BIODBLINK: MULTI-LEVEL DATA MATCHING FOR AUTOMATIC GENERATION OF CROSS LINKS AMONG BIOCHEMICAL PATHWAY DATABASES

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Abstract: Most of biological databases provide cross links that point to data records describing the same object in other databases. However, as more and more databases are available, manually creating and maintaining cross links becomes very time consuming, if not impossible. Existing databases provide only a small portion of all possible links. In this paper, we present a database cross link server BioDBLink that can automatically collect and generate cross links among biological databases. The core of BioDBLink is a data matching technique that identifies and matches data records or elements describing the same object among pathway databases. Experiment on a data set collected from several pathway, enzyme and compound databases shows that our approach is able to identify most of the cross links provided by current databases, discover a large number of missing links, and detect inconsistency and duplicate errors.

1 INTRODUCTION

Recently, most of the pathway databases provide cross links to help users to navigate from one database to another. However, as more and more databases are available, existing databases often provide only a small portion of all possible links. Manually creating and maintaining cross links becomes very time consuming, tedious and incomplete. In this paper, we present a software system BioDBLink that aims to provide a database link server, and can automatically collect and generate cross links among biological databases.

The core of BioDBLink is a data matching technique that identifies and matches data records or elements describing the same object among pathway databases. Note that matching of data elements in pathway databases is by no means easy, and faces the following sources of problems: errors in databases, aliases in mames, missing data, and heterogeneous pathway representations. Errors in pathway databases are inevitable. A large portion of pathway information is obtained by literature curation. There may be errors made in the curated literatures. In addition, some information is predicted by computer software. Different databases may use different software that makes different and possibly wrong predictions. Synonyms, aliases, and homonyms are common in biological science. For example, a compound may have several different names, and even different formula. Compound matching simply by names or formula does not work well. In reaction level, we need to deal with missing data. For example, some reactions may miss EC-number or part of compounds. In pathway level, we need to deal with heterogeneous definitions and representations of pathways. For example, KEGG combine the same pathways from different organisms into the same map. MetaCyc keeps a separate pathway for each organism.

Several approaches have been proposed to integrate different types of biological databases (Birkland and Yona, 2006; Garcia, Chen and Ragan, 2005; Macauley J., Wang, Goodman, 1998; Krishnamurthy et al., 2003; Chen and Chen, 2006; Rajasimha, 2004; Tsay, Wu and Chen 2009). Data matching has played a central role in physical integration of databases. In this paper, we propose a multi-level data matching approach that utilizes three levels of information provided in pathway databases: compounds, reactions and pathways. We first use attributes of compounds to identify matching between compounds, which is then used to induce matching between reactions. Reaction

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matching is used to induce pathway matching as well as to enhance compound matching.

We experiment our approach on a data set collected from two well-known pathway databases KEGG and MetaCyc, and a number of compound and enzyme databases, including PubChem, ChEBI, KNApSAcK, LIPIDMAPS, LipidBank, PDB-CCD, 3DMet, NIKKAJI, NCI, and UM-BBD, ExplorEnz, IUBMB ExPASy and BRENDA. The experiment shows that our approach is very promising. For example, between KEGG and MetaCyc, our approach identifies 6129 pairs of compound matching, 3608 pairs of reaction matching, and 1483 pairs of pathway relations. According to our matching result, we assign EC-numbers to 315 reactions in MetaCyc that do not have EC-numbers, and discover several duplicate errors in both databases. We use the unification links provided by MetaCyc to evaluate the matching performance of our approach. MetaCyc provides 4268 unification links to KEGG for compounds, and 24 of them are invalid links. Our approach discovers 4098 of 4244 valid links. The recall with respect to the set of unification links in MetaCyc is 0.966.

2 BIODBLINK OVERVIEW

As in Figure 1, BioDBLink (Biological Database Link) is a database link server that automatically collects and generates cross links among biological databases. It provides a query interface for searching compounds, enzymes, reactions and pathways. For compound query, it accepts a compound name as the input, and returns a compound description as well as a list of database links. Figure 2 gives an illustration of compound query for compound CPD-1125. A link marked by symbol "(+)" indicates that it is discovered by data matching but not provided in the database. Symbol "(-)" indicates that the link is provided in the database but is suggested to remove by data matching. For link correction, the old link will be marked by "(-)", and a newly discovered link marked by "(+)" will be added to replace the old one.

The current version of BioDBLink available at http://140.123.102.75:8080/pathway/index.jsp provides links generated from the following databases.

