FOM - Hochschule für Oekonomie & Management

Hamburg

Master-Studiengang Big Data & Business Analytics

2. Semester

Development of a solution for genetic analysis of ALL genomes by implementing Latent Dirichlet allocation

Betreuer:

Prof. Dr. Martin Münstermann

Autor: Jacqueline Franßen

Matrikel-Nr: 496804

2. Fachsemester

Hamburg, den 25.07.2019

Contents

List of Figures

List of Tables

1 Abstract

1

2 Introduction

3 Related work

Zhao et al. [Zhao et al. 2016] describe how topic modeling can be used to analyze NGS. By implementing topic modelling, text corpus are generated [Zhao et al. 2016]. In the beginning of every genome analysis, there are several important questions to ask. Jurca et al. [Jurca et al. 2016] recommend to ask the following questions: What are the top studied genes in breast cancer? How regulated blood cancer research is in each country? Which countries have studied the largest number of breast cancer? Which are the popular genes mentioned together by countries every year? Where do key genes lie in the soft clusters?

Jurca et al. describe a process to use large-scale text analysis of biomedical abstracts in order to generate new hypothesis about cancer biomarkers [Jurca et al. 2016]. The target is to develop a data minng methodology that patterns in genes associated with cancer. By analyzing disease-specific gene expression data, experimental data is being checked whether a gene has indeed been upregulated or downregulated with respect to a disease.

According to Xu et al. [Xu et al. 2013], micro Ribonucleic Acid (MIRNA)s build a class of 17-27 nucleotides single-stranded Ribonucleic Acid (RNA) molecules that regulate gen expression post-transcriptionally. In the described text-mining process, Xu et al. identified nine MIRNAs in bladder cancer and adopted protein-protein interaction sites between these miRNAs and target genes. The results of the analyzation process lead to two relationship types between bladder cancer and its MIRNA: casual and unspecified.

Topic modelling is not only used to analyze relationships between genomes but also to improve diagnoses for stroke disease. Djatna et al. [Djatna, Hardhienata, and Masruriyah 2018] describe an 'Intuitionistic Fuzzy Based Decision Tree' to diagnose different types of stroke disease. To be precise, the different types of stroke diseases can be calculated by Hamming distance. The term 'Fuzzy logic' means logic that

underlies the reasoning of data by way of precise estimates. It is the fastest way to map input space into output space using a degree of membership.

Lloret et al. [Lloret and Palomar 2012] built an automatic summarization algorithm for literature. It can includes three steps: First, topic identification, second topic interpretation and third summary generation. While describing the process of textual analyzation, Lloret et al. mention a specific term: term frequency/inverse document frequency (TFIDF) which is important for topic modelling. In addition to topic-based approaches, there are graph-based approaches and discourse-based approaches. Graph-based approaches implicate nodes that represent text elements and the edges/links refer to synonymy [Lloret and Palomar 2012]. Discourse-based approaches include Rhethorical Structure Theory (RST), Hidden-Markov-Models (HMM), RST or Bayesian models (BM).

Yang et al. [Yang et al. 2018] describe a process of 'constructing a database for relations between human copy number variant (CNV)s and human genetic disease via systematic text mining'. In general, CNV can cause disease by gene dosage, disruption, fusion or other genetic position effects. To be more precise, there can CNV can lead to two types of autosomal variants: They can either cause deletion or amplification of the long or broken arm region of chromosomes 1-22 or can build multiples of chromosomes 1-21 (e.g. as in disease trisomy 21).

According to their article, Yang et al. used CNV database which linked the CNV information to the NCBI Gene and Ontology database. In their article, Yang et al.[Yang et al. 2018] mention three steps in the text mining process. First, during the preprocessing step, unstructured fields are split into separated sentences by using Natural Language Toolkit (NLTK), a python package [*Natural Language Toolkit — NLTK 3.4.1 documentation* 2019]. After that, in the named entity recognition (NER) step, all disease mentions within DNorm system, such as MeSH IDs are recognized. In the third step, Relation extraction (RE), the positions in sentences and entities are compared to generate instances that constist of two candidate entities within one single sentence.

Yang et al. mention two more processing methods: Parallel Processing and Post Processing which includes data cleaning and statistics [Yang et al. 2018]. The term 'data cleaning' is explained as 'de-duplicating data after each step of the process to reduce repetitive operations and prevent statistical errors'. This is a very useful step

in biomedicine since as a common problem, biomedical databases contain errors. For that reason, users can give feedback through a feedback mechanism to improve the quality of the databases.

4 LDA

4.1 General description

According to Jurca et al. [Jurca et al. 2016] the text mining process can be divided into four steps: First, the information has to be retrieved by user queries (Information Retrieval (IR)). Second, different vocabularies and ontologies have to be integrated (NER). Third, during Information extraction (IE), relationships between biological entities in the texts are extracted by either use co-occurence processing or Natural Language Processing (NLP). Last, there has to be gained biologically meaningful knowledge about how biological entities are related by using Knowledge Discovery (KD) methods.

