PuReD-MCL: a graph-based PubMed document clustering methodology

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ABSTRACT

Motivation: Biomedical literature is the principal repository of biomedical knowledge, with PubMed being the most complete database collecting, organising, and analysing such textual knowledge. There are numerous efforts that attempt to exploit this information by using text mining and machine learning techniques. We developed a novel approach, called PuReD-MCL (Pubmed Related Documents-MCL), which is based on the graph clustering algorithm MCL and relevant resources from PubMed.

Methods: PuReD-MCL avoids using natural language processing (NLP) techniques directly; instead, it takes advantage of existing resources, available from PubMed. PuReD-MCL then clusters documents efficiently using the MCL graph clustering algorithm, which is based on graph flow simulation. This process allows users to analyse the results by highlighting important clues, and finally to visualise the clusters and all relevant information using an interactive graph layout algorithm, for instance BioLayout Express 3D.

Results: The methodology was applied to two different datasets, previously used for the validation of the document clustering tool TextQuest. The first dataset involves the organisms \textit{E. coli} and yeast, whereas the second is related to \textit{Drosophila} development. PuReD-MCL successfully reproduces the annotated results obtained from TextQuest, while at the same time provides additional insights into the clusters and the corresponding documents.

Availability: Source code in perl and R are available from http://tartara.csd.auth.gr/~theodos/

1 INTRODUCTION

There is an overwhelming amount of textual knowledge recorded in the biomedical literature, with the number of articles published each year increasing exponentially, following the advances in high-throughput experimental and computational methods. The PubMed database, which is considered one of the most complete repositories of biomedical articles, contains more than 11 million abstracts and receives more than 70 million queries each month.

The vast amount of documents available in the biomedical literature makes the manual handling, analysis and interpretation of textual information a daunting task. Automated methods that assist users to sift through this unstructured heap of valuable archives are becoming increasingly important in scientific research. There have been numerous attempts to develop systems that analyse textual resources and contribute towards the discovery of key facts with minimum user interaction and guidance. These approaches need to be scalable, as automatic as possible, as well as user-friendly (Ananiadou et al. 2006). Most text mining systems use natural language processing (NLP), machine learning and data mining techniques in order to process text, usually in the form of document abstracts. Examples include maximum entropy (Raychaudhuri et al. 2002), support vector machines (Izumitani et al. 2004) and linear discriminant analysis (LDA) (Theodosiou et al. 2007), all representing different classification methods based on a training set of documents. These training sets assist the creation of models, which are subsequently used for the categorization of new documents from so-called test sets. Avoiding the training/test set paradigm is advantageous, especially in cases where the partitioning of the document space is not known \textit{a priori}. For instance, the TextQuest document clustering system uses lists of keywords (Iliopoulos et al. 2001) and thus is independent of a training set or a specific algorithm. More complicated text mining techniques involve information extraction from documents. These make extensive use of syntactic and semantic analysis in order to recognize the logical entities described in the text, like in (Hu 2005) and (Neadic et al. 2003). The drawback is that they are computationally demanding, and they typically require a predefined ontology for the domain of discourse (Iliopoulos et al. 2001), (Ananiadou et al. 2006). In summary, the main feature of biomedical text mining methods is the use of NLP techniques, in order to process textual information. Usually, documents are represented using the Vector Space Model (VSM) (Salton 1970, Manning and Schutze 1999), where each document is encoded as a vector of weighted words. In information extraction, the syntax and the semantics of text are also taken into account for each document, using more complex structures than VSM (Ananiadou et al. 2006).

The motivation behind the current work was to create an approach that is able to cluster arbitrarily large quantities of biomedical text from the PubMed database and exploit useful information by extracting, filtering and organizing it, without directly relying on sophisticated NLP techniques. Another important aspect was the visualisation of the extracted information alongside the relationships between documents thus allowing users to interact with results, leading to better understanding and enhanced knowledge.

The methodology we put forward has a number of desirable advantages:

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It relies on robust and pre-computed information provided by PubMed curators and computational infrastructure, thus avoiding cumbersome calculations.

(2) It uses an efficient and scalable graph clustering algorithm, previously applied to very large and diverse datasets other than text.

(3) It uses a statistical methodology, based on $\chi^2$ testing and bootstrap procedures, for assessing the quality of the document clusters.

