BINF 731

Protein Structure Analysis

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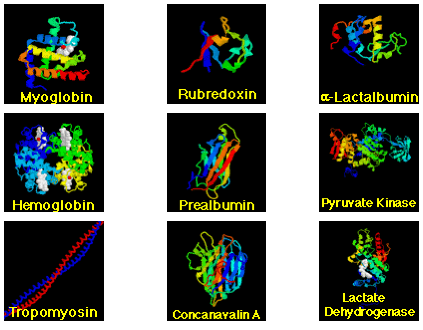
Secondary Structure: Computational Problems

Secondary structure characterization
Secondary structure assignment
Secondary structure prediction
Protein structure classification

Structural classes of proteins



all α all β α/β

Protein Structure Classification

SCOP - Structural Classification of Proteins

FSSP - Fold classification based on Structure-Structure alignment of Proteins

CATH - Class, architecture, topology and homologous superfamily

SCOP: Structural Classification of Proteins

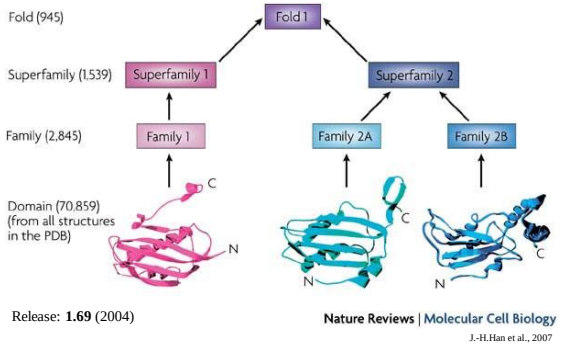
Current release: 1.75
38221 PDB Entries (June 2009). 110800 Domains.

http://scop.mrc-lmb.cam.ac.uk/scop/

The **SCOP** database aims to provide a detailed and comprehensive description of the structural and evolutionary relationships between all proteins whose structure is known. Proteins are classified to reflect both structural and evolutionary relatedness. Many levels exist in the hierarchy; the principal levels are family, superfamily and fold

Family: *Clear evolutionarily relationship*
Superfamily: *Probable common evolutionary origin*
Fold: *Major structural similarity*

SCOP: Structural Classification of Proteins



SCOP: Structural Classification of Proteins

Family: *Clear evolutionarily relationship*

Proteins clustered together into families are clearly evolutionarily related. Generally, this means that pairwise residue identities between the proteins are 30% and greater. However, in some cases similar functions and structures provide definitive evidence of common descent in the absense of high sequence identity; for example, many globins form a family though some members have sequence identities of only 15%.

SCOP: Structural Classification of Proteins

Superfamily: *Probable common evolutionary origin*

Proteins that have low sequence identities, but whose structural and functional features suggest that a common evolutionary origin is probable are placed together in superfamilies. For example, actin, the ATPase domain of the heat shock protein, and hexakinase together form a superfamily.

SCOP: Structural Classification of Proteins

Fold: *Major structural similarity*

Proteins are defined as having a common fold if they have the same major secondary structures in the same arrangement and with the same topological connections. Different proteins with the same fold often have peripheral elements of secondary structure and turn regions that differ in size and conformation. In some cases, these differing peripheral regions may comprise half the structure. Proteins placed together in the same fold category may not have a common evolutionary origin: the structural similarities could arise just from the physics and chemistry of proteins favoring certain packing arrangements and chain topologies.

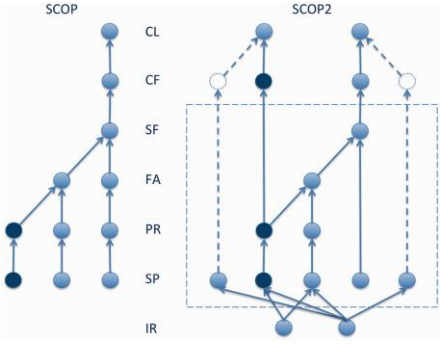
SCOP Statistics (2003)

