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FEDRR: fast, exhaustive detection of redundant hierarchical relations for quality improvement of large biomedical ontologies

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Abstract

Background: Redundant hierarchical relations refer to such patterns as two paths from one concept to another, one with length one (direct) and the other with length greater than one (indirect). Each redundant relation represents a possibly unintended defect that needs to be corrected in the ontology quality assurance process. Detecting and eliminating redundant relations would help improve the results of all methods relying on the relevant ontological systems as knowledge source, such as the computation of semantic distance between concepts and for ontology matching and alignment.

Results: This paper introduces a novel and scalable approach, called FEDRR – Fast, Exhaustive Detection of Redundant Relations – for quality assurance work during ontological evolution. FEDRR combines the algorithm ideas of Dynamic Programming with Topological Sort, for exhaustive mining of all redundant hierarchical relations in ontological hierarchies, in $O(c \cdot |V| + |E|)$ time, where $|V|$ is the number of concepts, $|E|$ is the number of the relations, and $c$ is a constant in practice. Using FEDRR, we performed exhaustive search of all redundant is-a relations in two of the largest ontological systems in biomedicine: SNOMED CT and Gene Ontology (GO). 372 and 1609 redundant is-a relations were found in the 2015-09-01 version of SNOMED CT and 2015-05-01 version of GO, respectively. We have also performed FEDRR on over 190 source vocabularies in the UMLS - a large integrated repository of biomedical ontologies, and identified six sources containing redundant is-a relations. Randomly generated ontologies have also been used to further validate the efficiency of FEDRR.

Conclusions: FEDRR provides a generally applicable, effective tool for systematic detecting redundant relations in large ontological systems for quality improvement.

Keywords: Redundant relations, Dynamic programming, SNOMED CT, Gene ontology, UMLS

Background

Ontologies are shared conceptualizations of a domain represented in a formal language. They represent not only the concepts (nodes) but the relationships (edges) between the concepts. Ontologies have become a critical knowledge source in informatics and data intensive applications, such as information retrieval [1], data integration [2], data management [3], and decision support [4].

This paper focuses on a particular type of ontological structural defect: redundant relations. Redundant hierarchical relations refer to such patterns as two paths from concept
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X to concept Y, one with length one (direct) and the other with length greater than one (indirect). For hierarchical relations such as subsumption (is-a), relations implied by transitivity should not be explicitly stated. For example, in Gene Ontology (GO 2015-05-01 version) we have (see Table 1). A (hormone secretion) is-a B (hormone transport), B (hormone transport) is-a C (regulation of hormone levels), C (regulation of hormone levels) is-a D (regulation of biological quality), D (regulation of biological quality) is-a E (biological regulation), E (biological regulation) is-a F (biological process).

However, “A (GO:0046879) is-a F (GO:0008150)” is directly asserted as well (Fig. 1). This represents redundant relations to be studied in this paper: two paths exist between A and F: one directly between A and F, and the other indirectly through B, C, D, and E as intermediate concept nodes.

The principle of parsimony in ontological modeling refers to the omission of relations implied by the transitive property of a relationship, such as “is-a” relations in GO. By violating this principle, redundant relations may increase maintenance burden for ontology curators. It can also cause inaccurate methods and algorithms based on this general principle. For example, semantic distance between concepts is a widely used technique [5]. Ontological mapping and alignment methods rely on the ordered structure of the hierarchical relation [6], with notions of neighborhood and proximity serving as their foundation. The presence of redundant relations induces a short-circuit: two concepts with a larger semantic distance may result in a smaller distance by mistake; and concepts not within a neighborhood may be counted as such.

Using brute force, exhaustive detection of redundant relations can be computationally expensive for large ontologies. For example, SNOMED CT (2015-03-01 version) contains over 300,000 active concepts. A naive approach would be to find the longest paths between the end nodes of each of the over 500,000 edges (relations). Assuming each edge takes 100 ms, processing a single version of SNOMED CT would take 14 hours. Finding all paths between all possible pairs among the 300k nodes would take over 10,000 days if each pair takes 10 ms.

This paper introduces a novel and scalable approach, called FEDRR, Fast, Exhaustive Detection of Redundant Relations, for quality assurance work during ontological evolution. In contrast to the 14 hours naive approach required for each SNOMED CT version, FEDRR needed <20 seconds (see Table 2).

Using FEDRR, we performed exhaustive search of all redundant is-a relations in two of the largest ontological systems in biomedicine: SNOMED CT and GO. 372 and 1609 redundant is-a relations were found in the SNOMED CT (2015-09-01 version) and GO (2015-05-01 version), respectively. Each redundant relation represents a possibly unintended defect that needs to be corrected in the ontology quality assurance process. We further performed longitudinal analyses using FEDRR on 5 versions of SNOMED CT Table 1

| GO Id       | Relation | GO Id       |
|-------------|----------|-------------|
| A GO:0046879| is-a     | B GO:0009914|
| B GO:0009914| is-a     | C GO:0010817|
| C GO:0010817| is-a     | D GO:0065008|
| D GO:0065008| is-a     | E GO:0065007|
| E GO:0065007| is-a     | F GO:0008150|
and 10 versions of GO. We also investigated redundant is-a relations in the UMLS, an integrated repository of biomedical terminologies, including SNOMED CT and GO.

**SNOMED CT**

SNOMED CT is the world’s largest clinical terminology [7, 8]. It provides broad coverage of clinical medicine, including findings, diseases, and procedures for use in electronic medical records.

