Mining Relational Paths in Integrated Biomedical Data

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Abstract

Much life science and biology research requires an understanding of complex relationships between biological entities (genes, compounds, pathways, diseases, and so on). There is a wealth of data on such relationships in publicly available datasets and publications, but these sources are overlapped and distributed so that finding pertinent relational data is increasingly difficult. Whilst most public datasets have associated tools for searching, there is a lack of searching methods that can cross data sources and that in particular search not only based on the biological entities themselves but also on the relationships between them. In this paper, we demonstrate how different graph-theoretic algorithms for mining relational paths can be used together with a previous integrative data resource we developed called Chem2Bio2RDF to extract new biological insights about the relationships between such entities. In particular, we use these methods to investigate the genetic basis of side-effects of thiazolinedione drugs, and in particular make a hypothesis for the recently discovered cardiac side-effects of Rosiglitazone (Avandia) and a prediction for Pioglitazone which is backed up by recent clinical studies.

Introduction

The emerging fields of chemogenomics [1] and systems chemical biology [2] require examination of critical associations between individual entities (genes, compounds, etc.). Identification of semantic associations can utilize many of the methods of graph theory, such as finding shortest paths between entities, and along with Semantic Web methods forms the basis of our work here. However, the complex structure of the ontologies involved, the heterogeneity of the data sources, and sheer size of some of the datasets make this a non-trivial problem: one requires a highly efficient and scalable framework to identify semantic associations in the biomedical field. Additionally, there are usually many linked paths between two instances; thus providing contextual evaluation of those different linked paths is also a critical problem.

The Semantic Web provides machine-understandable semantics for resources, establishing a common platform to integrate heterogeneous data sources, and tools for searching and data mining these sources in an integrative fashion. Semantic Web methods have been adopted in various areas of life sciences, healthcare, and drug discovery [3–4], through various projects including Chem2Bio2RDF (developed in our labs) [3], Bio2RDF [6], Linking Open Drug Data (LODD) project [7], and Linked Life Data, which convert data to a common syntax and specify the meaning of the data through formal, logic-based ontologies or schemas. In particular, discovering and ranking complex links and relationships between resources are critical steps toward knowledge discovery. In the biomedical domain, there is a vital need for cross-domain data mining. Recent technological and experimental advances in genomics, compound screening in particular have resulted in an explosion of public data of chemical compounds, drugs, genomes, biological molecules, and in scholarly publications that pertain to these entities. Consequently, new informatics-based integrative domains have emerged, including cheminformatics [8], chemogenomics [1] and systems chemical biology [2]. Cheminformatics pertains to the large-scale analysis of chemical structures and their relationships to biological entities; chemogenomics to the relationships between chemical compounds and genes or protein targets, and systems chemical biology to the system-wide application of these techniques (where the system is a cell or organism as a whole).

In this paper, we first describe an algorithm for tackling this: a scalable path finding algorithm that works on RDF (the basis on describing relationships in the Semantic Web) and an algorithm based on LDA [9] which we call Bio-LDA, that extracts topics from large quantities of biomedical literature and gives the probabilistic distribution of biological terms (e.g., compounds, diseases, and genes) among different topics, so as to provide contextual information for those identified semantic associations. Through the integration of the path finding algorithm and a Bio-LDA algorithm we have developed for ranking paths using literature associations [10] with our prior work to develop an integrated RDF systems chemical biology resource [5], we demonstrate how important semantic and literature-contextualized paths can be identified and evaluated. We discuss this process using two biomedical case studies.

In the context of Semantic Web as a whole, the problem of discovering and reasoning complex relationships between resources has been studied by many researchers, most of which studied a specific subset of such relationships, or relationships that bear
certain properties. Anyanwu et al. [11–13] originally formalized an important subset of complex relationships called Semantic Associations that are mainly based on undirected or directed paths. Anyanwu et al. [11,13] define three types of complex relationships based on Property Sequence (PS) that is a finite sequence of properties defined in RDFS: \( \rho – Path \) association capturing the connectivity feature between two resources; \( \rho – Join \) association indicating that resources \( r_1 \) and \( r_2 \) relate to the same resource; \( \rho – ISO \) association identifying the similarity between \( r_1 \) and \( r_2 \). A following-up work [13] formalized the definition of semantic associations and presented outlines of two implementations of \( \rho – operator \). The first approach is to build a separate \( \rho – query \) processing layer from a storage system. The \( \rho – query \) processing layer maintains an index called PathGuide that keeps the path information among classes extracted from schema. However, this is not very scalable when a large index size and number of queries for validation is needed. The second approach is to use graph algorithms on memory-resident RDF graphs. However, the RDF graphs are usually too large to fit into memory. Sheth et al. [14] combined novel academic research and commercialized semantic web technology to provide capabilities of semantic association identification. Faloutsos et al. proposed an algorithm to identify an informative subgraph between two nodes [15]. Mulla et al. proposed three heuristics to calculate weights of edges and assigned weights to edges of the RDF graph [16] and applied the algorithm proposed in [15]. Perry et al. introduced a system for computing Semantic Associations over distributed RDF data stores in a peer-to-peer setting [17]. For semantic association finding in the biomedical domain, Dong et al. described a prototype system for mining the semantic associations in ontology structure and search for instances that belong to the nodes and edges along the identified path through SPARQL [18].

