SEPHYRES 1: A Symptom Checker based on Semantic Pain Descriptors and Weight Spreading

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Abstract
Semantic-enabled medical diagnostic systems, which have exploited an ontology in their internal engines, have failed to perfectly describe disease profiles, especially in complex medical terms having a variant generality level or certainty in the medical literature. The main objective of this paper was to present an ontology with a highly matching grade of proeminent medical concepts able to analyze the patient's descriptive medical condition. Focusing on semantic pain descriptors and weight spreading techniques, we proposed a semantic-pseudo-fuzzy engine entitled SEPHYRES, with which we tried to present an ontology-based solution using not only a generic semantic reasoner but also complementary domain-heuristic reasoning. Having applied the valid evidence-based references along with local experts, we illustrated how the resilient expressive model represents the complex medical term relations. The twenty test cases were extracted from the MEDSCAPE and PubMed databases and the precision and recall were calculated. Finally, the results were compared against the Isabel symptom checker and performed the Wilcoxon signed-rank test. The recall measures indicated that the accuracy was equal to 75%, if the system was adjusted to only ten results as differential diagnoses. Moreover, the Wilcoxon signed-rank test showed that there was significant difference between SEPHYRES and Isabel symptom checker (P= 0.016) so that this method is sufficiently able to improve semantic expressiveness in both professional medical diagnosis and patient decision aid systems.

Keywords: Clinical information systems; Clinical decision support; Computer assisted decision making; Knowledge modeling and representation; Telemedicine and telehealth; Computer assisted diagnosis

Introduction

In recent years, there has been a marked increase in the growth of conceptual networks to transform human-centric information into machine-understandable knowledge bases. One of the biggest limitations on this route happens when the application domain is mostly semantic-fuzzy and uncertain by nature, as is in medicine. Additionally, several medical recommender applications have applied semantic technologies as a key factor to avoid syntax matching [1] that has been a prominent problem to analyze descriptive medical literature. Hence, the implicit relations between domain concepts and their attributes are established in the form of an ontology, to turn them into concepts which are machine-understandable [2]. In spite of the exciting opportunities in the ontology-based solutions, we refer to some concerns about both semantic representation details and fuzzy-enabled concepts. The flexible representation of semantic-fuzzy-enabled medical terms could have a significant effect on both professional medical diagnostic systems and patient decision aids [3,4].

Applying clinical decision support systems were seen in early expert systems from as far back as the 1970s, when the deDombal's system called AAPHelp (1972) was a primary decision support system for acute abdominal pain based on naive Bayesian approach [5]. Another study, INTERNIST I (1974) was a rule based expert system for general internal medicine [6]. It resulted in such a valuable product that it was applied as a basis for other medical diagnostic systems such as CADUCEUS and QMR. Similarly, considering certain blood infections, Buchanan and Shortliffe developed a rule-based expert system, namely MYCIN (1976) in which they applied not only a set of IF-THEN rules but also certainty factors [7,8]. Also, we can point to DXplain that included 2,200 diseases and 5,000 symptoms, likewise, the Quick Medical Reference (QMR) was developed with 700 diseases and 5,000 symptoms [9]. Considering the newer systems, we refer to the system called MET1 that was developed to manage pediatric emergency triage [10,11].

Over the past decades, the uses of semantic technologies for computer-aided medical diagnosis have become ubiquitous in a clinical setting. For example, the study of Musen (1998) was powered with the idea of separating ontologies and solvers in the EON system [11,12]. Also, references can be made to the research of Crespo et al. (2010) which proposed a diagnostic system that had been turned on rules and probabilities into the ontology [13]. Another study, Mohammed et al. (2012) presented a method for merging both of symptom and disease ontologies due to use in the medical diagnostic systems [14]. Considering other research, Schriml et al. (2012) explained a prominent Disease Ontology (DO) that the relations of signs and symptoms have been established on descriptions in the absence of full semantic modelling [15]. Also, the research of Gounot et al. (2012) implemented a method to produce a disease ontology along with relations to signs and symptoms [16]. In research Brochhausen et al. (2011), they suggested an ontology called ACGT-MO for breast cancer using the combination of three terminologies including SNOMED-CT, UMLS, and NCIT [17]. In addition, there are several studies that have used case profile ontology developed in K4CARE project [18,19]. The K4CARE project provided an amazingly well-known ontology with all healthcare terms related to the care of chronically ill patients at home [20]. Even though the above mentioned published works and newer studies have used ontologies, their applications were different and none of them used flexibly, variant generality matching of symptoms or weight spreading according to prominent medical terminologies [21-26].

