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# Reactome knowledgebase of human biological pathways and processes

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## ABSTRACT

Reactome (<http://www.reactome.org>) is an expert-authored, peer-reviewed knowledgebase of human reactions and pathways that functions as a data mining resource and electronic textbook. Its current release includes 2975 human proteins, 2907 reactions and 4455 literature citations. A new entity-level pathway viewer and improved search and data mining tools facilitate searching and visualizing pathway data and the analysis of user-supplied high-throughput data sets. Reactome has increased its utility to the model organism communities with improved orthology prediction methods allowing pathway inference for 22 species and through collaborations to create manually curated Reactome pathway datasets for species including *Arabidopsis*, *Oryza sativa* (rice), *Drosophila* and *Gallus gallus* (chicken). Reactome's data content and software can all be freely used and redistributed under open source terms.

## EXPANDED COVERAGE OF HUMAN PATHWAYS

The current release of Reactome (version 26, September 2008) covers approximately 12.5% of 20 000 curated UniProt human proteins, a 2.7-fold increase over the last three years. Forty-six major domains of human

biology, such as apoptosis, the HIV and influenza life cycles, DNA replication, transcription, hemostasis and carbohydrate metabolism are annotated, as are normal functions of 1005 proteins associated with OMIM disease phenotypes (<http://www.ncbi.nlm.nih.gov/omim/>).

## IMPROVED TOOLS, SOFTWARE AND DATA MODEL

### Revised orthology prediction methods

The OrthoMCL clustering procedure (1,2) ([http://reactome.org/electronic\\_inference.html](http://reactome.org/electronic_inference.html)) applied to data from OrthoMCL DB (<http://www.orthomcl.org/cgi-bin/OrthoMclWeb.cgi>), Version 2, is used to identify orthologs of curated human proteins in each of 22 evolutionarily divergent species for which high-quality whole-genome sequence data are available (3). In line with changes in the OrthoMCL clustering procedure, only the longest transcript of each gene is considered, and a gene-based rather than a protein-based method is used to map the Ensembl identifiers used by OrthoMCL to the UniProt accessions used in Reactome. These changes have improved our success rate for electronic inference without measurably affecting accuracy.

### Improved tools for analysis of large-scale data sets, data-mining and modeling

*SkyPainter*. The current version of the SkyPainter tool allows users to more effectively visualize the functional relationships among genes identified in large-scale

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The authors wish it to be known that, in their opinion, the first two authors should be regarded as joint First Authors

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experiments (Figure 1A and B). For a user-submitted list of genes, each reaction arrow on the reaction map is colored according to the number of user-specified genes whose products participate in the reaction. In addition, hypergeometric testing is now used to display statistically over-represented events in the event hierarchy. Statistically over-represented events may also be viewed as an ordered list and a mapping from submitted identifiers to reactions is provided. The colored reaction maps can be downloaded in publication quality PNG, SVG or PDF format.

**Biomart.** The newly implemented Reactome BioMart tool ([www.biomart.org](http://www.biomart.org)) facilitates data mining, cross-database analysis and large-scale analysis of gene function. A user can formulate queries across selected data sets (pathways, reactions and complexes) specifying data attributes and filters to narrow searches. For example, querying the Reactome dataset, a user can identify all complexes that contain a given protein (Figure 1C). Alternatively, a user can link a query of the Reactome 'complexes' dataset to a UniProt proteome query and retrieve sequences of all the proteins in these complexes.

Popular searches, e.g. all reactions or proteins or genes in a given pathway, all pathways inferred for a given species or all reactions or pathways involving a set of specified genes can be launched with predefined 'canned' queries. Additional context-sensitive help documentation is under construction.

**Changes in the Reactome data model.** These have been minimized, to facilitate data curation and use of the knowledgebase. Two additions are a 'black box' reaction class to allow the annotation of events for which not all defining attributes can be provided and an 'entityOnOtherCell' attribute to allow description of individual events and complexes that span two cells.

