Support decision system for diagnosing rare diseases using vector space model and medical text mining

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Abstract

It can be time consuming for a physician to diagnose a disease and even more so if it is a rare disease. Many rare disease have a high fatality rate so a quick diagnosis is vital to the health of the patient. We therefore propose a prototype support decision system for diagnosing rare diseases with a specialized database. For this we will be using a vector space model to look for similarity between input symptoms and gathered information. Given a list of symptoms, the system will calculate a similarity score between the search query and the documents in the matrix. The system was tested using 13 test cases from BMJ [1], 29 test cases from Orpha.net and 5 blind tests cases provided by chief physician Henrik Jørgensen and Lennart Friis-Hansen. In a top 20 the system returned the correct results for 8 out of 13 for BMJ, 20 out of 29 for Orpha.net and 3 out of 5 during the blind test. The system places 61.5% of the BMJ cases, 68% of Orpha.net and 60% of the blind test cases in top 20. This proves the potential of the system, and suggests that further work within this area of research should be performed.

Acknowledgements

We would like to thank our supervisor for letting us take on this project, even though the project was not clearly defined from the beginning. His ideas and thoughts helped us a lot when we ran into corners.

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We would like to thank Lennart Friis-Hansen for coming up with the original idea for the project, and hope that others — in the future — will continue our project, or work on similar ones.

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Changes from Original Synopsis

The project has changed title from *"Support decision system for diagnosing rare diseases using machine learning for medical text mining"* to ``‘‘Support decision system for diagnosing rare diseases using vector space model and medical text mining’’``. This was because the original project was focused on gathering and organizing information using clustering algorithms, to help physicians locate the right PubMed article to identify a disease. The new focus was to providing a list of 20 suggestions for possible diseases given a list of symptoms, this was best carried out using information retrieval techniques such as the vector space model.

The system original success criteria were

1. The ability to correctly diagnose 50 rare diseases by search terms provided by chief physician Henrik L. Jørgensen. A successful hit is the correct diagnosis being among the top 20 search results.
2. The use of as few references (clicks) as possible to narrow in the search. This should be 5 or fewer.
3. The use of as few search terms as possible. This should be 5 or fewer depending on the rarity of the disease.
4. How quickly the physician can locate the correct article compared to when using PubMed.

Reasons for changing the success critera

Ad 1. This has been changed because we did not receive the 50 golden standard diseases on which to test our system. We received 5 test cases upon which we performed a blind test. The lack of test cases made us look into alternatives which we found in BMJ, and some randomly chosen strings characterizing symptoms from Orpha.net.

Ad 2. The system is to deliver a suggestion list of top 20 diseases given a symptom list, therefore is does not make sense to talk about using as few references as possible.

Ad 3. The use of as few symptoms as possible, is partially still in effect, though we have misinterpreted the word few. The symptoms lists we received for blind test from Henrik L. Jørgensen can be seen in table 4.3. These are comprehensive, so the phrase "few symptoms" is relative to the observer.

Ad 4. Our system never reached a state where it was possible for the physicians to test it, therefore the last of the original success criteria was not met.

Therefore only a single success criteria has been specified for the revised edition, and that is the ability of the system to correctly place rare diseases amongst top 20, given a symptom list, which will be the main focus of the project.

Contents

Chapter 1

Introduction

Due to the vast amount of information available on the Internet today, it is near impossible for researchers to have an 'up-to-date' knowledge on anything but their own specific field. Even that seems to become more and more difficult, as new information is added each day[1] [2]. Therefore it can be necessary to employ tools to help gather, structure and look for relations or hypotheses within the masses of information. One very popular method of finding new relations in data is through the use of *text mining*.

"The whole is greater than the sum of its parts" $\sim$ Aristotle (384–322 BC)

Text mining refers to the automated search for meaningful patterns in structured or unstructured text documents, stored in very large digital databases or distributed over the Web. A good example of this is "Fish oil, Raynaud's syndrome and undiscovered public knowledge" by D.R. Swanson [3]. Here, Swanson was referring to published knowledge buried deeply in disjoint topical domains[2]. Swanson was one of the first to propose using text mining on biomedical literature. In 1986, he found evidence of a relation between the use of fish oil and the development of Raynaud's syndrome, by looking at seemingly unrelated documents. This was done years before there actually were any scientific documents supporting this.

Throughout recent years, the use of text mining has grown tremendously. In the biomedical field, research is divided into highly specialized sections and subsections, often too complex to enable for interdisciplinary work. For instance, the recent sequencing of the human genome has introduced a whole new level of detail to genetic research. It is likely that new discoveries in this area could affect other areas concerned with health and diseases, as genomic mechanisms play a major role in the various branches of medicine [4]. Text mining is a way of making these important connections in a world of increasing complexity and hidden patterns. This method of making new, unseen discoveries also introduces text mining as a major potential aid in the diagnosis of rare or (to the physician) unknown diseases.

[1]Take for instance the biomedical database MedLine that grows with over half a million citations per year

[2]Here 'disjoint' refers to articles written by researchers unaware of each others work

This project aims to make it easier and more efficient for physicians to diagnose rare diseases. Through the use of text mining, information retrieval and clustering algorithms, it attempts to increase the likelihood of getting the correct article based upon a search of symptoms, environmental and/or human factors. We use a list of rare diseases and synonyms acquired from Rarediseases.info [5]. Based on this, we extract a series of MedLine records [6] using the Python module Bio.Entrez [7] and process the text for a more optimized search.

1.1 Inspiration

The list of rare diseases numbers over 6,000 and increases by 5 each week [8]. A rare (or orphan) disease is classified by the Orpha.net Encyclopedia [9] as being a disease that affects less than 1 out of 2,000 people in Europe, and which has severe chronic or terminal outcomes (or less than 200,000 affected in the USA by standard of Rarediseases.info [5]). These diseases may not be fatal if treated promptly. However, given the amount of knowledge a physician would need to carry around to make a correct diagnosis (or correctly exclude other potential candidates), quick (and correct) treatment isn't always the case.

When affected by a rare disease, the lack of a correct diagnosis — or the delay spent going from one specialist to another — will often lead to a fatal outcome. When it comes to rare, and often dangerous diseases, the typical physician has little or no prior experience with similar cases. It is therefore important that the diagnosing physician has as much help at hand as possible in this intrinsic task.

In a dialogue with Henrik L. Jørgensen [10] — chief physician at Bispebjerg Hospital — we found that — even though many systems already exist to help physicians in their diagnosis — there seemed to be a lack of a system for specifically diagnosing rare diseases. Systems such as PubMed returns numerous results if the symptoms are even slightly non-specific (more on this in the following chapters). The advantage of a specialized system for rare diseases would be that the physician — when in doubt — would have a chance to quickly look the symptoms up, before referring or discharging the patient. According to Henrik L. Jørgensen, time is a great issue, when treating patients and, in the rare event of a patient being affected by something unknown, he or she is referred to a specialist.

The inspiring task of creating an efficient support decision system for diagnosing rare diseases was what drove us to initiate this project.

1.2 Objectives

Aim

Our system will be based on machine learning concepts and will hopefully add something new to the arena of medical support decision systems. Using various techniques to optimize our system, we aim to design a system that — if successful — also has the generic potential of being expanded to other domains than that of rare diseases.

Overall process

The list of rare disease names (along with synonyms and optional descriptions) will be mined from the Rarediseases.info website. Some of these diseases will have specialized PubMed search strings that we mine along with the names. Using these names, predefined search strings and synonyms, we search PubMed for a maximum of 500 PMID's[3] per disease, representing MedLine records containing an abstract. We then download the corresponding records.

The intention is to preprocess the data using a vector space model and various heuristics in order optimize the probability of getting a correct hit. The heuristics are described in the following chapter but revolve mainly around the Term Frequency - Inverse Document Frequency (TF-IDF). Since a graphical user interface will not be made for the prototype system, a correct hit is when an article defining the disease is among the top 20 returned results from a given query of symptoms.

We will be running tests on three different test cases. The first set of cases are derived from a subset of tests in the BMJ article [1] relevant to our database[4] The second set of cases come from a random select of disease descriptions on the Orpha.net website [11]. The third and final set of test cases come from a blind test provided by Henrik L. Jørgensen.

Primary tools

We will be using Python 2.6.2 [12] in this project. For access to PubMed, we use the Python module Bio.Entrez [7] while BeautifulSoup [13] is used for parsing of HTML/XML combined with Urllib2 [14] these are used for crawling the websites. For construction of the term document matrix we use the SciPy package [15], which supports sparse matrix structures. For auxiliary vector functions we use the Numpy package [16].

1.3 Roadmap

Chapter 2 covers the different databases that we harvest our data from, and how we intend to model the information. We provide a background on Rarediseases.info, PubMed and the MedLine database, our primary data sources. We examine various advantages and disadvantages of the models and heuristics that we use, how we measure the similarities used to provide a disease score for queries, we also look into the data types used to handle the large amounts of information. Lastly, we look at an alternative that may be able to provide more information on each mined disease.

Chapter 3 deals with the methods that we have used to implement the first prototype and the following branches of the system. We present an overview

[3]PMID's are unique article identifiers used by PubMed

[4]We only run tests on the diseases present in our database

of the implementation, amplify the flexibility of the data exchange between the modules, and show how we have applied several heuristics/filters to the data and the vector space. The chapter finishes with details of the data and technical discussion of the implementation.

Chapter 4 contains all the primary tests and results of the different schemes used to find the most efficient model for looking up rare diseases. The cosine similarity measure and the simple sum similarity measure are tested, measured and put up against each other to see which performs the best. This is done on both the classical term document matrix and on a document-summed version called the *disease matrix*. It also deals with aspects and tests of clustering and some of the potential noise in the data set.

Chapter 5 is the conclusion of the project, it contains a summary of the results, along with some comment on the usefulness of a system such as this from Henrik L. Jørgensen.

Chapter 6 contains future perspectives of the project, what could it become and which features could be useful if the system were to be made available for use by physicians all over the world.

Chapter 2

Background

This chapter examines the challenges of diagnosing rare diseases, of the databases we harvest data from and of the data models we intend to use, including applied optimized heuristics. We will reason our choices through the preliminary work of others and look at alternatives to some of the choices made. We will also go through selected parts of the theoretical aspects of the methods used in our prototype system.

2.1 Diagnosing Rare Diseases

In theory, clinical decision-making is a complicated process based upon experience, judgement and a reasoning coming from a large body of medical literature and clinical trials. In practise though, a physician may have very little time per patient and — when in doubt — must come with a qualified guess based on personal experience and judgement. But with the tremendous amount of knowledge available today, the physician should not stand alone with this decision-making. If the symptoms of the patient seem strange or out of the ordinary, a quick list of qualified diagnostic guesses from an automated supporting decision-system would be able to help the physician in contradicting or justifying the diagnosis.

Though existing sources like Orpha.net (see section 2.6.4) and Rarediseases.info (see section 2.2.1) aims to aid researchers and physicians in dealing with rare diseases, these sites are primarily based on human information retrieval. This gives them a higher accuracy but it also renders them unable to keep up with the growing amounts of research and information available.

Today, PubMed (see section 2.2.2) is one of the largest and most used biomedical article database-interfaces. It provides access to millions of abstracts and citations. Though rich in information, this is also its Achilles heel when it comes to describing less common subjects like rare diseases.

The prototype of the supporting decision-system presented in this paper will be based on a specialized database for rare diseases that harvests its information from MedLine (see section 2.2.3) by using information gathered from the Rarediseases.info. It will be easily extendable to other sources (like Orpha.net) and — through implemented text mining and machine learning methods — have the ability to present the physician with a list of highly potential diagnoses given a list of symptoms.

2.2 Retrieval of Biomedical Literature

In the following, we will go through the main sources of information that we intend to retrieve data from. We will be looking at advantages and disadvantages of each system and how we might use them. We also describe Orpha.net which — as mentioned above — is an obvious source of additional data.

2.2.1 Rarediseases.info

Overview

Rarediseases.info is a website from the National Institute of Health [17] that provides resources in relation to rare diseases. These resources include links to patient support groups, glossary, research, PubMed searches, OMIM (Online Mendelian Inheritance in Man [18]) searches and a description of the disease. However, none of the resources are mandatory, and in certain cases nearly all that is mentioned on a disease is its name.

The Rarediseases.info website contains — at the time of writing — a list of 6881 diseases classified as being rare. It defines a rare disease as one that is prevalent in fewer than 200,000 individuals in the United States [19]. This also means that diseases such as malaria are included on the list, even though it might not be considered rare in other places in the world, say, Africa. Sites such as Rarediseases.info provide an excellent base for creating a database of rare diseases.

Database Interface

There are two main types of links available at Rarediseases.info for use in relation to MedLine. The first is a handcrafted PubMed search string. An example of this is:
http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=DetailsSearch&Term=Ledderhose[All+Fields]+AND+("disease"[MeSH+Terms]+OR+"disease"[All+Fields])

Handcrafted search strings can be more or less specific. The given example is rather standard - simply searching for the disease name and a condition being that either the MeSH-terms should contain “disease” or that “disease” should be present in any of the fields (for a description of fields see [20]). This type of link can return anything from zero to several thousand articles, based on the search within PubMed.

The second type of link is an OMIM link. These links only return one MedLine record and are primarily concerned with diseases linked to the human genome. They usually contain several links to gene sequences and literature references and are mostly research-oriented.

Rarediseases.info also lists synonyms of the disease which can be used to search PubMed for more information on the disease. If a search on the disease name gives no or few results, there might be a chance that a search on its synonyms will.

Last, there is a handcrafted description of the disease which could be useful for later classification of the disease in a specialized database.

Keeping in mind that none of the extra information above might be present, we will be using one of the available links and the name of the disease for primary information retrieval, and the synonyms of the disease in a secondary information retrieval. Since the OMIM link only links to one article, (in order to get more information to work with) we select all the related articles to the OMIM link (See section 3.2.2), hoping these also will contain valuable information relevant to the disease. The handcrafted descriptions are retrieved, but are not currently used in our system, though this could provide valuable information about the diseases.

As mentioned, Rarediseases.info is far from complete in its level of detail and is based solely on rare diseases from an American view. Though focused on Europe and thereby perhaps incomparable, an alternative such as Orpha.net (section 2.6.4) seems to be containing more information per disease than Rarediseases.info and it contains a longer list of rare diseases. We do not use Orpha.net as we sought permission to text mine their site, but have received no answer to the request.

2.2.2 PubMed and Entrez

Overview

PubMed [21] is the worlds largest resource of free information on biomedical literature, containing abstracts and citations of more than 19 million articles. This makes PubMed the ideal candidate for text mining biomedical research.

Information is retrieved from PubMed through Entrez [22]. Entrez is provided by the National Center for Biotechnology Information [23] and is a text-based search and retrieval system providing access to services such as PubMed, nucleotide and protein sequences, protein structure, complete genomes, OMIM and many others (currently a total of 35 different databases).

PubMed is a popular source of information when it comes to text mining and there are many projects that use the available information to extract knowledge and make relations. A good example is Chilibot [24] that can be used to extract relations between genes, proteins or keywords by searching through PubMed abstracts. Another example is iHOP [25] (information-Hyperlinked Over Proteins) that allows the user to search for protein-networks. In iHOP, the user types in a protein name and the system then searches PubMed for occurrences of that name. A snippet of the found abstracts is returned to the user along with the information on where it was found and protein names are marked out. When marking the protein name, it provides a confidence level to the identified proteins names, based on evidence in relation to the protein name.

Since the human genome project, many text mining systems deal with mining or identifying gene or protein interactions. Some data mining and machine learning systems exist, that are used for diagnosing and classifying diseases. These are usually very specific, like a system for diagnosing heart diseases [26]. It deals with diagnosing the Ischaemic heart disease using machine learning techniques on four diagnostic levels: ECG[1] at rest, sequential ECG during controlled exercise, myocardial scintigraphy and coronary angiography. Where the diagnosis is performed as 'heart disease' vs. 'no heart disease' [27].

Most diagnosis systems that function well today are based on machine learning and image analysis. Wang et. al looks at the performance of a system to diagnose breast cancer using either image features, non-image features or both. The hybrid system combining both feature sets in diagnosis, performed the best [28].

Text mining systems are concerned with hypothesis generation, building knowledge bases, identifying gene/proteins and their interaction or with identifying malignancy terms in MedLine records. All of these things are done by structuring the information and looking for patterns within it.

We have not been able to find other articles on the subject of automated diagnosis of rare diseases (i.e. many different rare diseases given a symptom list). There are systems that deals with rare diseases, but these are specialized and only deal with a specific disease, not multiple. An example of this is a system using neural network to diagnose Lyme borreliosis disease [29]

Database Interface

Searching in PubMed is done by Boolean queries using the keywords AND, OR and NOT operators on record fields (see section 2.2.3) which provides a very powerful way to search since it's possible to retrieve any subset of the database. Graham L. Poulter has constructed a classifier that ranks nearly 17 million documents from the MedLine database of biomedical literature [30]. He remarks that the Boolean search also presents a major problem when it comes to the amount of information returned. If a search is even slightly non–specific, the results will tend to be numerous — a problem when, for example, diagnosing a rare disease.

We use Entrez to search PubMed for article information represented as records from the MedLine database. These records contain abstracts and other kinds of useful information and are described in the following section. The searches will be based on the retrieved information from Rarediseases.info (see section 2.2.1).

The figure 2.1 shows the structure of Entrez and visualize how many resources there are available at the different sub components[2].

[1]electrocardiogram

[2]Go to http://www.ncbi.nlm.nih.gov/Database/datamodel/index.html for an interactive model in Flash.