Another approach to the discovery of semantic association is to use a query language that supports semantic association queries. Kochut and Janik [19] present SPARQLeR, a novel extension of the SPARQL query language which adds the support for semantic path queries. The proposed extension fits seamlessly within the overall syntax and semantics of SPARQL and allows easy and natural formulation of queries involving a wide variety of regular path patterns in RDF graphs. SPARQLeR’s path patterns can capture many low-level details of the queried associations. Other similar studies include SPARQ2L, PSPARQL [path RDF query language] [20].

In the field of topic identification and text mining, since Blei et al. [9] introduced the LDA model, various extended LDA models have been used in automatic topic extraction from text corpora. LDA and its extended models have been broadly used in many areas including the biomedical domain. Zheng et al. [21] applied the classic LDA model to protein-related MEDLINE titles and abstracts and extracted 300 major topics. They further mapped those topics to Gene Ontology (GO) terms. Blei et al. [22] examined 5,225 free-text items in the Caenorhabditis Genetic Center (CGC) Bibliography using the classic LDA model. They found that the LDA model had better predictive performance than two standard models (unigram and mixture of unigrams) trained using the same data. Bundschus et al. [23] presented a Topic-Concept model, which extends the basic LDA framework to reflect the generative process of indexing a PubMed abstract with terminological concepts from an ontology.

In this paper, we propose a scalable path finding algorithm that can not only detect paths between instances belonging to different classes but also between instances belonging to the same class. In addition, we complement the algorithm with a Bio-LDA model which extracts contextual information on topics of bio-terms, which helps to evaluate and interpret the semantic associations. This paper is organized as follows: Section 2 describes the materials and methods; Section 3 presents the results, including two case studies; section 4 presents a discussion of the results.

**Materials and Methods**

### 2.1 Datasets

The work reported in this paper uses the Chem2Bio2RDF resource [5]. Chem2Bio2RDF covers 25 biomedical datasets, grouped into 6 domains, namely chemical (PubChem Compound, ChEBI, PDB Ligand), chemogenomics (KEGG Ligand, CTD Chemical, BindingDB, MATADOR, PubChem BioAssay, Qsar, TTD, DrugBank, ChEMBL, Binding MOAD, PDSP, PharmGKB), biological (UNIPROT, HGNC, PDB, GI), systems (KEGG Pathway, Reactome, PPI, DIP, phenotype (OMIM, Diseasesome, SIDER, CTD diseases)) and literature (MEDLINE/PubMed). At the time of writing, the numbers of triples (i.e., relationships encoded) is about 78 million. Provenance information has been added and the data has been linked to LODD and Bio2RDF [6] using owl:sameAs constructs.

Additionally, biological terms that are found in these datasets (compounds, drugs, genes, diseases and side-effects; collectively we call these **BioTerms**) are identified in scholarly journal abstracts in PubMed, and these terms are used to link publications (as identified by a PubMed ID) with entries in Chem2Bio2RDF datasets. The BioTerm PubMed-datASET relationships are converted to RDF triples and integrated with Chem2Bio2RDF. Table 1 gives some statistics on the extracted BioTerms. The data schema used in our system is designed based on the category of bio-terms (compound, drug, gene, disease, side effect, pathway) and DTD (Document Type Definition) provided by National Library of Medicine (NLM). Bio-term dictionaries are generated from the following data sources listed in Chem2Bio2RDF: the compound dictionary is generated from PubChem Synonym with the PubChem Compound identifier (CID); the drug dictionary is generated from DrugBank and used DBID as the identifier; the gene dictionary is generated from the HGNC and used UniprotID as the identifier; the disease dictionary is generated from the CTD (the comparative toxicogenomics database) and used MeshID as the identifier; the side effect dictionary is generated from the Sider and used UMLSISD as the identifier; the pathway dictionary is generated from the KEGG pathway and used KeggID as the identifier. We parsed the XML file and extracted the terms based on the pre-generated dictionaries.

### 2.2 Algorithm for Pathfinding in RDF data

We have developed a scalable and efficient path finding algorithm that is designed to find all of the paths between any two entities in the RDF network. In the area of network analysis, the task of association search can be formalized as a task of path search in the graph. Algorithms for shortest path [24–25], efficient shortest paths in sparse networks [26], top-k shortest paths [27–28], and near-shortest paths [29] have been proposed. See [30–32] for overviews. See also [33]. The algorithms for shortest path have been applied to, for instance, find the best routines of vehicles or messages, find optimal flows in networks (treated for example in [34] and traffic-light networks [35], and find the k most likely state sequences from the HMM graph given the observed acoustic data [36].

