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Data and Text Processing for Health and Life Sciences

an example driven introductory guide using shell scripting

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Aos meus pais, Francisco de Oliveira Couto e Maria Fernanda dos Santos Moreira Couto.

Preface

During the last decades, I witnessed the growing importance of computer science skills for career advancement in Health and Life Sciences. However, not everyone has the skill, inclination, or time to learn computer programming. The learning process is usually time-consuming and requires constant practice, since software frameworks and programming languages change substantially overtime. This is the main motivation for writing this book about using shell scripting to address common Health and Life data and text processing tasks. Shell scripting has the advantages of being: i) nowadays available in almost all personal computers; ii) almost immutable for more than four decades; iii) relatively easy to learn as a sequence of independent commands; iv) an incremental and direct way to solve many of the data problems that Health and Life professionals face.

During the last decades, I had the pleasure to teach introductory computer science classes to Health and Life Sciences undergraduates. I used programming languages, such as Perl and Python, to address data and text processing tasks, but I always felt to loose a substantial amount of the time teaching the technicalities of these languages, which will probably change over time and are uninteresting for the majority of the students that do not intend to pursue advanced bioinformatics courses. Thus the purpose of this book is to motivate and help specialists to automate common data and text processing tasks after a short learning period. If they become interested (and I hope some do), the book presents pointers to where they can acquire more advanced computer science skills.

This book does not intend to be a comprehensive compendium of shell scripting commands, but instead a introductory guide for Health and Life specialists. This book introduces the commands as they are required to automate data and text processing tasks. The selected tasks have a strong focus on text mining and biomedical ontologies given my research experience and their growing relevance for Health and Life studies. Nevertheless, the same type of solutions presented in the book are also applicable to many other research fields and data sources.

Lisboa, January 2019 *Francisco Couto*

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Acronyms

ChEBI	Chemical Entities of Biological Interest
CSV	Comma-Separated Values
cURL	Client Uniform Resource Locator
DAG	Directed Acyclic Graph
DBMS	Database Management System
DiShIn	Semantic Similarity Measures using Disjunctive Shared Information
DO	Disease Ontology
EBI	European Bioinformatics Institute
GO	Gene Ontology
HTTP	Hypertext Transfer Protocol
HTTPS	HTTP Secure
ICD	International Classification of Diseases
MER	Minimal Named-Entity Recognizer
MeSH	Medical Subject Headings
NCBI	National Center for Biotechnology Information
NER	Named-Entity Recognition
OBO	Open Biological and Biomedical Ontology
OWL	Web Ontology Language
PMC	PubMed Central
RDFS	RDF Schema
SNOMED CT	Systematized Nomenclature of Medicine - Clinical Terms
SQL	Structured Query Language
TSV	Tab-Separated Values
UMLS	Unified Medical Language System
UniProt	Universal Protein Resource
URI	Uniform Resource Identifier
URL	Uniform Resource Locator
XLS	Microsoft Excel file format
XML	Extensible Markup Language
XPath	XML Path Language

Chapter 1
Introduction

Health and Life studies are well known for the huge amount of data they produce, such as high-throughput sequencing projects [Stephens et al., 2015, Hey et al., 2009]. However, the value of the data should not be measured by its amount, but instead by the possibility and ability of researchers to retrieve and process it [Leonelli, 2016]. Transparency, openness, and reproducibility are key aspects to boost the discovery of novel insights into how living systems work [Nosek et al., 2015].

Biomedical data repositories

Fortunately, a significant portion of the biomedical data is already being collected, integrated and distributed through central repositories, such as European Bioinformatics Institute (EBI) and National Center for Biotechnology Information (NCBI) repositories [Cook et al., 2017, Coordinators, 2018]. Nonetheless, researchers cannot rely on available data as mere facts, they may contain errors, can be outdated, and may require a context [Ferreira et al., 2017]. Most facts are only valid in a specific biological setting and should not be directly extrapolated to other cases. In addition, different research communities have different needs and requirements, which change over time [Tomczak et al., 2018].

Scientific text

Structured data is what most computer applications require as input, but humans tend to prefer the flexibility of text to express their hypothesis, ideas, opinions, conclusions [Barros and Couto, 2016]. This explains why scientific text is still the preferential means to publish new discoveries and to describe the data that support them [Holzinger et al., 2014, Lu, 2011]. Another reason

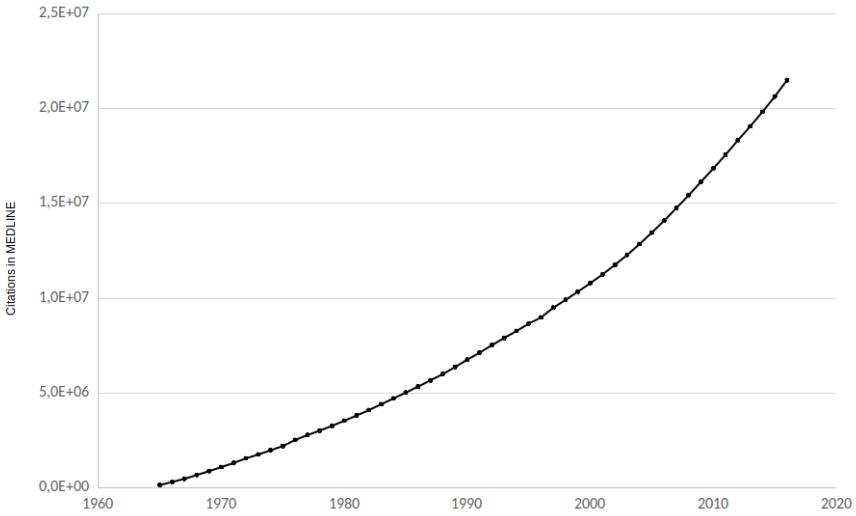


Fig. 1.1 Chronological listing of the total number of citations in MEDLINE (Source: `https://www.nlm.nih.gov/bsd/`)

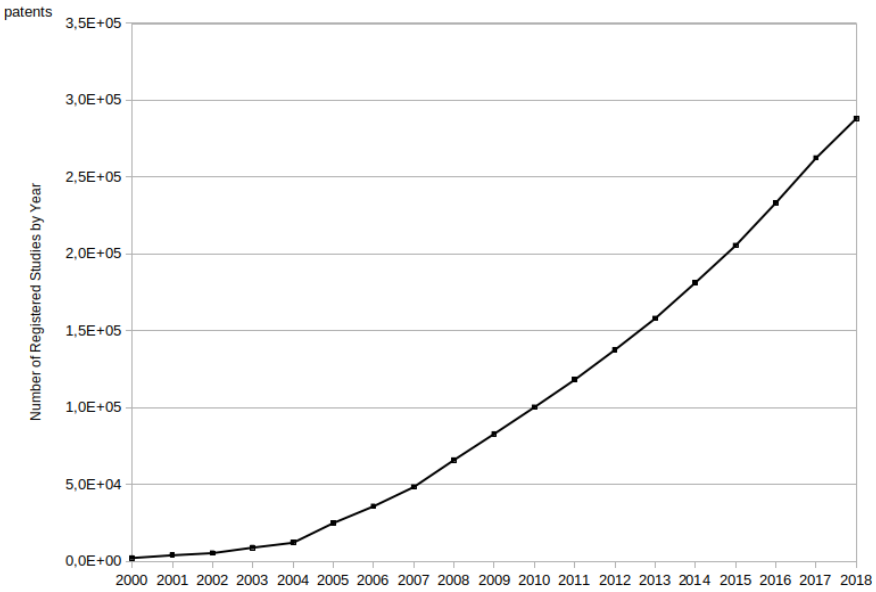


Fig. 1.2 Chronological listing of the total number of registered studies (clinical trials) (Source: `https://clinicaltrials.gov`)

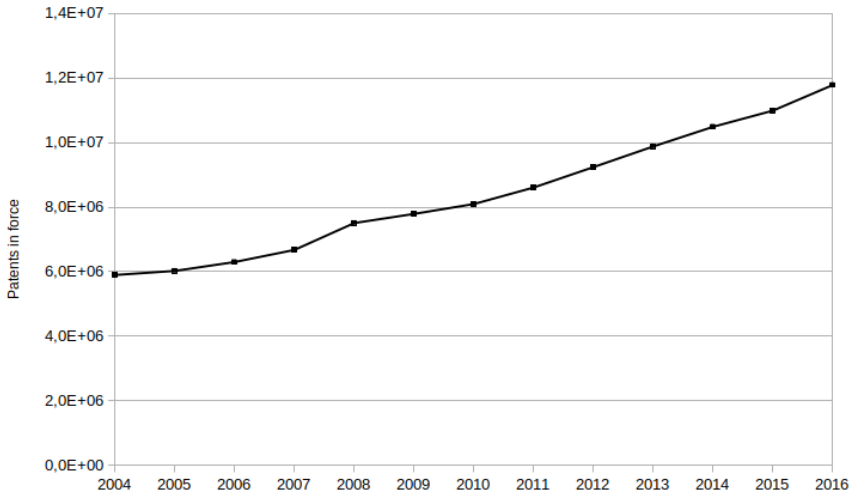


Fig. 1.3 Chronological listing of the total number of patents in force (Source: WIPO statistics database `http://www.wipo.int/ipstats/en/`)

is the long-established scientific reward system based on the publication of scientific articles [Rawat and Meena, 2014].

Amount of text

The main problem of analyzing biomedical text is the huge amount of text being published every day [Hersh, 2008]. For example, 952,919 citations [1] were indexed in 2020 in MEDLINE, a bibliographic database of Health and Life literature [2]. If we read 10 articles per day, it will take us takes more than 261 years to just read those articles. Figure 1.1 presents the number of citations added to MEDLINE in the past decades, showing the increasing large amount of biomedical text that researchers must deal with.

Moreover, scientific articles are not the only source of biomedical text, for example clinical studies and patents also provide a large amount of text to explore. They are also growing at a fast pace, as Figures 1.2 and 1.3 clearly show [Aras et al., 2014, Jensen et al., 2012].

[1] `https://www.nlm.nih.gov/bsd/medline_pubmed_production_stats.html`

[2] `https://www.nlm.nih.gov/bsd/medline.html`

Ambiguity and contextualization

Given the high flexibility and ambiguity of natural language, processing and extracting information from texts is a painful and hard task, even to humans. The problem is even more complex when dealing with scientific text, that requires specialized expertise to understand it. The major problem with Health and Life Sciences is the inconsistency of the nomenclature used for describing biomedical concepts and entities [Hunter and Cohen, 2006, Rebholz-Schuhmann et al., 2005]. In biomedical text, we can often find different terms referring to the same biological concept or entity (synonyms), or the same term meaning different biological concepts or entities (homonyms). For example, many times authors improve the readability of their publications by using acronyms to mention entities, that may be clear for experts on the field but ambiguous in another context.

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. Understanding the underlying message in such articles normally requires years of training to create in our brain a semantic model about the domain and to know how to interpret the highly specialized terminology specific to each domain. Finally, the multilingual aspect of text is also a problem, since most clinical data are produced in the native language [Campos et al., 2017].

Biomedical ontologies

To address the issue of ambiguity of natural language and contextualization of the message, text processing techniques can explore current biomedical ontologies [Robinson and Bauer, 2011]. These ontologies can work as vocabularies to guide us in what to look for [Couto et al., 2006]. For example, we can select an ontology that models a given domain and find out which official names and synonyms are used to mention concepts in which we have an interest [Spasic et al., 2005]. Ontologies may also be explored as semantic models by providing semantic relationships between concepts [Lamurias et al., 2017].

Programming skills

The success of biomedical studies relies on overcoming data and text processing issues to take the most of all the information available in biomedical data repositories. In most cases, biomedical data analysis is no longer possible using an in-house and limited dataset, we must be able to efficiently process all this data and text. So, a common question that many Health and Life specialists face is:

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

This is the goal of this book, to provide a low-cost, long-lasting, feasible and painless answer to this question.

1.1 Why this book?

State-of-the-art data and text processing tools are nowadays based on complex and sophisticated technologies, and to understand them we need to have special knowledge on programming, linguistics, machine learning or deep learning [Holzinger and Jurisica, 2014, Ching et al., 2018, Angermueller et al., 2016]. Explaining their technicalities or providing a comprehensive list of them are not the purpose of this book. The tools implementing these technologies tend to be impenetrable to the common Health and Life specialists and usually become outdated or even unavailable some time after their publication or the financial support ends. Instead, this book will equip the reader with a set of skills to process text with minimal dependencies to existing tools and technologies. The idea is not to explain how to build the most advanced tool, but how to create a resilient and versatile solution with acceptable results.

In many cases, advanced tools may not be most efficient approach to tackle a specific problem. It all depends on the complexity of problem, and the results we need to obtain. Like a good physician knows that the most efficient treatment for a specific patient is not always the most advanced one, a good data scientist knows that the most efficient tool to address a specific information need is not always the most advanced one. Even without focusing on the foundational basis of programming, linguistics or artificial intelligence, this book provides the basic knowledge and right references to pursue a more advanced solution if required.

Third-party solutions

Many manuscripts already present and discuss the most recent and efficient text mining techniques and the available software solutions based on them that users can use to process data and text [Cock et al., 2009, Gentleman et al., 2004, Stajich et al., 2002]. These solutions include stand-alone applications, web applications, frameworks, packages, pipelines, etc. A common problem with these solutions is their resiliency to deal with new user require-

ments, to changes on how resources are being distributed, and to software and hardware updates. Commercial solutions tend to be more resilient if they have enough customers to support the adaptation process. But of course we need the funding to buy the service. Moreover, we will be still dependent on a third-party availability to address our requirements that are continuously changing, which vary according to the size of the company and our relevance as client.

Using open-source solutions may seem a great alternative since we do not need to allocate funding to use the service and its maintenance is assured by the community. However, many of these solutions derive from academic projects that most of the times are highly active during the funding period and then fade away to minimal updates. The focus of academic research is on creating new and more efficient methods and publish them, the software is normally just a means to demonstrate their breakthroughs. In many cases to execute the legacy software is already a non-trivial task, and even harder is to implement the required changes. Thus, frequently the most feasible solution is to start from scratch.

Simple pipelines

If we are interested in learning sophisticated and advanced programming skills, this is not the right book to read. This book aims at helping Health and Life specialists to process data and text by describing a simple pipeline that can be executed with minimal software dependencies. Instead of using a fancy web front-end, we can still manually manipulate our data using the spreadsheet application that we already are comfortable with, and at the same time be able to 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.

1.2 How this book helps Health and Life specialists?

So, if this book does not focus on learning programming skills, and neither on the usage of any special package or software, how it will help specialists processing biomedical text and data?

Shell scripting

The solution proposed in this book has been available for more than four decades [Ritchie, 1971], and it can now be used in almost every personal computer [Haines, 2017]. Even with all the recent computational advances such ancient technology is still the most efficient solution to many problems, the same way that face masks used a century ago to deal with the 1918 Spanish flu pandemic are still being used today to deal with the COVID-19 pandemic.

The idea is to provide an example driven introduction to shell scripting [3] that addresses common challenges in biomedical text processing using a Unix shell [4]. Shells are software programs available in Unix operating systems since 1971 [5], but nowadays are available is most of our personal computers using 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?

It is different in the sense that most solutions are based on the usage of single command line tools, that sometimes are combined as simple pipelines. This book does not intend to create experts in shell scripting, by the contrary, the few scripts introduced are merely direct combinations of simple command line tools individually explained before.

The main idea is to demonstrate the ability of a few command line tools to automate many of the text and data processing tasks. The solutions are presented in a way that comprehending them is like conducting a new laboratory protocol i.e. testing and understanding its multiple procedural steps, variables, and intermediate results.

Text files

All the data will be stored in text files, which command line tools are able to efficiently process [Baker and Milligan, 2014]. Text files represent a simple and universal medium of storing our data. They do not require any special encoding and can be opened and interpreted by using any text editor application. Normally, text files without any kind of formatting are stored using a *txt* extension. However, text files can contain data using a specific format, such as:

---

[3] `https://en.wikipedia.org/wiki/Shell_script`

[4] `https://en.wikipedia.org/wiki/Unix_shell`

[5] `https://www.in-ulm.de/~mascheck/bourne/#origins`

CSV : Comma-Separated Values [6];
TSV : Tab-Separated Values [7];
XML : eXtensible Markup Language [8].

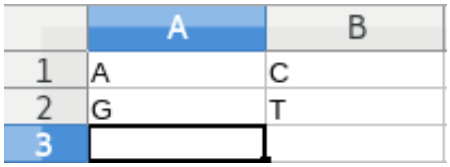


Fig. 1.4 Spreadsheet example

All the above formats can be open (import), edited and saved (export) by any text editor application. and common spreadsheet applications [9], such as LibreOffice Calc or Microsoft Excel [10]. For example, we can create a new data file using LibreOffice Calc, like the one in Figure 1.4. Then we select the option to save it as CSV, TSV, XML (Microsoft 2003), and XLS (Microsoft 2003) formats. We can try to open all these files in our favorite text editor.

When opening the CSV file, the application will show the following contents:

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

Each line represents a row of the spreadsheet, and column values are separated by commas.

When opening the TSV file, the application will show the following contents:

```
A C
G T
```

The only difference is that instead of a comma it is now used a tab character to separate column values.

When opening the XML file, the application will show the following contents:

```
...
<Table ss:StyleID="ta1">
<Column ss:Span="1" ss:Width="64.01"/>
```

[6] https://en.wikipedia.org/wiki/Comma-separated_values
[7] https://en.wikipedia.org/wiki/Tab-separated_values
[8] https://en.wikipedia.org/wiki/XML
[9] https://en.wikipedia.org/wiki/Spreadsheet
[10] To save in TSV format using the LibreOffice Calc, we may have to choose CSV format and then select as field delimiter the tab character

```
<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>
...
```

Now the data is more complex to find and understand, but with a little more effort we can check that we have a table with two rows, each one with two cells.

When opening the XLS file, we will get a lot of strange characters and it is humanly impossible to understand what data it is storing. This happens because XLS is not a text file is a proprietary format [11], which organizes data using an exclusive encoding scheme, so its interpretation and manipulation could only be done using a specific software application.

Comma-separated values is a data format so old as shell scripting, in 1972 it was already supported by an IBM product [12]. 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 to automate some of the tasks.

Relational databases

If there is a need to use more advanced data storage techniques, such as using a relational database [13], we may still be able to use shell scripting if we can import and export our data to a text format. For example, we can open a relational database, execute Structured Query Language (SQL) commands [14], and import and export the data to CSV using the command line tool `sqlite3` [15].

Besides CSV and shell scripting being almost the same as they were four decades ago, they are still available everywhere and are able to solve most of our data and text processing daily problems. So, these tools are expected to continue to be used for many more decades to come. As a bonus, we will look like a true professional typing command line instructions in a black background window! ☺

---

[11] https://en.wikipedia.org/wiki/Proprietary_format

[12] http://bitsavers.trailing-edge.com/pdf/ibm/370/fortran/GC28-6884-0_IBM_FORTRAN_Program_Products_for_OS_and_CMS_General_Information_Jul72.pdf

[13] https://en.wikipedia.org/wiki/Relational_database

[14] https://en.wikipedia.org/wiki/SQL

[15] https://www.sqlite.org/cli.html

1.3 What is in the book?

First, the Chapter 2 presents a brief overview of some of the most prominent resources of biomedical data, text, and semantics. The chapter discusses what type of information they distribute, where we can find them, and how we will be able to automatically explore them. Most of the examples in the book use the resources provided by the European Bioinformatics Institute (EBI) and use their services to automatically retrieve the data and text. Nevertheless, after understanding the command line tools, it will not be hard to adapt them to the formats used by other service provider, such as the National Center for Biotechnology Information (NCBI). In terms of semantics, the examples will use two ontologies, one about human diseases and the other about chemical entities of biological interest. Most ontologies share the same structure and syntax, so adapting the solutions to other domains are expected to be painless.

As an example, the Chapter 3 will describe the manual steps that Health and Life specialists may have to perform to find and retrieve biomedical text about *caffeine* using publicly available resources. Afterwards, these manual steps will be automatized by using command line tools, including the automatic download of data. The idea is to go step-by-step and introduce how each command line tool can be used to automate each task.

Command line tools

The main command line tools that this book will introduce are the following:

- `curl`: a tool to download data and text from the web;
- `grep`: a tool to search our data and text;
- `gawk`: a tool to manipulate our data and text;
- `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.

Other command line tools are also presented to perform minor data and text manipulations, such as:

- `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

A fundamental technique introduced in Chapter 3 is how to redirect the output of a command line tool as input to another tool, or to a file. This enables

the construction of pipelines of sequential invocations of command line tools. Using a few commands integrated in a pipeline is really the maximum shell scripting that this book will use. Scripts longer than that would cross the line of not having to learn programming skills.

Chapter 4 is about extracting useful information from the text retrieved previously. The example consists in finding references to *malignant hyperthermia* in these *caffeine* related texts, so we may be able to check any valid relation.

Regular Expressions

A powerful pattern matching technique described in Chapter 4 is the usage of regular expressions [16] in the `grep` command line tool to perform Named-Entity Recognition (NER) [17]. Regular expressions originated in 1951 [Kleene, 1951], so they are even older than shell scripting, but still popular and available in multiple software applications and programming languages [Forta, 2018]. A regular expression is a string that include special operators represented by special characters. For example, the regular expression `A|C|G|T` will identify in a given string any of the four nucleobases adenine (A), cytosine (C), guanine (G), or thymine (T).

Another technique introduced is tokenization. It addresses the challenge of identifying the text boundaries, such as splitting a text into sentences. So, we can keep only the sentences that may have something we want. Chapter 4 also describes how can we try to find two entities in the same sentence, providing a simple solution to the relation extraction challenge [18].

