1bg503



1bg5



The full protein has 9 helices.
The domain 1bg503 is here:

CATH Levels: **A**rchitecture

- The architecture level defines the overall shape of the domain structure as defined by the orientations of the secondary structure.
  - E.g.: barrel, sandwich, etc.
  - Connectivity between secondary structures is ignored.
  - Classification at this level is done by inspection appealing to the literature for descriptions of various architectures.

CATH Levels: **T**opology

- These are essentially fold families.
  - Classification depends on the overall shape and connectivity of the secondary structures.
    - Done by using the structure comparison algorithm (SSAP) of Taylor and Orengo (1989).
    - SSAP assigns a score to a pair-wise comparison.
      - A score of 70 and a matching that indicates that at least 60% of the larger protein is contained in the smaller protein means that the two proteins are in the same fold family.
      - The score threshold is raised for some families if they are highly populated.

CATH Levels: **H**omologous superfamily

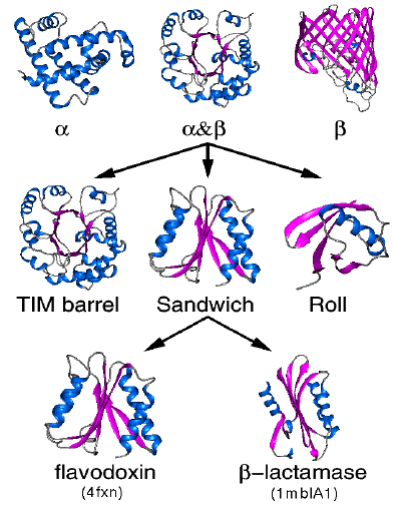
- Homologous ==> a common ancestor
  - Similarities are determined by sequence comparison and then by structure comparison.
    - using SSAP
  - Two structures are in the same homologous superfamily if any of the following hold:
    - sequence identity $\geq$ 35%
    - SSAP score $\geq$ 80 and sequence identity $\geq$ 20%
    - SSAP score $\geq$ 80, 60% of larger structure is equivalent to the smaller structure and the domains have related functions.

CATH Levels: **S**equence families

- Structures within an H level are clustered into smaller groups based on sequence identity.
  - Domains clustered in the same S level have sequence identities greater than 35% with at least 60% of the larger domain equivalent to the smaller domain.
    - indicates highly similar structure and function.

A Portion of the Hierarchy

- Class:
- Architecture:
- Topology:



PubChem: http://pubchem.ncbi.nlm.nih.gov/

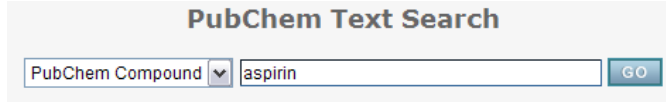
- PubChem is a database holding structural information for millions of molecules.
  - Maintained by the NCBI
    - National Center for Biotechnology Information
    - within the National Library of Medicine, NIH (National Institute of Health).
  - Data is free and can be downloaded via FTP.
    - The American Chemical Society (ACS) claims the database competes with its Chemical Abstracts Service (CAS).
      - A publishing operation that had $400m/year revenues.
    - The ACS tried to get the U.S. Congress to restrict the operation of PubChem.
      - This was resolved in the summer of 2005.
      - Congress did not censure the NIH.

PubChem Overview PubChem

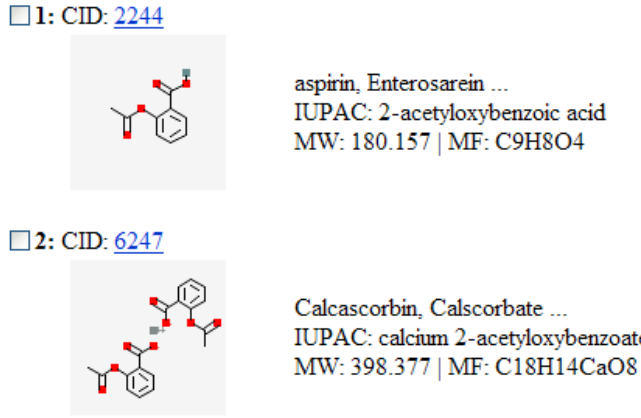
- Currently PubChem has over 90 million compounds.
- Different searches:
  - PubChem Compound
    - Search for compounds using names, synonyms or keywords.
  - PubChem Substance
    - Search for chemical substances
  - PubChem BioAssay
    - Search on bioassay results
  - Structure Search
    - Search using chemical structure (eg. SMILES) as a query.