(4) It only uses the document title and Medical Subject Headings (MeSH) terms, selected by a simple yet effective scoring and filtering scheme, to describe the knowledge in documents and clusters.

(5) It embeds the results and relationships interactively, in 2D and 3D space.

2 METHODS

The general idea of our methodology is to represent the relationships between the documents with a graph, and cluster them using the Markov Clustering algorithm (MCL) (van Dongen 2000). In order to avoid the direct use of NLP techniques, pre-computed relationships from PubMed are utilised to build the association graph between documents. The clusters are visualized in 2D or 3D space and are described using the document titles and the MeSH terms.

Specifically, the methodology involves the following main steps (Fig. 1):

(1) The retrieval of a set of documents (abstracts) through the query system of PubMed.

(2) The retrieval of pre-computed related documents for each document of the previous set, again from PubMed.

(3) The creation of a graph between the documents of the first step, with vertices representing documents and edges representing document relatedness.

(4) The clustering of the graph using the Markov Cluster algorithm (MCL).

(5) The annotation of the clusters and their documents using an efficient in-house algorithm.

(6) The statistical validation of the clustering results.

(7) The visualization of the results using BioLayout Express 3D.

Steps 1 & 2:

A user query is performed at PubMed, and for each of the returned documents its pre-computed related documents are retrieved using the e-utilities module of Entrez (Wheeler et al. 2007).

The algorithm for calculating the related documents is based on comparing words from the title, the abstract and the MeSH terms of the documents. It uses Natural Language Processing (NLP) techniques and the Vector Space Model in order to represent each document as a vector of weighted words and apply vector scoring (Wilbur and Yang 1996).

In this step, there is a possibility that some documents do not relate to any of the other. These documents are represented in the graph as stand-alone, disconnected nodes and do not affect the next step of the clustering, since they have no connections to the rest of the documents.

Step 4:

The MCL algorithm is used to uncover clusters in the graph. MCL performs unsupervised clustering (i.e. there is no need to predefine the number of clusters) on weighted graphs. It has previously been used successfully in biology for detecting protein families (Enright et al. 2002), and has also been shown to perform better than other algorithms when used in protein-protein interaction networks (Brohee 2006).

MCL is based on the idea that natural clusters in a graph have many edges between the members of each cluster and few across clusters. Once inside a cluster, a hypothetical entity moving around randomly will have little chance to escape that cluster. MCL simulates random walks (flow) within the entire graph and augments flow where it is already strong and weakens it where it is weak. After many iterations of this process, the underlying cluster structure of the graph gradually becomes visible. Regions of the graph with high flow describe clusters that are separated by boundaries with no flow. MCL simulates the random walks within a graph by two algebraic operations, called expansion and inflation that are applied to a stochastic matrix. The matrix representing the graph is used as input, while expansion and inflation are applied for many rounds, until there is little or no change in the matrix. The final matrix then represents the clustering of the graph nodes (documents in this context). Expansion refers to the power of a stochastic matrix, using the normal matrix product. Inflation is the entry-
wise Hadamard-Schur product (Radhakrishna and Bhaskara 1998) combined with diagonal scaling, and is responsible for both the strengthening and the weakening of the flow. The value of the inflation parameter controls cluster granularity (van Dongen 2000).

The MCL algorithm is considered to be very fast and scalable (van Dongen 2000), since its worst case time complexity is \(O(N^*L^2)\), where \(N\) is the number of documents and \(L\) is an MCL parameter usually between 500 and 1000. The space complexity is \(O(N^*L)\) (van Dongen, 2000).

**Step 5:**

Each cluster and included documents are annotated using the document titles and a selected number of MeSH terms and chemical substances. The MeSH terms form a controlled structured vocabulary, used for indexing PubMed documents. The chemical substances are supplementary concept records of the MeSH hierarchy that are not used for indexing. MeSH terms have been shown to be good indicators for representing the contents of a cluster (Yamamoto et al. 2007), and are generally considered to be useful for the extraction of contents from whole documents without using complex NLP techniques (Strube et al. 2004).

The titles of the documents are used as they are without any further processing. On the other hand, the MeSH terms and the chemical substances (collectively defined as ‘terms’ hereafter) to be used for annotation are chosen for each cluster based on a scoring and filtering scheme.