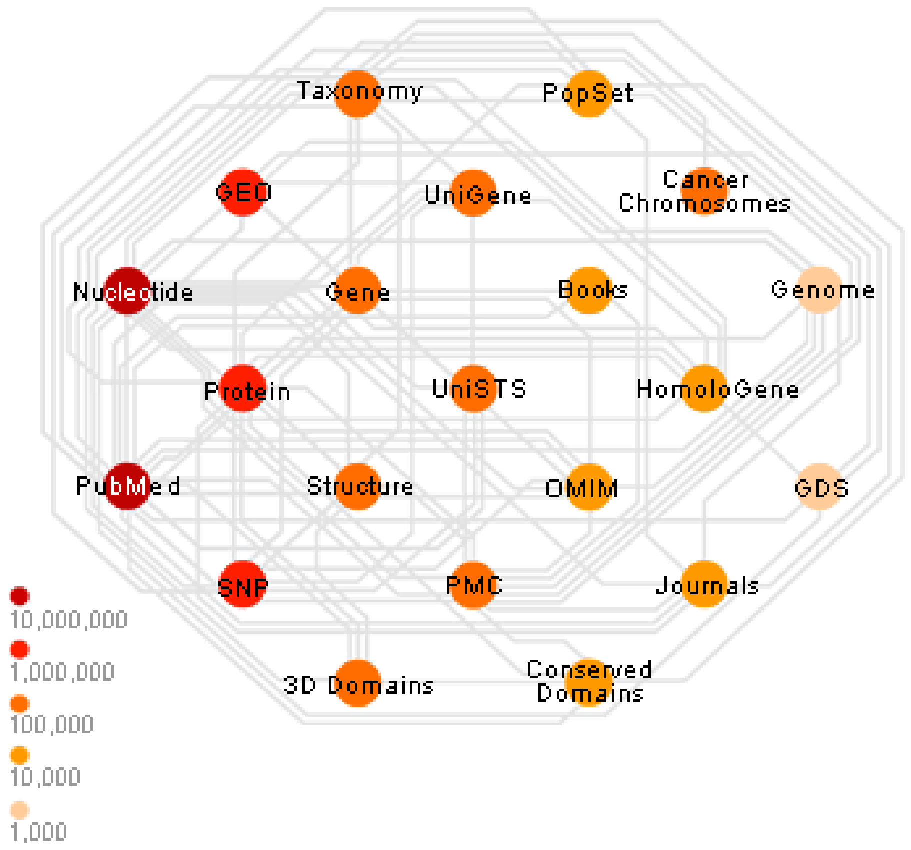


Figure 2.1: Shows the structure of the Entrez data model

2.2.3 MedLine Records and MeSH

Overview

MedLine (Medical Literature Analysis and Retrieval System Online) [6] is the U.S. National Library of Medicine's foremost bibliographic database, containing over 16 million references to journal articles from approximately 5,200 journals worldwide, dating from 1949 to the present. Since 2005 between 2,000-4,000 references have been added each Tuesday through Sunday and over 670,000 references were added in 2007.

MedLine records are built from various fields such as title, abstract, language, author, publication data and many others (for complete list see [20]). Using these search fields, it is possible to specify exactly what is to be searched for. As an example, the article could be one that needs to have an abstract, has to have a specific author and is dated from 2005 and later.

The records of MedLine are indexed with Medical Subject Headings (MeSH) which is a controlled vocabulary thesaurus. MeSH describes a hierarchical structure with the possibility of searching at different levels of specificity. MeSH descriptors are very general at the top-level (such as 'anatomy' or 'mental disorder') and gradually become more and more specific when moving down its 11 levels (for more information see their fact sheet on MeSH [31]).

Database Interface

When MeSH is used by experienced users, it can be a powerful tool to extract information on a specific subject. But when used by less experienced users, these tend to get long lists of hits, which results in an overload of information. For instance, a search on "Parkinson's Disease" returns 21,000 results according to Panos et. al [32]. Panos et. al proposes a system that divides MeSH into three categories, allowing the information to be view from different perspectives [32]. They cluster the results by using a Self-Organizing Map thereby creating a concept hierarchy to improve information retrieval.

Many different opinions exist when it comes to dealing with MeSH in the context of information retrieval. W.R. Hersh and D.H. Hickham found that text word indexing is more effective than MeSH term indexing [33], while G. Sophie et. al suggest that both MeSH and text search should be considered in the search strategy [34].

Roger P. Smith describes how MeSH can be used to explode searches and manipulate them to include the more specific sub levels of the MeSH [35]. For instance, a search for 'Filovirus' will include the more specific searches 'Ebola virus' and 'Marburg virus'. The system tries to correct user input errors through a system of mappings (e.g. "adverse reaction", "side effects" and "undesirable effects" all map to "adverse effects"). It is also possible to use simple patterns when searching on PubMed, for example 'bacter*' searches for bacteria, bacterium, bacteriophage etc. When using truncation, the search will not find search strings containing white-space, for example a search for 'infection*' will find 'infections', but not 'infection control'.

Though MedLine records are rich in information, we will in the system be focusing on information given by the abstract, title and MeSH terms. We require the records to have an abstract but MeSH terms might not always be present. For an expansion of the prototype system, it would be natural to take in account the information given with potential keywords, publication dates, authors and other optional MedLine information (And example of a MedLine record can be seen in figure 2.2).

Figure 2.2: Example of a MedLine record for the disease Cerebral cavernous hemangioma

```
PMID- 19634751
OWN - NLM
STAT- MEDLINE
DA  - 20090728
DCOM- 20090914
IS  - 1542-8877 (Print)
IS  - 1542-8877 (Linking)
VI  - 40
IP  - 4
DP  - 2009 Jul-Aug
TI  - Labor-induced hemorrhage of a retinal cavernous hemangioma.
PG  - 419-20
AB  - The authors present a case of a previously undiagnosed retinal cavernous
      hemangioma that hemorrhaged during labor. There are previous reports of
      labor-induced intracranial hemorrhage from central nervous system vascular
      malformations, but none have demonstrated intraocular hemorrhage during labor.
      The case emphasizes a need to screen patients with retinal cavernous hemangioma
      and to warn them of possible vision loss during Valsalva maneuvers such as labor.
AD  - Barnes Retina Institute, Washington University School ofMedicine, Department of
      Ophthalmology and Visual Sciences, St. Louis, Missouri, USA.
FAU - Smith, Bradley T
AU  - Smith BT
FAU - Joseph, Daniel P
AU  - Joseph DP
LA  - eng
PT  - Case Reports
PT  - Journal Article
PL  - United States
TA  - Ophthalmic Surg Lasers Imaging
JT  - Ophthalmic surgery, lasers & imaging : the official journal of the International
      Society for Imaging in the Eye
JID - 101155780
SB  - IM
MH  - Female
MH  - Fluorescein Angiography
MH  - Hemangioma, Cavernous/*pathology
MH  - Humans
MH  - *Obstetric Labor Complications
MH  - Pregnancy
MH  - Retinal Hemorrhage/*diagnosis
MH  - Retinal Neoplasms/*pathology
MH  - Vision Disorders/etiology
MH  - Young Adult
EDAT- 2009/07/29 09:00
MHDA- 2009/09/15 06:00
CRDT- 2009/07/29 09:00
PST - ppublish
SO  - Ophthalmic Surg Lasers Imaging. 2009 Jul-Aug;40(4):419-20.
```

2.2.4 Searching the Information

Having gathered information about rare diseases, our system needs to be able to efficiently search and retrieve information given a query string. Various approaches to retrieve the information needed exist. One possibility is using Boolean queries, where it is possible to use the standard operators like “AND”, “OR” and “NOT” to perform queries in a system — this is how PubMed works. Many professional users prefer using Boolean queries, because it offers them precise control over what is returned. Either a document matches or it does not.

But this does not mean that using Boolean queries are the most efficient, not even for professional searchers [36]. A problem is that the use of the "AND" operator tends to produce high precision, but in turn lowers the recall of information [36]. As the Boolean query model only record term presence or absence, it lacks the ability to produce ranked ordered results. In order to rank the query results the different terms needs to be given a weight describing how important the term is to the document. In order to incorporate the use of term weights, we need to be able to calculate a relevance score for a document given a query. A very popular way of doing this, is to represent the query and documents in the collection as vectors. This leads to us choosing the vector space model to represent our gathered information.

2.3 The Vector Space Model

This model represents the way we structure all the retrieved information that we use. It forms the backbone for the heuristics we apply in the following chapters to model our data for an improved search. We will in this section shortly describe its model (as used in the prototype system), advantages and disadvantages.

Model Description

The vector space model is a matrix representation of our information. As shown in figure 2.3, each row represents a document and each column a term.

Terms / PMID	hemangioma	hemorrhage	cavernous	intracranial	blood
19634751	3	4	3	1	0
17447932	0	5	0	0	4
14838147	0	3	0	3	2

Figure 2.3: Example of term document matrix

In our case, the abstract, MeSH terms and title of a Mealing record will represent a document vector in the model. The first index is saved for a hash of the document id (PMID) while the remaining India's make up the term (or word) frequencies of each term in the abstract, MeSH and title in the record. The choice of putting the title of the record together with its abstract is appropiate, as these (often long) titles has a tendency of containing a lot of information in the MedLine records. As described in section 2.2.3, the optional MeSH also contains valuable information on the record.

Note also that the first index of each of the term vectors is saved for the hash of the term.

Advantages

Representing our data in this model simplifies further processing. It is a well known and well documented model (especially due to its assumption of term independence which enables the use of naive Bayes for document classification). It has several well researched and used heuristics attached to it (like TF-IDF, section 2.4.2 and LSA in section 2.4.9), and it is relatively easy to implement.

Disadvantages

As a basic model, the term vector scheme has several limitations. First, it is very calculation intensive. We will try to improve performance by using pre-calculated hashes of vector norms, by stemming the terms and by removing outliers, but it still requires a lot of processing time. Furthermore — when we use schemes like calculating the inverse document frequency — updating the term space leads to a recalculation of the entire matrix.

The matrix will also be very sparse, containing a lot more zeroes than term frequencies. We will try to improve computational time and memory by using data structures built for sparse matrices (see section 2.6.1).

Another main disadvantage of the vector space model is that it does not capture polysemy[3] or synonymity, since every term is assumed to be independent. Thus some irrelevant documents have high similarities with a query because they share some words with the query (polysemy) while other relevant documents have a low similarity with the query since they have different terms (synonymy). Lack of polysemy comprehension affects the recall of a search on the model. Lack of synonymy comprehension affects the precision of a search. Some synonyms can be caught by stemming the terms but this is far from all. We will also to create a semantic space using SVD (see section 2.4.9) to capture the most meaningful words.

2.4 Applied Heuristics

Many heuristics exist for information processing that can be used when dealing with term-document matrices and the vector space model. In this section, we will go through some of the most commonly used schemes for enhancing the performance (recall and precision) of a search in the model. We will also go through some less common schemes used for the prototype system and justify these decisions.

2.4.1 Mitigating the Problem of Term Burstiness

The term 'burstiness' describes the behavior of a rare word appearing many times in a single document according to REMs E. Madsen ed. al [37]. This is under the general assumption that if a word appears once in a document, it is

[3]Polysemy describes terms that can be used to express different things in different contexts, e.g. *driving a car* and *driving results*.

more likely to appear again. This assumption breaks with the independence assumption of the vector space model and a high raw count of a word often seems to exaggerate the significance of that word. Derived from [37], our first heuristic is the log-transformation of the term frequency:

$$x_{MW}^{log} = \log(1 + x_{dw})$$

Where x_{dw} is the number of times the term w appears in document d. This helps reduce the problem of burstiness by smoothing the term counts.

2.4.2 Term Frequency - Inverse Document Frequency

This heuristic is commonly known under the acronym TF-IDF and is probably the most used heuristic in the vector space model and information retrieval in general. It is as follows (note also the log-transformation of the term frequency from section 2.4.1):

$$x_{iv}^{tfidf} = \log(1 + x_{dw}) * \log \frac{D}{\sum_{d\prime=1}^{D} \delta_{d\prime w}}$$

Where δ_{dw} is 1 if w is present in document d and D are the document corpus. Term frequency (TF) is also referred to as the *recall* component while the inverse document frequency (IDF) is the *precision* component. In other words, IDF gives us a higher weight for rare terms and the log-transformation of IDF helps to smooth the data. With TF-IDF the importance increases proportionally to the number of times a term appears in the document but is offset by the frequency of the word in the corpus.

One clear disadvantage of TF-IDF is its inability to capture the importance of a term. Though rare words are promoted, there is no real guarantee that these words are as relevant and that they classify the document as one would hope. A lot of research have been laid into explaining the advantages and disadvantages of TF-IDF and there are many interesting discussions going on — like the one at the blog [38] — in this discussion, E. Garcia mentions that it would make sense to work with some measure of the entropy of a term but — as also noted — such methods are computationally expensive, especially when dealing with large scale web search engines. It would be reasonable to assume that the same applies when dealing with large term document matrices and — due to the limited resources available in this project — we believe it is reason enough to only consider the relatively simple transformations.

2.4.3 Normalization

After the TF-IDF transformation, there is a need to normalize the vectors using L_2 normalization[4]. This makes all the document vectors have the same length and therefore the same influence on the search result.

[4]Also known as the Euclidean norm

$$x_{dw}^{norm} = \frac{x_{dw}^{tfidf}}{\sqrt{\sum_{w\prime=1}^{W} {x_{dw}^{tfidf}}^2}}$$

Where $\sqrt{\sum_{w\prime=1}^{W} {x_{dw}^{tfidf}}^2}$ is the normalization factor of the x_{dw}^{tfidf} - using the usual vector normalization to make the length 1.

2.4.4 Square Root Transformation

Like the log-transformation in section 2.4.1, the square root transformation represents a method for smoothing burstiness in data. The most important difference is that using the square root on data smooths the data towards 1 opposed to the more aggressive log-transformation. Numbers of 1 and above behave differently than numbers between 0.00 and 0.99. The square root of numbers above 1 always become smaller, 1 and 0 remain constant, and numbers between 0.00 and 1.00 become larger (the square root of 4 is 2, but the square root of 0.40 is 0.63). Thus the square root transformation should only be used on data that is either below or above 1. For illustration of square root transformation see figure 2.4

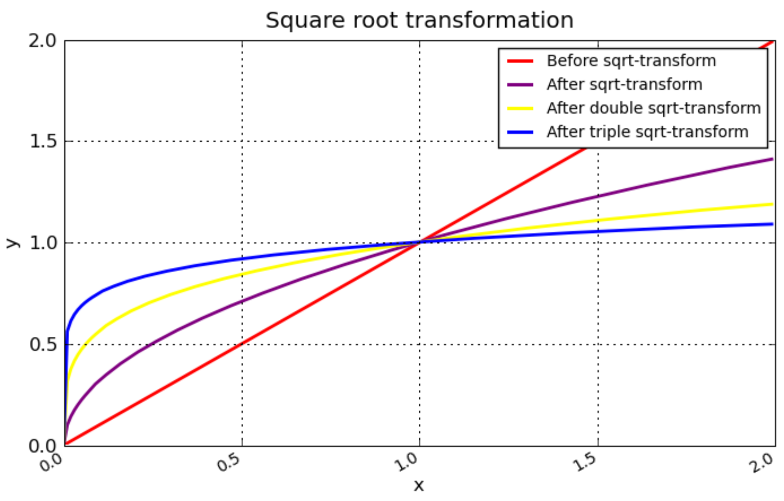


Figure 2.4: Square root transformations

We will be using the square root transformation to analyse the data coming from the TF-IDF scheme. We will describe transformation in further detail in chapter 4. For now, the basic idea is that — if the TF-IDF works as supposed — a square root 'upping' of the lower data will result in poorer search results.

2.4.5 Stop Word Removal

We will be removing English stop words in the prototype to limit the number of too common words that interfere with searches. In recent years there has been a tendency to avoid using stop word removal due to the small impact that it has on a search [36]. But taking into consideration that most searches performed on this system will consist of a list of symptoms, it seems that it will not damage the performance of the system to remove the insignificant terms (remember the assumption of term independence). In any case, these terms — like 'and' or 'this' — would be present in nearly all of the MedLine records and therefore be assigned very low weight by TF-IDF. Let us for instance say that the term 'a' was present in every document. The IDF-factor would be $\log 1 = 0$ which results in $tf \cdot idf = tf \cdot 0 = 0$. The term will therefore be deemed irrelevant in relation to the information retrieval.

2.4.6 Stemming

Performing stemming on textual information will increase the recall of information at the price of lowering the precision[5] [36]. Considering that our system will be dealing with domain specific information, it should not pose a problem. Our choice of stemmer has fallen on Porter's stemmer which has also been shown empirically to be very efficient [36]. Other stemmers exist — like Lovins which is the first stemmer to be made and is very aggressive in its stemming [39]. Or like the simple S stemmer — for English words — where only endings of common words are stemmed such as 'ies', 'es' and 's'. A complete alternative using a stemmer could be to use a lemmatizer. A lemmatizer performs a full morphological analysis to accurately identify the lemma of a word. Performing lemmatization seems to have only very limited benefits for the retrieval [36]. For our system, we have chosen to stick with only testing stemming.

2.4.7 Outlier Detection

Outlier detection on the retrieved information of each disease could concentrate the knowledge that we have on the disease. But care needs to be taken when removing information, since there is the risk of removing specific terms required to identify the correct disease. There are multiple ways of performing outlier detection, the most interesting generally being the most computationally expensive. One way could be to make a centroid vector for each disease and then remove a percentage of the MedLine records farthest away from the centroid by choosing some similarity/distance measure on which to score them. Cosine Similarity (see section 2.5) would be well suited for the purpose. Another way could be to calculate a distance matrix from each document vector to all others, again using an appropriate distance measure like the cosine similarity (see section 2.5). This is then followed by taking the sum of each document vector and removing the percentage that score the lowest, that

[5]Remembering from section 2.4.2 could be defined as TF and precision as IDF in the TF-IDF vector space model

is the ones that — summed over all distances to every other document vector — score the lowest.

2.4.8 Clustering

Performing clustering on the diseases within our database could provide valuable information to the physician using our system. Which diseases are similar to each other, which could easily be mistaken for one another. This is, unfortunately, very computationally intensive and is beyond the scope of this project. But performing clustering on a limited subset, such as the top 20 returned results is possible. This should reflect the diseases similarity to the query vector. A number of clustering algorithms exist, such as k-nearest neighbour (knn) or hierarchical clustering, the latter begin the most computational heavy, but it tends to give better results than knn as it is not based on randomized centroids, such as those knn relies on. This means that every time a dendrogram is made, it looks the same. Because we only need to cluster 20 diseases, we have chosen to use hierarchical clustering.

2.4.9 Latent Semantic Analysis

Additional preprocessing that could be interesting, would be to create a latent semantic space on the information on each disease. This can be done by performing latent semantic analysis (LSA)/latent semantic indexing (LSI). With this scheme, it should be possible to extract a keyword list describing each disease or summarizing the information we have available about the disease. The keyword list could then be used to provide the physician using the system with a more comprehensive list of characteristics for the most likely diseases, given the original symptoms. It could be used for later disease classification schemes.

LSA is done by performing Singular Value Decomposition (SVD). SVD decomposes the original matrix X, with shape m x n, into a product of three new matrices U, S and V^t. Here U is an m x n matrix, S is an n x n diagonal matrix and V^t is an n x n matrix. The column of U is called left singular vectors, and the rows of V^t is called right singular vectors. The elements of S are only nonzero on the diagonal and these are called singular values. The singular values are the square root of the eigenvalues of X^tX, arranged in decreasing order. A dimension reduction is performed by removing the k least significant singular values, the k last columns of U, and the k last rows of V^t. The result is an $n - k = l$ matrix where l is the remaining dimensions. Due to the reduction, the dimensions are now U_r is m x l, S_r is l x l, and V_r^t is l x n. SVD — and the dimensionality reduction — is then followed by calculating the product of $U_rS_rV_r^t$ (where the subscribtion $_r$ means reduced), hence putting the three reformed pieces back together:

$$X_r = U_rS_rV_r^t, \text{ where } X \text{ is } m \text{ x } n$$

X_r is also called the semantic space, and should — in theory — be able capture some of the semantic relation between terms.