PubChem Sample Search (1)

- Search for aspirin:

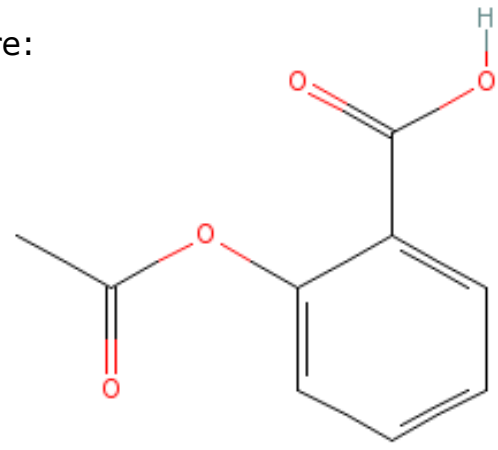


A partial list of results:



PubChem Sample Search (2)

Aspirin 2D structure:

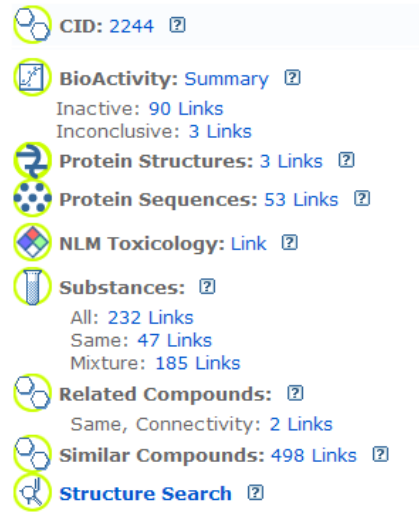


CID: 2244

PubChem identifier

PubChem Sample Search (3)

- As well as 2D structure several links are made available:



PubChem Sample Search (4)

- Following the "Protein Structures" link eventually leads to proteins that bind with aspirin, in this case 1TGM:

PubChem Sample Search (5)

- Description for **Aspirin**:
  The prototypical analgesic used in the treatment of mild to moderate pain. It has anti-inflammatory and antipyretic properties and acts as an inhibitor of cyclooxygenase which results in the inhibition of the biosynthesis of prostaglandins. Aspirin also inhibits platelet aggregation and is used in the prevention of arterial and venous thrombosis. (From Martindale, The Extra Pharmacopoeia, 30th ed, p5)

- **Pharmacological Action:**
  Anti-Inflammatory Agents, Non-Steroidal
  Fibrinolytic Agents
  Platelet Aggregation Inhibitors
  Cyclooxygenase Inhibitors

PubChem Sample Search (6)

- Research references for **Aspirin**:

PubMed via MeSH Choose by Subheadings:

administration and dosage	adverse effects	analogs and derivatives
analysis	antagonists and inhibitors	blood
cerebrospinal fluid	chemical synthesis	chemistry
classification	contraindications	diagnostic use
economics	history	immunology
isolation and purification	metabolism	pharmacokinetics
pharmacology	physiology	poisoning
radiation effects	standards	supply and distribution
therapeutic use	therapy	toxicity
urine		

PubChem Sample Search (7)

- **Properties Computed from Structure:**

  - **Molecular Weight:** 180.157g/mol
    Molecular Formula: C9H8O4

    XLogP: 1.4

    Hydrogen Bond Donor Count: 1
    Hydrogen Bond Acceptor Count: 4
    Rotatable Bond Count: 3
    Topological Polar Surface Area: 63.6

PubChem Sample Search (8)