1. Pathway databases: KEGG and MetaCyc.
2. Compound databases: PubChem, ChEBI, KNApSAcK, LIPIDMAPS, LipidBank, PDB-CCD, 3DMet, NIKKAJI, NCI, and UM-BBD.
3. Enzyme databases: ExplorEnz, IUBMB, ExPASy, UM-BBD, and BRENDA.

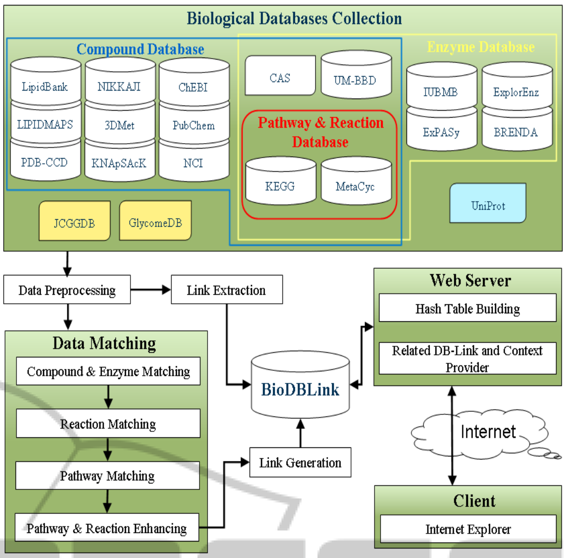
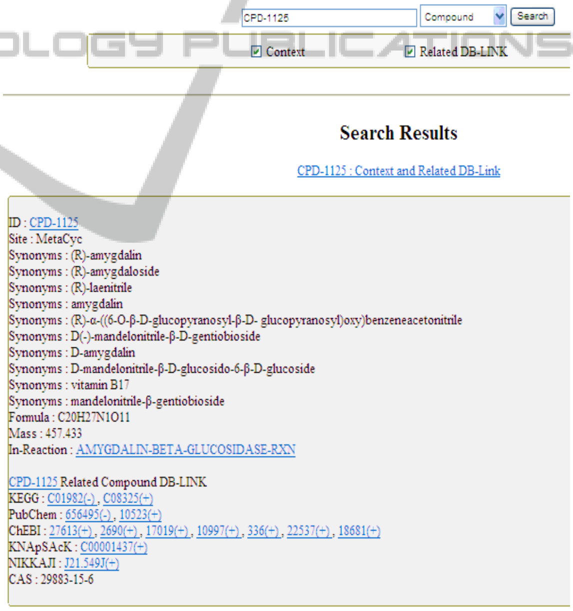


Figure 1: BioDBLink system overview.



☑ Context ☑ Related DB-LINK

Search Results

CPD-1125 : Context and Related DB-Link

ID : CPD-1125
Site : MetaCyc
Synonyms : (R)-amygdalin
Synonyms : (R)-amygdaloside
Synonyms : (R)-laenitrile
Synonyms : amygdalin
Synonyms : (R)-α-((6-O-β-D-glucopyranosyl-β-D- glucopyranosyl)oxy)benzeneacetonitrile
Synonyms : D(-)-mandelonitrile-β-D-gentiobioside
Synonyms : D-amygdalin
Synonyms : D-mandelonitrile-β-D-glucosido-6-β-D-glucoside
Synonyms : vitamin B17
Synonyms : mandelonitrile-β-gentiobioside
Formula : C20H27N1O11
Mass : 457.433
In-Reaction : AMYGDALIN-BETA-GLUCOSIDASE-RXN

CPD-1125 Related Compound DB-LINK
KEGG : C01982(-) , C08325(+)
PubChem : 656495(-) , 10523(+)
ChEBI : 27613(+) , 2690(+) , 17019(+) , 10997(+) , 336(+) , 22537(+) , 18681(+)
KNApSAcK : C00001437(+)
NIKKAJI : J21.549J(+)
CAS : 29883-15-6

Figure 2: BioDBLink web query interface.

3 BIODBLINK TECHNIQUES

In this section, we present details of our data matching approach. At first, we download data descriptions of compounds, enzymes, reactions and pathways from collected databases. Because those databases don't have common data format, we preprocess those data to a common format.

