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SDADB: a functional annotation database of protein structural domains

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Abstract

Annotating functional terms with individual domains is essential for understanding the functions of full-length proteins. We describe SDADB, a functional annotation database for structural domains. SDADB provides associations between gene ontology (GO) terms and SCOP domains calculated with an integrated framework. GO annotations are assigned probabilities of being correct, which are estimated with a Bayesian network by taking advantage of structural neighborhood mappings, SCOP-InterPro domain mapping information, position-specific scoring matrices (PSSMs) and sequence homolog features, with the most substantial contribution coming from high-coverage structure-based domain-protein mappings. The domain-protein mappings are computed using large-scale structure alignment. SDADB contains ontological terms with probabilistic scores for more than 214 000 distinct SCOP domains. It also provides additional features include 3D structure alignment visualization, GO hierarchical tree view, search, browse and download options.

Database URL: http://sda.denglab.org

Introduction

A protein domain is a conserved and functional unit of a protein that can fold independently and has distinct functions. Most proteins consist of one or several domains. A unique domain may appear in a variety of different proteins that capture specific functions. Usually, specific functions of protein domains are highly independent, and they are, in many cases, conserved across species (1). For example, the catalytic domain of serine/threonine/tyrosine protein kinases is highly conserved from *E. coli* to human containing the catalytic function, and shares conserved catalytic regions with both serine/threonine and tyrosine protein kinases (2). The N-terminal of the catalytic domain has been shown to be involved in ATP binding, while the central part of the catalytic domain plays important roles in the catalytic activity of the enzyme (3, 4). A broad range of approaches has been developed to the problem of automatically identifying domain regions in protein sequences based on some degree of relatedness shared between domain sequences. InterPro (5, 6) is the widely used sequence-based domain database, which collates important resources for protein domain classifications: Pfam (7), CATH-Gene3D (8), SMART (9), ProDom (10), SUPERFAMILY (11) and PROSITE (12). The Conserved Domain Database (CDD) (13) maintains domain annotations for sequences. It produces representative sequence fragments, which are in agreement with domain boundaries as observed in protein 3D structure. A more reliable way to assign structures to the domain families is using the structural information. As the widely used hierarchical classification scheme of proteins, SCOP (14) groups protein domains into Class, fold, superfamily and family according to structural and evolutionary relationships (15). The current version of SCOPe version 2.06 (16, 17) contains over 240 000 structural domains.

Assigning ontological terms to specific domains are important for fully understanding functions of proteins. Gene ontology (GO) has been a de facto standard for describing gene and protein function (18, 19). It arranges in a directed acyclic graph and discriminates between molecular function and biological process, as well as subcellular localization. The GO terms in top levels describe general functions such as catalytic activity and binding. While deeper GO terms in the hierarchy represent more specific functions. For sequence-based domains, a few have been manually annotated with GO terms, and several computational prediction methods have been developed. The InterPro2GO mapping (20) is curated manually by the InterPro team, who compare InterPro and protein entries, check the statistic and conservation information, and assign most appropriate and specific GO terms to the InterPro domain. The Pfam2GO mapping is subsequently created by mapping InterPro domains to Pfam domains. Forslund and Sonnhammer (21) developed a probabilistic model to predict the relationship between multiple Pfam domain and annotation GO terms. Rentzsch and Orengo (22) use domain functional families (FunFams) to predict the functions of whole proteins. They group domain sequences into FunFams based on the GO annotations and associate the FunFams with GO terms probabilistically.

Although sequence-based domain annotation and domain-centric protein function prediction have been extensively studied, predicting functions for protein structural domains is, even more, difficult given the lack of comprehensive structural domain information for proteins. Only a few previous efforts have been performed to computationally predict structural domain functions (11, 23, 24). The SUPERFAMILY database (11) contains SCOP domain architecture and classification assignments to sequences at the superfamily level by using hidden Markov models. Based on the sequence homology to SCOP structural domain mapping in SUPERFAMILY, the dcGO database (24) provides GO annotations for SCOP domains in a probabilistic framework at the superfamily and family levels. Daniel and Florencio (23) proposed a scop2go approach, which annotates SCOP domains with molecular function GO terms based on the fold distribution of PDB structures associated with given GO terms. Although these resources are valuable, they only have coarse-grained level function annotation and are largely incomplete in that many domains are still not annotated.