Many healthcare studies have variously developed ontologies to apply in semantic applications, due to the different domains of interest. Hence, having reused previous works, we investigated several ontologies in the medical diagnostic field, including but not limited to ODDIN [13], Ontology Merging [14], DO [15], ACGT-MO [16] on breast cancer, HAIKU [22], MedDRA [23] and those which applied the best case profile ontology developed in the K4Care project [18-20]. However, some ontologies did not tackle a vast range of medical concepts (e.g. DO, ODDIN) and some others (e.g. K4Care Project) considered neither completely detailed pain descriptors nor weighting strategies and interested diseases. Eventually, considering manageability and showing contributions practically, it was preferred to manually represent medical-related concepts in the new limited ontology exploiting the earlier ontologies and evidence-based references at this stage of the SEPHYRES.

The aim of the study was to create a semantic-pseudo-fuzzy model which has more powerful expressivity than other models regarding complex medical concepts, it was called SEPHYRES that stands for SEmantic Physician HYbrid Recommender Expert System.

Methods and Materials

The Ontology and its Creation

To keep the domain manageable, we enforced two constraints, including pain-only descriptors and abdominal-pain-related diseases. In this regard, two types of evidence were studied: firstly, local expert's opinion, including a general practitioner, a medical student of fellowship and two gastroenterologist physicians; secondly, both of the most referred sources of internal medicine knowledge, Harrison's Principles of Internal Medicine [27] and UpToDate offline application [28]. After that, an initial list of 115 identified diseases associated with abdominal pain was extracted that all were coded using ICD10 [29]. Consulting the local experts, the weights for every association was assigned and inserted into the knowledge base. Finally, 90 diseases were selected with a higher prevalence and importance. Thereafter, every entry of pain was linked to a list of pain descriptors recommended using our sources of evidence that have been mostly ignored in previous works (Table 1 and Figure 1). According to Figure 2, the main basic concepts of ontology include *Specs*, *Location,* and *Disease*. The *Specs* tackled any characteristic values used along with various properties (Figure 2: relations 1 and 2). Some relations were defined as weighted (Figure 2: relation 3), which reflected the importance of its relationship. The *Disease* concept has been classified in terms of ICD10 using the *hasParent* features (Figure 2: relations 8 and 9).

Table 1. The SEPHYRES pain descriptors extracted from evidence-based references related to abdominal pain

Predicate	Sample values (Object)
Location	upper abdomen in Gastric Ulcer Disease
Focus Location	Epigastrium in Gastric Ulcer Disease
Radiation	to Groin, to Genitals for kidney Stone disease
Diffusion	Localized, Widespread
Frequency	Continues, Intermittent
Chronic State	Acute, Chronic
Sharpness	Sharp, Dull
Activity Response	With Activity Increase, With Activity Decrease
Eating Relation	Relate to Eating, Not Relate to Eating
Start State	Suddenly, Progressive
Severity	Mild, Moderate, Intense, Severe
Pulsation	Pulselike, Pulseless
Aggravating	Emptional Stress, Menstrution, Cold
Alleviating	After Drink, Eating Food, Flatus
Evolution Speed	Gradually, Rapidly
Intensity	Mild, Moderate, Severe
Reach Peak Speed	Gradually, Rapidly
Duration	From 6 to 8 Weeks, Over 24 Hours, Days to Weeks
Other Sense	Burning, Colicky, Crampy, Crawling, Fullness, Heat, Icy Coldness, Numbing, Pressure, Tenderness, Tingling, Weakness, Vaguely Uncomfortable ,Onset

Another important part of the ontology was devoted to the concept of *Location* which required a complex network transforming the locality into a semantic relation. In other words, the element of semantic in this concept helps the machine perception of location. For example, the *Right Lower Quadrant (RLQ)* has a child-parent relation with the *Right Abdomen* and *Lower Abdomen*, using *hasParent* feature (Figure 2: relation 4).