We then perform a multilevel data matching to identify data records from different databases that describe the same object. We classify information in pathway databases into 3 levels: compounds, reactions and pathways. The matching process consists of two phases: the identification phase and the enhancing phase. In identification phase, we identify data matching from lower levels to higher levels, using matching in lower levels to infer matching in higher levels. In the enhancing phase, we use matching identified in higher levels to enhance matching in lower levels. Finally, we use our matching result to generate new links and correct existing links. We next present details of our data matching methods.

3.1 Compound Matching

We define a formula to evaluate the matching score between any pair of compound descriptions. Two compound descriptions are matched if their matching score is larger than the threshold (1.5 in our experiment). The compound matching score is a combination of the name score and formula score.

Given two name sets ns_1 and ns_2, the name score $nscore(ns_1, ns_2)$ between them is defined as the maximum of matching scores between any pair of names from them.

$$nscore(ns_1, ns_2) = \max_{n_1 \in ns_1, n_2 \in ns_2} match(n_1, n_2)$$

The matching score between two names is 1.5 if they are the same string, is 1 if they become the same after special words, such as -D-, -L-, -O-, alpha, beta and gamma, are removed, is 0.8 if they are partially matched, and is 0 otherwise.

To evaluate formula score, we classify and count the number of atoms in the following 3 types. Type 1 consists of atoms appearing in both formulas with the same number, type 2 consists of atoms appearing in both formulas with different numbers, and type 3 consists of atoms appearing in only one of the two formulas. Consider two formula f_1 and f_2. Let m_1, m_2, m_3 denote the number of atoms in type 1, 2 and 3, respectively. The formula score $fscore(f_1, f_2)$ is defined as follows.

$$fscore(f_1, f_2) = \frac{m_1}{m_1 + 1.2m_2 + 1.5m_3}$$

Given two compound descriptions $d_1 = (ns_1, f_1)$ and $d_2 = (ns_2, f_2)$, their compound matching score is defined as follows.

$$CompScore(d_1, d_2) = nscore(ns_1, ns_2) + fscore(f_1, f_2)$$

3.2 Enzyme Matching

Given two enzyme name sets ens_1 and ens_2, the enzyme score $EnzymeScore(ens_1, ens_2)$ between them is defined as the maximum of matching scores between any pair of names from them.

$$EnzymeScore(ens_1, ens_2) = \max_{en_1 \in ens_1, en_2 \in ens_2} match(en_1, en_2)$$

The matching score between two names is 2.2 if they are the same string, is 1.2 if they become the same after special words, such as -D-, -L-, -O-, alpha, beta and gamma, are removed, and is 0 otherwise.

3.3 Reaction Matching

Each reaction description consists of a set EC of EC-numbers, a set $Cset$ of compounds and a set $PCset$ of primary compounds. Each compound is labelled as substrates or products. Let $r_1 = (EC_1, Cset_1, PCset_1)$ and $r_2 = (EC_2, Cset_2, PCset_2)$ be two reactions. The reaction matching score $RScore(r_1, r_2)$ is derived from EC-numbers, compound sets and primary compound sets as follows.

$$\begin{aligned} RScore(r_1, r_2) = {} & 0.5 \times ECscore(EC_1, EC_2) + \\ & 0.5 \times PCscore(PCset_1, PCset_2) + \\ & Cscore(Cset_1, Cset_2), \end{aligned}$$

If $PCset_1 = 0$ or $PCset_2 = 0$, the reaction matching score $RScore(r_1, r_2)$ is derives as follows.

$$\begin{aligned} RScore(r_1, r_2) = {} & 0.5 \times ECscore(EC_1, EC_2) + \\ & 1.5 \times Cscore(Cset_1, Cset_2), \end{aligned}$$

$PCscore(PCset_1, PCset_2)$, denotes the ratio of matched compounds in $PCset_1$ and $PCset_2$. Let $PCM(Cset_1, Cset_2)$ denote the set of matching pairs between $PCset_1$ and $PCset_2$.

$$PCscore(Cset_1, Cset_2) = \frac{|PCM(PCset_1, PCset_2)|}{\max(|PCset_1|, |PCset_2|)}$$

$Cscore(Cset_1, Cset_2)$ denotes the ratio of matched compounds in $Cset_1$ and $Cset_2$. Let $CM(Cset_1, Cset_2)$ denote the set of matching pairs between $Cset_1$ and $Cset_2$.

$$Cscore(Cset_1, Cset_2) = \frac{|CM(Cset_1, Cset_2)|}{\max(|Cset_1|, |Cset_2|)}$$

Each EC-number consists of 4 digital numbers. The matching score between two EC-numbers is assigned to 1 if they match all 4 numbers, 0.75 if they match the first 3 numbers, 0.5 if they match the first 2 numbers, 0.25 if they match the first number, and 0 otherwise. The matching score $ECscore(EC_1, EC_2)$ is defined as the maximum of matching scores between any pair of EC-numbers in EC_1 and EC_2.