From a structural perspective, SNOMED CT can be seen as a series of large directed acyclic graphs, one for each of its 19 “sub-hierarchies” including Procedure, Substance, Body structure, Specimen, Clinical finding, and Organism. No concept is shared across sub-hierarchies except for the root. Each concept comes with a SNOMED CT identifier, which is an integer. SNOMED CT concepts are linked by hierarchical relations within each sub-hierarchy.

**Gene ontology**

The Gene Ontology (GO) [9] is a collection of three ontologies to describe attributes of gene products in three non-overlapping domains of molecular biology: Cellular Component, the parts of a cell or its extracellular environment; Molecular Function, the elemental activities of a gene product at the molecular level, such as binding or catalysis; and Biological Process, operations or sets of molecular events with a defined beginning and end, pertinent to the functioning of integrated living units (cells, tissues, organs, and organisms). Within each ontology, terms have free text definitions and unique identifiers. GO terms can be related to each other by is-a and part-of relationships, forming a directed acyclic graph. The GO vocabulary is designed to be species-agnostic, and is intended to capture multiple organisms.

| Table 2 Summary of the results for 5 versions of SNOMED CT |
|---------------------------------|-------------|---------|---|---------|--------|
| Version                        | # Concepts | # is-a Relations | TC   | RR     | RR %   | T(ms)  |
| 2013-09-01                     | 300,485    | 447,442 | 5,226,630   | 240 | 0.00459 | 10,472 |
| 2014-03-01                     | 300,409    | 446,603 | 5,188,221   | 277 | 0.00534 | 10,335 |
| 2014-09-01                     | 302,902    | 449,564 | 5,222,506   | 305 | 0.00584 | 10,074 |
| 2015-03-01                     | 315,904    | 467,799 | 5,408,010   | 235 | 0.00435 | 15,264 |
| 2015-09-01                     | 320,911    | 476,226 | 5,511,334   | 372 | 0.00675 | 16,077 |

TC: number of transitive closure pairs, RR: number of redundant is-a relations, T(ms): time taken in milliseconds
UMLS
The Unified Medical Language System (UMLS) [8], produced and distributed by US
National Library of Medicine (NLM), is a large integrated repository of biomedical con-
trolled vocabularies to facilitate interoperability among disparate systems in biomedicine
and health. The source vocabularies include SNOMEDCT_US (SNOMED CT US Edi-
tion), SCTSPA (SNOMED CT Spanish Language Edition), GO, FMA (Foundational
Model of Anatomy), HPO (Human Phenotype Ontology), and NCI (NCI Thesaurus).

Knowledge in the UMLS Metathesaurus is organized by concept (or meaning). Term
variants from source vocabularies are clustered together to form a concept, and each con-
cept is assigned a unique concept identifier (CUI). The basic building blocks (or atoms) of
the UMLS Metathesaurus are the concept names or strings from each source vocabulary.
Every occurrence of a string in each source is assigned a unique atom identifier (AUI).
For instance, concept names *Hypertension*, *High blood pressure*, and *Hypertensive disor-
der* from SNOMEDCT_US have AUIs A2882711, A2876587, and A3501627, respectively.
*Hypertension* and *Vascular Hypertensive Disorder* from NCI has AUIs A7571194 and
A7628940, respectively. Such concept names from different sources represent the same
meaning and are assigned a unique CUI: C0020538. Moreover, relationships between
terms in source vocabularies are preserved in the UMLS as relationship attributes.

The 2015AB release of the UMLS contains over 3.2 million concepts and 12.8 million
unique concept names from more than 190 source vocabularies.

Ontology quality assurance
Large, comprehensive terminological systems such as SNOMED CT and GO continue
to evolve over time. They are often incomplete, under-specified, and non-static, for rea-
sons such as the evolving state of knowledge in a domain, the involvement of manual
curation work, and the progressive nature of ontological engineering itself. New appli-
cations are calling for new ontologies or expansion and enhancement of existing ones.
Many additional factors, such as merging or reusing existing ontologies and porting to a
common representation framework, may introduce inconsistencies and unintended arti-
facts. Thus Ontology Quality Assurance (OQA) is an indispensable part of the ontological
engineering lifecycle [10–21]. OQA attempts to assess and improve the overall quality of
ontologies in aspects such as the consistency of the ontological structure with respect to
the explicit and implicit knowledge they capture; the coverage of the ontology in terms of
classes and properties needed to support specific applications; and the non-redundancy
of classes and properties.

The basic premise of OQA is a mixed closed-world assumption (CWA) and open-
world assumption (OWA). In a formal system of logic used for knowledge representation,
such as ontological systems, CWA refers to the assumption that a relationship holds true
between two concepts is also explicitly asserted to be true, unless they are implied by log-
ical properties such as transitivity. It dictates that, in reverse, a relationship between two
concepts that is not asserted explicitly, must be false. OWA, on the other hand, refers to
the assumption that lack of knowledge does not imply falsity.

In the context of OQA, OWA refers to the evolving state of knowledge in a domain, in
the sense that new concepts may be included in an ontological system in a continuous
fashion. The lack of a concept in an ontological system does not imply that such a concept
does not exist. CWA, on the other hand, implies that, among existing concepts in an
ontological system, the lack of an explicit relationship of a known relation-type between two concepts means that such a relationship does not exist between the two concepts.