Moreover, there can be distinguished between three types of clustering: hard clustering, hierarchical clustering and soft clusternig. Hard clustering describes the process of separating items into distinct groups where each item is exactly in one cluster. Hierarchical clustering implicates single-link (how similar the items are to one another) and complete-link (how dissimilar the items are). Soft clustering means that items cannot be distinctly separated into clusters and partly are member of two or more clusters at a time [Jurca et al. 2016].

Besides, Djatna et al. [Djatna, Hardhienata, and Masruriyah 2018] mention data mining techniques, such as Classification and Regression Tree (CART), Iterative Dichotomized 3 (IDB), Decision Tree (DT) and two classification techniques: Principal Component Analysis (PCA) and LDA.

LDA was developed by David Blei et. al in the year 2003 and is a clustering algorithm for text mining. It counts to the most popular topic modelling algorithms [Zhao et al. 2016]. According to [Zhao et al. 2016], topic modelling requires of a number documents which represent each of them a mixture of latent topics. Moreover, each topic

is expressed by a distribution of words. During LDA, two relationships are analyzed: First, the relationship between documents and words, also called 'per-document topic distributions'. Second, the relationship between words and topics ('per-topic word distributions'). To measure the relationships exactly and to make inference about topics and documents for text mining, probability matrices are calculated.

4.2 Examples and possible use cases

Zhao et al. describe the process of analyzing genomes as follows: First, each document corresponds to one of the total number of Desoxyribonucleic acid (DNA) straints. Second, all documents had the same number of words. Third, the distribution of words for topics as well as the distribution of topics in documents were described by random variables obeying Dirichlet distributions with parameters α and β. After that, nucleotides and their orders in NGS sequences coudl be treated as words and the genetic information in sequences was translated and exhibited as a 'bag of words' [Zhao et al. 2016]. By using the strain-topic matrix derived from topic modelling, relationships or similarities between the strains serotypes can be found out.
images and schemes

4.3 Python package 'Gensim'

5 Acute Lymphoblastic Leukemia

5.1 Types of Leukemia and its causes

According to Jurca et al. [Jurca et al. 2016], cancer is the result of damage, especially of mutations to cell's DNA which leads to a cell losing its normal functionality and gains the ability to indefinitely multiply until normal tissue funtions are impaired. This is also why malitious cancer is distributing so fast. Besides, each patient develops a different set of cancerous mutations in various genes which lead to multiple subtypes of cancer. Furthermore, some genes can be up-regulated (which means that they are transcribed more and are expressed), down-regulated (which means that they are not expressed) or can be co-expressed (which means that they are expressed at the same time [Jurca et al. 2016].

5.2 Examples for Genome Analysis: NGS

NGS refers to post-Sanger sequencing methods [Zhao et al. 2016]. Since NGS produces large volumes of sequence data it might be very useful to use topic modelling techniques to maintain the flexibility for the level of resolution required for given experiments. According to Gasperskaja et al. [Gasperskaja and Kučinskas 2017], NGS does not require a priori knowledge about genomic feature, it only requires a low amount of DNA or RNA as input.

The step before analyzing two or more (multiple) genomes is called alignment which includes a comparison of two genomes. There are many different types of alignments, but Zhao et al. refer to the Multiple Sequence Alignment (MSA) by describing Multiple Sequence Comparison by Log- Expectation (MUSCLE) and CLUSTAL.

Gasperskaja et al. [Gasperskaja and Kučinskas 2017] mention an important question

which should be asked before every genome analysis: 'Is the variance pathogenic?' and whether there is any relationship between genotype and phenotype which means that it can lead to disease or can cause a number of disorders. Furthermore, Gasperskaja et al. [Gasperskaja and Kučinskas 2017] describe Clustered Regularly Interspaced Short Palindromic Repeats Cas-9 (CRISPR-CAS9) as an example for systems to explain functions of genes and proteins or research relationship between genotype and phenotype. Moreover, there can be distinguished between beneficial (Single Nucleotide Polymorphism (SNP)) and pathogenic (nonsense variant) single nucleotide changes, large microscopically visible or chromosomal aberation. To find out whether a genome mutation is pathogenic, Gasperskaja et al. [Gasperskaja and Kučinskas 2017] explain that substantial information about functional genomics can be found through analysis of messenger RNA (MRNA) or complementary Ribonucleic Acid (CRNA) (which is a copy from MRNA by reverse transcription Polymerase Chain Reaction (PCR). Methods to measure RNA expression are for example: Serial Analysis of Gene Expression (SAGE) or Quantitative real-time Polymerase Chain Reaction (QPCR). By using complementary Desoxyribonucleic acid (CDNA) microarray assays important genome-wide information about changes of gene expression in various cell lines can be found out.

5.3 Data sources: NCBI and Ensembl genome browser 96

6 Development of a solution for genetic analysis of ALL genomes by implementing LDA

6.1 Problems and challenges of genetic analysis

6.2 First steps: Draft of developed solution

To get useful data, the [Information et al. 2019] was used to get all currently detected mutations of genomes which may cause LDA.
The first idea was to build a parsing application, which iterates over the found 582 genomes. After the iteration, it compares the oncogenes with the healthy genomes and to figure out where the differences are. The results might be displayed in a diagram. It might be possible to create clusters from the differences between the two groups or practice LDA on the differences.

