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RESEARCH ARTICLE

Generative Topic Modeling in Taxonomic Structure of Genomic Data using LDA

Dnyati.S.Randhave[1], S.N.Deshmukh[2]

[1]Department of Computer Science and IT & Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India
[2]Department of Computer Science and IT & Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, India
[1] dnyati.randhave@gmail.com; [2] sndeshmukh@hotmail.com

Abstract- Probabilistic topic models have been developed for applications in various domains such as text mining, information retrieval. In this work, we focus on developing probabilistic topic models for LDA and specifically, a probabilistic topic model is proposed for data analysis and function analysis using homogenous approach and composite approach. In this paper, we aim to develop a new method that is able to analyze the genome-level composition of DNA sequences, in order to characterize a set of common genomic features shared by the same species and tell their functional roles. To achieve this end, we firstly apply a We firstly show that generative topic model can be used to model the taxon abundance information obtained by homology based approach and study the microbial core. The model considers each sample as a 'document', which has a mixture of functional groups, while each functional group (also known as a 'latent topic') is a weight mixture of species. Therefore, estimating the generative topic model for taxon abundance data will uncover the distribution over latent functions (latent topic) in each sample. Secondly composition-based approach to break down DNA sequences into sub-reads called the 'N-mer' and represents the sequences by N-mer frequencies. Then, we introduce the Latent DirichletAllocation (LDA) model to study the genome-level statistic patterns (a.k.a. latent topics) of the 'N-mer' features. Each estimated latent topic represents a certain component of the whole genome.

Keyword— Data mining, Bioinformatics (genome or protein) databases, Language models, Metagenomics

I. INTRODUCTION

The developed sequencing techniques and meta-genomics has dramatically changed the way of genomics data acquiring and analyzing. Next generation methods (such as Roche/454 Sequencing and Illumina Sequencing) are able to extract very large amount (100 ~ 1000 MB) of DNA fragment sequences from an environmental sample (like the ocean, soil and human body) in only a single run (the acquired data is also known a 'meta-genomic data'). The next generation sequencing methods not only provides efficient ways to generate genomic data, but also enable bioinformatics researchers to exploit genomic data [1]from very large amount of uncultured microbial samples instead of from isolated organism and culture. In analysis meta-genomics data both, taxonomic categorization and functional explanation are difficult because the obtained large amount of DNA remains are always relatively short and may from mixture of very large amount it's usually difficult and to laborites to assemble and annotate the meta-genomic reads. Microbial genome sequencing started in the late 1990s, and now, one decade later, we researchers have access to hundreds of genome sequences.[2] This advance has revolutionized the way research is conducted, and microbial biology has solidly transitioned into the era of post-genomics. Researchers routinely have access to the full catalog of the genes within a genome, thereby eliminating any misperception that genes function in isolation, and thus facilitating the discovery and characterization of genes as parts of genetic networks. This paradigm shift, inspired by DNA sequencing, has led to the development of other high-throughput genomic techniques such as the DNA microarray. The major challenge of the post-genomic era is to interpret the overwhelming amount of data that is now available to all microbial life scientists. Functional genomics and systems biology seek to address this challenge by utilizing enormous genome-scale datasets to predict functional interactions between genes, both within a genetic network and within a genome. Many of the most advanced techniques and algorithms used to make these predictions require a large variety of genomic datasets that are currently only available to the most well-studied model organisms; for the majority of prokaryotic model organisms, the only available types of genomic data exist in the form of a genome sequence and a DNA microarray

In this review, we will focus on the homology-based approach of functional and taxonomic structure of genomics by describing how the most common types of genomic data can be utilized to construct an experimental pipeline. We will summarize the different forms of genomics datasets, with emphasis on how these data are used to make functional predictions. We also present a case study for the integration of datasets into an experimental pipeline for the identification and verification of functional interactions, including how these datasets can be applied to bacterial systems biology. Finally, we describe the relationship between functional genomics and the evolution of model organism databases, with emphasis on genome annotation. Functional genomics data can be subdivided into sequenced-based and experiment based sets. Sequence-based datasets apply fundamental genetic principles to entire genomes the genome. For example, the principle of conserved operons can be used to predict the function and functional interactions of unknown open reading frames (ORFs) based on the clustering of ORFs into putative operons. Experiment-based datasets, on the other hand, are adaptations of established molecular biology protocols scaled-upto become 'high throughput. For example, DNA microarrays represent the adaptation of standard hybridization techniques applied on a genomic scale. While there is a clear delineation between sequenced-based and experiment-based datasets, the primary utilization of these datasets is identical: the large-scale prediction of functional interactions. From a systems biology perspective, the de facto structure of a functional interaction can be reduced to a binary construct between two proteins or genes. Although this construct is a drastic over simplification, it allows for both sequence-based and experiment-based datasets to be converted and combined into interaction sets. Stripe do fall subtlety that exists in. within a genome, every pair of genes either interacts (1) or does not (0).Because this binary characterization of an interaction bears little resemblance to reality, any interaction predict educing functional genomics data set must be experimentally verified and characterized with respect to spatial and temporal variables; at present, this process still occurs one interaction at a time. Further complicating this process is a lack of consensus regarding the definition of the term “functional interaction”. The problem lies in the literal interpretation of the word “interaction” and, by extension, the purpose of its modifier, “functional”.