Recently, we proposed a functional annotation approach for structural domains (SDA) that is largely based on 3D structure-based domain-protein mappings (25). We used a Bayesian network to integrate heterogeneous information: (i) protein-to-domain mappings calculated using all-against-all structural alignment of SCOP domains and protein structures from the PDB database; (ii) SCOP-to-InterPro domain mappings calculated using the InterProScan software; (iii) SVM models generated based on the position-specific scoring matrix (PSSM) profiles; (iv) sequence homologs mapped to SCOP domains using a Bayesian network. We showed the advantages of integrating large-scale structure-based mappings and other heterogeneous information sources for structural domain function prediction.

Here, we present the SDA database, which provides domain GO annotations predicted from our integrated method, and also includes links to other databases. The server allows users to query functional annotations for input proteins or domains. The results can be visualized in an interactive 3D viewer and a tree viewer. SDADB is available at http://sda.denglab.org.

Methods and data sources

Structural domains are downloaded from SCOPe version 2.06 (16, 17). GO annotations for the SCOP domains are generated by our structure-based integrative function prediction approach that combines structural mappings with other sequence and evolutionary clues (25). A detailed illustration of the data sources and framework is shown in Figure 1. Briefly, for a query SCOP domain, GO annotations are predicted with four component methods (structure-based, InterPro-based, PSSM-based and sequence homology-based methods). A probability for each annotation is calculated using a Bayesian network trained on a dataset of SCOP domains (ending in dash) generated from single-domain proteins.