Class	Folds	Super families	Families
All alpha proteins	179	299	480
All beta proteins	126	248	462
Alpha and beta proteins (a/b)	121	199	542
Alpha and beta proteins (a+b)	234	349	567
Multi-domain proteins	38	38	53
Membrane and cell surface proteins	36	66	73
Small proteins	66	95	150
Total	**800**	**1294**	**2327**

SCOP Statistics (2009 – current release)

Class	Number of folds	Number of superfamilies	Number of families
All alpha proteins	284	507	871
All beta proteins	174	354	742
Alpha/beta proteins (a/b)	147	244	803
Alpha+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**

SCOP2



Andreeva et al., 2014

SCOP2

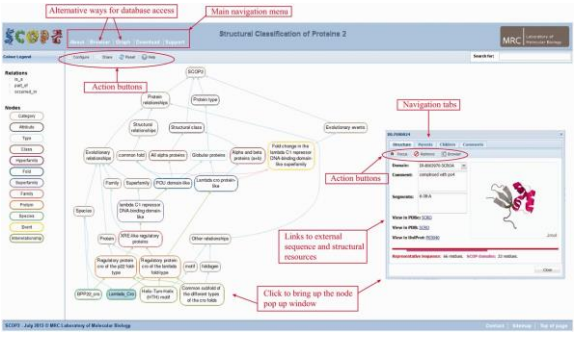
SCOP2 retains the evolutionary levels of SCOP, **Species, Protein, Family,** and **Superfamily** but their content and definitions are different.

- **Species** corresponds to the individual gene product and is represented by its full-length sequence
- **Protein** groups together orthologous proteins and is defined as a subsequence that can be found on its own
- **Family** corresponds to the conserved sequence region shared by closely related proteins
- **Superfamily** is represented by the common structural region shared by different protein families

Importantly, the domains representing Family and Superfamily levels can span over more than one structural domain. In addition to these levels, SCOP2 contains a new level, **Hyperfamily**. The Hyperfamily level is introduced mainly to deal with the most populated and structurally diverse SCOP superfamilies. One of the striking differences between SCOP and SCOP2 is that these distinct levels are not obligatory; e.g., family could be the highest evolutionary relationship to which a protein domain belongs since there are no other distantly related protein domains that could form a superfamily.

Andreeva et al., 2014

SCOP2



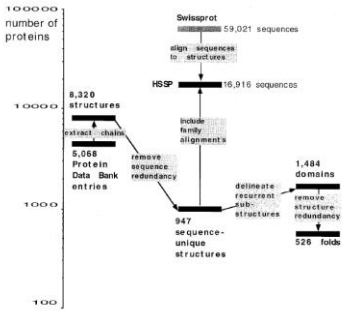
Andreeva et al., 2014

FSSP (DALI) Database

Current release: April 2009

The FSSP database is based on exhaustive all-against-all 3D structure comparison of protein structures currently in the Protein Data Bank (PDB). The classification and alignments are automatically maintained and continuously updated using the Dali search engine.

Structure processing for Dali/FSSP



Adopted from Holm and Sander, 1998

Dali Domain Dictionary

http://www2.ebi.ac.uk/dali/domain

Structural domains are delineated automatically using the criteria of recurrence and compactness. Each domain is assigned a Domain Classification number DC_l_m_n_p , where:

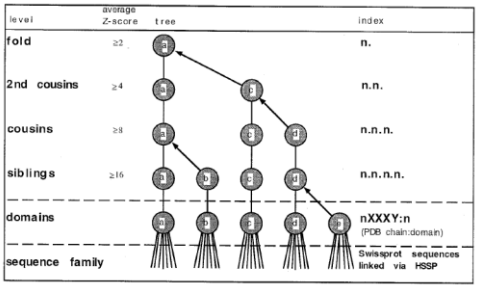
l - fold space attractor region

m - globular folding topology

n - functional family

p - sequence family

Hierarchical clustering of folds in Dali/FSSP

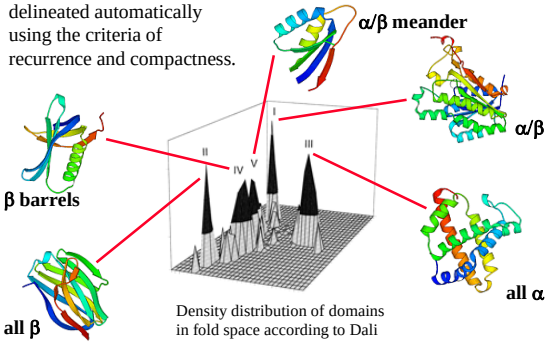


Adopted from Holm and Sander, 1998

Dali Domain Dictionary

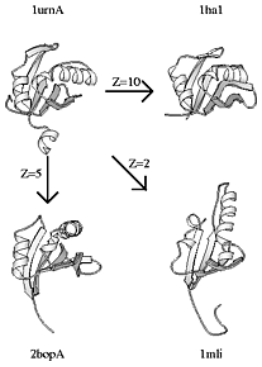
Structural domains are delineated automatically using the criteria of recurrence and compactness.

Fold space attractor regions



Density distribution of domains in fold space according to Dali

Dali Domain Dictionary



Fold types

Fold types are defined as clusters of structural neighbors in fold space with average pairwise Z-scores (by Dali) above 2.

Structural neighbours of 1urnA (top left). 1mli (bottom right) has the same topology even though there are shifts in the relative orientation of secondary structure elements

Dali Domain Dictionary

Functional families

The third level of the classification infers plausible evolutionary relationships from strong structural similarities which are accompanied by functional or sequence similarities. Functional families are branches of the fold dendrogram where all pairs have a high average neural network prediction for being homologous. The neural network weighs evidence coming from: overlapping sequence neighbours as detected by PSI-Blast, clusters of identically conserved functional residues, E.C. numbers, Swissprot keywords.

Dali Domain Dictionary

Sequence families

The fourth level of the classification is a representative subset of the Protein Data Bank extracted using a 25 % sequence identity threshold. All-against-all structure comparison was carried out within the set of representatives. Homologues are only shown aligned to their representative.

CATH - Protein Structure Classification

Current release: 3.5 (September 20, 2011)

http://www.cathdb.info

CATH is a novel hierarchical classification of protein domain structures, which clusters proteins at four major levels:

- **C**lass
- **A**rchitecture
- **T**opology
- **H**omologous superfamily

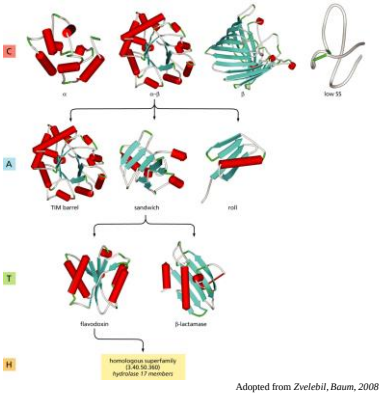
CATH - Protein Structure Classification

Class

Architecture

Topology

Homologous superfamily



Adopted from *Zvelebil, Baum, 2008*

CATH - Protein Structure Classification

Class, C-level

Class is determined according to the secondary structure composition and packing within the structure. It can be assigned automatically (90% of the known structures) and manually.

Three major classes:

mainly-alpha

mainly-beta

alpha-beta (alpha/beta and alpha+beta)

A fourth class is also identified which contains protein domains which have low secondary structure content.

CATH - Protein Structure Classification

Architecture, A-level

This describes the overall shape of the domain structure as determined by the orientations of the secondary structures but ignores the connectivity between the secondary structures.

It is currently assigned manually using a simple description of the secondary structure arrangement e.g. barrel or 3-layer sandwich. Reference is made to the literature for well-known architectures (e.g the beta-propellor or alpha four helix bundle).

Procedures are being developed for automating this step.

CATH - Protein Structure Classification

Topology (Fold family), T-level

Structures are grouped into fold families at this level depending on both the overall shape and connectivity of the secondary structures. This is done using the structure comparison algorithm SSAP.

Some fold families are very highly populated and are currently subdivided using a higher cutoff on the SSAP score.

CATH - Protein Structure Classification

Homologous Superfamily, H-level

This level groups together protein domains which are thought to share a common ancestor and can therefore be described as homologous. Similarities are identified first by sequence comparisons and subsequently by structure comparison using SSAP.