We are given a semantic network (e.g., Chem2Bio2RDF), which can be represented as a graph \( G = (V, E) \), where \( e \in E \) represents an entity in the network; \( e \) represents a relationship with property \( r \) (e.g., drug interaction) between entities \( v_i \) and \( v_j \) the relationship...
Table 1. Statistics of the bio-terms extraction.

| Bio-Terms     | # of unique terms | # of term-citation pairs | # of unique citations |
|---------------|-------------------|--------------------------|-----------------------|
| Compound      | 56,383            | 11,775,891               | 5,856,084             |
| Drug          | 2,820             | 5,624,529                | 3,427,067             |
| Gene          | 13,022            | 5,252,844                | 3,735,517             |
| Disease       | 3,848             | 12,612,636               | 7,066,084             |
| Side Effect   | 1,363             | 10,489,676               | 6,310,741             |
| Pathway       | 180               | 916,754                  | 838,090               |

Figure 1 summarizes the proposed algorithm. In the rest of the section, we will explain the two main stages (Step 2 and Step 3). Figure 1 shows the network, where the conventional Dijkstra algorithm results in a high time complexity of $O(n^3)$. We propose using a heap-based Dijkstra algorithm (heap-Dijkstra) which has a complexity of $O((\log n))^2)$. The heap-Dijkstra is summarized in Figure 2.

In the heap-Dijkstra algorithm, we firstly create a minimal heap. Then, in each iteration of the algorithm, we use the heap to find the minimal value. The function is in heap[u] in line 14 to determine whether the node $u$ has been inserted into the heap or not. The operations “moveUp” and “insert” are respectively used to resort the heap and to insert a node into the heap. This focuses on finding the shortest path from each node to a specified target node. This is different from the traditional use of the Dijkstra algorithm where the objective is usually to find the shortest path from a specified source node to each of the other nodes. We conducted complexity analysis of the algorithm. As all nodes may be inserted into heap, the complexity of the loop from line 5 is $O(|V|)$. In the loop, the algorithm requires enumerating all edges $E(n_{min})$ pointing to the selected node $v_{min}$. Usually, we have $|E(n_{min})| < |V|$, where $|E(n_{min})|$ is the number of edges pointing to the node $v_{min}$ and $|V|$ is the number of nodes in graph G. In our research network, the average number of edges pointing to a node is about 3. Hence, we view the complexity of the loop in line 9 as $O(1)$. The running time of the operation “moveUp” in line 15 is $log(n)$, necessitating the operation “insert” in line 17. Therefore, the final complexity of the algorithm is $O((\log n))^2)$. More intuitively, search processes starts at the starting node and ending node at the same time. The process systematically explores all the neighboring nodes in sequence; then for each of those nearest neighboring nodes, it visits their unexplored neighbor nodes and records/updates all those stretching-out paths. The two processes end when they first explored the same node in the graph. Thus the shortest path is identified by combining the recorded path between the starting node and the coincidental node and between the coincidental node and the ending node. An example showing how the algorithm runs on Chem2Bio2RDF data are shown in Figure 3.

In the above example, we want to find the path between node 1 and node 26 (Figure 3-a):

1. Breadth First Search (BFS) explores the nearest neighbor of node 1 and it reaches nodes 3, 4, 6, 7, 10 (Figure 3-b);
2. Meanwhile, another BFS explores the nearest neighbor of node 26 similarly and it reaches nodes 19, 21, 23, 24, 25 (Figure 3-c);
3. Explore all the nearest neighbors of node 3, 4, 6, 7, 10, and it reaches nodes 2, 5, 8, 9, 11, 14, 18 (Figure 3-d);
4. Meanwhile, explore all the nearest neighbors of node 19, 21, 22, 23, 24, 25, and it reaches nodes 15, 16, 18, 22 (Figure 3-e);
5. One node (i.e., node 18) first gets visited by both BFS processes; algorithm ends. The shortest path between node 1 and node 26 is 1–10–18–21–26 (marked in red in Figure 3-f).

2.2.2 Near-Shortest Association Finding

In the previous step, we obtain the shortest association from each source entity to the target entity \( v_j \), including the shortest association with the length \( L_{\min} \) from the source entity \( v_i \) to the target entity \( v_j \). In this step, based on the depth-first search, we try to find the near-shortest associations. The algorithm runs a straightforward \( v_i \rightarrow v_j \) association enumeration algorithm (depth-first search). The depth-first search itself has an exponential complexity. We apply several strategies to reduce the computational cost. First we use an indicator \( c(v) \) to avoid loop in the association. Next we utilize the shortest associations \( d^9(v) \) found in Step 2 to prune the search space. Specifically, we extend an \( v_i \rightarrow v_j \) association to \( u \) along the relationship \( e=(s,u) \) if and only if \( d(s)+d(u)+d^9(v)<1+\beta L_{\min} \), where \( d(s) \) is the length the current \( v_i \rightarrow v_j \) association and \( d(u) \) is the shortest association from the entity \( u \) to the target entity \( v_j \) (cf. line 11 in Figure 1).