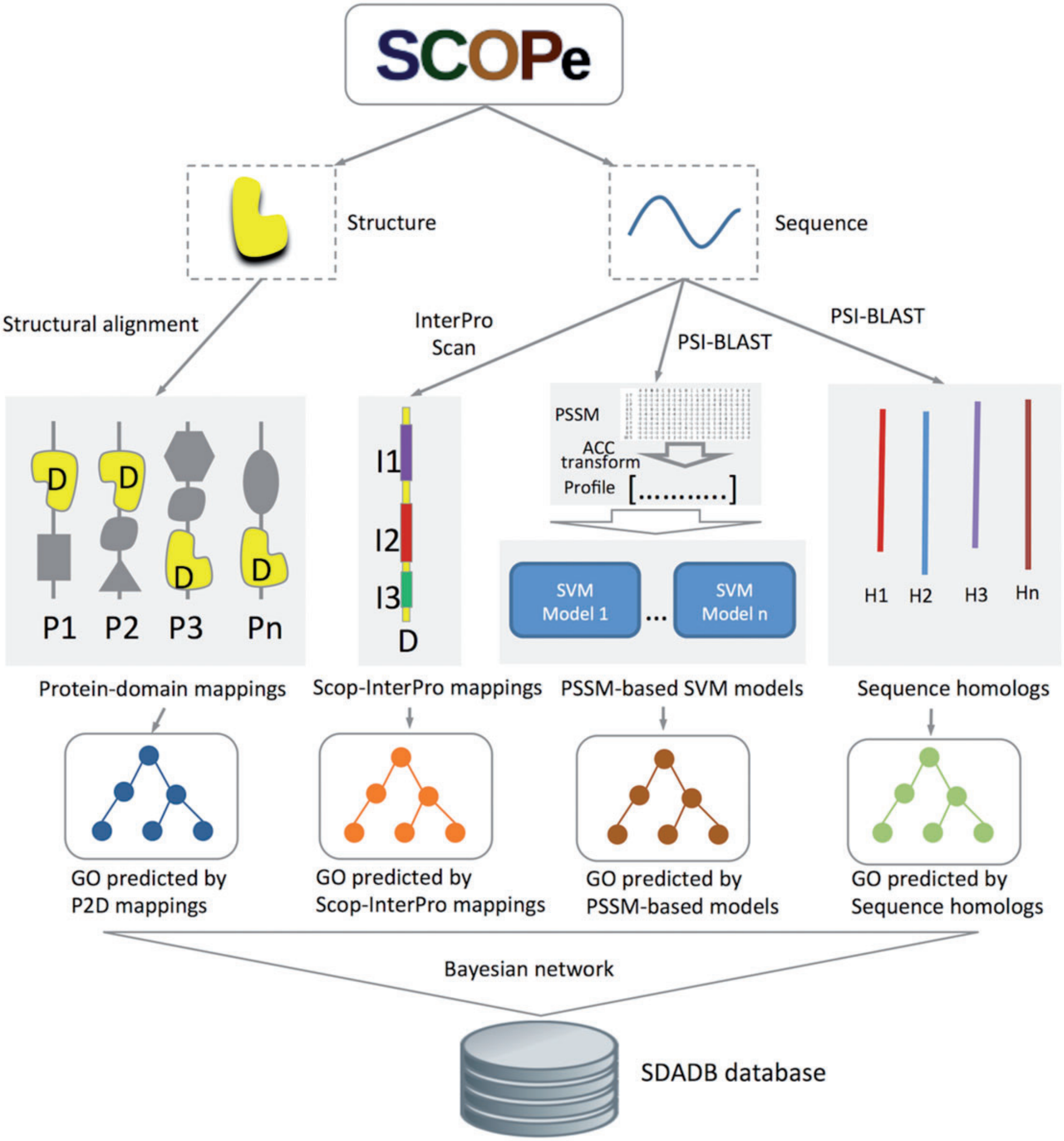


Figure 1. Flowchart of SDADB construction. For each domain in the SCOPe database, GO annotations are predicted with the four component methods: (i) GO annotations predicted using P2D mappings: protein-SCOP domain mappings are calculated by large-scale structure alignment, then the probability that a domain annotated by a specific function is computed; (ii) GO annotations predicted using Scop-InterPro mappings: we use InterProScan to search InterPro domains for the SCOP domain, and transfer the annotations of these InterPro domains in the InterPro2GO database to the target SCOP domain; (iii) GO annotations predicted using PSSM profiles: SVM models for GO function annotation are trained with fixed length of PSSM vectors, which are calculated using ACC transformation; (iv) GO annotations predicted using sequence homologs: we transfer the GO annotations of the sequence homologs in UniProt-GOA to the target SCOP domain. Finally, the SDADB database is built by integrating the outputs of the four component methods with a Bayesian network.

GO annotations predicted using protein-domain structural mappings

We use a structure alignment algorithm (26, 27) to search structural neighbors for SCOP domains against the PDB database, and obtain a significant number of protein-domain (P2D) mappings. The structural similarity between proteins and domains is measured by protein structure distance (PSD) (26). The PSD score integrates the RMSD (root mean square deviation) and the secondary structural alignment score to measure the similarity of two structures and is applicable both when two structures are very similar, and when they are very different. Lower PSD score corresponds to a good fit or better alignment between the structures. A protein is defined as the structural neighbor of a SCOP domain when the PSD score is lower than 0.1. We assign GO annotations to SCOP domains based on the assumption that the most populated SCOP domain in the mappings corresponds to the structural neighbor proteins which are responsible for the function (25). The GO annotations of proteins are extracted from the PDB-GOA database (28). The probabilities of transferring protein function annotations to SCOP domains are computed as shown in the following equation:

$$P_1(g|d) = \frac{P(d,g)}{P(d)},$$

where d is a SCOP domain, g denotes a GO term, $P(d, g)$ is the number of PDB proteins containing domain d and having function g, $P(d)$ is the number of PDB proteins containing domain d calculated on the P2D mapping data.

GO annotations predicted using Scop-InterPro domain mappings

We use the InterProScan tool (6) to search the InterPro domains (5) against the SCOP sequences. GO terms of InterPro domains in the InterPro2GO database (28) are transferred to the corresponding SCOP domains. The probability of a GO term (g) assigned to the SCOP domain is calculated based on the number of InterPro domains that have the function:

$$P_2(g) = \frac{1}{n}\sum_{i=1}^{n} I(g),$$

where n is the number of InterPro domains owned by the SCOP domain. If an InterPro domain has the function g, $I(g)$ is 1; otherwise 0.