A functional interaction can be narrowly defined as only those proteins that engage in direct physical contact or it can be broadly defined to include all of the proteins that are involved in a response or pathway. Both of these definitions represent extremes and, as such, contradictory examples abound. This lack of consensus does not represent a failure of the scientific community; it is possible that no rigorous definition exists. The difficulty in constructing a universally accepted definition for ‘functional interaction’ is similar to the current controversy in finding a definition for a bacterial species or a planetary body Rather than commit to specific pair wise functional interactions, ontologies have been developed to categorize proteins into functional groups including Clusters of Orthologous Groups (COGs) Gene Ontology (GO), the Kyoto Encyclopedia of Genes and Genomes (KEGG), and Protein Families (Pfam). Although every ontology uses an independent schema for their classifications, the fact that a computer script can convert data from one ontology to another, is a strong indication of convergence. Ontological analysis provides insight into the relationship that exists between a gene and its genome by reducing the set of possible interaction partners from the whole genome to a subset.

In the following section, we characterize the most common types of sequence-based and experiment based functional.

II. Homology – Based Approaches

The critical first step in homology modeling is the identification of the best structure, if indeed any are available. The simplest method of identification relies on serial pair wise sequence alignments aided by database search techniques such as FASTA and BLAST.[2] More sensitive methods based on multiple sequence alignment – of which PSI-BLAST is the most common example – iteratively update their position-specific scoring matrix to successively identify more distantly related homolog’s. This family of methods has been shown to produce a larger number of potential and to identify better for sequences that have only distant relationships to any solved structure. Protein threading, also known as fold recognition or 3D-1D alignment, can also be used as a search technique for identifying templates to be used in traditional homology modeling methods. . When performing a BLAST search, a reliable first approach is to identify hits with a sufficiently low *E*-value, which are considered sufficiently close in evolution to make a reliable homology model. Other factors may tip the balance in marginal cases; A better approach is to submit the primary sequence to fold-recognition servers or, better still, consensus meta-servers which improve upon individual fold-recognition servers by identifying similarities (consensus) among independent predictions. Often several candidate template structures are identified by these approaches. Although some methods can generate hybrid models with better accuracy from multiple. most methods rely on a single template. Therefore, choosing the best template from among the candidates is a key step, and can affect the final accuracy of the structure significantly. This choice is guided by several factors, such as the similarity of the query and template sequences, of their functions, and of the predicted query and observed template secondary structures. Perhaps most importantly, the coverage of the aligned regions: the fraction of the query sequence structure that can be predicted from the template, and the plausibility of the resulting model. Thus, sometimes several homology models are produced for a single query sequence, with the most likely candidate chosen only in the final step. It is possible to use the sequence alignment generated by the database search technique as the basis for the subsequent model production; however, more sophisticated approaches have also been explored. One proposal generates an ensemble of stochastically defined pair wise alignments between the target sequence and a single identified template as a means of exploring "alignment space" in regions of sequence with low local similarity. "Profile-profile" alignments that first generate a sequence profile of the target and systematically compare it to the sequence profiles of solved structures; the coarse-graining inherent in the profile construction is thought to reduce noise introduced by sequence drift in nonessential regions of the sequence. We present a www server for homology-based gene. The user enters a pair of evolutionary related genomic sequences. The homology-based approaches assign meta-genomic reads into NCBI taxonomy based on the alignment between these reads and standard reference (of known species) in standard databases (such as NCBI NR database). One example of homology-based classification approach is the Meta genome Analyzer (a.k.a. MEGAN) [9]. MEGAN is computer software that achieves taxonomical analysis over large databases. It compares DNA fragments against the database of reference sequence, and extracts taxonomical information from the high score BLAST hits. Based on the taxonomical information, the BLAST hits will be matched to different species and strains of the NCBI taxonomy (the algorithm collect all high score BLAST hits and assign taxon ID to each hit based on NCBI taxonomy, the NCBI Taxonomy contains over 460,000 taxa from different taxonomical ranks such as Kingdom, Phylum, Class, Order,...,). After that, the algorithm Will look for the lowest common ancestor (LCA) taxon of all those BLAST hits and then assigned the input sequence fragment with that taxon. In practice, BLASTX algorithm will be used to compare all reads against the standard references database (like the NR (non-redundant) protein database from NCBI). Before loading BLASTX hits of a specific meta-genomic fragment to perform a LCA algorithm, the MEGAN algorithm uses a bit-score threshold to limit the number of BLAST hits. It also discards all the “isolated assignment” by looking into the number of hit with regard to each taxon. Despite these efforts, however, the number of resulting hits may still be up to tens of thousands. The LCA algorithm used in MEGAN is able to visualize the hierarchical structure of the phylogenetic tree. However, it should be pointed out that the resulting taxon assignment may only has a limited resolution, as reads with too much BLAST hits may always be assigned to relative high taxon levels such as genus, family instead of species and strains [8].