2.5 Calculation of Vector Similarity

When working with the vector space model, the most used measure of similarity is the cosine similarity. In the prototype system, we use this measure for scoring and clustering diseases based on queries. We also use a simpler *sum* score in comparison with the cosine measure.

The Cosine Similarity Measure

When using this measure, the resulting similarity score of two vectors can be thought of as the angle between two vectors (though the angle measure is only visible for up to three dimensions and can not readily be applied to the hyper dimensional space of the matrix), that is the angle between the query vector and the document vector. The usual equation for cosine similarity can then be used:

$$\cos\theta_{D_j} = \frac{Q \cdot D_j}{|Q| \times |D_j|}$$

Where D_j is document j as a vector, Q is the query vector and $\cos\theta_{D_j}$ is the cosine similarity between document j and query Q.

Since we assume that no values in the vector space model are below zero, this measure results in a value of 0 if the vectors have no terms in common and 1 if they are exactly like each other. The latter case is most improbable in our proposed system since the query vector usually consists of a limited list of symptoms, measured up against the document vector consisting of a long list of terms derived from the title, the abstract and the potential MeSH terms of a MedLine record.

With a TF-IDF transformation and L_2 normalization the above calculation can be rewritten as follows:

$$\text{score}_d = \frac{1}{|I|}\frac{1}{|x_d|}\sum_{i\in I} x_{dw}$$

Where score_d is the similarity score for document d, $\frac{1}{|I|}$ is the normalization factor of the query vector and $\frac{1}{|x_d|}$ is the normalization factor of the document vector. Due to the fact that length of the query vector is the same for all the document vectors in a given search, this acts as a scalar for all scores. Because of this, we choose to disregard the $\frac{1}{|I|}$ factor in our system, meaning we can rewrite the formula as:

$$\propto \frac{\sum_{i\in I} x_{dw}}{|x_d|}$$

Since the denominator is the norm of the document vector, the division above simply represents a normalization of the document vector so that it is unit length. To improve query processing time, the normalization of the document corpus matrix — that we will be working on — can be preprocessed before the calculation of the cosine similarity. Assuming that the document vectors are on unit length, we can now rewrite the cosine similarity function to be of the simple form:

$$\propto \sum_{i \in I} \widehat{x_{dw}}$$

Where I is the set of indices where query vector and document vector overlap. And $\widehat{x_{dw}}$ is the normalized version of x_{dw}

Should the need to compare two searches arise, there is of course a need to normalize the search score in accordance with the length of the query vector.

How we use the cosine similarity measure to test and score our data will be described in chapter 4.

The Simple Sum Measure

When using this measure, we simply sum the vectors values returned by a query. In other words, this works like the cosine measure described above but it deals with non-normalized vector spaces as opposed to the cosine measure. This will also be described in 4.1.1

2.6 Data Structures

When constructing a term document matrix, it is essential to use the correct data structures to save the information. Creating a term document matrix from diverse MedLine records tends to produce very large sparse matrix. One of the matrices (a stemmed version) that we have created has shown itself to contain only about 0.026% non-zero entries, corresponding to about 61,520,349 term counts in a matrix for size 602,467(documents)x390.766(terms) with a total capacity of 235,423,619,722 entries. In short, this means a lot of zeroes. Working with a matrix that takes all these zeroes into account is simply not an option. In order to save time and space we have chosen to work with three main data structures.

2.6.1 SciPy.sparse

The SciPy.sparse module is used to make sparse matrices. It offers seven different forms of data structures to represent sparse matrices - the interested reader can have a look at the SciPy documentation accessible on their website [15]. The different types each have pros and cons. We primarily use the “lil” format, which is a sparse matrix using linked lists. For traversal through the matrix, we use the “coo” format which is coordinate format. Coo matrices also facilitate fast conversion to the other matrix format. For a quick look-up of individual elements, it is advantageous to use the “dok” format which is a dictionary of keys. This allows O(1) time access to matrix elements. And the “csc” and “csr” formats can be used when dealing with arithmetic operations, since these are efficient for column and row operations.

Linked list matrices are slow when it comes to arithmetic operations but efficient when it comes to incrementally constructing matrices. Therefore it is ideal to construct a large matrix from a number of smaller matrices using linked list format. It also permits the usage of fancy slicing, which makes manipulations of the content very flexible. Once the construction is completed, it can be converted to another format for efficient arithmetic operations (usually csc or csr). The lil format also tends to have a higher memory usage than the other sparse matrix formats.

Coordinate matrices are memory efficient but do not allow for direct access of the elements it contains. It is, however, possible to traverse over all the elements which is useful when constructing a term document matrix. This is especially fast when combined with the dok format which allows fast access for elements.

Compressed sparse row or column allows for fast matrix arithmetic operations like, addition, multiplication, matrix matrix product, vector matrix product and so on. The csr allow fast row slicing but is slow when column slicing, and csc vice versa.

The two remaining sparse matrix formats in SciPy are not relevant to the project.

2.6.2 Matrix Market

Revisiting the discussion on how to save the term document matrix, the Scipy package [15] offers an I/O-module that allows matrices to be exported to "Matrix Market" (MM) format. MM only saves non-zero entries via coordinate/-value. When reading from an MM file, the matrix is read in is in coo format for obvious reasons[6]. More information can be found at their website [40].

2.6.3 cPickle

cPickle is a standard Python module that is used for serializing Python objects. It can be used to save objects to the hard drive and later read them back into memory - without bothering with type transformations. cPickle has the unfortunate property that it saves all the zeroes that reside within the term document matrix which results in large files. Fortunately cPickle is very efficient when it comes to saving and reading the hashes that we use for the matrices. The I/O time is pretty quick and it enables a much quicker read of the hashes than, say a plain text file would have. More on cPickle can be found at Python's documentation site [41].

2.6.4 The Orpha.net Alternative

Although we have chosen to harvest much of our data from Rarediseases.info, we have also come across another website worthy of mention as it seems this site is more rich in information than Rarediseases.info - though focused on rare diseases in Europe.

Orpha.net defines a rare disease as one that affects 1 person out of every 2,000 in Europe and it lists 12,191 different rare diseases at the time of writing.

[6]The exception being the "dense" format, which is similar NumPy's matrix format.

A quick overview suggests more of the detailed descriptions than Rarediseases.info and it has highlighted data such as “Prevalence of rare diseases” and “Age of onset” which could be very useful for disease classification. Like Rarediseases.info, it is — however — variable in the amount of information per disease and not all diseases have any information on them, save for its name.

Since Orpha.net focuses on diseases that are rare in Europe, a combination of data from Raredisease.info and Orpha.net could enable a physician using the system to enhance the precision by defining the continental origin of the disease. It could also up the number of diseases with a description to a large enough amount for a classifier to use them for priors in a statistical model.

Chapter 3

Methods

This chapter deals with the design of our system, an overview of the implementation and technical aspects on the data that we work with. We will be taking a look at how the first prototype was designed and how it branched out to several different versions due to experiments with various heuristics applied to the data. We will go through the individual modules of the system and how they communicate through the data formats. After giving a thorough description on the data we work with in the system, we finally round off the chapter with some of the technical conclusions that we got from building the system.

3.1 System Overview and Design

In this section, we lay out the design of the system. In section 3.1.1, we describe how the first prototype is put together while in section 3.1.2, we describe the different ways we have tried to structure the system. Finally, in section 3.1.3, we mention how the applied filters have led to several different versions of the matrices that make up the heart of the system. For full overview see figure 3.1

3.1.1 The First Prototype

We have made a modular design that is divided into five major components representing our system. The first module is a web crawler called *Disease-Crawler*. It gathers preliminary data from Rarediseases.info and saves it in a specified data format on the disk (see section 3.2.1), allowing the next module to read it in and process it. *The Search and Information Retrieval* (SIR) module searches and retrieves MedLine records from PubMed.org in accordance to the data gathered in the crawler module. SIR saves its data in a file under the disease name, containing up 500 MedLine records per disease-search and a description if one is found (see section 3.2.2). This allows the third module *TermDoc* to read in the data, convert all the disease to sub term document matrices and construct a large term document matrix from the data from the sub-matrices, saving the term document matrix in Matrix Market format (see section 2.6.2). As an option one can include a filter just before the construction of the large term document matrix (or on the sub-matrices), e.g. a stemmer and/or stop word remover or other kinds of filters, like log-transformation of the term counts and the much used term frequency - inverse document frequency (TF-IDF). The resulting data from the TermDoc module can now be used for querying. This is done through the *QueryInterface* module that implements the cosine measure to perform correlation between vectors, i.e. between a query vector and a document vector in our term document matrix. To be able to give a disease name instead of just a MedLine record, we need to score the disease in relation to the given query vector. This is done by a consensus method, where we select the number of MedLine records to use a basis of the consensus so that each MedLine record has one or more disease names attached to it (the same MedLine record can be returned from different diseases). We then sum the score from each MedLine record under the given disease names and sort the total scores. Those with the highest total score have the greatest correlation with the search query, and therefore these are the most likely to be our disease.

The modular design of the prototype system allows the different modules to be replaced with more efficient modules or modules that gather data from different sources - as long as the new module conforms to the specified data formats. It allows for an easy addition of new heuristics and filtering modules to specific points in the data modelling.

3.1.2 Branching the Prototype

A major branch in our design sprung when we realised the potential of building a disease matrix instead of a term document. Though severely simplifying our data, this model is a reduced version of the term document matrix and is a lot easier and faster to work with.

The disease matrix is based on the same data as the term document matrix. It differs in the way that it contains all the information that we have about each disease from the MedLine records, summed into one vector describing the disease. The new disease matrix still needs to contain the same terms as the term document matrix but is now made of a disease vectors instead of document vectors. This makes the individual disease vector less sparse than a document vector. The same preprocessing options that run on the term document matrix, can be applied to the disease matrix just as easily.

3.1.3 Filtering for New Matrices

Adding filters to the prototype system spawns new matrices to work on (as shown on in the figure below 3.1). The sub-matrices generated from the MedLine records are generated both as stemmed and non-stemmed. From these, two large term document matrices and two different disease matrices are generated. Adding another heuristic, the large matrices are TF-IDF transformed (with and without normalization).

Yet another pool of sub-matrices are created by SVD and dimensionality reduction, leading to yet another large disease matrix to perform tests and potential keyword extractions on.

Again we mention that filters and heuristics should be pretty easy to add since only the data formats in between the modules needs to be kept in order.

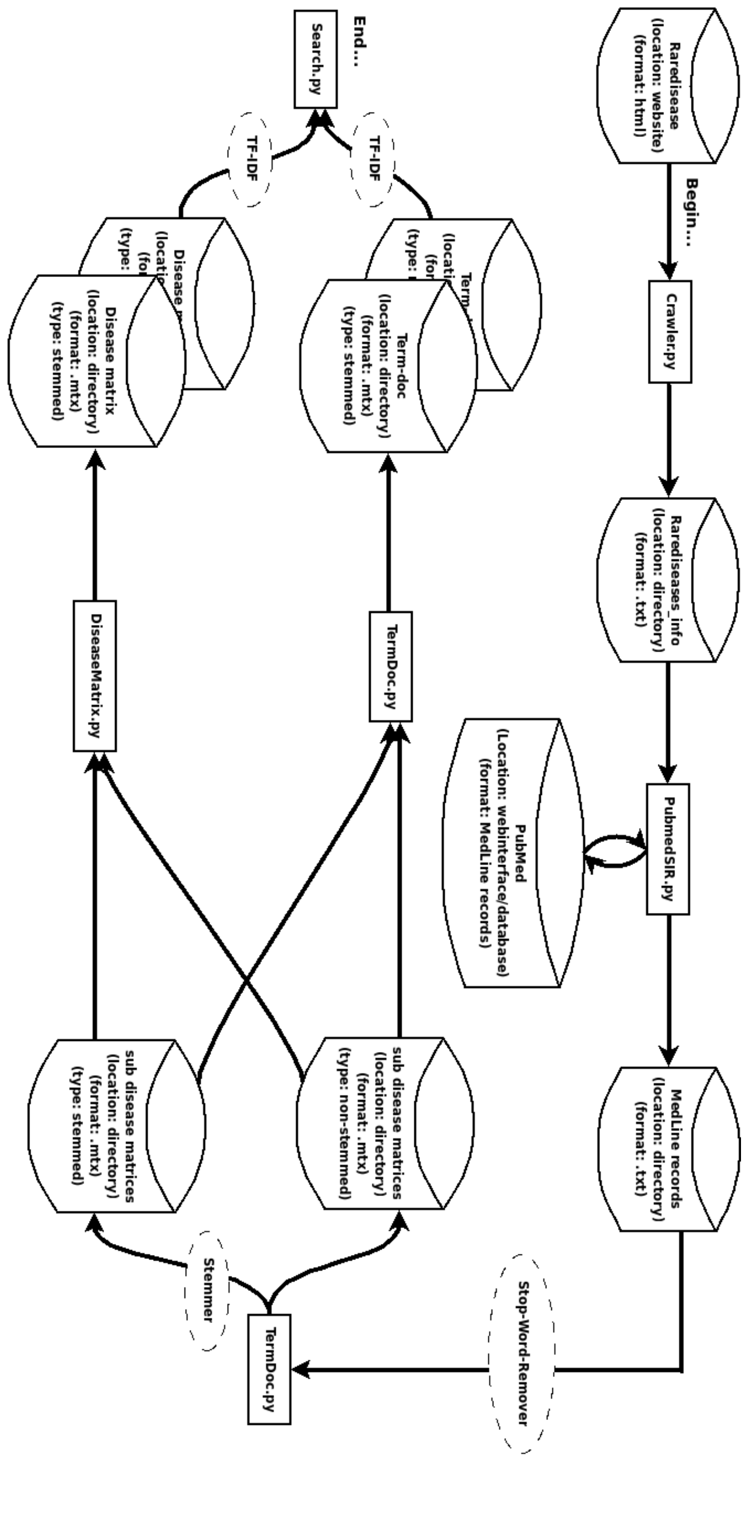


Figure 3.1: Overview diagram of the system

3.2 Modules

In this section, we will go through the individual modules described in section 3.1. We will provide an overview of the module, its parts and the way that the data — in between the modules — is structured. We will also be looking at the filter modules, the auxiliary modules and the modules used for data analysis.

3.2.1 Crawler

Overview and Purpose

The crawler is the first step in creating a database of MedLine records, containing information about rare diseases, since its main purpose is to gather information about what to search for in PubMed.

As described in 2.2.1, Raredisease.info contains a list of rare diseases and a varying degree of information on each specific disease. We were referred to the website by Henrik L. Jørgensen [10]. A Crawler to collect information from the site, was the first module to be made. The crawler goes through every disease from A to Z and 0-49 and saves the names of the diseases and (if any exist) the synonyms, the specialized search string for PubMed and a description of the disease. This information is then used by a SIR-module which is described in the following section 3.2.2.

Our main module is named *DiseaseCrawler*. It crawls the Rarediseases.info web page and gathers information as described above. It is a rather large module since it has to take a series of anomalies into account when crawling Rarediseases.info (like dysfunctional sub pages, strange characters and unexpected white-spaces). It utilizes the auxiliary modules *TextCleaner* and *IOmodule*, described in section 3.2.5.

Methods and data description

The crawler accepts a list of letters for which to gather information from, e.g. ['A'] means gather all diseases beginning with A. It utilizes the HTML parser library Beautifulsoup [13] to parse the web pages, looking for disease names, synonyms, handcrafted searches and uids. The crawled data is all stored in database of dictionaries on the form:

{'terms': '', 'desc': '', 'db': u'omim', 'syn': [u'Pectus excavatum', u' macrocephaly and dysplastic nails', u'Familial short stature', u' developmental delay', u' pectus abnormalities', u' distinctive facies', u' and dysplastic nails'], 'uid': u'600399'}

The name of the file — that each of the data sets are stored in — is the name of the disease. The above shows a example for the disease 'Zori Stalker Williams syndrome'. The key 'terms' will contain the handcrafted search string for PubMed if one is found while 'desc' contains the description of the disease if one is available (unfortunately on Rarediseases.info only 6.94% contain one). 'db' represents the choice of database to use and refers to either PubMed or OMIM in our current cases. It is necessary to know how to search for the disease in Entrez, as described in the following section. 'syn' is a list containing the various synonyms associated with the disease and used for finding more relevant information about the disease. 'uid' is a unique identifier found on all OMIM links and in some cases on pre-calculated PubMed searches.

3.2.2 SIR (Search and Information Retrieval)

Overview and Purpose

The *PubMedSIR*-module reads in the information saved by the crawler (or any other crawler). It uses Entrez for accessing, searching and retrieving MedLine records from PubMed. The information contained within the MedLine record represents our knowledge base about the diseases. The *PubMedSIR*-module is set to search in such a way that we hope to optimizes the retrieval of records that are actually relevant to the given disease. A maximum of 500 MedLine records are downloaded per disease using a two phase search - all containing an abstract.

The main module is called *PubMedSIR* and is used to search and retrieve MedLine records from the PubMed database.

As mentioned above the searching is split into two phases, where at most 250 MedLine records are looked for in each phase. It first examines whether there is a handcrafted search string to search for or whether the disease has a PubMed or OMIM unique-id (uid). When searching for the handcrafted search string, *PubMedSIR* automatically adds the additional search options "AND hasabstract[text]" to the string. This makes sure that all the MedLine records, that are returned, contain an abstract. This is unfortunately not possible when dealing with PubMed/OMIM uids which means that we have to employ other means to ensure that the returned MedLine records contain an abstract. This is carried out by the method `getMedLineList` which takes a list of PMIDs, downloads them from PubMed and runs through all the MedLine records, selecting only those containing an abstract. Making a local clean to ensure that the MedLine records contain abstracts also means that we can not guarantee 500 MedLine abstracts for a disease even thought they are available. This is a minor fault in our system that should have been corrected if time allowed it but we have chosen to continue with the information we have available. Alternatively additional search options could be to also include constraints for getting only abstracts in English, only records published after a certain date etc. For options see the site PubMed help search [42]

PubMedSIR relies primarily on the function `getArticleIDsFromMultipleSources` for searching across the two major databases of Entrez - PubMed and OMIM. We have chosen not to remove duplicate MedLine records between the first and second phase of the search because it is our belief that — if a record is present in both searches — the terms are worth counting twice. The searches are done as the described below.

First phase of the search:

- Search for term if it is present, OR
- Search for PubMed/omim uid.

- If we have obtained less than 250 MedLine records,
  - Search for the disease name on PubMed.
  - Eliminate duplicates.

Second phase of the search:

- Calculate all possible combinations of the synonyms.
- Search for the combined synonym. If a combination returns 0 results then eliminate all future searches that contains this combination since PubMed put 'AND' in between search terms (meaning that future searches containing this combination will also return 0 results).
- Fill up until we get at most 500 MedLine records.

Method and data description

The primary function of the module is `gatherOfAllThings`, which reads in the information that was saved by the crawler. This information is passed onto `getArticleIDs` that in turn calls `getArticleIDsFromMultiSource` which searches the items specified within the disease dictionary. `getArticleIDs` is also the function that keeps track of the number of MedLine records that are downloaded for each disease.

