New developments in the InterPro database

Nicola J. Mulder1,*, Rolf Apweiler1, Teresa K. Attwood3, Amos Bairoch4,5, Alex Bateman2, David Binns1, Peer Bork6, Virginie Buillard4, Lorenzo Cerutti4, Richard Copley7, Emmanuel Courcelle8, Ujjwal Das1, Louise Daugherty1, Mark Dibley9, Robert Finn2, Wolfgang Fleischmann1, Julian Gough10, Daniel Haft11, Nicolas Hulo4, Sarah Hunter1, Daniel Kahn12, Alexander Kanapin1, Anish Kejariwal13, Alberto Labarga1, Petra S. Langendijk-Genevaux4, David Lonsdale1, Rodrigo Lopez1, Ivica Letunic6, Martin Madera14, John Maslen1, Craig McAnulla1, Jennifer McDowall1, Jaina Mistry2, Alex Mitchell1,13, Anastasia N. Nikolskaya15, Sandra Orchard1, Christine Orengo9, Robert Petryszak1, Jeremy D. Selengut11, Christian J. A. Sigrist4, Paul D. Thomas13, Franck Valent1, Derek Wilson14, Cathy H. Wu15 and Corin Yeats9

1EMBL Outstation—European Bioinformatics Institute and 2Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK, 3Faculty of Life Sciences and School of Computer Science, University of Manchester, Manchester, UK, 4Swiss Institute for Bioinformatics, Geneva, Switzerland, 5Department of Structural Biology and Bioinformatics, University of Geneva, Switzerland, 6Biocomputing Unit EMBL, Heidelberg, Germany, 7Wellcome Trust Centre for Human Genetics, Oxford, UK, 8CNRS/INRA, Toulouse, France, 9Biochemistry and Molecular Biology Department, University College London, University of London, UK, 10Genomic Sciences Centre, RIKEN Yokohama Institute, Suehiro-cho, Tsurumi-ku, Yokohama, Japan, 11The Institute for Genomic Research, Rockville, MD, USA, 12Laboratoire de Biométrie et Biologie Evolutive and INRIA HELIX Project, University Lyon 1, France, 13Evolutionary Systems Biology Group, SRI International, Menlo Park, CA, USA, 14MRC Laboratory of Molecular Biology, Cambridge, UK and 15Protein Information Resource, Georgetown University Medical Center, Washington, DC, USA

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ABSTRACT

InterPro is an integrated resource for protein families, domains and functional sites, which integrates the following protein signature databases: PROSITE, PRINTS, ProDom, Pfam, SMART, TIGRFAMs, PIRSF, SUPERFAMILY, Gene3D and PANTHER. The latter two new member databases have been integrated since the last publication in this journal. There have been several new developments in InterPro, including an additional reading field, new database links, extensions to the web interface and additional match XML files. InterPro has always provided matches to UniProtKB proteins on the website and in the match XML file on the FTP site. Additional matches to proteins in UniParc (UniProt archive) are now available for download in the new match XML files only. The latest InterPro release (13.0) contains more than 13 000 entries, covering over 78% of all proteins in UniProtKB. The database is available for text-and-sequence-based searches via a webserver (http://www.ebi.ac.uk/interpro), and for download by anonymous FTP (ftp://ftp.ebi.ac.uk/pub/databases/interpro). The InterProScan search tool is now also available via a web service at http://www.ebi.ac.uk/Tools/webservices/WSInterProScan.html.

INTRODUCTION

InterPro (1) incorporates the major protein signature databases into a single resource. These include: PROSITE (2), which uses regular expressions and profiles, PRINTS (3), which uses Position Specific Scoring Matrix-based (PSSM-based) fingerprints, ProDom (4), which uses automatic sequence clustering, and Pfam (5), SMART (6), TIGRFAMs (7), PIRSF (8), SUPERFAMILY (9), Gene3D (10) and PANTHER (11), all of which use hidden Markov models (HMMs). Table 1 shows the coverage of each of these member

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*To whom correspondence should be addressed. Tel: +44 1223 494 602; Fax: +44 1223 494 468; Email: mulder@ebi.ac.uk

Present address: Julian Gough, Unite de Bioinformatique Structurale, Institut Pasteur, Paris, France

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Annotation

Two new member databases have been integrated into InterPro, PANTHER and Gene3D. PANTHER (http://www.pantherdb.org) (11) HMMs define protein families and subfamilies modelled on the divergence of specific functions within the families, which permits more accurate association with function based on ontology terms and pathways, as well as inference of amino acids important for functional specificity. PANTHER currently has high coverage of all families that contain at least one metazoan protein, including homologous proteins from all taxa. Consequently, coverage is very high for proteins found in animals and less so for other groups, such as plants, fungi and bacteria. The addition of PANTHER HMMs to InterPro is facilitating more fine-grained annotation of functionally and evolutionarily related subfamilies. Gene3D (http://cath.wbi.ac.uk:8080/Gene3D/) (10) is a library of HMMs that represent all proteins of known structure. The seed alignments for the models are derived from the proteins found within the homologous superfamly (H-level) classification level in CATH, which groups together domains that are thought to share a common ancestor. Gene3D models are being integrated to complement the SUPERFAMILY models that are based on SCOP superfamilies.