The principle of parsimony in ontological modeling is a direct consequence of CWA. It refers to the fact that relations implied by the transitive property of a relationship, such as the example given in Fig. 1, must not be explicitly stated. By violating this principle, redundant relations can cause methods and algorithms based on this general principle inaccurate. Detecting redundant relations is an important task for OQA, which is the focus of this paper.

Methods

The general mathematical abstraction of an ontological structure is a graph-theoretic one: nodes correspond to concepts, and edges correspond to relations (between nodes). For hierarchical relations in ontological systems such as “is-a,” which obeys the transitivity property that

\[
\text{if } A \text{ is-a } B \text{ and } B \text{ is-a } C, \text{ then } A \text{ is-a } C,
\]

one can model the structure of an ontological system as a directed acyclic graph (DAG, as shown in part in Fig. 1).

**Definition 1.** Suppose \(G = (V, E)\) is a directed acyclic graph with \(V\) a set of nodes, and \(E\) a set of edges between the nodes. A redundant relation in \(G\) is a pair of nodes \((s, t)\) such that \((s, t) \in E\), and there is an indirect path (i.e., length more than 1) from \(s\) to \(t\).

The closely related known algorithm for computing redundant relations in the literature is all-pair longest path [22]. Although fixed source longest path can be solved in time-complexity \(O(|V| + |E|)\) in a DAG [22], all-pair longest path requires iteration over \(V\), resulting in an \(O(|V| \cdot |E| + |V|^2)\) time-complexity algorithm. For large ontological systems such as SNOMED CT, such a running time amounts to an intractable amount of processing time (requiring 10,000 days if all-pair paths were to be computed).

FEDRR solves this problem in time-complexity \(O(c \cdot |V| + |E|)\), where \(c\) is the average number of descendants of a node. For the latest version of SNOMED CT, we have \(c = 17.12\) (see Time Complexity Analysis). For a single version of SNOMED CT, the actual processing time is less than 20 seconds.

There are two key algorithmic ideas behind FEDRR. One is avoidance of repeated computations by remembering the set of directly reachable nodes as well as the set of indirectly reachable nodes, for each node. The second is to completely skip node pairs that are not connected by a directed path. These ideas are reflected in FEDRR using a novel combination of dynamic programming with topological sort. The sparsity of most ontological structures, viewed as a DAG, is a particularly suitable property for the second idea to take advantage of.

For a node \(u\) in a DAG \(G = (V, E)\), we introduce two sets, \(D_u\) and \(I_u\), where

- \(D_u = \{v \mid (v, u) \in E\}\), called the **D-set**, consists of the direct descendants (i.e. children) of \(u\); and
- \(I_u\), called the **I-set** of \(u\), is the set of all indirect descendants of \(u\).

The design of our algorithm is based on the following observation.

**Lemma 1.** For each node \(v \in D_u \cap I_u\), \((v, u)\) is redundant.
Our algorithm amounts to the computation of \((D_u, I_u)\) for each node \(u\). To utilize the idea of dynamic programming, we update \((D_u, I_u)\) for each node \(u\) according to the order by topological sort. The basic update scheme is illustrated in the following diagram:

Suppose we have obtained \((D_{v_i}, I_{v_i})\) for each \(i = 1, \ldots, k\), where \(\{v_1, v_2, \ldots\} = \{v \mid (v, u) \in E\}\). Then we set \(D_u = \{v_1, v_2, \ldots\}\) and \(I_u = \bigcup_{i=1}^{k} (D_i \cup I_i)\). The pseudo-code of FEDDR appears in Algorithm 1.

**Algorithm 1** FEDRR: Dynamic programming using topological sort to compute the \(D\)-set and \(I\)-set of each node

1: Input: \(G(V)\)
2: \(q := \text{new Queue()}\)
3: for all \(v \in V\) do
4: \(I[v] := \emptyset\)
5: \(D[v] := \emptyset\)
6: if no incoming edge for \(v\) then
7: \(q.enqueue(v)\)
8: end if
9: end for
10: while \(q\) not empty do
11: \(s := q.dequeue()\)
12: for all \(t \in s.to\) do
13: \(I[t] := I[t] \cup I[s] \cup D[s]\)
14: \(D[t] := D[t] \cup \{s\}\)
15: mark edge \((s, t)\)
16: if no unmarked incoming edge for \(t\) then
17: \(q.enqueue(t)\)
18: end if
19: end for
20: end while

FEDDR starts by initializing an empty queue to hold the nodes that will be sorted (line 2). Then nodes with no incoming edges are put to the queue, with the \(D\)-set and \(I\)-set initialized as empty (lines 3 - 9). In the next phase (lines 10 - 20), the nodes are dequeued one at a time, with the \(I\)-sets and \(D\)-sets (for \(t\)) updated according to the mechanism described in Fig. 2.

We illustrate the steps of Algorithm 1 using an example. The input DAG is given in Fig. 3 (top left), and there is a redundant edge (colored in red) that FEDDR is supposed to detect. The algorithm starts with setting initial values for the \(D\)-set and the \(I\)-set and enqueuing those node with no incoming edges, as shown on the top right of Fig. 3. The result is shown on the bottom right of Fig. 3.

**Correctness**

The correctness of the algorithm can be proved using mathematical induction by showing \(I[v_i] = I_{v_i}\) and \(D[v_i] = D_{v_i}\) after node \(v_i\) is dequeued (line 11) for \(i = 1 \ldots |V|\).
Proof $i = 1$. The first dequeued node must be a node with no incoming edges. This means $I_{v_1} = \emptyset$ and $D_{v_1} = \emptyset$. As both $I[v_1] = \emptyset$ and $D[v_1] = \emptyset$ from lines 4 and 5, we have

$I[v_1] = I_{v_1}$ and $D[v_1] = D_{v_1}$.