III. GENERATIVE TOPIC MODEL FOR TAXONOMIC DATA ANALYSIS

In this modeling work on functional groups in microbial communities. The approach is based on taxon large quantity data acquired from homology based approaches. In this paper the generative topic modeling is an unsupervised probabilistic learning method that is able to extract useful information from unlabeled data. Various domain using a text mining has been developed for generative topic models. The bioinformatics or computational biology various domain generative topic model has been previously used to protein- protein relation from MEDLINE abstract of biomedical literature [2] [5]; we use LDA (Latent Dirichlet Allocation) Model [3]

Latent Dirichlet allocation (LDA) is a generative probabilistic model. The basic idea is that documents are represented as random mixtures over latent topics, where each topic is characterized by a distribution over words

LDA assumes the following generative process for each document

1**.** Choose N ~Poisson (ξ)

2. Choose θ~Dir (α).

3. for each of the N words w_n:

(a) Choose a topic Z_n~Multinomial (θ).

(b) Choose a word w_n from p(w_n | Z_n ,β), a multinomial probability conditioned of the topic Z_n.

Several simplifying assumptions are made in this basic model, some of which we remove in subsequent sections. First, the dimensionality D of the Dirichlet distribution (and thus the dimensionality of the topic variable z) is assumed known and fixed. Second, the word probabilities are parameterized by a k X V matrix β,

Where β_{ij} =p (w^j =1 | Z^j = 1) which for now we treat as a fixed quantity that is to be estimated. Finally, the Poisson assumption is not critical to anything that follows and more realistic document length distributions can be used as needed. Furthermore, note that *N* is independent of all the other data generating variables (q and **z**). It is thus an ancillary variable and we will generally ignore its randomness in the subsequent development.

IV. Results

By conducting a generative topic modeling experiment for taxonomic analysis, following the methods as shown in above section 2.4, we apply the LDA topic model to the taxon abundance data of human gut microbial samples. The human gut microbial community taxon abundance data is generated by [14], the Illumina GA reads from human gut microbial samples are firstly assembled into longer contigs.

General Concept for Original BLAST Program

- Sequence (query) is broken into words of ***length W***
- Align all words with sequences in the database
- Calculate ***score T*** for each word that aligns with a sequence in the database using a substitution matrix
- Discard words whose T value is below a ***neighborhood score threshold***
- Extend words in both directions until score falls by ***drop-off value X*** when compared to previous best Score

BLAST is one of the most widely used bioinformatics programs, because it addresses a fundamental problem and the heuristic algorithm it uses is much faster than calculating an optimal alignment. This emphasis on speed is vital to making the algorithm practical on the huge genome databases currently available, although subsequent algorithms can be even faster.

