Data and Text Processing
for
Health and Life Sciences

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Book website: `http://labs.rd.ciencias.ulisboa.pt/book/`

First Edition: `https://link.springer.com/book/10.1007/978-3-030-13845-5`

Introduction

Health and Life studies known for the huge amount of data they produce

Value of the data should not be measured by its amount

- possibility and ability of researchers to retrieve and process it

Transparency, openness, and reproducibility are key aspects

Biomedical data repositories

Examples: European Bioinformatics Institute (EBI)
National Center for Biotechnology Information (NCBI) repositories

Researchers cannot rely on available data as mere facts
they may contain errors
can be outdated
and may require a context

Scientific text

Structured data is what most computer applications require as input

Humans tend to prefer the flexibility of text to express
their hypothesis, ideas, opinions, conclusions

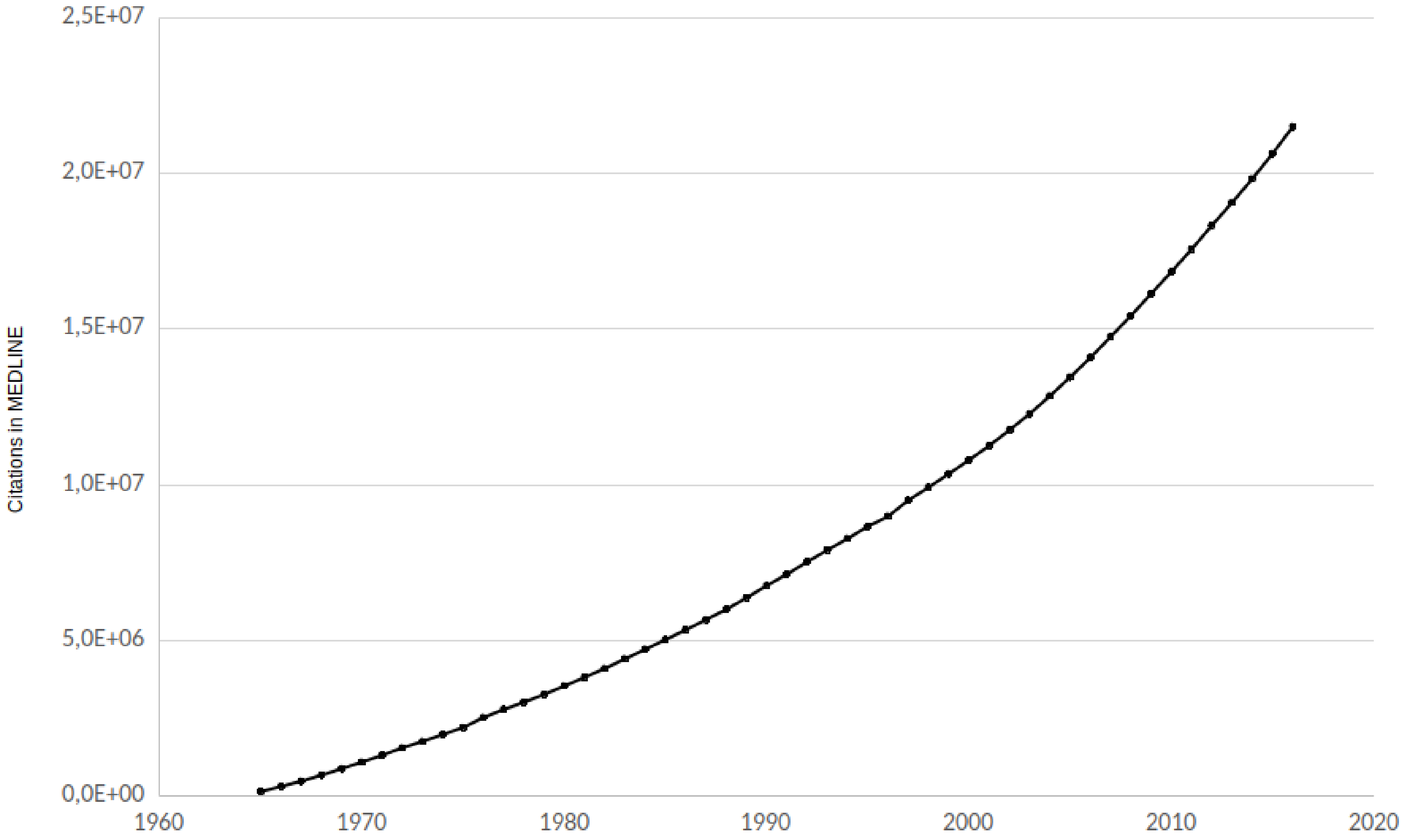
Text is still the preferential means to publish new discoveries
and to describe the data that support them

Amount of text

Huge amount of text being published every day

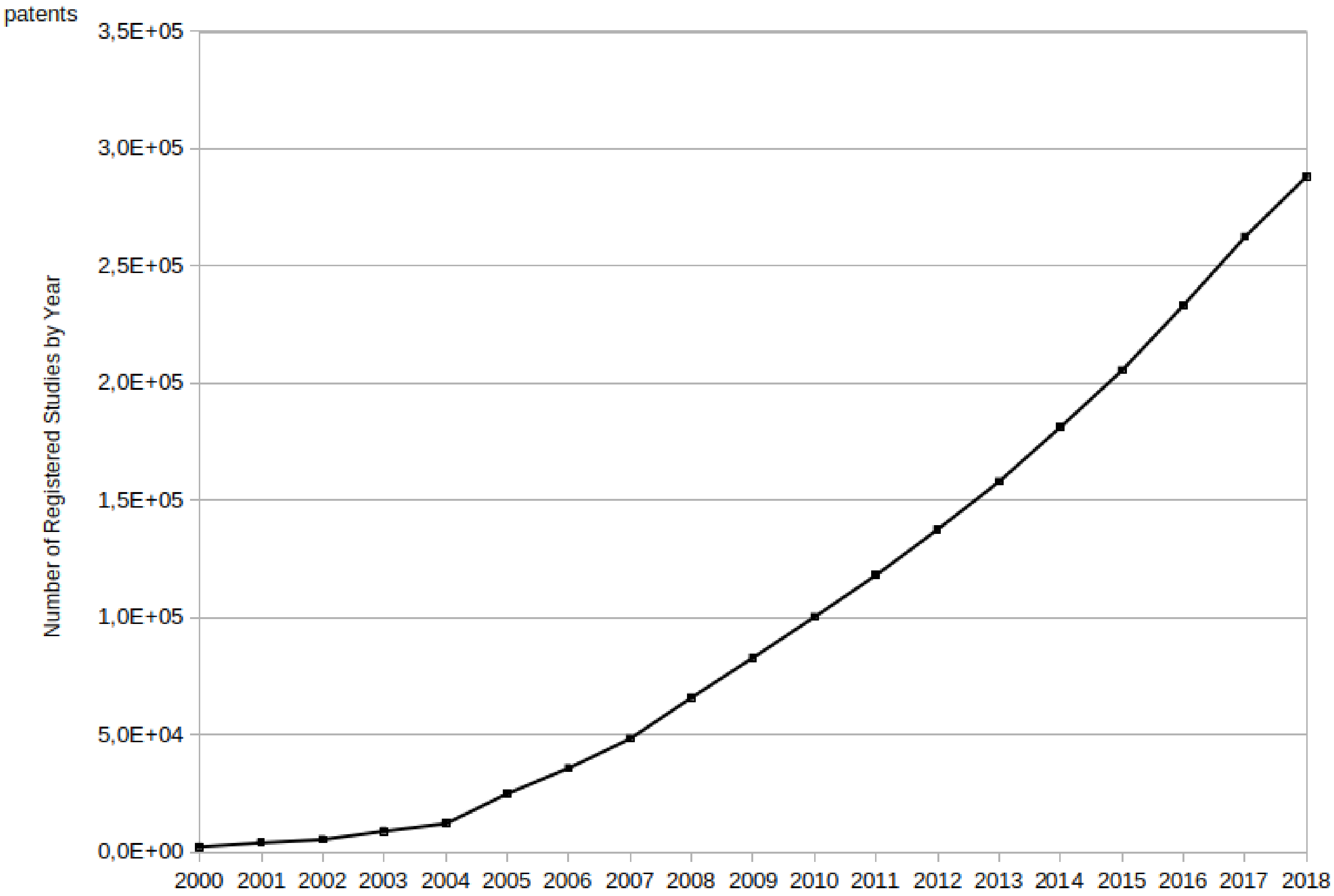
For example, 952,919 citations were added in 2020 to MEDLINE
- 10 articles per day
- more than 261 years to read those articles

Scientific articles are not the only source of biomedical text
- for example clinical studies and patents



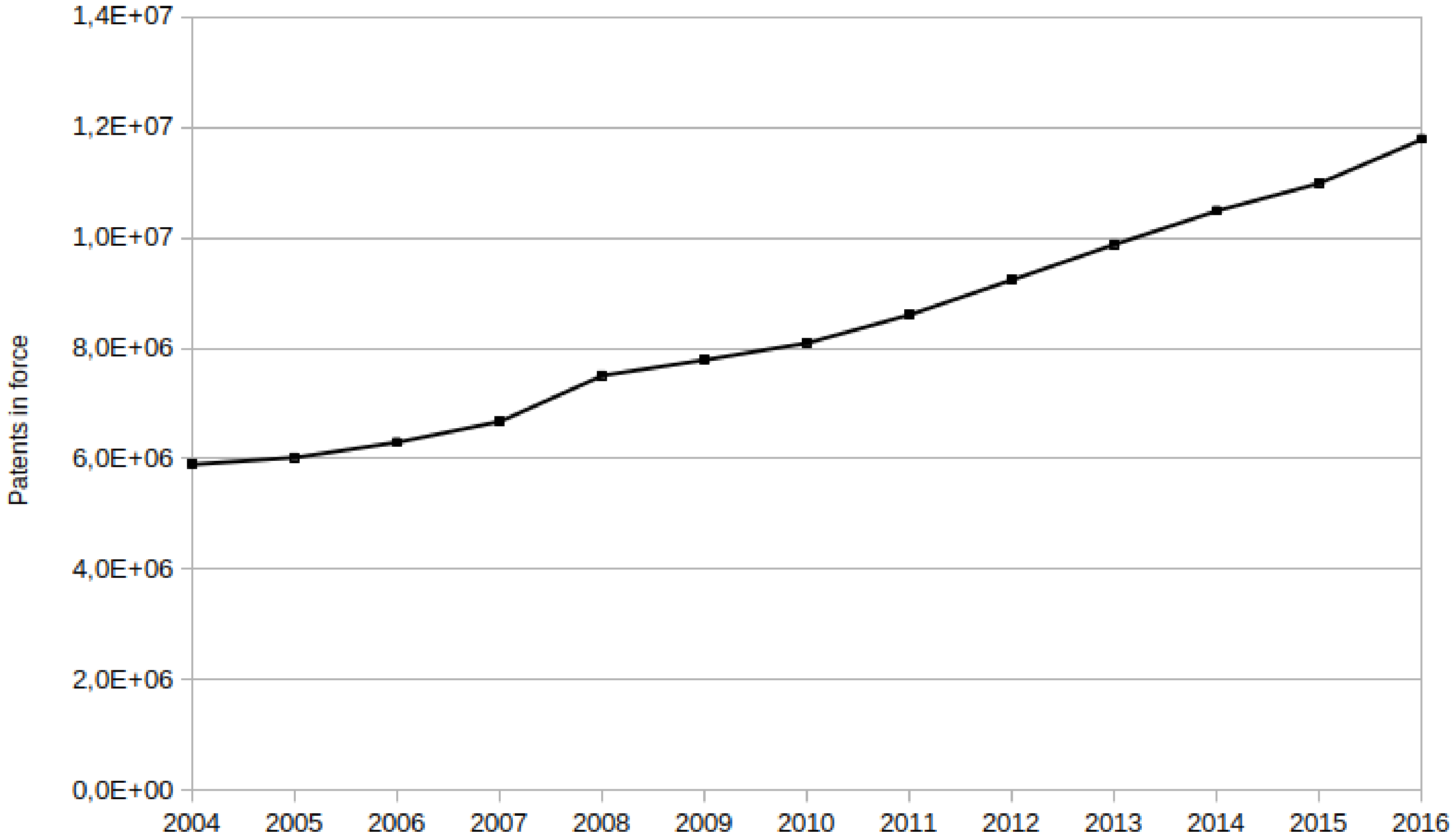
Total number of citations in MEDLINE

(Source: `https://www.nlm.nih.gov/bsd/`)



Total number of registered studies (clinical trials)

(Source: `https://clinicaltrials.gov`)



Total number of patents in force

(Source: WIPO statistics database `http://www.wipo.int/ipstats/en/`)

Ambiguity and contextualization

Inconsistency of the nomenclature
- Different terms referring to the same biological entity (synonyms)
- or the same term meaning different biological entities (homonyms)

The second problem is the complexity of the message
- Almost everyone can read and understand a newspaper story
- but just a few can really understand a scientific article

Finally the multilingual aspect of text is also a problem
- since most clinical data are produced in the native language

Biomedical ontologies

Address the issue of ambiguity of natural language
    and contextualization of the message

Vocabularies to guide what to look for
    official names and synonyms are used to mention concepts

Semantic models by providing semantic relationships between concepts

Programming skills

Data analysis is no longer possible using an in-house and limited dataset

How can I deal with such huge amount of data and text without having the necessary expertise, time and disposition to learn computer programming?

Why this book?

State-of-the-art tools based on complex and sophisticated technologies
require knowledge on programming, linguistics,
machine learning or deep learning
impenetrable to the common Health and Life specialists
and usually become outdated or even unavailable

Set of skills to process text with minimal dependencies
to existing tools and technologies

Create a resilient and versatile solution with acceptable results

Physician knows that the most efficient treatment for
a specific patient is not always the most advanced one

Data scientist knows that the most efficient tool to
address a specific information need
is not always the most advanced one

Provides basic knowledge and right references to pursue
a more advanced solution if required

Third-party solutions

A common problem is their resiliency to deal with
  - new user requirements
  - changes on how resources are being distributed
  - software and hardware updates

Commercial solutions tend to be more resilient
  - need the funding to buy the service
  - dependent on a third-party availability

Open-source solutions may seem a great alternative
  - derive from academic projects that fade away to minimal updates
  - using legacy software is a non-trivial task

Simple pipelines

Build a simple pipeline with minimal software dependencies
- not a fancy web front-end
- manipulate our data using the spreadsheet application
- automatize some of the repetitive tasks

In summary, this book is directed mainly towards Health and Life specialists and students that need to know how to process biomedical data and text, without being dependent on continuous financial support, third-party applications, or advanced computer skills

Shell scripting

Available for more than four decades

- and now in almost every personal computer
- Linux, macOS or Windows operating systems

But a shell script is still a computer algorithm, so how is it different from learning another programming language?

Usage of single command line tools
    combined as simple pipelines
    not intend to create experts in shell scripting

Demonstrate the ability of a few command line tools

Comprehending them is like conducting a new laboratory protocol
    testing and understanding its multiple procedural steps
    variables, and intermediate results

Text files

Data will be stored in text files

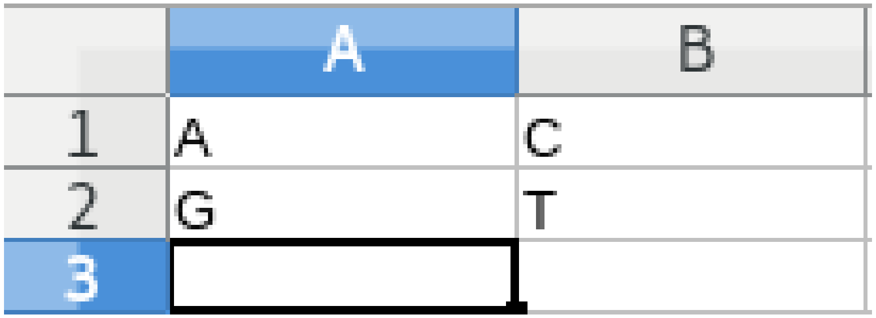
- that command line tools efficiently process
- simple and universal medium of storing data
- opened and interpreted by using any text editor
- *txt* extension without any kind of formatting

Specific formats:

- **CSV** : Comma-Separated Values
- **TSV** : Tab-Separated Values
- **XML** : eXtensible Markup Language

Open (import), edited and saved (export) by

- any text editor application
- spreadsheet applications:
- such as LibreOffice Calc or Microsoft Excel



	A	B
1	A	C
2	G	T
3		

Spreadsheet example

CSV file contents:

```
A,C
G,T
```

TSV file contents:

```
A	C
G	T
```

XML file contents:

```
...
<Table ss:StyleID="ta1">
<Column ss:Span="1" ss:Width="64.01"/>
<Row ss:Height="12.81"><Cell><Data ss:Type="String">A</Data></
  Cell><Cell><Data ss:Type="String">C</Data></Cell></Row>
<Row ss:Height="12.81"><Cell><Data ss:Type="String">G</Data></
  Cell><Cell><Data ss:Type="String">T</Data></Cell></Row>
</Table>
...
```

XLS file a lot of strange characters
- not a text file is a proprietary format

Comma-separated values is a data format so old as shell scripting
- in 1972 it was already supported by an IBM product

Using CSV or TSV enables us to manually manipulate the data
- using our favorite spreadsheet application
- and at the same time use command line tools

Relational databases

More advanced data storage techniques,
- still be able to use shell scripting
- import and export the data to CSV using `sqlite3`

What is in the book?

Chapter Resources
- most prominent resources of biomedical data, text, and semantics
- type of information they distribute
- where we can find them
- how we will be able to automatically explore them

Most of the examples use the resources provided by
- the European Bioinformatics Institute (EBI)
- using their services to automatically retrieve data

Not hard to adapt them to other service provider
- such as the National Center for Biotechnology Information (NCBI).

Examples use two ontologies

- one about human diseases
- the other about chemical entities of biological interest.
- share the same structure and syntax

Chapter Data Retrieval

  manual steps to retrieve text about *caffeine*

  then automated by using command line tools

Step-by-step and introduce how each command line tool

  can be used to automate each task

Command line tools

- `curl`: a tool to download data and text from the web;
- `grep`: a tool to search our data and text;
- `cut`: a tool to filter sections of each data item;
- `sed`: a tool to edit our data and text;
- `xargs`: a tool to repeat the same step for multiple data items;
- `xmllint`: a tool to search in XML data files.

- `cat`: a tool to get the content of file;
- `tr`: a tool to replace one character by another;
- `sort`: a tool to sort multiple lines;
- `head`: a tool to select only the first lines.

Pipelines

Redirect the output of a command line tool
- as input to another tool, or to a file
- sequential invocations of command line tools

Chapter Text Processing

- extracting useful information from the text
- finding references to *malignant hyperthermia*
- *caffeine* related texts

Regular Expressions

Powerful pattern matching technique
- `grep` command line tool
- perform Named-Entity Recognition (NER)

Regular expressions originated in 1951
- even older than shell scripting
- still popular and available

String that include special operators
- represented by special characters
- For example: `A|C|G|T`

Tokenization

identifying the text boundaries

such as splitting a text into sentences

Relation Extraction

find two entities in the same sentence,

Semantics

Ontologies

- construct large lexicons
- all entities of a domain (humans diseases)
- expand search using ancestors and related classes

Entity Linking

- each entity recognized is mapped to a ontology class
- deals with the ambiguity issue
- same label can be mapped to multiple classes

Resources

Biomedical Text

Text preferential means publishing knowledge
- multiple types of sources
- main being scientific articles and patents
- less formal texts: electronic health records

What?

Statement: a short piece of text
  - personal remarks
  - evidence about a biomedical phenomenon

Abstract: a short summary of a larger scientific document

Full-text: the entire text present in a scientific document

Statements

- more syntactic and semantic errors
- not peer-reviewed
- directly linked to data
- brief and succinct form

Abstracts

- intellectual exercise to summarize
- may be insufficient to draw a solid conclusion
- details in a full-text document

Full-text documents

- may have restricted access.
- structure and format varies
- more information does not mean is beneficial
- may even induce us in error
- a fact in the Results vs. Related Work

Where?

PubMed
- an information retrieval system
- search and find biomedical texts
- developed and maintained by NCBI

More than 28 million citations from MEDLINE
- with title, abstract, authors, journal, publication date

EBI services
- Europe PMC
- Universal Protein Resource (UniProt) citations service

Alternative tools:
- Google Scholar
- Google Patents
- ResearchGate
- Mendeley

Tools also integrate semantic links

- GOPubMed categorized texts using Gene Ontology
- PubTator annotated with biological entities

Open Access Publications

- full-texts freely available with unrestricted use
- PubMed Central (PMC) more than 5 million documents

Electronic health records
- stored in health institutions and linked to patients
- access is restricted due to ethical and privacy issues

THYME corpus
- more than one thousand de-identified clinical notes (Mayo Clinic)
- only available for text processing research

Social networks
- identify new trends and insights about a disease
- processing tweets to predict flu outbreaks

How?

Programmatic access to it
    restrictions only manual access is granted
    face a CAPTCHA challenge (humans or not)

NCBI and EBI online services
    such as PubMed, Europe PMC, or UniProt Citations
    allow programmatic access with Web APIs

RESTful web services (simple uniform interface)
    Uniform Resource Locator (URL) self-explanatory
    enough to retrieve the data using command line

Semantics

Lack of use of standard nomenclatures

- different labels (synonyms, acronyms)
- sharing the same label (homonyms)
- requires sense disambiguation to select the correct meaning

Disease acronym *ATS* may represent

- *Andersen-Tawil syndrome*
- or the *X-linked Alport syndrome*

Solution: ontologies and semantic similarity

What?

In 1993 definition of ontology:

> an explicit specification of a conceptualization

In 1997 and 1998 refined to:

> a formal, explicit specification of a shared conceptualization

Conceptualization
  an abstract view of the concepts
  and the relationships of a given domain

Shared conceptualization
  a group of individuals agree (common agreement)

Specification is a representation of that conceptualization
  using a given language.
  needs to be formal and explicit
  so computers can deal with it

Languages

Web Ontology Language (OWL)
- most common languages to specify ontologies

Open Biomedical Ontology (OBO)
- principles to ensure high quality, formal rigor
- and interoperability between other OBO ontologies

Concepts are defined as OWL classes
    that may include multiple properties, such as labels
    official name, acronyms, exact synonyms, and even related terms

Class *malignant hyperthermia*
    synonym *anesthesia related hyperthermia*.

Andersen-Tawil syndrome and *X-linked Alport syndrome*
    share *ATS* as an exact synonym

Formality

Different levels of formality
such as controlled vocabularies, taxonomies
and thesaurus may include logical axioms.

Controlled vocabularies are list of terms
without specifying any relation between them

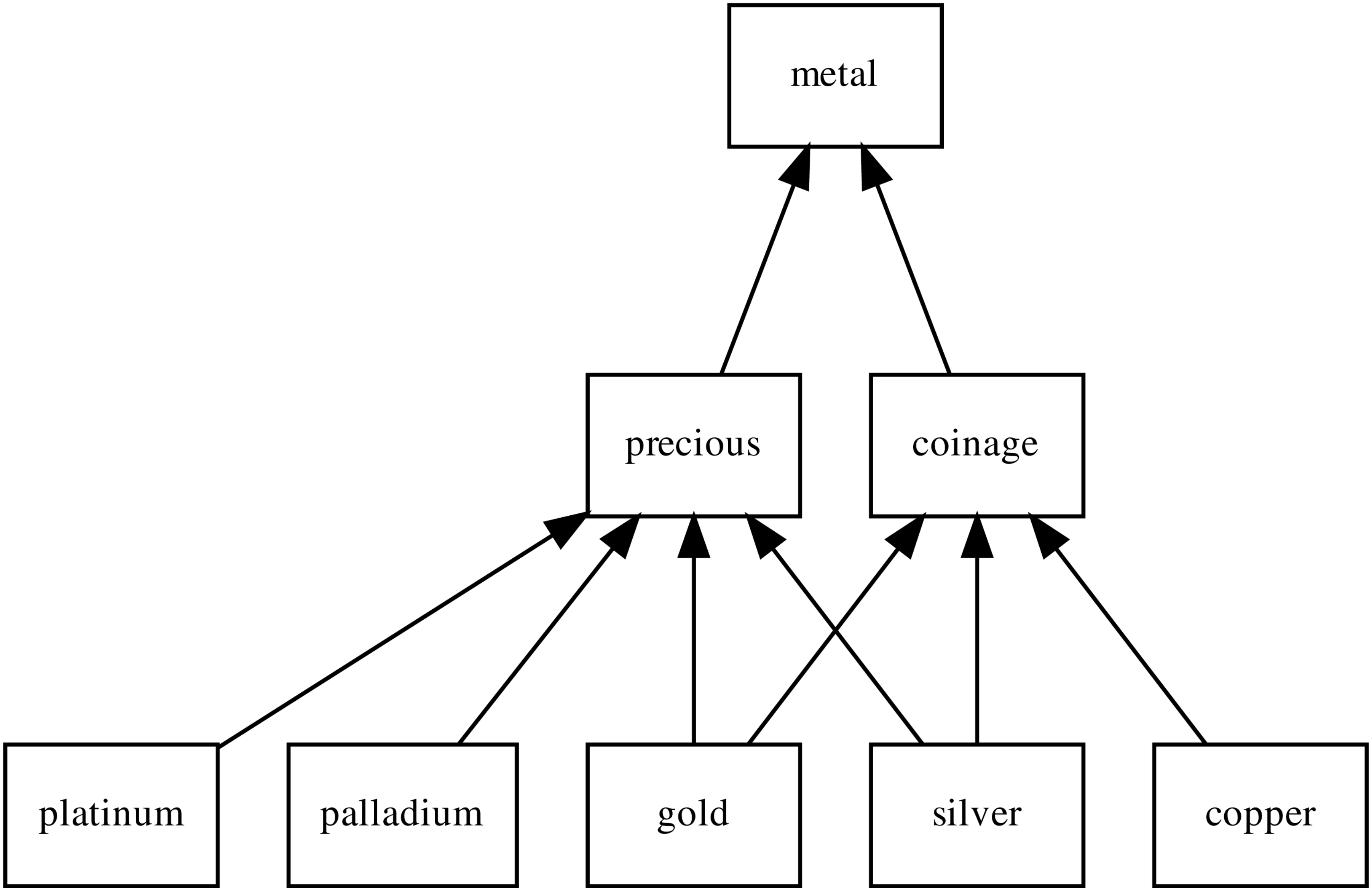
Taxonomies are controlled vocabularies
that include subsumption relations
malignant hyperthermia is a *muscle tissue disease*

is-a or subclass relations

- are normally the backbone of ontologies.
- include multiple inheritance
- organized as a directed acyclic graphs (DAG)

Thesaurus

- includes other types of relations besides subsumption
- *caffeine* has role *mutagen*.


metal

precious

coinage

platinum

palladium

gold

silver

copper

DAG representing a classification of metals with multiple inheritance

Gold related documents

Find texts related to *gold*
- a corpus with one distinct document mentioning each metal
- except for *gold* that no document mentions
- which documents should we read first?

silver is probably the most related
- shares two parents, *precious* and *coinage*.

platinum, *palladium* or *copper*?
    depends on our information need
    previous searches or reads

Last searches were *coinage*
    copper is probably the second-most related

Importance of these semantic resources
    development of the knowledge graph by Google

Where?

BioPortal (April 2021)
- 858 ontologies
- more than 10 million classes

Search for *caffeine*
- large list of ontologies that define it
- conceptualizations of *caffeine* in different domains
- alternative perspectives
- Interoperability property with links to similar classes

OBO initiative
- tackle this somehow disorderly spread of definitions
- each OBO ontology covers a clearly specified scope

OBO ontologies

Success of Gene Ontology (GO)
- describe molecular function, biological process and cellular component
- gene-products for different species

Disease Ontology (DO)
- human disease terms
- phenotype characteristics
- and related medical vocabulary disease concepts

Chemical Entities of Biological Interest (ChEBI)
- classification of molecular entities
- with biological interest
- focus on small chemical compounds

Popular controlled vocabularies

- International Classification of Diseases (ICD)
  - by World Health Organization (WHO)
  - generic clinical terms
- Systematized Nomenclature of Medicine - Clinical Terms (SNOMED CT)
  - highly comprehensive and detailed
- Medical Subject Headings (MeSH)
  - classifying biomedical and health-related information and documents
- Unified Medical Language System (UMLS)
  - large resource integrate most biomedical vocabularies
  - 2015AB release more than three million concepts

Ontobee

- repository of ontologies (most OBO ontologies)
- 231 ontologies (April 2021)

Outside the biomedical domain

- W3C SWEO Linking Open Data community project
- W3C Library Linked Data Incubator Group

How?