Semantics

Instead of trying to recognize a limited list of entities, Chapter 5 explains how can we use ontologies to construct large lexicons that include all the entities of a given domain, e.g. humans diseases. The chapter also explains how the semantics encoded in an ontology can be used to expand a search by adding the ancestors and related classes of a given entity. Finally, a simple solution to the Entity Linking [19] challenge is given, where each entity recognized is mapped to a class in an ontology. A simple technique to solve the ambiguity issue when the same label can be mapped to more than one class is also briefly presented.

---

[16] `https://en.wikipedia.org/wiki/Regular_expression`

[17] `https://en.wikipedia.org/wiki/Named-entity_recognition`

[18] `https://en.wikipedia.org/wiki/Relationship_extraction`

[19] `https://en.wikipedia.org/wiki/Entity_linking`

Chapter 2
Resources

The previous chapter presented the importance of text and semantic resources for Health and Life studies. This chapter will describe what kind of text and semantic resources are available, where they can be found, and how they can be accessed and retrieved.

2.1 Biomedical Text

Text is still the preferential means of publishing novel knowledge in Health and Life Sciences, and where we can expect to find all the information about the supporting data. Text can be found and explored in multiple types of sources, the main being scientific articles and patents [Krallinger et al., 2017]. However, less formal texts are also relevant to explore, such as the ones present nowadays in electronic health records [Blumenthal and Tavenner, 2010].

2.1.1 What?

In the biomedical domain, we can find text in different forms, such as:

Statement	: a short piece of text, normally containing personal remarks or an evidence about a biomedical phenomenon;
Abstract	: a short summary of a larger scientific document;
Full-text	: the entire text present in a scientific document including scattered text such as figure labels and footnotes.

Statements contain more syntactic and semantic errors than abstracts, since they normally are not peer-reviewed, but they are normally directly linked to data providing useful details about it. The main advantage of using state-

ments or abstracts is the brief and succinct form on which the information is expressed. In the case of abstracts, there was already an intellectual exercise to present only the main facts and ideas. Nevertheless, a brief description may be insufficient to draw a solid conclusion, that may require some important details not possible to summarize in a short piece of text [Schuemie et al., 2004]. These details are normally presented in the form of a full-text document, which contains a complete description of the results obtained. For example, important details are sometimes only present in figure labels[Yeh et al., 2003].

One major problem of full-text documents is their availability, since their content may have restricted access. In addition, the structure of the full-text and the format on which is available varies according to the journal in where it was published. Having more information does not mean that all of it is beneficial to find what we need. Some of the information may even induce us in error. For example, the relevance of a fact reported in the Results Section may be different if the fact was reported in the Related Work Section. Thus, the usage of full-text may create several problems regarding the quality of information extracted [Shah et al., 2003].

2.1.2 Where?

Access to biomedical literature is normally done using the internet through PubMed [1], an information retrieval system released in 1996 that allows researchers to search and find biomedical texts of relevance to their studies [Canese, 2006]. PubMed is developed and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH). Currently, PubMed provides access to more than 28 million citations from MEDLINE, a bibliographic database with references to a comprehensive list of academic journals in Health and Life Sciences [2]. The references include multiple metadata about the documents, such as: title, abstract, authors, journal, publication date. PubMed does not store the full-text documents, but it provides links where we may find the full-text. More recently, biomedical references are also accessible using the European Bioinformatics Institute (EBI) services, such as Europe PMC [3], or the Universal Protein Resource (UniProt) with its UniProt citations service [4].

[1] `https://www.nlm.nih.gov/bsd/pubmed.html`

[2] `https://www.nlm.nih.gov/bsd/medline.html`

[3] `http://europepmc.org/`

[4] `https://www.uniprot.org/citations/`

Other generic alternative tools have been also gaining popularity for finding scientific texts, such as Google Scholar [5], Google Patents [6], ResearchGate [7] and Mendeley [8].

More than just text some tools also integrate semantic links. One of the first search engines for biomedical literature to incorporate semantics was GOPubMed [9], that categorized texts according to Gene Ontology terms found in them [Doms and Schroeder, 2005]. These semantic resources will be described in a following section. A more recent tool is PubTator [10] that provides the text annotated with biological entities generated by state-of-the-art text-mining approaches [Wei et al., 2013].

There is also a movement in the scientific community to produce Open Access Publications, making full-texts freely available with unrestricted use. One of the main free digital archives of free biomedical full-texts is PubMed Central [11] (PMC), currently providing access to more than 5 million documents.

Other relevant source of biomedical texts is the electronic health records stored in health institutions, but the texts they contain are normally directly linked to patients and therefore their access is restricted due to ethical and privacy issues. As example, the THYME corpus [12] includes more than one thousand de-identified clinical notes from the Mayo Clinic, but is only available for text processing research under a data use agreement (DUA) with Mayo Clinic [Styler IV et al., 2014].

From generic texts we can also sometimes find relevant biomedical information. For example, some recent biomedical studies have been processing the texts in social networks to identify new trends and insights about a disease, such as processing tweets to predict flu outbreaks [Aramaki et al., 2011]
.

2.1.3 How?

To automatically process text, we need programmatic access to it, this means that from the previous repositories we can only use the ones that allow this kind of access. These limitations are imposed because many biomedical documents have copyright restrictions hold by their publishers. And some restric-

[5] http://scholar.google.com/

[6] http://www.google.com/patents

[7] https://www.researchgate.net/

[8] https://www.mendeley.com/

[9] https://gopubmed.org/

[10] http://www.ncbi.nlm.nih.gov/CBBresearch/Lu/Demo/PubTator/

[11] https://www.ncbi.nlm.nih.gov/pmc/

[12] http://thyme.healthnlp.org/

tions may define that only manual access is granted, and no programmatic access is allowed. These restrictions are normally detailed in the terms of service of each repository. However, when browsing the repository if we face a CAPTCHA [13] challenge to determine whether we are humans or not, probably means that some access restrictions are in place.

Fortunately, NCBI [14] and EBI [15] online services, such as PubMed, Europe PMC, or UniProt Citations, allow programmatic access [Li et al., 2015]. Both institutions provide Web APIs [16] that fully document how web services can be programmatically invoked. Some resources can inclusively be accessed using RESTful web services [17] that are characterized by a simple uniform interface that make any Uniform Resource Locator (URL) almost self-explanatory [Richardson and Ruby, 2008]. The same URL shown by our web browser is the only thing we need to know to retrieve the data using a command line tool.

For example, if we search for *caffeine* using the UniProt Citations service [18], select the first two entries, and click on Preview, the browser will show information about those two documents using a tabular format.

```
Citation Id Title Authors Publication date Journal
   First page Last page Statistics
20520601 Association of the anxiogenic ...
29522901 The influence of CYP1A2 genotype ...
```

We can also click on Generate URL for API and check the URL to access the information:

```
https://rest.uniprot.org/citations/stream?compressed=
   true&fields=id%2Ctitle%2Cauthors%2Cpublication_date
   %2Cjournal%2Cfirst_page%2Clast_page%2Cstatistics&
   format=tsv&query=id%3A20520601%20OR%20id%3A29522901
```

We can check that the URL has three main components: the scheme (`https`), the hostname (`rest.uniprot.org`), the service (`citations`) and the data parameters. The scheme represents the type of web connection to get the data, and usually is one of these protocols: Hypertext Transfer Protocol (HTTP) or HTTP Secure (HTTPS) [19]. The hostname represents the physical site where the service is available. The list of parameters depends on the data available from the different services.

---

[13] `https://en.wikipedia.org/wiki/CAPTCHA`

[14] `https://www.ncbi.nlm.nih.gov/home/develop/api/`

[15] `https://www.ebi.ac.uk/seqdb/confluence/display/JDSAT/`

[16] `https://en.wikipedia.org/wiki/Web_API`

[17] `https://www.ebi.ac.uk/seqdb/confluence/pages/viewpage.action?pageId=68165098`

[18] `https://www.uniprot.org/citations/`

[19] `https://en.wikipedia.org/wiki/Hypertext_Transfer_Protocol`

We can change any value of the parameters (arguments) to get different results. For example, we can replace the two PubMed identifiers by the following one 29029291:

```
https://rest.uniprot.org/citations/stream?compressed=
    true&fields=id%2Ctitle%2Cauthors%2Cpublication_date
    %2Cjournal%2Cfirst_page%2Clast_page%2Cstatistics&
    format=tsv&query=id%3A29029291
```

With this link our browser will now download a file with the information about this new document:

```
PubMed ID Title Authors/Groups Abstract/Summary
29029291 Nutrition Influences ...
```

The good news is that we can use this link with a command line tool and automatize the retrieval of the data, including extracting the abstract to process its text.

2.2 Semantics

Lack of use of standard nomenclatures across biological text makes text processing a non-trivial task. Often, we can find different labels (synonyms, acronyms) for the same biomedical entities, or, even more problematic, different entities sharing the same label (homonyms) [Rebholz-Schuhmann et al., 2005]. Sense disambiguation to select the correct meaning of an expression in a given piece of text is therefore a crucial issue. For example, if we find the disease acronym *ATS* in a text, we may have to figure out if it representing the *Andersen-Tawil syndrome* [20] or the *X-linked Alport syndrome* [21]. Further in the book, we will address this issue by using ontologies and semantic similarity between their classes [Couto and Lamurias, 2019].

2.2.1 What?

In 1993, [Gruber, 1993] proposed a short but comprehensive definition of ontology as an:

> an explicit specification of a conceptualization

In 1997 and 1998, [Borst and Borst, 1997] and [Studer et al., 1998] refined this definition to:

[20] http://purl.obolibrary.org/obo/DOID_0050434

[21] http://purl.obolibrary.org/obo/DOID_0110034

a formal, explicit specification of a shared conceptualization

A conceptualization is an abstract view of the concepts and the relationships of a given domain. A shared conceptualization means that a group of individuals agree on that view, normally established by a common agreement among the members of a community. The specification is a representation of that conceptualization using a given language. The language needs to be formal and explicit, so computers can deal with it.

Languages

The Web Ontology Language (OWL) [22] is nowadays becoming one of the most common languages to specify biomedical ontologies [McGuinness et al., 2004]. Another popular alternative is the Open Biomedical Ontology (OBO) [23] format developed by the OBO foundry. OBO established a set of principles to ensure high quality, formal rigor and interoperability between other OBO ontologies [Smith et al., 2007]. One important principle is that OBO ontologies need to be open and available without any constraint other than acknowledging their origin.

Concepts are defined as OWL classes that may include multiple properties. For text processing important properties include the labels that may be used to mention that class. The labels may include the official name, acronyms, exact synonyms, and even related terms. For example, a class defining the disease *malignant hyperthermia* may include as synonym *anesthesia related hyperthermia*. Two distinct classes may share the same label, such as *Andersen-Tawil syndrome* and *X-linked Alport syndrome* that have *ATS* as an exact synonym.

Formality

The representation of classes and the relationships may use different levels of formality, such as controlled vocabularies, taxonomies, and thesaurus that even may include logical axioms.

Controlled vocabularies are list of terms without specifying any relation between them. Taxonomies are controlled vocabularies that include subsumption relations, for example specifying that *malignant hyperthermia* is a *muscle tissue disease*. This *is-a* or subclass relations are normally the backbone of ontologies. We should note that some ontologies may include multiple inheritance, i.e. the same concept may be a specialization of two different concepts. Therefore, many ontologies are organized as a directed acyclic graphs (DAG) and not as hierarchical trees, as the one represented in Figure 2.1. A

[22] `https://en.wikipedia.org/wiki/Web_Ontology_Language`

[23] `https://en.wikipedia.org/wiki/Open_Biomedical_Ontologies`

thesaurus includes other types of relations besides subsumption, for example specifying that *caffeine* has role *mutagen*.

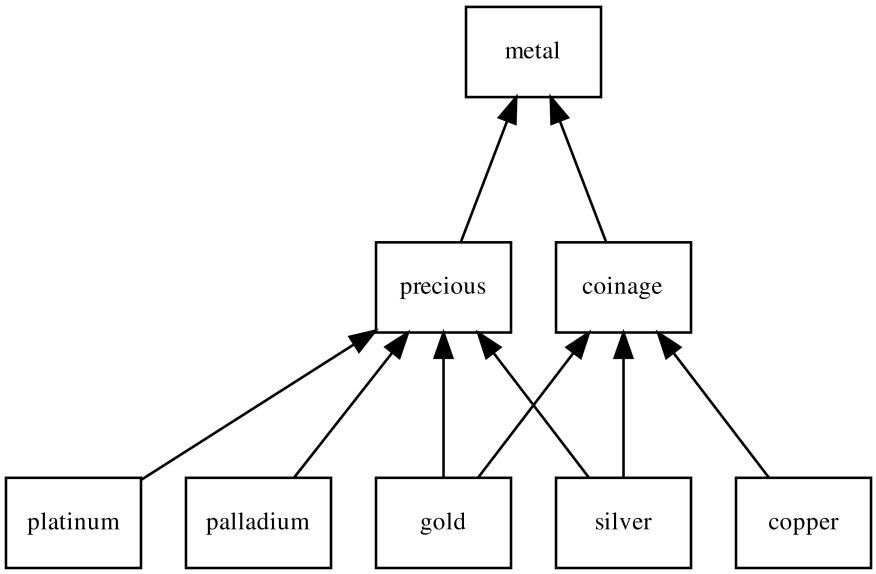


Fig. 2.1 A DAG representing a classification of metals with multiple inheritance, since *gold* and *silver* are considered both precious and coinage metals (All the links represent *is-a* relations)

Gold related documents

The importance of these relations can be easily understood by considering the domain modeled by the ontology in Figure 2.1, and the need to find texts related to *gold*. Assume a corpus with one distinct document mentioning each metal, except for *gold* that no document mentions. So, which documents should we read first?

The document mentioning *silver* is probably the most related since it shares with *gold* two parents, *precious* and *coinage*. However, choosing between the documents mentioning *platinum* or *palladium* or the document mentioning *copper* depends on our information need. This information can be obtained by our previous searches or reads. For example, assuming that our last searches included the word *coinage*, then document mentioning *copper* is probably the second-most related. The importance of these semantic

resources is evidenced by the development of the knowledge graph [24] by Google to enhance their search engine [Singhal, 2012].

2.2.2 Where?

Most of the biomedical ontologies are available through BioPortal [25]. In April of 2021, BioPortal provided access to 859 ontologies representing more than 10 million classes. BioPortal allows us to search for an ontology or a specific class. For example, if we search for *caffeine*, we will be able to see the large list of ontologies that define it. Each of these classes represent conceptualizations of *caffeine* in different domains and using alternative perspectives. To improve interoperability some ontologies include class properties with a link to similar classes in other ontologies. One of the main goals of the OBO initiative was precisely to tackle this somehow disorderly spread of definitions for the same concepts. Each OBO ontology covers a clearly specified scope that is clearly identified.

OBO ontologies

A major example of success of OBO ontologies is the Gene Ontology (GO) that has been widely and consistently used to describe the molecular function, biological process and cellular component of gene-products, in a uniform way across different species [Ashburner et al., 2000]. Another OBO ontology is the Disease Ontology (DO) that provides human disease terms, phenotype characteristics and related medical vocabulary disease concepts [Schriml et al., 2018]. Another OBO ontology is the Chemical Entities of Biological Interest (ChEBI) that provides a classification of molecular entities with biological interest with a focus on small chemical compounds[Degtyarenko et al., 2007].

Popular controlled vocabularies

Besides OBO ontologies, other popular controlled vocabularies also exist. One of them is the International Classification of Diseases (ICD) [26], maintained by the World Health Organization (WHO). This vocabulary contains a list of generic clinical terms mainly arranged and classified according to anatomy or etiology. Another example is the Systematized Nomenclature of

[24] https://en.wikipedia.org/wiki/Knowledge_Graph
[25] http://bioportal.bioontology.org/
[26] https://www.who.int/classifications/icd/en/

Medicine - Clinical Terms (SNOMED CT) [27], currently maintained and distributed by the International Health Terminology Standards Development Organization (IHTSDO). The SNOMED CT is a highly comprehensive and detailed set of clinical terms used in many biomedical systems. The Medical Subject Headings (MeSH) [28] is a comprehensive controlled vocabulary maintained by the National Library of Medicine (NLM) for classifying biomedical and health-related information and documents. Both MeSH and SNOMED CT are included in the Metathesaurus of the Unified Medical Language System (UMLS) [29], maintained by the U.S National Library of Medicine. This is a large resource that integrates most of the available biomedical vocabularies. The 2015AB release covered more than three million concepts.

Another alternative to BioPortal is Ontobee [30], a repository of ontologies used by most OBO ontologies, but it also includes many non-OBO ontologies. In April 2021, Ontobee provided access to 231 ontologies [Ong et al., 2016]

Other alternatives outside the biomedical domain include the list of vocabularies gathered by the W3C SWEO Linking Open Data community project [31], and by the W3C Library Linked Data Incubator Group [32]

2.2.3 How?

After finding the ontologies that cover our domain of interest in the previous catalogs, a good idea is to find their home page and download the files from there. This way, we will be sure that we get the most recent release in the original format and select the subset of the ontology that really matter for our work. For example, ChEBI provides three versions: LITE, CORE and FULL [33]. Since we are interested in using the ontology just for text processing, we are probably not interested in chemical data and structures that is available in CORE. Thus, LITE is probably the best solution, and it will be the one we will use in this book. However, we may be missing synonyms that are only included in the FULL version.

---

[27] `https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct`

[28] `https://www.nlm.nih.gov/mesh/`

[29] `https://www.nlm.nih.gov/research/umls/`

[30] `http://www.ontobee.org/`

[31] `http://www.w3.org/wiki/TaskForces/CommunityProjects/LinkingOpenData/CommonVocabularies`

[32] `http://www.w3.org/2005/Incubator/lld/XGR-lld-vocabdataset-20111025`

[33] `https://www.ebi.ac.uk/chebi/downloadsForward.do`

OWL

The OWL language is the prevailing language to represent ontologies, and for that reason will be the format we will use in this book. 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 that stores information in statements represented as triples of the form subject, predicate and object. Originally, W3C recommended RDF data to be encoded using Extensible Markup Language (XML) syntax, also named RDF/XML. XML is a self-descriptive mark-up language composed of data elements.

For example, the following example represents an XML file specifying that *caffeine* is a drug that may treat the condition of sleepiness, but without being an official treatment:

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

The information is organized in an hierarchical structure of data elements. `treatment` is the parent element of `drug` and `condition`. The character `<` means that a new data element is being specified, and the characters `</` means that a specification of data element will end. The `treatment` element has a property named `category` with the value `non-official`. The `drug` and `condition` elements have as values `caffeine` and `sleepiness`, respectively. This is a very simple XML example, but large XML files are almost unreadable by humans.

To address this issue other encoding languages for RDF are now being used, such as N3 [34] and Turtle [35]. Nevertheless, most biomedical ontologies are available in OWL using XML encoding.

URI

The Uniform Resource Identifier (URI) was defined as the standard global identifier of classes in an ontology. For example, the class `caffeine` in ChEBI is identified by the following URI :

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

If a URI represents a link to a retrievable resource is considered a Uniform Resource Locator, or URL. In other words, a URI is a URL if we open it in a web browser and obtain a resource describing that class.

---

[34] `https://en.wikipedia.org/wiki/Notation3`

[35] `https://en.wikipedia.org/wiki/Turtle_(syntax)`

Sometimes, ontologies are also available as database dumps. These dumps are normally SQL files that need to be fed to a DataBase Management System (DBMS) [36]. If for any reason we must deal with these files, we can use the simple command line tool named `sqlite3`. The tool has the option to execute the SQL commands to import the data into a database (`.read` command), and to export the data into a CSV file (`.mode` command) [Allen and Owens, 2011].

2.3 Further Reading

One important read if we need to know more about biomedical resources is the Arthur Lesk's book about bioinformatics [Lesk, 2014]. The book has entire chapters dedicated to where data and text can be found, providing a comprehensive overview of the type of biomedical information available, nowadays .

A more pragmatic approach is to explore the vast number of manuals, tutorials, seminars and courses provided by the EBI [37] and NCBI [38].

[36] `https://en.wikipedia.org/wiki/Database#Database_management_system`

[37] `https://www.ebi.ac.uk/training`

[38] `https://www.ncbi.nlm.nih.gov/home/learn/`

Chapter 3
Data Retrieval

This chapter starts by introducing an example of how we can retrieve text, where every step is done manually. This chapter will describe step-by-step how we can automatize each step of the example using shell script commands, which will be introduced and explained as long as they are required. The goal is to equip the reader with a basic set of skills to retrieve data from any online database and follow the links to retrieve more information from other sources, such as literature.

3.1 Caffeine Example

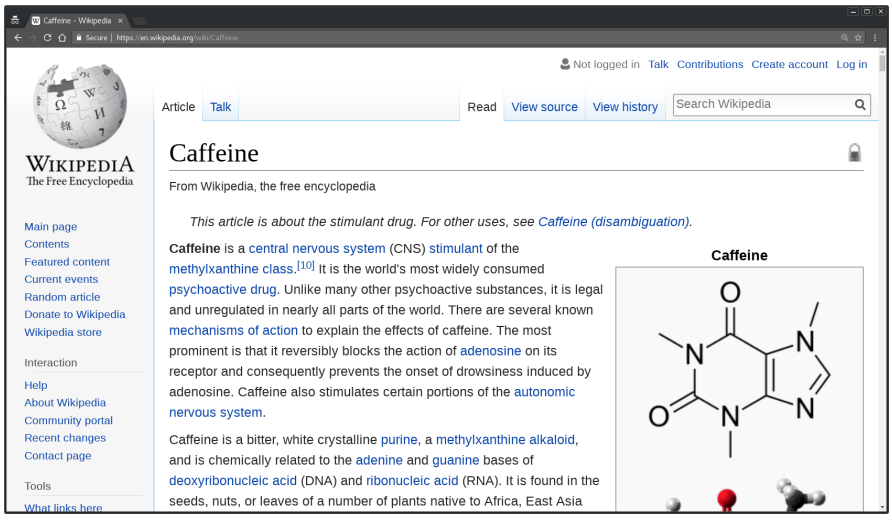


Fig. 3.1 Wikipedia page about caffeine

As our main example, let us consider that we need to retrieve more data and literature about *caffeine*. If we really do not know anything about *caffeine*, we may start by opening our favorite internet browser and then searching *caffeine* in Wikipedia [1] to know what it really is (see Figure 3.1). From all the information that is available we can check in the infobox that there are multiple links to external sources. The infobox is normally a table added to the top right-hand part of a web page with structured data about the entity described on that page.