To further extend the publications section of InterPro entries, we have introduced the ‘additional reading’ field. This field lists any publications provided by the member databases for the methods associated with each InterPro entry, which are not directly referenced in the InterPro abstract. Additionally, a maximum of five references per entry are taken from the PDB when one or more of the proteins in the entry has had its structure determined. These references provide the user with additional publications to visit to find out more about the proteins in the entry, and also provide InterPro curators with a list of references to consult when updating abstracts.

Table 1. Coverage of protein sequences and amino acid residues for each member database

<table>
<thead>
<tr>
<th>Member database</th>
<th>Number of methods in InterPro</th>
<th>Total number of proteins hit by database</th>
<th>Total number of residues covered</th>
<th>Number of unique proteins hit by database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene3D</td>
<td>1465</td>
<td>1 736 593</td>
<td>395 970 746</td>
<td>18 504</td>
</tr>
<tr>
<td>PANTHER</td>
<td>39 648</td>
<td>582 799</td>
<td>173 969 368</td>
<td>6355</td>
</tr>
<tr>
<td>PIRSF</td>
<td>1347</td>
<td>161 248</td>
<td>58 525 186</td>
<td>851</td>
</tr>
<tr>
<td>PRINTS</td>
<td>1900</td>
<td>645 272</td>
<td>55 137 257</td>
<td>3936</td>
</tr>
<tr>
<td>PROSITE patterns</td>
<td>1336</td>
<td>766 422</td>
<td>16 861 589</td>
<td>14 229</td>
</tr>
<tr>
<td>PROSITE profiles</td>
<td>632</td>
<td>763 334</td>
<td>153 498 831</td>
<td>2131</td>
</tr>
<tr>
<td>Pfam</td>
<td>8296</td>
<td>2 502 476</td>
<td>570 591 566</td>
<td>289 062</td>
</tr>
<tr>
<td>ProDom</td>
<td>3538</td>
<td>506 284</td>
<td>61 153 722</td>
<td>19 926</td>
</tr>
<tr>
<td>SMART</td>
<td>706</td>
<td>514 466</td>
<td>94 310 609</td>
<td>2252</td>
</tr>
<tr>
<td>SUPERFAMILY</td>
<td>1122</td>
<td>1 929 112</td>
<td>484 789 136</td>
<td>51 282</td>
</tr>
<tr>
<td>TIGRFAMs</td>
<td>2625</td>
<td>501 897</td>
<td>170 121 752</td>
<td>7306</td>
</tr>
</tbody>
</table>

*aNot all the methods are integrated into InterPro entries, e.g. for PANTHER, but InterPro provides matches to them in the match XML file.

*bThis is the number of proteins hit by one database only.
A clan contains two or more Pfam families that have arisen from a single evolutionary origin, based on evidence from structure, function, profile–profile comparisons and whether the sequences are matched by more than one HMM. Clans were introduced to resolve the issue of Pfam HMMs overlapping on a sequence, as this is forbidden in the Pfam database. Clan information is used in post-processing of matches to remove these overlaps. The link from InterPro entries to clans provides a popup display of the Pfam clan name and all Pfam clan members with their corresponding InterPro accession numbers. These InterPro entries will not necessarily be related to each other through parent/child or contains/found in relationships.

Links to IntAct (http://www.ebi.ac.uk/intact/site/) (16), the molecular interaction database, have been incorporated into InterPro, providing manually curated examples of domain–domain interactions. IntAct incorporates protein–protein interaction data derived from the literature and direct submissions, and provides a query interface and modules to analyze the data. Links from InterPro to IntAct are provided at the level of individual UniProtKB accessions, and are restricted to 20 randomly chosen examples. There are currently 135 InterPro entries with links to 1180 IntAct entries, involving 400 proteins. This number is likely to remain low, compared to the total number of interactions in IntAct, as these links are based on well curated domain interactions, rather than every protein–protein interaction.

New positional links are available for UniProtKB proteins to MODBASE (http://modbase.compbio.ucsf.edu/modbase-cgi-new/index.cgi) (17) and SWISS-MODEL (http://swissmodel.expasy.org/) (18). MODBASE is a database of 3D protein models calculated by comparative modelling using ModPipe, an automated modelling pipeline relying on programs, such as PSI-BLAST and MODELLER. MODBASE matches to protein sequences are shown in the detailed graphical view as yellow and white striped bars. SWISS-MODEL is a repository of annotated 3D protein structure models from the UniProtKB sequence database, and provides a protein structure homology modelling server. Matches to protein sequences are shown in the detailed graphical view as red and white striped bars. These cross-references, as well the other links to more than 30 different databases, increase the value of InterPro with respect to its interoperability and integration with other data sources.