Whenever an association \( (v_i,v_j) \) is found using the above method, we calculate the length of the association \( d((v_i,v_j)) \) and add the association with its length to the association set \( A \). The search terminates when no more association can be found. Then we rank all \( (v_i,v_j) \in A \) with the lowest \( d((v_i,v_j)) \) on the top. Finally, we return the ranked associations. It is not easy to accurately analyze the complexity of the algorithm in this step. Depth-first search itself has an exponential complexity. However, in our algorithm we utilized several strategies to heuristically guide the search. The number of search steps is greatly reduced. An empirical analysis of the experimental results on the researcher network (with half million nodes and 2 millions edges) shows that the average search steps in this sub-process is 14,418 and the average time cost in this step is 0.34s which takes only 16.49% of the total time cost (about 3 seconds on average).

2.3 Bio-LDA

Natural language processing (NLP) has been widely used to mine literatures in biomedical domain [37,38]. Compared to traditional NLP techniques, which bases on linguistic rules of the documents, modern probabilistic models...
focus on the topical features of the documents. For example, LDA, a hierarchical Bayesian model, and its assorted variations, can capture groups of words that tend to be used to discuss the same topics. Applications of LDA in the biomedical domain have already produced promising results. However, few of those applications take bio-terms (including genes, compounds, diseases, etc.) into a customized LDA model as the hidden variables. The Bio-LDA model used in this paper not only uncovers the topical feature of common words, but more importantly, also the bio-terms. The similarity of bio-terms are then measured using KL-divergence, which, compared to the co-occurrence-based methods, is more helpful for identifying hidden associations.

The Bio-LDA model extracts latent topics of bio-terms from biomedical literature, and which further provides semantically contextual evaluation for those associations identified by the path finding algorithm.

Our Bio-LDA model extends the ACT model proposed by [45] as shown in Figure 4. Based on the results of Bio-LDA, we calculate entropy and KL divergence for any given two RDF nodes in the RDF graph to identify their semantic association.

The generative process can be summarized as follows:

1. For each topic \( z \), draw \( \psi_z \) and \( \phi_i \) respectively from Dirichlet priors \( \beta \) and \( \mu \).
2. For each word \( w_{id} \) in paper \( d \):
   - draw a bio-term \( x_{id} \) from \( b_d \) uniformly;
   - draw a topic \( z_{id} \) from a multinomial distribution \( \theta_{z_i} \);
   - specific to bio-term \( x_{id} \), where \( \theta \) is generated from a Dirichlet prior \( \alpha \);
   - draw a word \( w_{id} \) from multinomial \( \phi_{z_i} \);
   - draw a journal stamp \( j_{id} \) from multinomial \( \psi_{z_i} \).

In our model, Gibbs sampling is chosen for inference. As for the hyperparameters \( \alpha \), \( \beta \), and \( \mu \), we take a fixed value (i.e., \( \alpha = 50 = T \), \( \beta = 0.01 \), and \( \mu = 0.1 \)). In the Gibbs sampling procedure, we first estimate the posterior distribution on just \( x \) and \( z \) and then use the results to infer \( \theta, \phi \), and \( \psi \). The posterior probability is calculated by the following equation:

\[
P(z_{id}, x_{id}|z_{-id}, x_{-id}, w_{id}, j_{id}, \theta, \beta, \mu) \propto \sum_{z}(m_{z_{-id}}^{z_{id}} + \beta) \sum_{w_{id}}(n_{z_{-id}}^{w_{id}} + \beta_{w_{id}}) \sum_{j}(n_{j_{-id}}^{z_{id}} + \mu_{j_{id}})
\]

where the superscript \( -id \) denotes a quantity, excluding the current instance (e.g., the \( d \)-th word token in the \( d \)-th paper). After Gibbs sampling, the probability of a word given a topic \( \phi \), the probability of a journal given a topic \( \psi \), and the probability of a topic given a bio-term \( \theta \) can be estimated as follows:

\[
\phi_{z_{id}} = \frac{n_{z_{id}}^{w_{id}} + \beta_{w_{id}}}{n_{z_{id}}^{w_{id}} + \beta_{w_{id}}}
\]

\[
\psi_{z_{id}} = \frac{n_{z_{id}}^{j_{id}} + \beta_{j_{id}}}{n_{z_{id}}^{j_{id}} + \beta_{j_{id}}}
\]
3. Bio-term Entropy over Topics

In information theory, entropy is a measure of the uncertainty associated with a random variable. It is also a measure of the average information content one is missing when one does not know the value of random variable. In our Bio-LDA model, we can compute the bio-term entropies over topics as shown in equation 5, which indicates that bio-terms tend to address a single topic or cover multiple topics. The

\[ \psi_{zd} = \frac{n_{zd} - d + \mu_{zd}}{n_{zd} + \mu_z} \]  
\[ \theta_{sz} = \frac{m_{sz} + \alpha_z}{\sum_j (m_{sz'} + \alpha_{z'})} \]  

Figure 3. An intuitive example of the path finding algorithm.

