

Enzyme Resources: IntEnz, Rhea and BRENDA

Partners

IntEnz and Rhea are produced by EMBL-EBI in collaboration with the Swiss Institute of Bioinformatics (www.isb-sib.ch). This collaboration is responsible for the production of the ENZYME.dat resource, now an integral part of IntEnz.

BRENDA is produced by the Department of Bioinformatics at the Technische Universität Braunschweig.

Need help with IntEnz or Rhea?

Support for IntEnz:
www.ebi.ac.uk/intenz
intenz-help@lists.sourceforge.net

Support for Rhea:
www.ebi.ac.uk/rhea
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Need help with BRENDA?

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Published by the
EMBL-EBI – a part
of the European
Molecular Biology
Laboratory

EBI's new enzyme portal

The EBI's forthcoming enzyme portal will provide access to data from several resources, including IntEnz, Rhea, ChEBI, UniProtKB, Reactome and PDB. Its search, browse and download services will be complimented by enzyme comparison tools and customised reporting. Users have helped guide the design and content selection of this new interface.

IntEnz – www.ebi.ac.uk/intenz

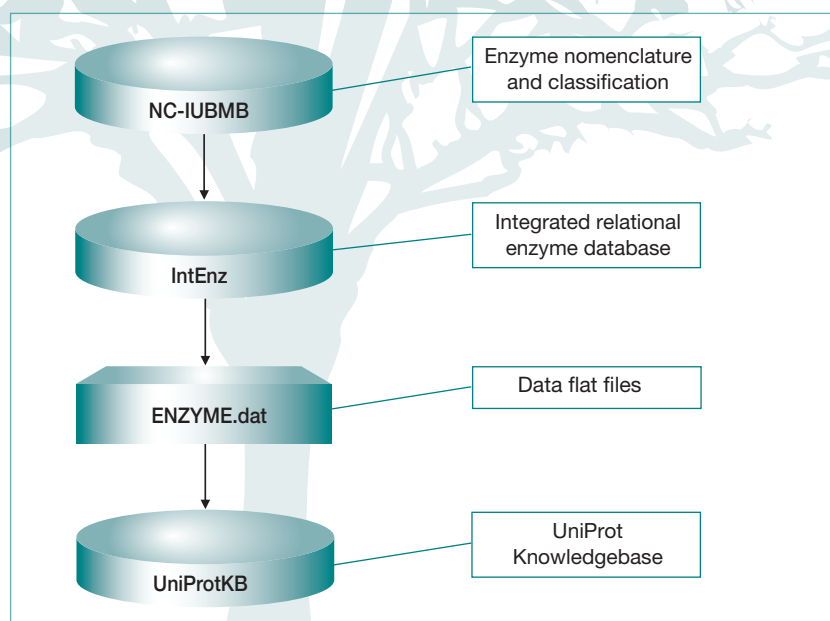
Enzyme nomenclature and classification are two distinct but interrelated systems for categorising enzyme activity. In the past, enzyme nomenclature and classification were provided by different organisations either as a plain text file (e.g. ENZYME.dat by the Swiss Institute of Bioinformatics, SIB) or HTML pages (e.g. the enzyme web pages of the NC-IUBMB and the data held in the BRENDA resource). IntEnz combines these distinct data sources, providing a unified data flow from NC-IUBMB via ENZYME.dat to UniProtKB, the world's gold-standard database for protein information.

What is IntEnz?

IntEnz, the integrated relational enzyme database, is a freely available resource that follows the recommendations of the NC-IUBMB for enzyme nomenclature and classification. It is the master data source for ENZYME.dat, which is the main reference resource for enzymes in UniProtKB. All of the data is curated within IntEnz by SIB and then exported daily for production in UniProtKB.

What can I do with IntEnz?

- Use it as a dictionary and thesaurus of enzyme names. IntEnz keeps track of synonyms or ambiguous names to aid identification.
- Find the biochemical reaction associated with an EC number, or vice versa.



Data flow relationships between IntEnz, NC-IUBMB and UniProtKB.