## COLLABORATIONS

We are actively collaborating in the creation of model organism Reactome projects for *Arabidopsis*, rice, *Drosophila* and chicken. The Arabidopsis Reactome (<http://arabidopsisreactome.org/>), developed with the human Reactome data model, software and curation tools, contains seven manually curated pathways and 311 pathways inferred from data in KEGG (<http://www.genome.ad.jp/kegg/pathway.html>) (4) and MetaCyc (<http://metacyc.org/>) (5). Arabidopsis Reactome events have been electronically projected onto five other predicted plant proteomes using the OrthoMCL prediction method described above (6). Curation of *Drosophila* and chicken reactions is underway in collaboration with FlyBase and the Gallus Knowledge Extraction and Annotation project using the Reactome infrastructure and curation protocols; the first releases of these databases are planned for late 2008.

In collaboration with the BioHealthbase group at University of Texas Southwestern Medical College, the life cycle of Influenza virus has been curated and reviewed and is publicly accessible as a segment of Reactome (7).

In collaboration with the Protein Ontology group—PRO (8), Reactome annotations of complexes and physiological states of proteins are being applied to build a hierarchy of proteins and their functional forms. For example, protein objects used to illustrate TGF- $\beta$  signaling in PRO use corresponding protein objects in the Reactome annotated pathway. The Reactome and PRO collaboration, as a source for curated annotations of proteins, extends the application of Reactome to a larger ontology community.

## INCREASED DATA INTEGRATION AND USER SUPPORT

We are increasing the accessibility of Reactome data through data integration and improved online documentation. Reactome pathway annotations are now included in the Pathway Interaction Database (<http://pid.nci.nih.gov/>) (9). Reactome's online documentation is now available as WIKI pages that provide easy access to user, author and curator guides as well as glossaries and standard operating procedure (SOP) guidelines. In addition, an Editorial Calendar lists modules being prepared for the knowledgebase, their planned release dates and contact information for module curators.

To support data mining, analysis and modeling of Reactome content by other groups, individual reactions and pathways can be exported in SBML ([http://sbml.org/Main\\_Page](http://sbml.org/Main_Page)) (10), Protégé (<http://protege.stanford.edu/>), Cytoscape (<http://www.cytoscape.org/>) (11) and BioPax (<http://www.biopax.org/>) (levels 2 and 3) formats. The entire data content of Reactome can be downloaded as a MySQL database or in SBML or BioPax 2 and 3 formats. A SOAP based Web Services API is now available to access the Reactome data. Details about this API are provided in many forms including a 'Flash' tutorial and a PDF user's guide at <http://www.reactome.org/download/index.html>.

## FUTURE DIRECTIONS

A long-term objective of the Reactome project is to provide users with intuitive graphical representations of pathways and reactions. Toward this goal, Reactome has developed a beta version of an entity-level pathway visualization tool: through enhanced navigation features including improved zooming, scrolling and event highlighting, this tool provides a detailed graphical representation of the relationships among the molecules participating in reactions (Figure 1D).

Hover-over molecule/reaction descriptions allow quick and easy scanning of the molecular details of each reaction. An improved search option with an auto-complete feature at the top of the page allows directed queries over reaction and pathway names, entity names, identifiers and GO molecular function terms.

### New author tool with pathway diagram editing capability

We are in the process of developing a user interface that couples the powerful navigation and search features of the entity level pathway visualization tool with software that



draws intuitive ‘textbook style’ illustrations of pathways. To this end, we have recently developed an SBGN (<http://www.sbgm.org>) based version of the Reactome author tool that can create such diagrams (Figure 1E). Currently, this has been released as a beta test version and is available as a Java Web Start application at the Reactome development site: (<http://brie8.cshl.edu:8080/ReactomeTools/AuthorTool/authorToolLaunch.html>).

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