The scoring is based on TF.IDF (Text Frequency – Inverse Document Frequency) (Manning and Schutze 1999), which expresses the specificity and the coverage that the terms confer to the clusters. Specificity corresponds to in-cluster frequency, i.e. the probability of a term to belong to a cluster of interest. Coverage corresponds to out-cluster frequency, i.e. the probability of a term to belong to any other cluster. The score is the product of the in-cluster and the out-cluster probability. Formally,

\[
TF = \frac{n^c}{n^m} \quad (1)
\]

and

\[
IDF = -\log \left( \frac{n_n}{N} \right) \quad (2)
\]

where \(N\) is the total number of documents, \(n_n\) the number of documents in the whole set (corpus) containing term \(m\), \(n^c\) the number of documents in cluster \(c\) and \(n^m\) the number of documents in cluster \(c\) containing term \(m\). Then the score \(s_n\) of each term \(m\) is

\[
s_n = TF \times IDF \quad (3)
\]

Consequently, a ranked list of terms is generated, according to these scores.

In order to annotate the documents of a cluster, and subsequently the cluster itself, in a clutter-free manner, we manage the document coverage of each term in the ranked list using a threshold. The threshold controls how many new documents the candidate term describes, compared to the already accepted (and higher-scoring) ones in the ranked list. In other words, we want to avoid complete overlap between the documents described by the candidate term and all the documents described by the already accepted terms. In our experiments, we set this threshold to one document.

**Step 6:**

The biological coherence of the MCL clusters is then validated by randomizing the assignment of the documents to the clusters (random clustering). Coherence is assessed by the \(\chi^2\) statistic (Weiss 2002) and the counts of each term in each cluster, symbolized as \(n^c_m\), where \(C_i\) is cluster \(k\) with \(k\) signifying the number of clusters. \(m\) is the \(v\)th term. The terms used in this step are all terms contained in all documents of our set and not only the ones selected in the previous step of our methodology (Step 5), thus avoiding any bias. Using the bootstrap method, we create 10,000 random clusterings (samples), where the number of clusters and their size remain the same as in the solution produced by MCL. The documents are randomly assigned to each cluster. Then for each cluster we count the number of documents that contain each term (Table 1 – contingency table) and we calculate the \(\chi^2\) statistic for every sample (random clustering). Using the \(\chi^2\) statistic from the 10,000 samples, we build a histogram and a distribution graph based on kernel density estimation. If the \(\chi^2\) statistic calculated for the MCL clustering is at the edge of our graphs, we can conclude that the terms are not independent of the clusters. Furthermore, we calculate the P-value for the \(\chi^2\) statistic for the MCL clustering.

<table>
<thead>
<tr>
<th>Clusters</th>
<th>(m_1)</th>
<th>(m_2)</th>
<th>...</th>
<th>(m_v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_1)</td>
<td>(n^c_{11})</td>
<td>(n^c_{12})</td>
<td>...</td>
<td>(n^c_{1v})</td>
</tr>
<tr>
<td>(C_2)</td>
<td>(n^c_{21})</td>
<td>(n^c_{22})</td>
<td>...</td>
<td>(n^c_{2v})</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>(C_k)</td>
<td>(n^c_{k1})</td>
<td>(n^c_{k2})</td>
<td>...</td>
<td>(n^c_{kv})</td>
</tr>
</tbody>
</table>

**Table 1** A contingency table of clusters and MeSH terms

**Step 7:**

The final step of the methodology involves the visualisation of the clustering, documents and their titles, and selected terms. This is achieved with BioLayout Express 3D (Goldovsky et al. 2005) that also allows the user to interact with results, for instance by searching for keywords, highlighting relevant documents, analyzing graph connectivity, linking nodes with external databases, and so forth.

It must be made clear that 2D or 3D space is only used for the presentation of the documents and the clusters to the end-user, and that coordinates of a citation have no further use. BioLayout uses a modified version of the Fuchtermann and Rheingold graph layout algorithm in order to produce an “aesthetically pleasing” layout of complex graphs (Goldovsky et al. 2005). Based on this algorithm, two documents that are similar, meaning they have a mutual connection with a high similarity score obtained from the “related articles” tool of PubMed, will end up closer in the final graph than two documents which are weakly similar. Consequently, highly connected groups of similar documents will form tight clusters in the final graph.

In our methodology, apart from MCL and BioLayout Express 3D, we use perl scripts for processing the documents, as in Step 5, and the R statistical software package (R development Core team 2007) for the statistical procedures as in Step 6.
3 RESULTS

In order to evaluate our methodology, we performed control experiments based on two different datasets that have already been used for evaluating the performance of TextQuest (Iliopoulos et al. 2001).