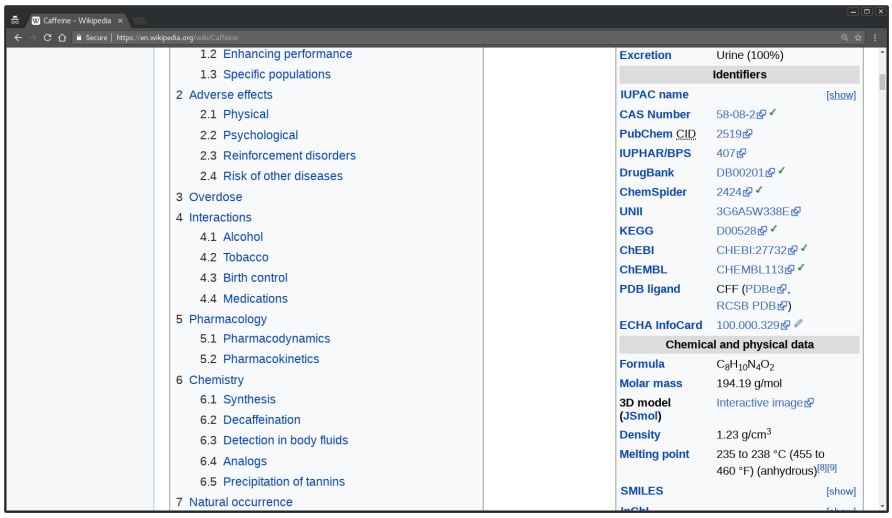


Fig. 3.2 Identifiers section of the Wikipedia page about caffeine

From the list of identifiers (see Figure 3.2), let us select the link to one resource hosted by the European Bioinfomatics Institute (EBI), the link to CHEBI:27732 [2].

CHEBI represents the acronym of the resource Chemical Entities of Biological Interest (ChEBI) [3] and 27732 the identifier of the entry in ChEBI describing *caffeine* (see Figure 3.3). ChEBI is a freely available database of molecular entities with a focus on "small" chemical compounds. More than a simple database, ChEBI also includes an ontology that classifies the entities according to their structural and biological properties.

By analyzing the CHEBI:27732 web page we can check that ChEBI provides a comprehensive set of information about this chemical compound. But

[1] `https://en.wikipedia.org/wiki/Caffeine`

[2] `https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:27732`

[3] `http://www.ebi.ac.uk/chebi/`

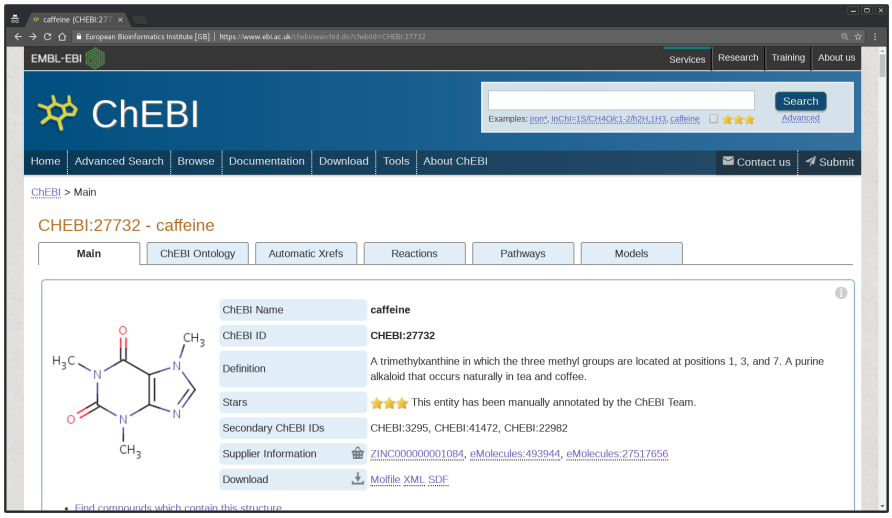


Fig. 3.3 ChEBI entry describing caffeine

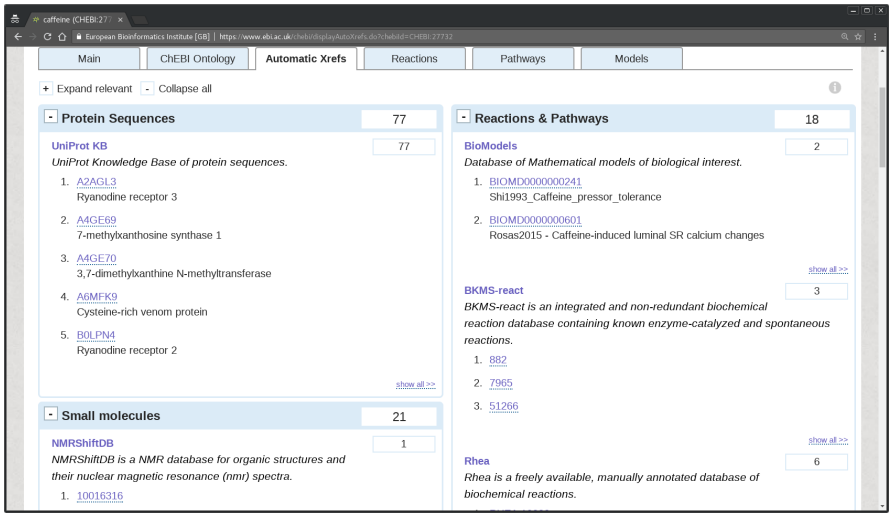


Fig. 3.4 External references related to caffeine

let us focus on the *Automatic Xrefs* tab [4]. This tab provides a set of external links to other resources describing entities somehow related to *caffeine* (see Figure 3.4).

In the Protein Sequences section, we have 77 proteins (in September of 2018) related to *caffeine*. If we click on *show all* we will get the complete

[4] `http://www.ebi.ac.uk/chebi/displayAutoXrefs.do?chebiId=CHEBI:27732`

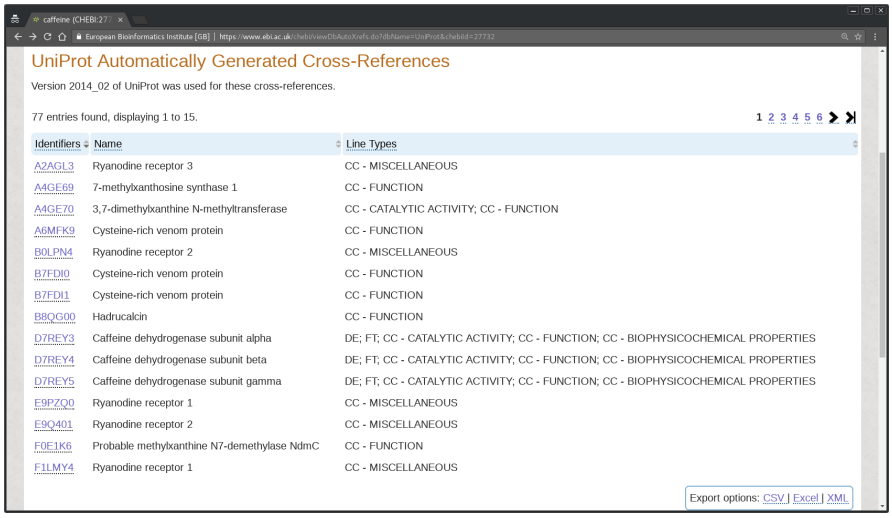


Fig. 3.5 Proteins related to caffeine

list [5] (see Figure 3.5). These links are to another resource hosted by the EBI, the UniProt, a database of protein sequences and annotation data.

The list includes the identifiers of each protein with a direct link to respective entry in UniProt, the name of the protein and some topics about the description of the protein. For example, DISRUPTION PHENOTYPE means some effects caused by the disruption of the gene coding for the protein are known [6].

We should note that at bottom-right of the page there are *Export options* that enable us to download the full list of protein references in a single file. These options include:

CSV : Comma Separated Values, the open format file that enable us to store data as a single table format (columns and rows).

Excel : a proprietary format designed to store and access the data using the software Microsoft Excel.

XML : eXtensible Markup Language, the open format file that enable us to store data using a hierarchy of markup tags.

We start by downloading the CSV, Excel and XML files. We can now open the files and check its contents in a regular text editor software [7] installed in our computer, such as notepad (Windows), TextEdit (macOS) or gedit (Linux).

---

[5] `http://www.ebi.ac.uk/chebi/viewDbAutoXrefs.do?dbName=UniProt&chebiId=27732`

[6] `https://web.expasy.org/docs/userman.html#CC_line`

[7] `https://en.wikipedia.org/wiki/Text_editor`

The first lines of the *chebi_27732_xrefs_UniProt.csv* file should look like this:

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

The first lines of the *chebi_27732_xrefs_UniProt.xls* file should look like this:

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

As we can see, this is not the proprietary format XLS but instead a TSV format. Thus, the file can still be open directly on *Microsoft Excel*.

The first lines of the *chebi_27732_xrefs_UniProt.xml* file should look like this:

```
<?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>
...
```

We should note that all the files contain the same data they only use a different format.

If for any reason, we are not able to download the previous files from UniProt, we can get them from the book file archive [8].

In the following sections we will use these files to automatize this process, but for now let us continue our manual exercise using the internet browser. Let us select the *Ryanodine receptor 1* with the identifier P21817 and click on the link [9] (see Figure 3.6). We can now see that UniProt is much more than

[8] http://labs.rd.ciencias.ulisboa.pt/book/

[9] https://www.uniprot.org/uniprotkb/P21817

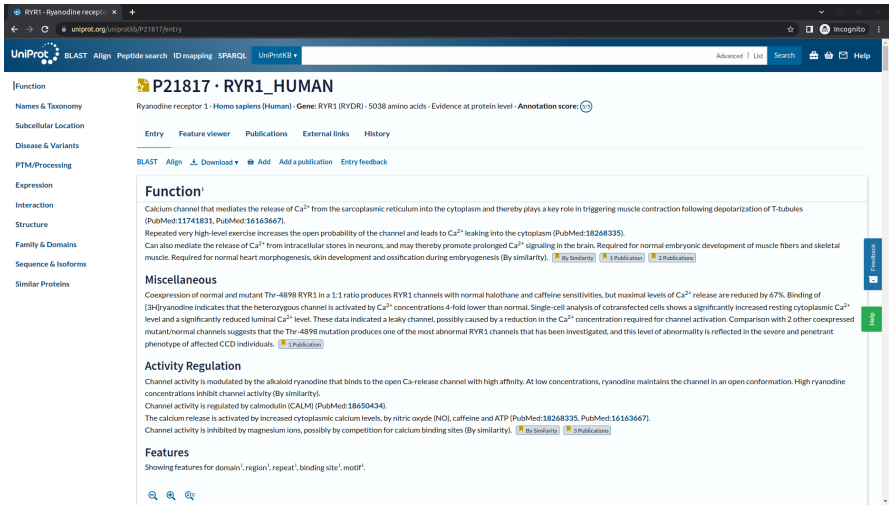


Fig. 3.6 UniProt entry describing the Ryanodine receptor 1

just a sequence database. The sequence is just a tiny fraction of all the information describing the protein. All this information can also be downloaded as a single file by clicking on Download and on XML. Then, save the result as a XML file to our computer.

Again, we can use our text editor to open the downloaded file named *P21817.xml*, which first lines should look like this:

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

We can check that this entry represents a *Homo sapiens (Human)* protein, so if we are interested only in Human Proteins, we will have to filter them. For example, the entry E9PZQ0 [10] in the ChEBI list also represents a *Ryanodine receptor 1* protein but for the *Mus musculus (Mouse)*.

Going back to the browser in the top side of the UniProt entry we have a link to publications [11]. If we click on it, we will see a list of publications somehow related to the protein (see Figure 3.7).

Let us assume that we are interested in finding phenotypic information, the first title that may attract our attention is: *Polymorphisms and deduced amino acid substitutions in the coding sequence of the ryanodine receptor*

[10] `https://www.uniprot.org/uniprotkb/E9PZQ0`

[11] `https://www.uniprot.org/uniprotkb/P21817/publications`

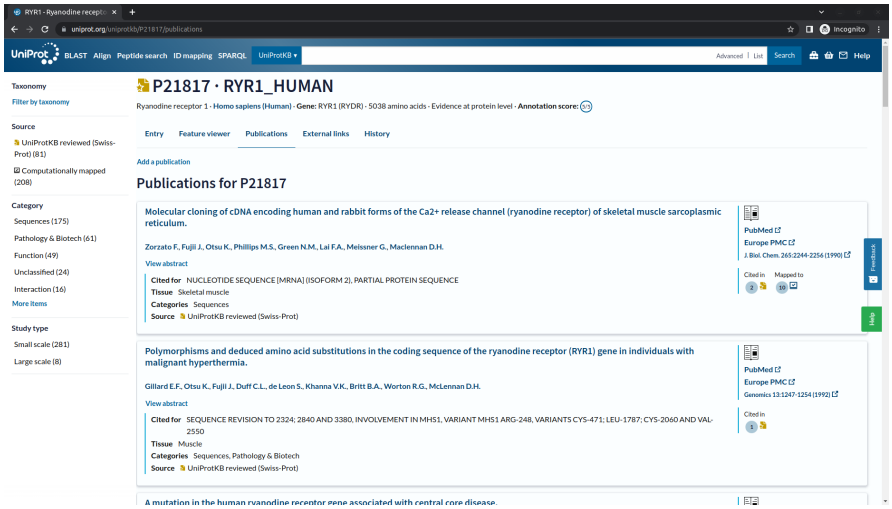


Fig. 3.7 Publications related to Ryanodine receptor 1

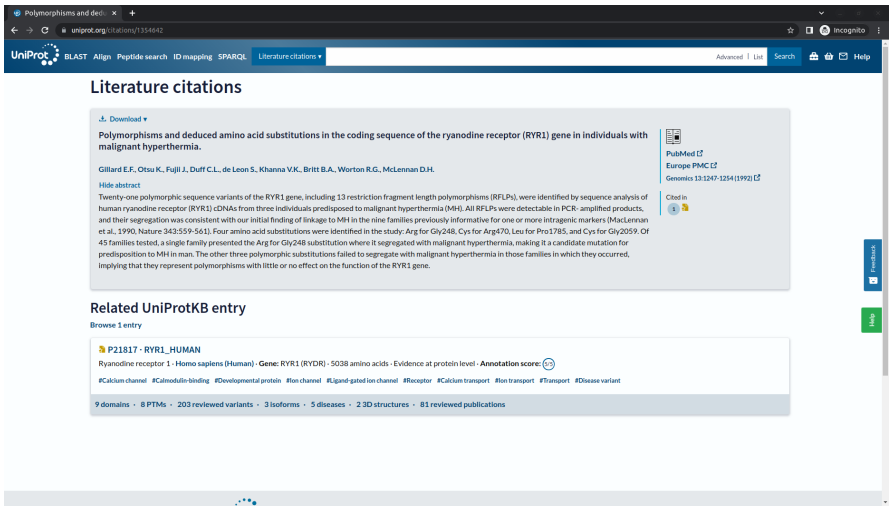


Fig. 3.8 Abstract of the publication entitled *Polymorphisms and deduced amino acid substitutions in the coding sequence of the ryanodine receptor (RYR1) gene in individuals with malignant hyperthermia*

(RYR1) gene in individuals with malignant hyperthermia. To know more about the publication, we can use the UniProt citations service by clicking on the Abstract link [12] (see Figure 3.8).

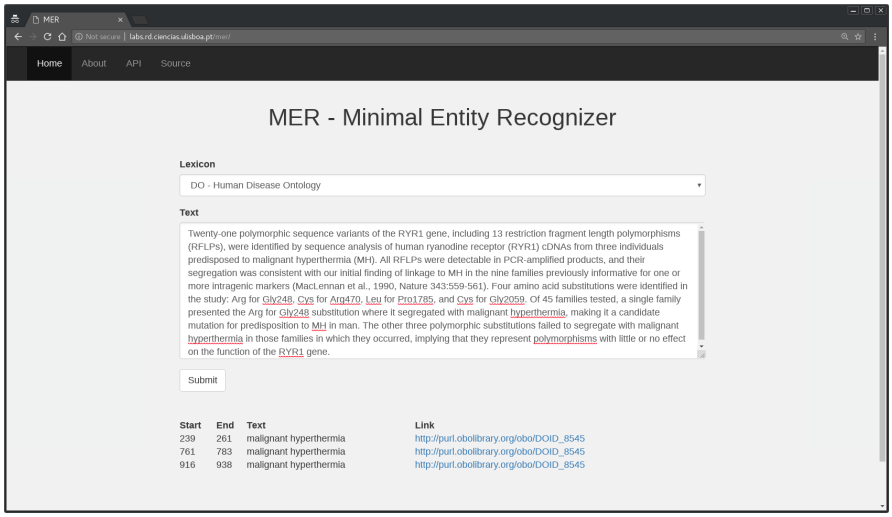


Fig. 3.9 Diseases recognized by the online tool MER in an abstract

To check if the abstract mentions any disease we can use an online text mining tool, for example the Minimal Named-Entity Recognizer (MER) [13]. We can copy and paste the abstract of the publication into MER and select *DO - Human Disease Ontology* as lexicon (see Figure 3.9).

We will see that MER detects three mentions of *malignant hyperthermia*, giving us another link [14] about the disease found (see Figure 3.10).

Thus, in summary, we started from a generic definition of *caffeine* and ended with an abstract about hyperthermia by following the links in different databases. Of course, this does not mean that by taking *caffeine* we will get hyperthermia, or that we will treat hyperthermia by taking *caffeine* (maybe as a cold drink ◡̈ [15]). However, this relation has a context, a protein and a publication, that need to be further analyzed before drawing any conclusions.

We should note that we only analyzed one protein and one publication, we now need to repeat all the steps to all the proteins and to all the publications related to each protein. And this could even be more complicated if we were interested in other central nervous system stimulants, for example by looking

[12] `https://www.uniprot.org/citations/1354642`

[13] `http://labs.rd.ciencias.ulisboa.pt/mer/`

[14] `http://purl.obolibrary.org/obo/DOID_8545`

[15] `https://en.wikipedia.org/wiki/Hyperthermia#Treatment`

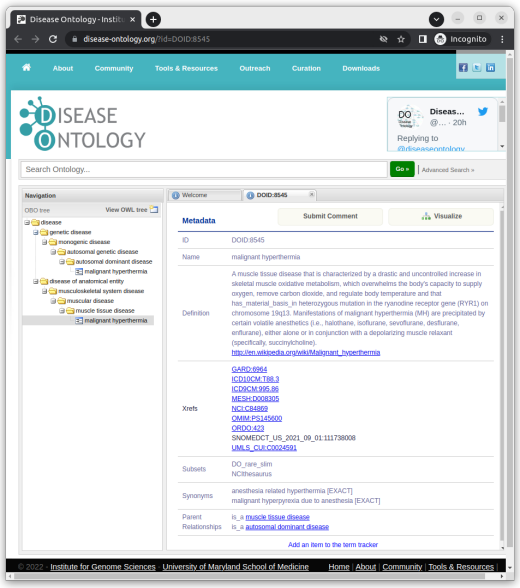


Fig. 3.10 Disease ontology entry for the class *malignant hyperthermia*

in the ChEBI ontology [16]. This is of course the motivation to automatize the process, since it is not humanly feasible to deal with such large amount of data, that keeps evolving every day.

However, if the goal was to find a relation between *caffeine* and hyperthermia, we could simply have searched these two terms in PubMed. We did not do that because some relations are not explicitly mention in the text, thus we have to navigate through database links. The second reason is because we needed an example using different resources and multiple entries to explain how we can automate most of these steps using shell scripting. The automation of the example will introduce a comprehensive set of techniques and commands, which with some adaptation Health and Life specialists can use to address many of their text and data processing challenges.

3.2 Unix shell

A shell is a software program that 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. This manuscript will introduce a few command line tools, which

[16] `https://www.ebi.ac.uk/chebi/chebiOntology.do?chebiId=35337`

will allow us to automatize the previous example. Unix shell was developed to manage Unix-like operating systems, but due to their usefulness nowadays they are available is most personal computers using Linux, macOS or Windows operating systems. There are many types of Unix shells with minor differences between them (e.g. sh, ksh, csh, and tcsh), but the most widely available is the Bourne-Again shell (bash [17]). The examples in this manuscript were tested using bash.