Suppose $I[v_i] = I_{v_i}$ and $D[v_i] = D_{v_i}$ is true for $i = 1 \ldots k - 1$. For $i = k$, then we have $D[v_k] = \{v \mid (v, v_k) \in E\}$ and $I[v_k] = \bigcup_j (D[v_k] \cup I[v_k])$, where $v_k \in \{v \mid (v, v_k) \in E\}$.
Based on the definition of $D_v$, we have $D_{vk} = \{ v \mid (v, v_k) \in E \} = D[v_k]$. From the induction hypothesis, we have $I[v_i] = I_{vi}$ and $D[v_i] = D_{vi}$ for $i = 1 \ldots k - 1$. This means $I[v_k] = \bigcup_i \left( D[v_k] \cup I[v_k] \right) = \bigcup_i \left( D_{vk} \cup I_{vk} \right) = I_{vk}$.

**Time complexity analysis**

The topological sorting itself takes $O(|V| + |E|)$ time [23]. With the computation of $D$-set and $I$-set, the total time is $O(\sum_{(u,v) \in E}(|D_u| + |I_u|) + |V| + |E|)$. When $|E| = O(|V|)$ (which is the case for both SNOMED CT and GO), the running time is $O(\sum_v(|D_v| + |I_v|) + |V| + |E|)$. If we let $c = \sum_v(|D_v| + |I_v|) / |V|$, then the running time is in $O(c \cdot |V| + |E|)$. Based on the definition of $D_v$ and $I_v$, $\sum_v(|D_v| + |I_v|)$ is the size of transitive closure pairs shown in Tables 2 and 4. Even though the worst-case running time is $O(|V|^2)$ (when $c = |V|$), $c$ is a relatively small constant for ontological systems in practice. This is validated by our experimental results shown in Tables 2 and 4. For the 2015-03-01 version of SNOMED CT, $c = \frac{5,408,010}{315,904} = 17.12$, and for the 2015-05-01 version of GO, $c = \frac{557,550}{42,979} = 12.97$.

**Results**

**Experimental environment**

To detect redundant is-a relations from SNOMED CT and Gene Ontology, we ran the FEDRR method on a MacBook Pro running the Mac OS X Yosemite with 16 GB RAM and Intel Core i7 processor. FEDRR was implemented in Java programming language based on JDK7.

**Redundant is-a relations in SNOMED CT**

We ran the FEDRR method on 5 versions of SNOMED CT (U.S. edition) from 2013 to 2015 dated on 2013-09-01, 2014-03-01, 2014-09-01, 2015-03-01, and 2015-09-01. Table 2 summarizes the result of each version including numbers of concepts, is-a relations, and transitive closure pairs (TC), and number of redundant is-a relations (RR); percentage of redundant is-a relations (RR%) among transitive closure pairs; and computing time in milliseconds to detect redundant is-a relations. For example, for the 2015-09-01 version, there were 320,911 concepts, 476,226 is-a relations, 5,511,334 transitive closure pairs, and 372 redundant is-a relations; the percentage of the redundant is-a relations among the transitive closure pairs is 0.00675%; and it took about 16 seconds to complete. For each version, it only took a few seconds to identify all the redundant is-a relations, indicating the efficiency of FEDRR.

Table 3 shows the numbers of redundant is-a relations in 5 versions of SNOMED CT with respect to the length of the indirect path. For each version, $I_i$ ($i = 2, 3, 4$) is the number of redundant is-a relations in length of $i$ regarding to the indirect path. For example, in the version of 2015-09-01, there were 358 redundant is-a relations in length of 2, 13 in length of 3, and 1 in length of 4. In general, most redundant is-a relations were in length of 2, and no redundant is-a relations exceeding length of 4 was identified.

**Redundant is-a relations in gene ontology**

We ran the FEDRR method to detect redundant is-a relations in 10 versions of Gene Ontology from 2014-08-01 to 2015-05-01 updated monthly. Table 4 summarizes the basic results of each version. For instance, for the 2015-05-01 version, there were 42,979 concepts, 71,954 is-a relations, 557,550 transitive closure pairs, and 1,609 redundant is-a
Numbers of redundant is-a relations in 5 versions of SNOMED CT regarding to the length of the indirect path. \( l_i \) represents the number of redundant is-a relations in length of \( i \) regarding to the indirect path.

| Version   | \( l_2 \) | \( l_3 \) | \( l_4 \) | Total |
|-----------|-----------|-----------|-----------|-------|
| 2013-09-01| 233       | 7         | 0         | 240   |
| 2014-03-01| 264       | 11        | 2         | 277   |
| 2014-09-01| 291       | 13        | 1         | 305   |
| 2015-03-01| 224       | 10        | 1         | 235   |
| 2015-09-01| 358       | 13        | 1         | 372   |

relations; the percentage of the redundant is-a relations among the transitive closure pairs is 0.2886 %; and it took 1,538 milliseconds to complete. As the number of concepts and is-a relations were increasing, the number and percentage of redundant is-a relations (RR) were monotonically increasing every month and increased more than twice from the 2014-08-01 version (497; 0.0961 %) to the 2015-05-01 version (1,609; 0.2886 %). For each version, it only took a couple of seconds to identify all the redundant is-a relations, indicating the efficiency of FEDRR.