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higher the entropy is, the more diverse the bio-term is over topics.

\[
\text{Entropy}(b_t) = - \sum_{z=1}^{T} \theta_{b_t} \log \theta_{b_t}
\]

(5)

4. Semantic Association

Kullback-Leibler divergence (KL divergence) is a non-symmetric measure of the difference between two probability distributions. In our Bio-LDA model, we used the KL divergence as the non-symmetric distance measure for two bio-terms over topics, as shown in equation 6.

\[
KL(b_t, b_j) = \sum_{z=1}^{T} \theta_{b_t} \log \left( \frac{\theta_{b_t}}{\theta_{b_j}} \right)
\]

(6)

The symmetric distance measure of two bio-terms over topics is the sum of two non-symmetric distances, as shown in equation 7.

\[
sKL(b_t, b_j) = \sum_{z=1}^{T} \left( \theta_{b_t} \log \left( \frac{\theta_{b_t}}{\theta_{b_j}} \right) + \theta_{b_j} \log \left( \frac{\theta_{b_j}}{\theta_{b_t}} \right) \right)
\]

(7)

\(sKL\) divergence measures the similarity between two probability distributions. In our Bio-LDA model, each bio-term is represented by a probability distribution which designates the strength of the semantic association between the bio-terms and a set of topics (or research issues). Thus \(sKL\) divergence is used to calculate the similarity between a pair of bio-terms by means of measuring the similarity between the two probability distributions associated with each bio-term of the pair. The smaller the \(sKL\) score is, the more semantically relevant the two bio-terms are in terms of their involvements with a set of research issues. This association score can combined with the pre-knowledge of bio-terms (i.e. Chem2Bio2Rdf) for novel knowledge discovery. The score of a given directed semantic association is simply given by the accumulated distance between bio-terms on a path, as shown in equation 8. The score of an undirected path is given by the accumulated symmetric distance between bio-terms, as shown in equation 9. In this study, we do not evaluate the direction of the associations, focusing only on the association score calculated by the symmetric distances. The association search in Bio-LDA model is finding the associations with the smallest score.

Results

We implemented the path finding algorithm described in section 2.2 using C++ and created a tool called associationsearch which will find paths of given length between any two items in our Chem2Bio2Rdf dataset. These items can be compounds, drugs, genes, pathways, diseases, or side-effects. These paths are then ranked (i.e., evaluated) by the Bio-LDA model described in section 2.3, and the user can select a maximum number of paths to return. The paths are then visualized using a flash interface within a browser.

We present two case studies that apply this method to address biological research problems.

3.1 Finding gene associations between thiazolidinediones and cardiac side-effects

Insulin-sensitizing drugs from the thiozalinedione class have revolutionized the treatment of insulin-dependent diabetes yet have been beset by rare but serious side effects. The drugs Troglitazone, Rosiglitazone and Pioglitazone are thought to work...
Figure 5. Ranked association graphs between myocardial infarction and Rosiglitazone (top) or Troglitazone (bottom) identify SAA2, APOE, ADIPOQ, and CYP2C8 genes as significant for Rosiglitazone. The red-outlined box is the starting node and ending node, that is, the bio-terms associations that we are searching for. Yellow-outlined boxes are the intermediate bio-terms. Other boxes indicate the types of the connection between the two intermediate bio-terms that it is connected to, which gives a hint on which database this connection is originated from.

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Figure 6. Ranked association graphs between Ibuprofen and Parkinson Disease (top) as well as Aspirin and Parkinson Disease. The red-outlined box is the starting node and ending node, that is, the bio-terms associations that we are searching for. Yellow-outlined boxes are the intermediate bio-terms. Other boxes indicate the types of the connection between the two intermediate bio-terms that it is connected to, which gives a hint on which database this connection is originated from. doi:10.1371/journal.pone.0027506.g006

by binding to the PPAR-gamma receptor, one of several nuclear receptors involved in fatty acid and glucose uptake. However, these receptors are also known to be involved in much larger scale regulation and metabolic processes including metabolism of xenobiotics (foreign substances in the body). Interference of some of these processes may be responsible for the side effects that have caused these drugs to “fall from grace”: Troglitazone was withdrawn from the U.S. market in 2000 due to adverse liver side effects; Rosiglitazone was until recently believed to be safe as it does not appear to have the hepatic side effects of Troglitazone, however it was restricted in the U.S. in 2011 and removed from the European market entirely in September 2010 due to increased risk of myocardial infarction in patients. Pioglitazone is currently under review.