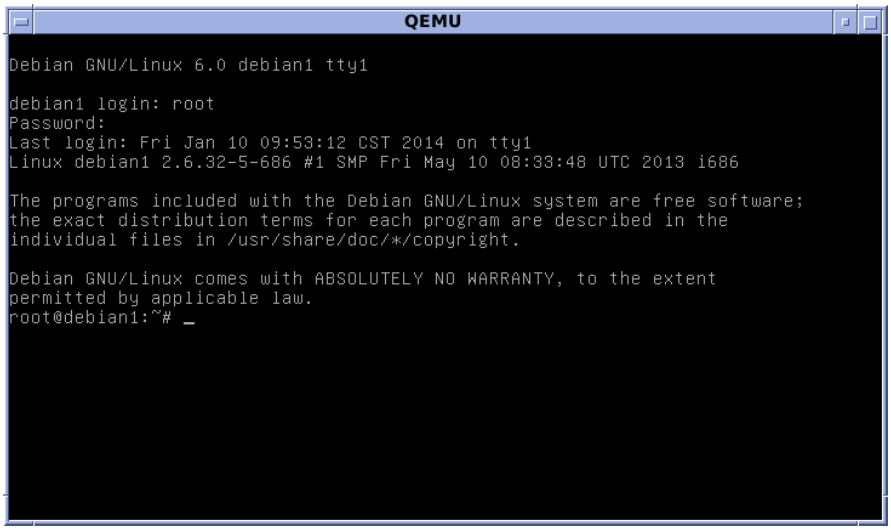


Fig. 3.11 Screenshot of a Terminal application (Source: `https://en.wikipedia.org/wiki/Unix`)

So, the first step is to open a shell in our personal computer using a terminal application (see Figure 3.11). If we are using Linux or macOS then this is usually not new for us, since most probably we have a terminal application already installed, that opens a shell for us. In case we are using a Microsoft Windows operating system, then we have several options to consider. If we are using Windows 10, then we can install a Windows Subsystem for Linux [18] or just install a third-party application, such as MobaXterm [19]. No matter which terminal application we end up using, the shell will always have a common look: a text window with a cursor blinking waiting for our first command line. We should note that most terminal applications allow the usage of the up and down cursor keys to select, edit, and execute previous commands, and the usage of the tab key to complete the name of a command or a file.

[17] `https://en.wikipedia.org/wiki/Bash_(Unix_shell)`

[18] `https://docs.microsoft.com/en-us/windows/wsl/about`

[19] `https://mobaxterm.mobatek.net/`

Current directory

As our first command line, we can type:

```
$ pwd
```

After hitting enter, the command will show the full path of the directory (folder) of our computer in which the shell is working on. The dollar sign in the left is only to indicate that this is a command to be executed directly in the shell. A curved arrow can appear in the right each time 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, such as `pwd`, we can type `man` followed by the name of the tool. For example, we can type `man pwd` to learn more about `pwd` (do not forget to hit enter, and press `q` to quit). We can also learn more about `man` by typing `man man`. A shorter alternative to `man`, is to add the `--help` option after any command tool. For example, we can type `pwd --help` to have a more concise description of `pwd`.

As our second command line, we can type `ls` and hit enter. It will show the list of files in the current directory. For example, we can type `ls --help` to have a concise description of `ls`. Since we will work with files, that we need to open with a text editor or a spreadsheet application [20], such as LibreOffice Calc or Microsoft Excel, we should select a current directory that we can easily open in our file explorer application. A good idea is to open our favorite file explorer application, select a directory, and then check its full path [21].

Windows directories

Notice that in Windows the full path to a directory each name is separated by a backslash (`\`) while in a Unix shell is a forward slash (`/`). For example, a Windows path to the Documents folder may look like:

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

If we are using the Windows Subsystem for Linux [22], the previous folder must be accessed using the path:

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

If we are using MobaXterm [23], the following path should be used instead:

---

[20] https://en.wikipedia.org/wiki/Spreadsheet

[21] https://en.wikipedia.org/wiki/Path_(computing)

[22] https://www.howtogeek.com/261383/how-to-access-your-ubuntu-bash-files-in-windows-and-your-windows-system-drive-in-bash/

[23] https://mobaxterm.mobatek.net/documentation.html

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

Change directory

To change the directory, we can use another command line tool, the `cd` (change directory) followed by the new path. In a Linux system we may want to use the *Documents* directory. If the *Documents* directory is inside our current directory (shown using `ls`), we only need to type:

```
$ cd Documents
```

Now we can type `pwd` to see what changed.

And if we want to return to the parent directory, we only need to use the two dots `..`:

```
$ cd ..
```

And if we want to return to the home directory, we only need to use the tilde character (∼):

```
$ cd ~
```

Again, we should type `pwd` to double check if we are in the directory we really want.

In Windows we may need to use the full path, for example:

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

We should note that we need to enclose the path within single (or double) quotes in case it contains spaces:

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

Later on, we will know more about the difference between using single or double quotes. For now, we may assume that they are equivalent. To know more about `cd`, we can type `cd --help`.

Useful key combinations

Every time the terminal is blocked by any reason, we can press both the control (Ctrl) and C key at the same time [24]. This usually cancels the current tool being executed. For example, try using the *cd* command with only one single quote:

```
$ cd '
```

[24] `https://en.wikipedia.org/wiki/Control`

This will block the terminal, because it is still waiting for a second single quote that closes the argument. Now press Ctrl-c, and the command will be aborted.

Now we can type again the previous command, but instead of pressing Ctrl-c we may also press Ctrl-d [25]. The combination Ctrl-d indicates the terminal that it is the end of input. So, in this case, the `cd` command will not be canceled, but instead it is executed without the second single quote and therefore a syntax error will be shown on our display.

Other useful key combinations are the Ctrl-l that when pressed cleans the terminal display, and the control-insert and shift-insert that when pressed copy and paste the selected text, respectively.

Shell version

The following examples will probably work in any Unix shell, but if we want to be certain that we are using bash we can type the following command, and check if the output says bash.

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

`ps` is a command line tool that shows information about active processes running in our computer. The `-p` option selects a given process, and in this case `$$` represents the process running in our terminal application. In most terminal applications bash is the default shell. If this is not our case, we may need to type `bash`, hit enter and now we are using bash.

Now that we know how to use a shell, we can start writing and running a very simple script that reverse the order of the lines in a text file.

Data file

We start by creating a file named *myfile.txt* using any text editor, and adding the following lines:

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

We cannot forget to save it in our working directory, and check if it has the proper filename extension.

[25] `https://en.wikipedia.org/wiki/End-of-Transmission_character`

File contents

To check if the file is really on our working directory, we can type:

```
$ cat myfile.txt
```

The contents of the file should appear in our terminal. `cat` is a simple command line tool that receives a filename as argument and displays its contents on the screen. We can type `man cat` or `cat --help` to know more about this command line tool.

Reverse file contents

An alternative to `cat` tool is the `tac` tool. To try it, we only need to type:

```
$ tac myfile.txt
```

In macOS the `tac` tool may not be available, but we can replace it by `tail -r`.

The contents of the file should also appear in our terminal, but now in the reverse order. We can type `man tac` or `tac --help` to know more about this command line tool.

My first script

Now we can create a script file named *reversemyfile.sh* by using the text editor, and add the following lines:

```
1 tac $1
```

We cannot forget to save the file in our working directory. `$1` represents the first argument after the script filename when invoking it. Each script file presented in this manuscript will include the line numbers in the left. This will helps us not only to identify how many lines the script contains, but also to distinguish a script file from the commands to be executed directly in the shell.

Additionally, we could add the shebang [26] `#!/bin/bash` as the first line of the script, which would specify that it should be executed using the Bash shell. However, for simplicity we will not use any shebang in this book.

[26] https://en.wikipedia.org/wiki/Shebang_(Unix)

Line breaks

A Unix file represents a single line break by a line feed character, instead of two characters (carriage return and line feed) used by Windows [27]. So, if we are using a text editor in Windows, we must be careful to use one that lets us save it as Unix file, for example the open source Notepad++ [28]. If we are using a text editor in macOS we also need to be careful in saving it in text format[29].

In case we do not have such text editor, we can also remove the extra carriage return by using the command line tool `tr`, that replaces and deletes characters:

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

The `-d` option of `tr` is used to remove a given character from the input, in this case `tr` will delete all carriage returns (`r`). Many command line options can be used in short form using a single dash (`-`), or in a long form using two dashes (`--`). In this tool, using the `--delete` option is equivalent to the `-d` option. Long forms are more self-explanatory, but they take longer to type and occupy more space. We can type `man tr` or `tr --help` to know more about this command line tool.

Redirection operator

The > character represents a redirection operator [30] that moves the results being displayed at the standard output (our terminal) to a given file. The < character represents a redirection operator that works on the opposite direction, i.e. opens a given file and uses it as the standard input.

We should note that `cat` received the filename as an input argument, while `tr` can only receive the contents of the file through the standard input. Instead of providing the filename as argument, the `cat` command can also receive the contents of a file through the standard input, and produce the same output:

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

The previous `tr` command used a new file for the standard output, because we cannot use the same file to read and write at the same time. To keep the same filename, we have to move the new file by using the `mv` command:

---

[27] https://en.wikipedia.org/wiki/Newline

[28] https://notepad-plus-plus.org/

[29] https://beebom.com/how-save-files-txt-format-textedit-mac/

[30] https://www.gnu.org/software/bash/manual/html_node/Redirections.html

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

We can type `man mv` or `mv --help` to know more about this command line tool.

Installing tools

These last two commands could be replaced by the `dos2unix` tool:

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

If not available, we have to install the `dos2unix` tool.

For example, in the Ubuntu Windows Subsystem we need to execute:

```
$ apt install dos2unix
```

The `apt` (Advanced Package Tool) command is used to install packages in many Linux systems [31]. Another popular alternative is the `yum` (Yellowdog Updater, Modified) command [32].

In macOS we can install the *The Missing Package Manager* [33], and then execute:

```
$ brew install dos2unix
```

To avoid fixing line breaks each time we update our file when using Windows, a clearly better solution is to use a Unix friendly text editor

When we are not using Windows, or we are using a Unix friendly text editor, the previous commands will execute, but nothing will happen to the contents of *reversemyfile.sh*, since the `tr` command will not remove any character. To see the command working replace `'r'` by `'$'` and check what happens.

Permissions

A script also needs permission to be executed, so every time we create a new script file we need to type:

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

The command line tool `chmod` just gave the user (`u`) permissions to execute (`+x`). We can type `man chmod` or `chmod --help` to know more about this command line tool.

Finally, we can execute the script by providing the *myfile.txt* as argument:

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

[31] `https://en.wikipedia.org/wiki/APT_(Debian)`

[32] `https://en.wikipedia.org/wiki/Yum_(software)`

[33] `https://brew.sh/`

The contents of the file should appear in our terminal in the reverse order:

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

Congratulations, we made our first script work! ☺

In case the terminal responds with a *Permission denied* error message, we need to check if the `chmod` was done correctly.

In case the terminal responds with a *failed to open myfile.txt* error message, we need to check if the *reversemyfile.sh* file was saved as a Unix text file, as explained above.

If we give more arguments, they will be ignored:

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

The output will be exactly the same because our script does not use `$2` and `$3`, that in this case will represent *myotherfile.txt* and *my other file.txt*, respectively. We should note that when containing spaces, the argument must be enclosed by single quotes.

Debug

If something is not working well, we can debug the entire script by typing:

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

Our terminal will not only display the resulting text, but also the command line tools executed preceded by the plus character (+):

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

Alternatively, we can add the `set -x` command line in our script to start the debugging mode, and `set +x` to stop it.

Save output

We can now save the output into another file named *mynewfile.txt* by typing:

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

Again, to check if the file was really created, we can use the `cat` tool:

```
$ cat mynewfile.txt
```

Or, we can reverse it again by typing:

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

Of course, the result should exactly be the original contents of *myfile.txt*.

3.3 Web Identifiers

The input argument(s) of our retrieval task is the chemical compound(s) of which we want to retrieve more information. For the sake of simplicity, we will start by assuming that the user knows the ChEBI identifier(s), i.e. the script does not have to search by the name of the compounds. Nevertheless, finding the identifier of a compound by its name is also possible, and this manuscript will describe how to do it later on.

So, the first step, is to automatically retrieve all proteins associated to the given input chemical compound, that in our example was *caffeine* (CHEBI:27732). In the manual process, we downloaded the files by manually clicking on the links shown as *Export options*, namely the URLs:

```
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
```

for downloading a CSV, Excel, or XML file, respectively.

We should note that the only difference between the three URLs is a single numerical digit (1, 2, and 3) after the first equals character (=), which means that this digit can be used as an argument to select the type of file. Another parameter that is easily observable is the ChEBI identifier (27732). Try to replace 27732 by 17245 in any of those URLs by using a text editor, for example:

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

Now we can use this new URL in the internet browser, and check what happens. If we did it correctly, our browser downloaded a file with more than seven hundred proteins, since the 17245 is the ChEBI identifier of a popular chemical compound in life systems, the *carbon monoxide*.

In this case, we are not using a fully RESTful web service, but the data path is pretty modular and self-explanatory. The path is clearly composed of:

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

The order of the parameters in the URL is normally not relevant. They are separated by the ampersand character (&) and the equals character (=) is used to assign a value to each parameter (argument). This modular structure of these URLs allows us to use them as data pipelines to fill our local files with data, like pipelines that transport oil or gas from one container to another.

Single and double quotes

To construct the URL for a given ChEBI identifier, let us first understand the difference between single quotes and double quotes in a string (sequence of characters). We can create a script file named *getproteins.sh* by using a text editor to add the following lines:

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

The command line tool `echo` displays the string received as argument. Do not forget to save it in our working directory and add the right permissions with `chmod` as we did previously with our first script.

Now to execute the script we will only need to type:

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

The output on the terminal should be:

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

This means that when using single quotes, the string is interpreted literally as it is, whereas the string within double quotes is analyzed, and if there is a special character, such as the dollar sign (`$`), the script translates it to what it represents. In this case, `$1` represents the first input argument. Since no argument was given, the double quotes displays nothing.

To execute the script with an argument, we can type:

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

The output on our terminal should be:

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

We can check now that when using double quotes `$1` is translated to the string given as argument.

Now we can update our script file named *getproteins.sh* to contain only the following line:

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

Comments

Instead of removing the previous lines, we can transform them in comments by adding the hash character (#) to the beginning of the line:

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

Commented lines are ignored by the computer when executing the script.

Now, we can execute the script giving the ChEBI identifier as argument:

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

The output on our terminal should be the link that returns the CSV file containing the proteins associated with *caffeine*.

3.4 Data Retrieval

After having the link, we need a web retrieval tool that works like our internet browser, i.e. receives as input a URL for programmatic access and retrieves its contents from the internet. We will use Client Uniform Resource Locator (cURL), which is available as a command line tool, and allows us to download the result of opening a URL directly into a file (`man curl` or `curl --help` for more information).

For example, to display in our screen the list of proteins related to *caffeine*, we just need to add the respective URL as input argument:

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

In some systems the `curl` command needs to be installed [34]. Since we are using a secure connection *https*, we may also need to install the *ca-certificates* package [35].

The output on our terminal should be the long list of proteins:

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

An alternative to `curl` is the command `wget`, which also receives a URL as argument but by default `wget` writes the contents to a file instead of displaying it on the screen (`man wget` or `wget --help` for more information). So, the equivalent command, is to add the `-O-` option to select where the contents is placed:

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

We should note that dash – character after `-O` represents the standard output. The equivalent long form to the `-O` option is `--output-document=file`.

Instead of using a fixed URL, we can update the script named *getproteins.sh* to contain only the following line:

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

We should note that now we are using double quotes, since we replaced the *caffeine* identifier by `$1`.

Now to execute the script we only need to provide a ChEBI identifier as input argument:

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

The output on our terminal should be the long list of proteins:

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

Or, if we want the proteins related to *carbon monoxide*, we only need to replace the argument:

```
$ ./getproteins.sh 17245
```

---

[34] `apt install curl`

[35] `apt install ca-certificates`

And the output on our terminal should be an even longer list of proteins:

```
...
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
```

If we want to analyze all the lines we can redirect the output to the command line tool `less`, which allows us to navigate through the output by using the arrow keys. To do that we can add the bar character (`|`) between two commands, which will transfer the output of the first command as input of the second:

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

To exit from `less` just press `q`.

However, what we really want is to save the output as a file, not just printing some characters on the screen. Thus, what we should do is redirect the output to a CSV file. This can be done by adding the redirect operator `>` and the filename, as described previously:

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

We should note that `curl` still prints some progress information into the terminal.

Standard error output

This happens because it is displaying that information into the standard error output, which was not redirected to the file [36]. The `>` character without any preceding number by default redirects the standard output. The same happens if we precede it by the number `1`. If we do not want to see that information, we can also redirect the standard error output (`2`), but in this case to the null device (`/dev/null`):

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

We can also use the `-s` option of `curl` in order to suppress the progress information, by adding it to our script file named *getproteins.sh*:

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

[36] `https://www.gnu.org/software/bash/manual/html_node/Redirections.html`

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

Now when executing the script, no progress information is shown:

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

To check if the file was really created and to analyze its contents, we can use the `less` command:

```
$ less chebi_27732_xrefs_UniProt.csv
```

We can also open the file in our spreadsheet application, such as LibreOffice Calc or Microsoft Excel.

As an exercise execute the script to get the CSV file with the associated proteins of water [37] and gold [38].

3.5 Data Extraction

Some data in the CSV file may not be relevant regarding our information need, i.e. we may need to identify and extract relevant data. In our case, we will select the relevant proteins (lines) using the command line tool `grep`, and secondly, we will select the column we need using the command line tool `gawk`, which is the GNU implementation of `awk` [39]. We should note that if we are using MobaXterm [40] or macOS [41] we may need to install the *gawk* package. We can also replace `gawk` by `awk` in case another implementation is available [42].

Since our information need is about diseases related to *caffeine*, we may assume that we are only interested in proteins that have one of these topics in the third column:

```
CC - MISCELLANEOUS
CC - DISRUPTION PHENOTYPE
CC - DISEASE
```

Extracting lines from a text file is the main function of `grep`. The selection is performed by giving as input a pattern that `grep` tries to find in each line, presenting only the ones where it was able to find a match. The pattern is the same as the one we normally use when searching for a word in our text editor. The `grep` command also works with more complex patterns such as regular expressions, that we will describe later on.

---

[37] `https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:15377`

[38] `https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:30050`

[39] `http://www.gnu.org/software/gawk/`

[40] `apt install gawk`

[41] `brew install gawk`

[42] `https://en.wikipedia.org/wiki/AWK#Versions_and_implementations`

Single and multiple patterns

We can execute the following command that selects the proteins with the topic `CC - MISCELLANEOUS`, our pattern, in our CSV file:

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

The output will be a shorter list of proteins, all with `CC - MISCELLANEOUS` as topic:

```
A2AGL3,Ryanodine receptor 3,CC - MISCELLANEOUS
B0LPN4,Ryanodine receptor 2,CC - MISCELLANEOUS
E9PZQ0,Ryanodine receptor 1,CC - MISCELLANEOUS
E9Q401,Ryanodine receptor 2,CC - MISCELLANEOUS
F1LMY4,Ryanodine receptor 1,CC - MISCELLANEOUS
P11716,Ryanodine receptor 1,CC - MISCELLANEOUS
P21817,Ryanodine receptor 1,CC - DISEASE; CC -
    MISCELLANEOUS
P54867,Protein SLG1,CC - MISCELLANEOUS
Q9TS33,Ryanodine receptor 3,CC - MISCELLANEOUS
Q15413,Ryanodine receptor 3,CC - MISCELLANEOUS
Q92736,Ryanodine receptor 2,CC - MISCELLANEOUS
```

To use multiple patterns, we must precede each pattern with the `-e` option:

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

The equivalent long form to the `-e` option is `--regexp=PATTERN`.

The output on our terminal should be a longer list of proteins:

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

We should note that as previously, we can add `| less` to check all of them more carefully. The `less` command also gives the opportunity to find lines based on a pattern. We only need to type `/` and then a pattern.

We can now update our script file named *getproteins.sh* to contain the following lines:

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

```
2 grep -e 'CC - MISCELLANEOUS' -e 'CC - DISRUPTION
    PHENOTYPE' -e 'CC - DISEASE'
```

We should note that we added the `-s` option to suppress the progress information of `curl`, and the characters `| \` to the end of line to redirect the output of that line as input of the next line, in this case the `grep` command. We need to be careful in ensuring that `\` is the last character in the line, i.e. spaces in the end of the line may cause problems.

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

Now we need to select just the first column, the one that contains the protein identifiers. Selecting columns from a tabular file is one easy task for `gawk`, that besides performing pattern scanning also provides a complex processing language (AWK [43]). This processing language can be highly complex [44] and it is out of our scope for this introductory manuscript. The `gawk` command can receive as arguments the character that divides each data element (column) in a line using the `-F` option, and an instruction of what to do with it enclosed by single quotes and curly brackets. The equivalent long form to the `-F` option is `--field-separator=fs`.

For example, we can get the first column of our CSV file:

```
$ gawk -F, '{ print $1 }' <
    chebi_27732_xrefs_UniProt_relevant.csv
```

We should note that comma (`,`) is the character that separates data elements in a CSV file, and that `print` is equivalent to `echo`, and `$1` represents the first data element.

The command will display only the first column of the file, i.e. the protein identifiers:

```
...
```

[43] `https://en.wikipedia.org/wiki/AWK`

[44] `https://www6.software.ibm.com/developerworks/education/au-gawk/au-gawk-a4.pdf`

```
Q9VSH2
Q15413
Q92736
```

For example, we can get the first and third columns separated by a comma:

```
$ gawk -F, '{ print $1 ", " $3}' < ↩
    chebi_27732_xrefs_UniProt_relevant.csv
```

Now, the output contains both the first and third column of the file:

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

We can update our script file named *getproteins.sh* to contain the following lines:

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

The last line is the only that changes, except the `| \` in the previous line to redirect the output.

To execute the script, we can type again:

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

The output should be similar of what we got previously, but now only the protein identifiers are displayed.