Find ontology home page
- download the most recent release
- the original format
- select the subset of the ontology

ChEBI provides three versions:
- LITE, CORE and FULL

If not interested in chemical data and structures
- that is available in CORE
- LITE is probably the best solution
- may miss synonyms from FULL version

OWL

OWL language prevailing language to represent ontologies

OWL extends RDF Schema (RDFS)
    with more complex statements using description logic

RDFS is an extension of RDF
    with additional statements
    such as class-subclass or property-subproperty relationships

RDF is a data model
- stores information in statements
- represented as triples: subject, predicate and object

RDF data encoded using Extensible Markup Language (XML)
- named RDF/XML

XML is a self-descriptive mark-up language
- composed of data elements

XML example

- *caffeine* is a drug
- may treat the condition of sleepiness
- without being an official treatment:

```
<treatment category="non-official">
  <drug>caffeine</drug>
  <condition>sleepiness</condition>
</treatment>
```

Hierarchical structure of data elements:

- `<` - new data element
- `</` - data element will end
- property `category` with value `non-official`

Large XML files are almost unreadable by humans

N3 and Turtle
- legible encoding languages for RDF

Most biomedical ontologies in OWL using XML encoding

URI

The Uniform Resource Identifier (URI)

- standard global identifier of classes
- class `caffeine` in ChEBI identified by:
  `http://purl.obolibrary.org/obo/CHEBI_27732`

A URI is a URL if we open it in a web browser

- and obtain a resource describing that class

Ontologies are also available as database dumps.
- normally SQL files
- in a DataBase Management System (DBMS)

Use command line tool `sqlite3`
- execute the SQL commands
- import data (`.read` command)
- export data to CSV (`.mode` command)

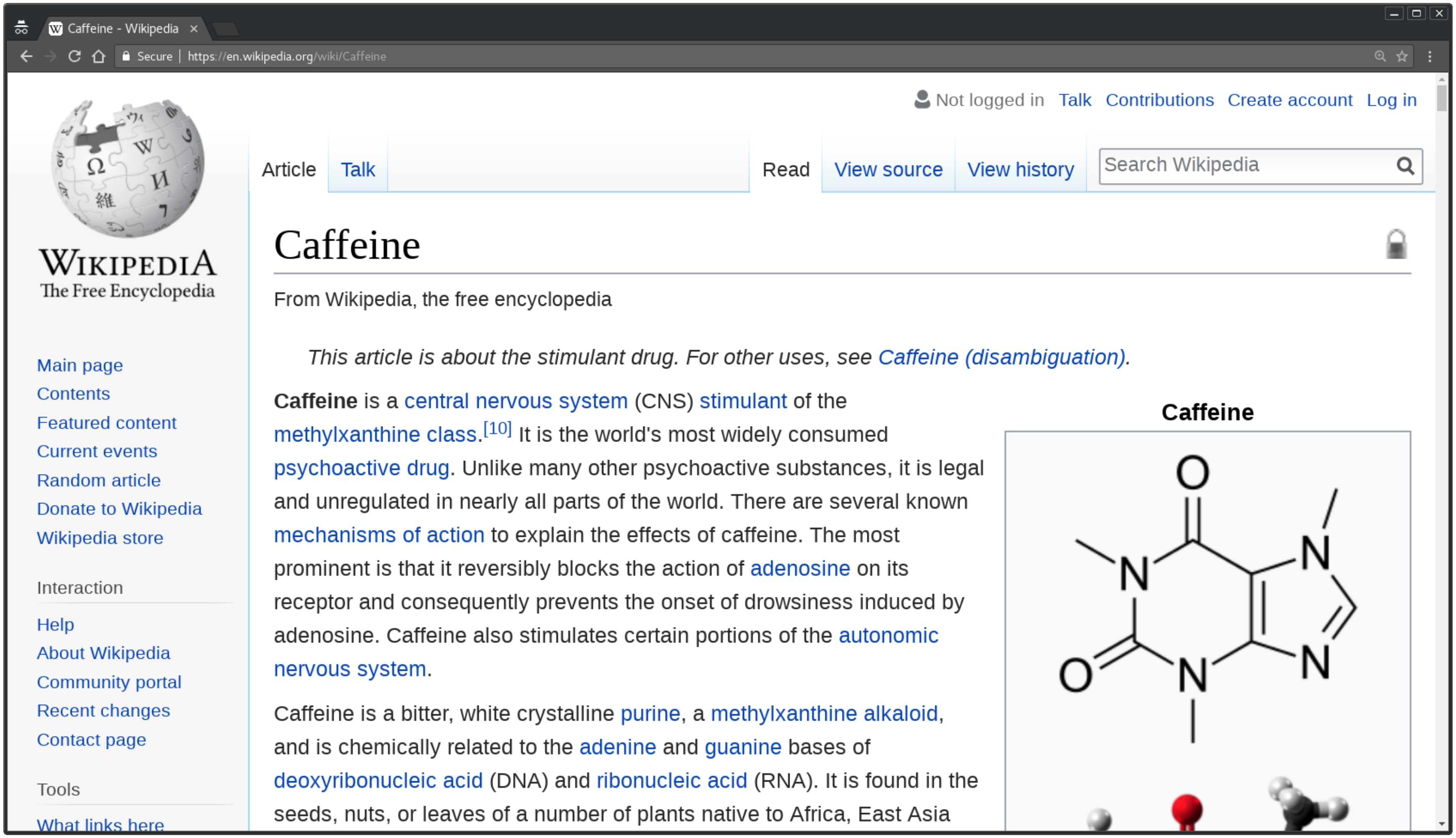
Data Retrieval

Example of how we can retrieve text manually and then automatize using shell script commands

Caffeine Example

Retrieve data and literature about *caffeine*
- searching *caffeine* in Wikipedia
- information available in the infobox
- multiple links to external sources

Link to resource hosted by the European Bioinfomatics Institute (EBI)
- CHEBI:27732 - Chemical Entities of Biological Interest
- includes an ontology with structural and biological properties



Caffeine

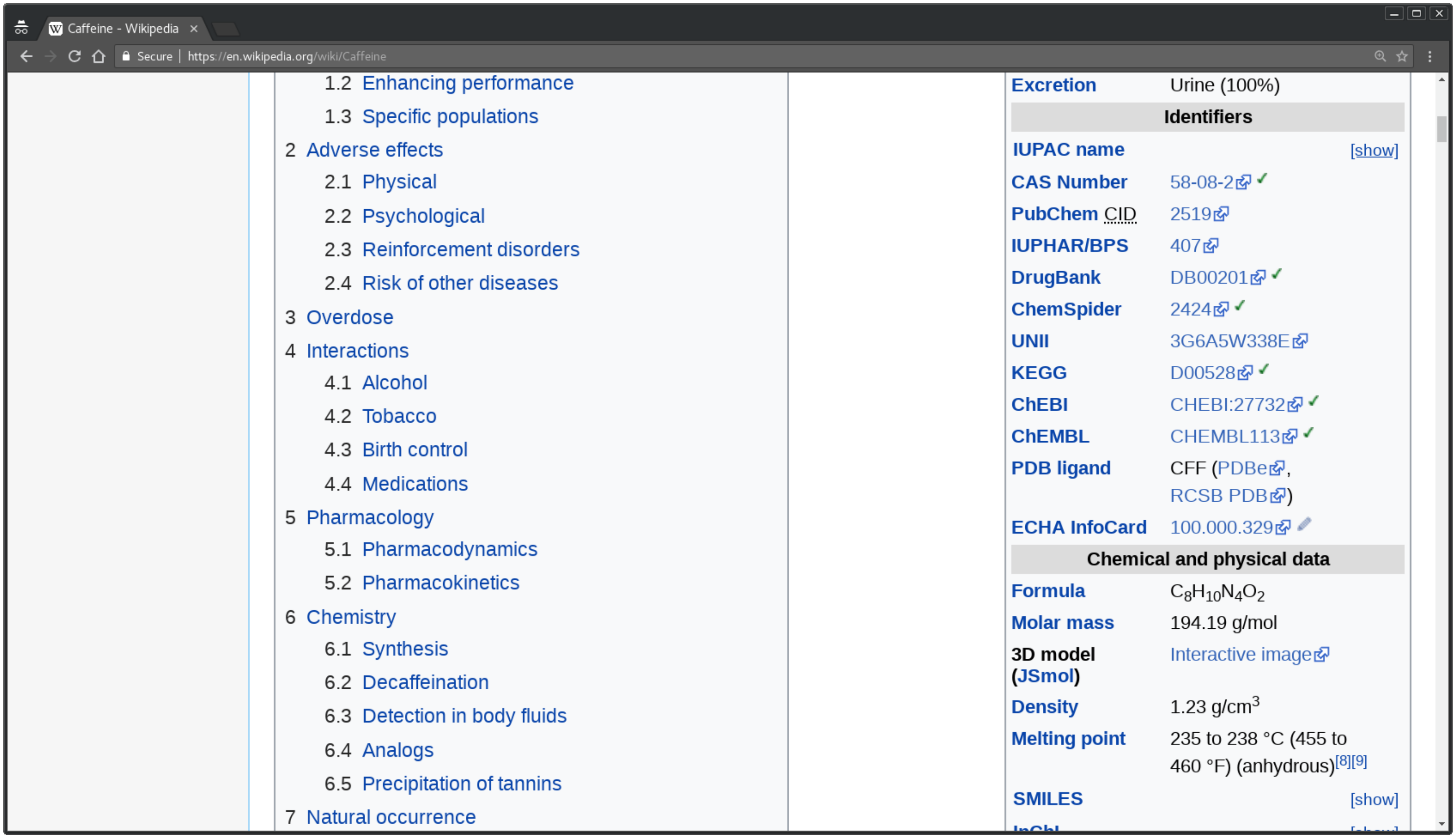
From Wikipedia, the free encyclopedia

This article is about the stimulant drug. For other uses, see Caffeine (disambiguation).

Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class.[10] It is the world's most widely consumed psychoactive drug. Unlike many other psychoactive substances, it is legal and unregulated in nearly all parts of the world. There are several known mechanisms of action to explain the effects of caffeine. The most prominent is that it reversibly blocks the action of adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine. Caffeine also stimulates certain portions of the autonomic nervous system.

Caffeine is a bitter, white crystalline purine, a methylxanthine alkaloid, and is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It is found in the seeds, nuts, or leaves of a number of plants native to Africa, East Asia

Wikipedia page about caffeine



- 1.2 Enhancing performance
- 1.3 Specific populations

2 Adverse effects
- 2.1 Physical
- 2.2 Psychological
- 2.3 Reinforcement disorders
- 2.4 Risk of other diseases

3 Overdose

4 Interactions
- 4.1 Alcohol
- 4.2 Tobacco
- 4.3 Birth control
- 4.4 Medications

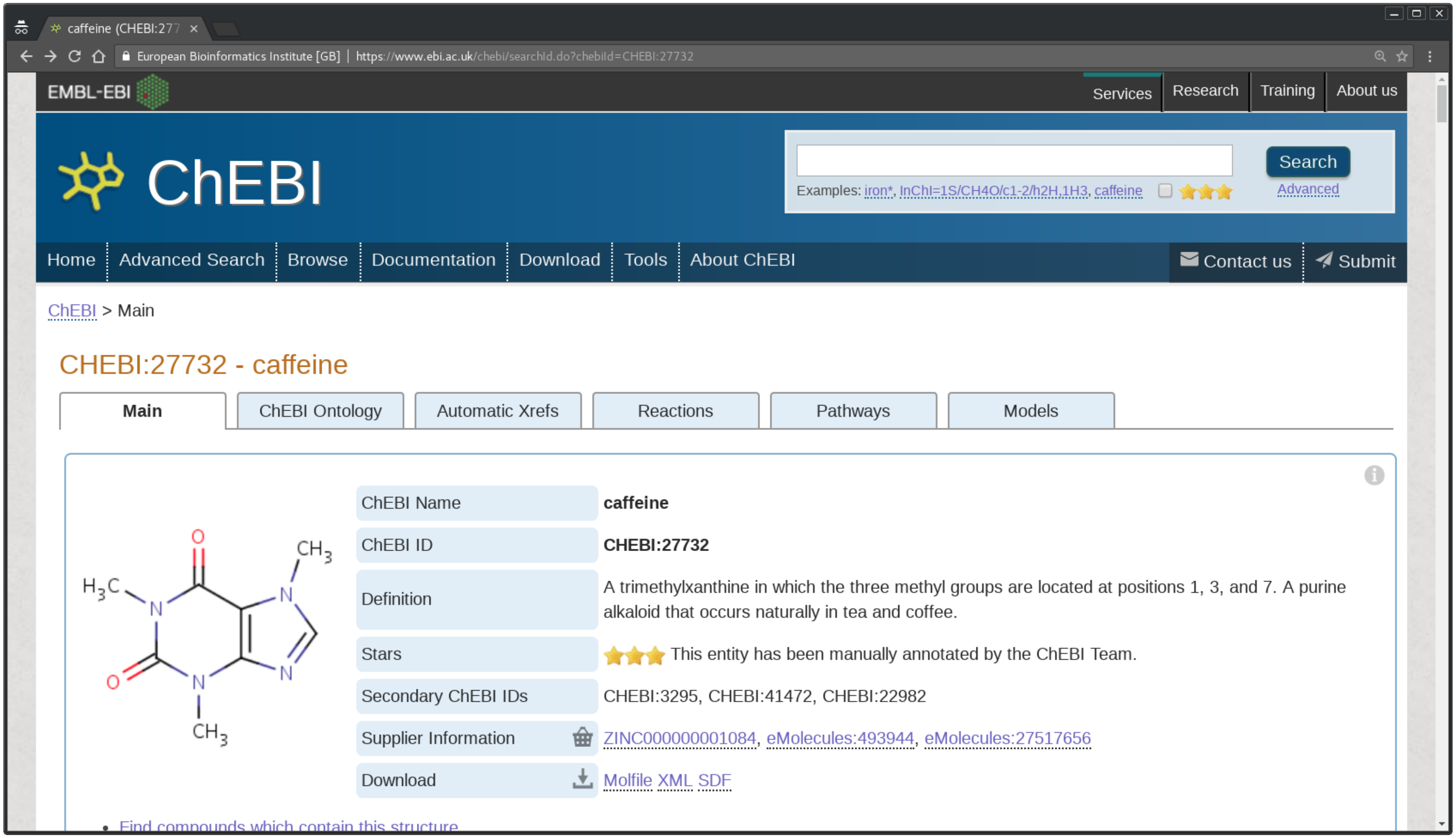
5 Pharmacology
- 5.1 Pharmacodynamics
- 5.2 Pharmacokinetics

6 Chemistry
- 6.1 Synthesis
- 6.2 Decaffeination
- 6.3 Detection in body fluids
- 6.4 Analogs
- 6.5 Precipitation of tannins

7 Natural occurrence

Excretion	Urine (100%)
Identifiers	
IUPAC name	[show]
CAS Number	58-08-2 ✓
PubChem CID	2519
IUPHAR/BPS	407
DrugBank	DB00201 ✓
ChemSpider	2424 ✓
UNII	3G6A5W338E
KEGG	D00528 ✓
ChEBI	CHEBI:27732 ✓
ChEMBL	CHEMBL113 ✓
PDB ligand	CFF (PDBe, RCSB PDB)
ECHA InfoCard	100.000.329
Chemical and physical data	
Formula	$C_8H_{10}N_4O_2$
Molar mass	194.19 g/mol
3D model (JSmol)	Interactive image
Density	1.23 g/cm^3
Melting point	235 to 238 °C (455 to 460 °F) (anhydrous)[8][9]
SMILES	[show]

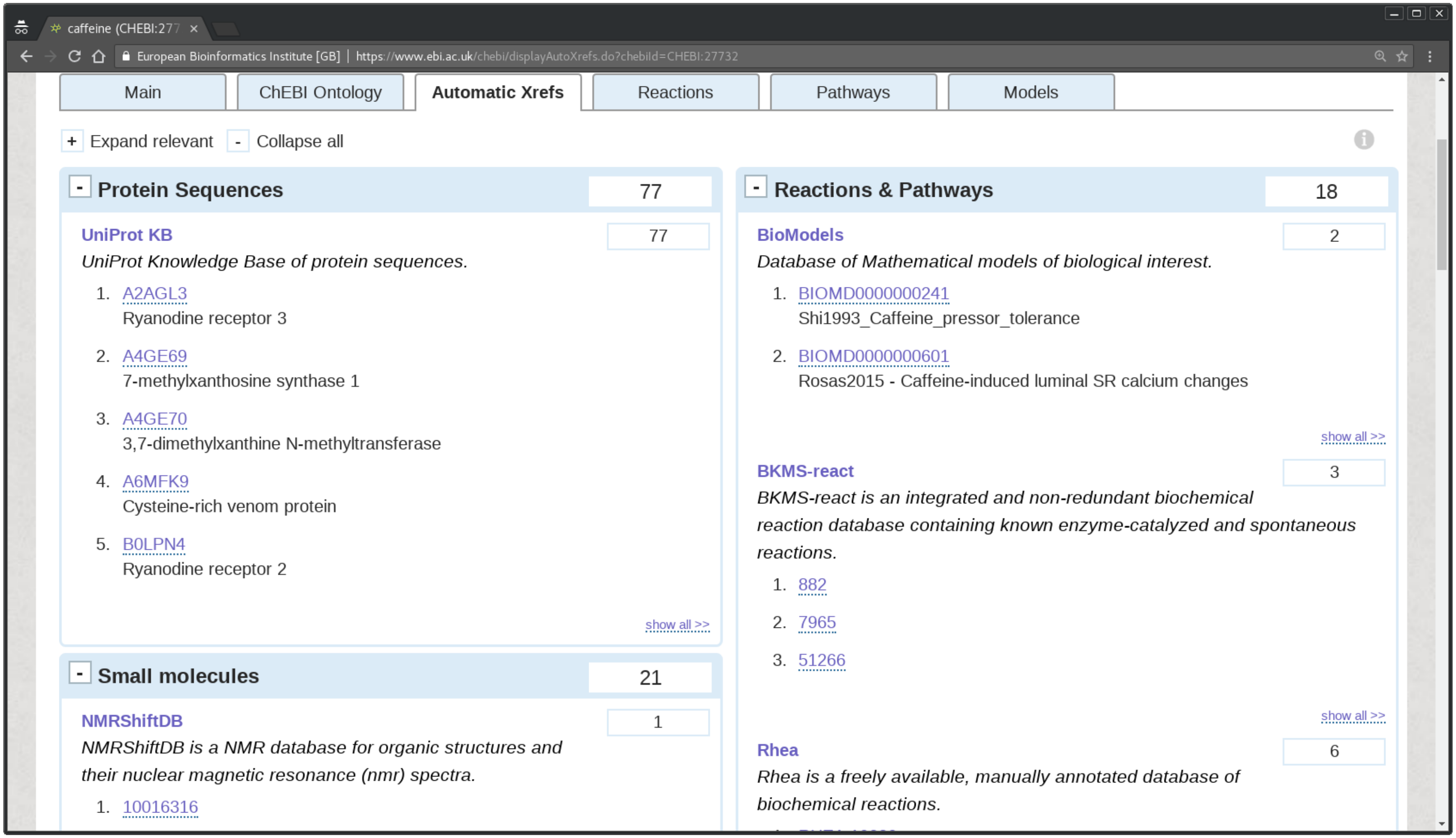
Identifiers section of the Wikipedia page about caffeine



CHEBI:27732 - caffeine

ChEBI Name	**caffeine**
ChEBI ID	**CHEBI:27732**
Definition	A trimethylxanthine in which the three methyl groups are located at positions 1, 3, and 7. A purine alkaloid that occurs naturally in tea and coffee.
Stars	★★★ This entity has been manually annotated by the ChEBI Team.
Secondary ChEBI IDs	CHEBI:3295, CHEBI:41472, CHEBI:22982
Supplier Information	ZINC000000001084, eMolecules:493944, eMolecules:27517656
Download	Molfile XML SDF

ChEBI entry describing caffeine



Protein Sequences 77

UniProt KB 77

UniProt Knowledge Base of protein sequences.

1. A2AGL3
   Ryanodine receptor 3
2. A4GE69
   7-methylxanthosine synthase 1
3. A4GE70
   3,7-dimethylxanthine N-methyltransferase
4. A6MFK9
   Cysteine-rich venom protein
5. B0LPN4
   Ryanodine receptor 2

Small molecules 21

NMRShiftDB 1

NMRShiftDB is a NMR database for organic structures and their nuclear magnetic resonance (nmr) spectra.

1. 10016316

Reactions & Pathways 18

BioModels 2

Database of Mathematical models of biological interest.

1. BIOMD0000000241
   Shi1993_Caffeine_pressor_tolerance
2. BIOMD0000000601
   Rosas2015 - Caffeine-induced luminal SR calcium changes

BKMS-react 3

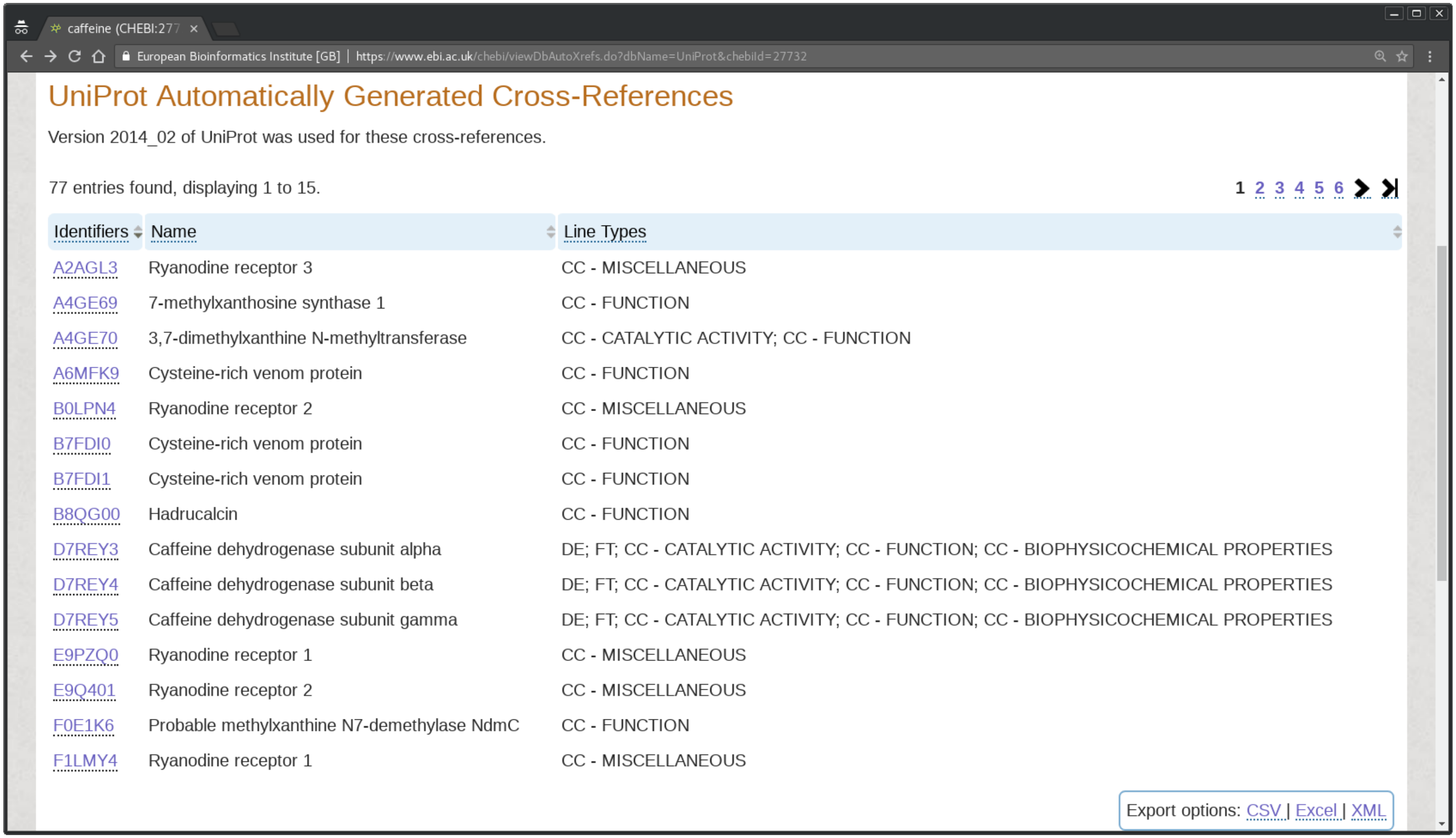
BKMS-react is an integrated and non-redundant biochemical reaction database containing known enzyme-catalyzed and spontaneous reactions.

1. 882
2. 7965
3. 51266

Rhea 6

Rhea is a freely available, manually annotated database of biochemical reactions.

External references related to caffeine



UniProt Automatically Generated Cross-References

Version 2014_02 of UniProt was used for these cross-references.

77 entries found, displaying 1 to 15.