Table 5 shows the numbers of identified redundant is-a relations for the 10 versions with respect to the length of the indirect path. For each version, \( l_i \ (i = 2, \ldots, 7) \) is the number of redundant is-a relations in length of \( i \) regarding to the indirect path. For example, in the version of 2015-05-01, there were 1,238 redundant is-a relations in length of 2 and 255 in length of 3. Most redundant is-a relations were in length of 2 or 3 regarding to the indirect path. There were only a couple of redundant is-a relations in length of 7. No redundant is-a relations exceeding length of 7 was identified.

### Redundant is-a relations in UMLS

We ran the FEDRR method to detect redundant is-a relations from over 190 source vocabularies integrated in the UMLS (2015AB release). Since the original occurrences of concept names are preserved and identified as AUIs in the UMLS, we used AUIs and relations between AUIs to detect redundant is-a relations. We also filtered out inactive is-a relations in the UMLS before applying the FEDRR method (obsolete relations are indicated by a value of ‘O’ in the SUPPRESS field in the relation file MRREL.RRF).

| Version   | # Concepts | # is-a Relations | TC   | RR  | RR%  | T(ms) |
|-----------|------------|------------------|------|-----|------|-------|
| 2014-08-01| 41,436     | 66,544           | 517,092 | 497 | 0.0961 | 1,372 |
| 2014-09-01| 41,694     | 66,995           | 522,741 | 502 | 0.0960 | 1,472 |
| 2014-10-01| 41,867     | 67,536           | 528,821 | 631 | 0.1193 | 1,455 |
| 2014-11-01| 42,012     | 69,300           | 541,718 | 1,031 | 0.1903 | 1,497 |
| 2014-12-01| 42,189     | 69,887           | 545,168 | 1,193 | 0.2188 | 1,425 |
| 2015-01-01| 42,329     | 70,272           | 544,210 | 1,277 | 0.2347 | 1,510 |
| 2015-02-01| 42,466     | 70,724           | 546,158 | 1,420 | 0.2600 | 1,549 |
| 2015-03-01| 42,588     | 71,032           | 548,006 | 1,463 | 0.2670 | 1,542 |
| 2015-04-01| 42,805     | 71,549           | 552,367 | 1,552 | 0.2810 | 1,437 |
| 2015-05-01| 42,979     | 71,954           | 557,550 | 1,609 | 0.2886 | 1,538 |

\( TC \): number of transitive closure pairs; \( RR \): number of redundant is-a relations; \( RR\% \): percentage of redundant is-a relations among transitive closure pairs; \( T\)(ms): time taken in milliseconds.
Table 5 Numbers of redundant is-a relations in 10 different versions of Gene Ontology regarding to the length of the indirect path. $l_i$ represents the number of redundant is-a relations in length of $i$ regarding to the indirect path

| Version       | $l_1$ | $l_2$ | $l_3$ | $l_4$ | $l_5$ | $l_6$ | Total |
|---------------|-------|-------|-------|-------|-------|-------|-------|
| 2014-08-01    | 421   | 40    | 23    | 11    | 1     | 1     | 497   |
| 2014-09-01    | 419   | 44    | 24    | 13    | 1     | 1     | 502   |
| 2014-10-01    | 512   | 72    | 29    | 15    | 2     | 1     | 631   |
| 2014-11-01    | 771   | 164   | 64    | 27    | 4     | 1     | 1,031 |
| 2014-12-01    | 921   | 174   | 63    | 27    | 7     | 1     | 1,193 |
| 2015-01-01    | 980   | 202   | 62    | 24    | 8     | 1     | 1,277 |
| 2015-02-01    | 1,098 | 220   | 68    | 24    | 8     | 2     | 1,420 |
| 2015-03-01    | 1,119 | 237   | 72    | 25    | 8     | 2     | 1,463 |
| 2015-04-01    | 1,198 | 238   | 78    | 29    | 7     | 2     | 1,552 |
| 2015-05-01    | 1,238 | 255   | 78    | 29    | 7     | 2     | 1,609 |

Based on our experiment, the concept graph in terms of AUI is acyclic, and FEDRR completes the exhaustive search for all the sources in our experiments. Six sources were found to have redundant is-a relations (see Table 6): SNOMEDCT_US (2015_09_01), SNOMEDCT_VET (2015_04_01), GO (2015_04_04), NCI (1502D), HPO (2015_04_20), and UMD (2015AA). For instance, in HPO, there were 18,175 AUIs, 14,762 is-a relations, 117,366 transitive closure pairs, and 101 redundant is-a relations. Moreover, it took FEDRR less than 30 seconds to detect redundant is-a relations for each of these source vocabularies.

As can be seen from Table 6, SNOMEDCT_US in the UMLS shows the same number (372) of redundant is-a relations compared to the result obtained based on its original source (version 2015_09_01 in Table 2). GO in the UMLS has slightly more redundant is-a relations (1,576 v.s. 1,552) compared to the result obtained based on its original source of GO (version 2015_04_01 in Table 4). This difference may be caused by the a different version of GO (version 2015_04_04) integrated in the 2015AB release of the UMLS.

**Redundant is-a relations in randomly generated ontology**

We have also tested FEDRR on randomly generated ontologies. There are two goals in testing FEDRR on randomly generated ontologies.

- To test the efficiency of FEDRR on arbitrarily large ontologies, and
- To compare the ratio of redundancy relations in real world biomedical ontologies with random ontologies with similar properties.