The first dataset consisted of 1660 documents obtained from two different queries. The first query was “escherichia AND pili”, returned 830 documents and is relevant to the organism Escherichia coli and pili, which are surface organelles. The second query was “cerevisiae AND cdc*”, returned the same number of documents (830) and is relevant to the cell division control genes of yeast.

The second dataset was derived by using the following terms in the queries: “anterior-posterior AND drosophila” plus “dorsal-ventral AND drosophila”. Both queries are relevant to the developmental axes of Drosophila. Since the queries are closely related some documents returned by the two queries were the same. Thus, the number of unique documents in the second dataset was 465.

The two datasets reflect two control tests of increasing difficulty: in the first dataset, the desired solution would clearly be two large, disconnected clusters since the concepts are drastically different; in the second dataset, the desired solution is less clear although it should reflect some biologically relevant concept groups (Iliopoulos et al. 2001).

3.1 First dataset

Thirty documents were not related to the other 1630 documents according to PubMed. Using an inflation value of 1.2 for the MCL algorithm, the 1630 documents were divided in two clusters. The first cluster included 818 documents referring to the E. coli query, while the second cluster contained 812 documents referring to yeast and the cdc genes (Fig. 2).

<table>
<thead>
<tr>
<th>Cluster 1</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bacterial Adhesion</td>
<td></td>
</tr>
<tr>
<td>2. Bacterial Proteins</td>
<td></td>
</tr>
<tr>
<td>3. Conjugation, Genetic</td>
<td></td>
</tr>
<tr>
<td>4. Escherichia coli infections</td>
<td></td>
</tr>
<tr>
<td>5. Escherichia coli</td>
<td></td>
</tr>
<tr>
<td>6. Fimbriae proteins</td>
<td></td>
</tr>
<tr>
<td>7. Fimbriae, bacterial</td>
<td></td>
</tr>
<tr>
<td>8. Genes, Bacterial</td>
<td></td>
</tr>
<tr>
<td>9. Humans</td>
<td></td>
</tr>
<tr>
<td>10. Mannose</td>
<td></td>
</tr>
<tr>
<td>11. Plasmids</td>
<td></td>
</tr>
<tr>
<td>12. Analysis</td>
<td></td>
</tr>
<tr>
<td>13. Immunology</td>
<td></td>
</tr>
<tr>
<td>14. Microbiology</td>
<td></td>
</tr>
<tr>
<td>15. Pathogenicity</td>
<td></td>
</tr>
<tr>
<td>16. Ultrastructure</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cluster 2</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CDC28 Protein Kinase, S. cerevisiae</td>
<td></td>
</tr>
<tr>
<td>2. Cell Cycle Proteins</td>
<td></td>
</tr>
<tr>
<td>3. Cell Cycle</td>
<td></td>
</tr>
<tr>
<td>4. Cyclins</td>
<td></td>
</tr>
<tr>
<td>5. Fungal Proteins</td>
<td></td>
</tr>
<tr>
<td>6. Genes, Fungal</td>
<td></td>
</tr>
<tr>
<td>7. Mutation</td>
<td></td>
</tr>
<tr>
<td>8. Saccharomyces cerevisiae Proteins</td>
<td></td>
</tr>
<tr>
<td>9. Saccharomyces cerevisiae</td>
<td></td>
</tr>
<tr>
<td>10. Sequence Homology, Amino Acid</td>
<td></td>
</tr>
<tr>
<td>11. Cytology</td>
<td></td>
</tr>
<tr>
<td>12. Enzymology</td>
<td></td>
</tr>
<tr>
<td>13. Metabolism</td>
<td></td>
</tr>
<tr>
<td>14. Ras-GRF1</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 The selected terms describing each cluster for dataset 1

Table 2 contains the terms selected using Step 5 of our methodology. Originally Cluster 1 contained 1349 unique terms and Cluster 2 1551, but the selected ones were only 16 and 14 respectively. The terms described general concepts relevant to each query, like bacterial adhesion, fimbriae proteins, cell cycle proteins etc.