1 2 3 4 5 6

Identifiers	Name	Line Types
A2AGL3	Ryanodine receptor 3	CC - MISCELLANEOUS
A4GE69	7-methylxanthosine synthase 1	CC - FUNCTION
A4GE70	3,7-dimethylxanthine N-methyltransferase	CC - CATALYTIC ACTIVITY; CC - FUNCTION
A6MFK9	Cysteine-rich venom protein	CC - FUNCTION
B0LPN4	Ryanodine receptor 2	CC - MISCELLANEOUS
B7FDI0	Cysteine-rich venom protein	CC - FUNCTION
B7FDI1	Cysteine-rich venom protein	CC - FUNCTION
B8QG00	Hadrucalcin	CC - FUNCTION
D7REY3	Caffeine dehydrogenase subunit alpha	DE; FT; CC - CATALYTIC ACTIVITY; CC - FUNCTION; CC - BIOPHYSICOCHEMICAL PROPERTIES
D7REY4	Caffeine dehydrogenase subunit beta	DE; FT; CC - CATALYTIC ACTIVITY; CC - FUNCTION; CC - BIOPHYSICOCHEMICAL PROPERTIES
D7REY5	Caffeine dehydrogenase subunit gamma	DE; FT; CC - CATALYTIC ACTIVITY; CC - FUNCTION; CC - BIOPHYSICOCHEMICAL PROPERTIES
E9PZQ0	Ryanodine receptor 1	CC - MISCELLANEOUS
E9Q401	Ryanodine receptor 2	CC - MISCELLANEOUS
F0E1K6	Probable methylxanthine N7-demethylase NdmC	CC - FUNCTION
F1LMY4	Ryanodine receptor 1	CC - MISCELLANEOUS

Export options: CSV | Excel | XML

Proteins related to caffeine

Protein Sequences section

- Click on *show all* to complete list
- includes the identifiers of each protein

UniProt

- a database of protein sequences and annotation data.
- resource hosted EBI

DISRUPTION PHENOTYPE

- effects caused by the disruption of the gene coding

Bottom-right *Export options*

- CSV, Excel and XML files

Open in a text editor software

- notepad (Windows), TextEdit (macOS) or gedit (Linux).

chebi_27732_xrefs_UniProt.csv:

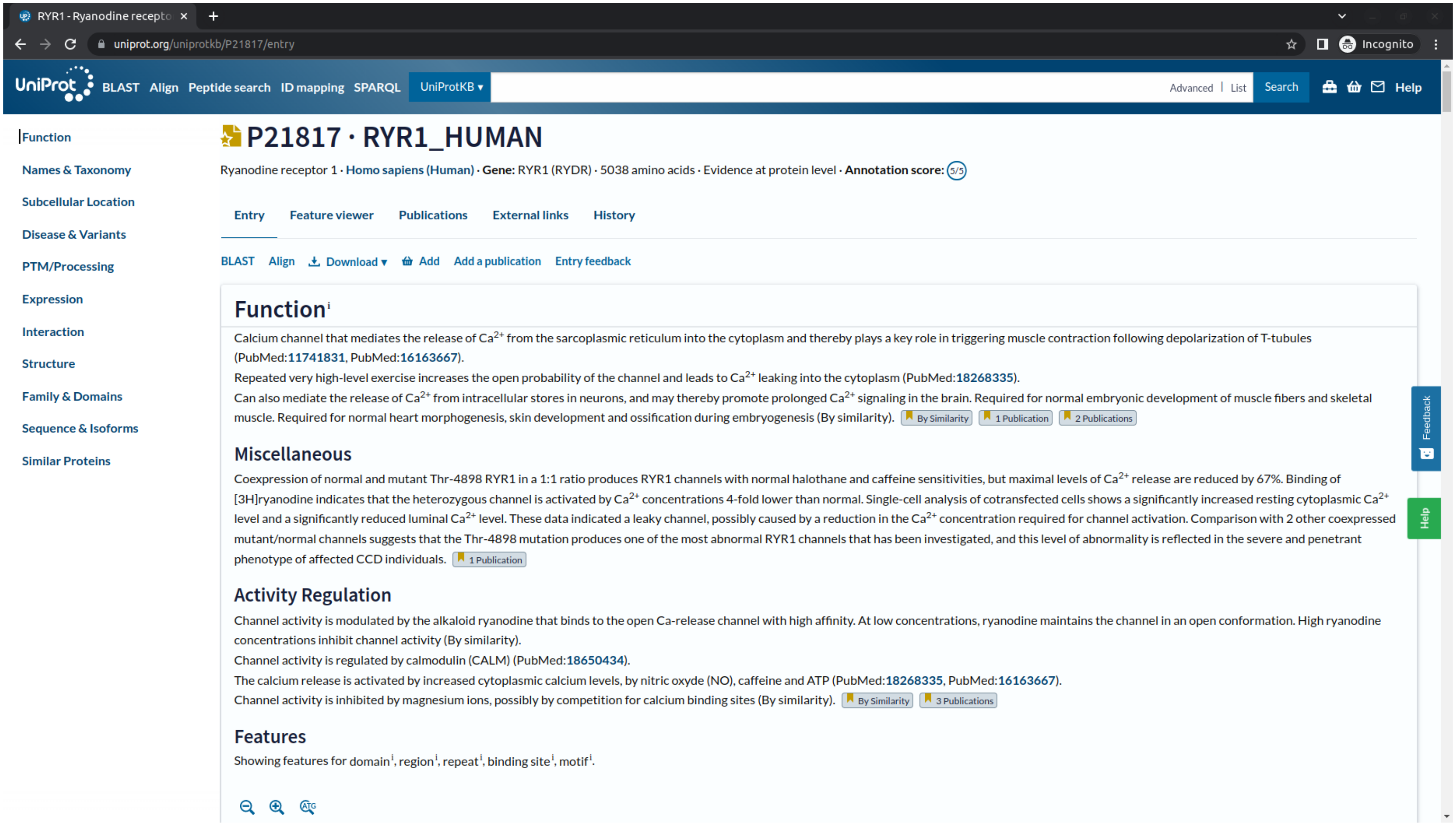
```
A2AGL3,Ryanodine receptor 3,CC - MISCELLANEOUS
A4GE69,7-methylxanthosine synthase 1,CC - FUNCTION
...
```

chebi_27732_xrefs_UniProt.xls:

```
"Identifiers" "Name"                             "Line Types"
"A2AGL3"      "Ryanodine receptor 3"             "CC - MISCELLANEOUS
  "
"A4GE69"      "7-methylxanthosine synthase 1" "CC - FUNCTION"
...
```

chebi_27732_xrefs_UniProt.xml:

```
<?xml version="1.0"?>
<table>
<row>
<column>A2AGL3</column>
<column>Ryanodine receptor 3</column>
<column>CC - MISCELLANEOUS</column>
</row>
<row>
<column>A4GE69</column>
<column>7-methylxanthosine synthase 1</column>
<column>CC - FUNCTION</column>
</row>
...
```



P21817 · RYR1_HUMAN

Ryanodine receptor 1 · Homo sapiens (Human) · **Gene:** RYR1 (RYDR) · 5038 amino acids · Evidence at protein level · **Annotation score:** 5/5

Function

Calcium channel that mediates the release of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm and thereby plays a key role in triggering muscle contraction following depolarization of T-tubules (PubMed:11741831, PubMed:16163667).

Repeated very high-level exercise increases the open probability of the channel and leads to Ca^{2+} leaking into the cytoplasm (PubMed:18268335).

Can also mediate the release of Ca^{2+} from intracellular stores in neurons, and may thereby promote prolonged Ca^{2+} signaling in the brain. Required for normal embryonic development of muscle fibers and skeletal muscle. Required for normal heart morphogenesis, skin development and ossification during embryogenesis (By similarity). By Similarity 1 Publication 2 Publications

Miscellaneous

Coexpression of normal and mutant Thr-4898 RYR1 in a 1:1 ratio produces RYR1 channels with normal halothane and caffeine sensitivities, but maximal levels of Ca^{2+} release are reduced by 67%. Binding of [3H]ryanodine indicates that the heterozygous channel is activated by Ca^{2+} concentrations 4-fold lower than normal. Single-cell analysis of cotransfected cells shows a significantly increased resting cytoplasmic Ca^{2+} level and a significantly reduced luminal Ca^{2+} level. These data indicated a leaky channel, possibly caused by a reduction in the Ca^{2+} concentration required for channel activation. Comparison with 2 other coexpressed mutant/normal channels suggests that the Thr-4898 mutation produces one of the most abnormal RYR1 channels that has been investigated, and this level of abnormality is reflected in the severe and penetrant phenotype of affected CCD individuals. 1 Publication

Activity Regulation

Channel activity is modulated by the alkaloid ryanodine that binds to the open Ca-release channel with high affinity. At low concentrations, ryanodine maintains the channel in an open conformation. High ryanodine concentrations inhibit channel activity (By similarity).

Channel activity is regulated by calmodulin (CALM) (PubMed:18650434).

The calcium release is activated by increased cytoplasmic calcium levels, by nitric oxyde (NO), caffeine and ATP (PubMed:18268335, PubMed:16163667).

Channel activity is inhibited by magnesium ions, possibly by competition for calcium binding sites (By similarity). By Similarity 3 Publications

Features

Showing features for domain, region, repeat, binding site, motif.

UniProt entry describing the Ryanodine receptor 1

Select *Ryanodine receptor 1* P21817
  more than just sequence database

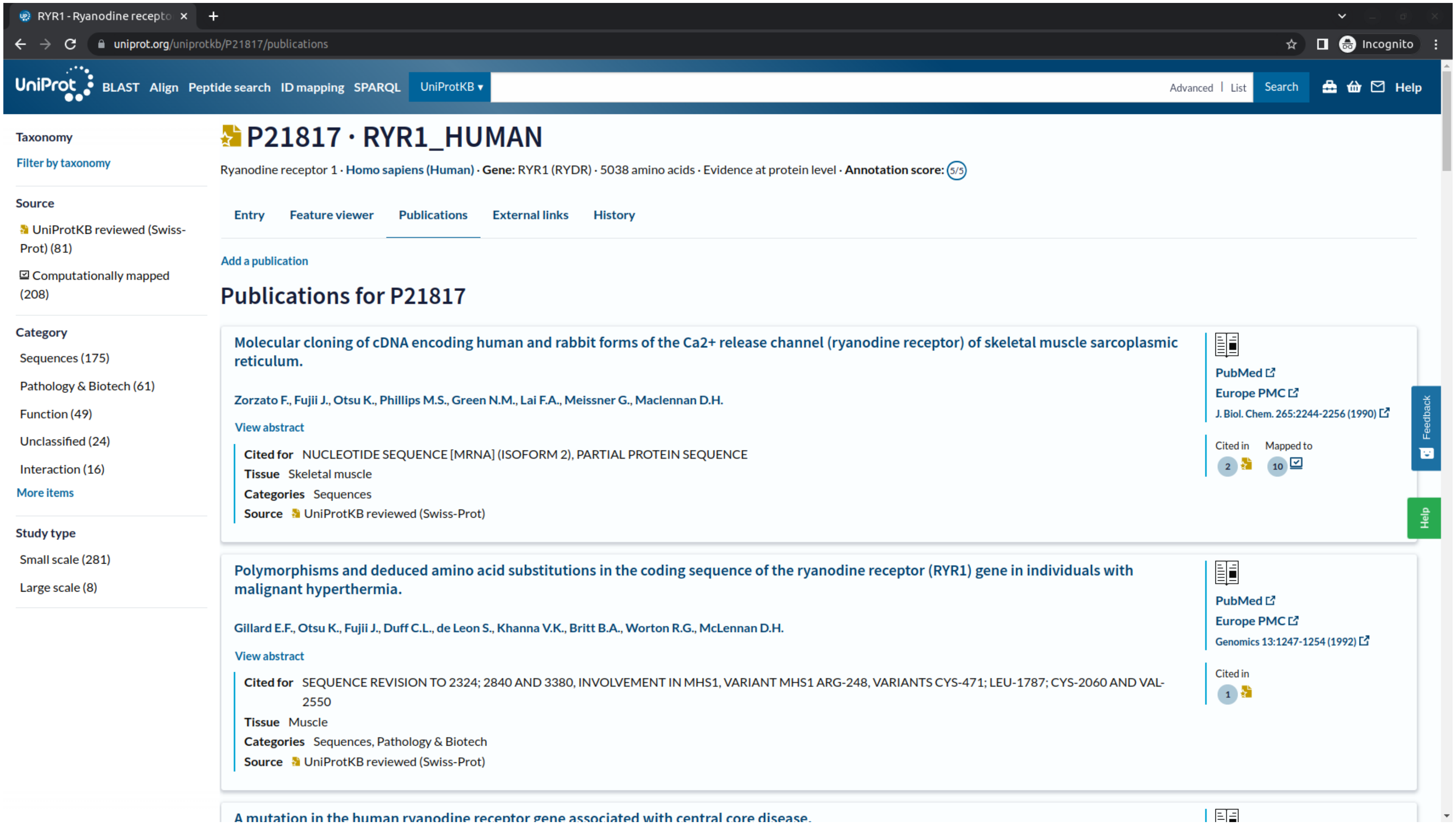
Click on Format and on XML.
  save the result as a XML file

P21817.xml:

```
<?xml version='1.0' encoding='UTF-8'?>
<uniprot xmlns="http://uniprot.org/uniprot" ...
<entry dataset="Swiss-Prot" created="1991-05-01" ...
<accession>P21817</accession>
...
```

Homo sapiens (Human) protein
- interested only in Human Proteins
- filter them

Entry E9PZQ0
- *Ryanodine receptor 1* protein
- but *Mus musculus (Mouse)*



Taxonomy
Filter by taxonomy

Source
UniProtKB reviewed (Swiss-Prot) (81)
☑ Computationally mapped (208)

Category
Sequences (175)
Pathology & Biotech (61)
Function (49)
Unclassified (24)
Interaction (16)
More items

Study type
Small scale (281)
Large scale (8)

P21817 · RYR1_HUMAN

Ryanodine receptor 1 · Homo sapiens (Human) · **Gene:** RYR1 (RYDR) · 5038 amino acids · Evidence at protein level · **Annotation score:** 5/5

Entry | Feature viewer | Publications | External links | History

Add a publication

Publications for P21817

Molecular cloning of cDNA encoding human and rabbit forms of the Ca2+ release channel (ryanodine receptor) of skeletal muscle sarcoplasmic reticulum.

Zorzato F., Fujii J., Otsu K., Phillips M.S., Green N.M., Lai F.A., Meissner G., Maclennan D.H.

View abstract

Cited for NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 2), PARTIAL PROTEIN SEQUENCE
Tissue Skeletal muscle
Categories Sequences
Source UniProtKB reviewed (Swiss-Prot)

PubMed
Europe PMC
J. Biol. Chem. 265:2244-2256 (1990)
Cited in 2 Mapped to 10

Polymorphisms and deduced amino acid substitutions in the coding sequence of the ryanodine receptor (RYR1) gene in individuals with malignant hyperthermia.

Gillard E.F., Otsu K., Fujii J., Duff C.L., de Leon S., Khanna V.K., Britt B.A., Worton R.G., McLennan D.H.

View abstract

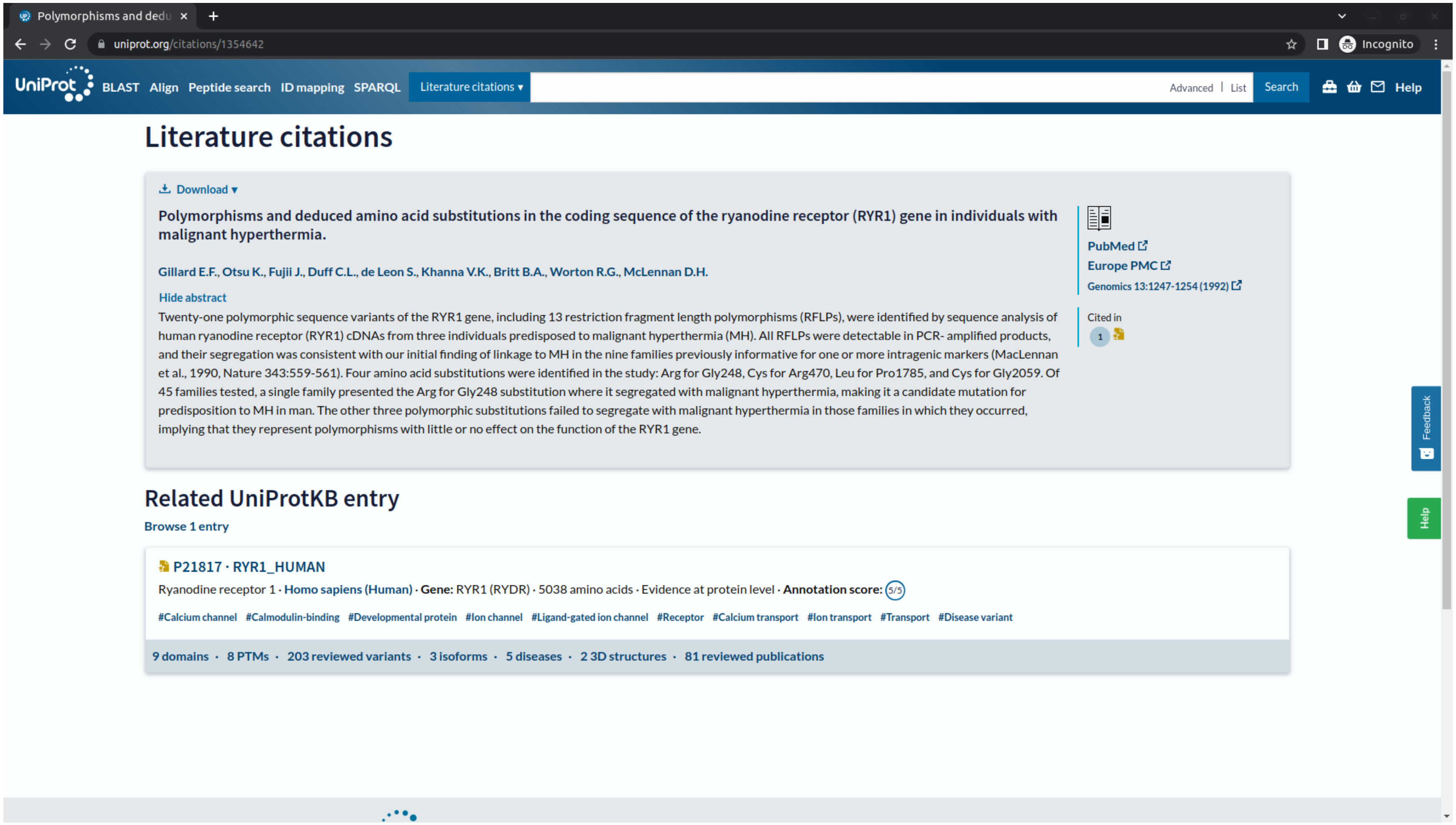
Cited for SEQUENCE REVISION TO 2324; 2840 AND 3380, INVOLVEMENT IN MHS1, VARIANT MHS1 ARG-248, VARIANTS CYS-471; LEU-1787; CYS-2060 AND VAL-2550
Tissue Muscle
Categories Sequences, Pathology & Biotech
Source UniProtKB reviewed (Swiss-Prot)

PubMed
Europe PMC
Genomics 13:1247-1254 (1992)
Cited in 1

A mutation in the human ryanodine receptor gene associated with central core disease.

Publications related to Ryanodine receptor 1

Top-left link to publications
- click on it
- list of publications somehow related to the protein



Literature citations

Download ▾

Polymorphisms and deduced amino acid substitutions in the coding sequence of the ryanodine receptor (RYR1) gene in individuals with malignant hyperthermia.

Gillard E.F., Otsu K., Fujii J., Duff C.L., de Leon S., Khanna V.K., Britt B.A., Worton R.G., McLennan D.H.

Hide abstract

Twenty-one polymorphic sequence variants of the RYR1 gene, including 13 restriction fragment length polymorphisms (RFLPs), were identified by sequence analysis of human ryanodine receptor (RYR1) cDNAs from three individuals predisposed to malignant hyperthermia (MH). All RFLPs were detectable in PCR- amplified products, and their segregation was consistent with our initial finding of linkage to MH in the nine families previously informative for one or more intragenic markers (MacLennan et al., 1990, Nature 343:559-561). Four amino acid substitutions were identified in the study: Arg for Gly248, Cys for Arg470, Leu for Pro1785, and Cys for Gly2059. Of 45 families tested, a single family presented the Arg for Gly248 substitution where it segregated with malignant hyperthermia, making it a candidate mutation for predisposition to MH in man. The other three polymorphic substitutions failed to segregate with malignant hyperthermia in those families in which they occurred, implying that they represent polymorphisms with little or no effect on the function of the RYR1 gene.

PubMed
Europe PMC
Genomics 13:1247-1254 (1992)

Cited in
1

Related UniProtKB entry

Browse 1 entry

P21817 · RYR1_HUMAN

Ryanodine receptor 1 · Homo sapiens (Human) · **Gene:** RYR1 (RYDR) · 5038 amino acids · Evidence at protein level · **Annotation score:** 5/5

#Calcium channel #Calmodulin-binding #Developmental protein #Ion channel #Ligand-gated ion channel #Receptor #Calcium transport #Ion transport #Transport #Disease variant

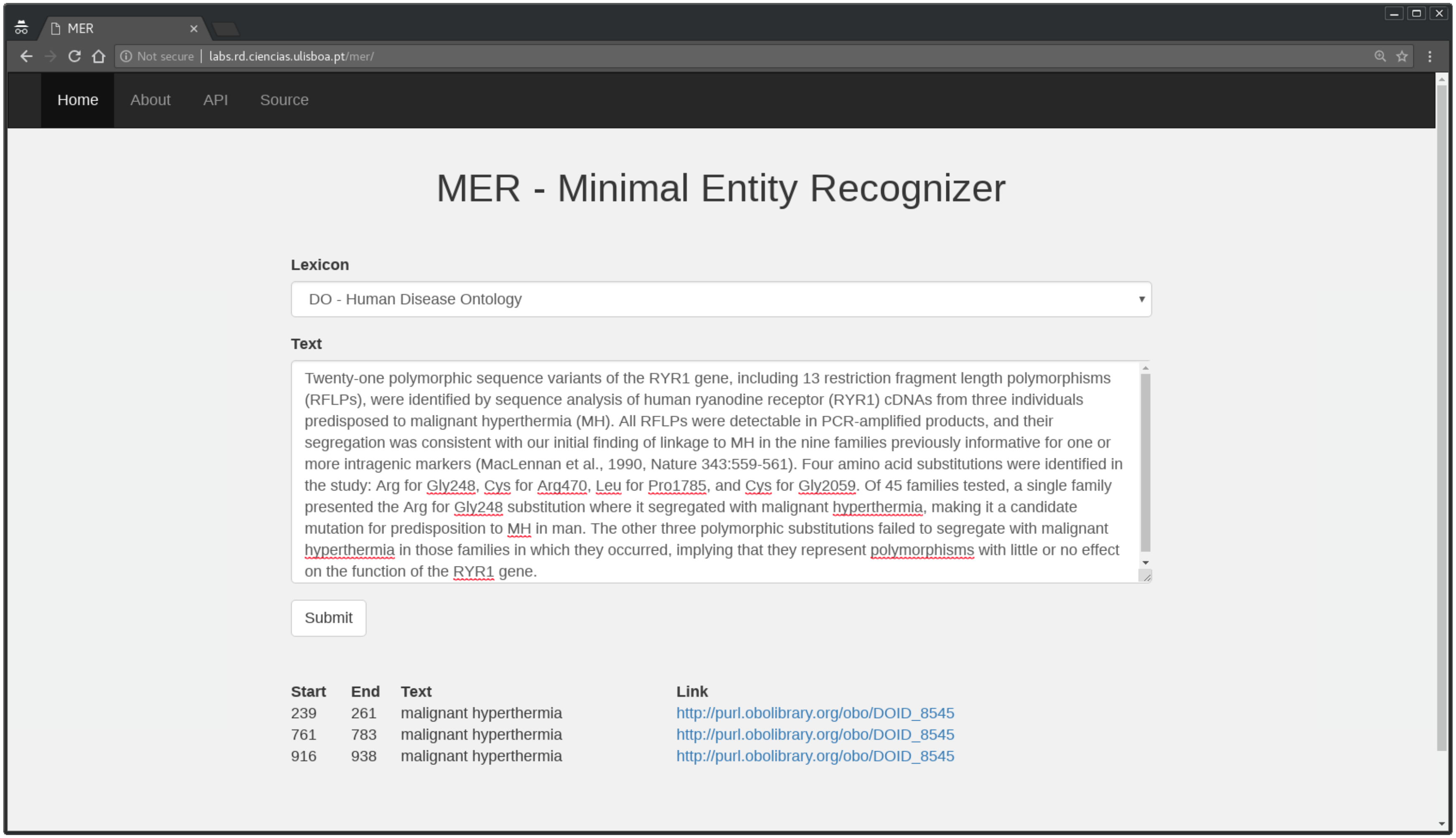
9 domains · 8 PTMs · 203 reviewed variants · 3 isoforms · 5 diseases · 2 3D structures · 81 reviewed publications

Abstract of the publication entitled *Polymorphisms and deduced amino acid substitutions in the coding sequence of the ryanodine receptor (RYR1) gene in individuals with malignant hyperthermia*

Finding phenotypic information,
the first title that may attract our attention:

Polymorphisms and deduced amino acid substitutions in the coding sequence of the ryanodine receptor (RYR1) gene in individuals with malignant hyperthermia

Clicking on the Abstract link



MER - Minimal Entity Recognizer

Lexicon

DO - Human Disease Ontology

Text

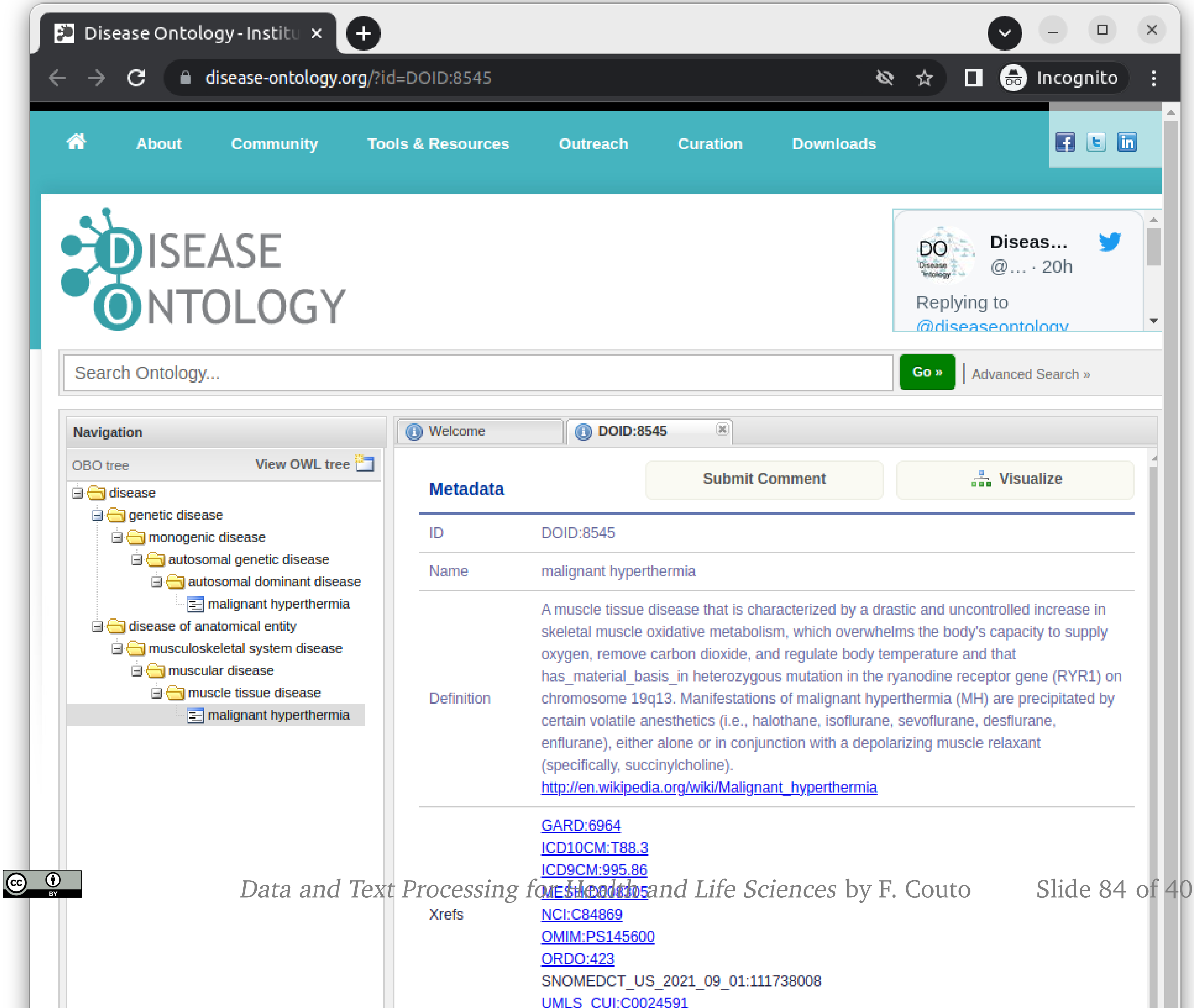
Twenty-one polymorphic sequence variants of the RYR1 gene, including 13 restriction fragment length polymorphisms (RFLPs), were identified by sequence analysis of human ryanodine receptor (RYR1) cDNAs from three individuals predisposed to malignant hyperthermia (MH). All RFLPs were detectable in PCR-amplified products, and their segregation was consistent with our initial finding of linkage to MH in the nine families previously informative for one or more intragenic markers (MacLennan et al., 1990, Nature 343:559-561). Four amino acid substitutions were identified in the study: Arg for Gly248, Cys for Arg470, Leu for Pro1785, and Cys for Gly2059. Of 45 families tested, a single family presented the Arg for Gly248 substitution where it segregated with malignant hyperthermia, making it a candidate mutation for predisposition to MH in man. The other three polymorphic substitutions failed to segregate with malignant hyperthermia in those families in which they occurred, implying that they represent polymorphisms with little or no effect on the function of the RYR1 gene.