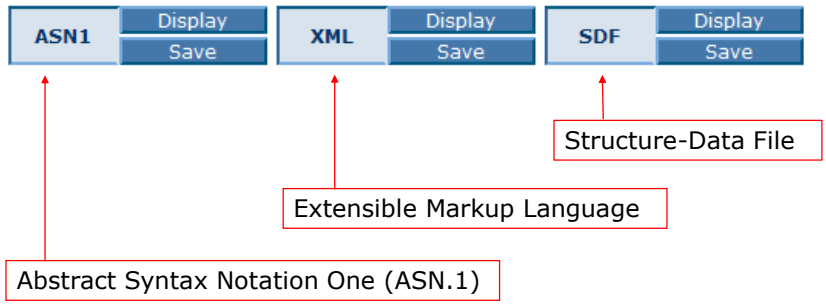
International Union of Pure and Applied Chemistry

- **Descriptors Computed from Structure:**
- **IUPAC Name:** 2-acetyloxybenzoic acid
  Canonical SMILES: CC(=O)OC1=CC=CC=C1C(=O)O
  InChI: InChI=1/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3,(H,11,12)/f/h11H

- **Substance Category:**
  - **Biological Properties:** 28 Links
    Journal Publishers: 1 Link
    Metabolic Pathways: 2 Links
    Molecular Libraries Screening Center Network: 4 Links
    Physical Properties: 4 Links
    Protein 3D Structures: 4 Links
    Substance Vendors: 1 Link
    Theoretical Properties: 1 Link
    Toxicology: 3 Links

PubChem Sample Search (9)

- Links to structure files:



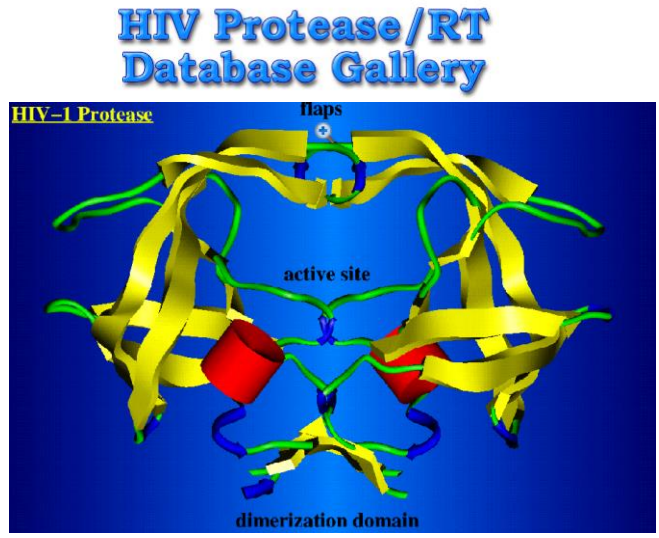
Specialized Databases: HIVSDB (1)

HIV Structural Database & Chem-BLAST

http://xpdb.nist.gov/hivsdb/hivsdb.html

- NIST (National Institute of Standards and technology) provides this database as a central structural information resource for AIDS related molecules.
  - Proteins and ligands
- Related publications:
  - Prasanna, M.D., Vondrasek, J., Wlodawer, A., Bhat, T. N. Application of InChI to curate, index and query 3-D structures. *PROTEINS: Structure, Function, and Bioinformatics* **60**, 1-4 (2005).
  - 2.Prasanna M.D, Vondrasek J, Wlodawer A, Rodriguez H, Bhat T.N. Chemical compound navigator: a web-based Chem-BLAST, chemical taxonomy-based search engine for browsing compounds. Proteins **63**(4), 907-917(2006).

Specialized Databases: HIVSDB (2)