A typical dictionary read in from the crawler looks as follows:

{'disease x': {'syn' : [xx, yy, zz], 'term' : string, 'uid' : string, 'description' : string, 'db' : pubmed | omim}, 'disease y': {'syn' : [aa, bb], 'term' : string, 'uid' : string, 'description' : string, 'db' : pubmed | omim}, ...}

`gatherOfAllThings` completes by performing a write out of the MedLine records to the disk in the following format:

{'disease a': [pmid1, pmid2, pmid3...], 'disease b' : [pmidx, pmidy,...], ...}

The *PubMedSIR* module uses the following auxiliary modules (see section3.2.5):

- *SearchTermCombiner* which is a simple module that is used to combine search terms in all possible unique combinations.
- *IOmodule* handles Input/Output.
- *TextCleaner* is used to sanitize the input strings.

For more information about the gathered data set, see section 3.3.

3.2.3 TermDoc

Overview and Purpose

The information gathered from the *PubMedSIR*-module now needs to be processed to allow queries to be made on it. An often used method in Information Retrieval (IR) is the vector space model 2.3 that represents the gathered information as document vectors (in a term document matrix). The result is that queries to the system can be made using a query vector, getting a similarity score/measure against all documents contained within the model. In the following, we will go through the creation of the sub term document matrices, the large term document matrix and the compressed disease matrix.

We use a two-phase approach to construct the complete term document matrix.

In the first phase, we make a sub term document matrix for each disease containing the information from the MedLine records. We split up the abstract, title and MeSH terms if present. Various filters can be applied to the terms, e.g. stemming and stop word removal. We choose to remove any kind of punctuation and the like because otherwise the terms remain very noisy ("blood" and "blood." would be two different terms). We keep single letters (except for 'a' which counts as a stop word), because many diseases contains single letters as identification of which type they are, e.g. 'Hemoglobin C disease'. It is an fault in our system that we do not keep 'a', but this was discovered to late.

The second phase simply goes through the sub term document matrices and fill the term count values into complete term document matrix.

There are two main modules. The first — called *TermDoc* — is able to make sub term document matrices from a folder containing MedLine records and to combine a folder containing sub term document matrices into a complete term document matrix. The second one is called *DiseaseMatrix* and makes a matrix with disease vectors instead of document vectors.

Method and data description

The main function for creating the sub term document matrices from a folder containing MedLine records is `MedLineDir2MatrixDir`. This function requires a hash table containing hashes for all the terms and pmids of the MedLine record. The need for hash tables comes from the fact that the data structures, we have chosen, do not support string entries. So hashes can be made by the `createTermAndPmidHashes`. This function goes through a folder containing MedLine records, while building a term and pmid hash table. When `MedLineDir2Matrix` has read in the hash, it proceeds by calling *gatherMatrixData* on each file within the MedLine record folder. `gatherMatrixData` extracts information from the file by the use of the auxiliary module *RecordHandler* (see section 3.2.5). The information can be specified by the user; title, abstract and MeSH terms are chosen by default, as these seem to give a good overall description of a disease. This is also the place to perform stop word removal and stemming. We have chosen to create both a stemmed and an unstemmed matrix in order to test what performs best. `MedLineDir2Matrix` then calls `populateMatrix` with the data from `gatherMatrixData`. This creates and returns a term document matrix. Last it calls *IOmodule* (see section 3.2.5) to write the created term document matrix to the disk in Matrix Market format (see section 2.6.2).

For creation of the large term document matrix, the function `createTermDoc` is used. This goes through the folder containing the sub term matrices and places the term count for each of the MedLine records in the right place in the term document matrix. This is basically done by looking up where to place them in the hash table. them. If the same MedLine record exists in two different diseases, the term counts are summed. When completed, it is written to the disk in Matrix Market format.

The disease matrix is created by calling `constructDiseaseMatrix` with a folder of sub term document matrices as input. It then runs through every of the sub term document matrices and calls `getColumnSum` for each of them. This sums the sub-matrices to a single vector and returns one row for each of the diseases which can be used to represent it. `getColumnSum` has the option of making the average column sum instead of just summing them. This option can be used to normalize the disease vectors, should it be needed. The disease matrix is (like the term document matrix) based on hash tables. These can be created by running `createDiseaseHash` on a folder containing sub term document matrices.

The *TermDoc* module uses the following auxiliary modules (see section 3.2.5):

- *RecordHandler*, which is used for extraction with the records contained within the MedLine records, e.g. 'AB' for abstract etc.
- *FilterInterface* used to get access to Porter stemmer and stop word removal of string.
- *IOmodule* and *TextCleaner* as mentioned in the previous section.

3.2.4 FilterInterface and Heuristics

Overview and Purpose

When dealing with the amounts of information — in a system like this — there is a need to make some modifications to the data. We choose to sanitize the input information to our system by removal of punctuations, and by making every term lowercase. This helps reduce the number of different terms in the system. This has the side-effect that it also removes punctuation within description of e.g. chromosome errors. Taking an example, the string "1q42.4-qter duplication" will be split into '1q42', '4', 'qter' 'duplication'. We do, however, not consider this to be a problem since the query receives the same preprocessing as the term document matrix and it should still be possible to retrieve the right information[1]. The simple string cleaning also allows the user to use other notations for the same gene[2].

[1]Using regular expression, it is possible to preserve the above string as: '1q42.4-qter', 'duplication' but we do not believe it important for the prototype

[2]'1q42.4-qter' and 1q42-4-qter amounts to the same

Another common technique in IR is to use stop word removal. This is because words like 'this', 'the' and 'a' are very common and thereby do not contain any information in the term-independent vector space model. In some circumstances, it is also normal to remove single letter characters but as some diseases are characterized by having a special type (as mentioned in 3.2.3), we choose not to remove single letters. However, our stop word remover does unfortunately remove 'a' due to its frequency in the English language. As mentioned earlier, we did not have time to correct this error.

Some Numbers about Filtering

Making a 'raw' term document matrix, without any filtering results in 1,945,966 terms. After sanitizing the information there are 465,220 terms and after stemming there is a further reduction to 390,766 terms. There are a couple of modules involved with filtering. We have made a *FilterInterface* module to provide easy access to the different filters.

FilterInterface

This is simply a gateway to various filters that are implemented in separate modules. It is designed to return e.g. a stemmer or a stop word remover that can be run on the abstracts before the term document matrix is constructed. In the current prototype, it contains the modules *StopwordRemover*, *Stemmer* and *TFIDFMatrix*.

StopwordRemover

The stop word remover allows for list of stop words to be supplied by the user. By default it uses the nltk.corpus.stopwords of English stop words which contains 127 stop words. There are other languages present in the stop word corpus for a total of 2431 words, e.g. German, Danish, Swedish, Norwegian and others. We do not know if any important words are removed due in a multiple language stop word removal. We assume that most of our information is in English and have chosen only to remove English stop words. It is possible to setup additional options within the *PubMedSIR* module (section 3.2.2) so that it will only gather MedLine records containing abstracts in English but this is preserved for a later version of the system.

Stemmer

To preserve flexibility our system allows another stemmer to be sent to the function replacing the default stemmer. The default stemmer is *nltk.PorterStemmer().stem* that performs stemming on our abstract, title and MeSH terms to "smooth" out the terms. It is only advisable to run the stemmer after the stop word remover. This is mainly because the stemmer changes some stop words so that they will not be recognised by the stop word remover, e.g. performing stemming on 'this' results in 'thi' which is not included in the default stop word corpus.

TFIDFMatrix

The *TFIDFMatrix* module is used to perform the TF-IDF transformation of a term document matrix using the equation from section 2.4.2. It performs the transformation by reading the term frequency (tf) from an original matrix only containing term counts and then by making a log-transformation of the tf. For finding the inverse document frequency (IDF), we have made a precalculated hash table containing the number of documents that the different terms are present in such that $idf = \frac{D}{\sum_{d'=1} \delta_{d'w}}$. We then store the calculation of $tf \cdot idf$ at the term's position within the term document matrix. The transformed term document matrix is then saved to the disk. The module then performs normalization of the document vector to make sure that each document has the same influence upon the result of a query (and is used for the enhancing the speed of the cosine similarity calculation described in section 2.5). The normalization is carried out as usual vector normalization $\frac{\overrightarrow{a}}{||a||}$.

3.2.5 Auxiliary modules

Auxiliary modules are used by the different modules to perform tasks such as input/output, stemming, stop word removing, cleaning text string or combining synonyms into search queries.

IOmodule

Performs various I/O functions. For instance, when a module is writing or reading objects like hash tables to/from the disk, it simply calls the `pickleIn` or `pickleOut` function with a path. The object is then written or read. It is also able to return a sorted list of file references from a folder, which is very useful when one needs to keep track of how far the process has come. This module also allows for term document matrices to be written or read from the disk using the Matrix Market format (see section2.6.2).

TextCleaner

This module performs string manipulation like removing tags from HTML code, sanitizing strings for punctuation and all other special characters, and decoding various HTML characters. Most of these task are obtained by returning a regular expression for the specific task.

RecordHandler

The *RecordHandler* module is used to read information fields from MedLine records which it returns as a dictionary containing the requested fields.

3.2.6 SearchInterface

The search interface implements different approaches of measuring similarity/distance between the query vector and document vector in our term document matrix. Our two choices of measure in the vector space model are the cosine similarity measure and a simple sum measure. Instead of going through all the rows (documents) in our matrix, we take the terms from the query vector and only look up the the documents containing one or more of the queried terms. This limits our search space and significantly enhances the time it takes to process a query.

SearchInterface

This is the simple search interface that allows the different search methods to be called, hence acting as a gateway like the *FilterInterface* described earlier.

CosineMeasure

This module is used to perform a search using the cosine measure for distance calculations between the query vector and the rows of our term document matrix. It uses *SearchTermDoc* to get the row indices of which rows the query terms are present in. It then sums the scores in accordance to the occurrence of the query term. This should resemble usual cosine measuring between vector when performed on a pre-normalized vector space (see section 2.5).

SumMeasure

The *SumMeasure* module is used to perform a different kind of measure. It performs a summing of the entries in the in the document vector according to the terms of the query vector. It basically acts as the cosine measure but is used on a vector space that is not normalized. Again note that the reason we can compare the two measures is because of the simplifications made in 2.5.

SearchTermDoc

This module is used as a support module for performing searches. Given a search vector, it will return the row indices of the term document vectors that contain any of the terms. It can extract the term columns with the relevant documents indices and it can create the hashes needed for normalization and for column element counts. It is also performs reverse look up of pmids (documents) given a pmidhash value.

3.2.7 Data Analysis Tools

In order keep track of the amount of information that we have collected, we have made a "crude" module for gathering information. It can be used to get the total number of pmids including duplicates, the number of MedLine records containing a title or the number of diseases that contain a description. In addition to this, we made a module to perform hierarchical clustering of the diseases of top 20 results returned by our system.

The modules, that are part of the data analysis suite, is *Cluster* which performs the clustering, *DistanceMeasure* which implements different distance/similarity measures to be used within *Cluster* and *Stat* which is able to count various information fields contained within the MedLine records.

Cluster

The *Cluster* module contains various functions in relation to hierarchical clustering and drawing of dendrograms of the returned clusters. The hierarchical clustering has unfortunately not been made as generic as it could be. For now, slight modifications are required between running either on a disease matrix / term document matrix or a sub term document matrix. We have no intentions of performing a full clustering on a term document matrix, as it simply contains too many entries to consider clustering - at least with the resources available currently. The hierarchical clustering and dendrogram functionality are based on Collective Intelligence [43] with slight modification to adopt it for our data.

DistanceMeasure

This module simply implements its own cosine measure functions for sparse and dense matrices.

Stat

This module is able to count the various different fields within the MedLine records, e.g. how many a title, a MeSH, etc. It is also able to count how many duplicate pmids there are.

3.3 The database

Our raw data set consists mainly of two parts that are gathered independently. The first part is the information gathered from Rarediseases.info. The files reside in a sub folder called *rarediseases_info* containing 6881 text files. Looking at one of these files it is possible to see exactly what information have been used to retrieve the MedLine records for a specific disease. The second part of our raw data set is the information gathered from PubMed by the *PubMedSIR* module. This information can be find in the sub folder *MedLine_records*. Again we have chosen to store it as plain text files which enable the use of GNU unix/linux command line tools for a quick look inside or using grep to look for specific words inside a disease file.

Due to the limit on 500 abstracts per disease and with a total of 6,881 different rare diseases from Raredisease.info, the theoretical upper limit on the number of abstract is 3,440,500. But since the diseases are rare and the crawled information from Rarediseases.info faulty at times, in reality the number of returned MedLine records is much smaller. In fact, we only have 602,466 unique MedLine records (about 2.8 million from the theoretical limit) and approximately 1,036,432 when counting duplicates. One of the MedLine records is even shared among 240 diseases which indicates that it is an overview over many diseases. There are also 505 diseases that do not return any information at all. This means the remaining 6,376 diseases, on average, have 94.49 MedLine records each. When searching PubMed, we need to impose the 500-limit on the number of abstracts because (even though the diseases are rare) some of them will return a lot of information. Kidney cancer, though on the list of rare diseases, will return 51,393 hits (January 3, 2010) with a search on PubMed (only those with an abstract) and this is without considering any synonyms or possibly handcrafted search terms.

We have chosen to remove the 505 empty disease entries from our data set because, without any information about these diseases, our system will be unable to find/diagnose them.

More statistics on the data

Out of the 1,036,432 MedLine records, 1,036,417 have a title. This is nearly 100% (99.99%). Not all of the MedLine records have MeSH terms although 924,026 has. This is 89.15% of all the entries.

3.4 Technical Conclusions

When performing text mining, robustness is needed to be able to handle various situations. This became apparent to us after having written the first version of it. Due to the inconsistency of Rarediseases.info, it crashed every time that it ran into a new special case on Rarediseases.info. Therefore, when crawling website based on incomplete topics like rare diseases, its important to carry out proper error handling and logging which diseases were missed in the first run as the presence of errors is almost certain. As a related side note, the BeautifulSoup module is a really useful tool when crawling HTML since it is able to correct and prettify many common website errors.

Gathering data from PubMed was performed by the Entrez module which on several occasions crashed. This created the need to gather the MedLine records in chunks to be able to resume them at any point. When collecting data from OMIM- or PubMed-uid links, there is no way to ensure that the returned MedLine records contains abstract and this needs to be dealt with locally (as mentioned in 3.2.2). Before performing text or data mining, ALWAYS seek the permission of those running the site or sites. During this project, we got banned from Rarediseases.info once and from Orpha.net twice. This was not because we broke any laws or rules but because most websites today protects themselves from harmful bots, replay attacks and other risks to the website. If you do not have permission to find information on the website, at least make sure you give your credentials, browser type, etc. with the crawler.

Constructing a term document matrix requires a sparse data structure for being stored on disk and in memory but when working with document vectors, making them dense can give a huge speed up on arithmetic operations. Choosing to rewrite some of the more computational parts to a low level language like C would also increase performance. Saving intermediate steps along the way while making term document matrices also allows other preprocessing steps to be performed, if needed later in the project and is recommendable for large projects.

When querying the matrices, it is important to try several different methods since the most well known or obvious one, might not be the best choice (as we shall see in the following chapter).

Chapter 4

Experiments and Results

In this section, we introduce the test cases that we intend to use. We go through the details of our cosine and sum measure scoring schemes that we will be using to test our system's ability to rank a correct disease given a list of symptoms. By comparing the individual top scores of each different measure tested on a given matrix (stemmed or non-stemmed), we find the most efficient measure to score data on our system. It should here be noted that each time we score a given disease, we do it by taking the top 3000[1] of the documents returned by the similarity measure and the *SearchCases* module. Using the most efficient measure, we try to score 5 blind tests provided by a chief physician.

We also discuss clustering of the results, protein/gene filtering improvements, the noise of overview articles and the effect of concensus normalization.

4.1 Test cases

BMJ

In order to test our system we must find some suitable test cases that are not biased towards our own system. We have chosen to first of all test our system against a subset of the disease cases in BMJ [1], that is disease cases which can be found in our system[2]. However, there is one major difference between the tests conducted by the people behind the BMJ article - they have a medical background (a respiratory and sleep physician and a rheumatologists) contrary to our computer science background. This means that we have no bias or knowledge about selecting symptoms and — as they explain — given some of the symptoms, the correct diagnosis was evident to them. Note that we will (in the following sections) be referring to the subset of the test cases as BMJ since this is were it was found.

The subset of the BMJ test cases include the following 13 diseases (Table 4.1):

[1]A number chosen at random in between our total number of different diseases

[2]As mentioned earlier in 3.3 our system can only help diagnose the diseases contained in the system

Disease	Symptoms
Infective endocarditis	Acute, aortic, regurgitation, depression, abscess
Cushing's syndrome	hypertension, adrenal, mass
Eosinophilic granuloma	Hip, lesion, older, child
Ehrlichiosis	fever, bilateral, thigh, pain, weakness
Neurofibromatosis type 1	multiple, spinal, tumours, skin, tumours
Pheochromocytoma	hypertension, papilledema, headache, renal, mass, cafe, au, lait
Creutzfeldt-Jakob disease	ataxia, confusion, insomnia, death
Churg-Strauss syndrome	Wheeze, weight, loss, ANCA, haemoptysis, haematuria
Dermatomyositis	myopathy, neoplasia, dysphagia, rash, periorbital, swelling
Cat Scratch Disease	renal, transplant, fever, cat, lymphadenopathy
TEN	bullous, skin, conditions, respiratory, failure, carbamazepine
MELAS	seizure, confusion, dysphasia, T2, lesions
Brugada syndrome	cardiac arrest sleep

Table 4.1: Disease / Symptoms list for the 13 BMJ cases

Orpha.net

To examine significance of the test result, we have additionally selected some diseases at 'random' from Orpha.net. We require that the disease has a description on Orpha.net containing a sentence with 'characterized by'. Occasionally we have meant that the 'characterized by' contained too many specific symptoms (e.g. derivatives of the name of the disease or a several sentences long list of symptoms) and have removed certain symptoms from the list. Examples of reductions would be[3]

congenital anomalies (microcephaly, specific facial characteristics, broad thumbs and halluces and postnatal growth retardation), intellectual deficit and behavioural characteristics

has been reduced to

congenital anomalies, intellectual deficit, behavioural

and

congenital malformations: hydrocephalus (due to Dandy-Walker anomaly), cleft palate, and severe joint contractures

has been reduced to

congenital malformations: hydrocephalus, cleft palate, severe joint contractures

The test cases from Orpha.net, which includes 29 different diseases, can be found in table 4.2.

[3]Note that this is based solely on our own judgement as non-physicians.