### Protein matches

Protein matches in InterPro are pre-calculated using the InterProScan software (14). InterProScan is a tool that combines different protein signature recognition methods of the InterPro member databases into one resource, and provides the corresponding InterPro accession numbers and GO annotation in the results. InterProScan can be used via a web interface or email server, which allows searching of a sequence against InterPro, or it can be installed and run locally for bulk searches. A new development has been the establishment of a web service for running single or multiple sequences through InterProScan. More information about the web service and example clients in Perl and Java for accessing the service is available from http://www.ebi.ac.uk/Tools/webservices/WSInterProScan.html. This service provides programmatic access to the tool for users who want to run bulk searches or use InterProScan as part of a pipeline.

Over the past two years, additional protein matches have become available in InterPro. Previously, InterPro matches were available only for UniProtKB proteins, but now InterPro provides additional matches to alternative splice products and UniParc proteins. Matches to splice variant sequences associated with UniProtKB accession numbers can be accessed through the ‘protein with splice variants’ link from the Matches field, and are available through the compact and detailed displays. The matches for the master sequence are shown at the top with the splice variant matches below them, so it is easy to identify where matches differ between isoforms. The splice variant sequences originate from UniProtKB, and of the 25 927 splice variants available, 24 268 have hits to a total of 3483 InterPro entries.

The UniProt archive (UniParc) is a repository of all protein sequences, with each unique sequence stored once. These sequences are then cross-referenced to the relevant databases, e.g. UniProtKB, and include data submitted from metagenomics projects. This repository contains 7.5 million protein sequences, including UniProtKB proteins, and therefore the calculation of InterPro matches is slow. These calculations are ongoing, and the data provided incorporates the most up-to-date matches available at that point in time. Currently, there are just over 50 million InterPro matches to UniParc proteins. UniParc matches are not yet visible in InterPro entries, but are available in XML format from the FTP site and are searchable in SRS. An additional match XML file, match_complete.xml, is provided with each release, and contains UniProtKB sequence matches for all member database signatures, including those that have not yet been integrated into InterPro. This is to ensure that the public has access to all protein signature matches that have been calculated. All protein matches are updated on each major InterPro release (approximately every 3 months).

### Web interface

The web interface has been extended to provide additional searching options. From the text search page (http://www.ebi.ac.uk/interpro/search.html) the user can search within
InterPro entries or protein matches. One can retrieve matches for a UniProtKB accession number by pasting the accession number in the search box and selecting ‘Find protein matches’. This returns the matches in a combination of formats. The protein match views can also be selected in the Matches section of an InterPro entry, which provides options for displaying the matches in different tabular or graphical views. From any of these views, the user can then select a set of proteins by UniProtKB accession number(s) or InterPro accession, and can refine the set to show splice variants or proteins with known structure or both. Alternatively, the user can filter the protein set by taxonomy using the ‘tax ID’. Once the protein set has been defined, the user can select the output display format from ‘compact’, ‘detailed’, ‘architectures’ or ‘table’, and can specify the order of proteins in the display by UniProtKB accession or identifier.

In addition to links to complete match lists, each InterPro entry page contains a taxonomy wheel showing the taxonomic range of proteins matching the entry. The numbers on the wheel for each taxonomic group are now ‘clickable’. Clicking on a particular lineage returns only the protein matches for the selected taxonomy. In this view, the species are sorted and displayed alphabetically and the lineage is shown at the top. The numbers on the phylogeny show the number of proteins associated with each taxonomic group that match the entry.

DISCUSSION

InterPro now integrates protein signatures from 10 different member databases, and links >20 additional resources, including UniProtKB, structural data and specialized protein family databases. It has proven its usefulness in the functional characterization of proteins, and is used by genome annotation projects (19–22) and individual researchers worldwide. In the last year, the InterPro website received ~3 million hits per month from up to 35 000 unique hosts. Through the mapping of InterPro entries to GO terms, InterPro contributes the majority of annotations of proteins to GO terms. Approximately 68% of all UniProtKB proteins are annotated with GO terms from a combination of manual annotation and the use of mappings, such as InterPro2GO, Swiss-Prot keyword2GO, etc. InterPro2GO alone provides GO annotations for 61% of UniProtKB proteins, thus accounting for a significant proportion of the total number of annotations currently available. These GO mappings are also available via InterProScan, which facilitates GO annotation to query proteins. The current release of InterPro contains more than 13 000 entries, with its signatures covering over 78% of UniProtKB proteins. The integration of new protein signatures from the existing and new member databases will continue to increase the coverage, as well as the depth, of InterPro.

The InterPro database will continue to develop and increase its functionality. Future plans include the provision of protein match views for UniParc matches, facilitating the searching and browsing of InterPro entries by function, and the provision of data for unintegrated protein signatures via the InterPro web interface. Integration of signatures into InterPro entries and subsequent annotation of the entries is done manually and is thus of high-quality, but is time-consuming. In order to make the signatures awaiting integration available to the public via the web interface, new entries will be created automatically for the unintegrated signatures and will be searchable by their member database accession numbers. The protein matches will be available in the same format as match views from InterPro entries so that the user can see how the new signature relates to existing entries. These new features will increase the usefulness of this already popular high-quality resource.

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REFERENCES