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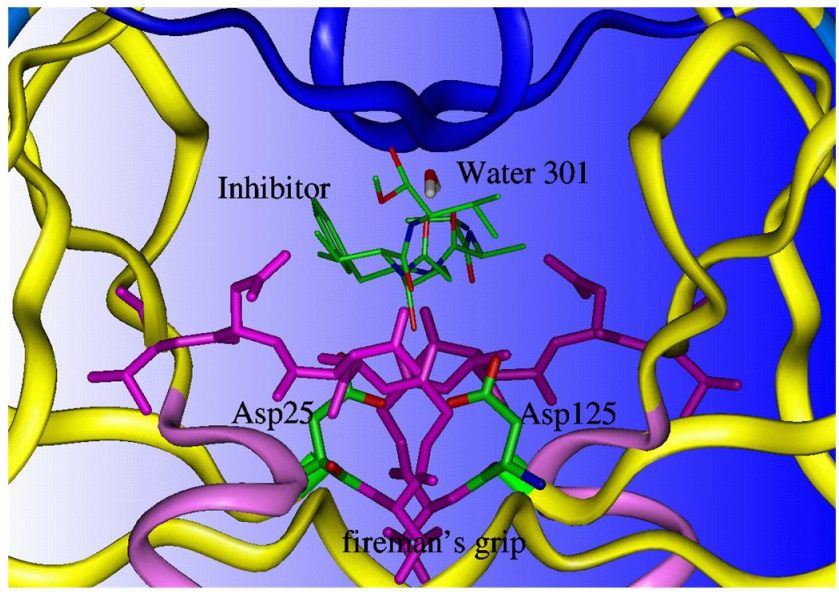
Specialized Databases: HIVSDB (3)



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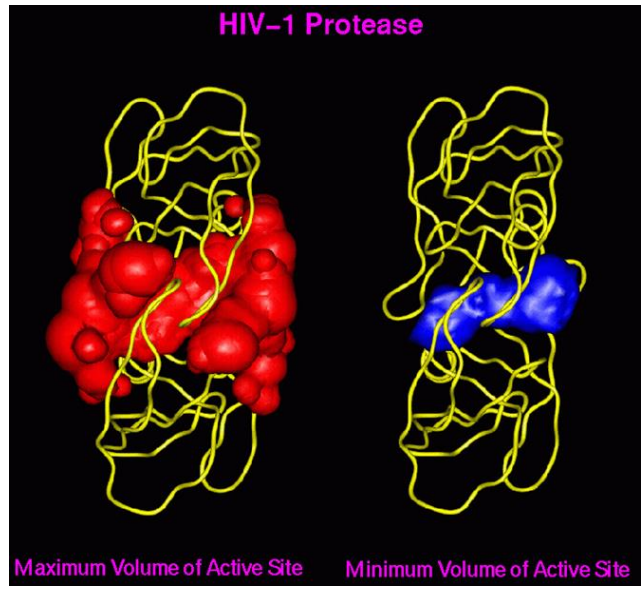
Specialized Databases: HIVSDB (4)



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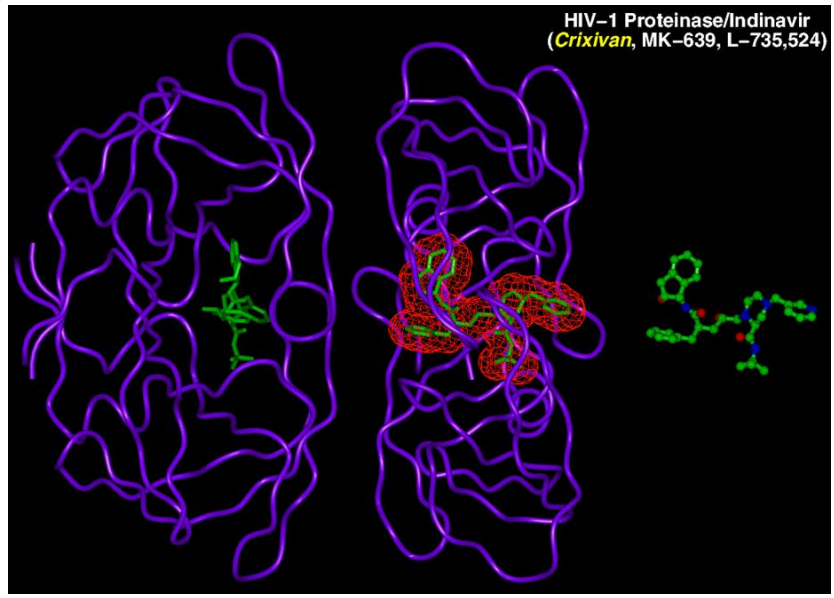
Specialized Databases: HIVSDB (5)



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