Significantly, for different inflation values we observed clusterings with different granularities. For example, when we used an inflation value of 1.3, MCL produced four clusters. The first of the two additional clusters contained four documents relevant to gonococcal pili antigens and described by the MeSH term Neisseria gonorrhoeae. All the documents were from the query related to E.coli and pili. The second additional cluster contained three documents from the yeast query and is described by the MeSH terms Ribonucleoprotein, U1 Small Nuclear and Schizosaccharomyces. It is thus encouraging that PuReD-MCL is able, through the tweaking of a single parameter, to produce clusterings of variable detail. In this case two small subclusters were extracted from the original two clusters describing more specialised concepts.

3.2 Second dataset

Out of the 465 documents of the second dataset, 18 did not relate to any of the remaining 447 documents. Since we wanted to compare our results with those of TextQuest, where the clusters were three, we experimented with MCL and inflation values that resulted in a similar number of clusters. An inflation value of 1.2 yielded two clusters, as described in the original control experiments (Iliopoulos et al. 2001). The first cluster contained 443 documents and corresponded mainly to the dorsal-ventral development of Drosophila, while the second cluster...
(four documents) covered the homeobox pbx1 protein, uncovering parts of development along the anterior-posterior axis. In more detail, three abstracts (PubMed ID: 7791786, 7565734, 10067897) in this cluster were fully interconnected, while the fourth document (PubMed ID: 7914870) connected also to documents outside the cluster, because it referred generally to homeotic proteins in Drosophila, as expected. Furthermore, using an inflation value of 1.3, we separated the documents to six, more granular, clusters. We chose to keep this last clustering solution, since it provided more details about the biological information in the documents and was directly comparable with a previous study (Iliopoulos et al. 2001).

Cluster 5 described the morphogenesis of the zebrafish (tropical fish) brain and the genes that regulate it (Schier et al. 1996). It also included information about the genetic regulation of the somite formation in vertebrates (Rawls et al. 2000). Finally, Cluster 6 contained documents that described the binding of pbx1 protein (homeoprotein Extradenticle) to DNA and homeotic (Hox) protein Ultrabithorax; thus, the pbx1 protein affects development across the anterior-posterior axis of animals, as is already known (Passner et al. 1999).

It is intriguing to note that the documents related to the dorsal-ventral development axis were assigned to cluster 1, whereas development in both axis was described by cluster 4 (Wnt/Wg pathway) and cluster 5 (in vertebrates).

Fig. 3 presents a graph of the six clusters where the dark nodes are the documents and the light ones the selected terms. Also, Table 3 includes details about the number of documents and a short description of each cluster. We can see that the first cluster contained most of the documents and described the process of segmentation and embryonic patterning in general. Interestingly, the second cluster contained documents specifically related to the genetic machinery for the concept in cluster 1, the homeobox genes (Hox), which are the subject of intense research on merit: the Hox genes control the formation of segment specific structures in the anterior-posterior axis, are highly conserved, crucial for the development of Drosophila, and exhibit unique behavior, like colinearity (Lappin et al. 2006). Cluster 3 involved the sonic hedgehoc proteins (Shh) and their role in the zone of polarizing activity (ZPA), which are related to the differentiation in the anterior-posterior axis (Marigo et al. 1996). Cluster 4 contained documents about the Wnt/Wg signaling pathway studied in C. elegans, Xenopus and Drosophila. The Wng/Wg pathway is evolutionary conserved and plays an important role in normal development and cancer for many organisms, including Drosophila and human (Xiang 2003). Wg is required to establish the anterior-posterior axis during embryogenesis, but it is also necessary for correct dorsal-ventral axis patterning in the wing imaginal disc, at different steps of development (Zhang et al. 1998).

Fig. 3 The six clusters from the second dataset.

Table 3 Cluster description of dataset 2

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Size</th>
<th>Short Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>322</td>
<td>Segmentation and embryonic patterning</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>88</td>
<td>Homeobox genes</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>19</td>
<td>Sonic Hedgehog proteins (Shh) &amp; Zone of Polarizing Activity (ZPA)</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>10</td>
<td>C. elegans, Xenopus and Drosophila Wnt/Wg signaling pathway</td>
</tr>
<tr>
<td>Cluster 5</td>
<td>4</td>
<td>Morphogenesis of zebrafish brain &amp; Somitogenesis</td>
</tr>
<tr>
<td>Cluster 6</td>
<td>4</td>
<td>Binding properties of pbx1 protein</td>
</tr>
</tbody>
</table>

Table 4 The selected terms describing each cluster for dataset 2. Original number of terms obtained is indicated in parentheses.