Start	End	Text	Link
239	261	malignant hyperthermia	http://purl.obolibrary.org/obo/DOID_8545
761	783	malignant hyperthermia	http://purl.obolibrary.org/obo/DOID_8545
916	938	malignant hyperthermia	http://purl.obolibrary.org/obo/DOID_8545

Diseases recognized by the online tool MER in an abstract

Mentions any disease
    use an online text mining tool
    Minimal Named-Entity Recognizer (MER)
    `http://labs.rd.ciencias.ulisboa.pt/mer/`.
    copy and paste the abstract
    select *DO - Human Disease Ontology* as lexicon

Detects three mentions of *malignant hyperthermia*,
    link about the disease



- disease
  - genetic disease
    - monogenic disease
      - autosomal genetic disease
        - autosomal dominant disease
          - malignant hyperthermia
  - disease of anatomical entity
    - musculoskeletal system disease
      - muscular disease
        - muscle tissue disease
          - malignant hyperthermia

Metadata

ID	DOID:8545
Name	malignant hyperthermia
Definition	A muscle tissue disease that is characterized by a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature and that has_material_basis_in heterozygous mutation in the ryanodine receptor gene (RYR1) on chromosome 19q13. Manifestations of malignant hyperthermia (MH) are precipitated by certain volatile anesthetics (i.e., halothane, isoflurane, sevoflurane, desflurane, enflurane), either alone or in conjunction with a depolarizing muscle relaxant (specifically, succinylcholine). http://en.wikipedia.org/wiki/Malignant_hyperthermia
Xrefs	GARD:6964 ICD10CM:T88.3 ICD9CM:995.86 MESH:D008305 NCI:C84869 OMIM:PS145600 ORDO:423 SNOMEDCT_US_2021_09_01:111738008 UMLS_CUI:C0024591

Entry for the class *malignant hyperthermia*

Need to repeat all the steps to all the proteins
    all publications of each protein

More complicated if all central nervous system stimulants

Motivation to automatize the process,
    not humanly feasible

Goal relation between *caffeine* and hyperthermia,
simply search these two terms in PubMed

1 - Some relations are not explicitly mention in the text

2 - Example using different resources and multiple entries
to automate using shell scripting

Unix shell

A shell is a software program
    interprets and executes command lines
    given by the user in consecutive lines of text

A shell script is a list of such command lines

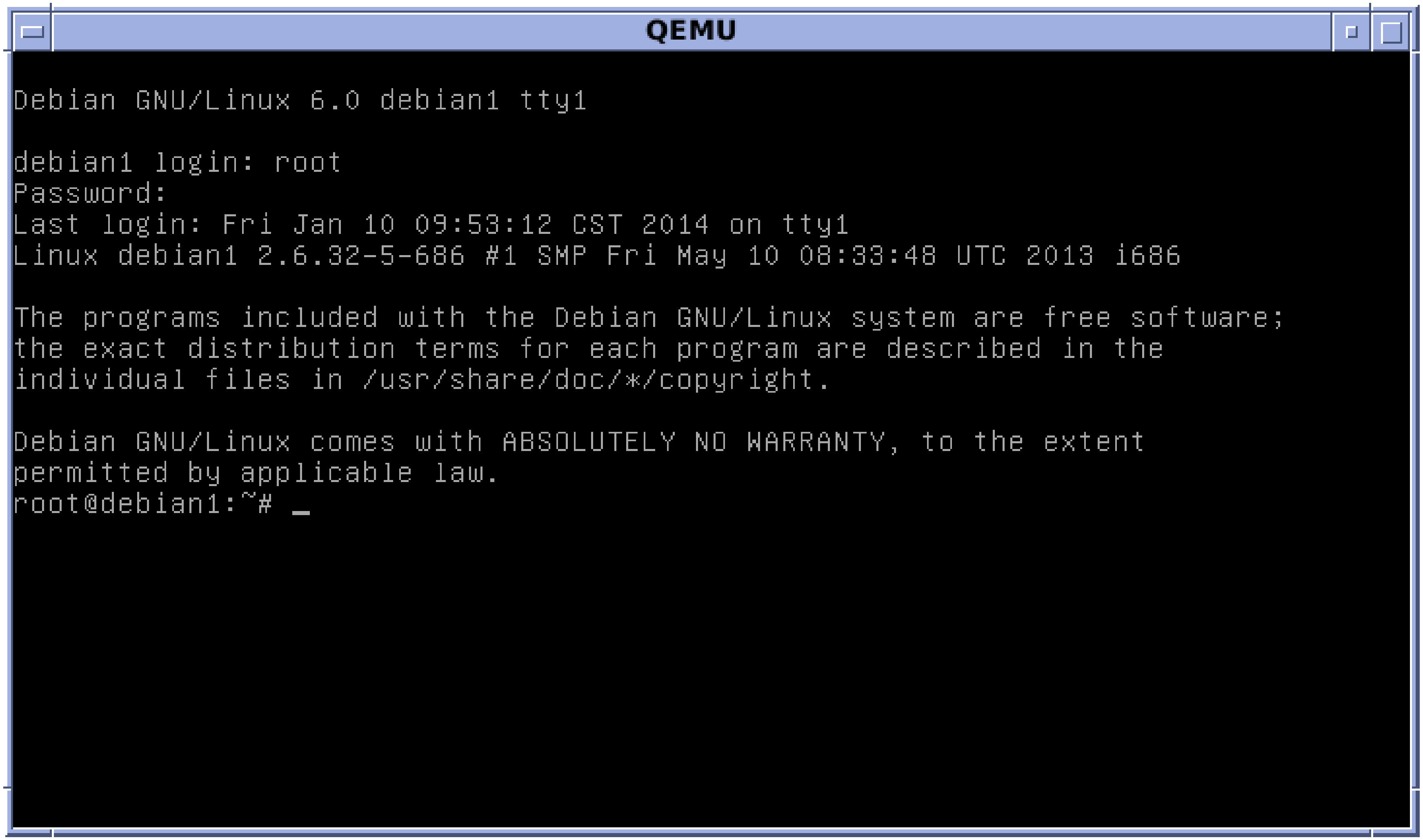
The command line usually starts by invoking a command line tool.

Unix shell was developed to manage Unix-like operating systems,

- nowadays available is most computers
- Linux, macOS or Windows operating systems.

Types of Unix shells with minor differences between them

- sh, ksh, csh, and tcs
- most widely available is the Bourne-Again shell (bash)



```
Debian GNU/Linux 6.0 debian1 tty1

debian1 login: root
Password:
Last login: Fri Jan 10 09:53:12 CST 2014 on tty1
Linux debian1 2.6.32-5-686 #1 SMP Fri May 10 08:33:48 UTC 2013 i686

The programs included with the Debian GNU/Linux system are free software;
the exact distribution terms for each program are described in the
individual files in /usr/share/doc/*/copyright.

Debian GNU/Linux comes with ABSOLUTELY NO WARRANTY, to the extent
permitted by applicable law.
root@debian1:~# _
```

Screenshot of a Terminal application

(Source: `https://en.wikipedia.org/wiki/Unix`)

Linux or macOS
- terminal application already installed
- that opens a shell for us.

Microsoft Windows operating system
- Windows 10 install a Windows Subsystem for Linux
- or a third-party application, such as MobaXterm

Current directory

First command line:

```
$ pwd
```

Shows the full path of the directory (folder) in which the shell is working on.

The dollar sign in the left

    a command to be executed directly in the shell

A curved arrow in the right

    a command does not fit in the available width of a page
    and has to be presented in multiple lines

To understand a command line tool

type `man` followed by the name of the tool.

For example `man pwd`

Or type `pwd --help`

a more concise description of `pwd`.

`ls`

shows list of files in the current directory.

Type `ls --help`

a concise description of `ls`

Select a current directory

we can easily open in our file explorer application

Windows directories

Separated by a backslash (`\`)
in a Unix shell is a forward slash (`/`).

Windows path to the Documents folder:

```
C:\Users\MyUserName\Documents
```

Windows Subsystem for Linux:

```
/mnt/c/Users/MyUserName/Documents
```

MobaXterm:

```
/drives/c/Users/MyUserName/Documents
```

Change directory

Type `cd` (change directory) followed by the new path:

```
$ cd Documents
```

Type `pwd` to see what changed.

Return to the parent directory:

```
$ cd ..
```

Return to the home directory:

```
$ cd ~
```

Windows full path:

```
$ cd /mnt/c/Users/MyUserName/Documents
```

Enclose the path within single (or double) quotes
in case it contains spaces:

```
$ cd '/mnt/c/Users/MyUserName/Documents'
```

Later on difference between using single or double quotes.
we may assume that they are equivalent.

Useful key combinations

Terminal is blocked
- press Ctrl-c cancels the current tool

For example: try using the *cd* command with only one single quote:

```
$ cd '
```

- Now press Ctrl-c, and the command will be aborted.

Ctrl-d indicates the terminal that it is the end of input.
- command will not be canceled,
- executed without the second single quote
- a syntax error will be shown on our display

Ctrl-l cleans the terminal display

control-insert and shift-insert
    copy and paste the selected text

Shell version

Check if the output says bash;

```
$ ps -p $$
```

`ps` shows information about active processes

The `-p` option selects a given process,

`$$` represents the process running in our terminal

Data file

Create a file named *myfile.txt* using any text editor:

```
line 1
line 2
line 3
line 4
```

Save it in working directory
- check proper filename extension.

File contents

Type:

```
$ cat myfile.txt
```

`cat` receives a filename as argument
displays its contents on the screen.

Reverse file contents

Type:

```
$ tac myfile.txt
```

The contents of the file in the reverse order

In macOS use `tail -r`

My first script

Create a script file named *reversemyfile.sh*:

```
tac $1
```

`$1` represents the first argument

Each script will include the line numbers in the left
helps identify how many lines
and distinguish from commands directly in the shell

Line breaks

A Unix file a line break
- is a line feed character
- instead of two characters (carriage return and line feed)
- used by Windows

Text editor in Windows
- save it as Unix file,
- open source Notepad++

Text editor in macOS
- save it in text format

Remove the extra carriage return:

```
$ tr -d '\r' < reversemyfile.sh > reversemyfilenew.sh
```

The `-d` option of `tr`

- removes a given character from the input
- this case delete all carriage returns (`r`)

Command line options can be used

- in short form using a single dash (`-`)
- or in a long form using two dashes (`--`)

`--delete` is equivalent to `-d`

Redirection operator

> character
    moves the results being displayed at the standard output (our terminal) to a given file.

< character
    works on the opposite direction
    opens a given file
    uses it as the standard input

`cat` filename as an input argument
while `tr` through the standard input

`cat` can also receive contents through the standard input:

```
$ cat < myfile.txt
```

`tr` a new file for the standard output
cannot use the same file to read and write

To keep the same filename use `mv`:

```
$ mv reversemyfilenew.sh reversemyfile.sh
```

Installing tools

Two last two commands replaced by `dos2unix`:

```
$ dos2unix -n reversemyfile.sh
```

If not available, install the `dos2unix` tool:

```
$ apt install dos2unix
```

In macOS:

```
$ brew install dos2unix
```

Avoid fixing line breaks
- each time update file using Windows,
- better solution is a Unix friendly text editor

Using a Unix friendly text editor,
- the previous commands nothing will happen
- since `tr` not remove any character

Permissions

A script also needs permission to be executed:

```
$ chmod u+x reversemyfile.sh
```

`chmod` just gave the user (`u`)
permissions to execute (`+x`)

Finally, execute the script:

```
$ ./reversemyfile.sh myfile.txt
```

Result:

```
line 4
line 3
line 2
line 1
```

More arguments will be ignored:

```
$ ./reversemyfile.sh myfile.txt myotherfile.txt 'my other file.txt'
```

The output will be exactly the same

- does not use `$2` and `$3`

When containing spaces

- the argument enclosed by single quotes

Debug

Not working well debug the entire script:

```
$ bash -x reversemyfile.sh myfile.txt
```

Command line tools executed preceded by +:

```
+ tac myfile.txt
line 4
line 3
line 2
line 1
```

Or add `set -x` in script to start debug
and `set +x` to stop debug

Save output

Save output into another file:

```
$ ./reversemyfile.sh myfile.txt > mynewfile.txt
```

Check if the file was really created:

```
$ cat mynewfile.txt
```

Or reverse it again:

```
$ ./reversemyfile.sh mynewfile.txt
```

Web Identifiers

Input argument(s) of our task
- is the chemical compound(s)
- ChEBI identifier(s)
- finding the identifier by its name is also possible

Retrieve all proteins
- associated to *caffeine* (CHEBI:27732).

Links shown as *Export options*:

```
https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e
  =1&6578706f7274=1&chebiId=27732&dbName=UniProt
https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e
  =2&6578706f7274=1&chebiId=27732&dbName=UniProt
https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e
  =3&6578706f7274=1&chebiId=27732&dbName=UniProt
```

Downloading a CSV, Excel, or XML file, respectively.

The only difference

single numerical digit (1, 2, and 3)

after the first =

argument to select the type of file

Another parameter
the ChEBI identifier (27732).

Replace 27732 by 17245 in any of those URLs:

```
https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e
  =1&6578706f7274=1&chebiId=17245&dbName=UniProt
```

Downloads more than seven hundred proteins
since 17245 the ChEBI identifier
of *carbon monoxide*.

Not using a fully RESTful web service
but pretty modular and self-explanatory

The path is clearly composed of:

- the name of the database (chebi);
- the method (viewDbAutoXrefs.do);
- list of parameters and their value (arguments) after ?

Order of the parameters is normally not relevant
- separated by &
- = assigns a value to each parameter (argument).

As data pipelines to fill our local files with data
- like pipelines that transport oil or gas

Single and double quotes

Script *getproteins.sh*:

```
echo 'The input: $1'
echo "The input: $1"
```

```
$ ./getproteins.sh
```

```
The input: $1
The input:
```

With an argument:

```
$ ./getproteins.sh 27732
```

```
The input: $1
The input: 27732
```

Comments

```
#echo 'The input: $1'
#echo "The input: $1"
echo "https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e=1&6578706f7274=1&chebiId=$1&dbName=UniProt"
```

Commented lines are ignored

ChEBI identifier as argument:

```
$ ./getproteins.sh 27732
```

Output the link for CSV file with proteins associated with *caffeine*

Data Retrieval

Client Uniform Resource Locator (cURL)
- a command line tool
- download a URL directly into a file

List of proteins related to *caffeine*:

```
$ curl 'https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e↩
  =1&6578706f7274=1&chebiId=27732&dbName=UniProt'
```

```
...
Q15413,Ryanodine receptor 3,CC - MISCELLANEOUS
Q92375,Thioredoxin reductase,DE
Q92736,Ryanodine receptor 2,CC - MISCELLANEOUS
```

Alternative:

```
$ wget -O- 'https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d
    -1169080-e=1&6578706f7274=1&chebiId=27732&dbName=UniProt'
```

Instead of using a fixed URL, update *getproteins.sh*:

```
curl "https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e
    =1&6578706f7274=1&chebiId=$1&dbName=UniProt"
```

Using double quotes

Execute:

```
$ ./getproteins.sh 27732

  ...
  Q15413,Ryanodine receptor 3,CC - MISCELLANEOUS
  Q92375,Thioredoxin reductase,DE
  Q92736,Ryanodine receptor 2,CC - MISCELLANEOUS
```

Proteins related to *carbon monoxide*:

```
$ ./getproteins.sh 17245

...
Q58432,Phosphomethylpyrimidine synthase,CC - CATALYTIC ACTIVITY
Q62976,Calcium-activated potassium channel subunit alpha-1,CC -
  ENZYME REGULATION; CC - DOMAIN
Q63185,Eukaryotic translation initiation factor 2-alpha kinase 1,
  CC - ENZYME REGULATION
```

Command line tool `less`

navigate using the arrow keys

Bar character (`|`) between two commands

transfer the output of the first command as input of the second

```
$ ./getproteins.sh 27732 | less
```

To exit press `q`.

Save the output as a file:

```
$ ./getproteins.sh 27732 > chebi_27732_xrefs_UniProt.csv
```

Download progress information still displayed

Standard error output

Redirect the standard error output (`2`) to the null device:

```
$ ./getproteins.sh 27732 > chebi_27732_xrefs_UniProt.csv 2>/dev/null
```

Or use `-s` option of `curl`:

```
curl -s "https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e=1&6578706f7274=1&chebiId=$1&dbName=UniProt"
```

The equivalent long form to the `-s` option is `--silent`.

Check if created:

```
$ less chebi_27732_xrefs_UniProt.csv
```

Or use spreadsheet application
  such as LibreOffice Calc or Microsoft Excel

Exercise get the CSV file
  associated proteins of water and gold

Data Extraction

Select the relevant proteins (lines)
  using `grep`,

Select the column
  using `cut`

Diseases related to *caffeine*,

- only interested in proteins (lines) with topics:
  - `CC - MISCELLANEOUS`
  - `CC - DISRUPTION PHENOTYPE`
  - `CC - DISEASE`

Extracting lines from a text file

- main function of `grep`.
- giving as input a pattern

Single and multiple patterns

Selects proteins topic `CC - MISCELLANEOUS`:

```
$ grep 'CC - MISCELLANEOUS' chebi_27732_xrefs_UniProt.csv
```

```
A2AGL3,Ryanodine receptor 3,CC - MISCELLANEOUS
B0LPN4,Ryanodine receptor 2,CC - MISCELLANEOUS
...
Q15413,Ryanodine receptor 3,CC - MISCELLANEOUS
Q92736,Ryanodine receptor 2,CC - MISCELLANEOUS
```

Multiple patterns

precede with `-e` option:

```
$ grep -e 'CC - MISCELLANEOUS' -e 'CC - DISRUPTION PHENOTYPE' -e '↩
  CC - DISEASE' chebi_27732_xrefs_UniProt.csv
```

```
...
Q9VSH2,Gustatory receptor for bitter taste 66a,CC - FUNCTION; CC
  - DISRUPTION PHENOTYPE
Q15413,Ryanodine receptor 3,CC - MISCELLANEOUS
Q92736,Ryanodine receptor 2,CC - MISCELLANEOUS
```

Add `| less` to check carefully

`less` also find lines based on a pattern

- type `/`
- and then a pattern

Update *getproteins.sh*:

```
curl -s "https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e=1&6578706f7274=1&chebiId=$1&dbName=UniProt" | \
grep -e 'CC - MISCELLANEOUS' -e 'CC - DISRUPTION PHENOTYPE' -e 'CC - DISEASE'
```

Added `-s` to suppress the progress information

The characters `| \`

- redirect the output of that line
- as input of the next line
- ensure `\` is the last character

We can now execute the script again:

```
$ ./getproteins.sh 27732
```

The output should be similar of what we got previously, but the script downloads the data and filters immediately.

To save the file with the relevant proteins, we only need to add the redirection operator:

```
$ ./getproteins.sh 27732 > chebi_27732_xrefs_UniProt_relevant.csv
```

Data elements selection

Select first column

- the one that contains the protein identifiers
- one easy task for `cut`

Select character that divides each data element (column)

- with `-F` option,
- and instruction of what to do with it
- enclosed by single quotes and curly brackets

Get the first column of CSV file:

```
$ cut -d, -f1 < chebi_27732_xrefs_UniProt_relevant.csv
```

```
...
Q9VSH2
Q15413
Q92736
```

Comma (`,`) character that separates data elements

- `print` is equivalent to `echo`
- and `1` the first data element

Example for first and third columns:

```
$ cut -d, -f1,3 < chebi_27732_xrefs_UniProt_relevant.csv

  ...
  Q9VSH2,CC - FUNCTION; CC - DISRUPTION PHENOTYPE
  Q15413,CC - MISCELLANEOUS
  Q92736,CC - MISCELLANEOUS
```

Update *getproteins.sh*:

```
curl -s "https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e=1&6578706f7274=1&chebiId=$1&dbName=UniProt" | \
grep -e 'CC - MISCELLANEOUS' -e 'CC - DISRUPTION PHENOTYPE' -e 'CC - DISEASE' | \
cut -d, -f1
```

The last line is the only that changes except the `| \`

Execute:

```
$ ./getproteins.sh 27732
```

Output similar of what we got previously
but now only the protein identifiers

To save the output as a file:

```
$ ./getproteins.sh 27732 > ↩
    chebi_27732_xrefs_UniProt_relevant_identifiers.csv
```

Task Repetition

Given a protein identifier
- construct the URL
- download its information from UniProt
- RESTful web services provided by UniProt

URL starts by `https://www.uniprot.org/uniprot/`
- followed by the protein identifier
- ending with a dot and the data format
- `https://rest.uniprot.org/uniprotkb/P21817.xml`

Assembly line

Construct one URL for each protein
- from the previously list
- size can be large (hundreds of proteins)
- varies for different compounds
- and evolves with time

We need an assembly line
- list of proteins identifiers added as input
- construct one URL per protein
- and retrieve the respective file

`xargs` works as an assembly line
- executes a command per each line given as input

Display each identifier:

```
$ cat chebi_27732_xrefs_UniProt_relevant_identifiers.csv | xargs -I
    {} echo 'Another protein id {} to retrieve'
```

```
...
Another protein id Q9VSH2 to retrieve
Another protein id Q15413 to retrieve
Another protein id Q92736 to retrieve
```

Input the contents our CSV file

for each line displayed a message

`-I` replaces `{}` by the value of the line being processed

Create the URLs:

```
$ cat chebi_27732_xrefs_UniProt_relevant_identifiers.csv | xargs -I
    {} echo 'https://rest.uniprot.org/uniprotkb/{}.xml'
```

```
...
https://rest.uniprot.org/uniprotkb/Q9VSH2.xml
https://rest.uniprot.org/uniprotkb/Q15413.xml
https://rest.uniprot.org/uniprotkb/Q92736.xml
```

Try these links in our internet browser

Download using the `curl`:

```
$ cat chebi_27732_xrefs_UniProt_relevant_identifiers.csv | xargs -I {} curl 'https://rest.uniprot.org/uniprotkb/{}.xml' -o 'chebi_27732_{}.xml'
```

`-o` save the output to a given file
named after each protein identifier

Check using `ls`:

```
$ ls chebi_27732_*.xml
```

`*` represents any file
whose name starts with `chebi_27732_`
and ends with `.xml`

Check contents:

```
$ less chebi_27732_P21817.xml
```

File header

Content has to start with `<?xml`

- otherwise was download error
- run `curl` again for those entries

Check the header with `head`:

```
$ head -n 1  chebi_27732_*.xml | less
```

`-n` specifies how many lines to print

Not able to download from UniProt

- book file archive: `http://labs.rd.ciencias.ulisboa.pt/book/`

Variable

Update *getproteins.sh*:

```
ID=$1 # The CHEBI identifier given as input is renamed to ID
rm -f chebi\_$ID\_*.xml # Removes any previous files
curl -s "https://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?d-1169080-e=1&6578706f7274=1&chebiId=$ID&dbName=UniProt" | \
grep -e 'CC - MISCELLANEOUS' -e 'CC - DISRUPTION PHENOTYPE' -e 'CC - DISEASE' | \
cut -d, -f1 | xargs -I {} curl 'https://rest.uniprot.org/uniprotkb/{}.xml' -o chebi\_$ID\_{}.xml
```

Includes `xargs`, `curl` and `$ID` variable
- variable contains value of `$1`

Preceding character of `$ID` an underscore (_)
- add a backslash (`\`) before it

`rm` remove any files downloaded previously

Execute:

```
$ ./getproteins.sh 27732
```

Check results:

```
$ head -n 1  chebi_27732_*.xml | less
```

XML Processing

Only human diseases
  process the XML of each protein
  check if a *Homo sapiens (Human)* protein.

Human proteins

Use `grep`:

```
$ grep '<name type="scientific">Homo sapiens</name>' chebi_27732_*.xml
chebi_27732_P21817.xml:<name type="scientific">Homo sapiens</name>
chebi_27732_Q15413.xml:<name type="scientific">Homo sapiens</name>
chebi_27732_Q8N490.xml:<name type="scientific">Homo sapiens</name>
chebi_27732_Q92736.xml:<name type="scientific">Homo sapiens</name>
```

`-l` option just filename:

```
$ grep -l '<name type="scientific">Homo sapiens</name>' ⤸
    chebi_27732_*.xml
```

The output will now show only the filenames:

```
chebi_27732_P21817.xml
chebi_27732_Q15413.xml
chebi_27732_Q8N490.xml
chebi_27732_Q92736.xml
```

PubMed identifiers

Extract PubMed identifiers:

```
$ grep '<dbReference type="PubMed"' chebi_27732_P21817.xml

  ...
  <dbReference type="PubMed" id="11741831"/>
  <dbReference type="PubMed" id="16163667"/>
  <dbReference type="PubMed" id="27586648"/>
```

Just the identifier:

```
$ grep '<dbReference type="PubMed"' chebi_27732_P21817.xml | cut -d
    \" -f4

  ...
  11741831
  16163667
  27586648
  18318008
```

`"` as separation character

PubMed identifiers extraction

Apply to every protein:

```
$ grep -l '<name type="scientific">Homo sapiens</name>'
    chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed
    "' {} | cut -d\" -f4
```

Long list of PubMed identifiers

- including repetitions
- same publication cited in different entries

Duplicate removal

Identify the repetitions with `sort`

- repeated identifiers in consecutive lines

```
$ grep -l '<name type="scientific">Homo sapiens</name>' 
    chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed
    "' {} | cut -d\" -f4 | sort

...
9607712
9607712
9607712
```

`-u` option removes duplicates:

```
$ grep -l '<name type="scientific">Homo sapiens</name>'
    chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed
    "' {} | cut -d\" -f4 | sort -u
```

Check how many duplicates were removed

- word count `wc` command
- with and without the usage of `-u`:

```
$ grep -l '<name type="scientific">Homo sapiens</name>'
    chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed
    "' {} | cut -d\" -f4 | sort | wc
$ grep -l '<name type="scientific">Homo sapiens</name>'
    chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed
    "' {} | cut -d\" -f4 | sort -u | wc

263      263     2315
133      133     1172
```

`wc` prints the numbers of lines, words, and bytes

removed $263 - 133 = 130$ duplicates

```
$ expr 263 - 133
```

Create script *getpublications.sh*:

```
ID=$1 # The CHEBI identifier given as input is renamed to ID
grep -l '<name type="scientific">Homo sapiens</name>' chebi\_$ID\_*.xml | \
xargs -I {} grep '<dbReference type="PubMed"' {} | \
cut -d\" -f4 | sort -u
```

Execute:

```
$ ./getpublications.sh 27732
```

How many unique publications:

```
$ ./getpublications.sh 27732 | wc -l
```

133 as expected

Complex Elements

XML elements not in the same line
- use `xmllint`
- a parser to extract data
- using a XPath query
- instead of single line pattern

XPath (XML Path Language)
- a powerful tool to extract information from XML and HTML documents
- following their hierarchical structure

Namespace problems

Our protein XML files

- second line defines a specific namespace
- using the xmlns attribute:

```
<uniprot xmlns="http://uniprot.org/uniprot" xmlns:xsi="http://www
  .w3.org/2001/XMLSchema-instance" xsi:schemaLocation="http://
  uniprot.org/uniprot http://www.uniprot.org/support/docs/uniprot
  .xsd">
```

Complicates our XPath queries

- since need explicitly specify using local name
- for every element in a XPath query

Get the data in each `reference` element:

```
$ xmllint --nsclean --xpath "//*[local-name()='reference']" ⤸
    chebi_27732_P21817.xml
```

`//` means any path in the XML file
until reaching a reference element

The square brackets
normally represent conditions

Only local names

Avoid `local-name()`

- identify the top-level element
- extract all the data that it encloses:

```
$ xmllint --nsclean --xpath "//*[local-name()='entry']" ⤵
  chebi_27732_P21817.xml > chebi_27732_P21817_entry.xml
```

The new XML file:

```
<entry dataset="Swiss-Prot" created="1991-05-01" ...
<accession>P21817</accession>
...
</sequence>
</entry>
```

Apply any XPath query without explicitly say it represents a local name:

```
$ xmllint --xpath '//reference' chebi_27732_P21817_entry.xml
```

```
<reference key="1">
<citation type="journal article" date="1990" name="J. Biol. Chem.
  " volume="265" first="2244" last="2256">
<title>Molecular cloning of cDNA encoding human and rabbit forms
  of the Ca2+ release channel (ryanodine receptor) of skeletal
  muscle sarcoplasmic reticulum.</title>
...
<dbReference type="DOI" id="10.1111/cge.12810"/>
</citation>
<scope>VARIANTS CCD PRO-2963 AND ASP-4806</scope>
</reference>
```

Queries

`//dbReference`

elements of type `dbReference` descendants of something

```
<dbReference type="NCBI Taxonomy" id="9606"/>
...
<dbReference type="PubMed" id="27586648"/>
```