GO annotations predicted using PSSM profiles

PSSM (29–32) is a highly informative representation of protein sequences and is widely utilized in many applications. We use PSI-BLAST (33) to calculate PSSM profiles based on the NCBI NR database (34). The auto-cross covariance (ACC) transformation (35) is used to transform the PSSM profiles into fixed-length vectors. For a domain sequence, auto covariance (AC) describes the average interactions between residues, a certain distance (l) apart throughout the whole sequence. For a descriptor (one of the 20 basic residue types), the AC variable is calculated as:

$$AC = \frac{1}{DL-l}\sum_{i=1}^{DL-l} (X_i - \bar{X})(X_{i+l} - \bar{X}),$$

where l denotes the distance between one residue and its neighbor, DL is the length of domain sequence, X_i is the PSSM score of the descriptor at position i, $\bar{X}$ is the average score for the descriptor along the whole sequence. We use the AC variables to transform the numerical PSSM vectors of SCOP domain sequences into uniform matrices with the distance $l = 10$. Based on the PSSM vectors, we build SVM classifiers for each GO term. The probability score of a GO term (g) assigned to a SCOP domain is estimated based on the output of the SVM classifier by a sigmoid function:

$$P_3(g) \approx \frac{1}{1 + e^{Af(g)+B}},$$

where $f(g)$ is the SVM output score, A and B are estimated using the method of Lin *et al.* (36).

GO annotations predicted using sequence homologs

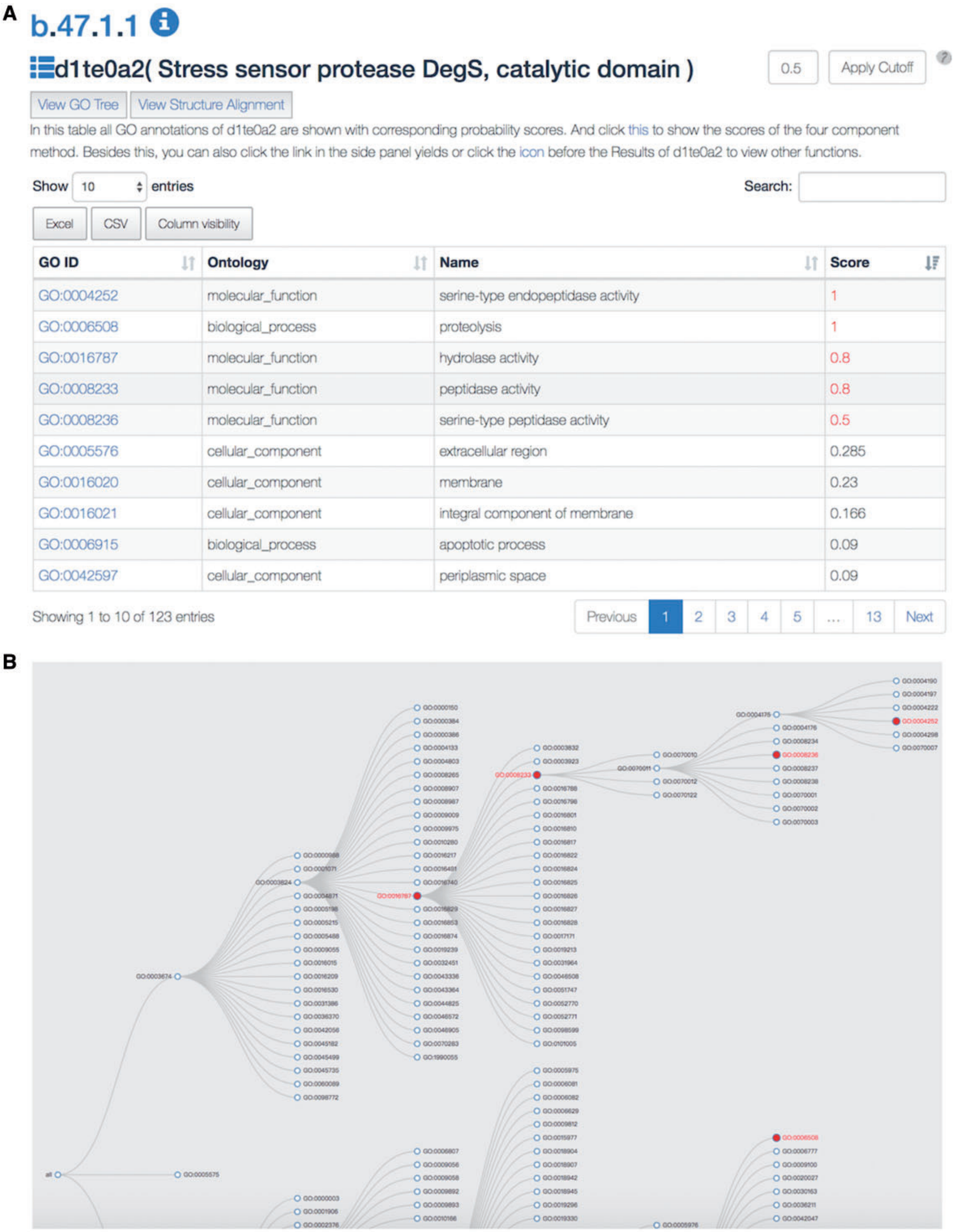
We also used PSI-BLAST to search sequence homologs for SCOP domains against the UniProt database. We only select the sequence homologs with alignment coverage >60%. The GO annotations of sequence homologs are obtained from the UniProt-GOA database (37). We use the sequence homolog's E-value (E) to estimate the weight of its GO term assigned to the query SCOP domain. The probability for a GO term (g) assigned to the query domain is the sum of weights of sequence homologs that have the GO annotation in UniProt-GOA:

$$P_4(g) = \sum_{i=1}^{n} \frac{-\log(E_i) + b}{\sum_{j=1}^{n} \{-\log(E_j) + b \cdot I(g)}$$

where n is the number of sequence homologs, b is a constant of log(10). If the sequence homolog has the function g, $I(g)$ is 1; otherwise 0.

Integration of the four component methods

We combine the output scores of the four component approaches using a Bayesian network (38). The Bayesian network represents the joint probability distribution of multiple variables and is especially suitable for integrating



b.47.1.1

d1te0a2(Stress sensor protease DegS, catalytic domain)

0.5 Apply Cutoff

View GO Tree View Structure Alignment

In this table all GO annotations of d1te0a2 are shown with corresponding probability scores. And click this to show the scores of the four component method. Besides this, you can also click the link in the side panel yields or click the icon before the Results of d1te0a2 to view other functions.

Show 10 entries Search:

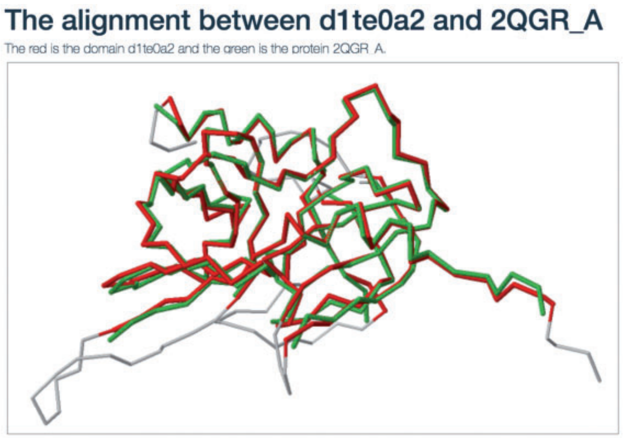
Excel CSV Column visibility

GO ID	Ontology	Name	Score
GO:0004252	molecular_function	serine-type endopeptidase activity	1
GO:0006508	biological_process	proteolysis	1
GO:0016787	molecular_function	hydrolase activity	0.8
GO:0008233	molecular_function	peptidase activity	0.8
GO:0008236	molecular_function	serine-type peptidase activity	0.5
GO:0005576	cellular_component	extracellular region	0.285
GO:0016020	cellular_component	membrane	0.23
GO:0016021	cellular_component	integral component of membrane	0.166
GO:0006915	biological_process	apoptotic process	0.09
GO:0042597	cellular_component	periplasmic space	0.09

Showing 1 to 10 of 123 entries

Previous 1 2 3 4 5 … 13 Next

Figure 2. A snapshot of the SDADB web interface. (A) The GO annotations of a query domain are listed. (B) The GO tree view shows the hierarchical architecture of GO for the query domain.