We used our algorithms to examine ranked associations between Rosiglitazone and myocardial infarction, and Troglitazone and myocardial infarction, to see if we could identify gene associations that may account for the cardiac effects of Rosiglitazone. The association graphs for these two drugs are shown in Fig. 5. The red-outlined box is the starting node and ending node, that is, the bio-terms associations that we are searching for. Yellow-outlined boxes are the intermediate bio-terms. Other boxes indicate the types of the connection between the two intermediate bio-terms that it is connected to, which gives a hint on which database this connection is originated from. Note that Fig. 5 and Fig. 6 are screenshots of the visualization provided by our application in which users can interactively moving the nodes and clicking the nodes to obtain more information about the node. The graphs show that there is a strong ranked association between Rosiglitazone and myocardial infarction which is not present for Troglitazone, particularly involving four genes: SLCO2 (Serum Amyloid A 2), APOE (Apolipoprotein E), ADIPOQ (Adiponectin) and CYP2C8 (Cytochrome P450 2C8). Examination of these genes indicates that all are involved in cardiovascular lipid metabolic processes. In particular, activation of ADIPOQ results in increased HDL (“good” cholesterol) and activation of APOE results in increased LDL levels (“bad” cholesterol), a potential mechanism that would account for Rosiglitazone’s cardiac side effects as has recently been reported in the literature [46]. The next obvious question is whether Pioglitazone interacts with these genes. Association graphs between Pioglitazone and myocardial infarction (and Pioglitazone and Rosiglitazone) show strong associations between Pioglitazone and APOE, but not with APOE, indicating that Pioglitazone should increase HDLs but not LDLs. This is confirmed clinically by recent literature [45].

We further evaluated these relationships by directly examining the ranked paths from the BioLDA algorithm. Table 2 and 3 shows the symmetric KL divergence for semantic associations for the two pairs of bio-terms.

3.2 Associations between non-steroidal anti-inflammatory drugs (NSAIDs), inflammation and Parkinson Disease

Recent research [47] has shown that use of Ibuprofen, a non-steroidal anti-inflammatory drug, is clinically associated with

### Table 2. Symmetric KL divergence for paths between Troglitazone and Myocardial infarction.

| Path | sKL divergence |
|------|----------------|
| Troglitazone→SLC29A1→Dipyridamole→Myocardial-infarction | 16.151 |
| Troglitazone→Edema→Iodixanol→Myocardial-infarction | 23.105 |
| Troglitazone→Edema→Diprydamole→Myocardial-infarction | 24.086 |
| Troglitazone→Congestive-heart-failure→Bisoprolol→Myocardial-infarction | 24.151 |
| Troglitazone→Edema→Bisoprolol→Myocardial-infarction | 24.744 |
| Troglitazone→PPARG→Rosiglitazone→Myocardial-infarction | 25.454 |
| Troglitazone→Diabetes-Mellitus-Type→Benazepril→Myocardial-infarction | 25.732 |
| Troglitazone→Syncope→Diprydamole→Myocardial-infarction | 26.176 |
| Troglitazone→Hyperglycemia→Rosiglitazone→Myocardial-infarction | 26.835 |
| Troglitazone→Syncope→Bisoprolol→Myocardial-infarction | 26.953 |
| Troglitazone→Hyperglycemia→Pioglitazone→Myocardial-infarction | 27.491 |
| Troglitazone→PPARG→Pioglitazone→Myocardial-infarction | 28.126 |
| Troglitazone→Edema→Nicardipine→Myocardial-infarction | 28.175 |
| Troglitazone→Edema→Betaxolol→Myocardial-infarction | 28.564 |
| Troglitazone→Weight-gain→Bisoprolol→Myocardial-infarction | 28.804 |
| Troglitazone→Edema→Fosinopril→Myocardial-infarction | 29.052 |
| Troglitazone→Edema→Amoxapine→Myocardial-infarction | 29.147 |
| Troglitazone→Edema→Oxaprozin→Myocardial-infarction | 29.222 |
| Troglitazone→Malaise→Betaxolol→Myocardial-infarction | 29.315 |
| Troglitazone→Edema→Cilazapril→Myocardial-infarction | 29.361 |

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### Table 3. Symmetric KL divergence for paths of Rosiglitazone and Myocardial infarction.

| Path                                           | sKL divergence |
|------------------------------------------------|----------------|
| Rosiglitazone → Myocardial-infarction          | 17.231         |
| Rosiglitazone → Congestive-heart-failure → Bisoprolol → Myocardial-infarction | 21.085         |
| Rosiglitazone → Heart-failure → Bisoprolol → Myocardial-infarction | 22.067         |
| Rosiglitazone → Hyperglycemia → Pioglitazone → Myocardial-infarction | 22.411         |
| Rosiglitazone → Hyperglycemia → Cilazapril → Myocardial-infarction | 24.814         |
| Rosiglitazone → Hyperglycemia → Betaxolol → Myocardial-infarction | 24.892         |
| Rosiglitazone → Hypoglycemia → Bisoprolol → Myocardial-infarction | 25.269         |
| Rosiglitazone → Hypoglycemia → Oxaprozin → Myocardial-infarction | 25.494         |
| Rosiglitazone → Hyperglycemia → Diazoxide → Myocardial-infarction | 25.767         |
| Rosiglitazone → Bilirubinemia → Eletriptan → Myocardial-infarction | 26.273         |
| Rosiglitazone → Bilirubinemia → Dolasetron → Myocardial-infarction | 26.439         |
| Rosiglitazone → Diabetes-Mellitus, Type → Benazepril → Myocardial-infarction | 26.634         |
| Rosiglitazone → Hyperglycemia → Bosentan → Myocardial-infarction | 26.683         |
| Rosiglitazone → Hyperglycemia → Candesartan → Myocardial-infarction | 26.688         |
| Rosiglitazone → Hyperglycemia → Quinapril → Myocardial-infarction | 27.381         |
| Rosiglitazone → Diabetes-Mellitus → Pioglitazone → Myocardial-infarction | 27.821         |
| Rosiglitazone → Hypoglycemia → Betaxolol → Myocardial-infarction | 27.832         |
| Rosiglitazone → Hypoglycemia → Pioglitazone → Myocardial-infarction | 28.316         |
| Rosiglitazone → Dizziness → Bisoprolol → Myocardial-infarction | 28.681         |
| Rosiglitazone → Nasopharyngitis → Bosentan → Myocardial-infarction | 28.699         |