Compounds are labelled as primary substrate, secondary substrate, primary product or secondary product. Primary substrates and primary products are the common substrates and products from one enzymatic reaction connected to other reactions. These common substrates are primary substrates, and the common products are primary products. The remaining substrates are secondary substrates. The remaining products are secondary products. In pathway view, primary compounds are more important than secondary compounds.

In reaction matching, $Cscore$, the ratio of matching compounds, is the main measure. $ECscore$ and $PCscore$ are added to handle missing data. While compounds are not fully matched due to compound missing, the score can be enhanced by matching in EC-numbers or primary compounds. The matching threshold is 1.5.

Note that, in our data set, there are more than 60% of reactions with primary compounds ratio larger than 0.5, 60% (5201/8711) in MetaCyc and 61% (4991/8172) in KEGG. This implies that as long as two reactions have the same set of primary compounds, their reaction score is often greater than 1.

3.4 Pathway Matching

Each pathway consists of a set of reactions and EC-numbers. Matching reactions are used to identify part-of relations between pathways in different databases as follows. Let D_1 and D_2 be two pathway databases. Let p be a pathway in D_1. We want to identify a candidate set M of pathways in D_2 for p. The candidate set is identified iteratively as follows. Let $R(p)$ be the set of reactions in p. In each iteration, find the pathway q in D_2 that has maximum of matching reactions in $R(p)$. Add q to M and remove q from D_2. Repeat above process until no more matched reactions exists between $R(p)$ and remaining pathways in D_2. We find

Let $EC(p)$ and $EC(q)$ denote the set of EC-number in p and q, respectively. out pathway matching from candidate set M. The pathway matching score $Pscore(p,q)$ is derived from the number of common reactions and EC-numbers as

$$\frac{|R(p)\cap R(q)|}{\min(|R(p)|,|R(q)|)}+\frac{|EC(p)\cap EC(q)|}{\min(|EC(p)|,|EC(q)|)}$$

Two pathways are matched if their pathway matching score is larger than the threshold (0.6 in our experiment).

3.5 Enhancing Compound Matching and Reaction Matching

For compound matching, the purpose of enhancing phase is to discover new matching not yet identified due to different names in different databases, and remove matching induced errors in the databases. Reaction matching is used to enhance compound matching. When two compounds participating in matched reactions, their compound matching score, $CompScore$, is increased 0.5. When two matched compounds do not participate in matched reaction, their score is decreased.

Pathway matching is used to enhance reaction matching. As illustrated in Figure 5, supposed in two matched pathways Pathway1 and Pathway2, R1 matches R1' and R3 matches R3'. We then increase the matching score between R2 and R4.

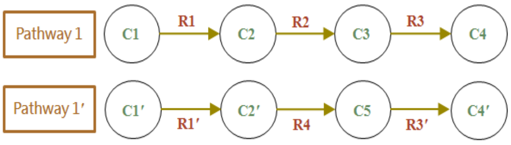


Figure 5: $RScore$ $(R2, R4)$ is increased.

4 EXPERIMENT

We experiment our approach over a collection of popular pathway, compound and enzyme databases, including KEGG, MetaCyc, PubChem, ChEBI, KNApSAcK, LIPIDMAPS, LipidBank, PDB-CCD, 3DMet, NIKKAJI, NCI, and UM-BBD, ExplorEnz, IUBMB, ExPASy, UM-BBD and BRENDA.

The version of MetaCyc which we use is 14.0. We use APIs provided by KEGG to retrieve pathway data from KEGG. Table 1 gives statistics of data collected from MetaCyc and KEGG. Furthermore, we use compound links collected from KEGG and MetaCyc to collect data from compound databases, such as PubChem, ChEBI, KNApSAcK, LIPIDMAPS, LipidBank, PDB-CCD, 3D-MET, NIKKAJI, NCI and UM-BBD-CPD. Table 2 gives statistics of compounds collected from each compound database.

Table 1: Database statistics between KEGG and MetaCyc.