Disease name	Symptom list
Apparent mineralocorticoid excess	early-onset, severe hypertension, associated, low renin levels, hypoaldosteronism
Rubinstein-Taybi syndrome	congenital anomalies, intellectual deficit, behavioural characteristics
Aagenaes syndrome	chronic severe lymphoedema, severe neonatal cholestasis, lessens during early childhood and becomes episodic
Aase Smith syndrome	congenital malformations: hydrocephalus, cleft palate, severe joint contractures
Achondroplasia	short limbs, hyperlordosis, short hands, macrocephaly, high forehead and saddle nose
Acalvaria	missing scalp and flat bones over an area of the cranial vault
Acrodysostosis	abnormally short and malformed bones of the hands and feet (peripheral dysostosis), nasal hypoplasia and mental retardation
Acromegaly	progressive somatic disfigurement (face and extremities) and systemic manifestations
Biliary atresia	biliary obstruction of unknown origin, neonatal period
Bronchiolitis obliterans with obstructive pulmonary disease	inflammatory and fibrosing thickening of bronchiolar walls, airflow obstruction
Cholera	severe diarrhea and vomiting
Choroideremia	progressive degeneration of the choroid, retinal pigment epithelium (RPE), and neural retina
Coats disease	abnormal development of retinal vessels (telangiectasia) with a progressive deposition of intraretinal or subretinal exudates
Omphalocele cleft palate syndrome lethal	omphalocele and cleft palate
Darier disease	keratotic papules in seborrheic areas and specific nail anomalies
Ichthyosis hepatosplenomegaly cerebellar degeneration	ichthyosis, hepatosplenomegaly and late-onset cerebellar ataxia
Emery-Dreifuss muscular dystrophy	muscular weakness and atrophy, with early contractures of the tendons and cardiomyopathy
Costello syndrome	postnatal growth retardation, coarse facies, intellectual deficit, skin anomalies and cardiac abnormalities
Fibrodysplasia ossificans progressiva	congenital malformation of great toes, progressive, disabling heterotopic osteogenesis in predictable anatomical patterns
Acropectorovertebral dysplasia	fusion of the carpal and tarsal bones, with complex anomalies of the fingers and toes
Osteogenesis imperfecta	increased bone fragility and low bone mass
Primary biliary cirrhosis	injury of the intrahepatic bile ducts
Hennekam syndrome	lymphoedema, intestinal lymphangiectasia, intellectual deficit and facial dysmorphism
Hyperlysinemia	elevated levels of lysine in the cerebrospinal fluid and blood
Jackson-Weiss syndrome	tarsal and/or metatarsal coalitions and variable craniosynostosis, accompanied by facial anomalies, broad halluces and normal hands
Jalili syndrome	amelogenesis imperfecta and cone-rod retinal dystrophy
Jeune syndrome	narrow thorax and short limbs
Multiple myeloma	overproduction of abnormal plasma cells in the bone marrow and manifested by skeletal destruction, bone pain, and presence of abnormous immunoglobulins
Trichodental syndrome	fine, dry and short hair with dental anomalies

Table 4.2: Disease / symptom list for 29 Orpha.net test cases

Note: In the tests that follows, the *Jackson-Weiss syndrome* will occur twice in all the case - hence producing 30 instead of 29 diseases. This error was discovered too late for a rerun of all the tests. However, *Jackson-Weiss* does not score in top 20 at any point and should not greatly affect the test results.

Blind Tests

In addition to the BMJ and Orpha.net test cases, we have performed a blind test on disease cases given by Henrik Jørgensen [10], disease name and symptoms can be in table 4.3. Here, we were given 5 different test cases and the queries made are based upon symptoms extracted from the cases based on our own judgement. The test is done with the highest performing measure and matrix - determined by the tests run on the BMJ and Orpha.net test cases in section 4.1.2. The results of the blind test can be found in section 4.1.5.

Disease name	Given case	Used symptom query
Fibrodysplasia ossificans progressiva	Dreng, normal ved fødslen bortset fra deformitet af begge storeter (de manglede et led). Udvikler sig normalt efterfløgende. Ved 5 års alderen der viser knoglevæv uden malignitetstegn. Kort tid efter biopsien udvikles mere knoglevækst, præcis der hvor man har skæret.	Boy, normal birth, deformity of both big toes (missing joint), quick development of bone tumor near spine and osteogenesis at biopsy.
Adrenoleukodystrophy autosomal neonatal form	Normally developed boy until age 5, where he progressively developed the following symptoms: Talking difficulties, seizures, ataxia, adrenal insufficiency and degeneration of visual and auditory functions.	Normally developed boy age 5, progessive development of talking difficulties, seizures, ataxia, adrenal insufficiency and degeneration of visual and auditory functions
Papillon Lefevre syndrome	A boy age 14 comes to the doctor with yellow, keratotic plaques on the skin of his palms and soles going up onto the dorsal side. Both hands and feet are affected. He equally had swollen and very vulnerable gums since the age of 4 with loss of most of his permanent teeth.	Boy age 14, yellow, keratotic plaques on the skin of palms and soles going up onto the dorsal side. Both hands and feet are affected.
Kleine Levin Syndrome	16-årig jødisk dreng har en til to gange om maaneden anfald, hvor han først og fremmest skal sove utroligt meget - ca. 18 timer om dagen. Anfaldene varer ca en uges tid. Han ændrer karakter under anfaldene og bliver irritabel og aggressiv, når han vækkes. Når han er vågen i anfaldsperioden spiser han helt utroligt store mængder mad, og hans appetit på sex er endvidere abnormt stor.	Jewish boy age 16, monthly seizures, sleep deficiency, aggressive and irritable when woken, highly increased sexual appetite and hunger.
Schinzel-Giedion Syndrome	The patient is a male child presenting at birth with numerous malformations. He had midfacial retraction with a deep groove under the eyes, and hypertelorism. A short nose with a low nasal bridge and large low-set ears were noted. He had a wide mouth and retrognathia. Hypertrichosis with bright reddish hair and a median frontal cutaneous angioma were present. The neck was short with redundant skin. Bilateral inguinal hernias, hypospadias with a megameatus, and cryptorchidism were noted.	Male child, malformations at birth, midfacial retraction with a deep groove under the eyes, and hypertelorism, short nose with a low nasal bridge and large low-set ears, wide mouth and retrognathia. Hypertrichosis with bright reddish hair and a median frontal cutaneous angioma, short neck with redundant skin, Bilateral inguinal hernias, hypospadias with a megameatus, and cryptorchidism

Table 4.3: Disease / Given case / Used query for the 5 blind test cases

4.1.1 Scoring Schemes

As mentioned in the previous chapters, we will employ two different kinds of scoring measures - the cosine and sum measure. The original idea behind using a sum measure was to test how much the cosine measure would outperform this simpler measure, but as we shall see in section 4.1.2 and section 4.1.3, the cosine measure is actually outperformed itself by the sum measure. We will try to explain this anomoly in the given section and for now focus the way we use the two different kinds of measure. The following cosine and sum score measures are described in accordance with how they function on the term document matrix. The exception of the disease matrix is described at the end of this section.

The Cosine Score

We will be testing the following three different approaches to using the cosine similarity measure: cosine mean, cosine median and cosine max.

Cosine Mean

Every disease has one or more documents attached to it (as described in section 3.3). This means that the same disease might be returned many times when looking at a top score of document similarity measures produced by, for example, the cosine score. Therefore — to give each disease a score — we use a form of consensus method where we sum the scores of each document belonging to that disease. This produces a mean score of each disease.

When the system (or more specifically the Query module) receives a query, it ranks the query vector of terms against all document vectors in which one or more of the terms has appeared. This results in a list of scores $\mathbf{x}_{\text{all diseases}} = \{x_1, x_2, \ldots, x_n\}$. It then runs through every scored document and adds the score to the disease from which the document came (in accordance with the consensus method just described). Since some documents appear in more than one disease (see section 3.3), several diseases may have the sum of a single document added to its score $\mathbf{x}_{\text{disease}_1} = \left\{x_{\text{sum for} x_2, x_7, x_i, \ldots, x_j}\right\}$, $\mathbf{x}_{\text{disease}_2} = \left\{x_{\text{sum for} x_1, x_2, x_9, \ldots, x_4 7, x_n}\right\}, \ldots$. Lastly, we evaluate the total ranking of each disease. We combine each x_{disease_1}, x_{disease_2} into a list of all the returned disease scores $SL = \{x_{\text{disease}_1}, x_{\text{disease}_2}, \ldots, x_{\text{disease}_n}\}$. These are then sorted and the highest scoring is deemed to be the most likely to be the correct disease given the query vector.

Cosine Median

The median is calculated much like the mean, apart from selecting the median of $\mathbf{x}_{\text{disease}_1} = \{x_2, x_7, x_i, \ldots, x_j\}, \mathbf{x}_{\text{disease}_2}, \ldots, \mathbf{x}_{\text{disease}_n}$, instead of summing the scores as we did above.

Cosine Max

Does the same as above, except that it selects the maximum scoring in each disease list and sorts the resulting list, selecting the highest scoring as the most probable.

The Sum Score

The sum measure works exactly like the cosine mean measure, except for running on non-normalized vectors. See 2.5 for reasoning.

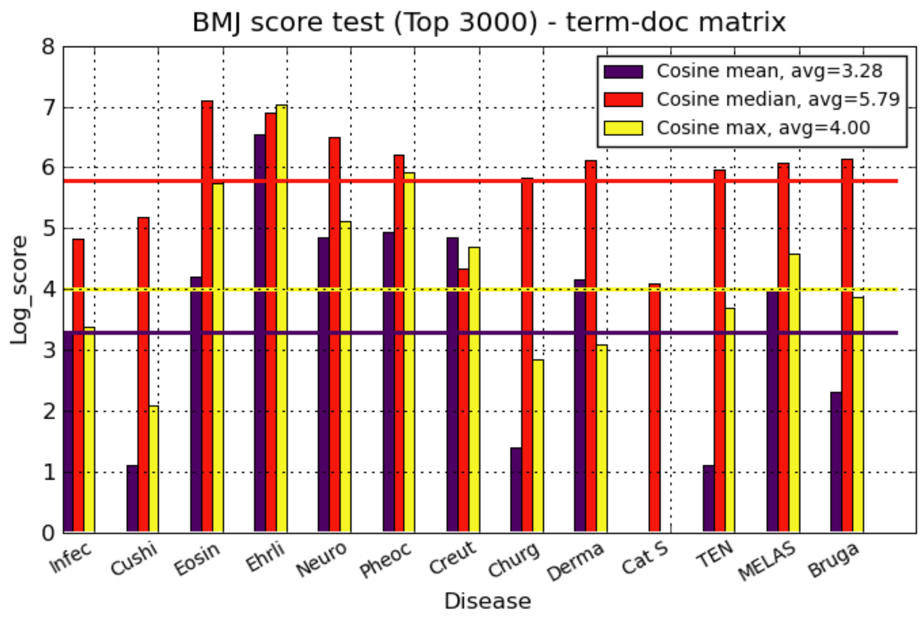
The Disease Matrix Exception

This is a short description of how we use the cosine and sum measures on the disease matrix. The disease matrix has no document vectors and is solely made up of summed disease vectors. This means that there is no point in using cosine mean, median or max, as there are no multiple label occurrences to run a consensus method over. Here, the score is either the cosine or sum measure calculated for each of the diseases that contain the queried term(s).

4.1.2 Testing the Cosine Similarity Measure

The first test we run is on the three different cosine scoring measures - mean, median and max. In the two bar charts below 4.1 and 4.2 the query scores of the BMJ and the Orhpa.net test cases are shown. These are run on the non-stemmed term document matrix. The scores a drawn on a logarithmic scale while the 'real' scores a shown below each chart. Note that the values are 0-indexed(!) and all tests are performed on TF-IDF preprocessed matrices.

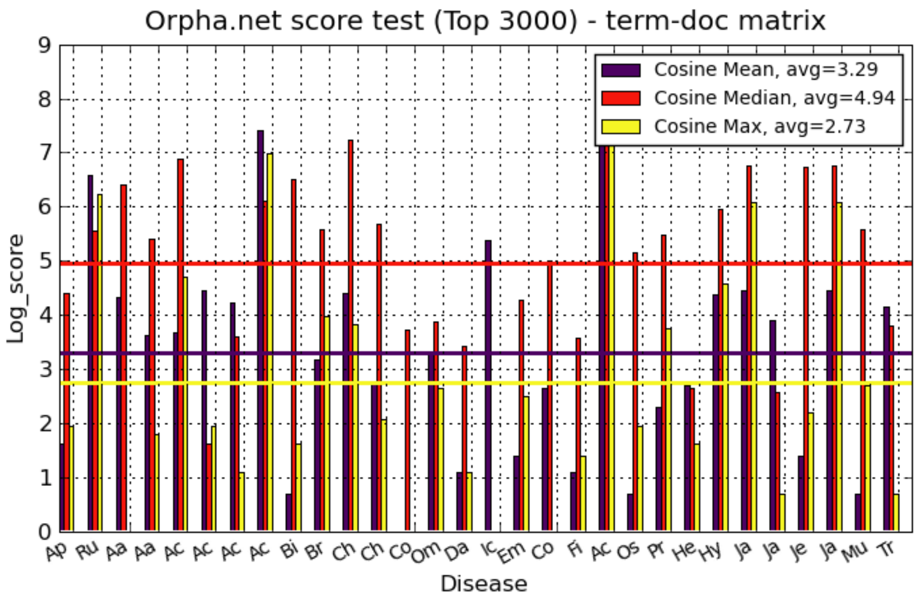
Figure 4.1: Test for mean, median and max cosine measure on a non-stemmed term-doc



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Cosine: mean	25	2	66	692	128	139	128
Cosine: median	123	179	1210	1004	665	502	76
Cosine: max	28	7	311	1123	166	375	109

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Cosine: mean non-stemmed	3	63	0	2	52	9	**5**
Cosine: mean stemmed	343	455	59	392	430	464	**0**
Cosine: max non-stemmed	16	21	0	39	96	47	**3**

Figure 4.2: Test of mean, median and max cosine measure on a non-stemmed term-doc



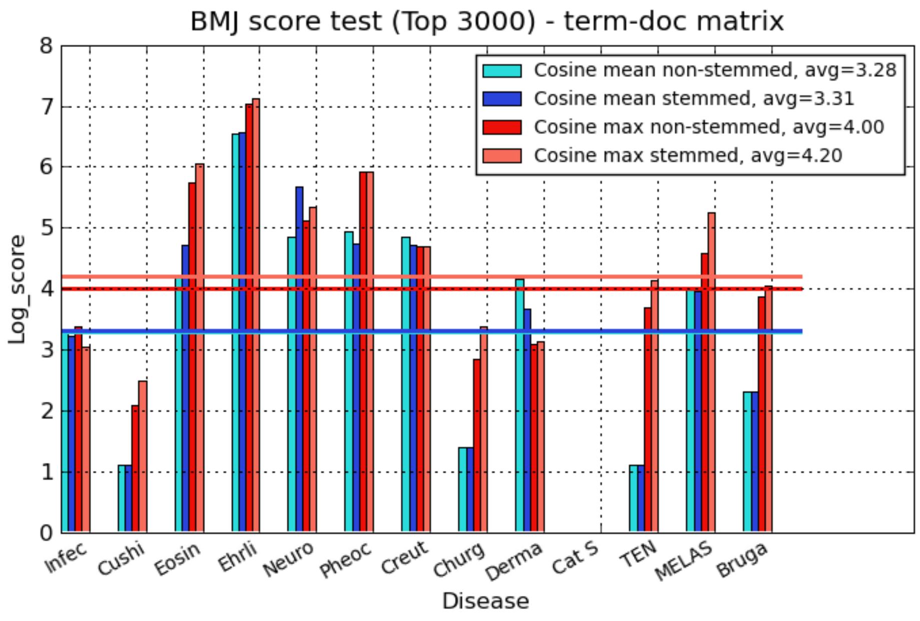
Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Cosine: mean	4	664	30	47	38	85	62	1371	1	32	83	15	0	26	2
Cosine: median	163	357	76	240	948	4	76	141	384	314	505	211	44	181	42
Cosine: max	4	858	0	10	44	15	2	541	4	116	99	18	0	6	2

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Cosine: mean	81	3	16	2	3000	4	10	13	24	66	35	3	66	4	34	**13**
Cosine: median	773	87	169	189	3000	179	265	21	491	692	37	435	692	358	233	**1**
Cosine: max	0	22	0	3	3000	9	67	5	63	201	1	8	201	9	0	**19**

As we see here, the mean cosine measure performs best in the BMJ test set, while the max cosine measure scores best in the Orpha.net test set. The median measure has an overall low score and running some quick tests on the different matrices quickly reveals that median is not well suited as a measure to be taken into consideration. Therefore we will not be carrying out further testing on the cosine median score and continues with the two remaining scores from here on. Note the score that has the worst performance in the Orpha.net test. It can and will happen that diseases are not found within the top 3000 documents that are returned. When this is the case — to avoid confusion in the bar charts and statistics — we simply set the score of any disease not found to the value 3000, representing a bad performance. Note also that a missing bar represents the top score of 0.

We now continue testing the scoring measures, this time comparing the non-stemmed and stemmed term document matrices. The results are shown in the figures 4.3 and 4.4 below.