`/entry//dbReference`

equivalent to the previous query

specifying `dbReference` descendants of `entry`

`/entry/reference/citation/dbReference`

similar to the previous query

specifying the full path

only `dbReference` descendants of `citation`

`//dbReference/*`

any child elements of `dbReference`

```
<property type="protein sequence ID" value="AAA60294.1"/> ... <
  property type="match status" value="5"/>
```

`//dbReference/property[1]`

first `property` of each `dbReference`

`<property type="protein sequence ID" value="AAA60294.1"/> ... <property type="entry name" value="MIR"/>`

`//dbReference/property[2]`

second `property` of each `dbReference`

`<property type="molecule type" value="mRNA"/> ... <property type="match status" value="5"/>`

`//dbReference/property[3]`

third `property` of each `dbReference`

`<property type="molecule type" value="Genomic_DNA"/> ... <property type="project" value="UniProtKB"/>`

`//dbReference/property/@type`

all type attributes of `property`

```
type="protein sequence ID" type="molecule type" type="protein
  sequence ID" ... type="entry name" type="match status"
```

`//dbReference/property[@type="protein sequence ID"]`

the previous `property` elements

with attribute type equal to *protein sequence ID*

```
<property type="protein sequence ID" value="AAA60294.1"/> ... <
  property type="protein sequence ID" value="ENSP00000352608"/>
```

`//dbReference/property[@type="protein sequence ID"]/@value`

string of each attribute *value* of previous `property` elements

`value="AAA60294.1" value="AAC51191.1" ... value="ENSP00000352608"`

`/entry/sequence/text()`

the contents inside `sequence`

`MGDAEGEDEVQF...DCFRKQYEDQLS`

Try previous queries:

```
$ xmllint --xpath '//dbReference' chebi_27732_P21817_entry.xml
```

Alternative o extract the PubMed identifiers:

```
$ xmllint --xpath '//dbReference[@type="PubMed"]/@id' ⤸
    chebi_27732_P21817_entry.xml

  ...
  id="11741831"
  id="16163667"
  id="27586648"
```

Need to extract only the identifiers

Extracting XPath results

To extract the identifiers using `cut`

value inside quotes

```
$ xmllint --xpath '//dbReference[@type="PubMed"]/@id' ⤸
   chebi_27732_P21817_entry.xml | cut -d\" -f2
```

Text Retrieval

Download the text
in titles and abstracts

UniProt citations service entry
`https://rest.uniprot.org/citations/1354642`
link to the RDF/XML version
deal like XML

Retrieve the publication entry:

```
$ curl https://rest.uniprot.org/citations/1354642.rdf
```

Using PubMed at NCBI:

```
$ curl 'https://eutils.ncbi.nlm.nih.gov/entrez/eutils/efetch.fcgi?
    db=pubmed&id=1354642&retmode=text&rettype=xml'
```

Update *getpublications.sh*:

```
ID=$1 # The CHEBI identifier given as input is renamed to ID
rm -f chebi\_$ID\_*.rdf # Removes any previous files
grep -l '<name type="scientific">Homo sapiens</name>' chebi\_$ID\_*.xml | \
xargs -I {} grep '<dbReference type="PubMed"' {} | \
cut -d\" -f4 | sort -u | \
xargs -I {} curl 'https://rest.uniprot.org/citations/{}.rdf' -o chebi\_$ID\_{}.rdf
```

Only the second and last lines updated

Execute:

```
$ ./getpublications.sh 27732
```

Take a while to download all the entries

Check files created:

```
$ ls chebi_27732_*.rdf
```

Not able to download from UniProt

- book file archive: `http://labs.rd.ciencias.ulisboa.pt/book/`

Title and Abstract

title and abstract

values of the `title`

and `rdfs:comment` elements

Extract them:

```
$ xmllint --xpath "//*[local-name()='title' or local-name()='⤸
    comment']" chebi_27732_1354642.rdf
```

```
<title>Polymorphisms ... hyperthermia.</title>
<rdfs:comment>Twenty-one ... gene.</rdfs:comment>
```

Remove the XML elements:

```
$ xmllint --xpath "//*[local-name()='title' or local-name()='↩
  comment']/text()" chebi_27732_1354642.rdf
```

```
Polymorphisms ... hyperthermia.
Twenty-one ... gene.
```

Create *gettext.sh*:

```
ID=$1 # The CHEBI identifier given as input is renamed to ID
xmllint --xpath "//*[local-name()='title' or local-name()='comment']/text()" chebi\_$ID\_*.rdf
```

Execute:

```
$ ./gettext.sh 27732 | less
```

Save the resulting text:

```
$ ./gettext.sh 27732 > chebi_27732.txt
```

Disease Recognition

Find sentences about a given disease by using `grep`:

```
$ grep 'malignant hyperthermia' chebi_27732.txt
```

To save the filtered text:

```
$ grep 'malignant hyperthermia' chebi_27732.txt > ⤸
    chebi_27732_hyperthermia.txt
```

Simple way of recognizing a disease

- next chapters more complex text processing

Text Processing

How process that text using shell script commands
  specifically extract information about diseases related to *caffeine*

Essential set of skills to extract meaningful information from any text

Pattern Matching

Searching for mentions of *malignant hyperthermia* using related expressions:

MH - acronym
MHS - acronym for *malignant hyperthermia susceptible*

Solve this problem by executing:

```
$ grep -e 'malignant hyperthermia' -e 'MH' -e 'MHS' chebi_27732.txt
```

Case insensitive matching

Case sensitive search
- good approach to avoid wrong matches
- acronyms are normally in upper case

While full name in lowercase
- sometimes the first letter of each word
- or only the first word in uppercase

Case sensitive `grep` for the acronyms

case insensitive `grep` for the disease words:

```
$ grep -e 'MH' -e 'MHS' chebi_27732.txt
$ grep -i -e 'malignant hyperthermia' chebi_27732.txt
```

Just one case sensitive `grep`

if *Malignant hyperthermia* only alternative case:

```
$ grep -e 'Malignant hyperthermia' -e 'malignant hyperthermia' -e '
  MH' -e 'MHS' chebi_27732.txt
```

Number of matches

Losing any match?

count number of matching lines

using the `-c` option:

```
$ grep -c -i 'malignant hyperthermia' chebi_27732.txt
$ grep -c -e 'malignant hyperthermia' -e 'Malignant hyperthermia' ⤸
    chebi_27732.txt
```

Output should show 100 and 98 matching lines

for the insensitive and sensitive patterns

two lines not caught by the case sensitive pattern

Invert match

`-v` option inverts matching returns lines not matched

Get our outlier mention:

```
$ grep -i 'malignant hyperthermia' chebi_27732.txt |  grep -v -e '
   Malignant hyperthermia' -e 'malignant hyperthermia'
```

```
...gene are associated with Malignant Hyperthermia (MH) and...
```

Obtain all matching lines by including missing matches:

```
$ grep -c -e 'malignant hyperthermia' -e 'Malignant hyperthermia' -
   e 'Malignant Hyperthermia' chebi_27732.txt
```

File Differences

`diff` input two files and identifies differences:

```
$ grep -i 'malignant hyperthermia' chebi_27732.txt > insensitive.⤸
    txt
$ grep -e 'Malignant hyperthermia' -e 'malignant hyperthermia' ⤸
    chebi_27732.txt > sensitive.txt
$ diff sensitive.txt insensitive.txt
```

Or

```
$ diff  <(grep -i 'malignant hyperthermia' chebi_27732.txt) <(grep ⤸
    -e 'Malignant hyperthermia' -e 'malignant hyperthermia' ⤸
    chebi_27732.txt)
```

The output should be the same text

Problem with case sensitive matching
    acronyms with lowercase in middle, e.g. ChEBI

Humans not consistent mentioning acronyms
    in original form
    or all letters in uppercase
    or just some of them.
    inconsistent mentions in same publication

Evaluation metrics

Online search engines

- use case insensitive searches as default
- favor recall
- while case sensitive search
- favor precision

Recall the proportion of
number of correct matches
over number of correct mentions in texts (found or not found)

Case insensitive searches avoid missing mentions
so favor recall

Precision the proportion of
number of correct matches
over number of matches found (correct or incorrect)

Case sensitive searches avoid incorrect matches
so favor precision

Trade-off between precision and recall

- technique improves precision decrease recall
- and vice-versa

How good the trade-off is?

- F-measure harmonic average of precision and recall

Word Matching

Acronyms appear inside common words
or longer acronyms:

Searching for *MH*
the word *victi**mh**ood* matches:

```
$ echo "victimhood" | grep -i 'MH'
```

Easily solved using case sensitive matching
but not longer acronym
acronym NEDMHM for *neurodevelopmental disorder with midbrain and hindbrain malformations*:

```
$ echo "NEDMHM" | grep 'MH'
```

`-w` option matches entire words
must be preceded and followed by
characters that are not letters, digits, or an underscore
or be at the beginning or end of the line

Neither produce a match:

```
$ echo "victimhood" | grep -w -i 'MH'
$ echo "NEDMHM" | grep -w -i 'MH'
```

Word matching improves precision but decreases recall

miss less common acronyms:

MHE - acronym for *malignant hyperthermia equivocal*

MHN - acronym for *malignant hyperthermia normal*

No match:

```
$ echo "MHE and MHN" | grep -w -i 'MH'
```

Not trivial problems to solve by exact pattern matching

Regular Expressions

Dealing with natural language text
- need more flexibility than exact matching

Regular expressions are an efficient tool
- extend exact matching with flexible patterns
- find different matches

Example finding all mentions of MHS or MHN
- regular expressions provide the alternation operator
- multiple alternatives to match
- an *S* or an *N* as the last character

Three distinct components:

- **input** - any string where to find
- **pattern** - what we are looking for
- **match** - a fragment of the input (a substring)

Input text file *chebi_27732.txt*
- or amino acid sequences

Pattern contains special characters
- not directly match
- operators specify different types of matches

Matches are not replicas of the pattern
- satisfy the specified pattern

Extended syntax

`grep` allows regular expression operators

- two syntax: basic and extended

Use the extended syntax for two reasons:

- the basic not support relevant operators, e.g. alternation
- differentiate exact matching from regular expression matching

The `-E` option

not affects matching with pattern without any operator:

```
$ echo -e 'MHS\nMHN' | grep 'MH'
$ echo -e 'MHS\nMHN' | grep -E 'MH'
```

Use `-e` option so `echo`

interpret `\n` as a newline.

outputs two lines

`grep` filters lines

Alternation

Alternation represented by `|`

- either the preceding or following characters
- can use parentheses specify scope

Example:

```
$ echo -e 'MHS\nMHN' | grep -E 'MH(S|N)'
```

Multiple patterns using `-E` option:

```
$ echo -e 'MHS\nMHN' | grep -E -e 'MH(S|X)' -e 'MH(X|N)'
```

Basic syntax

Basic syntax no match:

```
$ echo -e 'MHS\nMHN' | grep 'MH(S|N)'
```

Only if `|` and parentheses are in string:

```
$ echo -e 'MH(S|N)' | grep 'MH(S|N)'
```

Scope

Remove the parentheses and add `-w`:

```
$ echo -e 'MHS\nMHN' | grep -w -E 'MHS|N'
```

Only first line since operator applied to all preceding characters

If add a single *N* get another match:

```
$ echo -e 'MHS\nN' | grep -w -E 'MHS|N'
```

Move the opening parenthesis:

```
$ echo -e 'MHS\nMHN' | grep -E 'M(HS|N)'
```

Only *MHS* is now displayed

Multiple alternatives

Multiple `|`:

```
$ echo -e 'MHS\nMHN\nMHE' | grep -E 'MH(S|N|E)'
```

Transform previous multiple case sensitive patterns:

```
$ grep -c -e 'Malignant hyperthermia' -e 'Malignant Hyperthermia' -
    e 'malignant hyperthermia' chebi_27732.txt
```

in a single pattern:

```
$ grep -c -E '(M|m)alignant (H|h)yperthermia' chebi_27732.txt
```

Will obtain the same 100 matching lines

Multiple characters

Dot character (.) represents any character:

```
$ grep -o -w -E 'MH.' chebi_27732.txt | sort -u
```

`-o` option displays the matches, not the line

The output will be the following three-character lines:

```
MH
MH)
MH,
MH.
MH1
MH2
MHE
MHN
MHS
```

`-o` option counts total number of matches
not just number of lines matched:

```
$ grep -o -w -E 'MH.' chebi_27732.txt | wc -l
$ grep -c -w -E 'MH.' chebi_27732.txt
```

164 matches were found
in 47 lines

Match only the dot character use `\`:

```
$ grep -o -w -E 'MH\.' chebi_27732.txt | sort -u
```

Only *MH.* will be displayed

Some matches are not acronyms
- e.g. *MH)* and *MH,*

Spaces

MH appears because space can also be matched

following text includes *MH*␣

since parenthesis is word delimiter character:

`... susceptible to MH (MHS) ...`

Text not include a word match with *MH*␣:

`... markers and MH susceptibility ...`

Want matches where third character is letter or numerical digit

Other characters represent horizontal or vertical space

- e.g. tab character
- known as whitespaces
- represented by `\s`

Both space and tab characters are matched by `\s`:

```
echo -e 'space: :\ntab:\t:' | grep -E '\s'
```

Groups

Group operator specify a set of characters enclosed within square brackets

Previous command replaced by:

```
$ echo -e 'MHS\nMHN\nMHE' | grep -E 'MH[SNE]'
```

Ranges

Solving our need to only match letters or digits

- ranges with -

MH followed by any alphabet letter:

```
$ grep -o -w -E 'MH[A-Z]' chebi_27732.txt | sort -u

MHE
MHN
MHS
```

`A-Z` any alphabet letter in uppercase

lowercase letter will not be matched:

```
$ echo -e 'MHS\nMHs' | grep -E 'MH[A-Z]'

MHS
```

Keep case sensitive `grep`:

```
$ echo -e 'MHS\nMHs' | grep -E 'MH[A-Za-z]'

MHS
MHs
```

Dot character inside a range represents itself:

```
$ echo -e 'MHS\nMH.' | grep -E 'MH[.]'

MH.
```

End with a numerical digit:

```
$ grep -o -w -E 'MH[A-Z0-9]' chebi_27732.txt | sort -u
```

All three character acronyms starting with *MH*:

```
MH1
MH2
MHE
MHN
MHS
```

Negation

Match any character with exceptions
- *MH* followed by any character except a letter

Negation feature within a group operator
- represented by (^)
- next to left bracket
- all characters enclosed cannot be matched

Example:

```
$ grep -o -w -E 'MH[^A-Z]' chebi_27732.txt | sort -u
```

MHS, *MHE* or *MHN* missing:

```
MH
MH)
MH,
MH.
MH1
MH2
```

If we do not want the *MH␣* acronym, we can add the space character to the negative group:

```
$ grep -o -w -E 'MH[^A-Z ]' chebi_27732.txt | sort -u
```

The output should now contain one less acronym:

```
MH)
MH,
MH.
MH1
MH2
```

Quantifiers

Acronyms that start with *MH* independently of their length using quantifiers operators

Optional

Item followed by ?
- item can be character, operator or sub-pattern enclosed parentheses
- match can either contain item or not.

Example:

```
$ grep -o -w -E 'MH[A-Z0-9]?' chebi_27732.txt | sort -u
```

```
MH
MH1
MH2
MHE
MHN
MHS
```

Third character is optional

include two-character acronym *MH*

not *MH*␣

Add space character to group:

```
$ grep -o -w -E 'MH[A-Z0-9 ]?' chebi_27732.txt | sort -u
```

Now includes the two-character acronym *MH*:

```
MH
MH
MH1
MH2
MHE
MHN
MHS
```

Multiple and optional

Asterisk character *

- preceding item optional
- and be repeated multiple times

Example:

```
$ grep -o -w -E 'MH[A-Z0-9]*' chebi_27732.txt | sort -u
```

```
MH
MH1
MH2
MHE
MHN
MHS
MHS1
```

`grep` uses greedy approach

match as many characters as possible

Match *MH1* and not *MH*:

```
$ echo 'MH1' | grep -o -E 'MH[0-9]*'
```

Multiple and compulsory

Plus character +

Example:

```
$ grep -o -w -E 'MH[A-Z0-9]+' chebi_27732.txt | sort -u
```

```
MH1
MH2
MHE
MHN
MHS
MHS1
```

Not the two character acronym *MH*

All options

All can be reproduced by `{n,m}` where `n` and `m`

- specify minimal and maximum number of occurrences
- may also be omitted, no limit is imposed

Question mark ?

replaced by `{0,1}`:

Equivalent:

```
$ grep -o -w -E 'MH[A-Z0-9]?' chebi_27732.txt | sort -u
$ grep -o -w -E 'MH[A-Z0-9]{0,1}' chebi_27732.txt | sort -u
```

Asterisk character *

replaced by `{0,}`

both are equivalent:

Equivalent:

```
$ grep -o -w -E 'MH[A-Z0-9]*' chebi_27732.txt | sort -u
$ grep -o -w -E 'MH[A-Z0-9]{0,}' chebi_27732.txt | sort -u
```

Plus character +

- replaced by `{1,}`

Equivalent:

```
$ grep -o -w -E 'MH[A-Z0-9]+' chebi_27732.txt | sort -u
$ grep -o -w -E 'MH[A-Z0-9]{1,}' chebi_27732.txt | sort -u
```

Using `{1,1}`

same as not having any operator.

both are equivalent:

```
$ grep -o -w -E 'MH[A-Z0-9]' chebi_27732.txt | sort -u
$ grep -o -w -E 'MH[A-Z0-9]{1,1}' chebi_27732.txt | sort -u
```

```
MH1
MH2
MHE
MHN
MHS
```

Acronyms with exactly 4 characters:

```
$ grep -o -w -E 'MH[A-Z0-9]{2,2}' chebi_27732.txt | sort -u

MHS1
```

Position

Matches specific parts of input, examples:
- identify start and stop codons in sequence
- lines starting with a name of a disease

Regular expressions patterns can:
- start with `^`
- end with `$`

Beginning

Lines starting with *Malignant Hyperthermia*:

```
$ grep -E '^(M|m)alignant (H|h)yperthermia' chebi_27732.txt

  ...
  Malignant hyperthermia (MH) is a potentially fatal autosomal ...
  Malignant hyperthermia (MH) is a pharmacogenetic disorder ...
```

Check how many lines filtered:

```
$ grep -c -E '^(M|m)alignant (H|h)yperthermia' chebi_27732.txt
$ grep -c -E '(M|m)alignant (H|h)yperthermia' chebi_27732.txt
```

Only 20 of the 100 matches were considered

Ending

Lines ending with *Malignant Hyperthermia*,

```
$ grep -E '(M|m)alignant (H|h)yperthermia.$' chebi_27732.txt

  ...
  Mutations in the ryanodine receptor gene in central core disease
    and malignant hyperthermia.
  Detection of a novel mutation at amino acid position 614 in the
    ryanodine receptor in malignant hyperthermia.
  Novel mutations at a CpG dinucleotide in the ryanodine receptor
    in malignant hyperthermia.
```

Allow a punctuation character before the end of the line

- added the dot before the dollar

Check how many lines filtered:

```
$ grep -c -E '(M|m)alignant (H|h)yperthermia.$' chebi_27732.txt
$ grep -c -E '(M|m)alignant (H|h)yperthermia' chebi_27732.txt
```

Only 15 of the 100 matches were at the end of the line

Near the end

Mention not ending exactly at the last character
- allow a following expression
- or a given number of characters

Allow 10 other characters:

```
$ grep -c -E '(M|m)alignant (H|h)yperthermia.{0,10}$' chebi_27732.txt
```

The output will show that we have 20 matches.

Remove `-c` and check

families and *patients* are now allowed

```
...
Novel mutations in C-terminal channel region of the ryanodine
  receptor in malignant hyperthermia patients.
...
Novel missense mutations and unexpected multiple changes of RYR1
  gene in 75 malignant hyperthermia families.
...
```

Word in between

Allow a word in between
- independently of its length
- optional sequence of non-space characters (the word)
- preceded by a space:

```
$ grep -c -E '(M|m)alignant (H|h)yperthermia( [^ ]*)?.$' ⤸
  chebi_27732.txt
```

Only 24 matches

`[^ ]` operator avoids having two words

Remove `-c` and check

lengthy words (with more than 10 characters)

such as *susceptibility* are now allowed

```
...
Ryanodine receptor gene point mutation and malignant hyperthermia
   susceptibility.
...
```

Full line

Lines start with *Malignant Hyperthermia*
and end with an acronym:

```
$ grep -E '^(M|m)alignant (H|h)yperthermia' chebi_27732.txt | grep ⤸
    -w -E 'MHS?.$'
```

Or add both the circumflex and dollar operators:

```
$ grep -w -E '^(M|m)alignant (H|h)yperthermia.*MHS?.$' chebi_27732.⤸
    txt
```

`.*` to match anything in between them

Match all the text of the abstract

each abstract in a single line:

```
Malignant hyperthermia (MH) is a pharmacogenetical complication
  ... as for genetic diagnosis of MH.
Malignant hyperthermia susceptibility (MHS) is a subclinical
  pharmacogenetic disorder ... been tested positive for MHS.
```

Problem of tokenization

need to match a full sentence or a phrase

Match position

Knowing exact position of matches

using `-b`

```
$ echo 'MHS MHN MHE' | grep -b -o -w -E 'MH[SNE]'
```

```
0:MHS
4:MHN
8:MHE
```

Same result in multiple lines:

```
$ echo -e 'MHS\nMHN\nMHE' | grep -b -o -w -E 'MH[SNE]'
```

Tokenization

Work at the level of a sentence
    not use a full document as the input string

Tokenization is a Natural Language Processing (NLP) task
    identifying boundaries in the text
    to fragment it into basic units called tokens
    sentences, phrases, multi-word expressions, or words.

Character delimiters

Specific characters as accurate boundaries
- to fragment text into tokens.
- space character to identify words
- . ? ! to identify ending of sentence
- , ; : parenthesis to identify a phrase

More complex in languages without explicitly delimiters
- such as Chinese

Replace these delimiters by newline characters
result in a token per line:

```
$ tr '[.!?]' '\n' < chebi_27732.txt | wc -l
```

Get 1618 lines from the original 255 lines:

```
$ wc -l chebi_27732.txt
```

Wrong tokens

Not so simple, analyze:

```
$ tr '[.!?]' '\n' < chebi_27732.txt | less
```

i) many lines are empty

extra newline character added to last sentence

ii) the dot character also used as decimal mark

sentences split in multiple lines by having decimal numbers

Example:

```
These 10 mutations account for 21.9% of the North American MH-
  susceptible population
```

Split in two lines:

```
These 10 mutations account for 21
9% of the North American MH-susceptible population
```

String Replacement

One character not enough, need context

`sed` powerful version of `tr`

- stream editor receive as input a string
- perform basic text transformations
- replace one expression by another

Replace *caffeine* by its ChEBI identifier:

```
$ sed -E 's/caffeine/CHEBI:27732/gi' chebi_27732.txt
```

`'s/FIND/REPLACE/FLAGS'`

`FIND` pattern to find

`REPLACE` the expression to replace

`FLAGS` multiple options:

`g` replace all matches not just the first in line

`i` case insensitive.

`-E` use extended regular expressions

Original fragment of text:

```
... link between the caffeine threshold and tension ...
```

converted to:

```
... link between the CHEBI:27732 threshold and tension ...
```

Multi-character delimiters

Replace delimiter characters by a newline
when followed by at least one space:

```
$ sed -E 's/[.!?] +/\n/g' chebi_27732.txt
```

Avoids empty lines
not splits sentence in end of line, assuming no ghost spaces

Preserves decimal markers
followed by numerical digits, not spaces.

Get 1618 lines from original 255 lines:

```
$ sed -E 's/[.!?] +/\n/g' chebi_27732.txt | wc -l
```

Keep delimiters

Previous `sed` removes delimiter characters

- may cause other problems
- better solution is keep them

`sed` allows keep each match

- sub-pattern enclosed within parentheses
- and use backslash and its numerical order

```
$ sed -E 's/([.!?])( +)/\1\n\2/g' chebi_27732.txt
```

From:

```
... muscle relaxants. To date, ...
```

To:

```
... muscle relaxants.
 To date, ...
```

Some sentences include a HTML elements:

```
... bulk.&lt;h4&gt;Methods&lt;/h4&gt;Fetal ...
... sequencing.&lt;h4&gt;Results&lt;/h4&gt;Whole ...
```

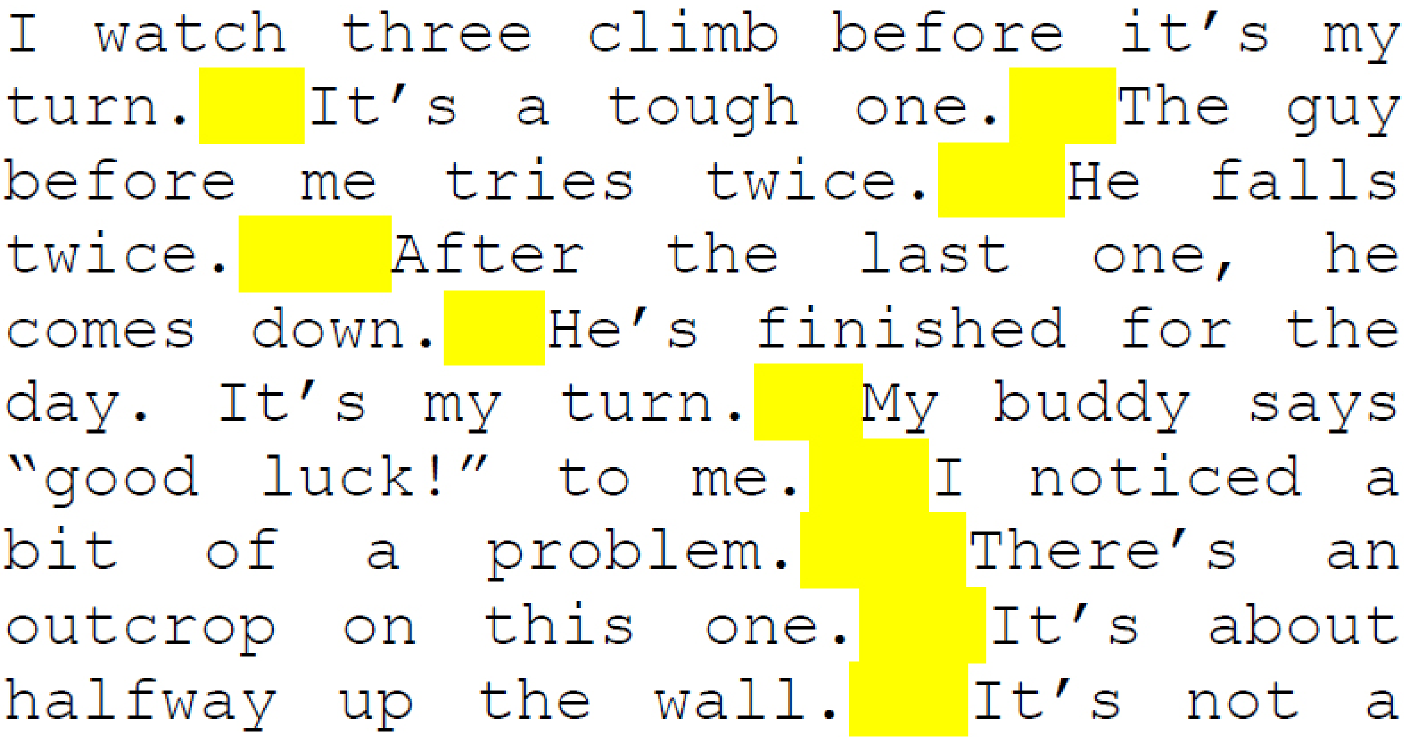
Add the option of `&` character:

```
$ sed -E 's/([.!?])([& ]+)/\1\n\2/g' chebi_27732.txt | wc -l
```

- Get 1179 lines
- able to split more 87 more sentences.