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### Table 4. Symmetric KL divergence for paths between Ibuprofen and Parkinson Disease.

| Paths                                                      | KL    |
|------------------------------------------------------------|-------|
| Ibuprofen PharmGKB CYP2C9 HPRD POR CTD Parkinson-Disease | 28.077|
| Ibuprofen Drugbank PTGS2 CTD-HUGE_Genopedia-HUGE_Phenopedia Parkinson-Disease | 30.409|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia HSP11L HUGEnoedia-HUGE_Phenopedia Parkinson-Disease | 36.573|
| Ibuprofen PharmGKB CYP2C9 PharmGKB Haloperidol PharmGKB Parkinson-Disease | 37.339|
| Ibuprofen PharmGKB Hemorrhage CTD GABRR1 CTD Parkinson-Disease | 37.791|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia HSPA4 CTD Parkinson-Disease | 37.842|
| Ibuprofen PharmGKB Hemorrhage CTD HRH1 HUGEnoedia-HUGE_Phenopedia Parkinson-Disease | 38.153|
| Ibuprofen PharmGKB Hemorrhage CTD RARG CTD Parkinson-Disease | 38.558|
| Ibuprofen PharmGKB Hemorrhage CTD MAPK2K2 CTD Parkinson-Disease | 38.858|
| Ibuprofen PharmGKB Hemorrhage CTD HSPH5 CTD-HUGE_Genopedia-HUGE_Phenopedia Parkinson-Disease | 39.055|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia MMP8 CTD Parkinson-Disease | 39.668|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia SCNN1A CTD Parkinson-Disease | 39.783|
| Ibuprofen PharmGKB Hemorrhage CTD GOT1 CTD Parkinson-Disease | 39.896|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia HSPA1A CTD-HUGE_Genopedia-HUGE_Phenopedia Parkinson-Disease | 40.331|
| Ibuprofen PharmGKB Hemorrhage CTD HSP90B1 CTD Parkinson-Disease | 40.886|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia IL1A HUGEnoedia-HUGE_Genopedia-HUGE_Phenopedia Parkinson-Disease | 41.056|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia MMP12 CTD Parkinson-Disease | 41.127|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia-HUGE_Phenopedia SELP CTD Parkinson-Disease | 41.278|
| Ibuprofen PharmGKB Hemorrhage CTD RARB CTD Parkinson-Disease | 41.455|
| Ibuprofen PharmGKB Hemorrhage HUGEnoedia-HUGE_Phenopedia SCGB1A1 CTD Parkinson-Disease | 41.47|

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reduced risk of Parkinson Disease. This effect is not found with other painkillers, such as Aspirin and Acetaminophen (Paracetamol). It is speculated that this effect may be due to the anti-inflammatory effects of Ibuprofen on neuroinflammation. We performed searches to (i) identify paths containing genes linking Ibuprofen, inflammation and Parkinson Disease (through three searches – Ibuprofen-Parkinson Disease, Ibuprofen-inflammation and inflammation-Parkinson Disease) and (ii) identify genes associated with Ibuprofen but not with other NSAIDS (in case this could be used to account for the differential activity with Aspirin, etc). Our searching identified 70 genes that are associated with Ibuprofen, inflammation and Parkinson Disease, 9 of which are known to be linked to inflammation: \( \text{IL1A, IL1B, IL1RN, IL6, LTA, NFKB1, NFKBIA, PTGS2 and TNF} \).

Of particular note, these searches identified a clear direct connection between the primary target of Ibuprofen (\text{PTGS2}, or Cox2) – Ibuprofen is a nonspecific inhibitor that also targets Cox1, and Parkinson Disease. This link maps to experimental data in the CTD dataset. The Cox2 link is supported by a variety of recent research [48–52] which indicates that neuroinflammation is implicated in Parkinson’s Disease, and that the Cox2 gene is implicated in this inflammation process. Indeed, selective and nonselective Cox2 inhibitors have been examined for their effect in this inflammatory process [52]. Selective Cox2 inhibitors may be of particular interest.