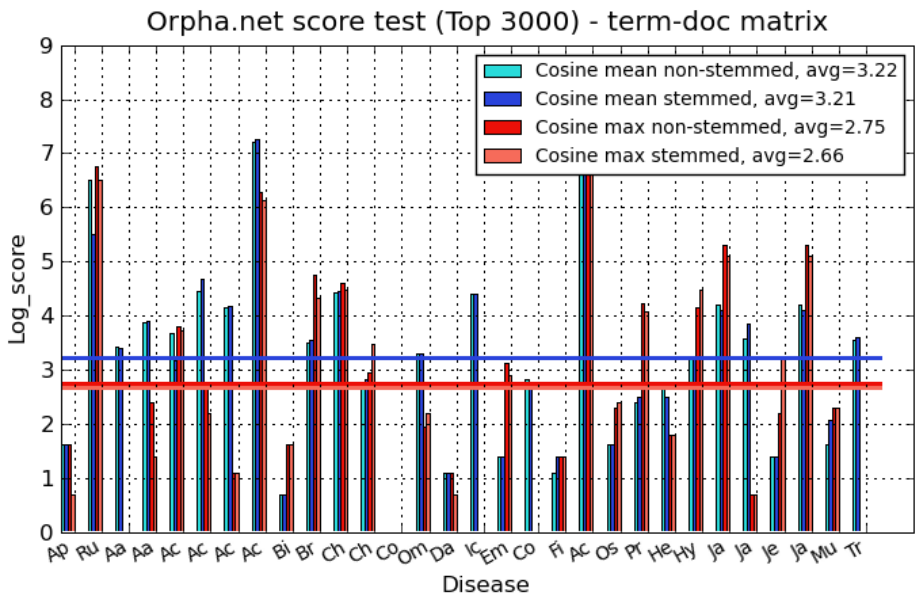
Figure 4.3: Comparison of mean and max cosine measure tests on non-stemmed and stemmed term-doc matrices



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Cosine: mean non-stemmed	25	2	66	692	128	139	128
Cosine: mean stemmed	24	2	110	710	292	113	110
Cosine: max non-stemmed	28	7	311	1123	166	375	109
Cosine: max stemmed	20	11	427	1232	210	370	108

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Cosine: mean non-stemmed	3	63	0	2	52	9	**5**
Cosine: mean stemmed	3	38	0	2	51	9	**5**
Cosine: max non-stemmed	16	21	0	39	96	47	**3**
Cosine: max stemmed	28	22	0	62	192	56	**2**

Figure 4.4: Comparison of mean and max cosine measure tests on non-stemmed and stemmed term-doc matrices



Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Cosine: mean non-stemmed	4	664	30	47	38	85	62	1371	1	32	83	15	0	26	2
Cosine: mean stemmed	4	248	29	48	23	106	64	1436	1	34	85	16	0	26	2
Cosine: max non-stemmed	4	858	0	10	44	15	2	541	4	116	99	18	0	6	2
Cosine: max stemmed	1	677	0	3	40	8	2	462	4	75	87	31	0	8	1

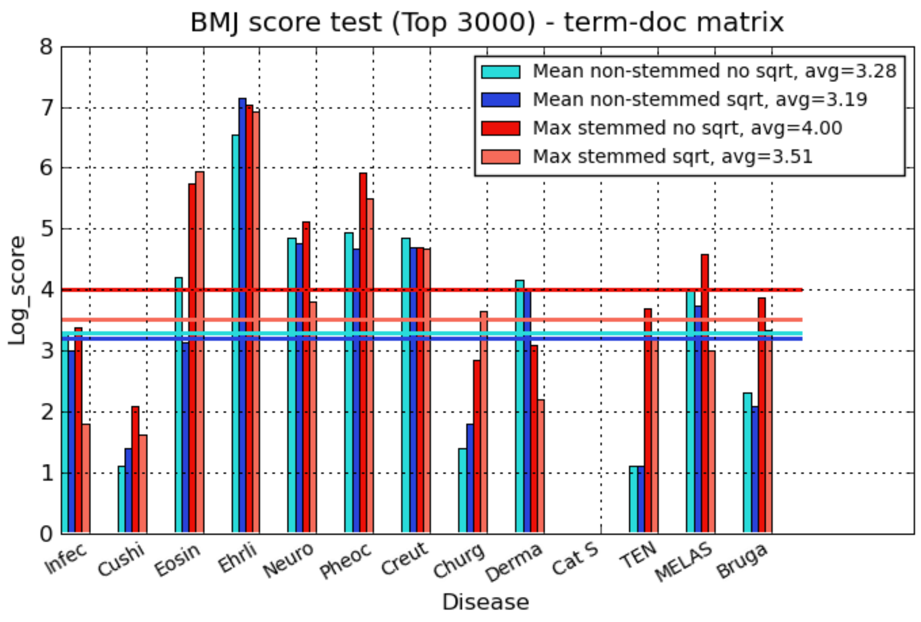
Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Cosine: mean non-stemmed	81	3	16	2	3000	4	10	13	24	66	35	3	66	4	34	**13**
Cosine: mean stemmed	81	3	15	3	3000	4	11	11	24	60	46	3	60	7	36	**13**
Cosine: max non-stemmed	81	3	15	3	3000	4	11	11	24	60	46	3	60	7	36	**19**
Cosine: max stemmed	0	22	0	3	3000	9	67	5	63	201	1	8	201	9	0	**18**

The two score tests just performed now presents us with a dilemma. In the BMJ test set the 'mean stemmed' and 'non-stemmed' scores perform best, while in the Orpha.net test set, it is just the opposite. We have chosen to cope with this by taking out the top score measure for each of the test sets - 'mean non-stemmed' from BMJ and 'max stemmed' from the Orpha.net.

The next step is to analyse our data by performing a square root transformation 2.4.4 of the TF-IDF preprocessed data above. Note that it is required that all values transformed are between 0 and 1, which in our case is guarenteed by the fact that the matrices we use for the cosine measure are normalized. The reason for the square root analysis is that it allows us to see whether the data has been correctly weighted. The square root transformation raises small values by a greater degree than it does large values. This means that if our scores improve, the information containing terms in the term document matrix have not been given high enough values by the applied heuristics.

The tests are shown in the figures below 4.5 and 4.6, where we compare the best measures from above with their square root transformation.

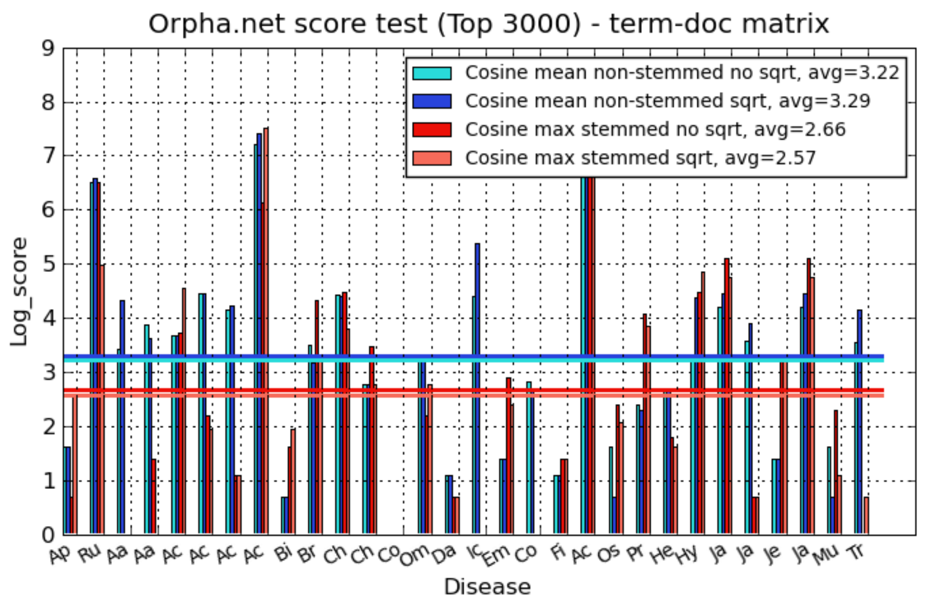
Figure 4.5: Comparison of mean (non-stemmed term-doc) and max (stemmed term-doc) cosine measure tests with and without sqrt-transformation



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Cosine: mean non-stemmed no sqrt	25	2	66	692	128	139	128
Cosine: mean non-stemmed sqrt	19	3	22	1268	115	105	108
Cosine: max stemmed no sqrt	20	11	427	1232	210	370	108
Cosine: max stemmed sqrt	2	10	136	1123	68	249	130

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Cosine: mean non-stemmed no sqrt	3	63	0	2	52	9	**5**
Cosine: mean non-stemmed sqrt	5	54	0	2	41	7	**6**
Cosine: max stemmed no sqrt	28	22	0	62	192	56	**2**
Cosine: max stemmed sqrt	44	8	0	47	65	25	**4**

Figure 4.6: Comparison of mean (non-stemmed term-doc) and max (stemmed term-doc) cosine measure tests with and without sqrt-transformation



Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Cosine: mean non-stemmed no-sqrt	4	664	30	47	38	85	62	1371	1	32	83	15	0	26	2
Cosine: mean non-stemmed sqrt	4	725	75	37	38	85	68	1651	1	23	80	15	0	26	2
Cosine: max stemmed no-sqrt	1	677	0	3	40	8	2	462	4	75	87	31	0	8	1
Cosine: max stemmed sqrt	12	145	0	0	93	6	2	1842	6	25	44	15	0	15	1

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Cosine: mean non-stemmed no-sqrt	81	3	16	2	3000	4	10	13	24	66	35	3	66	4	34	**13**
Cosine: mean non-stemmed sqrt	218	3	13	2	3000	1	9	14	78	84	48	3	84	1	62	**13**
Cosine: max stemmed no sqrt	0	17	0	3	3000	10	58	5	86	162	1	24	162	9	0	**18**
Cosine: max stemmed sqrt	0	10	0	3	3000	7	46	4	128	115	1	24	115	2	1	**19**

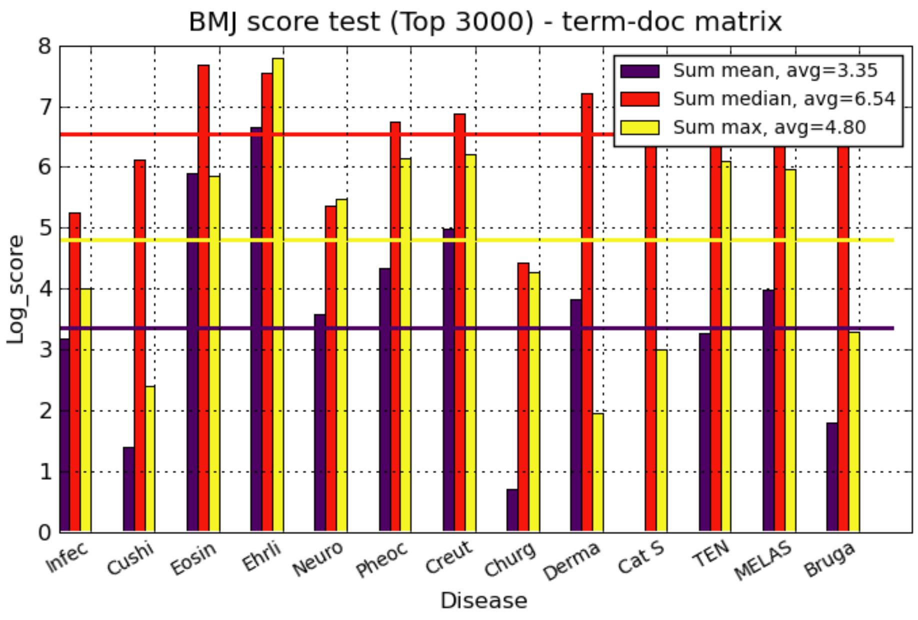
These tests reveal some interesting results. Looking at the BMJ test set, we see an overall improvement in the performance of the square root transformed measures. In Orpha.net test set there is an improvement in ′max stemmed′ measure, while a slight worsening of the ′mean non-stemmed′ measure is seen. However, there is no change in the number of top 20 results and the other measures show a more significant improvement than the worsening of the last mentioned measure. Based on these results, we will not deny that the data in the TF-IDF matrices are not as optimized as could have been expected. But we can not say if these anomalies stem from the data or the calculations themselves. For now, we choose to view the square root transformation as a general improvement.

In section 3.1.2, we will be using the best measure of the cosine scoring tests executed above - the ′mean stemmed sqrt′ and the ′max stemmed sqrt′ cosine similarity measures.

4.1.3 Testing the Sum Similarity Measure

In this section, we perform the same tests as described in the previous section, except for the square root transformation which would make no sense, as we will be running on non-normalized data. Or in other word on values above and below 1 (see section 2.4.4). The first test is run for the mean, median and max sum measures on a TF-IDF non-normalized term document matrix. The results are shown on the figures 4.7 below.

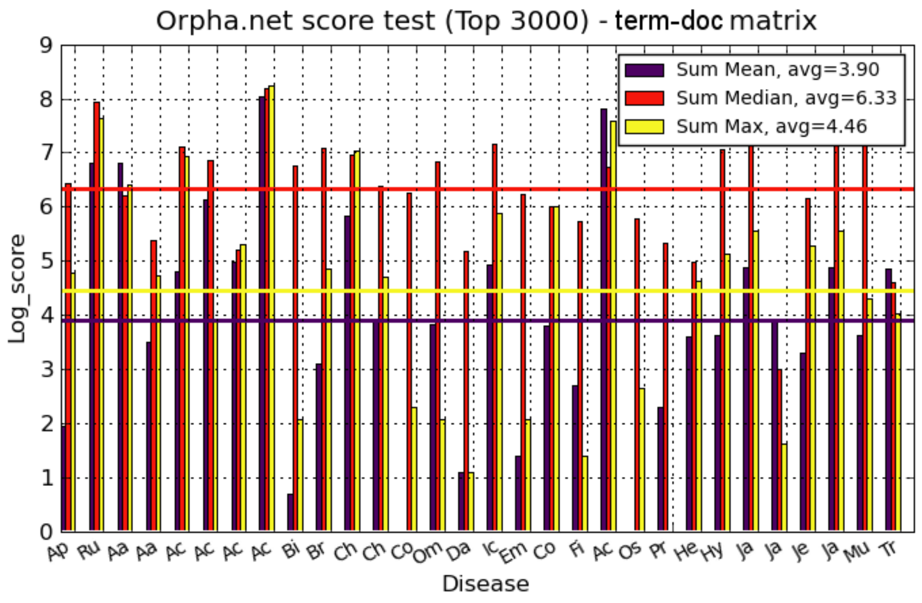
Figure 4.7: Test of mean, median and max sum measure on a non-stemmed term-doc matrix



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Sum: mean	23	3	362	772	35	76	144
Sum: median	188	459	2150	1878	213	852	974
Sum: max	54	10	344	2401	235	469	495

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Sum: mean non-stemmed	1	45	0	25	53	5	**4**
Sum: mean stemmed	83	1353	670	2193	689	1210	**0**
Sum: max non-stemmed	70	6	19	441	391	26	**3**

Figure 4.8: Test of mean, median and max sum measure on a non-stemmed term-doc matrix

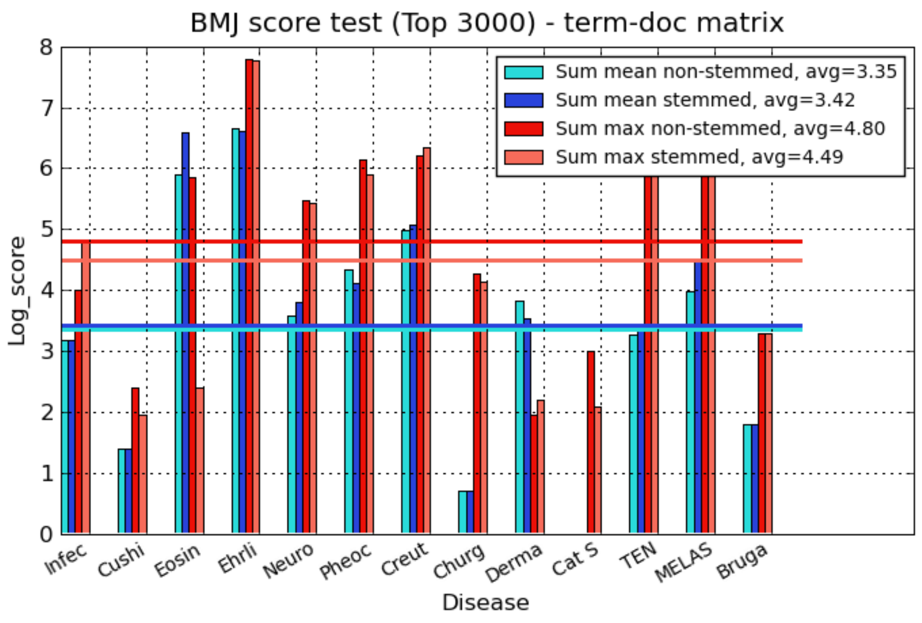


Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Sum: mean	6	910	917	32	122	460	145	3119	1	21	342	50	0	45	2
Sum: median	626	2814	495	219	1232	963	182	3590	872	1207	1056	595	526	940	179
Sum: max	119	2081	611	113	1031	48	203	3833	7	127	1139	109	9	7	2

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Sum: mean	137	3	44	14	2458	0	9	36	37	132	47	26	132	37	127	**8**
Sum: median	1292	503	408	304	845	320	204	143	1165	1763	19	467	1763	1532	100	**1**
Sum: max	357	7	401	3	1957	13	0	102	169	260	4	198	260	72	55	**9**

Like in the previous section, we again see the poor results given by the median measure and discard this for further testing. In the next tests, we compare the mean and sum measure in the stemmed and non-stemmed matrices. The tests are shown in the figures 4.9 and 4.10.

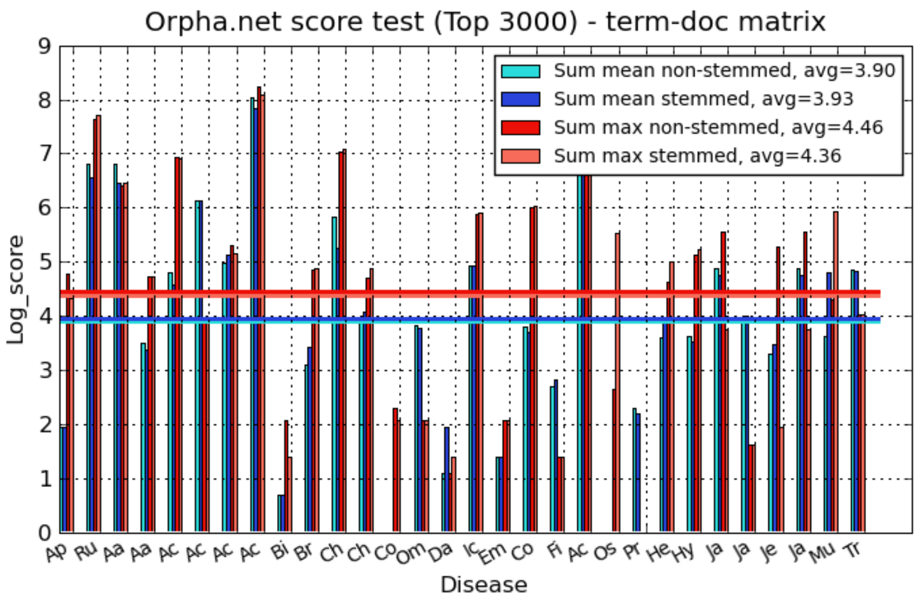
Figure 4.9: Comparison of mean and max sum measure tests on non-stemmed and stemmed term-doc matrices



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Sum: mean non-stemmed	23	3	362	772	35	76	144
Sum: mean stemmed	23	3	720	746	44	60	158
Sum: max non-stemmed	54	10	344	2401	235	469	495
Sum: max stemmed	120	6	10	2374	228	360	566

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Sum: mean non-stemmed	1	45	0	25	53	5	**4**
Sum: mean stemmed	1	33	0	27	88	5	**4**
Sum: max non-stemmed	70	6	19	441	391	26	**3**
Sum: max stemmed	62	8	7	394	496	26	**4**

Figure 4.10: Comparison of mean and max sum measure tests on non-stemmed and stemmed term-doc matrices



Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Sum: mean non-stemmed	6	910	917	32	122	460	145	3119	1	21	342	50	0	45	2
Sum: mean stemmed	6	708	644	28	97	460	170	2522	1	30	190	58	0	43	6
Sum: max non-stemmed	119	2081	611	113	1031	48	203	3833	7	127	1139	109	9	7	2
Sum: max stemmed	75	2228	638	113	993	48	171	3281	3	131	1194	131	7	7	3

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Sum: mean non-stemmed	137	3	44	14	2458	0	9	36	37	132	47	26	132	37	127	**8**
Sum: mean stemmed	136	3	39	16	2636	0	8	50	33	115	53	31	115	121	124	**8**
Sum: max non-stemmed	357	7	401	3	1957	13	0	102	169	260	4	198	260	72	55	**9**
Sum: max stemmed	365	7	414	3	2242	253	0	150	188	42	4	6	42	372	55	**9**

We see here that the ’mean sum’ similarity measure clearly outperforms the ’max sum’. In section 3.1.2, we compare this measure with the best of the cosine measure on both term document and the disease matrix.