The alignment between d1te0a2 and 2QGR_A

The red is the domain d1te0a2 and the green is the protein 2QGR A.

Figure 3. The structure alignment view for the domain-protein mappings.

heterogeneous data sources. We split the probability scores of the four component methods into individual bins. The likelihood ratio (LR) (39) for any bin is calculated as the ratio of the odds of a GO annotation to be true or false after and before knowing it is in this bin. The LR represents the increase of the chance that a GO prediction method with a particular set of scores corresponds to a positive GO annotation, compared with a random GO assignment. The final probability score is calculated by integrating the LR of the four component methods:

$$\mathrm{LR} = \prod_{i}^{N} \mathrm{LR}(f_i),$$

where f is the component method.

The final predicted GOA-SCOP (GO annotation for SCOP domains) data are stored in an MYSQL database. The website is developed using Perl, JavaScript, jQuery (AJAX), CSS and HTML5, and is deployed on an Apache web server. The BioJava (40) and JSmol (41) provide visuals of the P2D alignment. D3 (D3.js) (42) is used for visualizing GO hierarchical tree.

Web server interface

The SDADB database can be queried through the protein/domain accession number (e.g. 1te0/d1te0a2) or protein/domain name (e.g. Stress sensor protease DegS). The server will return a list of GO annotations with corresponding confidence scores (Figure 2A). The detailed annotation information, including GO accession ID, GO type, GO name and associated score, are shown in the table. The associated score denotes the probability of the SCOP domain certain having the GO function. The higher the score is, the more likely the SCOP domain has the function. The default cut-off of the associated score is 0.5. The GO annotations with scores over the cut-off are colored in red. The users can change the threshold according to their own needs. Also, users can search GO annotations in the results and download the detailed results in Excel or CSV file.

Users can view the annotations by clicking the 'view GO tree' button, which shows the hierarchical architecture of GO (Figure 2B). Users can expand or collapse the term nodes. The red nodes in the tree are annotated GO terms of the target SCOP domain. Users can view the GO name by putting the mouse over the node. Another unique feature is the visualization of structure alignment for the domain-protein mappings, which constitutes a major contribution to the function prediction. Users can choose to view the alignment between the target domain and its structural neighbors in 3D view (Figure 3).

Results

To evaluate the accuracy of domain functional annotations, we use the dataset obtained from GOA-PDB version 201010 in training and the independent test set from GOA-PDB version 201311 excluding those in GOA-PDB version 201010 for testing. Proteins of the test set that have >90% sequence identity to the proteins in the training set are removed. We use the precision–recall curve and maximum *F*-measure ($F_{\max}$) to measure the overall performance. The precision–recall curve shows the trade-off between precision and recall for different thresholds. A high area under the precision–recall curve denotes high overall performance. *F*-measure considers both the precision and the recall of the GO prediction results of SCOP domains. It is calculated as the harmonic average of the precision and recall. Maximum *F*-measure ($F_{\max}$) is the maximum value of the *F*-measure over a varying threshold. The coverage is computed by dividing the number of domains with predicted GO annotations by the total number of domains in SCOPe 2.06. For detailed descriptions of the datasets and performance measures, see Reference (25).