<table>
<thead>
<tr>
<th>Terms</th>
<th>Cluster 1 (683)</th>
<th>Cluster 2 (307)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bone Morphogenetic Proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Cadherins</td>
<td></td>
<td>1. Embryo, nonmamalian</td>
</tr>
<tr>
<td>3. Drosophila Proteins</td>
<td></td>
<td>2. Gene Expression Regulation</td>
</tr>
<tr>
<td>6. Female</td>
<td></td>
<td>5. Genes, regulator</td>
</tr>
<tr>
<td>8. Insect Hormones</td>
<td></td>
<td>7. Polycomb protein, Drosophila</td>
</tr>
<tr>
<td>9. Morphogenesis</td>
<td></td>
<td>8. Transcription factors</td>
</tr>
<tr>
<td>10. Mutation</td>
<td></td>
<td>9. Transcription, Genetic</td>
</tr>
<tr>
<td>11. Phenotype</td>
<td></td>
<td>10. Anatomy and Histology</td>
</tr>
<tr>
<td>12. Proteins</td>
<td></td>
<td><strong>Cluster 4 (102)</strong></td>
</tr>
<tr>
<td>14. Transcription factors</td>
<td></td>
<td>2. Cytoskeletal Proteins</td>
</tr>
<tr>
<td>15. Wing</td>
<td></td>
<td>3. Glycogen synthase Kinase 3</td>
</tr>
<tr>
<td>17. Metabolism</td>
<td></td>
<td><strong>Cluster 5 (44)</strong></td>
</tr>
<tr>
<td>18. Physiology</td>
<td></td>
<td>1. Somites</td>
</tr>
<tr>
<td><strong>Cluster 3 (146)</strong></td>
<td></td>
<td>2. Zebrafish</td>
</tr>
<tr>
<td>1. Chick Embryo</td>
<td></td>
<td><strong>Cluster 6 (52)</strong></td>
</tr>
<tr>
<td>2. Extremities</td>
<td></td>
<td>1. Pbx1 protein, human</td>
</tr>
<tr>
<td>4. Hedgehog Proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Limb bud</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Mice</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4 lists the selected terms from **Step 5** of the methodology for each cluster. Although the selected terms are rather generic, they can identify the different biological concepts of each cluster and help the user find specific information. Inside the parentheses there are the original number of terms contained in each cluster,
The assignment of documents to clusters. In the original clustering (see Table 3 for dataset 2) and randomiz-

cation in the whole document and not just the abstract or the title.

In future work, it will be crucial to devise more sophisticated

In order to statistically assess the biological coherence of the

classifiers/approaches, in the context of similar evaluations, for exam-

In order to provide a performance evaluation and further evi-

dence of the scalability of our methodology we used the query

The output includes (i) the elapsed real time between the invo-

cation and termination of the process (“real”), (ii) the user CPU
time (“user”) and (iii) the system CPU time (“sys”). The user time is
the time used by the program itself and any library subroutines it
calls. The system time is the time used by system calls invoked by
the program (directly or indirectly). The sum of user + system is
the total direct CPU cost of executing the program. To cluster a
dataset 1,000 times larger, the time requirement would be of the
order of 8,000 minutes, or 5 days or so – on a faster server, this
would be reduced to a matter of hours. Also note that the difference
between real and user + system time, is the sum of all of the factors
that may delay execution, for example delays due to network
speed. Furthermore, there are parameter dependencies, e.g. as the

<table>
<thead>
<tr>
<th>Type of time measured</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>real</td>
<td>26min 43.898s</td>
</tr>
<tr>
<td>user</td>
<td>8min 46.848s</td>
</tr>
<tr>
<td>sys</td>
<td>0min 18.464s</td>
</tr>
</tbody>
</table>

Table 5 UNIX “time” command results

The chi-squared test statistic for the random clustering of the
second dataset was $\chi^2 = 41556.39$, df = 17366, p-value =
0. We also performed a Monte Carlo simulation (Hope 1968) to
calculate the p-value and the result was also significant (p-value =
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30,000, which was much less than 41,556. Fig. 4 depicts a histo-
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around 30,000 while most of the scores are between 12,000 and
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We compared our clustering with the results from TextQuest in
order to explore the biological information revealed by each meth-
ology. TextQuest defined three clusters (Iliopoulos et al. 2001),
the first one containing documents about the process of segmenta-
tion and embryonic patterning, the second one about the embryonic
dorsoventral axis specification in
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ter referred to genes involved in both the anterior-posterior and the
dorsal-ventral axes, during oogenesis. In comparison, the PuReD-
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and thus better specificity for certain terms, e.g. pbx1, Shh & ZPA,
as shown (Table 3).