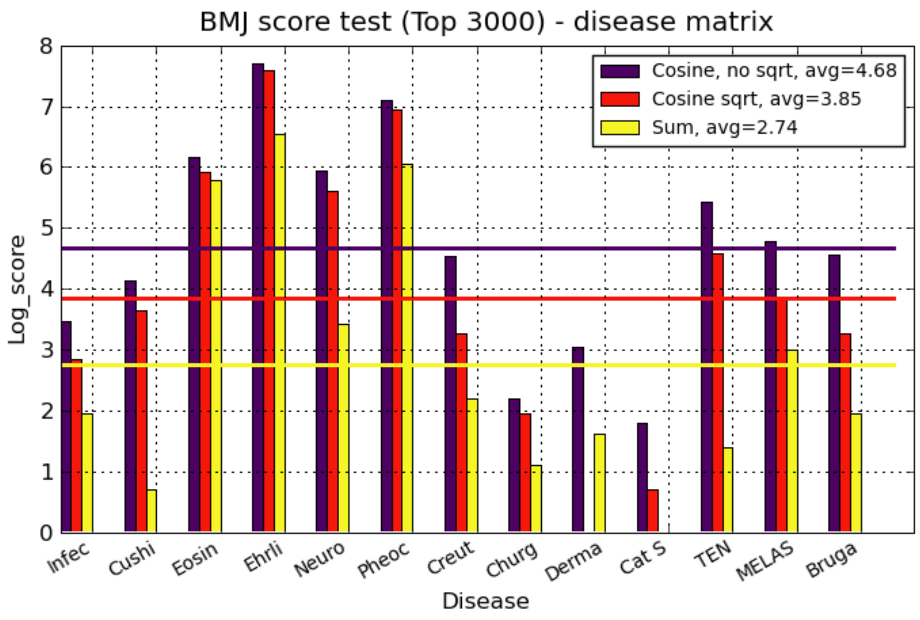
4.1.4 Disease and Term Document Matrix - Cosine, Sum and Final result

Now that we have found the results for the best measures to be used on the term document matrix, we focus our attention on the disease matrix. We will in the following test the sum and cosine measure on the disease matrix and — at the end of the section — compare these results to those of the term document matrix.

In the first test, we look at the performance of the cosine (mean), cosine-sqrt and the sum measure on the BMJ and Orpha.net test sets. These test are performed on both the non-stemmed and stemmed. The results are shown on the figures 4.11, 4.12, 4.13 and 4.14 below:

Non-stemmed:

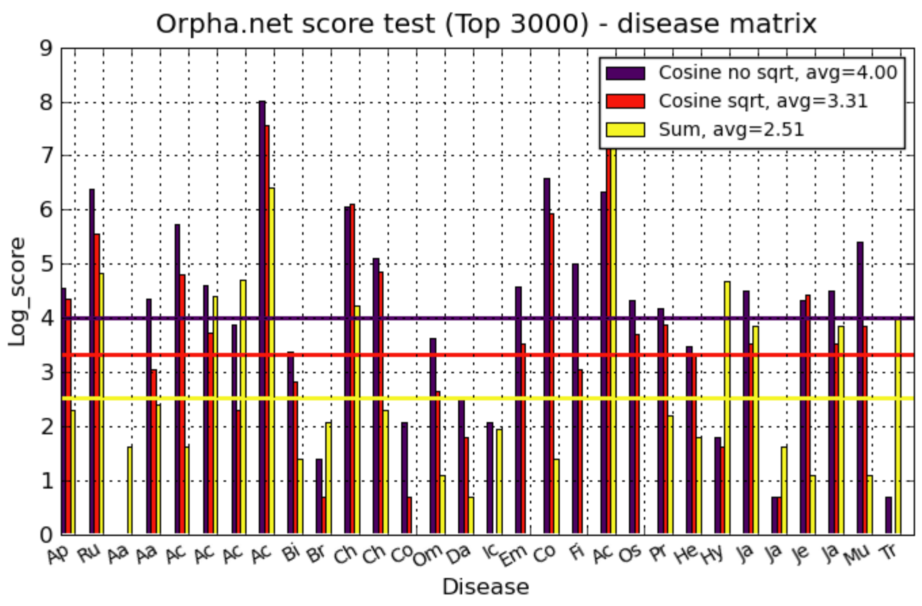
Figure 4.11: Test of cosine measure (with and without sqrt-transformation) and sum measure on a non-stemmed disease matrix



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Cosine no sqrt non-stemmed	31	62	474	2220	377	1225	93
Cosine sqrt non-stemmed	16	37	375	2001	270	1037	25
Sum non-stemmed	6	1	323	691	30	427	8

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Cosine no sqrt non-stemmed	8	20	5	227	118	94	**2**
Cosine sqrt non-stemmed	6	0	1	97	45	25	**4**
Sum non-stemmed	2	4	0	3	19	6	**9**

Figure 4.12: Test of cosine measure (with and without sqrt-transformation) and sum measure on a non-stemmed disease matrix

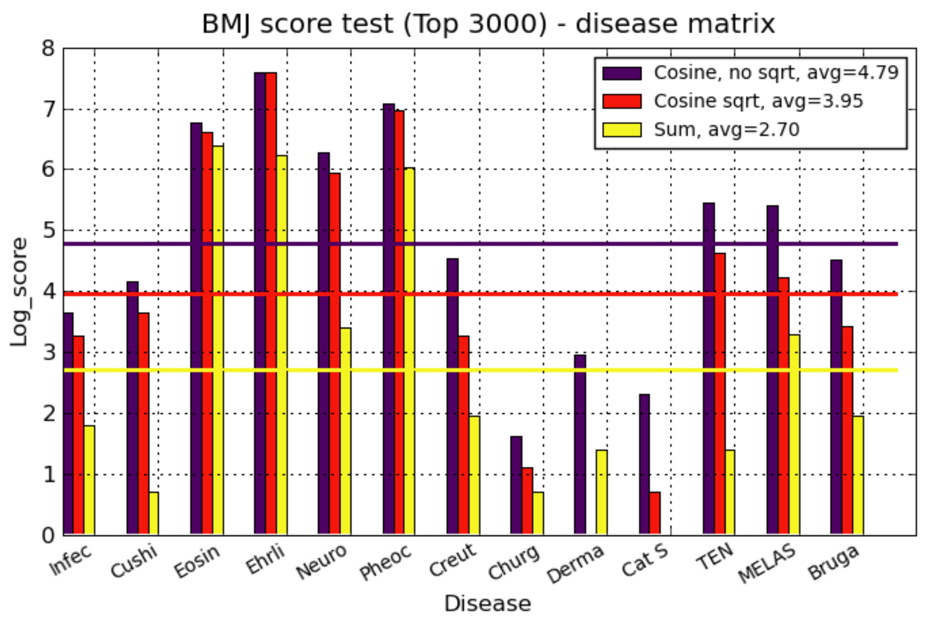


Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Cosine no sqrt non-stemmed	95	599	0	76	307	99	47	2989	28	3	430	165	7	37	11
Cosine sqrt non-stemmed	76	257	0	20	122	41	9	1912	16	1	448	128	1	13	5
Sum non-stemmed	9	123	4	10	4	81	109	601	3	7	68	9	0	2	1

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Cosine no sqrt non-stemmed	7	97	717	150	562	74	64	31	5	89	1	75	89	222	1	**8**
Cosine sqrt non-stemmed	0	33	380	20	1687	39	47	26	4	33	1	83	33	46	0	**11**
Sum non-stemmed	6	0	3	0	3000	0	8	5	107	46	4	2	46	2	55	**20**

Stemmed:

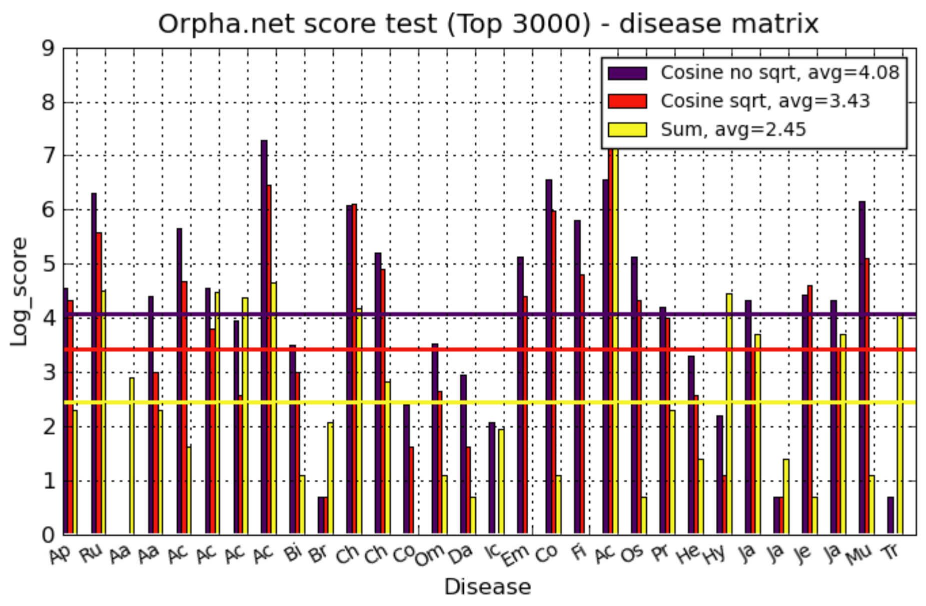
Figure 4.13: Test of cosine measure (with and without sqrt-transformation) and sum measure on a stemmed disease matrix



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Cosine no sqrt stemmed	37	63	872	1963	533	1198	93
Cosine sqrt stemmed	25	37	748	1970	384	1053	25
Sum stemmed	5	1	597	511	29	413	6

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Cosine no sqrt stemmed	4	18	9	230	221	91	**3**
Cosine sqrt stemmed	2	0	1	102	68	30	**3**
Sum stemmed	1	3	0	3	26	6	**8**

Figure 4.14: Test of cosine measure (with and without sqrt-transformation) and sum measure on a stemmed disease matrix



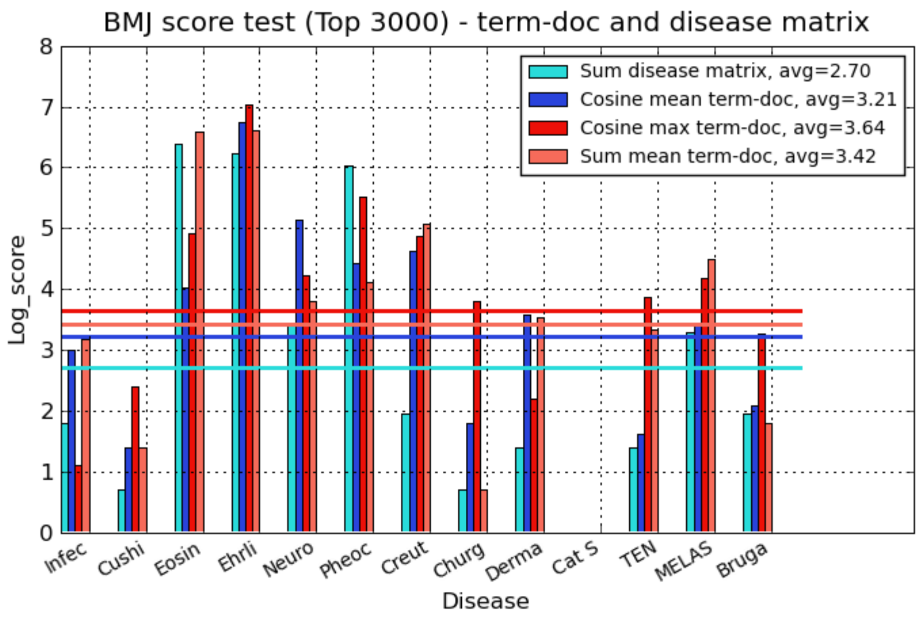
Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Cosine no sqrt stemmed	94	553	0	80	284	94	51	1454	32	1	433	181	10	33	18
Cosine sqrt stemmed	74	263	0	19	106	44	12	635	19	1	446	133	4	13	4
Sum stemmed	9	90	17	9	4	86	79	105	2	7	64	16	0	2	1

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Cosine no sqrt stemmed	7	169	710	334	704	167	65	26	8	74	1	83	74	468	1	**8**
Cosine sqrt stemmed	0	80	391	122	2137	74	54	12	2	30	1	99	30	162	0	**13**
Sum stemmed	6	0	2	0	3000	1	9	3	84	39	3	1	39	2	59	**20**

When it comes to scoring diseases on in the disease matrix, the sum measure greatly outrivals the cosine measure - with or without the square root transformation. If we look at the average values of the returned results, it seems that the stemmed version of the disease matrix is the best choice for optimized performance.

For the final test of measure and model, we compare the top results of the two matrices - term document and disease matrix. We will compare the different scores from the stemmed version of both matrix types since this seems to provide the overall best performance. In the figures 4.15 and 4.16 below are bar chart of the best scores found for the prototype system:

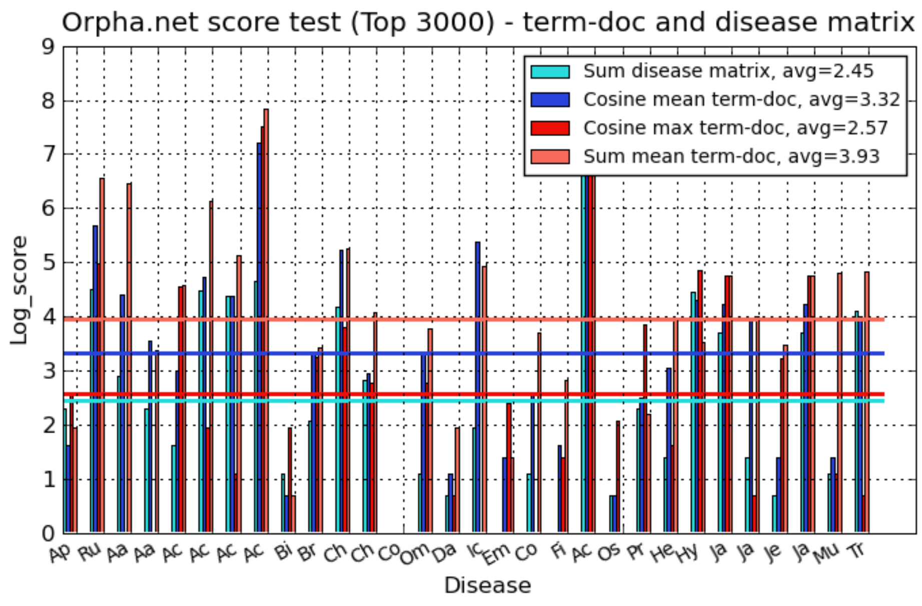
Figure 4.15: Comparison of the mean sum measure, and mean and max sqrt cosine measure, on a stemmed term-doc matrix, and of the sum measure on a stemmed disease matrix



Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Sum: disease matrix	5	1	597	511	29	413	6
Cosine: term-doc mean-sqrt	19	3	22	1268	115	105	108
Cosine: term-doc max-sqrt	2	10	136	1123	68	249	130
Sum: term-doc mean	23	3	720	746	44	60	158

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga	**# in top 20**
Sum: disease matrix	1	3	0	3	26	6	**8**
Cosine: term-doc mean-sqrt	5	54	0	2	41	7	**6**
Cosine: term-doc max-qrt	44	8	0	47	65	25	**4**
Sum: term-doc mean	1	33	0	27	88	5	**4**

Figure 4.16: Comparison of the mean sum measure, and mean and max sqrt cosine measure, on a stemmed term-doc matrix, and of the sum measure on a stemmed disease matrix



Measure	Ap	Ru	Aa	Aa	Ac	Ac	Ac	Ac	Bi	Br	Ch	Ch	Co	Om	Da
Sum: disease matrix	9	90	17	9	4	86	79	105	2	7	64	16	0	2	1
Cosine: term-doc mean-sqrt	4	725	75	37	38	85	68	1651	1	23	80	15	0	26	2
Cosine: term-doc max-sqrt	12	145	0	0	93	6	2	1842	6	25	44	15	0	15	1
Sum: term-doc mean	6	708	644	28	97	460	170	2522	1	30	190	58	0	43	6

Measure	Ic	Em	Co	Fi	Ac	Os	Pr	He	Hy	Ja	Ja	Je	Ja	Mu	Tr	**# in top 20**
Sum: disease matrix	6	0	2	0	3000	1	9	3	84	39	3	1	39	2	59	**20**
Cosine: term-doc mean-sqrt	218	3	13	2	3000	1	9	14	78	84	48	3	84	1	62	**13**
Cosine: term-doc max-sqrt	0	10	0	3	3000	7	46	4	128	115	1	24	115	2	1	**19**
Sum: term-doc mean	136	3	39	16	2636	0	8	50	33	115	53	31	115	121	124	**8**

Not only having the best average, but also the right disease 9 out 13 (BMJ) and 20 out of 29 (Oprha.net) in the top 20 out of over 3000 diseases returned from a top 3000 document scores, using the simple sum similarity measure on a disease matrix seems to give both best recall and precision. This result is very interesting since the document-summed disease matrix was originally made as model for fast tests before implementation in the large term document matrix. This could imply that a summation of the document vectors for each individual disease seems to enhance the values of information carrying terms with the TF-IDF taking care of too common and non-information containing terms. The summation also efficiently eliminates the problem of noisy overview articles 4.1.6.

One of the noteworthy things that can be learned from the bar charts made in this and the two previous sections is that there should be a lower bound on the number of documents per disease. Acropectorovertebral dysplasia is a prime example that the system needs to have a lower bound on the number of MedLine records that are gathered for each disease. This is in order to ensure that the system will be able make a reasonable qualified guess on the disease.

Clustering of the results

We perform a clustering of the top 20 results using hierarchical clustering. We have chosen to cluster the best disease from the sum similarity measure on the stemmed disease matrix which is the *Cat Scratch disease*. Remember that the 20 diseases are chosen based on the similarity to the query vector, not how similar they are to each other. From figure 4.17, it can be seen that *Cat Scratch disease* (near the top) is clustered together with *Cyclic Neutropenia* even though it is number 19 on the result list, this means these diseases are closest to each other in the list of 20 returned suggestions. And the disease ranked as number 2 is *Kikuchi disease* which is 6 sub clusters away from *Cat Scratch disease* - meaning that it requires merging 6 sub clusters to get them into the same cluster, the merging is performed by calculating a mean vector for the diseases (or sub clusters) being merged. The lowest ranking disease is *Chediak-Higashi syndrome*. To get this into the same cluster as *Cat Scratch* requires the merging of the entire cluster.