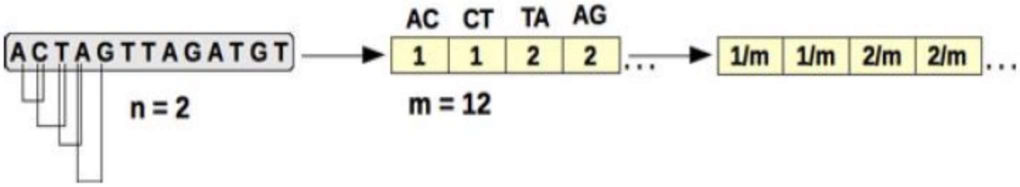
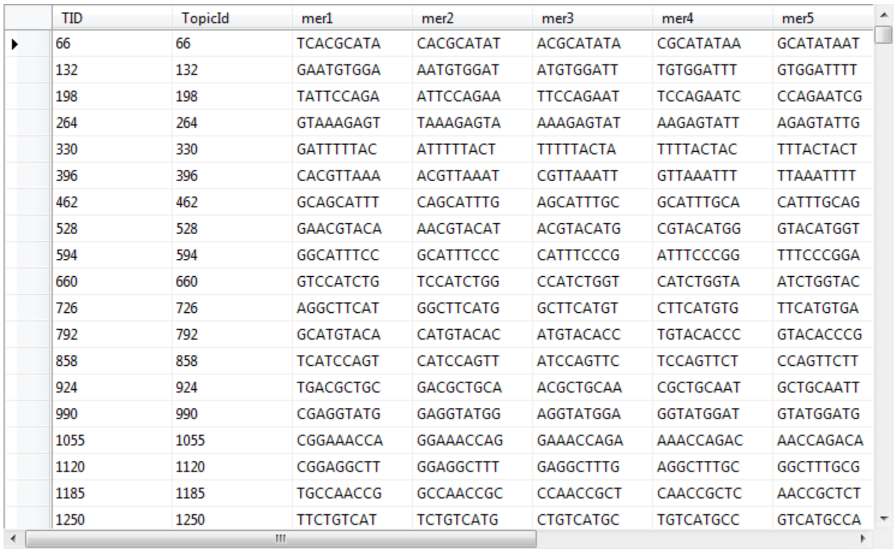
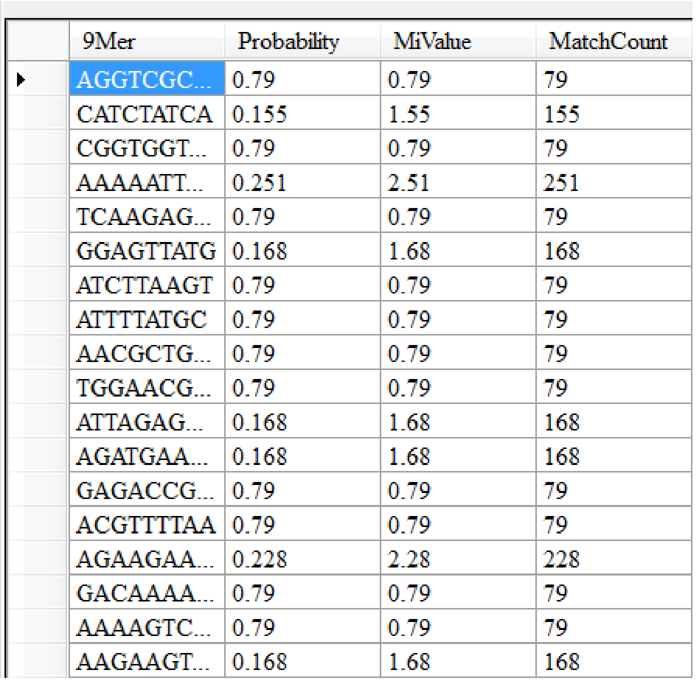


Fig. 'n-mer' example where n=2



TID	TopicId	mer1	mer2	mer3	mer4	mer5
66	66	TCACGCATA	CACGCATAT	ACGCATATA	CGCATATAA	GCATATAAT
132	132	GAATGTGGA	AATGTGGAT	ATGTGGATT	TGTGGATTT	GTGGATTTT
198	198	TATTCCAGA	ATTCCAGAA	TTCCAGAAT	TCCAGAATC	CCAGAATCG
264	264	GTAAAGAGT	TAAAGAGTA	AAAGAGTAT	AAGAGTATT	AGAGTATTG
330	330	GATTTTTAC	ATTTTTACT	TTTTTACTA	TTTTACTAC	TTTACTACT
396	396	CACGTTAAA	ACGTTAAAT	CGTTAAATT	GTTAAATTT	TTAAATTTT
462	462	GCAGCATTT	CAGCATTTG	AGCATTTGC	GCATTTGCA	CATTTGCAG
528	528	GAACGTACA	AACGTACAT	ACGTACATG	CGTACATGG	GTACATGGT
594	594	GGCATTTCC	GCATTTCCC	CATTTCCCG	ATTTCCCGG	TTTCCCGGA
660	660	GTCCATCTG	TCCATCTGG	CCATCTGGT	CATCTGGTA	ATCTGGTAC
726	726	AGGCTTCAT	GGCTTCATG	GCTTCATGT	CTTCATGTG	TTCATGTGA
792	792	GCATGTACA	CATGTACAC	ATGTACACC	TGTACACCC	GTACACCCG
858	858	TCATCCAGT	CATCCAGTT	ATCCAGTTC	TCCAGTTCT	CCAGTTCTT
924	924	TGACGCTGC	GACGCTGCA	ACGCTGCAA	CGCTGCAAT	GCTGCAATT
990	990	CGAGGTATG	GAGGTATGG	AGGTATGGA	GGTATGGAT	GTATGGATG
1055	1055	CGGAAACCA	GGAAACCAG	GAAACCAGA	AAACCAGAC	AACCAGACA
1120	1120	CGGAGGCTT	GGAGGCTTT	GAGGCTTTG	AGGCTTTGC	GGCTTTGCG
1185	1185	TGCCAACCG	GCCAACCGC	CCAACCGCT	CAACCGCTC	AACCGCTCT
1250	1250	TTCTGTCAT	TCTGTCATG	CTGTCATGC	TGTCATGCC	GTCATGCCA