To save the output as a file with the relevant proteins' identifiers, we only need to add the redirection operator:

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

3.6 Task Repetition

Given a protein identifier we can construct the URL that will enable us to download its information from UniProt. We can use the RESTful web services provided by UniProt [45], more specifically the one that allow us to retrieve a

[45] `https://www.uniprot.org/help/api`

specific entry [46]. The construction of the URL is simple, it starts always by `https://rest.uniprot.org/uniprotkb/`, followed by the protein identifier, ending with a dot and the data format. For example, the link for protein *P21817* using the XML format is: `https://rest.uniprot.org/uniprotkb/P21817.xml`

Assembly line

However, we need to construct one URL for each protein from the list we previously retrieved. The size of the list can be large (hundreds of proteins), varies for different compounds and evolves with time. Thus, we need an assembly line in which a list of proteins identifiers, independently of its size, are added as input to commands that construct one URL for each protein and retrieve the respective file.

The `xargs` command line tool works as an assembly line, it executes a command per each line given as input. We should note that if we are using MobaXterm we may need to install the *findutils* package [47], since the default `xargs` only has minimal options [48]

We can start by experimenting the `xargs` command by giving as input the list of protein identifiers in file *chebi_27732_xrefs_UniProt_relevant_identifiers.csv*, and display each identifier on the screen in the middle of a text message by providing the `echo` command as argument:

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

The `xargs` command received as input the contents our CSV file, and for each line displayed a message including the identifier in that line. The `-I` option tells `xargs` to replace `{}` in the command line given as argument by the value of the line being processed. The equivalent long form to the `-I` option is `--replace=R`.

The output should be something like this:

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

Instead of creating inconsequential text messages, we can use `xargs` to create the URLs:

---

[46] `https://www.uniprot.org/help/api_retrieve_entries`

[47] `apt install findutils`

[48] In some versions the scripts may have to use `xargs.exe` to invoke the new version. Or rename the `xargs` shortcut in the bin folder to other name, that way the right version will always be invoked.

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

The output should be something like this:

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

We can try to use these links in our internet browser to check if those displayed URLs are working correctly.

Now that we have the URLs, we can automatically download the files using the `curl` command instead of `echo`:

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

We should note that we now use the `-o` option to save the output to a given file, named after each protein identifier. The equivalent long form to the `-o` option is `--output <file>`.

To check if everything worked as expected we can use the `ls` command to view which files were created:

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

The asterisk character (`*`) is here used to represent any file whose name starts with `chebi_27732_` and ends with `.xml`.

To check the contents of any of them, we can use the `less` command:

```
$ less chebi_27732_P21817.xml
```

File header

We should note that the content of every file has to start with `<?xml` otherwise there was a download error, and we have to run `curl` again for those entries. To check the header of each file, we can use the `head` command together with `less`.

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

The `-n` option specifies how many lines to print, in the previous command just one.

If for any reason, we are not able to download the files from UniProt, we can get them from the book file archive [49].

[49] `http://labs.rd.ciencias.ulisboa.pt/book/`

Variable

We can now update our script file named *getproteins.sh* to contain the following lines:

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

We should note that the last line now includes the `xargs` and `curl` commands, and the `$ID` variable. This new variable is created in the first line to contain the first value given as argument (`$1`). So, every time we mention `$ID` in the script we are mentioning the first value given as argument. This avoids ambiguity in cases where `$1` is used for other purposes, like in the `gawk` command. Since the preceding character of `$ID` is an underscore (_), we have to add a backslash (\) before it. The second line uses the `rm` command to remove any files that were downloaded in a previous execution. We also now added two comments after # character, so we humans do not forget why these commands are needed for.

To execute the script once more:

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

And again, to check the results:

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

3.7 XML Processing

Assuming that our information need only concerns human diseases, we have to process the XML file of each protein to check if it represents a *Homo sapiens (Human)* protein.

Human proteins

For performing this filter, we can again use the `grep` command, to select only the lines of any XML file that specify the organism as *Homo sapiens*:

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

We should get in our display the filenames that represent a human protein, i.e. something like this:

```
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>
```

We should note that since the asterisk character (`*`) provides multiple files as argument to `grep`, the ones whose name starts with `chebi_27732_` and ends with `.xml`, the output now includes the filename (followed by a colon) where each line was matched.

We can use the `gawk` command to extract only the filename, but `grep` has the `-l` option to just print the filename:

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

The equivalent long form to the `-l` option is `--files-with-matches`.

The output will now show only the filenames:

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

These four files represent the four Human proteins related to *caffeine*.

PubMed identifiers

Now we need to extract the PubMed identifiers from these files to retrieve the related publications. For example, if we execute the following command:

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

The output is a long list of publications related to protein *P21817*:

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

To extract just the identifier, we can again use the `gawk` command:

```
$ grep '<dbReference type="PubMed"' chebi_27732_P21817.xml | gawk -F\" '{ print $4 }'
```

We should note that `"` is used as the separation character and, since the PubMed identifier appears after the third `"`, the `$4` represents the identifier.

Now the output should be something like this:

```
...
11741831
16163667
27586648
```

PubMed identifiers extraction

Now to apply to every protein we may again use the `xargs` command:

```
$ grep -l '<name type="scientific">Homo sapiens</name>' chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed"' {} | gawk -F\" '{ print $4 }'
```

This may provide a long list of PubMed identifiers, including repetitions since the same publication can be cited in different entries.

Duplicate removal

To help us identify the repetitions, we can add the `sort` command (`man sort` or `sort --help` for more information), which will display the repeated identifiers in consecutive lines (due by sorting all identifiers):

```
$ grep -l '<name type="scientific">Homo sapiens</name>' chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed"' {} | gawk -F\" '{ print $4 }' | sort
```

For example some repeated PubMed identifiers that we should easily be able to see:

```
...
9607712
9607712
9607712
```

Fortunately, we also have the `-u` option that removes all these duplicates:

```
$ grep -l '<name type="scientific">Homo sapiens</name>' chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed"' {} | gawk -F\" '{ print $4 }' | sort -u
```

To easily check how many duplicates were removed, we can use the word count `wc` command with and without the usage of the `-u` option:

```
$ grep -l '<name type="scientific">Homo sapiens</name>' chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed"' {} | gawk -F\" '{ print $4 }' | sort | wc
$ grep -l '<name type="scientific">Homo sapiens</name>' chebi_27732_*.xml | xargs -I {} grep '<dbReference type="PubMed"' {} | gawk -F\" '{ print $4 }' | sort -u | wc
```

In case we have in our folder any auxiliary file, such as `chebi_27732_P21817_entry.xml`, we should add the option `--exclude *entry.xml` to the first `grep` command.

The output should be something like:

```
263     263    2315
133     133    1172
```

`wc` prints the numbers of lines, words, and bytes, thus in our case we are interested in first number (`man wc` or `wc --help` for more information). We can see that we have removed $263 - 133 = 130$ duplicates.

Just for curiosity, we can also use the shell to perform simple mathematical calculations using the `expr` command:

```
$ expr 263 - 133
```

Now let us create a script file named *getpublications.sh* by using a text editor to add the following lines:

```
1 ID=$1 # The CHEBI identifier given as input is renamed to ID
2 grep -l '<name type="scientific">Homo sapiens</name>' chebi\_$ID\_*.xml | \
3 xargs -I {} grep '<dbReference type="PubMed"' {} | \
4 gawk -F\" '{ print $4 }' | sort -u
```

Again, do not forget to save it in our working directory, and add the right permissions with `chmod` as we did previously with the other scripts.

To execute the script again:

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

We can verify how many unique publications were obtained by using the `-l` option of `wc`, that provides only the number of lines:

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

The output will be 133 as expected.

Complex Elements

Not always the XML elements are in the same line, as fortunately was the case of the PubMed identifiers. In those cases, we may have to use the `xmllint` command, a parser that is able to extract data through the specification of a XPath query, instead of using a single line pattern as in `grep`.

XPath

XPath (XML Path Language) is a powerful tool to extract information from XML and HTML documents by following their hierarchical structure. Check W3C for more about XPath syntax [50]. We should note that `xmllint` may not be installed by default depending on our operating system, but it should be very easy to do it [51] If we are using MobaXterm, then we need to install the `xmllint` plugin [52].

Namespace problems

In the case of our protein XML files, we can see that their second line defines a specific namespace using the xmlns attribute [53]:

```
<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">
```

This complicates our XPath queries, since we need to explicitly specify that we are using the local name for every element in a XPath query. For example, to get the data in each `reference` element:

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

[50] `https://www.w3schools.com/xml/xpath_syntax.asp`

[51] `apt install libxml2-utils`

[52] `https://mobaxterm.mobatek.net/plugins.html`

[53] `https://www.w3schools.com/xml/xml_namespaces.asp`

We should note that `//` means any path in the XML file until reaching a reference element. The square brackets in XPath queries normally represent conditions that need to be verified.

Only local names

If we are only interested in using local names there is a way to avoid the usage of `local-name()` for every element in a XPath query. We can identify the top-level element, in our case `entry`, and extract all the data that it encloses using a XPath query. For example, we can create the auxiliary file `chebi_27732_P21817_entry.xml` by adding the redirection operator:

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

The `--nsclean` removes the redundant namespace declaration in `entry`.

The new XML file now starts and ends with the `entry` element without any namespace definition:

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

Now we can apply any XPath query, for example `//reference`, on the auxiliary file without the need to explicitly say that it represents a local name:

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

The output should contain only the data inside of each reference element:

```
<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

The XPath syntax allow us to create many useful queries, such as:

- `//dbReference` - elements of type `dbReference` that are descendants of something; Result:

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

- `/entry//dbReference` - equivalent to the previous query but specifying that the `dbReference` elements are descendants of the `entry` element;
- `/entry/reference/citation/dbReference` - similar to the previous query but specifying the full path in the XML file, i.e. only `dbReference` elements descendants of `citation`, `reference` and `entry` elements;
- `//dbReference/*` - any child elements of a `dbReference` element; Result:

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

- `//dbReference/property[1]` - first `property` element of each `dbReference` element; Result:

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

- `//dbReference/property[2]` - second `property` element of each `dbReference` element; Result:

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

- `//dbReference/property[3]` - third `property` element of each `dbReference` element; Result:

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

- `//dbReference/property/@type` - all type attributes of the `property` elements; Result:

```
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 that have an attribute type equal to *protein sequence ID*; Result:

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

- `//dbReference/property[@type="protein sequence ID"]/@value` - the string assigned to each attribute *value* of the previous `property` elements; Result:

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

- `/entry/sequence/text()` - the contents inside the `sequence` element; Result:

```
MGDAEGEDEVQF...DCFRKQYEDQLS
```

We should note that to try the previous queries we only need to replace the string after the `--xpath` option of the previous `xmllint` command, such as:

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

Thus, an alternative way to extract the PubMed identifiers using `xmllint` instead of `grep`, would be something like this:

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

However, the output contains all identifiers in the same line and with the id label:

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

Previous versions of `xmllint` may print all the output in the same line. In that case, we need to add an extra `tr ' ' 'n'` command to split the output in multiple lines (one line per identifier).

Extracting XPath results

To extract the identifiers, we can use the `gawk` command:

```
$ xmllint --xpath '//dbReference[@type="PubMed"]/@id' ↩
    chebi_27732_P21817_entry.xml | gawk -F\" '{ print ↩
    $2 }'
```

The `gawk` command extracts the value inside the double quotes.

3.8 Text Retrieval

Now that we have all the PubMed identifiers, we need to download the text included in the titles and abstracts of each publication.

Publication URL

To retrieve from the UniProt citations service the publication entry of a given identifier, we can again use the `curl` command and a link to the publication entry. For example, if we click on the Format button of the UniProt citations service entry [54], we can get the link to the RDF/XML version. RDF [55] is a standard data model that can be serialized in a XML format. Thus, in our case, we can deal with this format like we did with XML.

We can retrieve the publication entry by executing the following command:

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

Alternatively, we can use the web service provided by PubMed at NCBI[56], by still using curl but with another link:

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

The result is in XML and we can replace the PubMed identifier 135464 by a comma separated list of identifiers, such has *2298749,1354642,8220422*.

Thus, we can now update the script *getpublications.sh* to have the following commands:

```
1 ID=$1 # The CHEBI identifier given as input is renamed
      to ID
2 rm -f chebi\_$ID\_*.rdf # Removes any previous files
3 grep -l '<name type="scientific">Homo sapiens</name>'
    chebi\_$ID\_*.xml | \
4 xargs -I {} grep '<dbReference type="PubMed"' {} | \
5 gawk -F\" '{ print $4 }' | sort -u | \
6 xargs -I {} curl 'https://rest.uniprot.org/citations
    /{}.rdf' -o chebi\_$ID\_{}.rdf
```

We should note that only the second and last lines were updated to remove and retrieve the files, respectively.

Now let us execute the script:

---

[54] https://rest.uniprot.org/citations/1354642

[55] https://www.w3.org/RDF/

[56] https://www.ncbi.nlm.nih.gov/books/NBK25499/#chapter4.EFetch

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

It may take a while to download all the entries, but probably no more than one minute with a standard internet connection.

To check if everything worked as expected we can use the `ls` command to view which files were created:

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

If for any reason, we are not able to download the abstracts from UniProt, we can get them from the book file archive [57].

Title and Abstract

Each file has the title and abstract of the publication as values of the `title` and `rdfs:comment` elements, respectively. To extract them we can again use the `xmllint` command:

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

The output should be something like these two lines:

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

To remove the XML elements, we can again add `text()` to the XPath query:

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

The output should now be free of XML elements:

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

Thus, let us create the script *gettext.sh* to have the following commands:

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

Again do not forget to save it in our working directory, and add the right permissions.

Now to execute the script and see the retrieved text:

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

[57] `http://labs.rd.ciencias.ulisboa.pt/book/`

We can save the resulting text in a file named *chebi_27732.txt* that we may share or read using our favorite text editor, by adding the redirection operator:

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

Disease Recognition

Instead of reading all that text to find any disease related with *caffeine*, we can try to find sentences about a given disease by using `grep`:

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

To save the filtered text in a file named *chebi_27732_hyperthermia.txt*, we only need to add the redirection operator:

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

This is a very simple way of recognizing a disease in text. The next chapters will describe how to perform more complex text processing tasks.

3.9 Further Reading

If we really want to become an expert in shell scripting we may be interested in reading a book specialized in the subject, such as the book entitled *The Linux command line: a complete introduction* [Shotts Jr, 2012].

A more pragmatic approach is to explore the vast number of online tutorials about shell scripting and web technologies, such as the ones provided by W3Schools [58]

[58] `https://www.w3schools.com/`

Chapter 4
Text Processing

In the previous chapter we were able to automatically process structured data to retrieve biomedical text about any chemical compound, such as *caffeine*. This chapter will provide a step-by-step introduction to how we can process that text using shell script commands, specifically extract information about diseases related to *caffeine*. The goal is to equip the reader with an essential set of skills to extract meaningful information from any text.

4.1 Pattern Matching

We used the `grep` command in the last chapter to find a disease in the text, since `grep` receives as argument a pattern to find an exact match in the text, like any search functionality provided by conventional text editors. However, we may need to search for multiple patterns even when interested in a single disease. For example, when searching for mentions of *malignant hyperthermia*, we may also be interested in finding mentions using related expressions, such as:

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

Since we already know how to deal with multiple patterns by using the `-e` option, we may easily solve this problem by executing:

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

Case insensitive matching

When dealing with text, using a case sensitive search is usually a good approach to avoid wrong matches. For example, acronyms are normally in upper case, while the full name is usually in lowercase having sometimes the first letter of each word (or only the first word) in uppercase. So, instead of using a full case sensitive `grep`, we might think on performing a case sensitive `grep` for the acronyms and a case insensitive `grep` for the disease words using the `-i` option:

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

The equivalent long form to the `-i` option is `--ignore-case`. We should note that each execution of `grep` will produce two separate lists of matching lines that might be overlapped.

Alternatively, we can also convert it to just one case sensitive `grep`, if we are sure that *Malignant hyperthermia* is the only alternative case to *malignant hyperthermia* present in the text. So, we can add it as another pattern:

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

Number of matches

To be sure that we are not losing any match, we can count the number of matching lines for both cases. First we execute a case insensitive `grep` and then we execute a case sensitive `grep`, both using the `-c` option:

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

The equivalent long form to the `-c` option is `--count`.

In our case, the output should show 100 and 98 matching lines for the insensitive and sensitive patterns, respectively.

This means that there is two lines that were not caught by the case sensitive pattern. To identify them, we can manually analyze each of the 100 matching lines one by one. But the goal of this book is exactly avoiding these type of tedious tasks. One thing we can do to solve this issue is to find from the case insensitive matches the one that do not match the case sensitive patterns.

Invert match

Fortunately, the `grep` command has the `-v` option that inverts the matching and returns the lines of text that do not contain any matching. The equivalent long form to the `-v` option is `--invert-match`.

Thus, if we apply the inverted match with the case sensitive patterns to the output given by the case insensitive matching, we will get our outlier mention:

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

From the output, we can easily identify the missing matching lines:

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

We were missing the case where both words have the first letter in uppercase.

Thus, to obtain all the matching lines in a case sensitive match we just have to include the missing match as another pattern:

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

File Differences

Another alternative to compare different matches, is to use the `diff` command that receives as input two files and identifies their differences. So, we can create two auxiliary files and then apply the `diff` to them:

```
$ 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
```

The output should be the same text.

A problem that may occur with case sensitive matching is that some acronyms are defined with lowercase letters in the middle, such as ChEBI, and humans are not consistent with the way they mention them. The same acronym may be mentioned in their original form or with all letters in uppercase, or just some of them. Moreover, these inconsistent mentions sometimes may even be found in the same publication. We hope not in this book! ☺

Evaluation metrics

These inconsistencies made by humans when mentioning case sensitive expressions, is one of the reasons that most online search engines use case insensitive searches as default. This type of approach favors recall, while case sensitive search favor precision [1].

Recall is the proportion of the number of correct matches found by our tool over the total number of correct mentions in the texts (found or not found). Case insensitive searches avoid missing mentions, so they favor recall.

Precision is the proportion of the number of correct matches found by our tool over the total number of matches found (correct or incorrect). Case sensitive searches avoid incorrect matches, so they favor precision.

Normally, there is a trade-off between precision and recall. Using a technique that improves precision, most of the times, will decrease recall, and vice-versa. To know how good the trade-off is, we can use the F-measure, which is the harmonic average of the precision and recall [2].

Word Matching

Acronyms (or terms) may also appear inside common words or longer acronyms. For example, when searching for *MH*, the word *victi**mh**ood* will produce a match:

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

The problem with *victi**mh**ood* could be easily solved by using case sensitive matching, but not for a longer acronym. For example, the acronym NEDMHM for *neurodevelopmental disorder with midbrain and hindbrain malformations* will produce a case sensitive match:

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

One way to address this problem is to use the `-w` option of `grep` to only match entire words, i.e. the match 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). The equivalent long form to the `-w` option is `--word-regexp`.

Using this option, neither *victimhood* or *NEDMHM* will produce a match:

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

Word matching improves precision but decreases recall, since we may miss some less common acronyms that we are not aware of, but are still relevant

[1] https://en.wikipedia.org/wiki/Precision_and_recall

[2] https://en.wikipedia.org/wiki/F1_score

for our study. For example, consider that we may also be interested in the following acronyms:

MHE	: acronym for *malignant hyperthermia equivocal*
MHN	: acronym for *malignant hyperthermia normal*

If we apply word matching, we will not get a match, since both exact matches are followed by a letter:

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

These are not trivial problems to solve by exact pattern matching, we may need regular expressions to address some of these issues more efficiently.

4.2 Regular Expressions

When dealing with natural language text we may need more flexibility than the one provided by exact matching. Regular expressions are an efficient tool to extend exact matching with flexible patterns, that may find different matches. As an example, we may be interested in finding all the mentions of the acronym MHS or MHN in a text. For doing that, regular expressions provide the alternation operator that helps us to solve this issue easily by specifying multiple alternatives to match in a specific part of the pattern, in this case an *S* or an *N* as the last character.

Regular expressions can be better understood by clearly separating three distinct components:

input	: any string where we want to find something
pattern	: a string that specifies what we are looking for
match	: a fragment of the input (a substring) where the pattern can be found

In our examples, the input is the text file *chebi_27732.txt*, but it can be the amino acid sequences that we previously extracted from the UniProt file entries. Until now the pattern has represented an exact string to look for, where each match is an exact replica of the pattern occurring at a given position of the input string. When using regular expressions, the pattern contains special characters, whose purpose are not to directly match with the input but instead have a special meaning. These special characters represent operators that specify which different types of strings we want to find in the input. For example, strings that start with *MH* and end with *S* or an *N*. By using regular expressions, the matches are not replicas of the pattern, they can be different strings as long as they satisfy the specified pattern.

Extended syntax

The `grep` command allows us the possibility to include regular expression operators in the input pattern. `grep` understands two different versions of regular expression syntax: basic and extended [3]. We will use the extended syntax for two reasons: (i) the basic does not support relevant operators, such as alternation; (ii) and to clearly differentiate exact matching from regular expression matching. Thus, we will start to use the `-E` option, which makes the command interpret the pattern as an extended regular expression. The equivalent long form to the `-E` option is `--extended-regexp`. We should note that this option does not affects the matching when using a pattern without any regular expression operator, such as `MH`. For example, the following commands will produce the same results:

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

Note, that we use the `-e` option so the `echo` command interpret the `\n` characters as a newline. Thus, the `echo` command outputs two lines, that are given as input to the `grep` command. We should note that the `grep` command filters lines.