Table 6 Summary of the results for source vocabularies in UMLS (2015AB release) with redundant relations

| Version       | # AUIs | # is-a Relations | TC    | RR   | RR%   | T(ms) |
|---------------|--------|-----------------|-------|------|-------|-------|
| SNOMEDCT_US   | 846,444| 476,055         | 5,511,334| 372  | 0.00675| 28,977|
| SNOMEDCT_VET  | 85,939 | 19,832          | 29,688 | 7     | 0.024 | 954   |
| GO            | 148,900| 71,687          | 554,859| 1,576 | 0.2840| 9,128 |
| NCI           | 270,618| 119,707         | 701,986| 20    | 0.0028| 5,881 |
| HPO           | 18,175 | 14,762          | 117,366| 101   | 0.0861| 502   |
| UMD           | 34,124 | 10,750          | 37,732| 20    | 0.0530| 1,906 |

AUI: Atom Unique Identifier, TC: number of transitive closure pairs, RR: number of redundant is-a relations, T(ms): time taken in milliseconds
As each ontology can be represented as a DAG, we implemented Algorithm 2 to generate a random DAG\((N, E, C_{\text{min}}, C_{\text{max}})\), where \(N\) is the number of nodes, \(E\) is the number of edges, and \(C_{\text{min}}/C_{\text{max}}\) are the minimum/maximum number of children a node can have.

Algorithm 2 Procedure to generate a random ontology

\[
\begin{align*}
1: & \quad \text{Input: } N, E, C_{\text{min}}, C_{\text{max}} \\
2: & \quad q := \text{new Queue()} \\
3: & \quad \text{root} := \text{new node} \\
4: & \quad q.\text{enqueue}() \\
5: & \quad \text{numOfNodes} := 0 \\
6: & \quad \text{numOfEdges} := 0 \\
7: & \quad \text{edges} := \emptyset \\
8: & \quad \text{while numOfNodes} < N \text{ do} \\
9: & \quad \quad p := q.\text{dequeue()} \\
10: & \quad \quad c := \text{random}(C_{\text{min}}, C_{\text{max}}) \\
11: & \quad \quad \text{for } i \leq c \text{ do} \\
12: & \quad \quad \quad \text{child} := \text{new node} \\
13: & \quad \quad \quad \text{edges} := \text{edges} \cup \{(p, \text{child})\} \\
14: & \quad \quad \quad \text{numOfNodes}++ \\
15: & \quad \quad \quad \text{numOfEdges}++ \\
16: & \quad \quad \quad i++ \\
17: & \quad \quad \text{end for} \\
18: & \quad \text{end while} \\
19: & \quad \text{while numOfEdges} < E \text{ do} \\
20: & \quad \quad \text{src} := \text{random}(0, \text{numOfNodes}) \\
21: & \quad \quad \text{dest} := \text{random}(0, \text{numOfNodes}) \\
22: & \quad \quad \text{if src} \neq \text{dest} \text{ and } (\text{src}, \text{dest}) \notin \text{edges} \text{ then} \\
23: & \quad \quad \quad \text{edges} := \text{edges} \cup \{(\text{src}, \text{dest})\} \\
24: & \quad \quad \quad \text{numOfEdges}++ \\
25: & \quad \quad \text{end if} \\
26: & \quad \text{end while}
\]

Results of FEDRR on nine random ontologies are presented in Table 7. For each set of parameters, the median (using RR) of five runs is recorded. As can be seen from Table 7, FEDRR performs very well in terms of time efficiency and is suitable for online auditing of ontologies. It also scales very well to handle more than 1 million nodes and relations.

The results also clearly indicates that the number of redundant relations increases when the density of the edges increases. For comparable density of edges, the ratio of redundant relations in SNOMED CT (US edition) (ranging from 0.0039 to 0.0058 %) and GO (ranging from 0.096 to 0.289 %) is much higher than in randomly generated ontologies (ranging from 0.0001 to 0.0054 %).
### Table 7 Summary of the results for randomly generated ontologies

| $(N,E,C_{min},C_{max})$ | # Layers | TC     | RR | RR%  | T(ms) |
|------------------------|----------|--------|----|------|-------|
| (500,000, 550,000, 2, 5) | 12       | 5,957,690 | 6  | 0.0001 | 5,847 |
| (500,000, 550,000, 2, 10) | 8        | 4,036,792 | 12 | 0.0003 | 5,212 |
| (500,000, 600,000, 2, 20) | 6        | 3,000,751 | 7  | 0.0002 | 5,637 |
| (500,000, 700,000, 2, 20) | 6        | 3,567,691 | 13 | 0.00036 | 5,449 |
| (500,000, 900,000, 2, 20) | 6        | 4,190,494 | 34 | 0.00081 | 5,332 |
| (500,000, 1,300,000, 2, 20) | 6       | 7,104,749 | 109 | 0.00153 | 8,183 |
| (1,000,000, 1,200,000, 2, 20) | 7       | 7,071,813 | 21 | 0.0003 | 18,051 |
| (1,000,000, 1,400,000, 2, 20) | 7       | 8,694,703 | 133 | 0.0015 | 11,582 |

* $N$: number of concepts, $E$: number of is-a relations, $C_{min}/C_{max}$: minimum/maximum number of children a node can have, TC: number of transitive closure pairs, RR: number of redundant is-a relations, T(ms): time taken in milliseconds

### Change rates in ontology evolution

Most ontologies in life science evolve continuously to account for new discoveries [11, 13, 14]. Our experimental studies indicated that the change rates of redundant is-a relations are significantly higher than the change rates of all is-a relations for both SNOMED CT and Gene Ontology.