6.3 Proposed solution

6.4 Results

7 Conclusion and Outlook

7.1 Lessons learned

7.2 Conclusion

7.3 Outlook

Figure 7.1: Bildunterschrift

Ein Zitat

[]

Literaturverzeichnis

Djatna, Taufik, Medria Kusuma Dewi Hardhienata, and Anis Fitri Nur Masruriyah (Dec. 2018). “An intuitionistic fuzzy diagnosis analytics for stroke disease”. en. In: *Journal of Big Data* 5.1, p. 35. ISSN: 2196-1115. DOI: 10.1186/s40537-018-0142-7. URL: https://journalofbigdata.springeropen.com/articles/10.1186/s40537-018-0142-7 (visited on 04/07/2019).

Gasperskaja, Evelina and Vaidutis Kučinskas (2017). “The most common technologies and tools for functional genome analysis”. In: *Acta Medica Lituanica* 24.1, pp. 1–11. ISSN: 1392-0138. DOI: 10.6001/actamedica.v24i1.3457. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5467957/ (visited on 05/09/2019).

Information, National Center for Biotechnology et al. (2019). *National Center for Biotechnology Information*. en. URL: https://www.ncbi.nlm.nih.gov/ (visited on 05/09/2019).

Jurca, Gabriela et al. (Dec. 2016). “Integrating text mining, data mining, and network analysis for identifying genetic breast cancer trends”. en. In: *BMC Research Notes* 9.1. ISSN: 1756-0500. DOI: 10.1186/s13104-016-2023-5. URL: http://bmcresnotes.biomedcentral.com/articles/10.1186/s13104-016-2023-5 (visited on 04/06/2019).

Lloret, Elena and Manuel Palomar (Jan. 2012). “Text summarisation in progress: a literature review”. In: *Artificial Intelligence Review* 37.1, pp. 1–41. ISSN: 1573-7462. DOI: 10.1007/s10462-011-9216-z. URL: https://doi.org/10.1007/s10462-011-9216-z.

Natural Language Toolkit — NLTK 3.4.1 documentation (2019). URL: https://www.nltk.org/ (visited on 05/09/2019).

Xu, Yahong et al. (Sept. 2013). “RETRACTED ARTICLE: Integrated gene network analysis and text mining revealing PIK3R1 regulated by miR-127 in human bladder cancer”. In: *European Journal of Medical Research* 18.1, p. 29. ISSN: 2047-783X.

DOI: 10.1186/2047-783X-18-29. URL: https://doi.org/10.1186/2047-783X-18-29.

Yang, Xi et al. (Dec. 2018). “Constructing a database for the relations between CNV and human genetic diseases via systematic text mining”. en. In: *BMC Bioinformatics* 19.S19, p. 528. ISSN: 1471-2105. DOI: 10.1186/s12859-018-2526-2. URL: https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-018-2526-2 (visited on 04/11/2019).

Zhao, Weizhong et al. (May 2016). “A novel procedure on next generation sequencing data analysis using text mining algorithm”. In: *BMC Bioinformatics* 17.1, p. 213. ISSN: 1471-2105. DOI: 10.1186/s12859-016-1075-9. URL: https://doi.org/10.1186/s12859-016-1075-9.

Rechtsquellenverzeichnis

Bundesdatenschutzgesetz, BDSG, 1990, zuletzt geändert 2009

Gesetz gegen unlauteren Wettbewerb, UWG, 2004, zuletzt geändert 2013

Richtlinie 95/46/EG des Europäischen Parlaments und des Rates vom 24. Oktober 1995 NI. L 281/31 zum Schutz natürlicher Personen bei der Verarbeitung personenbezogener Daten und zum freien Datenverkehr

Telemediengesetz, TDG, 2007, zuletzt geändert 2010

Ehrenwörtliche Erklärung

Hiermit versichere ich, dass die vorliegende Arbeit von mir selbstständig und ohne unerlaubte Hilfe angefertigt worden ist, insbesondere dass ich alle Stellen, die wörtlich oder annähernd wörtlich aus Veröffentlichungen entnommen sind, durch Zitate als solche gekennzeichnet habe. Ich versichere auch, dass die von mir eingereichte schriftliche Version mit der digitalen Version übereinstimmt. Weiterhin erkläre ich, dass die Arbeit in gleicher oder ähnlicher Form noch keiner Prüfungsbehörde / Prüfungsstelle vorgelegen hat. Ich erkläre mich damit nicht einverstanden, dass die Arbeit der Öffentlichkeit zugänglich gemacht wird. Ich erkläre mich damit einverstanden, dass die Digitalversion dieser Arbeit zwecks Plagiatsprüfung auf die Server externer Anbieter hochgeladen werden darf. Die Plagiatsprüfung stellt keine Zurverfügungstellung für die Öffentlichkeit dar.

Ort, Datum (Vorname Nachname)