4.2.1 Alternation

The first regular expression operator we will test is the alternation, which we introduced above. An alternation is represented by the bar character (`|`) that specifies a pattern where any match must include either the preceding or following characters. The preceding and following characters can be enclosed within parentheses to better specify the scope of the alternation operator. For example, the pattern for finding strings that start with *MH* and end with *S* or an *N* can be written as:

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

We can also use multiple patterns using the `-E` option:

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

Basic syntax

If we use the basic regular expression syntax no match will be found, since the alternation operator is not supported:

[3] `https://www.regular-expressions.info/posix.html`

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

We will have a match only if the `|` and the parentheses are in the input string, since it is not interpreted as an operator:

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

Scope

To better understand the scope of an alternation, we can remove the parentheses from the pattern and add the `-w` option:

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

We only get the first line. This is explained because the alternation operator is applied to all the preceding characters, i.e. the `grep` will search for the *MHS* word or the *N* word. If we add a single *N* to the input string we already get another match:

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

We can also move the opening parenthesis one character to the left:

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

Only *MHS* is now displayed, since the alternative now represents *MN* without the *H*.

Multiple alternatives

We are not limited to two alternatives, we can have multiple `|` operators in a pattern. For example, the following command will find any of the three acronyms *MHS*, *MHE* or *MHN*:

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

We can now transform our previous `grep` command with multiple case sensitive patterns:

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

in a `grep` command with a single pattern using alternation:

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

And we will obtain the same 100 matching lines.

4.2.2 Multiple characters

A useful regular expression feature is that we can use the dot character (.) to represent any character, so if we want to find all the acronyms that start with *MH* we can execute the following command:

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

We should note that we use the `-o` option of the command `grep` so it just displays the matches and not all the line that includes the match. The equivalent long form to the `-o` option is `--only-matching`.

The output will be the following three-character lines:

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

The `-o` option also solves the problem of counting the total number of matches, and not just the number of lines with a match:

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

The output will show that 164 matches were found in 47 lines. The `-c` option overrides the `-o` option, i.e. if we use both in the same `grep` the output will be just the number of lines.

If we really want to match only the dot character, we have to precede it with a backslash character (`\`):

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

Now only the *MH.* will be displayed.

We can check that there are some matches that are not really acronyms, such as *MH)* and *MH,*.

Spaces

We should note that *MH* appears because the space character can also be matched. For example, the following text includes a word match with *MH*␣ since the parenthesis is considered a word delimiter character (not a letter, digit or underscore) :

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

On the other hand, the following text does not include a word match with *MH␣*:

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

Thus, what we really want is matches where the third character is a letter or a numerical digit.

Sometimes, the text includes other characters that also represent horizontal or vertical space in typography, such as the tab character. All these characters are known as whitespaces and can be represented by the expression `\s` in a pattern [4]. The following command demonstrates that both the space and the tab characters are matched by `\s`:

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

Groups

Fortunately, the regular expressions include the group operator that let us easily specify a set of characters. A group operator is represented by a set of characters enclosed within square brackets. Any of the enclosed characters can be matched.

For example, the previous command to find any of the three acronyms can be replaced by:

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

We should note that only one of the three letters, *S*, *N* or *E* will be matched in the input string.

Ranges

Still, this is not solving our need to only match letters or digits. However, we can also specify characters ranges with the dash character (-). For example, to find all the acronyms that start with *MH* followed by any alphabet letter:

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

This will result in only three acronyms:

```
MHE
MHN
MHS
```

We should note that `A-Z` represents any alphabet letter in uppercase, a lowercase letter will not be matched:

---

[4] `https://en.wikipedia.org/wiki/Whitespace_character`

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

The output will be only one line:

```
MHS
```

If we intend to keep the usage of a case sensitive `grep` and at the same time find lowercase matches, then we need to add the `a-z` range:

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

The output will be both lines:

```
MHS
MHs
```

We should note that the dot character inside a range represents itself and not any character:

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

The output will be only the last line:

```
MH.
```

Additionally, to include the acronyms that end with a numerical digit we need to add the `0-9` range:

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

Finally, we have the correct list of all three character acronyms starting with *MH*:

```
MH1
MH2
MHE
MHN
MHS
```

Negation

Another frequent case is the need to match any character with a few exceptions. For example, if we need to find all the matches that start with *MH* followed by any character except an alphabet letter. Fortunately, we can use the negation feature within a group operator. The negation feature is represented by the circumflex character (`^`) right next to the left bracket. The negation means that all the characters and ranges enclosed within the brackets are the ones that cannot be matched. Thus, a solution to the above example is to add the `A-Z` range after the circumflex:

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

We can see that all of the three acronyms *MHS*, *MHE* or *MHN* will be missing from the output:

```
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
```

4.2.3 Quantifiers

Above we were interested in finding acronyms composed of exactly three characters. However, we may need to find all acronyms that start with *MH* independently of their length. This functionality is also available in regular expressions using the quantifiers operators.

Optional

The simplest quantifier is the optional operator that is specified by an item followed by the question mark character (?). The item can be a character, an operator or a sub-pattern enclosed by parentheses. That item becomes optional for matching, i.e. a match can either contain that item or not.

For example, to find all the acronyms starting with *MH* and followed by one alphabetic letter or none:

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

Given that the third character is optional the output will include the two-character acronym *MH*, but not the *MH␣* match:

```
MH
MH1
```

```
MH2
MHE
MHN
MHS
```

We can add the space character to the group:

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

Now the output includes the two-character acronym *MH* and the *MH␣* match:

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

Multiple and optional

To find all the acronyms independently of their length, we can use the asterisk character (*). The preceding item becomes optional and can be repeated multiple times. For example, to find all the acronyms starting with *MH* and which may be followed any number of alphabetic letters or numeric digits:

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

The output now includes the four-character acronym *MHS1*:

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

We should note that the `grep` command uses a greedy approach, i.e. it will try to match as many characters as possible. For example, the following command will match *MH1* and not *MH*:

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

Multiple and compulsory

To make the preceding item compulsory and able to repeat it multiple times, we may replace the asterisk by the plus character (+). For example, the following pattern will find all the acronyms starting with *MH* followed by at least one alphabetic letter or numeric digit:

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

We should note that the output does not contain the two character acronym *MH*:

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

All options

The above quantifiers are the most popular, but the functionality of all of them can be reproduced by using curly braces to specify the minimal and maximum number of occurrences. The item is followed by an expression of the type `{n,m}` where `n` and `m` are to be replaced by a number specifying the minimum and maximum number of occurrences, respectively. `n` and `m` may also be omitted, which means that no minimum or maximum limit is to be imposed.

Using curly brackets, the question mark character (?) can be replaced by `{0,1}`. Thus, the following two patterns are 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
```

The asterisk character (*) can be replaced by `{0,}`. Thus, the following two patterns are 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
```

The plus character (+) can be replaced by `{1,}`. Thus, the following two patterns are 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
```

On the other hand using `{1,1}` is the same as not having any operator. Thus, the following two patterns 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
```

The previous commands display the all the three-character acronyms:

```
MH1
MH2
MHE
MHN
MHS
```

For example, if we are looking for acronyms with exactly 4 characters then we can apply the following pattern:

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

We should note that we use `2` as both the minimum and maximum since *MH* already count as 2 characters.

The output of the previous command is now the four-character acronym:

```
MHS1
```

4.3 Position

Sometimes besides the match, we are also interested in limiting the matches to specific parts of the input string. For example, to identify start and stop codons in a protein sequence, we need to limit the matches to the beginning or the end of the sequence. In text, we may for example be interested in lines starting with a name of a disease. To take in account the position of a match, regular expressions patterns can start with the circumflex character (`^`) and/or end with the dollar sign character (`$`).

If the pattern starts with a circumflex then only matches at the beginning of the line will be considered. On the other hand, if the pattern ends with a dollar then only matches at the end of the line will be considered.

Beginning

For example, if we are looking for lines starting with *Malignant Hyperthermia* we can use the following pattern:

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

The output will include the list of lines beginning with a mention to *Malignant Hyperthermia*:

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

To check how many of the matching lines were filtered, we can count the number of occurrences when using the circumflex and when not:

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

The output will show that only 20 of the 100 matches were considered.

Ending

If we are looking for lines ending with a mention to *Malignant Hyperthermia*, then we can add the dollar character to the end of the pattern:

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

To allow a punctuation character before the end of the line, we added the dot character before the dollar character in the pattern. The dot character matches any character, including the dot itself.

The output will be the list of lines ending with a mention to *Malignant Hyperthermia*:

```
...
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.
```

We can check how many lines were filtered by using again the `-c` option:

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

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

The output will show that only 15 of the 100 matches were at the end of the line.

Near the end

Sometimes we do not want the mention ending exactly at the last character. We may be more flexible and allow a following expression, or a given number of characters. For example, to allow 10 other characters between the end of the line and the mention of *Malignant Hyperthermia*, we can add a quantifier to the dot operator:

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

The output will show that we have 20 matches.

If we remove the `-c` option, we will be able to check that words, such as *families* and *patients*, are now allowed to appear between the mention of *Malignant Hyperthermia* and the end of the line:

```
...
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

To allow a word in between, independently of its length, we can add to the pattern an optional sequence of non-space characters (the word) preceded by a space:

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

The output will show that we have 24 matches. We should note that the `[^ ]` operator avoids having two words.

If we remove the `-c` option, we will be able to check that lengthy words (with more than 10 characters), such as *susceptibility*, are now allowed to

appear between the mention of *Malignant Hyperthermia* and the end of the line:

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

Full line

If we want lines that start with a mention to *Malignant Hyperthermia* and end with an acronym, *MH* or *MHS*, then we can execute two `grep` commands. The first gets the lines starting with *Malignant Hyperthermia* and the next filters the output of the latter with lines ending with an acronym:

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

Alternatively, we can add both the circumflex and dollar operators to the same pattern. However, we cannot forget to add `.*` to match anything in between them, since we are asking full line matches:

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

We can see that both commands match all the text of the abstract since each abstract is stored in a single line of the file:

```
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.
```

This demonstrates the problem of tokenization, since usually what we really need is to match a full sentence or a phrase. And in that case each line should represent a sentence or phrase from the abstract.

Match position

For more advanced processing, we may be interested in knowing the exact position of the matches in a given line. This can be done by using the `-b` option of `grep`, which provides the number of bytes in the line before the start of the match:

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

The equivalent long form to the `-b` option is `--byte-offset`.

The output shows the list of matches preceded by their position:

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

The same result happens if the input is given in multiple lines:

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

We have the exact same result because the newline character counts the same as the space.

4.4 Tokenization

As we have shown in the previous section, sometimes we need to work at the level of a sentence and not use a full document as the input string. Tokenization is a Natural Language Processing (NLP) task that aims at identifying boundaries in the text to fragment it into basic units called tokens. These tokens can be sentences, phrases, multi-word expressions, or words.

Character delimiters

In most languages, some specific characters can be considered as accurate boundaries to fragment text into tokens. For example, the space character to identify words; the period (.), the question mark (?) and the exclamation mark (!) to identify the ending of a sentence; and the comma (,), the semicolon (;), the colon (:) or any kind of parenthesis to identify a phrase within a sentence. However, this problem may be more complex in languages without explicitly delimiters, such as Chinese [Wu and Fung, 1994].

A common approach to tokenization is to use regular expressions to replace these delimiters by newline characters. This will result in a token per line. For example, we can replace the characters specifying the end of a sentence with a newline by using the `tr` command and then count the number of lines:

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

We get 1618 lines from the original 255 lines:

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

Unfortunately, this is not just so simple. We need to analyze the output:

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

Wrong tokens

We can check that: i) many lines are empty because an extra newline character will be added to the last sentence, and ii) the dot character is also used as a decimal mark in a number, then some sentences are split in multiple lines because they have decimal number in them. For example, the original sentence:

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

is split in two lines:

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

String Replacement

This means that looking at just one character is not enough, we need some context. For performing this, we will use the `sed` command that we may consider as a more powerful version of the `tr` command. The `sed` command is a stream editor that can receive as input a string and perform basic text transformations, such as replace one expression by another, that are available in almost all text editors. For example, we can use a simple `sed` to convert every mention of *caffeine* by its ChEBI identifier:

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

The `-E` option allow us to use extended regular expressions, like we used before in `grep`. The `s` option has the following syntax `'s/FIND/REPLACE/FLAGS'`, where: `FIND` is the pattern to find in the input string; `REPLACE` the expression to replace the matches; `FLAGS` are multiple options, such as `g` to replace all matches in each line and not just the first one, and `i` to be case insensitive.

For example, the original fragment of text:

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

will be converted to:

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

Multi-character delimiters

To replace the delimiter characters by a newline when followed by at least one space character, we can use the following command:

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

We should note that by making compulsory a space character, we avoid: i) empty lines by splitting a sentence that is already at the end of the line (assuming there are no ghost space characters at the end of each line), and ii) decimal markers because they are followed by numerical digits and not spaces.

We now get 1092 lines from the original 255 lines:

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

Keep delimiters

The previous `sed` command is removing the delimiter characters from the text, and this may cause other problems. A better solution is to keep the delimiter characters and just add the newline. The `sed` command allows us to keep each match for a specific part of the pattern (sub-pattern) by enclosing it within parentheses. To include the match of a sub-pattern in the replace expression, we can use the backslash and its numerical order. Thus, we can improve our `sed` command by using this technique so we do not remove any delimiter character:

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

The `\1` represents the match for the sub-pattern `([.!?])`, and the `\2` represents the match for the sub-pattern `( +)`. This means that a newline character is inserted right after each delimiter character found, and keeping the space characters.

For example, the original fragment of text:

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

will be converted to:

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

However, other common issues may still persist:

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

These sentences include a HTML elements.

To minimize this issue, we can change the pattern to add the option of `&` character besides the space:

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

We now get 1179 lines, i.e. this pattern is more flexible and was able to split more 87 sentences. *expr*1179 – 1092

This does not mean that is free of errors. It is almost impossible to derive a rule that covers all the possible typos humans can 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
```

Fig. 4.1 Identifying multiple spaces at the beginning of a sentence using regular expressions (Adapted from: `https://en.wikipedia.org/wiki/Regular_expression`)

As an example, the Figure 4.1 show a complex pattern adapted from Wikipedia. The pattern is equivalent to `\. {2,}[A-Z]`, and identifies multiples spaces at the beginning of a sentence. The pattern requires at least two spaces to be matched, but only after a period and before an uppercase letter.

Sentences file

Using our previous pattern, we can update our script named *gettext.sh* to provide the text already split in sentences by adding the `sed` command:

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

To save the output as a file named *chebi_27732_sentences.txt*, we only need to add the redirection operator:

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

Each line of the file *chebi_27732_sentences.txt* represents a sentence.

4.5 Entity recognition

To select the sentences with one of our acronyms, we can use the `grep` command and our sentences file:

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

The output will only include matching sentences:

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

Alternatively, we can use the `-n` option to get the number of the line and the `-o` option to get the acronym matched :

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

The equivalent long form to the `-n` option is `--line-number`. The output should be something like this:

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

We can also add the `-b` option to get the exact position of the acronym matched:

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

The output now contains the number of the line, the character position, and the match:

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

We can now make a script that receives a pattern as argument and the input text as the standard input, to display the line numbers and the matches in a TSV format. Thus, let us create a script file named *getentities.sh* with the following lines:

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

Again we should not forget to save the file in our working directory, and add the right permissions with `chmod`, as we did with our scripts in the previous chapter.

The first line stores the pattern given as argument in the variable `PATTERN`. The `grep` command finds the matches and the `tr` command replaces each colon by a tab character to produce TSV content.

We can now execute the script giving the pattern as argument and the sentences file as standard input:

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

The output should be something like this:

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

We should note that now we have the values separated by a tab character, i.e. the output is in TSV format.

The output can also be saved as a TSV file that we can open directly in our preferred spreadsheet application. For example, to save it as *chebi_27732.tsv*, we only need to add the redirection operator:

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

Select the sentence

If we want to analyze a specific matched sentence, we can use a text editor and go to that line number. A more efficient alternative is to use the print `p` option of `sed` to output a given line number. For example, to check the *MHS* match at line 2:

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

Now we can easily check the context of the match:

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

4.6 Pattern File

The script created in the previous section only accepts one pattern, however we may need to recognize different entities, or different mentions of the same entity, such as the official name, possible synonyms, and the acronyms. Fortunately, `grep` allows us to include a list of patterns directly from a file

using the `-f` option. The equivalent long form to the `-f` option is `--file=FILE`. For example, we can create a text file named *patterns.txt* with the following three patterns:

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

Then we can execute the previous `grep` but using multiple patterns specified in the pattern file:

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

Analyzing the output, we can check that the same sentences may include different entities:

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

We can now update our script named *getentities.sh* to receive as input not a single pattern but the filename where multiple patterns can be found.

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

We can execute the script giving as argument the file containing the patterns:

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

To save the output as a file named *chebi_27732.tsv*, we only need to add the redirection operator:

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

Using the *patterns.txt* file is very useful if for example we are not focused in a single disease, and we want to find any disease mentioned in the text. In these cases, we have to create a file with the full lexicon of diseases. This topic will be addressed in the following chapter.

4.7 Relation Extraction

Finding the relevant entities in text is sometimes not enough. We need to know which sentences may describe possible relationships between those entities, such as a relation between a disease and a compound.

This a complex text mining challenge, but a simple approach is to construct a pattern that allow any kind of characters between two entities:

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

The following sentence is one of the eight displayed sentences mentioning a possible relation:

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

However, we are missing all the sentences that have *caffeine* first:

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

We will be able to see that sometimes *caffeine* comes first:

```
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

The most flexible approach is use two `grep` commands. The first selects the sentences mentioning one of the entities, and the other selects from the previously selected sentences the ones mentioning the other entity. For example, we can first search for the acronyms and then for *caffeine*:

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

This will show all the ten sentences mentioning *caffeine* and an acronym.

Relation type

If we are interested in a specific type of relationship, we may have an additional filter for a specific verb. For example, we can add a filter for sentences with the verb *response* or *diagnosed*:

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

We should note that this does not take in account where the verb appears in the sentence. For example, in the following sentence the verb *response* appears first than any of the two entities:

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

If the verb needs to appear between the two entities, we have to construct a pattern that have these words in the middle of them:

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

We can see now that the previous sentence (line 50) is not presented as a match.

Remove relation types

We may also be interested in ignoring specific type of relations. To do that, we only need to use the `-v` (or `--invert-match`) option. For example, to ignore sentences with the word *response* or *diagnosed*:

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

All the resulting sentences do not mention *response* or *diagnosed*.

4.8 Further Reading

If we want to have a deeper knowledge about text processing tasks and challenges, we may be interested in reading some chapters of the book entitled *Speech and language processing* [Jurafsky and Martin, 2014]. The book is a highly specialized document explaining in full detail the topics here briefly described.

To have an overview about the state-of-art in text processing tools using biomedical literature, we should consider reading a recent and comprehensive survey [Lamurias and Couto, 2019].

Chapter 5
Semantic Processing

In the previous chapter we were able to automatically process text by recognizing a limited set of entities. This chapter will introduce the world of semantics, and present step-by-step examples to enhance text and data processing by using semantics. The goal is to equip the reader with the basic set of skills to explore semantic resources that are nowadays available using simple shell script commands.

5.1 Classes

In the previous chapters we searched for mentions of *caffeine* and *malignant hyperthermia* in text. However, we may miss related entities that may also be of our interest. These related entities can be found in semantic resources, such as ontologies. The semantics of *caffeine* and *malignant hyperthermia* are represented in *ChEBI* and *DO* ontologies, respectively.

OWL files

Thus, we can start by retrieving both ontologies, i.e. their 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
```

The `-O` option saves the content to a local file named according to the name of the remote file, usually the last part of the URL. The equivalent long form to the `-O` option is `--remote-name`. The option `-L` enables the `curl` com-

mand to follow a URL redirection [1]. The equivalent long form to the `-L` option is `--location`.

The previous commands will create the files *chebi_lite.owl* and *doid.owl*, respectively.

We should note that these links are for the specific releases used in this book. Using another release may change the output of the examples presented in this chapter.

To retrieve the most recent release we should use the following links:

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

To find other ontology links search for them on the BioPortal [2] or on the OBO Foundry [3] webpages. Alternatively, we can also get the OWL files from the book file archive [4].

Class label

Both OWL files use the XML format syntax. Thus, to check if our entities are represented in the ontology, we can search for ontology elements that contain them using a simple `grep` command:

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

For each `grep` the output will be the line that describes the property label (*rdfs:label*), which is inside the definition of the class that represents the entity:

```
<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>
```

Class definition

To retrieve the full class definition, a more efficient approach is to use the `xmllint` command, which we already used in previous chapters:

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

[1] https://en.wikipedia.org/wiki/URL_redirection

[2] http://bioportal.bioontology.org/

[3] http://www.obofoundry.org/

[4] http://labs.rd.ciencias.ulisboa.pt/book/

The XPath query starts by finding the label that contains *malignant hyperthermia* and then `..` gives the parent element, in this case the `Class` element.