Structures are clustered into the same homologous superfamily if they satisfy one of the following criteria:

- Sequence identity >= 35%, 60% of larger structure equivalent to smaller
- SSAP score >= 80.0 and sequence identity >= 20% 60% of larger structure equivalent to smaller
- SSAP score >= 80.0, 60% of larger structure equivalent to smaller, and domains which have related functions

CATH - Protein Structure Classification

Sequence families, S-level

Structures within each H-level are further clustered on sequence identity. Domains clustered in the same sequence families have sequence identities >35% (with at least 60% of the larger domain equivalent to the smaller), indicating highly similar structures and functions.

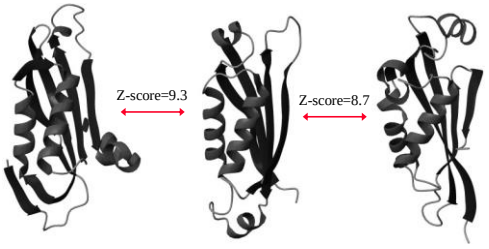
CATH Statistics

Version 3.5 **Date** 9-20-2011

Number of Domains	173,536
Number of Superfamilies	2,626
Number of PDBs	51,334

C	A	T	H	S	O	L	I	D
Mainly Alpha	5	305	652	1850	2329	3001	5587	19729
Mainly Beta	20	191	415	1860	2531	3846	6503	25537
Alpha Beta	14	496	922	3922	5303	6659	12998	47193
Few Sec Struct	1	92	102	162	200	275	403	1426
Total	**40**	**1084**	**2091**	**7794**	**10363**	**13781**	**25491**	**93885**

Classification limitations



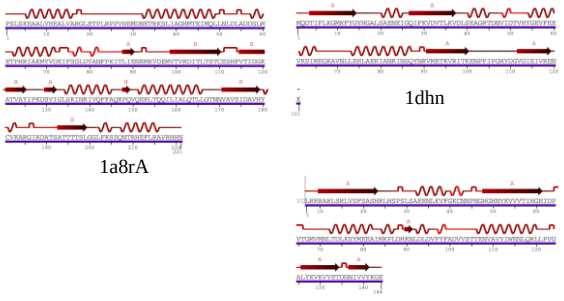
1a8rA, αβ three-layer (ββα) sandwich (CATH 3.50.11)

1dhn, αβ three-layer (ββα) sandwich (CATH 3.50.11)

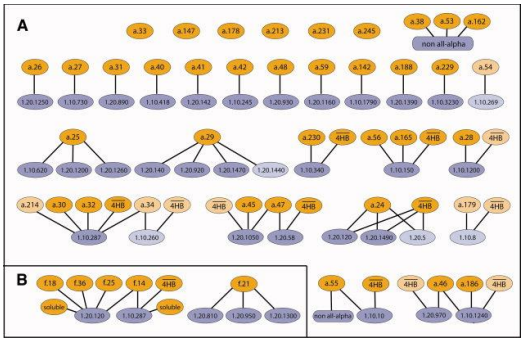
1b66A, αβ two-layer sandwich (CATH 3.30.479)

Adopted from Getz et al., 2002

Classification limitations



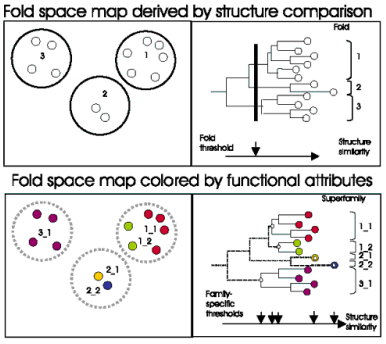
Classification limitations



Relationships between four helix bundle folds in SCOP (orange) and CATH (blue).

S. Neumann et al., 2010

Homologous and Analogous Proteins



Adopted from Dietmann & Holm, 2001

Homologous and Analogous Proteins

- Homologous: same fold, same or similar function, common ancestry.
- Analogous: same fold, different function, ancestral origin unknown.