Wherever possible, the reactions in IntEnz have been checked for mass and charge to make sure that reactions are accurately depicted using ChEBI (www.ebi.ac.uk/chebi) as a controlled vocabulary for compounds. These reactions are available from Rhea (see below).

- Retrieve information about cofactors, cross references to other databases (i.e. UniProtKB, PROSITE, KEGG and GO) and bibliographic references.
- Browse the EC classification system, finding relationships between enzymes by virtue of their substrates, products or the type of biochemical reaction they catalyse.

Retrieving data from IntEnz

Searching. IntEnz provides search tools that let you apply some constraints by field, such as Enzyme Commission (EC) number (including preliminary EC numbers issued by UniProt); name (accepted, systematic or synonym); reaction; cofactor; references; or a combination of terms. It also lets you search biochemical reactions using a Rhea identifier and compound names. Search results are shown as a simple table.

Browsing. IntEnz provides up-to-date EC classifications as a browsable tree, and includes deleted or transferred EC numbers. The location of a given enzyme within the tree structure reflects the type of reaction it catalyses.

Downloading IntEnz

IntEnz is downloadable from the IntEnz FTP site in three formats: the flat file ENZYME.dat format, IntEnzXML and BioPAX level 2, a standard data exchange format for data on biological pathways: www.ebi.ac.uk/intenz/downloads.jsp.

Submitting data to NC-IUBMB via IntEnz

The NC-IUBMB, in association with the Joint Commission on Biochemical Nomenclature (JCBN), updates its official enzyme classification and nomenclature list bimonthly. New enzymes – and corrections to existing ones – can be submitted to NC-IUBMB using the ‘Data submission’ menu on the IntEnz website. No registration is needed. To submit a new enzyme, you need to know the overall reaction equation; proposed name(s) for the enzyme; enzyme structure and cofactors; and full bibliographic citations (to be sent as PDF files).

Rhea – www.ebi.ac.uk/rhea

The ability to precisely describe biochemical reactions is essential for accurately modelling metabolic networks and calculating metabolite fluxes in biological systems. In the past, biochemical reactions were stored as plain text in IntEnz. This system had limitations: redundancy, ambiguity (a given compound might appear with different names) and isolation (reactions were not linked to any external resource). Rhea, a database of balanced reactions, was created to address these difficulties by analysing the equations in IntEnz and mapping every reactant and product to a compound in ChEBI, providing a controlled vocabulary for enzymatic reactions. Rhea can thus provide a way to accurately identify and discard redundant information about biochemical reactions.

What is Rhea?

Rhea is a manually annotated database of biochemical reactions that was developed in collaboration with the SwissProt group at SIB. Rhea is extensively cross-referenced to other reactions and compounds databases.

Every entry in Rhea is unique and stoichiometrically balanced, with a stable identifier and well defined directionality. Rhea was designed to incorporate reactions independently of spatial location and catalysts. It also holds other types of balanced reactions, including

those that occur spontaneously.

What can I do with Rhea?

- Use it as a controlled vocabulary for reactions.
- Find all EC numbers and publications associated with a particular reaction.
- Browse links to other sources of information about biochemical reactions: MACIE, UniPathway, Reactome, KEGG Reaction, MetaCyc and ChEBI.
- Find reactions related to each other via their directionality and whether the reactions are part of a multi-step process.

Retrieving data from Rhea

You can query all of the fields in the database using the simple search box on the homepage. Your search term can be a compound name or identifier (e.g. ChEBI ID), reaction identifier (Rhea ID), reaction equation, cross reference or a citation. The advanced search allows you to narrow the query by field, by cross-referenced database and by chemical structure, using the substructure search provided by ChEBI.

Downloading Rhea

The data held in Rhea is available in three formats: as a BioPAX level 2 file, in RXN format (chemical table files for individual reactions) and in RD (reaction data) format (either for the whole database or individual reactions).