From the output we can see that the semantics of *malignant hyperthermia* is 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>
```

A graphical visualization of this class is depicted in Figure 5.1.

For example, we can check that *malignant hyperthermia* is a subclass of (specialization) the entries 0050736 and 66. We can directly use the links [5]

[5] `http://purl.obolibrary.org/obo/DOID_0050736`

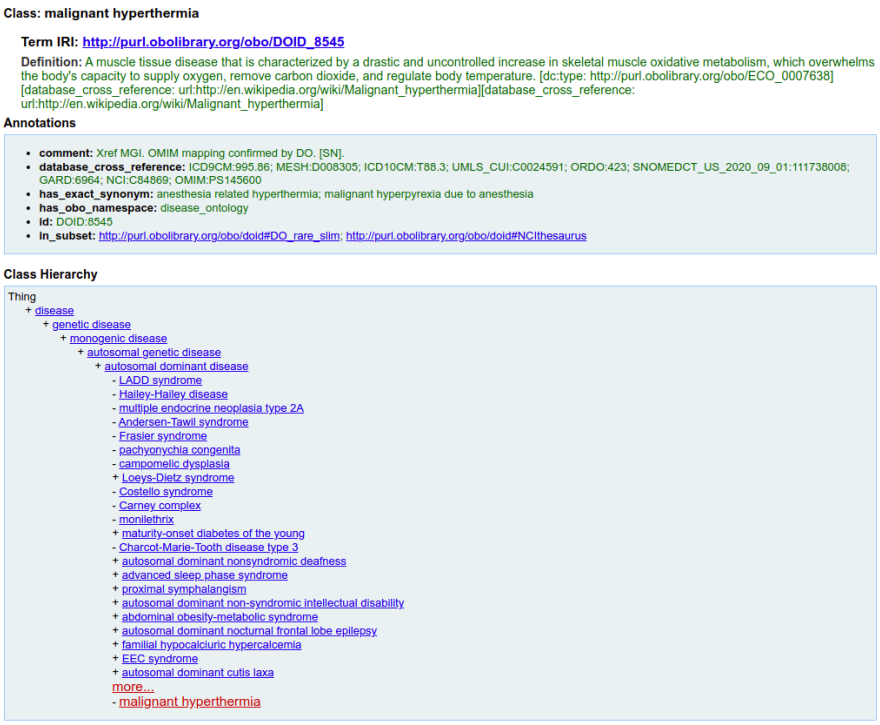


Fig. 5.1 Class description of *malignant hyperthermia* in the Human Disease Ontology (Source: `http://www.ontobee.org/`)

and [6] in our browser to know more about these parent diseases. We will see that *malignant hyperthermia* is a special case of a *autosomal dominant disease* and of a *muscle tissue disease*.

We can search for those specific relations between *malignant hyperthermia* and the entries 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
```

We added the `@*[local-name()='resource']` to extract the URI specified in an attribute `resource` of any descendant element `//*[...]`.

The relation specification uses the `subClassOf` element:

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

[6] `http://purl.obolibrary.org/obo/DOID_66`

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

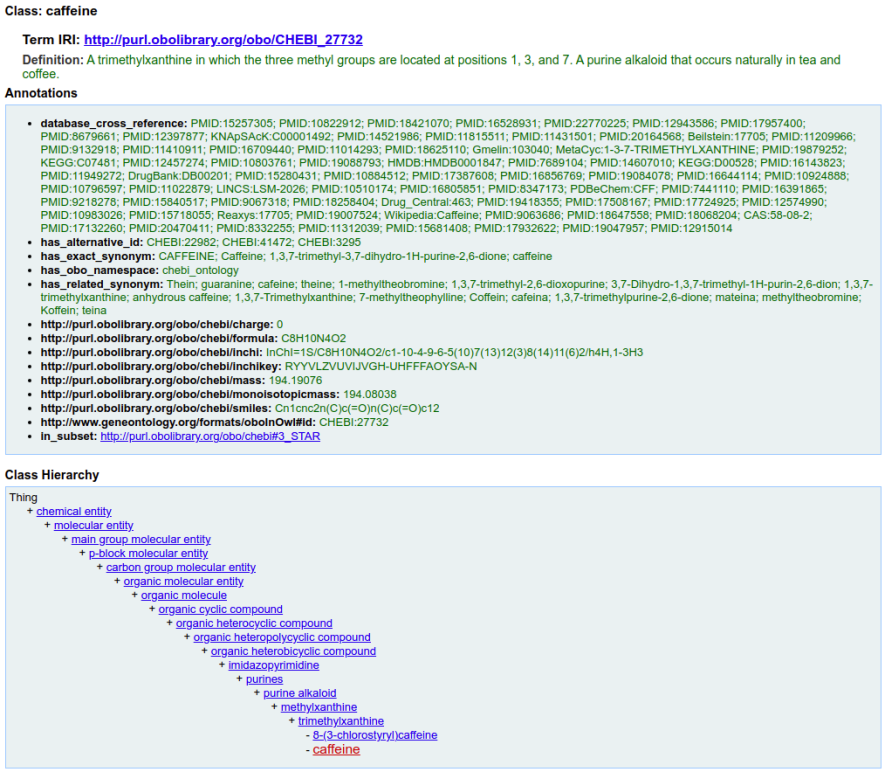
We can do the same to retrieve the full class definition of *caffeine*:

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

From the output we can see that the types of semantics available for *caffeine* differs from the semantics of *malignant hyperthermia*, but they still share many important properties, such as the definition of `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

Fig. 5.2 Class description of *caffeine* in ChEBI (Source: `http://www.ontobee.org/`)

A graphical visualization of this class is depicted in Figure 5.2.

The class *caffeine* is a specialization of two other entries: 26385 (*purine alkaloid* [7]), and 27134 (*trimethylxanthine* [8]).

We can search for those specific relations between *caffeine* and the entries 26385 and 27134:

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

[7] `http://purl.obolibrary.org/obo/CHEBI_26385`

[8] `http://purl.obolibrary.org/obo/CHEBI_27134`

```
    http://purl.obolibrary.org/obo/CHEBI_27134']]" doid
    .owl
```

The relation specification uses the `subClassOf` element:

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

Related Classes

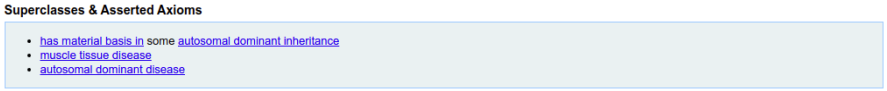


Fig. 5.3 Related classes of *malignant hyperthermia* in the Human Disease Ontology (Source: `http://www.ontobee.org/`)

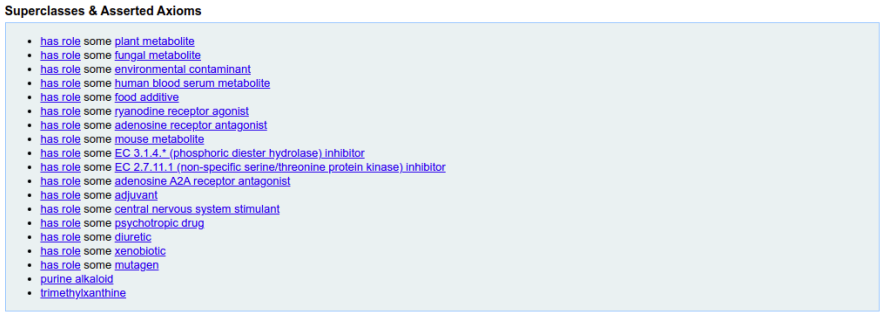


Fig. 5.4 Related classes of *caffeine* in ChEBI (Source: `http://www.ontobee.org/`)

There are additional subclass relationships that do not represent subsumption (*is-a*). Figures 5.3 and 5.4 show other related classes of *malignant hyperthermia* and *caffeine*, respectively.

For example, the relationship between *caffeine* and the entry 25435 (*mutagen* [9]) is defined by the entry 0000087 (*has role* [10]) of the *Relations Ontology*. This means that the relationship defines that *caffeine has role mutagen*.

We can search that specific relation between *caffeine* and *mutagen* (CHEBI:25435):

[9] `http://purl.obolibrary.org/obo/CHEBI_25435`
[10] `http://purl.obolibrary.org/obo/RO_0000087`

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

The specification uses the Restriction element:

```
<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>
```

We can now search in the OWL file for the definition of the type of relation *has role* (RO:0000087):

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

The XPath query starts by finding the elements `ObjectProperty` and then selects the ones containing the `about` attribute with the relation URI as value.

We can check that the relation is neither transitive or cyclic:

```
<owl:ObjectProperty rdf:about="http://purl.obolibrary.
    org/obo/RO_0000087">
 <oboInOwl:hasDbXref rdf:datatype="http://www.w3.org
    /2001/XMLSchema#string">RO:0000087</
    oboInOwl:hasDbXref>
 <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">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>
 <oboInOwl:shorthand rdf:datatype="http://www.w3.org
    /2001/XMLSchema#string">has_role</oboInOwl:shorthand
    >
 <rdfs:label rdf:datatype="http://www.w3.org/2001/
    XMLSchema#string">has role</rdfs:label>
```

```
</owl:ObjectProperty>
```

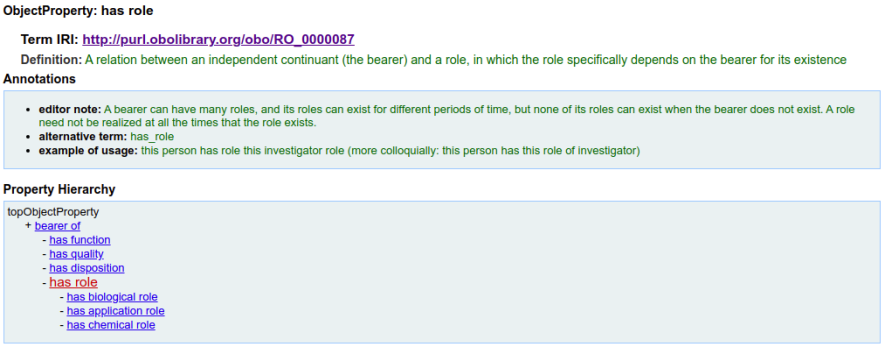


Fig. 5.5 Description of *has role* property (Source: `http://www.ontobee.org/`)

A graphical visualization of this property is depicted in Figure 5.5.

5.2 URIs and Labels

In the previous examples, we searched the OWL file using labels and URIs. To standardize the process, we will create two scripts that will convert a label into a URI and vice-versa. The idea is to perform all the internal ontology processing using the URIs and in the end convert them to labels, so we can use them in text processing.

URI of a label

To get the URI of *malignant hyperthermia*, we can use the following query:

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

We added the `@*[local-name()='about']` to extract the URI specified as an attribute of that class.

The output will be the name of the attribute and its value:

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

To extract only the value, we can add the `string` function to the XPath query:

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

The output will now be only the attribute value:

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

Unfortunately, the `string` function returns only one attribute value, even if many are matched. Nonetheless, we use the `string` function because we assume that *malignant hyperthermia* is an unambiguous label, i.e. only one class will match. To avoid this limitation we can add the `gawk` command using the character delimiting the URI, i.e. `"`.

```
$ xmllint --xpath "//*[local-name()='label' and text()='
    malignant hyperthermia']/../@*[local-name()='about
    ']" doid.owl | gawk -F\" '{ print $2 }'
```

Previous versions of `xmllint` may print all the output in the same line, and we may need to add extra commands [11].

To get the URI of *caffeine* is just about the same command:

```
$ xmllint --xpath "//*[local-name()='label' and text()='
    caffeine']/../@*[local-name()='about']"  chebi_lite
    .owl | gawk -F\" '{ print $2 }'
```

We can now write a script that receives multiple labels given as standard input and the OWL file where to find the URIs as argument. Thus, we can create the script named *geturi.sh* with the following lines:

```
1 OWLFILE=$1
2 xargs -I {} xmllint --xpath "//*[local-name()='label'
    and text()='{}']/../@*[local-name()='about']"
    $OWLFILE | \
3 gawk -F\" '{ print $2 }'
```

Again we cannot forget to save the file in our working directory, and add the right permissions using `chmod` as we did with our scripts in the previous chapters. The `xargs` command is used to process each line of the standard input.

Now to execute the script we only need to provide the labels as standard input:

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

The output should be the URIs of those classes:

[11] We need to split the result in multiple lines using the `tr '"' 'n'` command and filter the lines that contain the *http* keyword using the `grep 'http'` command.

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

We can also execute the script using multiple labels, one per line:

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

The output will be a URI for each label:

```
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

To get the label of the disease entry with the identifier 8545, we can also use the `xmllint` command:

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

We added the `@*[local-name()='label']` to select the element within the class that describes the label.

The output should be the label we were expecting:

```
malignant hyperthermia
```

We can do the same to get the label of the compound entry with the identifier 27732:

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

Again, the output should be the label we were expecting:

```
caffeine
```

We can now write a script that receives multiple URIs given as standard input and the OWL file where to find the labels. We can create a script named *getlabels.sh* with the following lines:

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

The `xargs` command is used to process each line of the standard input. Previous versions of `xmllint` may print all the output in the same line, and we may need to add extra commands [12].

Now to execute the script we only need to provide the URIs as standard input:

```
$ 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
```

The output should be the labels of those classes:

```
malignant hyperthermia
caffeine
```

We can also execute the script 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
```

The output will be a label for each URI:

```
malignant hyperthermia
muscle tissue disease

caffeine
purine alkaloid
trimethylxanthine
```

To test both scripts, we can feed the output of one as the input of the other, for example:

---

[12] We need to remove the `text()` function from the XPath. Then we have to split the result in multiple lines using the `tr '<>' 'n'` command and filter the lines that contain the `:label` keyword or are empty using the `grep -v -e ':label' -e '^$'` command. The pattern `^$` means that we cannot have any character between the beginning and the end of the line, only empty lines are matched.

```
$ 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
```

The output will be the original input, i.e. the labels given as arguments to the `echo` command:

```
malignant hyperthermia
muscle tissue disease

caffeine
purine alkaloid
trimethylxanthine
```

Now we can use the 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
```

Again the output will be the original input, i.e. the URIs given as arguments to the `echo` command:

```
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
```

5.3 Synonyms

Concepts are not always mentioned using the same official label. Frequently, we can find in text alternative labels. This is why some of the classes also specify alternative labels, such as the ones represented by the element `hasExactSynonym`.

For example, to find all the synonyms of a disease, we can use the same XPath as used before but replacing the keyword `label` by `hasExactSynonym` :

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

The output will be the two synonyms of *malignant hyperthermia*:

```
<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>
```

We can also get both the primary label and the synonyms. We only need to add an alternative match to the keyword label:

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

The output will include now the two synonyms plus the official label:

```
<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>
```

Thus, we can now update the script *getlabels.sh* to include synonyms:

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

We can test the script exactly in the same way as before:

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

But now the output will display multiple labels for this class:

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

URI of synonyms

Since the script now returns alternative labels, we may encounter some problems if we send the output to the *geturi.sh* script:

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

The previous command will display XPath warnings for the two synonyms:

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

If we do not want to know about these mismatches, we can always redirect them to the null device:

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

However, we can update the script *geturi.sh* to also include synonyms:

```
1 OWLFILE=$1
2 xargs -I {} xmllint --xpath "//*[(local-name()='hasExactSynonym' or local-name()='hasRelatedSynonym' or local-name()='label') and text()='{}']/../@*[local-name()='about']" $OWLFILE | \
3 gawk -F\" '{ print $2 }'
```

Now we can execute the same command:

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

Every label should now be matched exactly with the same class:

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

If we want to avoid repetitions, we can add the `sort` command with the `-u` option to the end of each command, as we did in previous chapters:

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

The output should now be only one URI:

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

5.4 Parent Classes

Parent classes represent generalizations that may also be relevant to recognize in text. To extract all the parent classes of *malignant hyperthermia*, we can use the following XPath query:

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

The first part of the XPath is the same as the above to get the class element, then `[local-name()='subClassOf']` is used to get the subclass element, and finally `@*[local-name()='resource']` is used to get the attribute containing its URI.

The output should be the URIs representing the parents of class 8545:

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

We can also execute the same command 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
```

The output will now include two parents:

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

We should note that we no longer can use the `string` function, because ontologies are organized as DAGs using multiple inheritance, i.e. each class can have multiple parents, and the `string` function only returns the first match. To get only the URIs, we can apply the previous technique of using the `tr` and `grep` commands:

```
$ xmllint --xpath "//*[local-name()='Class'][@*[local-name()='about']='http://purl.obolibrary.org/obo/CHEBI_27732']/*[local-name()='subClassOf']/@*[local-name()='resource']" chebi_lite.owl | gawk -F\" '{ print $2 }'
```

Now the output only contains the URIs:

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

We can now create a script that receives multiple URIs given as standard input and the OWL file where to find all the parents as argument. The script named *getparents.sh* should contain the following lines:

```
1 OWLFILE=$1
2 xargs -I {} xmllint --xpath "//*[local-name()='Class']
    [@*[local-name()='about']='{}']/*[local-name()='subClassOf']/@*[local-name()='resource']" $OWLFILE
    | \
3 gawk -F\" '{ print $2 }'
```

To get the parents of *malignant hyperthermia*, we will only need to give the URI as input and the OWL file as argument:

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

The output will include the URIs of the two parents:

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

Labels of parents

But if we need the labels we can redirect the output to the *getlabels.sh* script:

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

The output will now be the label of the parents of *malignant hyperthermia*:

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

Again, the same can be done with *caffeine*:

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

And now the output contains the labels of the parents of *caffeine*:

```
purine alkaloid
trimethylxanthine
```

Related classes

If we are interested in using all the related classes besides the ones that represent a generalization (*subClassOf*), we have to change our XPath to:

```
$ 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 | gawk -F\" '{ print $2 }'
```

We should note that these related classes are in the attribute *resource* of *someValuesFrom* element inside a *subClassOf* element.

The URIs of the 18 related classes of *caffeine* are now displayed:

```
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

To get the labels of these related classes, we only need to add the *getlabels.sh* script:

```
$ 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 | gawk -F\" '{ print $2 }' | ./getlabels.sh chebi_lite.owl
```

The output is now 18 terms that we could use to expand our text processing:

```
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
```

5.5 Ancestors

Finding all the ancestors of a class includes many chain invocations of the *getparents.sh* until we get no matches. We also should avoid relations that are cyclic, otherwise we will enter in a infinite loop. Thus, for identifying the ancestors of a class, we will only consider parent relations, i.e. subsumption relations.

Grandparents

In the previous section we were able to extract the direct parents of a class, but the parents of these parents also represent generalizations of the orig-

inal class. For example, to get the parents of the parents (grandparents) of *malignant hyperthermia* we need to invoke *getparents.sh* twice:

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

And we will find the URIs of the grandparents of *malignant hyperthermia*:

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

Or to get their labels we can add the *getlabels.sh* script:

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

And we find the labels of the grandparents of *malignant hyperthermia*:

```
autosomal genetic disease
muscular disease
```

Root class

However, there are classes that do not have any parent, which are called root classes. In Figures 5.1 and 5.2, we can see that *disease* and *chemical entity* are root classes of DO and ChEBI ontologies, respectively. As we can see these are highly generic terms.

To check if it is the root class, we can ask for their parents:

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

In both cases, we will get the warning that no matches were found, confirming that they are the root class.

```
XPath set is empty
```

Recursion

We can now build a script that receives a list of URIs as standard input, and invokes *getparents.sh* recursively until it reaches the root class.

The script named *getancestors.sh* should contain the following lines:

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

The second line of the script saves the standard input in a variable named `CLASSES`, because we need to use it twice: i) to check if the input as any classes or is empty (line 3) and ii) to get the parents of the classes given as input (line 4). If the input is empty then the script ends, this is the base case of the recursion [13]. This is required so the recursion stops at a given point. Otherwise, the script would run indefinitely until the user stops it manually.

The fourth line of the script stores the output in a variable named `PARENTS`, because we need also to use it twice: i) to output these direct parents (line 5), and ii) to get the ancestors of these parents (line 6). We should note that we are invoking the *getancestors.sh* script inside the *getancestors.sh*, which defines the recursion step. Since the subsumption relation is acyclic, we expect that at some time we will reach classes without parents (root classes) and then the script will end.

We should note that the `echo` of the variables `CLASSES` and `PARENTS` need to be inside commas, so the newline characters are preserved.

Iteration

Recursion is most of the times computational expensive, but usually it is possible to replace recursion with iteration to develop a more efficient algorithm. Explaining iteration and how to refactor a recursive script is out of scope of this book, nevertheless the following script represents an equivalent way to get all the ancestors without using recursion:

```
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
```

[13] `https://en.wikipedia.org/wiki/Recursion`

```
11 echo -e "$ANCESTORS"
```

The script uses the `while` command that basically implements iteration by repeating a set of commands (lines 6-8) while a given condition is satisfied (line 4).

To test the recursive script, we can provide as standard input the label *malignant hyperthermia*:

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

The output will be the URI of all its ancestors:

```
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
```

We should note that we will still receive the XPath warning when the script reaches the root class and no parents are found:

```
XPath set is empty
```

To remove this warning and just get the labels of the ancestors of *malignant hyperthermia*, we can redirect the warnings to the null device:

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

The output will now include the name of all 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
```

We should note that the first two ancestors are the direct parents of *malignant hyperthermia*, and the last one is the root class. This happens because the

recursive script prints the parents before invoking itself to find the ancestors of the direct parents.

We can do the same with *caffeine*, but be advised that given the higher number of ancestors in ChEBI we may now have to wait a little longer for the script to end.

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

The results include repeated classes that were found by using different branches, so that is why we need to add the `sort` command with the `-u` option to eliminate the duplicates.

The script will print the ancestors being found by the script:

```
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
```

5.6 My Lexicon

Now that we know how to extract all the labels and related classes from an ontology, we can construct our own lexicon with the list of terms that we want to recognize in text.

Let us start by creating the file *do_8545_lexicon.txt* representing our lexicon for *malignant hyperthermia* with all its labels:

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

Ancestors labels

Now we can add to the lexicon all the labels of the ancestors of *malignant hyperthermia* by adding the redirection operator:

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

We should note that now we use `>>` and not `>`, this will append more lines to the file instead of creating a new file from scratch.

Now we can check the contents of the file *do_8545_lexicon.txt* to see the terms we got:

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

We should note that we use the `sort` command with the `-u` option to eliminate any duplicates that may exist.

We should be able to see the following labels:

```
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
```

We can also apply the same commands for *caffeine* to produce its lexicon in the file *chebi_27732_lexicon.txt* by adding the redirection operator:

```
$ 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
```

We should note that it may take a while until it gets all labels.
Now let us check the contents of this new lexicon:

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

Now we should be able to see that this lexicon is much larger:

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

Merging labels

If we are interested in finding everything related to *caffeine* or *malignant hyperthermia*, we may be interested in merging the two lexicons in a file named *lexicon.txt*:

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

Using this new lexicon, we can recognize any mention in our previous file named *chebi_27732_sentences.txt*:

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

We added the `-F` option because our lexicon is a list of fixed strings, i.e. does not include regular expressions. The equivalent long form to the `-F` option is `--fixed-strings`.