Not free of errors

- almost impossible to derive a rule
- that covers all the possible typos humans produce



I watch three climb before it's my turn. It's a tough one. The guy before me tries twice. He falls twice. After the last one, he comes down. He's finished for the day. It's my turn. My buddy says "good luck!" to me. I noticed a bit of a problem. There's an outcrop on this one. It's about halfway up the wall. It's not a

Pattern equivalent to `\. {2,}[A-Z]`
identifies multiples spaces at the beginning of a sentence

(Adapted from: `https://en.wikipedia.org/wiki/Regular_expression`)

Sentences file

Update *gettext.sh*:

```
ID=$1 # The CHEBI identifier given as input is renamed to ID
xmllint --xpath "//*[local-name()='title' or local-name()='comment']/text()" chebi\_$ID\_*.rdf | \
sed -E 's/([.!?])([& ]+)/\1\n\2/g'
```

Save output:

```
$ ./gettext.sh 27732 > chebi_27732_sentences.txt
```

Each line is now a sentence

Entity recognition

Select sentences with acronyms:

```
$ grep -w -E 'MH[SNE]?' chebi_27732_sentences.txt

...
Interestingly, the data suggest a link between the caffeine
  threshold and tension values and the MH/CCD phenotype.
```

Use `-n` get the number of line:

```
$ grep -n -o -w -E 'MH[SNE]?' chebi_27732_sentences.txt

...
1129:MH
1131:MH
1132:MH
```

Add the `-b` option:

```
$ grep -b -n -o -w -E 'MH[SNE]?' chebi_27732_sentences.txt
```

Number of the line, the character position, and the match:

```
...
1129:174908:MH
1131:175340:MH
1132:175666:MH
```

Script receives pattern as argument

the input text as the standard input,

display the line numbers and the matches

in a TSV format

Create script *getentities.sh*:

```
PATTERN=$1
grep -n -o -w -E $PATTERN | \
tr ':' '\t'
```

First line stores the pattern

`grep` finds the matches

`tr` replaces each colon by tab

Execute:

```
$ ./getentities.sh 'MH[SNE]?' < chebi_27732_sentences.txt

  ...
  1129 MH
  1131 MH
  1132 MH
```

Values separated by tab (TSV format)

Saved as a TSV file

open in spreadsheet application:

```
$ ./getentities.sh 'MH[SNE]?' < chebi_27732_sentences.txt > ⤸
  chebi_27732.tsv
```

Select the sentence

Analyze a specific matched sentence

- text editor go to that line number

Or use `p` option of `sed`

- output a given line number

```
$ sed -n '2p' chebi_27732_sentences.txt
```

```
... in susceptible people (MHS) by volatile ...
```

Pattern File

Recognize different entities
- or different mentions of same entity
- the official name, synonyms, and acronyms

`grep` allows list of patterns from file
- using `-f` option

Create a text file *patterns.txt*:

```
(M|m)alignant (H|h)yperthermia
MH[SNE]?
(C|c)affeine
```

Execute:

```
$ grep -n -o -w -E -f patterns.txt chebi_27732_sentences.txt
```

```
...
1131:caffeine
1132:caffeine
1132:MH
```

Update *getentities.sh*:

```
PATTERNS=$1
grep -n -o -w -E -f $PATTERNS | \
tr ':' '\t'
```

Execute:

```
$ ./getentities.sh patterns.txt < chebi_27732_sentences.txt
```

Save output:

```
$ ./getentities.sh patterns.txt < chebi_27732_sentences.txt > chebi_27732.tsv
```

patterns.txt useful
- not focused in a single disease
- find any disease mentioned

Create file with the full lexicon of diseases
- addressed in the following chapter

Relation Extraction

Sentences describe possible relationships

- e.g. disease and compound.
- complex text mining challenge

Simple approach:

```
$ grep -n -w -E 'MH[SNE]?.*(C|c)affeine' chebi_27732_sentences.txt

  257: ... MHS families were investigated with a caffeine ...
```

One of the eight displayed sentences

Missing all with *caffeine* first:

```
$ grep -n -w -E '(C|c)affeine.*MH[SNE]?' chebi_27732_sentences.txt
```

```
837: ... caffeine-halothane contracture test were greater in
  those who had a known MH ...
1132: ... caffeine threshold and tension values and the MH ...
```

Multiple filters

Most flexible approach two `grep`

- first selects sentences mentioning one entity
- the other selects from the previously selected sentences
- the ones mentioning the other entity:

```
$ grep -n -w -E 'MH[SNE]?' chebi_27732_sentences.txt | grep -w -E ⤸
    '(C|c)affeine'
```

Shows ten sentences mentioning *caffeine* and an acronym

Relation type

Specific type of relationship

- additional filter for specific verb

Example filter with *response* or *diagnosed*:

```
$ grep -n -w -E 'MH[SNE]?' chebi_27732_sentences.txt | grep -w -E ⤸
    '(C|c)affeine' | grep -w -E 'response|diagnosed'
```

Not take in account where the verb appears

response appears first than the two entities:

```
58: The relationship between the IVCT response and genotype was
  ... the number of MHS discordants ... at 2.0 mM caffeine ...
```

Between the two entities:

```
$ grep -n -w -E 'MH[SNE]?.*(response|diagnosed).*(C|c)affeine' ⤸
  chebi_27732_sentences.txt
```

Previous sentence not a match

Remove relation types

Filering specific type of relations

use `-v`:

```
$ grep -n -w -E 'MH[SNE]?' chebi_27732_sentences.txt | grep -w -E ↩
    '(C|c)affeine' | grep -v -w -E 'response|diagnosed'
```

Resulting sentences not mention *response* or *diagnosed*

Semantic Processing

Introduce the world of semantics
    retrieve and enhance text and data processing
    by using semantics

Explore semantic resources
    nowadays available

Classes

Searched for *caffeine* and *malignant hyperthermia*
  miss related entities
  can be found in semantic resources
  such as ontologies.

Semantics of *caffeine* and *malignant hyperthermia*
  in *ChEBI* and *DO* ontologies

OWL files

Retrieving both ontologies (OWL files):

```
$ curl -L -O http://purl.obolibrary.org/obo/doid/releases
    /2021-03-29/doid.owl
$ curl -L -O http://purl.obolibrary.org/obo/chebi/198/chebi_lite.
    owl
```

`-O` saves to file name as remote file (last part of URL)

files *chebi_lite.owl* and *doid.owl*

`-L` follows redirects

Most recent release:

```
http://purl.obolibrary.org/obo/doid.owl
http://purl.obolibrary.org/obo/chebi/chebi_lite.owl
```

Class label

OWL files use XML syntax

check entities:

```
$ grep '>malignant hyperthermia<' doid.owl
$ grep '>caffeine<' chebi_lite.owl
```

```
<rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#string
  ">malignant hyperthermia</rdfs:label>
<rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#string
  ">caffeine</rdfs:label>
```

Property label (*rdfs:label*),

inside class definition

Class definition

Retrieve the full class definition with `xmllint`:

```
$ xmllint --xpath "//*[local-name()='label' and text()='malignant ⤸
    hyperthermia']/.." doid.owl
```

The XPath query

find the label *malignant hyperthermia*

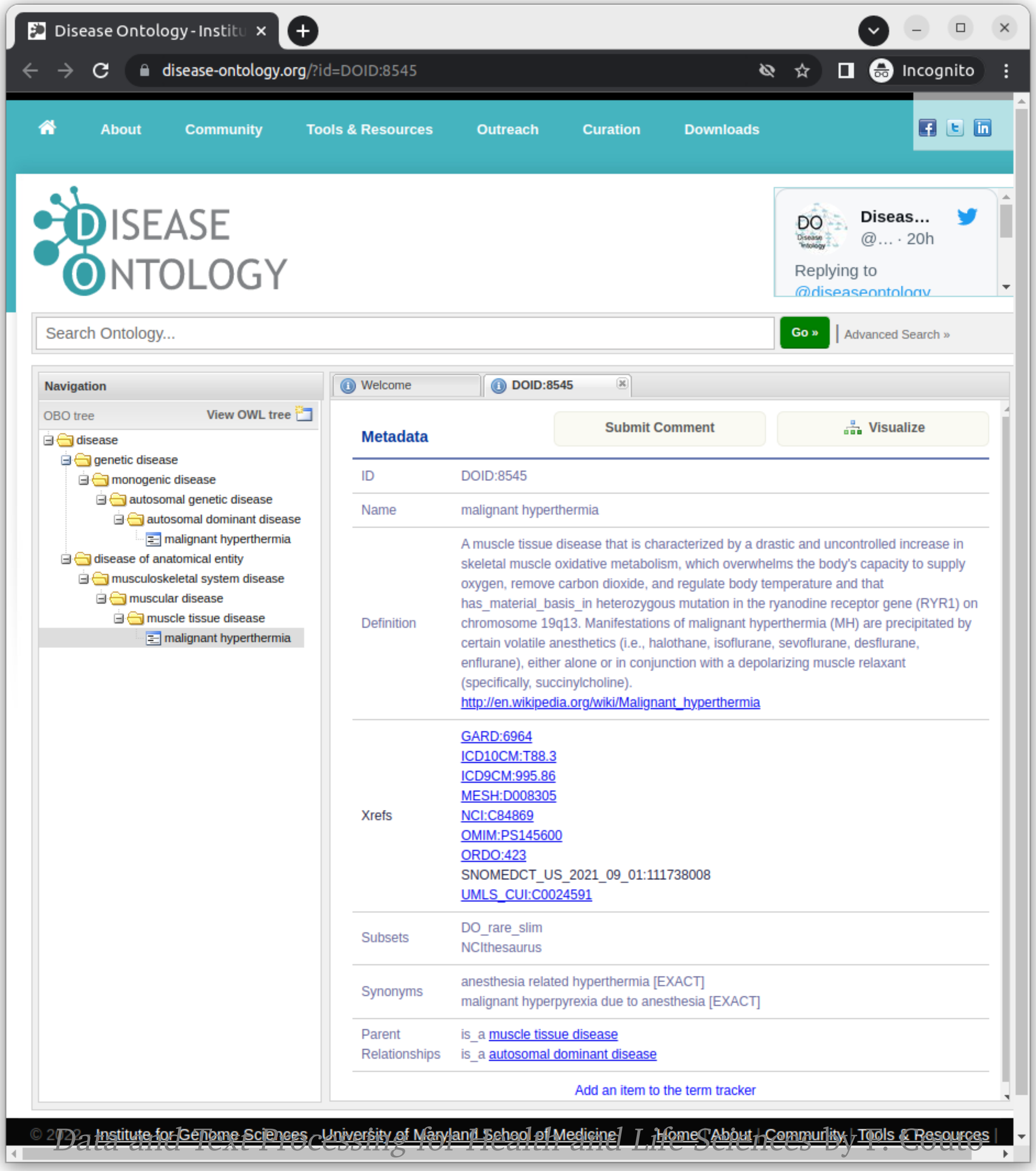
then `..` the parent element, `Class` element

Semantics of *malignant hyperthermia*

much more than its label:

```
<owl:Class rdf:about="http://purl.obolibrary.org/obo/DOID_8545">
 <rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  DOID_0050736"/>
 <rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  DOID_66"/>
 <rdfs:subClassOf>
     <owl:Restriction>
  <owl:onProperty rdf:resource="http://purl.obolibrary.org/obo/
  IDO_0000664"/>
  <owl:someValuesFrom rdf:resource="http://purl.obolibrary.org/
  obo/GENO_0000147"/>
     </owl:Restriction>
 </rdfs:subClassOf>
 ...
 <oboInOwl:hasExactSynonym xml:lang="en">anesthesia related
  hyperthermia</oboInOwl:hasExactSynonym>
 <oboInOwl:hasExactSynonym xml:lang="en">malignant hyperpyrexia
  due to anesthesia</oboInOwl:hasExactSynonym>
 <oboInOwl:hasOBONamespace rdf:datatype="http://www.w3.org/2001/
```

```
  XMLSchema#string">disease_ontology</oboInOwl:hasOBONamespace>
 <oboInOwl:id rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">DOID:8545</oboInOwl:id>
 <oboInOwl:inSubset rdf:resource="http://purl.obolibrary.org/obo/
  doid#DO_rare_slim"/>
 <oboInOwl:inSubset rdf:resource="http://purl.obolibrary.org/obo/
  doid#NCIthesaurus"/>
 <rdfs:comment rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">Xref MGI.
OMIM mapping confirmed by DO. [SN].</rdfs:comment>
 <rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">malignant hyperthermia</rdfs:label>
</owl:Class>
```



- disease
  - genetic disease
    - monogenic disease
      - autosomal genetic disease
        - autosomal dominant disease
          - malignant hyperthermia
  - disease of anatomical entity
    - musculoskeletal system disease
      - muscular disease
        - muscle tissue disease
          - malignant hyperthermia

ID	DOID:8545
Name	malignant hyperthermia
Definition	A muscle tissue disease that is characterized by a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature and that has_material_basis_in heterozygous mutation in the ryanodine receptor gene (RYR1) on chromosome 19q13. Manifestations of malignant hyperthermia (MH) are precipitated by certain volatile anesthetics (i.e., halothane, isoflurane, sevoflurane, desflurane, enflurane), either alone or in conjunction with a depolarizing muscle relaxant (specifically, succinylcholine). http://en.wikipedia.org/wiki/Malignant_hyperthermia
Xrefs	GARD:6964 ICD10CM:T88.3 ICD9CM:995.86 MESH:D008305 NCI:C84869 OMIM:PS145600 ORDO:423 SNOMEDCT_US_2021_09_01:111738008 UMLS_CUI:C0024591
Subsets	DO_rare_slim NCIthesaurus
Synonyms	anesthesia related hyperthermia [EXACT] malignant hyperpyrexia due to anesthesia [EXACT]
Parent Relationships	is_a muscle tissue disease is_a autosomal dominant disease

Add an item to the term tracker

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Class description of *malignant hyperthermia* in the Human Disease Ontology

malignant hyperthermia subclass of (specialization)
entries 0050736 *autosomal dominant disease*
and 66 *muscle tissue disease*

malignant hyperthermia a special case of *muscle tissue disease*
and of *autosomal dominant disease*

Search relations with 0050736 and 66:

```
$ xmllint --xpath "//*[local-name()='label' and text()='malignant ↩
    hyperthermia']/..//*[@*[local-name()='resource' and .='http://↩
    purl.obolibrary.org/obo/DOID_66' or .='http://purl.obolibrary.↩
    org/obo/DOID_0050736']]" doid.owl
```

`@*[local-name()='resource']`

extracts the URI specified

in an attribute `resource`

of any descendant `//*[...]`.

Uses the `subClassOf` element:

```
<rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  DOID_0050736"/>
<rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  DOID_66"/>
```

Retrieve full class definition of *caffeine*:

```
$ xmllint --xpath "//*[local-name()='label' and text()='caffeine
    ']/.." chebi_lite.owl
```

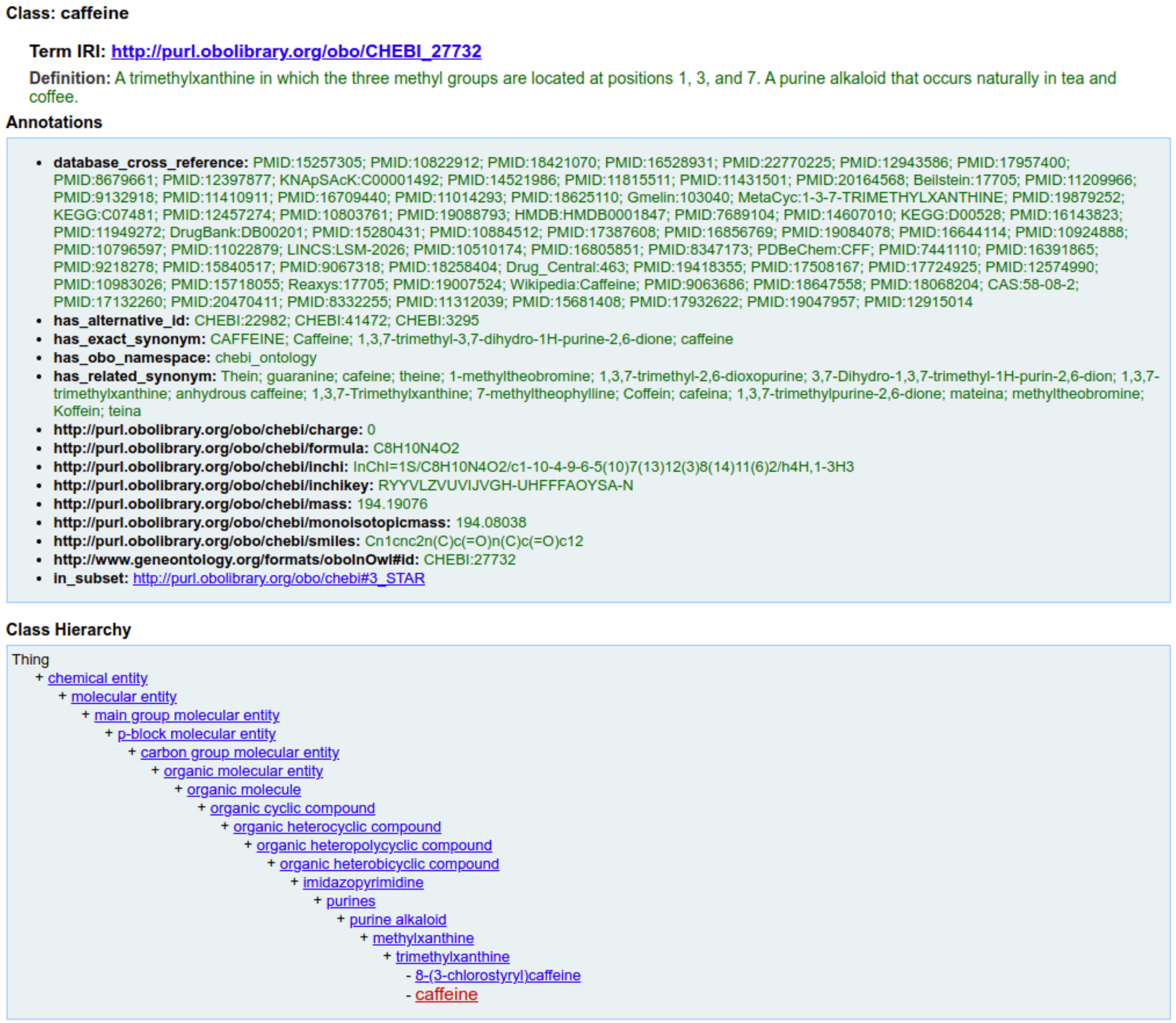
Semantics of *caffeine* differs from *malignant hyperthermia*

still share many properties

such as `subClassOf`

```
<owl:Class rdf:about="http://purl.obolibrary.org/obo/CHEBI_27732"
  >
 <rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  CHEBI_26385"/>
 <rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  CHEBI_27134"/>
 <rdfs:subClassOf>
     <owl:Restriction>
  <owl:onProperty rdf:resource="http://purl.obolibrary.org/obo/
  RO_0000087"/>
  <owl:someValuesFrom rdf:resource="http://purl.obolibrary.org/
  obo/CHEBI_25435"/>
     </owl:Restriction>
 </rdfs:subClassOf>
 <rdfs:subClassOf>
...
 </rdfs:subClassOf>
 <obo:IAO_0000115 rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">A trimethylxanthine in which the three methyl groups
  are located at positions 1, 3, and 7. A purine alkaloid that
  occurs naturally in tea and coffee.</obo:IAO_0000115>
```

```
 <oboInOwl:hasAlternativeId rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">CHEBI:22982</oboInOwl:hasAlternativeId>
 <oboInOwl:hasAlternativeId rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">CHEBI:3295</oboInOwl:hasAlternativeId>
 <oboInOwl:hasAlternativeId rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">CHEBI:41472</oboInOwl:hasAlternativeId>
 <oboInOwl:hasOBONamespace rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">chebi_ontology</oboInOwl:hasOBONamespace>
 <oboInOwl:id rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">CHEBI:27732</oboInOwl:id>
 <oboInOwl:inSubset rdf:resource="http://purl.obolibrary.org/obo/
  chebi#3_STAR"/>
 <rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">caffeine</rdfs:label>
</owl:Class>
```



Class: caffeine

Term IRI: http://purl.obolibrary.org/obo/CHEBI_27732

Definition: A trimethylxanthine in which the three methyl groups are located at positions 1, 3, and 7. A purine alkaloid that occurs naturally in tea and coffee.

Annotations

- **database_cross_reference:** PMID:15257305; PMID:10822912; PMID:18421070; PMID:16528931; PMID:22770225; PMID:12943586; PMID:17957400; PMID:8679661; PMID:12397877; KNApSAcK:C00001492; PMID:14521986; PMID:11815511; PMID:11431501; PMID:20164568; Beilstein:17705; PMID:11209966; PMID:9132918; PMID:11410911; PMID:16709440; PMID:11014293; PMID:18625110; Gmelin:103040; MetaCyc:1-3-7-TRIMETHYLXANTHINE; PMID:19879252; KEGG:C07481; PMID:12457274; PMID:10803761; PMID:19088793; HMDB:HMDB0001847; PMID:7689104; PMID:14607010; KEGG:D00528; PMID:16143823; PMID:11949272; DrugBank:DB00201; PMID:15280431; PMID:10884512; PMID:17387608; PMID:16856769; PMID:19084078; PMID:16644114; PMID:10924888; PMID:10796597; PMID:11022879; LINCS:LSM-2026; PMID:10510174; PMID:16805851; PMID:8347173; PDBeChem:CFF; PMID:7441110; PMID:16391865; PMID:9218278; PMID:15840517; PMID:9067318; PMID:18258404; Drug_Central:463; PMID:19418355; PMID:17508167; PMID:17724925; PMID:12574990; PMID:10983026; PMID:15718055; Reaxys:17705; PMID:19007524; Wikipedia:Caffeine; PMID:9063686; PMID:18647558; PMID:18068204; CAS:58-08-2; PMID:17132260; PMID:20470411; PMID:8332255; PMID:11312039; PMID:15681408; PMID:17932622; PMID:19047957; PMID:12915014
- **has_alternative_id:** CHEBI:22982; CHEBI:41472; CHEBI:3295
- **has_exact_synonym:** CAFFEINE; Caffeine; 1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione; caffeine
- **has_obo_namespace:** chebi_ontology
- **has_related_synonym:** Thein; guaranine; cafeine; theine; 1-methyltheobromine; 1,3,7-trimethyl-2,6-dioxopurine; 3,7-Dihydro-1,3,7-trimethyl-1H-purin-2,6-dion; 1,3,7-trimethylxanthine; anhydrous caffeine; 1,3,7-Trimethylxanthine; 7-methyltheophylline; Coffein; cafeina; 1,3,7-trimethylpurine-2,6-dione; mateina; methyltheobromine; Koffein; teina
- **http://purl.obolibrary.org/obo/chebi/charge:** 0
- **http://purl.obolibrary.org/obo/chebi/formula:** C8H10N4O2
- **http://purl.obolibrary.org/obo/chebi/inchi:** InChI=1S/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3
- **http://purl.obolibrary.org/obo/chebi/inchikey:** RYYVLZVUVIJVGH-UHFFFAOYSA-N
- **http://purl.obolibrary.org/obo/chebi/mass:** 194.19076
- **http://purl.obolibrary.org/obo/chebi/monoisotopicmass:** 194.08038
- **http://purl.obolibrary.org/obo/chebi/smiles:** Cn1cnc2n(C)c(=O)n(C)c(=O)c12
- **http://www.geneontology.org/formats/oboInOwl#id:** CHEBI:27732
- **in_subset:** http://purl.obolibrary.org/obo/chebi#3_STAR

Class Hierarchy

Thing
- + chemical entity
  - + molecular entity
    - + main group molecular entity
      - + p-block molecular entity
        - + carbon group molecular entity
          - + organic molecular entity
            - + organic molecule
              - + organic cyclic compound
                - + organic heterocyclic compound
                  - + organic heteropolycyclic compound
                    - + organic heterobicyclic compound
                      - + imidazopyrimidine
                        - + purines
                          - + purine alkaloid
                            - + methylxanthine
                              - + trimethylxanthine
                                - \- 8-(3-chlorostyryl)caffeine
                                - \- caffeine

Class description of *caffeine* in ChEBI

(Source: `http://www.ontobee.org/`)

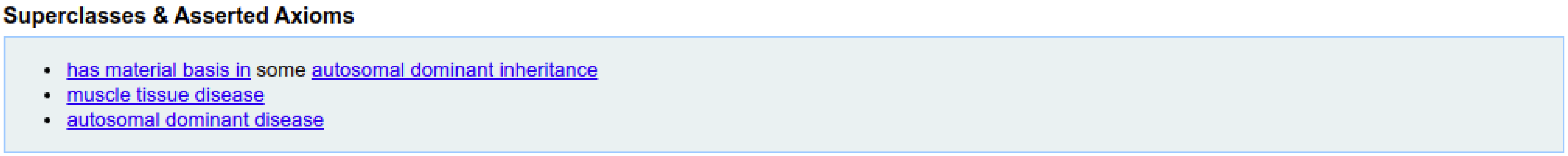
caffeine specialization of
26385 *purine alkaloid* and 27134 *trimethylxanthine*

Search relations:

```
$ xmllint --xpath "//*[local-name()='label' and text()='caffeine↩
    ']/..//*[@*[local-name()='resource' and .='http://purl.↩
    obolibrary.org/obo/CHEBI_26385' or .='http://purl.obolibrary.↩
    org/obo/CHEBI_27134']]" doid.owl
```

```
<rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  CHEBI_26385"/>
<rdfs:subClassOf rdf:resource="http://purl.obolibrary.org/obo/
  CHEBI_27134"/>
```

Related Classes

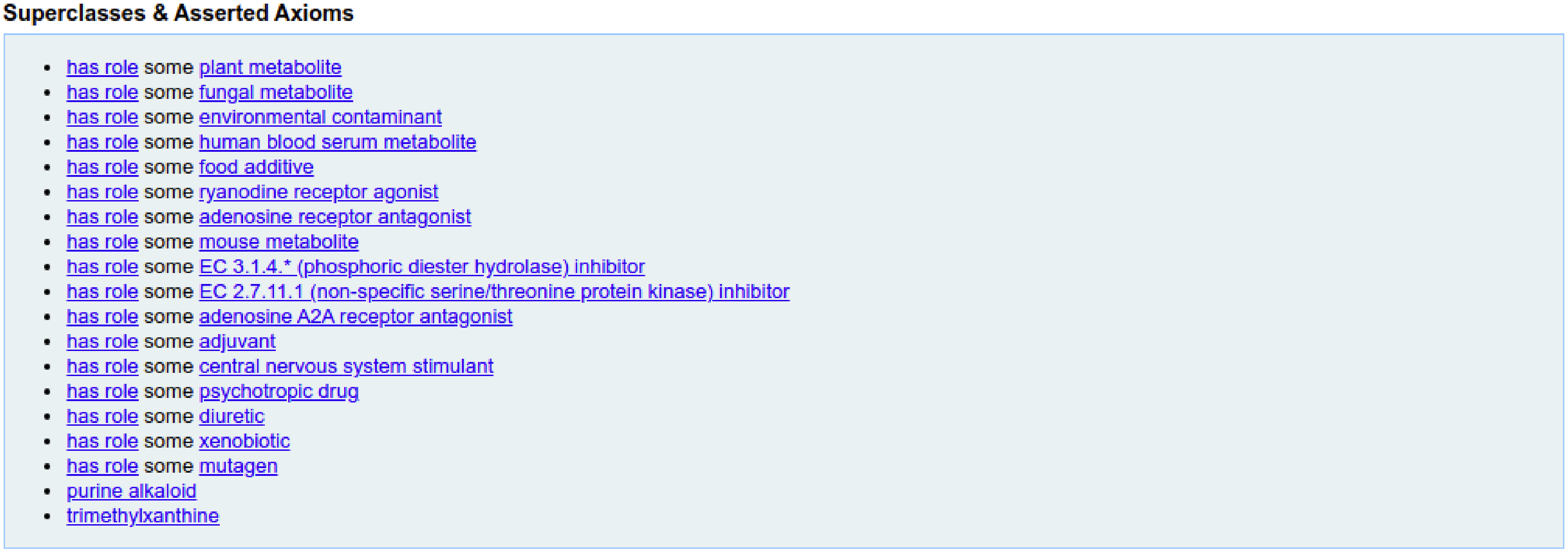


Superclasses & Asserted Axioms

- has material basis in some autosomal dominant inheritance
- muscle tissue disease
- autosomal dominant disease