In summary, the original question posed by TextQuest was how
are the two
Drosophila embryonic axes established. Thus, the
submitted queries in the PubMed had the keywords ‘anterior-
posterior’ and ‘dorsal-ventral’. Both, TextQuest and PuReD-MCL
answered the above question, but from a different perspective pro-
ducing more than two clusters.

In future work, it will be crucial to devise more sophisticated
learning sets to benchmark the performance of these algo-

The $\chi^2$ score for the solution was $41556.39$, df = 17366, p-value =
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### 3.3 Performance evaluation

In order to provide a performance evaluation and further evi-
dence of the scalability of our methodology we used the query
“microbial phenotype” in order to cluster 6524 documents from
PubMed. The UNIX command “time” was used in order to meas-
ure the time required to retrieve (download through an Internet
connection) the “related articles” xml files for each of the 6524
documents, process them, build the graph and cluster the graph
using the MCL algorithm. The hardware used was an Intel 2.16
GHz Core Duo processor, 2GB of RAM. The connection to the
Internet was through ADSL 1Mbps download and 256Kbps up-
load. The downloaded “related articles” information from PubMed
was approximately 112 Mbytes. The inflation value for MCL was
1.2. The “time” UNIX command produced the results in Table 5.

<table>
<thead>
<tr>
<th>Type of time measured</th>
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</tr>
</thead>
<tbody>
<tr>
<td>real</td>
<td>26min 43.898s</td>
</tr>
<tr>
<td>user</td>
<td>8min 46.848s</td>
</tr>
<tr>
<td>sys</td>
<td>0min 18.464s</td>
</tr>
</tbody>
</table>

Table 5 UNIX “time” command results

The output includes (i) the elapsed real time between the invo-
cation and termination of the process (“real”), (ii) the user CPU
time (“user”) and (iii) the system CPU time (“sys”). The user time is
the time used by the program itself and any library subroutines it
calls. The system time is the time used by system calls invoked by
the program (directly or indirectly). The sum of user + system is
the total direct CPU cost of executing the program. To cluster a
dataset 1,000 times larger, the time requirement would be of the
order of 8,000 minutes, or 5 days or so – on a faster server, this
could be reduced to a matter of hours. Also note that the difference
between real and user + system time, is the sum of all of the factors
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inflation value in MCL increases, the time required for the clustering decreases.

4 DISCUSSION & FUTURE WORK

PuRed-MCL can efficiently produce meaningful and interpretable clusters of PubMed documents by creatively using a combination of existing and well-established algorithms and tools. It is the first time that the MCL algorithm is used in the field of biomedical text mining, although it has been used before in the computational linguistics field for synonym dictionary improvement (Gfeller et al. 2005) and word sense disambiguation (Dorow et al. 2005) for the French language.

The fact that the method is unsupervised and relies mostly on existing systems is a major advantage, keeping its computational complexity to an absolute minimum. Although the use of pre-computed sets of “related articles” from PubMed enables us to avoid applying computationally expensive NLP techniques to the documents, this has two shortcomings. First, it makes the method suitable only for documents contained in the PubMed database. Second, the relatedness of the documents is based on an Euclidean distance (cosine), which suffers from severe defects as to keyword weightings and correlations (Mochihashi et al. 2006). Other measures, proposed elsewhere (Mochihashi et al. 2006), could reveal different relatedness between the same documents and thus affect the clustering.

Nevertheless, the ability of MCL to produce clusterings of different granularities with the adjustment of the inflation value allows a detailed analysis of the information contained in the documents through a form of controlled hierarchical clustering. In particular, starting from a graph where the documents are connected in the minimum number of clusters, the user can use MCL to start splitting the documents into subclusters. Gradually, an increase of the inflation value will produce an increasing number of clusters, until there are no more connections in the graph that can be eliminated, resulting to the maximum number of clusters.

In the future, we intend to cluster complete sets of PubMed-available documents for specific organisms, such as Drosophila, or human, to capture and explore different research topics and new discoveries through high-throughput text mining.

ACKNOWLEDGEMENTS

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