The above Table. Shows the merging of the browsed file & according to that it divide the original gene sequence into 9-mer



	9Mer	Probability	MiValue	MatchCount
▸	AGGTCGC...	0.79	0.79	79
	CATCTATCA	0.155	1.55	155
	CGGTGGT...	0.79	0.79	79
	AAAAATT...	0.251	2.51	251
	TCAAGAG...	0.79	0.79	79
	GGAGTTATG	0.168	1.68	168
	ATCTTAAGT	0.79	0.79	79
	ATTTTATGC	0.79	0.79	79
	AACGCTG...	0.79	0.79	79
	TGGAACG...	0.79	0.79	79
	ATTAGAG...	0.168	1.68	168
	AGATGAA...	0.168	1.68	168
	GAGACCG...	0.79	0.79	79
	ACGTTTTAA	0.79	0.79	79
	AGAAGAA...	0.228	2.28	228
	GACAAAA...	0.79	0.79	79
	AAAAGTC...	0.79	0.79	79
	AAGAAGT...	0.168	1.68	168

Above Table illustrates the top-ranked latent topics of different samples, in which the ID of latent topics are sorted by the probability with respect to different samples.

- After this, illustrations of top-ranked latent topics with respect to different microbial samples will be done.
- Commonly shared top-ranked latent topics for three different sample categories will be shown.

Gene functional Analysis

V. Feature Work: Online Generative Topic Modeling

Online processing of text streams is an essential task of many genuine applications. The objective is to identify the underlying structure of evolving themes in the incoming streams online at the time of their arrival. As many topics tend to reappear consistently in text streams, incorporating semantics that were discovered in previous streams would eventually enhance the identification and description of topics in the future. Latent Dirichlet Allocation (LDA) topic model is a probabilistic technique that has been successfully used to automatically extract the topical or semantic content of documents we investigate the role of past semantics in estimating future topics under the framework of LDA topic modeling, based on the online version implemented in Then, this model is incrementally updated according to the information inferred from the new stream of data with no need to access previous data. Since the proposed approach is totally unsupervised and data-driven, we analyze the effect of different factors that are involved in this model, including the window size, history weight, and equal/decaying history contribution. The proposed approach is evaluated using benchmark datasets. Our experiments show that the embedded semantics from the past improved the quality of the document modeling. We also found that the role of history varies according to the domain and nature of text data.

VI. CONCLUSIONS

In this paper, a set of novel probabilistic topic models have been proposed to address challenging issues text mining and bioinformatics studies. The contributions are as follows. In this section, we conduct a generative topic modeling experiment for taxonomic analysis. Following the methods in Section, we apply the LDA topic model to the taxon abundance data of human gut microbial samples. The human gut microbial community taxon abundance data is generated by [4], which is openly accessible via: http://gutmeta.genomics.org.cn/. According to [4], the Illumina GA reads from human gut microbial samples are firstly assembled into longer contigs. After that, the MetaGene program was used to predict open reading frames (ORFs) from those contigs. The predicted ORFs were then aligned to each other and grouped to a non-redundant gene set. The gene taxonomic assignment is achieved by carrying out BLASTP alignment against the NR database. The taxonomical level of each gene is determined by the lowest common ancestor (LCA). As a result of gene taxonomic assignment, the taxon abundance data for each sample can be produced.

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