Related classes of *malignant hyperthermia* in the Human Disease Ontology

(Source: `http://www.ontobee.org/`)



Superclasses & Asserted Axioms

- has role some plant metabolite
- has role some fungal metabolite
- has role some environmental contaminant
- has role some human blood serum metabolite
- has role some food additive
- has role some ryanodine receptor agonist
- has role some adenosine receptor antagonist
- has role some mouse metabolite
- has role some EC 3.1.4.* (phosphoric diester hydrolase) inhibitor
- has role some EC 2.7.11.1 (non-specific serine/threonine protein kinase) inhibitor
- has role some adenosine A2A receptor antagonist
- has role some adjuvant
- has role some central nervous system stimulant
- has role some psychotropic drug
- has role some diuretic
- has role some xenobiotic
- has role some mutagen
- purine alkaloid
- trimethylxanthine

Related classes of *caffeine* in ChEBI

(Source: `http://www.ontobee.org/`)

Search for relation with *mutagen* (25435)

```
$ xmllint --xpath "//*[local-name()='label' and text()='caffeine
  ']/..//*[@*[local-name()='resource' and .='http://purl.
  obolibrary.org/obo/CHEBI_25435']]/../.." chebi_lite.owl
```

Defined by RO:0000087 (*has role*) in *Relations Ontology*:

```
<rdfs:subClassOf>
 <owl:Restriction>
  <owl:onProperty rdf:resource="http://purl.obolibrary.org/obo/
  RO_0000087"/>
  <owl:someValuesFrom rdf:resource="http://purl.obolibrary.org/
  obo/CHEBI_25435"/>
 </owl:Restriction>
</rdfs:subClassOf>
```

Search *has role* in OWL:

```
$ xmllint --xpath "//*[local-name()='ObjectProperty'][@*[local-name⤸
   ()='about']='http://purl.obolibrary.org/obo/RO_0000087']" ⤸
   chebi_lite.owl
```

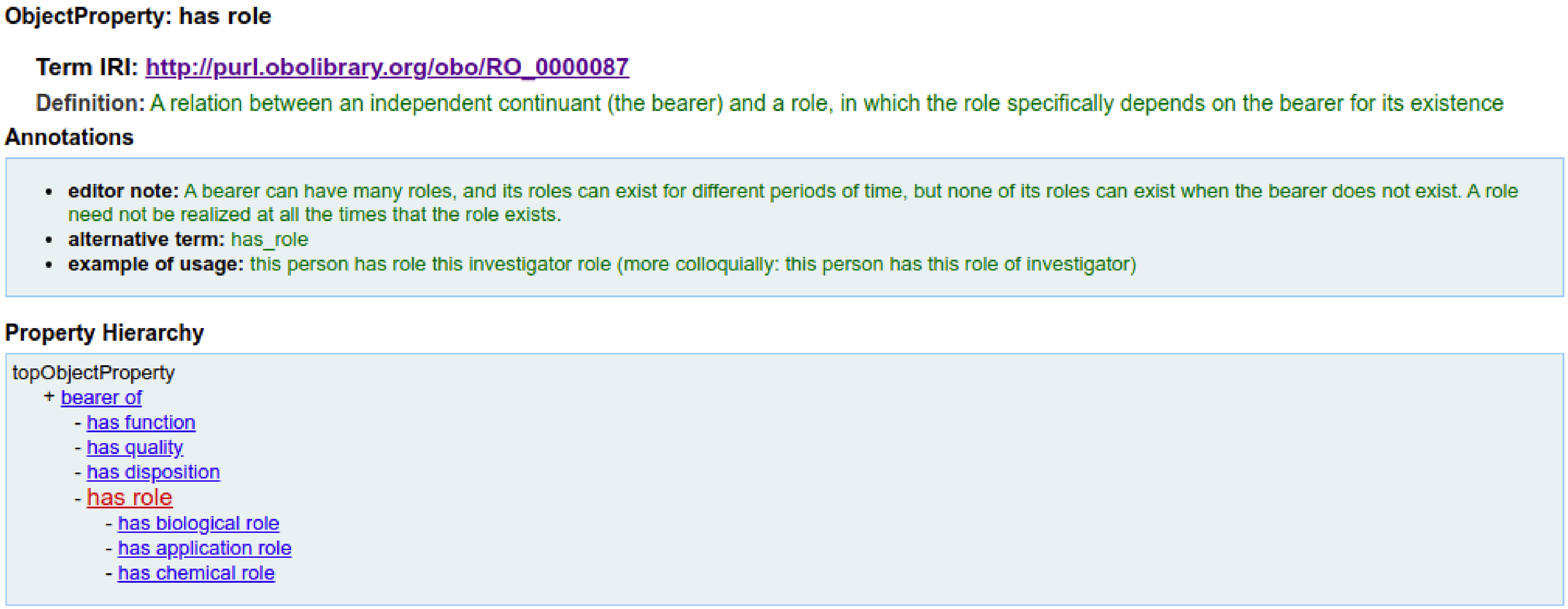
Finds `ObjectProperty`

selects the ones with `about` attribute

with the relation URI as value.

Neither transitive or cyclic:

```
<owl:ObjectProperty rdf:about="http://purl.obolibrary.org/obo/
  RO_0000087">
 ...
 <oboInOwl:id rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">has_role</oboInOwl:id>
 <oboInOwl:is_cyclic rdf:datatype="http://www.w3.org/2001/
  XMLSchema#boolean">false</oboInOwl:is_cyclic>
 <oboInOwl:is_transitive rdf:datatype="http://www.w3.org/2001/
  XMLSchema#boolean">false</oboInOwl:is_transitive>
 ...
 <rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#
  string">has role</rdfs:label>
</owl:ObjectProperty>
```



ObjectProperty: has role

Term IRI: http://purl.obolibrary.org/obo/RO_0000087

Definition: A relation between an independent continuant (the bearer) and a role, in which the role specifically depends on the bearer for its existence

Annotations

- **editor note:** A bearer can have many roles, and its roles can exist for different periods of time, but none of its roles can exist when the bearer does not exist. A role need not be realized at all the times that the role exists.
- **alternative term:** has_role
- **example of usage:** this person has role this investigator role (more colloquially: this person has this role of investigator)

Property Hierarchy

topObjectProperty
- + bearer of
    - - has function
    - - has quality
    - - has disposition
    - - has role
        - - has biological role
        - - has application role
        - - has chemical role

Description of *has role* property

(Source: `http://www.ontobee.org/`)

URIs and Labels

Standardize the process
  scripts convert label into URI
  and vice-versa

Internal ontology processing using URIs
  then convert to labels

URI of a label

Get URI of *malignant hyperthermia*:

```
$ xmllint --xpath "//*[local-name()='label' and text()='malignant
    hyperthermia']/../@*[local-name()='about']" doid.owl

  rdf:about="http://purl.obolibrary.org/obo/DOID_8545"
```

Only the value, add `string`:

```
$ xmllint --xpath "string(//*[local-name()='label' and text()='↩
    malignant hyperthermia']/../@*[local-name()='about'])" doid.owl
```

```
http://purl.obolibrary.org/obo/DOID_8545
```

`string` returns only one attribute value

even if many are matched

assuming *malignant hyperthermia* is unambiguous

Alternative:

add a `cut` to get the URI

```
$ xmllint --xpath "//*[local-name()='label' and text()='malignant hyperthermia']/../@*[local-name()='about']" doid.owl | cut -d\" -f2

$ xmllint --xpath "//*[local-name()='label' and text()='caffeine']/../@*[local-name()='about']" chebi_lite.owl | cut -d\" -f2
```

Script *geturi.sh*:

```
OWLFILE=$1
xargs -I {} xmllint --xpath "//*[local-name()='label' and text()
  ='{}']/../@*[local-name()='about']" $OWLFILE | \
cut -d\" -f2
```

Multiple labels as standard input

- OWL file to find URIs as argument

Execute:

```
$ echo 'malignant hyperthermia' | ./geturi.sh doid.owl
$ echo 'caffeine' | ./geturi.sh chebi_lite.owl
```

```
http://purl.obolibrary.org/obo/DOID_8545
http://purl.obolibrary.org/obo/CHEBI_27732
```

Execute using multiple labels:

```
$ echo -e 'malignant hyperthermia\nmuscle tissue disease' | ./
    geturi.sh doid.owl
$ echo -e 'caffeine\npurine alkaloid\ntrimethylxanthine' | ./geturi
    .sh chebi_lite.owl
```

```
http://purl.obolibrary.org/obo/DOID_8545
http://purl.obolibrary.org/obo/DOID_66
```

```
http://purl.obolibrary.org/obo/CHEBI_27732
http://purl.obolibrary.org/obo/CHEBI_26385
http://purl.obolibrary.org/obo/CHEBI_27134
```

Label of a URI

Get label disease 8545:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about
  ']='http://purl.obolibrary.org/obo/DOID_8545']/*[local-name()='
  label']/text()" doid.owl
```

```
malignant hyperthermia
```

`@*[local-name()='label']`

selects element describes label

Problem if multiple matches

- `text()` all labels in same line
- alternative add `tr` and `grep`

Get label of compound 27732:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about']='http://purl.obolibrary.org/obo/CHEBI_27732']/*[local-name()='label']/text()" chebi_lite.owl

caffeine
```

Script *getlabels.sh*:

```
OWLFILE=$1
xargs -I {} xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about']='{}']/*[local-name()='label']/text()" $OWLFILE
```

- Multiple URIs as standard input
  - OWL file to find labels as argument
  - `xargs` process each line of standard input

Execute:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getlabels.sh doid.owl
$ echo 'http://purl.obolibrary.org/obo/CHEBI_27732' | ./getlabels.sh chebi_lite.owl
```

```
malignant hyperthermia
caffeine
```

Execute with multiple URIs:

```
$ echo -e 'http://purl.obolibrary.org/obo/DOID_8545\nhttp://purl.obolibrary.org/obo/DOID_66' | ./getlabels.sh doid.owl

$ echo -e 'http://purl.obolibrary.org/obo/CHEBI_27732\nhttp://purl.obolibrary.org/obo/CHEBI_26385\nhttp://purl.obolibrary.org/obo/CHEBI_27134' | ./getlabels.sh chebi_lite.owl
```

```
malignant hyperthermia
muscle tissue disease
```

```
caffeine
purine alkaloid
trimethylxanthine
```

Test both scripts:

```
$ echo -e 'malignant hyperthermia\nmuscle tissue disease' | ./geturi.sh doid.owl | ./getlabels.sh doid.owl
$ echo -e 'caffeine\npurine alkaloid\ntrimethylxanthine' | ./geturi.sh chebi_lite.owl | ./getlabels.sh chebi_lite.owl
```

```
malignant hyperthermia
muscle tissue disease

caffeine
purine alkaloid
trimethylxanthine
```

URIs as input:

```
$ echo -e 'http://purl.obolibrary.org/obo/DOID_8545\nhttp://purl.
    obolibrary.org/obo/DOID_66' | ./getlabels.sh doid.owl | ./
    geturi.sh doid.owl
```

```
$ echo -e 'http://purl.obolibrary.org/obo/CHEBI_27732\nhttp://purl.
    obolibrary.org/obo/CHEBI_26385\nhttp://purl.obolibrary.org/obo/
    CHEBI_27134' | ./getlabels.sh chebi_lite.owl | ./geturi.sh
    chebi_lite.owl
```

```
http://purl.obolibrary.org/obo/DOID_8545
http://purl.obolibrary.org/obo/DOID_66
```

```
http://purl.obolibrary.org/obo/CHEBI_27732
http://purl.obolibrary.org/obo/CHEBI_26385
http://purl.obolibrary.org/obo/CHEBI_27134
```

Synonyms

Not always mentioned using official label
- text alternative labels
- represented by `hasExactSynonym`

Synonyms of a disease:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about
  ']='http://purl.obolibrary.org/obo/DOID_8545']/*[local-name()='
  hasExactSynonym']" doid.owl
```

```
<oboInOwl:hasExactSynonym rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">anesthesia related hyperthermia</
  oboInOwl:hasExactSynonym>
<oboInOwl:hasExactSynonym rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">malignant hyperpyrexia due to anesthesia</
  oboInOwl:hasExactSynonym>
```

Both primary label and synonyms:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about↩
  ']='http://purl.obolibrary.org/obo/DOID_8545']/*[local-name()='↩
  hasExactSynonym' or local-name()='label']" doid.owl
```

```
<oboInOwl:hasExactSynonym rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">anesthesia related hyperthermia</
  oboInOwl:hasExactSynonym>
<oboInOwl:hasExactSynonym rdf:datatype="http://www.w3.org/2001/
  XMLSchema#string">malignant hyperpyrexia due to anesthesia</
  oboInOwl:hasExactSynonym>
<rdfs:label rdf:datatype="http://www.w3.org/2001/XMLSchema#string
  ">malignant hyperthermia</rdfs:label>
```

Update *getlabels.sh*:

```
OWLFILE=$1
xargs -I {} xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about']='{}']/*[local-name()='hasExactSynonym' or local-name()='hasRelatedSynonym' or local-name()='label']/text()" $OWLFILE
```

Adding the `hasExactSynonym` keyword and `hasRelatedSynonym`

Execute:

```
$ echo -e 'http://purl.obolibrary.org/obo/DOID_8545' | ./getlabels.
  sh doid.owl
```

```
anesthesia related hyperthermia
malignant hyperpyrexia due to anesthesia
malignant hyperthermia
```

URI of synonyms

Send output to *geturi.sh*:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getlabels.sh ⤸
    doid.owl | ./geturi.sh doid.owl
```

XPath warnings for the two synonyms:

```
XPath set is empty
XPath set is empty
http://purl.obolibrary.org/obo/DOID_8545
```

Ignore these mismatches:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getlabels.sh doid.owl | ./geturi.sh doid.owl 2>/dev/null
```

Or update *geturi.sh* to include synonyms:

```
OWLFILE=$1
xargs -I {} xmllint --xpath "//*[(local-name()='hasExactSynonym' or local-name()='hasRelatedSynonym' or local-name()='label') and text()='{}']/../@*[local-name()='about']" $OWLFILE | \
cut -d\" -f2
```

Execute:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getlabels.sh doid.owl | ./geturi.sh doid.owl
```

```
http://purl.obolibrary.org/obo/DOID_8545
http://purl.obolibrary.org/obo/DOID_8545
http://purl.obolibrary.org/obo/DOID_8545
```

Avoid repetitions:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getlabels.sh ↩
    doid.owl | ./geturi.sh doid.owl | sort -u

http://purl.obolibrary.org/obo/DOID_8545
```

Parent Classes

Parent classes of *malignant hyperthermia*:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about⤸
   ']='http://purl.obolibrary.org/obo/DOID_8545']/*[local-name()='⤸
   subClassOf']/@*[local-name()='resource']" doid.owl
```

`[local-name()='subClassOf']` gets subclass

`@*[local-name()='resource']` gets attribute with URI

Output URIs parents of 8545:

```
rdf:resource="http://purl.obolibrary.org/obo/DOID_0050736"
rdf:resource="http://purl.obolibrary.org/obo/DOID_66"
```

Execute for *caffeine*:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about
  ']='http://purl.obolibrary.org/obo/CHEBI_27732']/*[local-name()
  ='subClassOf']/@*[local-name()='resource']" chebi_lite.owl
```

```
rdf:resource="http://purl.obolibrary.org/obo/CHEBI_26385"
rdf:resource="http://purl.obolibrary.org/obo/CHEBI_27134"
```

No longer can use `string`

multiple parents

and `string` only returns first match

Get only URIs:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about
   ']='http://purl.obolibrary.org/obo/CHEBI_27732']/*[local-name()
   ='subClassOf']/@*[local-name()='resource']" chebi_lite.owl |
   cut -d\" -f2
```

```
http://purl.obolibrary.org/obo/CHEBI_26385
http://purl.obolibrary.org/obo/CHEBI_27134
```

Script *getparents.sh*:

```
OWLFILE=$1
xargs -I {} xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about']='{}']/*[local-name()='subClassOf']/@*[local-name()='resource']" $OWLFILE | \
cut -d\" -f2
```

- Multiple URIs given as standard input
  - OWL file to find parents as argument

Parents of *malignant hyperthermia*:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getparents.sh
    doid.owl
```

```
http://purl.obolibrary.org/obo/DOID_0050736
http://purl.obolibrary.org/obo/DOID_66
```

Labels of parents

Redirect the output:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getparents.sh
    doid.owl | ./getlabels.sh doid.owl
```

```
autosomal dominant disease
muscle tissue disease
```

Same with *caffeine*:

```
$ echo 'http://purl.obolibrary.org/obo/CHEBI_27732' | ./getparents.
    sh chebi_lite.owl | ./getlabels.sh chebi_lite.owl
```

```
purine alkaloid
trimethylxanthine
```

Related classes

All related classes

besides *subClassOf*:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about']='http://purl.obolibrary.org/obo/CHEBI_27732']/*[local-name()='subClassOf']//*[local-name()='someValuesFrom']/@*[local-name()='resource']" chebi_lite.owl | cut -d\" -f2
```

Related classes are

in attribute *resource*

of *someValuesFrom* element

inside *subClassOf* element

Related classes of *caffeine*:

```
http://purl.obolibrary.org/obo/CHEBI_25435
http://purl.obolibrary.org/obo/CHEBI_35337
http://purl.obolibrary.org/obo/CHEBI_35471
http://purl.obolibrary.org/obo/CHEBI_35498
http://purl.obolibrary.org/obo/CHEBI_35703
http://purl.obolibrary.org/obo/CHEBI_38809
http://purl.obolibrary.org/obo/CHEBI_50218
http://purl.obolibrary.org/obo/CHEBI_50925
http://purl.obolibrary.org/obo/CHEBI_53121
http://purl.obolibrary.org/obo/CHEBI_60809
http://purl.obolibrary.org/obo/CHEBI_64047
http://purl.obolibrary.org/obo/CHEBI_67114
http://purl.obolibrary.org/obo/CHEBI_71232
http://purl.obolibrary.org/obo/CHEBI_75771
http://purl.obolibrary.org/obo/CHEBI_76924
http://purl.obolibrary.org/obo/CHEBI_76946
http://purl.obolibrary.org/obo/CHEBI_78298
http://purl.obolibrary.org/obo/CHEBI_85234
```

Labels of related classes

Add *getlabels.sh*:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about
  ']='http://purl.obolibrary.org/obo/CHEBI_27732']/*[local-name()
  ='subClassOf']//*[local-name()='someValuesFrom']/@*[local-name
  ()='resource']" chebi_lite.owl | cut -d\" -f2 | ./getlabels.sh
  chebi_lite.owl
```

```
mutagen
central nervous system stimulant
psychotropic drug
diuretic
xenobiotic
ryanodine receptor modulator
EC 3.1.4.* (phosphoric diester hydrolase) inhibitor
EC 2.7.11.1 (non-specific serine/threonine protein kinase)
  inhibitor
adenosine A2A receptor antagonist
adjuvant
```

```
food additive
ryanodine receptor agonist
adenosine receptor antagonist
mouse metabolite
plant metabolite
fungal metabolite
environmental contaminant
human blood serum metabolite
```

Ancestors

Chain invocations of *getparents.sh*

- until no matches (root)
- avoid cyclic relations (infinite loop)
- consider only parent relations

Grandparents

Parents of parents also generalizations

Grandparents of *malignant hyperthermia*:

```
$ echo 'malignant hyperthermia' | ./geturi.sh doid.owl | ./
  getparents.sh doid.owl | ./getparents.sh doid.owl
```

```
http://purl.obolibrary.org/obo/DOID_0050739
http://purl.obolibrary.org/obo/DOID_0080000
```

Their labels:

```
$ echo 'malignant hyperthermia' | ./geturi.sh doid.owl | ./getparents.sh doid.owl | ./getparents.sh doid.owl | ./getlabels.sh doid.owl
```

```
autosomal genetic disease
muscular disease
```

Root class

Not have any parent

- *disease* and *chemical entity*
- highly generic terms

Check root class:

```
$ echo 'disease' | ./geturi.sh doid.owl | ./getparents.sh doid.owl
$ echo 'chemical entity' | ./geturi.sh chebi_lite.owl | ./↩
    getparents.sh chebi_lite.owl
```

Warning confirming root class:

```
XPath set is empty
```

Recursion

Script *getancestors.sh*:

```
OWLFILE=$1
CLASSES=$(cat -)
[[ -z "$CLASSES" ]] && exit
PARENTS=$(echo "$CLASSES" | ./getparents.sh $OWLFILE | sort -u)
echo "$PARENTS"
echo "$PARENTS" | ./getancestors.sh $OWLFILE
```

List of URIs as standard input

- invokes *getparents.sh* recursively
- until reaches root class

Standard input in variable `CLASSES` to use twice:

- check input is empty (line 3)
- get parents classes (line 4).

Input empty then script ends

- base case of the recursion
- otherwise run indefinitely

Output in variable `PARENTS` to use twice

- output these direct parents (line 5)
- get ancestors of parents (line 6)

Invoking *getancestors.sh* inside *getancestors.sh*

- defines recursion step
- at some time reach classes without parents (root classes)
- then script ends

`echo` of variables `CLASSES` and `PARENTS`

- inside commas so newline chars preserved

Iteration

Recursion frequently computational expensive

- replace recursion with iteration
- and explaining iteration
- out of scope of this book

Nevertheless, script alternative:

```
 1 # iteration
 2 OWLFILE=$1
 3 CLASSES=$(cat -)
 4 ANCESTORS=""
 5 while [[ ! -z "$CLASSES" ]]
 6 do
 7    PARENTS=$(echo "$CLASSES" | ./getparents.sh $OWLFILE | sort -u)
 8    ANCESTORS="$ANCESTORS\n$PARENTS"
 9    CLASSES=$PARENTS
10 done
11 echo -e "$ANCESTORS"
```

`while` implements iteration

- repeating a set of commands (lines 6-8)
- while a condition is satisfied (line 4)

Test with *malignant hyperthermia*:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_8545' | ./getancestors.
    sh doid.owl
```

```
http://purl.obolibrary.org/obo/DOID_0050736
http://purl.obolibrary.org/obo/DOID_66
http://purl.obolibrary.org/obo/DOID_0050739
http://purl.obolibrary.org/obo/DOID_0080000
http://purl.obolibrary.org/obo/DOID_0050177
http://purl.obolibrary.org/obo/DOID_17
http://purl.obolibrary.org/obo/DOID_630
http://purl.obolibrary.org/obo/DOID_7
http://purl.obolibrary.org/obo/DOID_4
```

Warning when reaches root class:

```
XPath set is empty
```

Redirect warnings:

```
$ echo 'malignant hyperthermia' | ./geturi.sh doid.owl | ./↩
    getancestors.sh doid.owl 2>/dev/null | ./getlabels.sh doid.owl
```

Ancestors of *malignant hyperthermia*:

```
autosomal dominant disease
muscle tissue disease
autosomal genetic disease
muscular disease
monogenic disease
musculoskeletal system disease
genetic disease
disease of anatomical entity
disease
```

First two ancestors direct parents

last one the root class.

prints the parents before invoking itself

Same with *caffeine*:

```
$ echo 'caffeine' | ./geturi.sh chebi_lite.owl | ./getancestors.sh ⤸
    chebi_lite.owl | ./getlabels.sh chebi_lite.owl | sort -u
```

Repeated classes

- using different branches
- add `sort -u`

Ancestors of *caffeine*:

```
alkaloid
aromatic compound
bicyclic compound
carbon group molecular entity
chemical entity
cyclic compound
heteroarene
heterobicyclic compound
heterocyclic compound
heteroorganic entity
heteropolycyclic compound
imidazopyrimidine
main group molecular entity
methylxanthine
molecular entity
molecule
nitrogen molecular entity
organic aromatic compound
organic cyclic compound
organic heterobicyclic compound
```

```
organic heterocyclic compound
organic heteropolycyclic compound
organic molecular entity
organic molecule
organonitrogen compound
organonitrogen heterocyclic compound
p-block molecular entity
pnictogen molecular entity
polyatomic entity
polycyclic compound
purine alkaloid
purines
trimethylxanthine
```

My Lexicon

Labels and related classes from ontology

Create *do_8545_lexicon.txt*:

```
$ echo 'malignant hyperthermia' | ./geturi.sh doid.owl | ./↩
    getlabels.sh doid.owl > do_8545_lexicon.txt
```

Lexicon for *malignant hyperthermia*
with all its labels

Ancestors labels

Add to lexicon:

```
$ echo 'malignant hyperthermia' | ./geturi.sh doid.owl | ./getancestors.sh doid.owl | ./getlabels.sh doid.owl >> do_8545_lexicon.txt
```

`>>` and not `>`

append lines to file

Check contents:

```
$ cat do_8545_lexicon.txt | sort -u
```

```
anesthesia related hyperthermia
autosomal dominant disease
autosomal genetic disease
disease
disease of anatomical entity
genetic disease
malignant hyperpyrexia due to anesthesia
malignant hyperthermia
monogenic disease
muscle tissue disease
muscular disease
musculoskeletal system disease
```

Same for *caffeine* in *chebi_27732_lexicon.txt*:

```
$ echo 'caffeine' | ./geturi.sh chebi_lite.owl | ./getlabels.sh ⤸
    chebi_lite.owl > chebi_27732_lexicon.txt
```

```
$ echo 'caffeine' | ./geturi.sh chebi_lite.owl | ./getancestors.sh ⤸
    chebi_lite.owl | ./getlabels.sh chebi_lite.owl >> ⤸
    chebi_27732_lexicon.txt
```

Check contents:

```
$ cat chebi_27732_lexicon.txt | sort -u
```

```
alkaloid
aromatic compound
bicyclic compound
caffeine
...
polycyclic compound
purine alkaloid
purines
trimethylxanthine
```

This lexicon is much larger.

Merging labels

Merging two lexicons in *lexicon.txt*:

```
$ cat do_8545_lexicon.txt chebi_27732_lexicon.txt | sort -u > ⤸
    lexicon.txt
```

Recognize any mention in *chebi_27732_sentences.txt*:

```
$ grep -w -i -F -f lexicon.txt chebi_27732_sentences.txt
```

`-F` option

our lexicon is list of fixed strings

not includes regular expressions.

Some results not include direct mention
to *caffeine* or *malignant hyperthermia*

Example *molecule* ancestor of *caffeine*:

```
The remainder of the molecule is hydrophilic and presumably
  constitutes the cytoplasmic domain of the protein.
```

Example *disease* ancestor of *malignant hyperthermia*:

```
Our data suggest that divergent activity profiles may cause
  varied disease phenotypes by specific mutations.
```

Use the lexicon with *getentities.sh*:

- replace `-E` by the `-F` option

```
$ ./getentities.sh lexicon.txt < chebi_27732_sentences.txt
```

Ancestors matched

Ancestors being matched:

```
$ grep -o -w -F -f lexicon.txt chebi_27732_sentences.txt | sort -u
```

```
caffeine
disease
malignant hyperthermia
molecule
```

Text limited and using official labels

- missing acronyms and simple variations (plural)
- solution use a stemmer
- all ancestors besides subsumption
- add some regular expressions

Generic Lexicon

Recognizing any disease
represented in ontology
in our sentences
related to *caffeine*

Get all labels without restricting to any URI:

```
$ xmllint --xpath "//*[local-name()='Class']/*[local-name()='⤸
    hasExactSynonym' or local-name()='hasRelatedSynonym' or local-⤸
    name()='label']/text()" doid.owl
```

Script *getalllabels.sh*:

```
OWLFILE=$1
xmllint --xpath "//*[local-name()='Class']/*[local-name()='hasExactSynonym' or local-name()='hasRelatedSynonym' or local-name()='label']/text()" $OWLFILE | \
sort -u
```

Execute:

```
$ ./getalllabels.sh doid.owl
```

```
11-beta-hydroxysteroid dehydrogenase deficiency type 2
11p11.2 deletion
11p partial monosomy syndrome
...
Zoophilia
Zoophobia
zygomycosis
```

Redirect to *diseases.txt*:

```
$ ./getalllabels.sh doid.owl > diseases.txt
```

Check how many labels:

```
$ wc -l diseases.txt
```

More than 34 thousand labels

Recognize lexicon entries:

```
$ grep -n -w -E -f diseases.txt chebi_27732_sentences.txt

  grep: Unmatched ) or \)
```

Error because lexicon contains special characters
  also used by regular expressions (parentheses)

Replace `-E` by `-F`:

```
$ grep -n -o -w -F -f diseases.txt chebi_27732_sentences.txt
```

```
1:malignant hyperthermia
2:malignant hyperthermia
9:central core disease
10:disease
10:myopathy
...
1092:malignant hyperthermia
1092:central core disease
1103:malignant hyperthermia
1104:malignant hyperthermia
1106:central core disease
1106:myopathy
```

Problematic entries

Expressions enclosed by parentheses or brackets:

```
Post measles encephalitis (disorder)
Glaucomatous atrophy [cupping] of optic disc
```

Separation characters (commas or colons)
to represent a specialization

```
Tapeworm infection: intestinal taenia solum
Tapeworm infection: pork
Pemphigus, Benign Familial
ATR, nondeletion type
```

Comma also part of term:

```
46,XY DSD due to LHB deficiency
```

& to represent ampersand:

```
Gonococcal synovitis &amp;/or tenosynovitis
```

But alternatives already included:

```
Gonococcal synovitis and tenosynovitis
Gonococcal synovitis or tenosynovitis
```

Not trivial to devise rules

- that fully solve these issues
- will be exceptions to any rule

Special characters frequency

Check the impact:

```
$ grep -c -F '(' diseases.txt
$ grep -c -F ',' diseases.txt
$ grep -c -F '[' diseases.txt
$ grep -c -F ':' diseases.txt
$ grep -c -F '&amp;' diseases.txt
```

Parentheses and commas most frequent

more than one thousand entries

Completeness

Check presence of *ATR*

acronym *alpha thalassemia-X-linked intellectual disability syndrome*

```
$ grep -E '^ATR' diseases.txt
```

```
ATR-16 syndrome
ATR, nondeletion type
ATR syndrome, deletion type
ATR syndrome linked to chromosome 16
ATR-X syndrome
```

A single *ATR* mention will not be recognized:

```
$ echo 'The ATR syndrome is an alpha thalassemia that has material ⤸
    basis in mutation in the ATRX gene on Xq21' | grep -w 'ATR'
```

Removing special characters

Remove parentheses and brackets:

```
$ tr -d '[](){}' < diseases.txt
```

Miss shorter labels such as *Post measles encephalitis*,
but at least will recognize:

```
$ tr -d '[](){}' < diseases.txt | grep 'Post measles encephalitis ↩
    disorder'
```

Alternative create multiple entries in the lexicon
or transform the labels in regular expressions

Removing extra terms

Remove text after separation char:

```
$ tr -d '[](){}' < diseases.txt | sed -E 's/[,:;] .*$//'
```

Enforces a space after the separation char

avoids: *46,XY DSD due to LHB deficiency*

Recognize both *ATR* and *ATR syndrome*:

```
$ tr -d '[](){}' < diseases.txt | sed -E 's/[,:;] .*$//' | grep -E ⤸
    '^ATR'
```

Removing extra spaces

Remove leading or trailing spaces:

```
$ tr -d '[](){}' < diseases.txt | sed -E 's/[,:;] .*$//; s/^ *//; s/ *$//'
```

More replacement expressions to `sed`

- separated by semicolon

Update *getalllabels.sh*:

```
OWLFILE=$1
xmllint --xpath "//*[local-name()='Class']/*[local-name()='hasExactSynonym' or local-name()='hasRelatedSynonym' or local-name()='label']/text()" $OWLFILE | \
tr -d '[](){}' | \
sed -E 's/[,:;] .*$//; s/^ *//; s/ *$//' | sort -u
```

Generate fixed lexicon:

```
$ ./getalllabels.sh doid.owl > diseases.txt
```

Check number of entries:

```
$ wc -l diseases.txt
```

More than 13 thousand labels

- less because fixes made duplicate entries

Disease recognition

Recognize entries:

```
$ grep -n -o -w -F -f diseases.txt chebi_27732_sentences.txt
```

Labels recognized:

```
$ grep -o -w -F -f diseases.txt chebi_27732_sentences.txt | sort -u
```

```
47
Andersen-Tawil syndrome
arrhythmogenic right ventricular cardiomyopathy
...
scoliosis
syndrome
T cell
```

47 due to label *47, XXY*:

Performance

`grep` quite efficient

- but large lexicons and texts may give performing issues
- execution time proportional to lexicon size
- each entry an independent pattern to match

Inverted Recognition

- uses words of input text as patterns
- matched against lexicon
- input text smaller than lexicon
- `grep` fewer patterns to match
- applied to ChEBI 100 times faster

Case insensitive

Use the `-i` option:

```
$ grep -o -w -F -i -f diseases.txt chebi_27732_sentences.txt | sort -u | wc -l
```

66 labels being recognized.

Check new labels recognized:

```
$ grep -o -w -F -i -f diseases.txt chebi_27732_sentences.txt | sort -u > diseases_recognized_ignorecase.txt
```

```
$ grep -o -w -F -f diseases.txt chebi_27732_sentences.txt | sort -u > diseases_recognized.txt
```

```
$ grep -v -F -f diseases_recognized.txt diseases_recognized_ignorecase.txt
```

```
all
All
Arrhythmogenic right ventricular dysplasia
can
Catecholaminergic polymorphic ventricular tachycardia
Central Core Disease
defect
Disease
dyskinesia
face
fever
hypotonia
Malignant hyperthermia
Malignant Hyperthermia
March
ORF
total
```

Discard case variations with `-f`:

```
$ grep -o -w -F -i -f diseases.txt chebi_27732_sentences.txt | sort↩
    -u -f | wc -l
```

57 different labels

Correct matches

Some only recognized by case insensitive match

dyskinesia

Lexicon not include lowercase case:

```
$ grep -i -E '^dyskinesia$' diseases.txt
```

Lexicon only name with first character in uppercase:

```
Dyskinesia
```

Incorrect matches

Case insensitive match create other problems

CAN acronym of

Crouzon syndrome-acanthosis nigricans syndrome:

```
$ echo 'CAN' | ./geturi.sh doid.owl | ./getlabels.sh doid.owl
```

Check how many times *CAN* is recognized:

```
$ grep -n -o -w -i -F -f diseases.txt chebi_27732_sentences.txt | ⤸
    grep -i ':CAN' | wc -l
```

22 times

Which type of matches:

```
$ grep -o -w -i -F -f diseases.txt chebi_27732_sentences.txt | grep
    -i -E '^CAN$' | sort -u
```

Incorrect mentions:

```
can
```

22 mismatches by case insensitive match

Entity Linking

What recognized labels represent

Find what *AD2* represents:

```
$ echo 'AD2' | ./geturi.sh doid.owl
```

Only one URI:

```
http://purl.obolibrary.org/obo/DOID_0110035
```

Retrieve labels:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_0110035' | ./getlabels.⤸
    sh doid.owl
```

Clearly *Alzheimer disease*:

```
AD2
Alzheimer disease 2, late onset
Alzheimer disease associated with APOE4
Alzheimer disease-2
Alzheimer's disease 2
```

Modified labels

Labels modified by previous fixes:

```
$ echo 'ATR' | ./geturi.sh doid.owl

XPath set is empty
```

Solution keep track of the original label

Ambiguity

Classes acronym *KOS* may represent:

```
$ echo 'KOS' | ./geturi.sh doid.owl

 http://purl.obolibrary.org/obo/DOID_0111456
 http://purl.obolibrary.org/obo/DOID_0111712
```

Two distinct diseases:

Kaufman oculocerebrofacial syndrome (DOID:0111456)

Kagami-Ogata syndrome (DOID:0111712)

Alternative labels:

```
$ echo 'http://purl.obolibrary.org/obo/DOID_0111456' | ./getlabels.
    sh doid.owl
```

```
$ echo 'http://purl.obolibrary.org/obo/DOID_0111712' | ./getlabels.
    sh doid.owl
```

Both containing *KOS* as expected:

```
KOS
blepharophimosis ptosis intellectual disability syndrome
oculocerebrofacial syndrome, Kaufman type
Kaufman oculocerebrofacial syndrome

KOS
Kagami-Ogata syndrome
```

Surrounding entities

Select class closer in meaning
to other classes in surrounding text

Assuming entities in same text
semantically related

Example:

```
KOS is a syndromic intellectual disability
```

Identify the diseases:

```
$ echo 'KOS is a syndromic intellectual disability' | grep -o -w -F
    -f diseases.txt
```

```
KOS
syndromic intellectual disability
```

Find URIs:

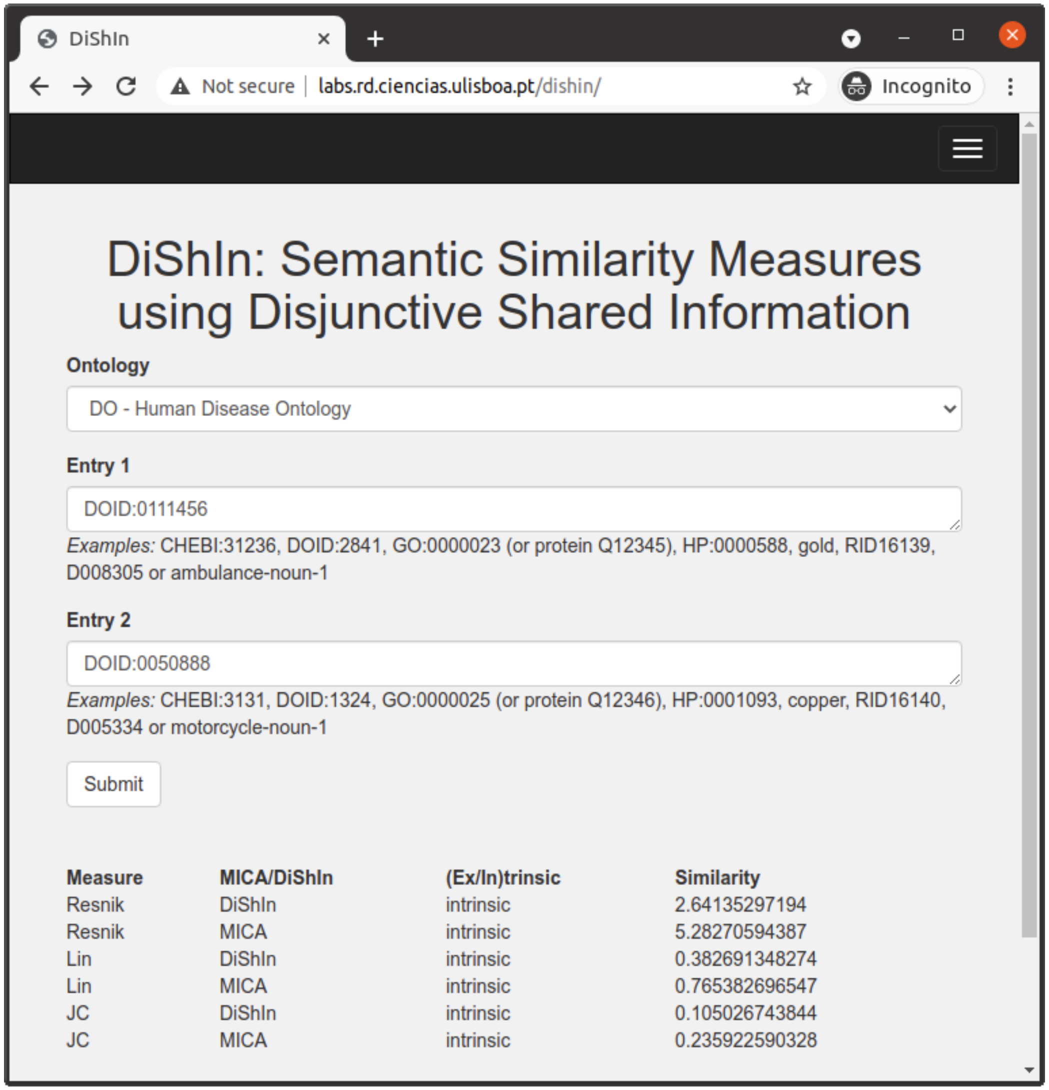
```
$ echo 'KOS is a syndromic intellectual disability' | grep -o -w -F
    -f diseases.txt | ./geturi.sh doid.owl

http://purl.obolibrary.org/obo/DOID_0111456
http://purl.obolibrary.org/obo/DOID_0111712
http://purl.obolibrary.org/obo/DOID_0050888
```

Syndromic intellectual disability (DOID:0050888)

Semantic similarity

Solve ambiguity problems
  quantify how close two classes are
  in terms of semantics
  encoded in a given ontology

Use `http://labs.rd.ciencias.ulisboa.pt/dishin/`
  to calculate semantic similarity between:
  Kaufman oculocerebrofacial syndrome (DOID:0111456)
  Syndromic intellectual disability (DOID:0050888)
  and
  Kagami-Ogata syndrome (DOID:0111712)
  Syndromic intellectual disability (DOID:0050888)



DiShIn: Semantic Similarity Measures using Disjunctive Shared Information

Ontology

DO - Human Disease Ontology

Entry 1

DOID:0111456

Examples: CHEBI:31236, DOID:2841, GO:0000023 (or protein Q12345), HP:0000588, gold, RID16139, D008305 or ambulance-noun-1

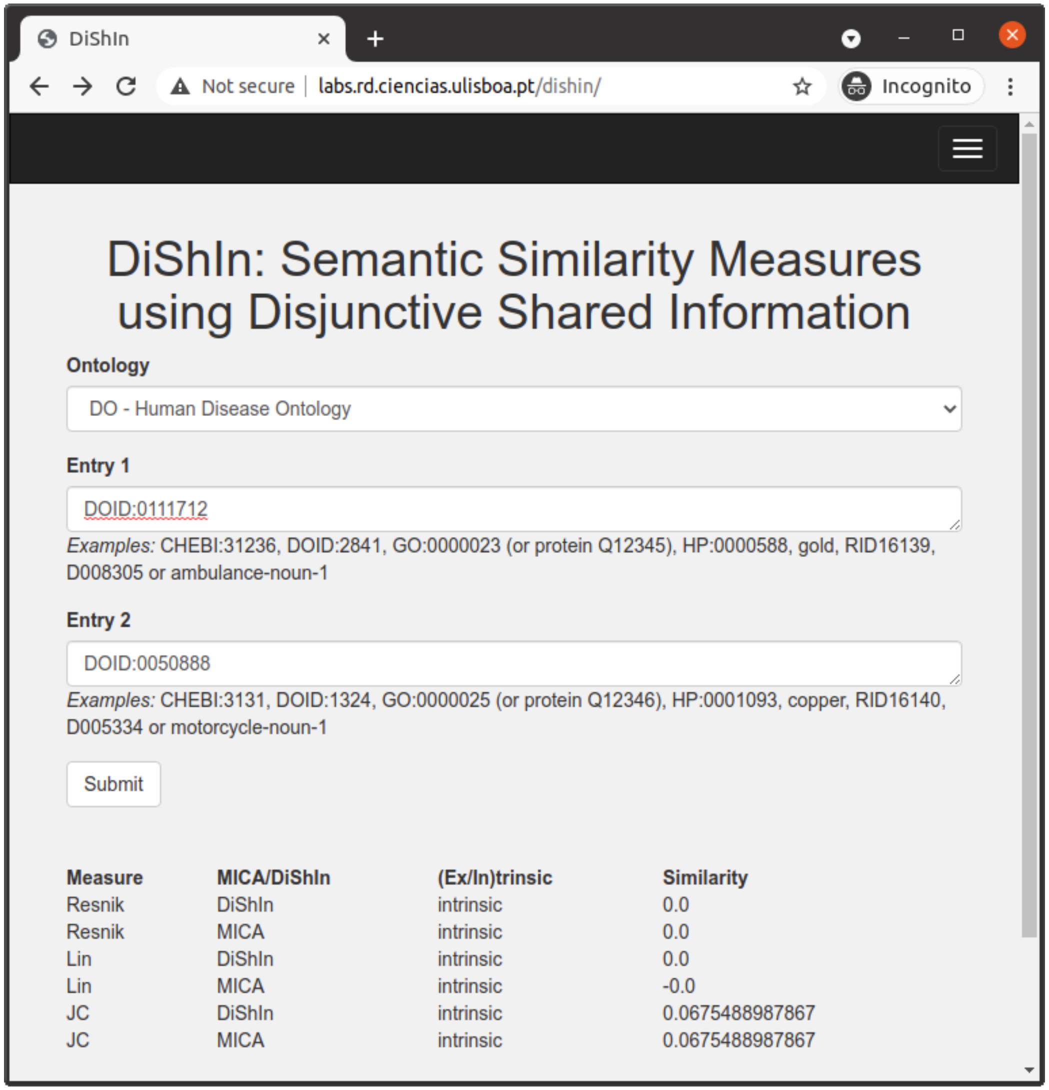
Entry 2

DOID:0050888

Examples: CHEBI:3131, DOID:1324, GO:0000025 (or protein Q12346), HP:0001093, copper, RID16140, D005334 or motorcycle-noun-1

Measure	**MICA/DiShIn**	**(Ex/In)trinsic**	**Similarity**
Resnik	DiShIn	intrinsic	2.64135297194
Resnik	MICA	intrinsic	5.28270594387
Lin	DiShIn	intrinsic	0.382691348274
Lin	MICA	intrinsic	0.765382696547
JC	DiShIn	intrinsic	0.105026743844
JC	MICA	intrinsic	0.235922590328

Semantic similarity between *Kaufman oculocerebrofacial syndrome* (DOID:0111456) and *Syndromic intellectual disability* (DOID:0050888)



DiShIn: Semantic Similarity Measures using Disjunctive Shared Information

Ontology

DO - Human Disease Ontology

Entry 1

DOID:0111712

Examples: CHEBI:31236, DOID:2841, GO:0000023 (or protein Q12345), HP:0000588, gold, RID16139, D008305 or ambulance-noun-1

Entry 2

DOID:0050888

Examples: CHEBI:3131, DOID:1324, GO:0000025 (or protein Q12346), HP:0001093, copper, RID16140, D005334 or motorcycle-noun-1

Measure	MICA/DiShIn	(Ex/In)trinsic	Similarity
Resnik	DiShIn	intrinsic	0.0
Resnik	MICA	intrinsic	0.0
Lin	DiShIn	intrinsic	0.0
Lin	MICA	intrinsic	-0.0
JC	DiShIn	intrinsic	0.0675488987867
JC	MICA	intrinsic	0.0675488987867

Semantic similarity between *Kagami-Ogata syndrome* (DOID:0111712) and *Syndromic intellectual disability* (DOID:0050888)

Measures

DiShIn provides three measures
- Resnik, Lin and Jiang-Conrath
- last two values between 0 and 1,
- Jiang-Conrath distance converted similarity

Syndromic intellectual disability more similar to
Kaufman oculocerebrofacial syndrome
than to *Kagami-Ogata syndrome*

Semantic similarity can identify
Kaufman oculocerebrofacial syndrome correct linked entity
for *KOS* in this text

DiShIn installation

Execute DiShIn as a command line
- need to install python (or python3)
- and SQLite

Download minimalist DiShIn and latest database:

```
$ curl -O http://labs.rd.ciencias.ulisboa.pt/dishin/dishin.py
$ curl -O http://labs.rd.ciencias.ulisboa.pt/dishin/ssm.py
$ curl -O http://labs.rd.ciencias.ulisboa.pt/dishin/doid202104.db.↩
    gz
$ gunzip -N doid202104.db.gz
```

Full version:

`https://github.com/lasigeBioTM/DiShIn`

DiShIn execution

Semantic similarity between:

Kaufman oculocerebrofacial syndrome (DOID:0111456)
Syndromic intellectual disability (DOID:0050888)
and
Kagami-Ogata syndrome (DOID:0111712)
Syndromic intellectual disability (DOID:0050888)

Execute:

```
$ python dishin.py doid.db DOID_0111456 DOID_0050888
$ python dishin.py doid.db DOID_0111712 DOID_0050888
```

Semantic similarity between *Kaufman oculocerebrofacial syndrome* (DOID:0111456) and *Syndromic intellectual disability* (DOID:0050888)

```
Resnik   DiShIn  intrinsic      2.64135297194
Resnik   MICA    intrinsic      5.28270594387
Lin      DiShIn  intrinsic      0.382691348274
Lin      MICA    intrinsic      0.765382696547
JC       DiShIn  intrinsic      0.105026743844
JC       MICA    intrinsic      0.235922590328
```

Semantic similarity between *Kagami-Ogata syndrome* (DOID:0111712) and *Syndromic intellectual disability* (DOID:0050888

```
Resnik   DiShIn  intrinsic      0.0
Resnik   MICA    intrinsic      0.0
Lin      DiShIn  intrinsic      0.0
Lin      MICA    intrinsic      -0.0
JC       DiShIn  intrinsic      0.0675488987867
JC       MICA    intrinsic      0.0675488987867
```

Learning python and SQL

out of scope of this book
but quite simple to execute

Large lexicons

Online tool MER

- a shell script
- easily executed as a command line
- efficiently recognize and link entities
- using large lexicons

MER installation

Install it locally:

```
$ curl -O -L https://github.com/lasigeBioTM/MER/archive/master.zip
$ unzip master.zip
$ mv MER-master MER
```

Copy Human Disease Ontology:

```
$ cp doid.owl MER/data/
$ cd MER
```

Lexicon files

Create lexicon:

```
$ (cd data; ../produce_data_files.sh doid.owl)
```

Check the contents:

```
$ tail data/doid_*
```

```
==> data/doid_links.tsv <==
ziziphus mauritiana fruit allergy http://purl.obolibrary.org/obo/
  DOID_0060507
zlotogora-ogur syndrome http://purl.obolibrary.org/obo/
  DOID_0080400
zlotogora-zilberman-tenenbaum syndrome http://purl.obolibrary.org
  /obo/DOID_0060773
zollinger-ellison syndrome http://purl.obolibrary.org/obo/
  DOID_0050782
zoophilia http://purl.obolibrary.org/obo/DOID_9336
zoophobia http://purl.obolibrary.org/obo/DOID_600
```

```
zunich-kaye syndrome http://purl.obolibrary.org/obo/DOID_0112152
zunich neuroectodermal syndrome http://purl.obolibrary.org/obo/
  DOID_0112152
zygodactyly 1 http://purl.obolibrary.org/obo/DOID_0111820
zygomycosis http://purl.obolibrary.org/obo/DOID_8485

==> data/doid_word1.txt <==
xpid
xpv
xrn
xscid
yaba
yaws
zaspopathy
zoophilia
zoophobia
zygomycosis

==> data/doid_word2.txt <==
zellweger syndrome
zemuron allergy
```

```
zika fever
zinacef allergy
zinsser.cole.engman syndrome
zlotogora.ogur syndrome
zlotogora.zilberman.tenenbaum syndrome
zollinger.ellison syndrome
zunich.kaye syndrome
zygodactyly 1

==> data/doid_words2.txt <==
y.linked monogenic
y.linked sertoli
y.linked spermatogenic
yolk sac
young adult.onset
zeta.associated.protein 70
zika virus
zikv congenital
ziziphus mauritiana
zunich neuroectodermal
```

```
==> data/doid_words.txt <==
yolk sac tumour
yolk sac tumour of the cns
young adult.onset dhmn
young adult.onset distal hereditary motor neuropathy
zeta.associated.protein 70 deficiency
zika virus congenital syndrome
zika virus disease
zikv congenital infection
ziziphus mauritiana fruit allergy
zunich neuroectodermal syndrome
```

MER execution

Execute MER:

```
$ cat ../chebi_27732_sentences.txt | tr -d "'" | xargs -I {} ./
    get_entities.sh '{}' doid
```

Removes single quotes

- special characters to `xargs`.

get_entities.sh script inside MER folder

- not the one created before

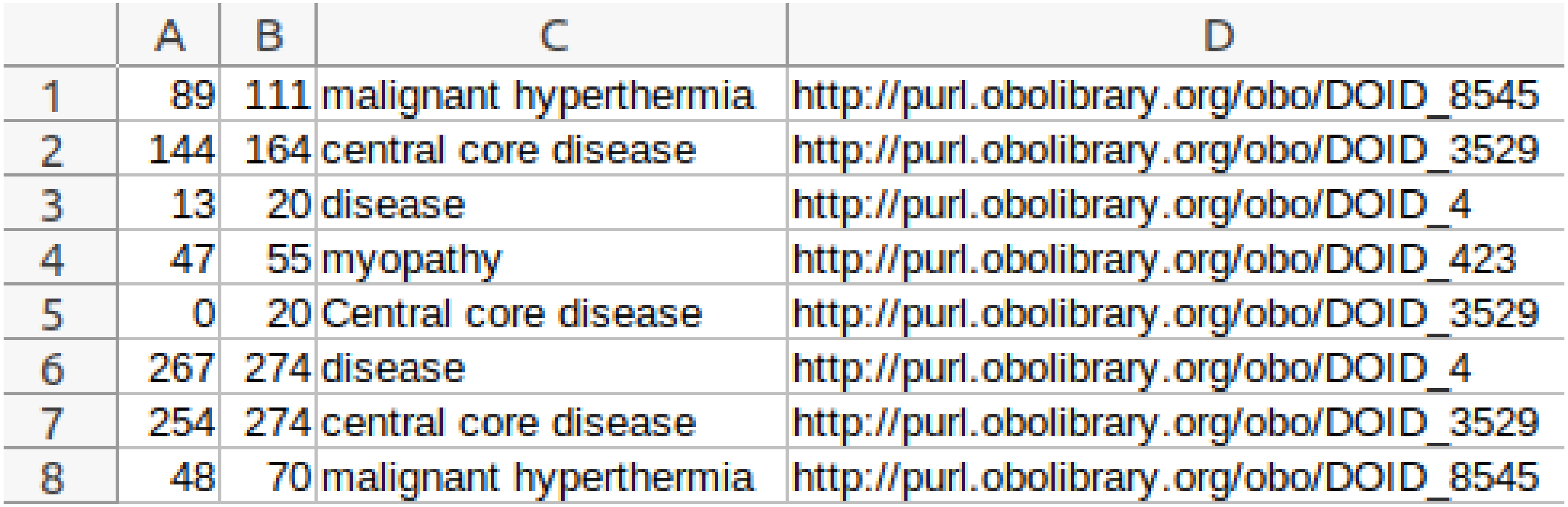
Large number of matches:

```
89      111     malignant hyperthermia  http://purl.obolibrary.
  org/obo/DOID_8545
74      96      malignant hyperthermia  http://purl.obolibrary.
  org/obo/DOID_8545
157     164     disease                 http://purl.obolibrary.
  org/obo/DOID_4
144     164     central core disease    http://purl.obolibrary.
  org/obo/DOID_3529
13      20      disease                 http://purl.obolibrary.
  org/obo/DOID_4
47      55      myopathy                http://purl.obolibrary.
  org/obo/DOID_423
...
```

First two numbers represent
  the start and end position of match
  followed by label and its URI

Create *diseases_recognized.tsv*:

```
$ cat ../chebi_27732_sentences.txt | tr -d "'" | xargs -I {} ./
    get_entities.sh '{}' doid > ../diseases_recognized.tsv
```



	A	B	C	D
1	89	111	malignant hyperthermia	http://purl.obolibrary.org/obo/DOID_8545
2	144	164	central core disease	http://purl.obolibrary.org/obo/DOID_3529
3	13	20	disease	http://purl.obolibrary.org/obo/DOID_4
4	47	55	myopathy	http://purl.obolibrary.org/obo/DOID_423
5	0	20	Central core disease	http://purl.obolibrary.org/obo/DOID_3529
6	267	274	disease	http://purl.obolibrary.org/obo/DOID_4
7	254	274	central core disease	http://purl.obolibrary.org/obo/DOID_3529
8	48	70	malignant hyperthermia	http://purl.obolibrary.org/obo/DOID_8545

The *diseases_recognized.tsv* file opened in a spreadsheet application

More:

`http://labs.rd.ciencias.ulisboa.pt/book/`