We now get more sentences, including some that do not include a direct mention to *caffeine* or *malignant hyperthermia*. For example, the following sentence was selected because it mentions *molecule*, which is an ancestor of *caffeine*:

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

Another example is the following sentence, which was selected because it mentions *disease*, which is an ancestor of *malignant hyperthermia*:

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

We can also use our script *getentities.sh* giving this lexicon as argument. However, since we are not using any regular expressions it would be better to replace the `-E` option by `-F` to the `grep` command in the script, so the lexicon is interpreted as list of fixed strings to be matched. Only then we can execute the script safely:

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

Ancestors matched

Besides these two previous examples, we can check if there other ancestors being matched by using the `grep` command with the `-o` option:

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

We can see that besides the terms *caffeine* and *malignant hyperthermia*, only one ancestor of each one of them was matched, *molecule* and *disease*, respectively:

```
caffeine
disease
malignant hyperthermia
molecule
```

This can be explained because our text is somehow limited and because we are using the official labels and we may be missing acronyms, and simple variations such as the plural of a term. To cope with this issue, we may use a stemmer [14], or use all the ancestors besides subsumption. However, if our lexicon is small is better to do it manually and maybe add some regular expressions to deal with some of the variations.

[14] `https://en.wikipedia.org/wiki/Stemming`

5.7 Generic Lexicon

Instead of using a customized and limited lexicon, we may be interested in recognizing any of the diseases represented in the ontology. By recognizing all the diseases in our *caffeine* related text, we will be able to find all the diseases that may be related to *caffeine*

All labels

To extract all the labels from the disease ontology we can use the same XPath query used before, but now without restricting it to any URI:

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

We can create a script named *getalllabels.sh*, that receives as argument the OWL file where to find all labels containing the following lines:

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

We should note that this script is similar to the *getlabels.sh* script without the `xargs`, since it does not receive a list of URIs as standard input.

Now we can execute the script to extract all labels from the OWL file:

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

The output will contain the full list of diseases:

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

To create the generic lexicon, we can redirect the output to the file *diseases.txt*:

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

We can check how many labels we got by using the `wc` command:

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

The lexicon contains more than 34 thousand labels.

We can now recognize the lexicon entries in the sentences of the file *chebi_27732_sentences.txt* by using the `grep` command:

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

However, we will get the following error:

```
grep: Unmatched ) or \)
```

This error happens because our lexicon contains some special characters also used by regular expressions, such as the parentheses.

One way to address this issue is to replace the `-E` option by the `-F` option, that treats each lexicon entry as a fixed string to be recognized:

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

The output will show the large list of sentences mentioning diseases:

```
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

Despite using the `-F` option, the lexicon contains some problematic entries. Some entries have expressions enclosed by parentheses or brackets, that represent alternatives or a category:

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

Other entries have separation characters, such as commas or colons, to represent a specialization. For example:

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

A problem is that not all have the same meaning. A comma may also be part of the term. For example:

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

Other case includes using *&* to represent an ampersand. For example:

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

However, most of the times the alternatives are already included in the lexicon in different lines. For example:

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

As we can see by these examples, it is not trivial to devise rules that fully solve these issues. Very likely there will be exceptions to any rule we devise and that we are not aware of.

Special characters frequency

To check the impact of each of these issues, we can count the number of times they appear in the lexicon:

```
$ 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
```

We will be able to see that parentheses and commas are the most frequent, with more than one thousand entries.

Completeness

Now let us check if the *ATR* acronym representing the *alpha thalassemia-X-linked intellectual disability syndrome* is in the lexicon:

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

All the entries include more terms than only the acronym:

```
ATR-16 syndrome
ATR, nondeletion type
```

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

Thus, a single *ATR* mention will not be recognized.

This is problematic if we need to match sentences mentioning that acronym, such as:

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

We will now try to mitigate these issues as simply as we can. We will not try to solve them completely, but at least address the most obvious cases.

Removing special characters

The first fix we will do, is to remove all the parentheses and brackets by using the `tr` command, since they will not be found in the text:

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

Of course, we may lose the shorter labels, such as *Post measles encephalitis*, but at least now, the disease *Post measles encephalitis disorder* will be recognized:

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

If we really need these alternatives, we would have to create multiple entries in the lexicon or transform the labels in regular expressions.

Removing extra terms

The second fix is to remove all the text after a separation character, by using the `sed` command:

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

We should note that the regular expression enforces a space after the separation character to avoid separation characters that are not really separating two expressions, such as: *46,XY DSD due to LHB deficiency*

We can see that now we are able to recognize both *ATR* and *ATR syndrome*:

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

Removing extra spaces

The third fix is to remove any leading or trailing spaces of a label:

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

We should note that we added two more replacement expressions to the `sed` command by separating them with a semicolon.

We can now update the script *getalllabels.sh* to include the previous `tr` and `sed` commands:

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

And we can now generate a fixed lexicon:

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

We can check again the number of entries:

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

We now have a lexicon with more than 13 thousand labels. We have less entries because our fixes made some entries equal to others already in the lexicon, and thus the `-u` option filtered them.

Disease recognition

We can now try to recognize lexicon entries in the sentences of file *chebi_27732_sentences.txt*:

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

To obtain the list of labels that were recognized, we can use the `grep` command:

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

We will get a list of 47 unique labels representing diseases that may be related to *caffeine*:

```
47
Andersen-Tawil syndrome
```

```
arrhythmogenic right ventricular cardiomyopathy
arthrogryposis
ARVD2
ataxia telangiectasia
ATR
atrial fibrillation
benign congenital myopathy
cancer
cardiac arrest
cardiomyopathy
catecholaminergic polymorphic ventricular tachycardia
central core disease
CFTD
chorea
congenital myopathy
contractures
deficiency
disease
dystonia
epilepsy
FHL1
hand
hepatitis C
HL
hypercholesterolaemia
hypokalemic periodic paralysis
Hypokalemic periodic paralysis
intellectual disability
long QT syndrome
LQT1
LQT2
LQT3
LQT5
LQT6
malignant hyperthermia
migraine
myopathy
myotonic dystrophy type 1
nemaline myopathy
nemaline rod myopathy
ophthalmoplegia
rod myopathy
scoliosis
syndrome
T cell
```

The reason why *47* appears is because there is a label *47, XXY*:

```
$ echo '47, XXY' | ./geturi.sh doid.owl
```

The URI of the disease with that label:

```
http://purl.obolibrary.org/obo/DOID_1921
```

Performance

The `grep` is quite efficient but of course when using large lexicons and texts we may start to feel some performing issues. Its execution time is proportional to the size of the lexicon, since each term of the lexicon will correspond to an independent pattern to match. This means that for large lexicons we may face serious performance issues.

A solution for dealing with large lexicons is to use the inverted recognition technique [Couto et al., 2017, Couto and Lamurias, 2018]. The inverted recognition uses the words of the input text as patterns to be matched against the lexicon file. When the number of words in the input text is much smaller than the number of terms in the lexicon, `grep` has much fewer patterns to match. For example, the inverted recognition technique applied to ChEBI has shown to be more than 100 times faster than using the standard technique.

Case insensitive

We may use the `-i` option to perform a case insensitive matching. To check how many labels are now being recognized we can execute:

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

We have now 66 labels being recognized.

To check which new labels were recognized, we can compare the results with and without the `-i` option:

```
$ 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
```

We are now able to see that the new labels are:

```
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
```

Some of them are just lower and upper case variations of the same label. To verify this, we can add the `-f` option to the `sort` command:

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

We really have 57 different labels being recognized. The equivalent long form to the `-f` option is `--ignore-case`.

Correct matches

Some important diseases could only be recognized by performing a case insensitive match, such as *dyskinesia*. This disease was missing because in the lexicon we had the uppercase case version of the labels, but not the lowercase version. We can check it by using the `grep` command:

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

The lexicon has only the disease name with the first character in uppercase:

```
Dyskinesia
```

Incorrect matches

However, using a case insensitive match may also create other problems, such as the acronym *CAN* for the disease *Crouzon syndrome-acanthosis nigricans syndrome*:

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

By using a case insensitive `grep` we will recognize the common word *CAN* as a disease. For example, we can 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
```

It is recognized 22 times.

And to see which type of matches they are, we can execute the following command:

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

We can verify that the matches are incorrect mentions of the disease acronym:

```
can
```

This means we created at least 22 mismatches by performing a case insensitive match.

5.8 Entity Linking

When we are using a generic lexicon, we may be interested in identifying what the recognized labels represent. For example, we may not be aware of what the matched label *AD2* represents.

To solve this issue, we can use our script *geturi.sh* to perform entity linking (aka entity disambiguation, entity mapping, normalization), i.e. find the classes in the disease ontology that may be represented by the recognized label. For example, to find what *AD2* represents, we can execute the following command:

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

Only one URI:

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

Now we can retrieve other labels:

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

In this case, the result clearly shows that *AD2* represents the *Alzheimer disease*:

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

Modified labels

However, we may not be so lucky with the labels that were modified by our previous fixes in the lexicon. For example, we can test the case of *ATR*:

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

As expected, we received the warning that no URI was found:

```
XPath set is empty
```

An approach to address this issue may involve keeping a track of the original label in a lexicon using another file.

Ambiguity

We may also have to deal with ambiguity problems where a label may represent multiple terms. For example, if we check how many classes the acronym *KOS* may represent:

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

We can see that it may represent two classes:

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

These two classes represent two distinct diseases, namely *Kaufman oculocerebrofacial syndrome* (DOID:0111456) and *Kagami-Ogata syndrome* (DOID:0111712), respectively.

We can also obtain their alternative labels by providing the two URI as standard input to the *getlabels.sh* script:

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

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

We will get the following two lists, both containing *KOS* as expected:

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

KOS
Kagami-Ogata syndrome
```

If we find a *KOS* mention in the text, the challenge is to identify which of the syndromes the mention refers to. For addressing this challenge, we may have to use advanced entity linking techniques that analyze the context of the text.

Surrounding entities

An intuitive solution is to select the class closer in terms of meaning to the other classes mentioned in the surrounding text. This assumes that entities present in a piece of text are somehow semantically related to each other, which is normally the case. At least the author assumed some type of relation between them, otherwise the entities would not be in the same sentence.

Let us consider the following sentence about *KOS*:

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

To identify the diseases in the previous sentence, we can execute the following command:

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

We have a list of labels that can help us decide which is the right class representing *KOS*:

```
KOS
syndromic intellectual disability
```

To find their URIs we can use the *geturi.sh* script:

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

The only ambiguity is for *KOS* that returns two URIs, one representing the *Kaufman oculocerebrofacial syndrome* (DOID:0111456) and the other representing the *Kagami-Ogata syndrome* (DOID:0111712):

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

The other URI represents the *Syndromic intellectual disability* (DOID:0050888).

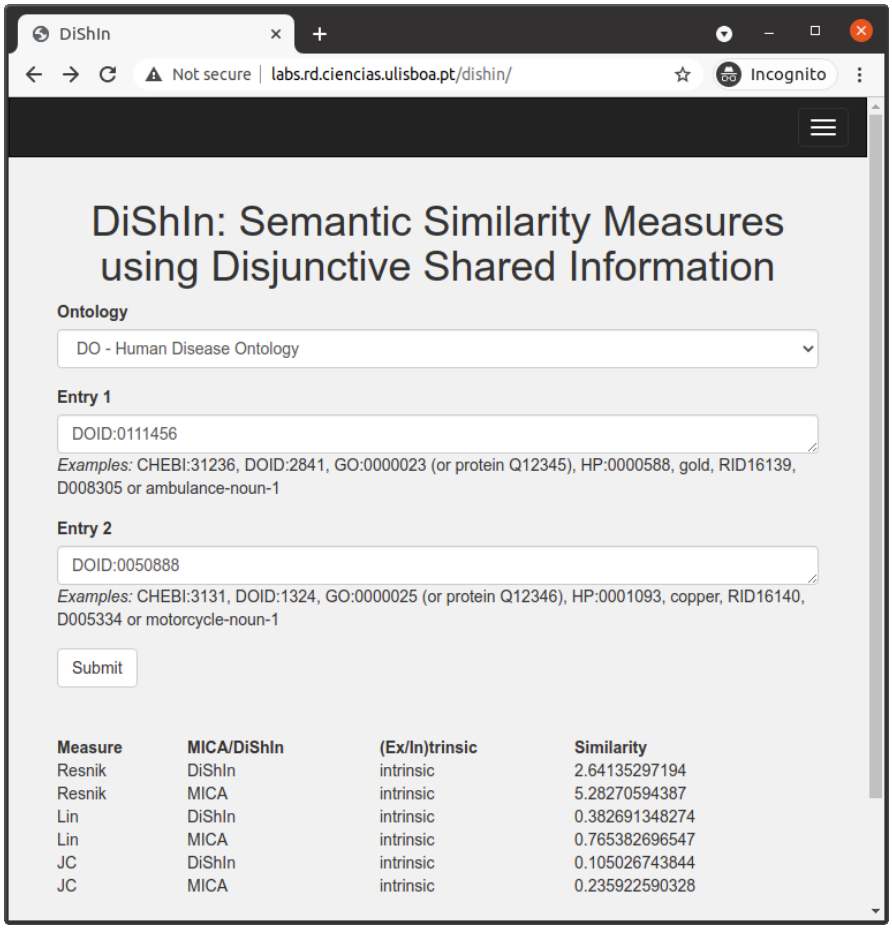


Fig. 5.6 Semantic similarity between *Kaufman oculocerebrofacial syndrome* (DOID:0111456) and *Syndromic intellectual disability* (DOID:0050888) using the online tool DiShIn

To decide which of the two URIs we should select, we can measure how close in meaning they are to the other diseases also found in the text.

Semantic similarity

Semantic similarity measures have been successfully applied to solve these ambiguity problems [Grego and Couto, 2013]. Semantic similarity quantifies how close two classes are in terms of semantics encoded in a given ontol-

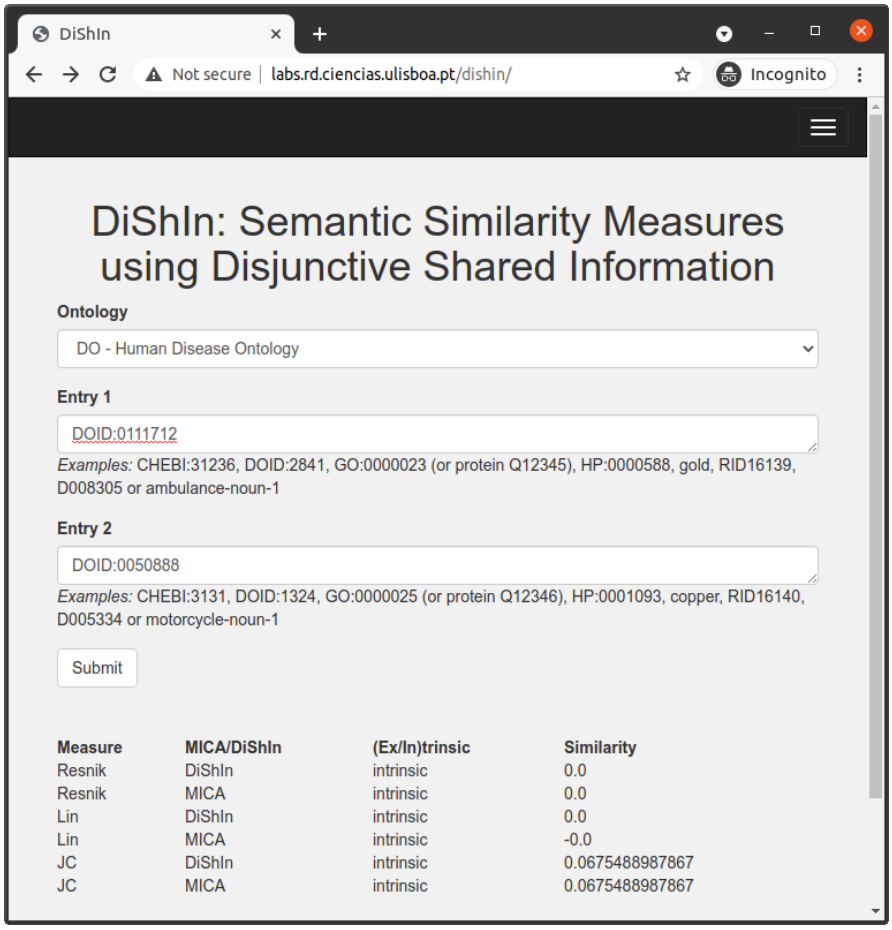


Fig. 5.7 Semantic similarity between *Kagami-Ogata syndrome* (DOID:0111712) and *Syndromic intellectual disability* (DOID:0050888) using the online tool DiShIn

ogy [Couto and Lamurias, 2019]. Using the web tool Semantic Similarity Measures using Disjunctive Shared Information (DiShIn) [15], we can calculate the semantic similarity between our recognized classes. For example, we can calculate the similarity between *Kaufman oculocerebrofacial syndrome* (DOID:0111456) and *Syndromic intellectual disability* (DOID:0050888) (see Figure 5.6), and the similarity between *Kagami-Ogata syndrome* (DOID:0111712) *Syndromic intellectual disability* (DOID:0050888) (see Figure 5.7).

[15] `http://labs.rd.ciencias.ulisboa.pt/dishin/`

Measures

DiShIn provides the similarity values for three measures, namely Resnik, Lin and Jiang-Conrath [Resnik, 1995, Lin et al., 1998, Jiang and Conrath, 1997]. The last two measures provide values between 0 and 1, and Jiang-Conrath is a distance measure that is converted to similarity.

We can see that for all measures *Syndromic intellectual disability* is much more similar to *Kaufman oculocerebrofacial syndrome* than to *Kagami-Ogata syndrome*. Moreover, Jiang-Conrath's measure gives the only similarity value larger than zero for *Kagami-Ogata syndrome*, since it is a converted distance measure. This means that by using semantic similarity we can identify *Kaufman oculocerebrofacial syndrome* as the correct linked entity for the mention *KOS* in this text.

DiShIn installation

To automatize this process we can also execute DiShIn as a command line [16], however we may need to install python (or python3) and SQLite [17].

We can download a minimalist version of DiShin and the latest database of the Human Disease Ontology:

```
$ 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
```

DiShIn execution

After being installed, we can execute DiShIn by providing the database and two classes identifiers:

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

The output of the first command will be the semantic similarity values between *LQT1* (DOID:0110644) and *Andersen-Tawil syndrome* (DOID:0050434):

```
Resnik   DiShIn  intrinsic      2.64135297194
Resnik   MICA    intrinsic      5.28270594387
```

[16] `https://github.com/lasigeBioTM/DiShIn`

[17] `apt install python sqlite3` or `apt install python3 sqlite3`

```
Lin      DiShIn  intrinsic      0.382691348274
Lin      MICA    intrinsic      0.765382696547
JC       DiShIn  intrinsic      0.105026743844
JC       MICA    intrinsic      0.235922590328
```

The output of the second command will be the semantic similarity values between *LQT1* (DOID:0110644) and *X-linked Alport syndrome* (DOID:0110034):

```
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 [18] and SQL [19] is out of scope of this book, but if we do not intend to make any modifications the above steps should be quite simple to execute.

5.9 Large lexicons

The online tool MER is based on a shell script [20], so it can be easily executed as a command line to efficiently recognize and link entities using large lexicons.

MER installation

We can start by downloading the latest compressed file (zip) version, and extract its contents:

```
$ curl -O -L https://github.com/lasigeBioTM/MER/archive/master.zip
$ unzip master.zip
$ mv MER-master MER
```

We now have to copy the Human Disease Ontology in to the data folder of MER, and then enter into the MER folder:

```
$ cp doid.owl MER/data/
$ cd MER
```

[18] https://www.w3schools.com/python/

[19] https://www.w3schools.com/sql/

[20] https://github.com/lasigeBioTM/MER

Lexicon files

To execute MER, we need first to create the lexicon files:

```
$ (cd data; ../produce_data_files.sh doid.owl)
```

This may take a few minutes to run. However, we only need to execute it once, each time we want to use a new version of the ontology. If we wait, the output will include the last patterns of each of the lexicon files.

We can check the contents of the created lexicons by using the `tail` command:

```
$ tail data/doid_*
```

These patterns are created according to the number of words of each term.

The output should be something like this:

```
==> 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

Now we are ready to execute MER, by providing each sentence from the file *chebi_27732_sentences.txt* as argument to its *get_entities.sh* script.

```
$ cat ../chebi_27732_sentences.txt | tr -d "'" | xargs -
    I {} ./get_entities.sh '{}' doid
```

We removed single quotes from the text, since they are special characters to the command line `xargs`. We should note that this is the *get_entities.sh* script inside the MER folder, not the one we created before.

Now we will be able to obtain a 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
...
```

The first two numbers represent the start and end position of the match in the sentence. They are followed by the name of the disease and its URI in the ontology.

We can also redirect the output to a TSV file named *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

Fig. 5.8 The *diseases_recognized.tsv* file opened in a spreadsheet application

We can now open the file in our spreadsheet application, such as LibreOffice Calc or Microsoft Excel (see Figure 5.8).

5.10 Further Reading

To know more about biomedical ontologies, the book entitled *Introduction to bio-ontologies* is an excellent option, covering most of the ontologies and computational techniques exploring them [Robinson and Bauer, 2011].

Another approach is to read and watch the materials of the training course given by Barry Smith [21].

[21] http://ontology.buffalo.edu/smith/IntroOntology_Course.html

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