Submitting data to Rhea

New reactions that are not currently annotated in Rhea can be submitted using the 'Reaction requests/updates' SourceForge tracker (www.sf.net/projects/rhea-ebi). Submissions must include: the reaction equation, all reactants and products that take part in the reaction (with their ChEBI ID or chemical structures) and any cross-references and bibliographic citations. For more information on the types of reactions held in Rhea, see www.ebi.ac.uk/rhea/manual.xhtm.

BRENDA – www.brenda-enzymes.org

BRENDA (the Braunschweig Enzyme Database) provides enzyme information for researchers in the life sciences, presenting it in a convenient, meaningful and easily searchable way. All of the information held in BRENDA, with the exception of enzyme nomenclature, is extracted from the primary scientific literature.

What is BRENDA?

BRENDA, a relational database, is one of the largest enzyme information resources, holding almost 5000 EC numbers. It contains biochemical and molecular information on all classified enzymes, and features software tools for querying the database and calculating molecular properties. The consistency of the data held in BRENDA is verified by computer programs, whilst each enzyme dataset is checked manually by at least one biologist and one chemist. BRENDA is curated by Professor Dietmar Schomburg's group at the Department of Biochemistry and Biotechnology at the Technische Universität Braunschweig.

What can I do with BRENDA?

BRENDA can be used to find information on enzyme features, such as:

- classification and nomenclature;
- reaction and specificity;
- functional and kinetic parameters such as k_{cat} or K_m ;
- organism-related information;
- enzyme structure and stability.

Retrieving data from BRENDA

BRENDA provides an intuitive search engine that offers:

- a simple, quick search;
- a full-text search that includes comments;
- an advanced, combinatorial search;
- a substrate search, featuring a graphical interface that allows you to enter a 2D molecular structure for enzyme ligands;
- a sequence search, which is useful for enzymes with a known protein sequence, or for searching specific sequence features (e.g. predicted membrane helices).

BRENDA provides a number of Explorer functions to browse the data.

- TaxTree Explorer is used to search for organisms in the tree of life.
- EC Explorer enables browsing or searching of the hierarchical enzyme classification system (classes, subclasses, sub-subclasses and serial numbers). The results are marked in the EC tree to provide a concise view of all functionally related enzymes. The EC numbers are linked to an enzyme flat file, containing all of the information held in BRENDA.
- Genome Explorer displays enzyme-coding genes in their genomic context.
- Ontology Explorer allows searching of all biochemically relevant ontologies, including the BTO (BrendaTissueOntology), which contains approximately 4000 terms on tissues, organs and cell types.

Downloading BRENDA

The complete set of manually curated BRENDA data can be downloaded in text format from the homepage (www.brenda-enzymes.org). Contact information needs to be supplied in order to download data from BRENDA. Registration is free.

BRENDA facilitates the creation of metabolic models by allowing researchers to create and download a species-specific SBML (Systems Biology Markup Language) file containing enzyme kinetic data (k_{cat} , K_m , k_i) and enzyme-catalysed reactions.

Programmatic access to BRENDA

BRENDA data can be accessed by SOAP at: www.brenda-enzymes.org/soap2

Submitting data to BRENDA

You can submit enzyme data via the BRENDA input page, which links from the homepage (www.brenda-enzymes.org). The EC number, a full scientific reference and details of the reaction participants are required. ●

Further reading

Alcántara, R. *et al.* (2007) IntEnz. Molecular Biology Database Collection entry number 508. *Nucleic Acids Res.* www.oxfordjournals.org/nar/database/summary/508

Scheer, M. *et al.* (2011) BRENDA, the enzyme information system in 2011. *Nucleic Acids Res.* 39, D670-D676

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Support

IntEnz and Rhea are funded by the European Molecular Biology Laboratory (EMBL). IntEnz is also funded by the European Commission under SLING, grant agreement number 226073 (Integrating Activity) within Research Infrastructures Action of the FP7 Capacities Specific Programme.

BRENDA is financially supported by the European Commission under FELICS, contract number 021902 (RII3) within Research Infrastructures Action of the FP6 'Structuring the European Research Area' Programme and SLING.