We compare our SDADB database with the four component methods, including structure alignment-based method (Str), Interpro domain-based method (IPR), PSSM profile-based method (PSSM) and sequence homolog-based approach (Seq). The results are summarized in Table 1. We observe that the combined SDADB significantly outperforms the four component methods, with a maximum *F*-score of 0.833 for MF (molecular function), a maximum *F*-score of 0.723 for BP (biological process) and a maximum *F*-score of 0.809 for CC (cellular component). For the coverage, SDADB has GO annotations for most SCOP domains (92.3%). We also compare SDADB with other state-of-the-art approaches on the independent test

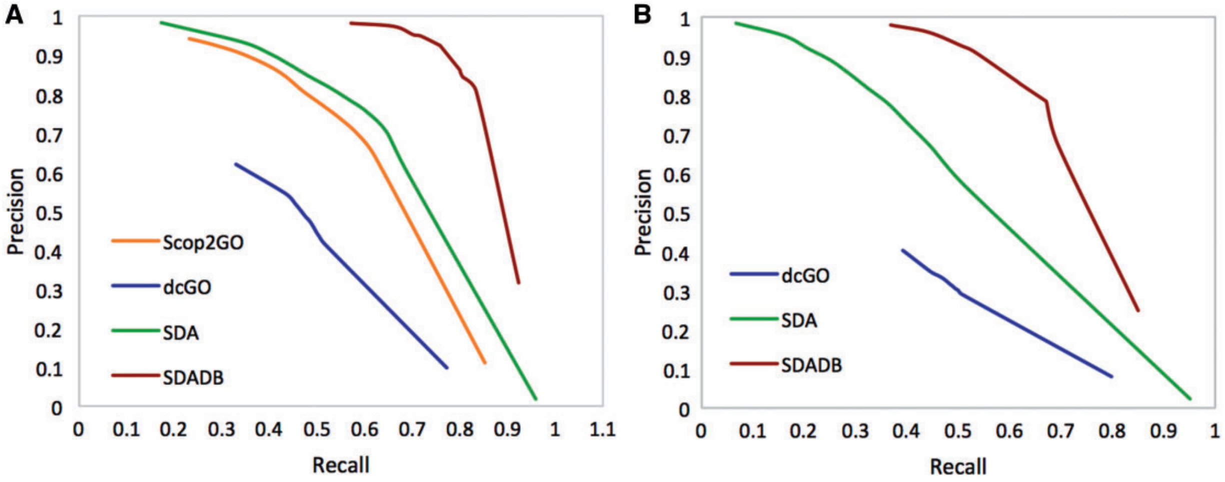


Figure 4. Precision–recall curve of SDADB versus existing methods for molecular function (A) and biological process (B).

Table 1. Prediction performance comparison of SDADB with the four component methods

Methods	Coverage	Fmax (MF)	F_{max} (BP)	F_{max} (CC)
Str	0.802	0.806	0.690	0.767
Blast	0.918	0.755	0.616	0.687
PSSM	0.509	0.491	0.364	0.507
IPR	0.555	0.711	0.508	0.263
SDADB	**0.923**	**0.833**	**0.723**	**0.809**

dataset. As shown in Figure 4, it is clear that SDADB significantly outperforms SDA and other methods for both MF and BP.

Conclusion

The SDADB database provides large-scale detailed GO annotations at the structural domain level. In contrast to the approaches based on sequence and homology information, an advantage of SDADB is that the method integrates structural neighborhood features together with a variety of heterogeneous information, including SCOP-InterPro domain mapping information, PSSMs and sequence homolog features. The SDADB database now contains 3 482 316 GO annotations for 211 282 SCOP domains with a probability >0.1. Of these, 1 479 652 annotations for 204 948 domains have a probability >0.5. Also, SDADB provides P2D mappings for over 191 060 PDB structures. The vast amount of P2D and domain-function mapping data in the SDADB database can help to investigate the functions of full-length proteins since domains are functional units of proteins. The database will also give valuable insights into protein domain evolution, which are not only likely to be fascinating but will also ultimately improve the power and accuracy of protein function prediction approaches.

It is worth pointing out that some common and multifunctional domains may be not well annotated since the presence of a common domain in several proteins does not necessarily imply that these proteins have the same function. Future developments will focus on combining more informative clues and analyzing tools. We also expect the interested user will be able to use the resources provided in the SDADB database as a basis for new efforts on expanding the functional space for both domains and full-length proteins.

Availability

The SDADB database is freely available at http://sda.denglab.org/.

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Conflict of interest. None declared.

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