Figure 4 is a graphical summary of the differences between SNOMED CT versions using the change rate of redundant is-a relations versus the change rate of all is-a relations. The change rate between two versions is defined as $\frac{|N - O| + |O - N|}{|O| + |N|}$, where $N$ is the set of relations in the new version, $O$ is the the set of relations in the old version, $N - O$ is the set of relations in the new version but not in the old version, and $O - N$ is the set of relations in the old version but not in the new version. It should be noted that $N - O \neq O - N$ and $|N - O| \neq |N| - |O|$ in general. Figure 5 shows the summary of the differences between Gene Ontology versions using the change rate of redundant is-a relations versus the change rate of all is-a relations.

As can be seen from Figs. 4 and 5, the change rates of redundant is-a relations between versions are consistently higher than that of all is-a relations for both SNOMED CT and

![Fig. 4 Change rate of redundant is-a relations compared to the change rate of all is-a relations during SNOMED CT evolution](image-url)
Gene Ontology. For SNOMED CT, the change rates of redundant is-a relations are 4 to 10 times higher than that of all is-a relations. For Gene Ontology, the change rates are 5 to 12 times higher. This indirectly validates the importance of eliminating redundant relations from ontologies during ontological evolution.

Revision reversals of redundant relations

A particular case of ontological changes during ontology evolution is the revision reversal of relations, which refers to the addition (removal) of a relation being reversed by a removal (addition) in later versions. For example, the relation “Telangiectasia of skin of face (disorder)” is-a “Disorder of skin of head (disorder)” was not present in the 2013-09-01 version. It was added in the 2014-03-01 version, but was subsequently removed in the 2015-03-01 version. The following is a list of redundant is-a relations added in the 2014-03-01 version, but removed from the 2015-03-01 version.

\[
\begin{align*}
131461000119105 & \text{ is } \rightarrow \text{ a } 275544003 \\
699056001 & \text{ is } \rightarrow \text{ a } 400082007 \\
699056001 & \text{ is } \rightarrow \text{ a } 118930001 \\
234140000 & \text{ is } \rightarrow \text{ a } 400082007
\end{align*}
\]

Clinically, such revision reversals may indicate the confusion about representing the relations among a group of concepts, which is closely related to the higher change ratio presented in Figs. 4 and 5. For SNOMED CT, we have observed much higher rate of revision reversals among the redundant is-a relations (19 out of 415; 4.58 %) compared to all is-a relations (1575 out of 491,825; 0.32 %). The revision reversal results in even higher rate when considering the segment induced by the redundant relation (59 out of 415; 14.22 %). For Gene Ontology, the rate of revision reversals among the redundant is-a relations (8 out of 1,614; 0.50 %) compared to all relations (188 out of 72,729; 0.26 %). The revision reversal results in even higher rate when considering the segment induced by the redundant relation (28 out of 1624 or 1.72 %).
Evaluation

Even though in most cases redundant edges should be removed, in some cases the redundancy is caused by a mistake of an edge along the indirect path. For example, in Fig. 6, the assertion that “Bilateral congenital dislocation of hip” is-a “Congenital dislocation of right hip” is most likely in error. This is because a concept involving “bilateral” should not be a subclass of a concept of limited laterality: “right” (but not “left”). Removing this edge would have automatically eliminated the redundancy of the detected relation.

To evaluate the performance of FEDRR’s detection of redundant is-a relations from original sources of SNOMED CT and GO, a random sample of 30 redundant relations from SNOMED CT (2015-03-01 version) and 50 from GO (2015-05-01 version) were selected and manually reviewed by two human annotators. One annotator was asked to manually verify if the redundant hierarchical relations identified by FEDRR are correct. The other annotator was asked to review each redundant relation and provide feedback if the redundant relation (direct edge) should be removed or an edge in the indirect path should be removed. For instance, Fig. 7 presents an example of redundant relation from GO manually reviewed by the second annotator. In this case, the annotator’s feedback is to remove the direct edge. For cases like the one shown in Fig. 6, the annotator’s feedback is to remove the indirect edge that is incorrect.

The first annotator verified that all of the redundant is-a relations identified by FEDRR are correct, that is, 100% accuracy. Table 8 shows the feedback of the second annotator.

Among 30 redundant is-a relations in SNOMED CT, 24 (80%) should have direct edge removed, and 6 (20%) should have indirect edge removed. Among 50 redundant is-a
Table 8 Numbers of direct edge and indirect edge that should be removed for 30 redundant is-a relations in SNOMED CT and 50 in Gene Ontology

|                | Remove direct edge | Remove indirect edge |
|----------------|--------------------|----------------------|
| SNOMED CT      | 24 (80%)           | 6 (20%)              |
| Gene Ontology  | 45 (90%)           | 5 (10%)              |

relations in GO, 45 (90 %) should have direct edge removed, and 5 (10 %) should have indirect edge removed.

To evaluate the performance of FEDRR’s detection of redundant hierarchical relations from UMLS, a random sample of 30 redundant relations detected from the SNOMEDCT_US in the UMLS was selected and manually reviewed by the first annotator. The annotator verified that all the 30 redundant relations identified by FEDRR are correct (100 % accuracy).