In our second search, we found a single gene, \text{AMBP}, which is differentially associated with Ibuprofen (and not with other NSAIDS), and which is associated with Parkinson disease (but not inflammation), based on a 1996 study which showed the potential of \text{AMBP} as a biomarker for the disease [53]. Several of the results searched are shown in Figure 6. The red-outlined box is the starting node and ending node, that is, the bio-terms associations that we are searching for. Yellow-outlined boxes are the intermediate bio-terms. Other boxes indicate the types of the connection between the two intermediate bio-terms that it is connected to, which gives a hint on which database this connection is originated from.

We further evaluated these relationships by directly examining the ranked paths from the BioLDA algorithm. Table 4 and 5 shows the symmetric KL divergence for semantic associations for the two pairs of bio-terms. The smaller the KL divergence is, the more thematically similar the bioterms along the path are in the literature. In Table 4, the path Ibuprofen-\text{PTGS2-PD} ranks high. Teismann et al. [54] studied the relationship between \text{COX-2}\text{PTGS2} and Parkinson Disease by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model. MPTP induces Parkinson Disease and \text{COX-2}. The authors claimed that \text{COX-2} inhibitors may be therapeutics for Parkinson Disease if the inhibitors have ability to penetrate the blood brain barrier. Many paths that connect Ibuprofen and Parkinson Disease through Hemorrhage and other genes have shown small KL divergence. Several studies have shown that Ibuprofen is helpful in preventing or decreasing susceptibility to different types of hemorrhage [55–50].

### Discussion

In this paper, we propose a scalable path finding algorithm and a topic model called Bio-LDA so as to mine semantic associations in integrated platform of various biomedical databases. The path finding algorithm can identify semantic paths between any two classes or instances in the linked open data in the biomedical domain. The Bio-LDA model extracts distributions of topics for bio-entities, which can provide topic-sensitive ranking of identified semantic associations. The two use cases presented in the paper demonstrate the rich possibilities that the proposed algorithm and

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**Table 5. Symmetric KL divergence for paths between Aspirin and Parkinson Disease.**

| Paths                                                                 | KL    |
|----------------------------------------------------------------------|-------|
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia CHEK1 CTD Parkinson-Disease | 25.682 |
| Aspirin PharmGKB UGT1A1 CTD Parkinson-Disease                          | 26.031 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia CASP9 CTD Parkinson-Disease | 26.771 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD IKBKB CTD Parkinson-Disease | 27.084 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia NFKB1 CTD Parkinson-Disease | 27.437 |
| Aspirin PharmGKB LTC4S HPRD MGST1 CTD Parkinson-Disease               | 27.678 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-DDIT3 CTD Parkinson-Disease | 27.919 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-CNBC2 CTD Parkinson-Disease | 27.979 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia TFRC CTD Parkinson-Disease | 28.226 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia GSTAA CTD-HUGe_Phenopedia Parkinson-Disease | 28.416 |
| Aspirin PharmGKB Colorectal-Neoplasms c2B2-CTD-HUGe_Phenopedia-PharmGKB MTR CTD-HUGe_Phenopedia Parkinson-Disease | 29.2  |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia NFE2L2 CTD Parkinson-Disease | 29.642 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD CCNA2 CTD Parkinson-Disease | 29.669 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD IRM2 CTD Parkinson-Disease | 30.126 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia TGFBI CTD Parkinson-Disease | 30.249 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia BCL2L1 CTD Parkinson-Disease | 30.357 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-GCLM CTD Parkinson-Disease | 30.386 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-MAPK8 CTD Parkinson-Disease | 30.58  |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia CHEK1 CTD Parkinson-Disease | 30.805 |
| Aspirin PharmGKB Colorectal-Neoplasms CTD-HUGe_Phenopedia Parkinson-Disease | 25.682 |

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model can contribute to crucial issues in biomedical domain, including Polypharmacology, drugs related to inhibition of a certain gene involved in diseases, and drug-like compounds. The application discussed in this paper is made available through http://cheminfoinformatics.indiana.edu/8090/yuyuan/chemistryspace.html.

In addition, based on the Bio-LDA model, we calculate the entropy and KL divergence for genes, compounds and diseases in the paths. The entropy shows to what extent the bio-terms are involved in multiple topics among biomedical literature; the KL divergence indicates the similarity between two bio-terms involved with different topics. Values extracted from another knowledge base (Medline) can be further integrated with user preferences to assign weight to semantic associations or to rank semantic associations. We also adopt expert and literature investigation to assess the result and value of the proposed algorithm, which indicates the algorithm can help discover invisible knowledge and identify potential research issues by obtaining and integrating existing knowledge.

For future work, we plan to further explore the potential of using the knowledge extracted through topic mining model to rank semantic associations. Moreover, we plan to design a parallel implementation of Bio-LDA and semantic association finding algorithm on MPI and MapReduce, which smoothes out storage and computation bottlenecks. Meanwhile, we would also like to establish an interactive searching system for semantic associations based on ChemBio2RDF database and extend our algorithm to incorporate heuristics from user preferences, context, or domain-specific rules.

**Author Contributions**

Conceived and designed the experiments: DW BJ YT YS JS BC. Performed the experiments: BH HW YS JS BC. Analyzed the data: GM PD DW. Wrote the paper: BH DW YD.

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