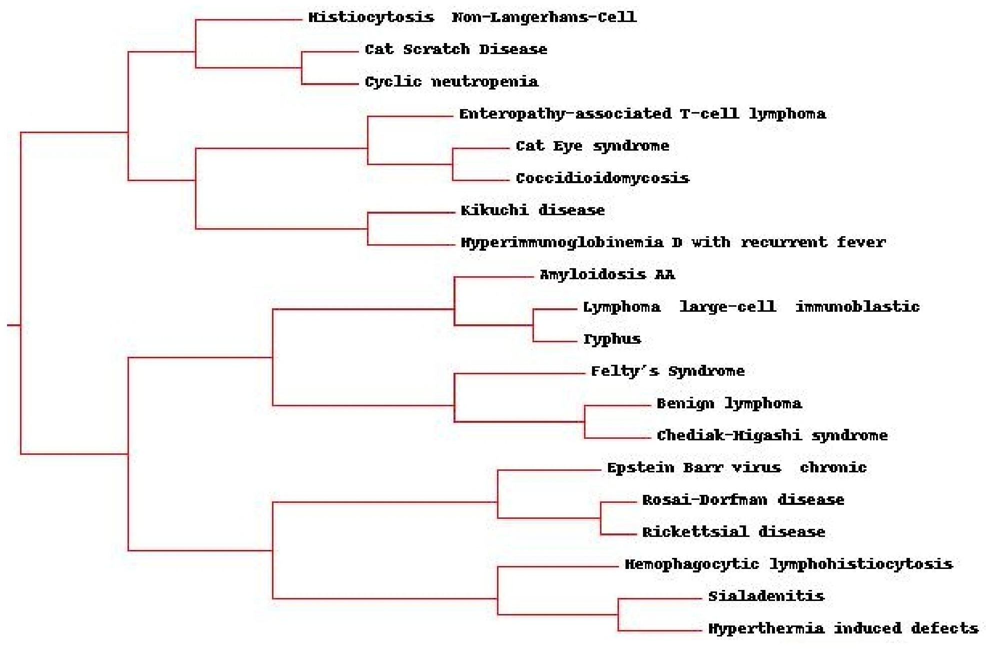

Histiocytosis Non-Langerhans-Cell
Cat Scratch Disease
Cyclic neutropenia
Enteropathy-associated T-cell lymphoma
Cat Eye syndrome
Coccidioidomycosis
Kikuchi disease
Hyperimmunoglobinemia D with recurrent fever
Amyloidosis AA
Lymphoma large-cell immunoblastic
Typhus
Felty's Syndrome
Benign lymphoma
Chediak-Higashi syndrome
Epstein Barr virus chronic
Rosai-Dorfman disease
Rickettsial disease
Hemophagocytic lymphohistiocytosis
Sialadenitis
Hyperthermia induced defects

Figure 4.17: Hierarchical clustering of best disease using sum, stemmed non-normalized

We have also chosen to cluster the disease where sum measure on the stemmed disease matrix produced the worst result. This is the test case *Eosinophilic granuloma* where the correct disease was ranked as number 597. Therefore it is not possible to find it in the dendrogram. Our system suggested Developmental Dysplasia of Hip as prime candidate given the query vector. Investigating the diseases present in the dendrogram 4.18 and comparing them to the correct diagnosis of the disease (if found) could provide helpful knowledge about why our system was so wrong in its suggestion of this disease, and might provides clues to correcting it. The problem might stem from bad or very noisy information about the correct disease, which therefore do not have enough similarity with the query vector.

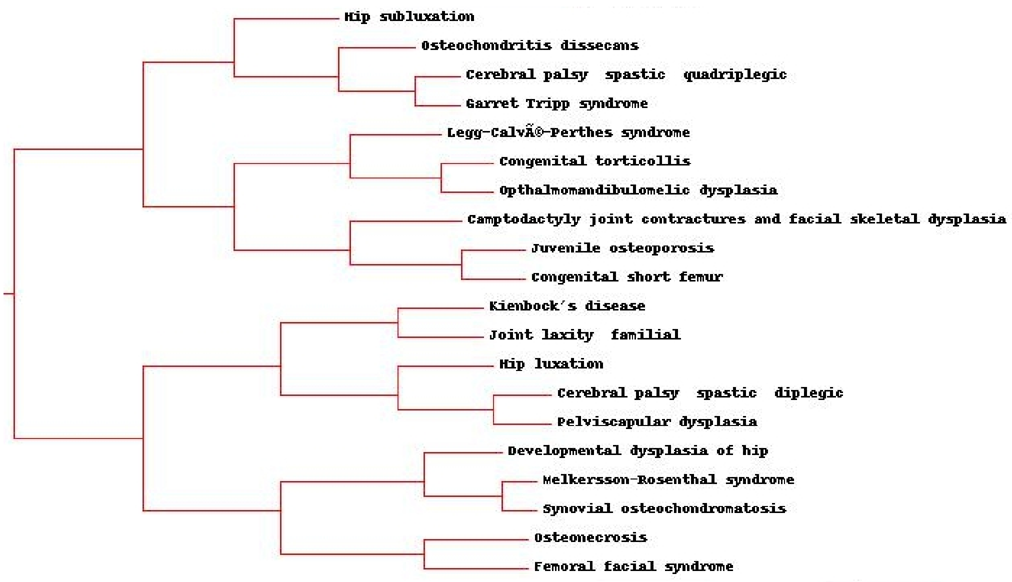
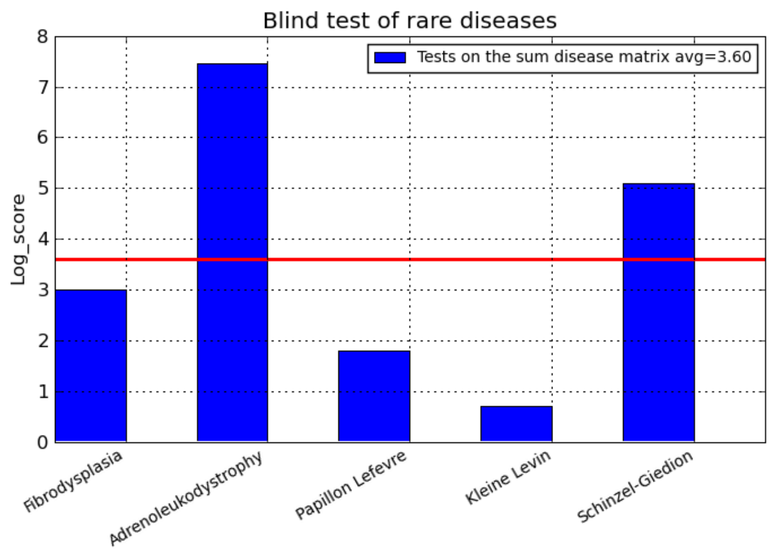

Hip subluxation
Osteochondritis dissecans
Cerebral palsy spastic quadriplegic
Garret Tripp syndrome
Legg-CalvÃ©-Perthes syndrome
Congenital torticollis
Opthalmomandibulomelic dysplasia
Camptodactyly joint contractures and facial skeletal dysplasia
Juvenile osteoporosis
Congenital short femur
Kienbock's disease
Joint laxity familial
Hip luxation
Cerebral palsy spastic diplegic
Pelviscapular dysplasia
Developmental dysplasia of hip
Melkersson-Rosenthal syndrome
Synovial osteochondromatosis
Osteonecrosis
Femoral facial syndrome

Figure 4.18: Hierarchical clustering of worst disease using sum, stemmed non-normalized

4.1.5 Results of the Blind Tests

Shown below are the results of the blind tests described in figure 4.19. Note that the scores below are 0-indexed as in the previous sections.

Figure 4.19: Blind test of a stemmed disease matrix using the sum measure



Measure	Fibrodysplasia	Adrenoleukodystrophy	Papillon Lefevre	Kleine Levin	Schinzel-Giedion	**# in top 20**
Sum: disease matrix	19	1717	5	1	164	**3**

As we see, *Adrenoleukodystrophy autosomal neonatal form* has a surprisingly poor score despite the many symptoms used in the query. We will try to analyse how this can be by looking at the most describing terms of the disease, as according to the used disease matrix. The disease matrix was TF-IDF transformed and thus the terms unique and classifying to the disease are those with a high term frequency and occurs few times in the corpus of diseases (high inverse document frequency). In table 4.4 below, we pull out the top 20 terms of the disease vector describing the worst (*Adrenoleukodystrophy autosomal neonatal form*) and the best (*Kleine Levin syndrome*) scored disease of the blind test.

Table 4.4: Top 20 terms

Adrenoleukodystrophy	Kleine Levin
pex26	lein
pex1	megaphagia
pex13	hypersomnia
pex5	levin
nald	hypersomn
pts1	kl
ldpex5	hypersomniac
pex12	hypersexu
pex5p	hypersomnol
peroxin	asmp
pex10	narcolepsi
zs	hypocretin
pbd	mslt
pex14	hyperphagia
g843d	pickwickian
pex12p	somnol
pex1p	ceretec
ird	parasomnia
pts1r	rem
pts2	smp

The top 20 terms on on the table above reveals a sginificant difference between the two diseases. *Adrenoleukodystrophy* is mainly classified by what seems to be protein names while *Kleine Levin* is more defined by what could seem to be symptoms like the ones a physician could be thougt to use. Let us expand the analysis and look at the ranks (from highest document-term value to lowest) of the symptoms that were actually used for the queries in the blind test. These are shown in table 4.5 below.

Table 4.5: Ranked quried symptoms

Adrenoleukodystrophy		Kleine Levin	
Rank	**Term**	**Rank**	**Term**
1367	normal	215	jewish
1668	develop	1053	boy
1383	boy	1585	age
1710	age	2247	16
1698	5	454	seizur
1668	develop	53	sleep
1891	difficulti	1771	aggress
440	seizur	389	irrit
524	adren	1682	highli
1474	insuffici	1301	increas
861	degener	202	sexual
1229	visual	83	appetit
731	auditori	172	hunger
1048	function		

Again we see a clear difference between the two diseases. *Adrenoleukodystrophy* has none of the queried terms below 440 in rank and in general the queried terms are not ranked very highly in the *Adrenoleukodystrophy* document. This could seem to indicate that the abstracts gathered for *Adrenoleukodystrophy* use many synonyms for the general terms while they might use the same protein/gene names for the disease, thus giving these a high term frequency (recall) in the disease's corpus of abstracts. This problem could probably be solved using a list of protein/gene names to filter away these to construct a disease matrix that could allow physicians to enable/disable protein/gene names before a query.

4.1.6 On Overview Article Noise and Consensus Normalization

Overview Articles

Unfortunately there are overview articles that can pollute the search results and if overview articles are found in many of the top scoring diseases, it could present a problem. When we run the consensus method as described in section 4.1.1, an overview article would potentially get an unfairly high score since it gets summed up to 240 times. Though overview articles represent an element of noise, the normalization of the vectors in the vector space model should in theory downweight the highly summed documents. We also tested to the most common overview article (240 occurrences) — to see if it could be a problem — using the Orpha.net disease cases among top 3000 (documents). The overview article was present in less than 1 out of 8 searches which is not a significant amount. The disease matrix on the other hand is less prone to the same problem, as it summarizes all information about a disease into one vector.

Consensus Normalization

While testing of the term document matrices, we got the idea to try and divide each label with the number of documents it had been summed over. This could in theory normalize the label in the top score of returned results, as labels being over-represented in, for example, the bottom of the top score list would be weighted down. However, as this might be a good theoretical idea, it did not quite amount to anything useful. The results for running this on the stemmed term document matrix, using the cosine measures, is seen in table 4.6.

Measure	Infec	Cushi	Eosin	Ehrli	Neuro	Pheoc	Creut
Mean:	99	210	804	1216	507	667	167
Median:	1036	989	1432	948	668	1301	1315
Max:	1034	989	1447	1084	635	1284	1293

Measure	Churg	Derma	Cat S	TEN	MELAS	Bruga
Mean:	309	502	50	330	695	424
Median:	1687	1429	1233	1696	1494	1322
Max:	1687	1414	1233	1696	1491	1321

Table 4.6: Show something something something

It does not take a bar chart to see that these values are pretty far off the top 20. The idea might be good enough, but it would have to be a different model or data set than the one we use.

Chapter 5

Conclusion

We choose to use the vector space model because it gives a good base upon which to perform different transformations on the data, and performing similarity scores.

When applying the square root transformation during calculation of similarity score on the TF-IDF matrix, our results improved. This suggests that other transformation to the data should be used. Unfortunately time constraints did not permit us to perform test on other transformations.

Using a disease matrix instead of a term-document matrix gave us the best results on the BMJ (61.5% correct in top 20) and the Orpha.net (68% correct in top 20) test cases. The blind tests provided by Henrik L. Jørgensen were also tested using our system, and the system placed 3 out of 5 within top 20 (60%). Further analysis of the blind tests indicate that protein/gene names can be a highly noisy factor, as it seemed to be in one of the blind tests.

The elimination of overview articles in the database could help reduce some of the noise found during testing the system. Combined with outlier detection, this could improve the results. Though a module for outlier detection has been implemented, this was not tested.

Latent Semantic Analysis could be a useful tool for reducing the amount noisy data by means of dimensionality reduction through SVD. SVD was implemented in the system but never fully tested.

There is a clear need for more control over the information gathered to describe the rare diseases in the database, this includes a lower bound on the information gather for a single disease. This is especially with *Acropectorovertebral dysplasia* in mind which never scores below 562 in any test.

We were unable to find any information about other system designed to perform automated diagnosis of rare diseases. In this relation the system build is (yet!) unique. Hopefully other systems will be made to assist physicians in diagnosing rare diseases.

When designing and testing a system for diagnosing rare diseases, it is imperative to be able to draw on the knowledge and ideas of domain specialists. When testing the system against the Orpha.net cases we choose the symptoms based on a strings from their web page described by "characterized by", a physician might not use the same description. The blind tests symptoms where received in Danish which meant that we had to translate them to English and some information may have been lost in the — perhaps non-medicinal — translation. A physician has a domain knowledge and intuition about searching for diseases that far exceeding that of computer scientists designing such a system.

We had a short correspondence with Henrik L. Jørgensen about the usefulness of the system. His opinion was that the system could become a helpful tool for physician because — through their carrier — they might only experience a single rare disease. So in case something did not quite fit with the diagnosis, they could type in a symptom list and receive a list of suggested diseases, which could result in more patients being given the correct treatment.

Considering the test results above, this provides evidence that a system for providing support decision with respects to diagnosing rare disease has high potential.

Chapter 6

Future Works

In this chapter, we present some ideas for improvements that could be implemented into the system.

Statistical Model

Gathering information about prior probabilities of the diseases could help produce better term weights for the term document matrix. The more information that could be found, the more specific the model. Also, gathering information about age, gender, racial and location dependencies of the diseases should be able to improve the systems ability to correctly find the correct disease. Further, it would present the physician with extra filtering options for a query.

Improved classification of the diseases. To begin with, one could use the MeSH term hierachy for a prior clustering of the diseases and — for better classification — remove outlier documents from each disease.

The outlier removal process might concentrate the remaining information, thereby making it more likely that the correct information is returned. Therefore, it might be advantageous to perform a clustering upon the abstracts and select some criteria upon which to remove outlying abstracts. The criteria could be either removal based on some distance (threshold) to the cluster average, or removal of some percentage of those abstracts that lie farthest away from the cluster center. The latter seems to be the most fair option - mainly because it removes abstracts in proportion to the size of the cluster. One fact that remains when it comes to outlier detection; care needs to be taken when removing outliers, as one might just remove that single piece of correct information needed to identify the right disease.

It could also be possible to strengthen a classifier by gathering disease domain keywords (e.g. coronary diseases), either from pre-existing lists or by text mining. The domain keywords have the strength that they can come from more common and well-described diseases. They can all-in-all be described as and expanded MeSH list to classify by.

Methods for keyword extraction — like LSA — should be tested.

Disease name	Keywords	Score	PMIDs
$Disease_1$	"Cancer, liver, blood, pressure ..."	0.8242	$18134923, \ldots, 3289472$
$Disease_2$ 0	"Cancer, coronary, blood, aortic ..."	0.2412	$17584932, \ldots, 16191394$

Construction of Other Term Document Matrices

Using SVD (LSA) to reduce noise and construct a term document matrix based on a semantic space.

Constructing a protein/gene name free matrix for a query based on general describing terms/symptoms. This would be most useful if the physician could enable/disable this functionality

Redesign of the storage and retrieval system. A database for storing and retrieving information that is more efficient than the current I/O that the system use. Much could probably be improved by writing certain data structures and methods in C - for instance the ones dealing with the large matrices.

Improvements upon Queries

The possibility of comparing two queries in the system could be useful for a physician. He could then compare the results from two slightly different queries and inspect the returned results. This functionality could be implemented with a cosine measure that L_2 normalizes the query vector.

Additional query options, like preferences for author, year, journal etc. could make it easier for a physician who has a small amount of prior knowledge as to what he is about to find.

Term mapping would be able to increase the recall of the system and help retrieve the correct information. Term mapping is the idea of mapping synonyms to each other include these in a query. This approach would most likely work best on a disease matrix to avoid overview articles that, for instance, contain many synonyms.

Boolean searches, allowing the physician to determine that some terms should be present and others should not. It could also be used to link certain terms together, like “adrenal insufficiency” that is split in two in the current system, thereby ensuring either both terms occur in a document or none does.

Visual representation of disease cluster, including keyswords extracted by LSA.

Visual representation of the results, perhaps like table 6 below. Here those terms that best describe the disease (“Keywords”) are presented to the physician to give him or her and idea of what the disease is dealing with. “Keyword” could also be related terms to the query terms themselves. “Score” is the calculated score that the system has given the query, and “PMID” is the list of PMIDs that the score is derived from. It should be possible to expand the PMIDs on different levels to see title, the abstract and perhaps the full information about the MedLine record.

Improvements Regarding Text/Data Retrieval

Locate more sources to gather information from. Orpha.net could be an ideal candidate. Furthermore, during the project, we also came across a rare diseases webpage from the Swedish Government's health care system [44], but the page was unfortunately unaccessable due to maintanence.

During this project, we also found that much of the data on the diseases were inadequate. Many diseases are only represented by one or a few more abstracts. Though these moght be correct, they do not contain enough synonyms and decribing terms to be hit by most queries. Therefore there should be a lower bound on the number of abstracts per disease.

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Appendix A

Source Code

Our source code is available at the opensource site http://github.com/ and can be cloned from the following repository: git://github.com/hmbachelor/bachelor.git

Appendix B

Raw test data

The raw test data are available in the github repository in the file called test-Module.py. This file needs some serious cleaning.