Discussion

Related work

There has been related work on exploring redundant relations in biomedical ontologies or terminologies [24–28]. Bodenreider [24] investigated the redundancy of hierarchical relations across biomedical terminologies in the UMLS. Different from Bodenreider’s work, FEDRR focuses on developing a fast and scalable approach to detect redundant hierarchical relations within a single ontology.

Gu et al. [25] investigated five categories of possibly incorrect relationship assignment including redundant relations in FMA. The redundant relations were detected based on the interplay between the is_a and other structural relationships (part_of, tributary_of, branch_of). A review of 20 samples from possible redundant part_of relations validated 14 errors, a 70 % correctness. FEDRR differs from this work in two ways. Firstly, FEDRR aims to provide an efficient algorithm to identify redundant hierarchical relations from large ontologies with 100 % accuracy. Secondly, FEDRR can be used for detecting redundant relations in all DAGs with the transitivity property.

Mougin [26] studied redundant relations as well as missing relations in GO. The identification of redundant relations was based on the combination of relationships including is_a and is_a and part_of, part_of and part_of, and is_a and positively_regulates. FEDRR’s main focus is to provide a generalizable and efficient approach to detecting redundant hierarchical relations in any ontology, which has been illustrated by applying it to all the UMLS source vocabularies. Moreover, the redundant hierarchical relations detected by FEDRR were evaluated by human experts, while only number of redundant relations was reported in [26] without human annotator’s validation.

Mougin et al. [27] exhaustively examined multiply-related concepts within the UMLS, where multiply-related concepts mean concepts associated through multiple relations. They explored whether such multiply-related concepts were inherited from source vocabularies or introduced by the UMLS integration. About three quarters of multiply-related concepts in the UMLS were found to be caused by the UMLS integration. Additionally, Gu et al. [28] studied questionable relationship triples in the UMLS following four cases: conflicting hierarchical relationships, redundant hierarchical relationships, mixed hierarchical/lateral relationships, and multiple lateral relationships. It was reported in [28]
that many examples indicated that questionable triples arose from the UMLS integration process.

Bodenreider [29], Mougin and Bodenreider [30], and Halper et al. [31] studied various approaches to removing cyclic hierarchical relations in the UMLS. Although no cycles have been detected in the current UMLS in terms of the AUI, such approaches ([29–31]) to detecting and removing cyclic relations are needed before FEDRR can be applied. This is because FEDRR is based on the topological sorting of a graph, which requires no cycles in a graph.

Future work

Although we have focused on investigating redundant is-a hierarchical relations in this paper, FEDRR is a general method and is applicable to detect redundant relations in other hierarchical structures. In future work, we plan to apply FEDRR on other hierarchical relationships such as part_of in SNOMED_CT and FMA, and branch_of in FMA.

Conclusions

Detecting and removing redundant relations is an important quality improvement task for biomedical ontologies because non-redundancy is the basic premise of all semantic measures derived from ontological structures, such as semantic distance between concepts and ontology mapping and alignment. We introduced FEDRR for fast and exhaustive detection of redundant hierarchical relations in ontological hierarchies. Our algorithm runs in linear time to the size of the ontological structure in practice.

Using FEDRR, we performed systematic and exhaustive search of redundant is-a relations in two large ontological systems in biomedicine: SNOMED CT and Gene Ontology, as well as all the source vocabularies in the UMLS. The algorithmic core of FEDRR is easy to implement and extremely efficient. In our extensive experiments on real-world, large ontological structures, it took less than 20 seconds for FEDRR to process SNOMED CT and Gene Ontology. Moreover, FEDRR is a general approach and can be applied to detect redundant relations in other hierarchical structures.

With these results, we believe that FEDRR is production ready. It is available at https://github.com/gmingx/fedrr.

Abbreviations

AUI: Unique atom identifier; CUI: Unique concept identifier; CWA: Closed-world assumption; DAG: Directed acyclic graph; FEDRR: Fast, exhaustive detection of redundant relations; FMA: Foundational model of anatomy; GO: Gene ontology; HPO: Human phenotype ontology; NLM: National library of medicine; NCI: NCI thesaurus; OQA: Ontology quality assurance; OWA: Open-world assumption; SNOMEDCT_US: SNOMED CT US edition; SCTSPA: SNOMED CT Spanish language edition; UMLS: Unified medical language system

Acknowledgements

We thank Shiqiang Tao for the SVG template which helped the rendering of the diagrams used for this work. We thank Dezhao Song, Adam Fermer, Cui Tao and Frank Schilder, Chairs of the International Workshop on Biomedical Data Mining, Modeling, and Semantic Integration: A Promising Approach to Solving Unmet Medical Needs, Co-located with the 2015 International Semantic Web Conference, for their work as Guest Editors for this submission.

Funding

The project described was supported by the National Center for Advancing Translational Sciences, UL1TR000117, and in part by the Software Solutions of Applied Research and Technology Program at Western Kentucky University. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Availability of data and materials

SNOMED CT, GO, and UMLS used in this paper are downloaded from their own websites, which are freely available. The source code of FEDRR is available at https://github.com/gmingx/fedrr.
Authors' contributions
GX, LC and GZ conceptualized the idea of this study. GX implemented the algorithm to detect redundant relations, and did experiment on SNOMED CT and UMLS. LC did experiment on Gene Ontology. LC prepared the materials for the evaluation on SNOMED CT and Gene Ontology. GZ performed the evaluation. LC analyzed the evaluation results. GX, LC and GZ developed the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

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Received: 2 March 2016 Accepted: 3 October 2016
Published online: 10 October 2016

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