Database context	KEGG	MetaCyc
Collected date	2010/06/11	v14.0 (2010/03/18)
Pathway	165	1719
Reaction	8172	8711
Enzyme	5184	9050
Compound	16250	8572
Undefined compound	-	1522

Table 2: Compound database statistics.

Compound database	Number of collected compounds (date: 2010/06/13)
PubChem	20711
ChEBI	6574
KNApSAcK	4204 (4246 links provided, but 24 are detected as dead links)
LIPIDMAPS	783
LipidBank	468 (490 links provided, but 22 are detected as dead links)
PDB-CCD	1424 (1449 links provided, but 25 are detected as dead links)
3D-MET	5640
NIKKAJI	6814 (6852 links provided, but 38 are detected as dead links)
NCI	222
UM-BBD-CPD	50

Table 3 gives the number of links predicted by compound matching, the number of links extracted from existing databases, and the precision and recall with respect to extracted links. Our approach achieves very high recall rate, and is able to identify more than 90% of cross links provided in current databases. For compound matching from MetaCyc to KEGG, our approach identifies 1174 more than the number of unification links provided by MetaCyc. This indicates that our approach has the potential to discover cross links not provided by current databases.

Table 4 gives statistics of each enzyme database. For enzyme matching, our experiment identifies 5846 matches from MetaCyc to KEGG. Enzyme matching result is given in Table 5.

For reaction matching, we identify 4097 matching pairs between MetaCyc and KEGG. Among them, 264 pairs have different EC-numbers, and 315 pairs have one reaction missing EC-number. For those missing EC-numbers, we assign EC-numbers to them according to their matched reactions. For those with different EC-numbers, we suggest them to biologists to check their correct EC-numbers. Note that MetaCyc v14.0 provides 3260 reaction links and 7 dead links to KEGG. Our approach identifies 2829 of them, and discovers 7 of them are invalid. The recall rate is 0.868.

Table 3: Compound matching result.

Databases	predicted links	existing links	Precision	Recall
MetaCyc to KEGG	6129	4244	0.984	0.966
KEGG to PubChem	13652	13607	0.999	0.997
KEGG to ChEBI	6386	5737	0.997	0.961
KEGG to KNApSAcK	4391	4151	0.992	0.951
KEGG to LIPIDMAPS	867	782	0.999	0.913
KEGG to LipidBank	699	427	0.982	0.934
KEGG to PDB-CCD	2309	1411	0.984	0.807
KEGG to 3D-MET	5689	5640	0.999	0.994
KEGG to NIKKAJI	7349	6754	0.993	0.974
MetaCyc to NCI	404	222	0.986	0.658
MetaCyc to UM-BBD-CPD	53	50	1	0.92

Table 4: Enzyme database statistics.

Enzyme database	Number of collected enzymes
Collected Date	2010/06/13
ExplorEnz	4257
IUBMB	4257
ExPASy	4257
UM-BBD	289
BRENDA	4257

For pathway matching, each matching denotes a part-of relation. Our approach identifies 1343 pathway relations. Among them, 1218 are one-to-one and 125 are one-to-many. MetaCyc v14.0 provided 24 pathway unification links to KEGG. Our approach identifies 15 of them, and discovers 4 of them are invalid. The recall rate is 0.75. If we set pathway matching threshold to 0.2, we can identify 1484 pathway matchings. Among them, 851 are one-to-one and 633 are one-to-many. We identify 16 links that MetaCyc provided, recall rate is 0.8.

Table 5: Enzyme matching result.

From DB 1 to DB 2	**Number of predicted links**	**Number of extracted links**	**Recall w.r.t. extracted links**
MetaCyc to KEGG	5855	7597	0.74
KEGG to ExplorEnz	4254	4257	0.999
KEGG to IUBMB	4253	4257	0.999
KEGG to ExPASy	4204	4257	0.99
KEGG to UM-BBD	318	289	0.98
KEGG to BRENDA	4155	4257	0.97

5 CONCLUSIONS

In this paper, we present a pathway database link server BioDBLink that can automatically collect and generate cross links among biological databases. The core of BioDBLink is a multi-level data matching technique that identifies and matches data records or elements describing the same object. Matching results can also be used to induce more accurate and complete object descriptions, remove data redundancy, and check data consistency. Experiment on a set of pathway, compound and enzyme databases shows that our approach is feasible, identifies a large number of matchings, and detect database inconsistency and duplicate errors. In the future, we will continue to extend our server to incorporate more databases available on internet, and develop data matching techniques to match other types of biological entities. Our goal is to provide a database link server for more biological databases.

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