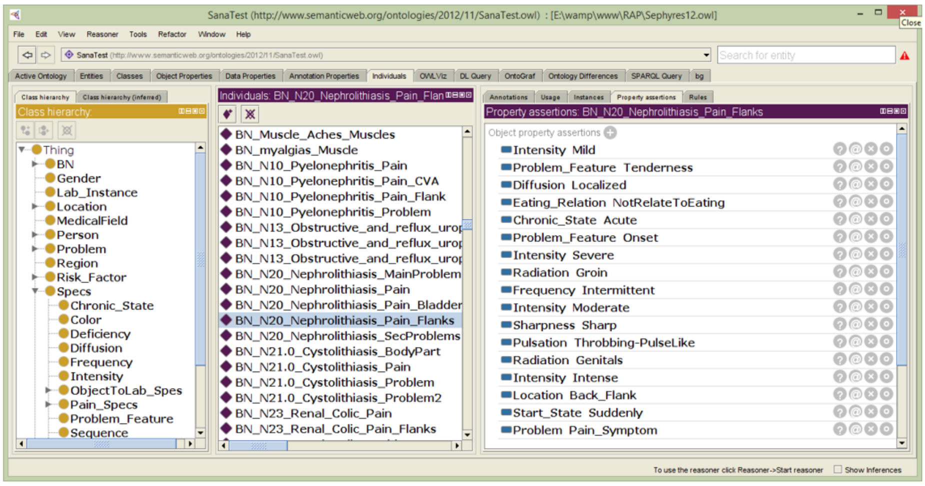


Figure 1. The semantic profile of *Kidney Stone* at SEPHYRES expressed by pain descriptors

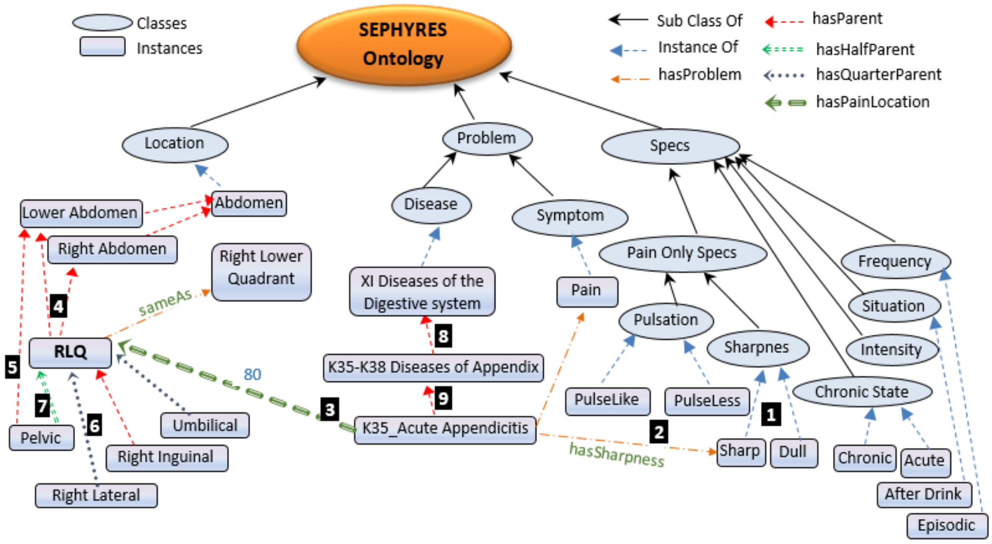


Figure 2. An excerpt of the SEPHYRES ontology

Additionally, we applied both 4-part and 9-part abdominal division standards known in medicine as well as other area-related terms which have semantic overlaps, such as *Right Lower Quadrant*, *Upper Abdomen*, and *Right Epigastric* (Figure 3). Complications appeared when there was no syntax similarity between them, such as between *Pelvic* and *Right Lower Quadrant* (*RLQ*). In that case, handling these problems, we applied two object properties, namely *hasHalfParent* and *hasQuarterParent*. Obviously, according to Figure 3, the *hasHalfParent* had established a relation between two concepts, *Pelvic* and *Right Lower Quadrant (RLQ)*, to realize a half (1/2) overlap, as it had done for *hasQuarterParent* (Table 2). Another example was made in Figure 2, relations of 6 and 7.

Table 2. The summarizing three kinds of parent-child relations in SEPHYRES

hasParent	hasHalfParent ~50% overlap	hasQuarterParent ~25% overlap
Pelvic *hasParent* Lower Abdomen	Pelvic *hasHalfParent* Right Lower Quadrant	Umbilical *hasQuarterParent* Left Upper Quadrant

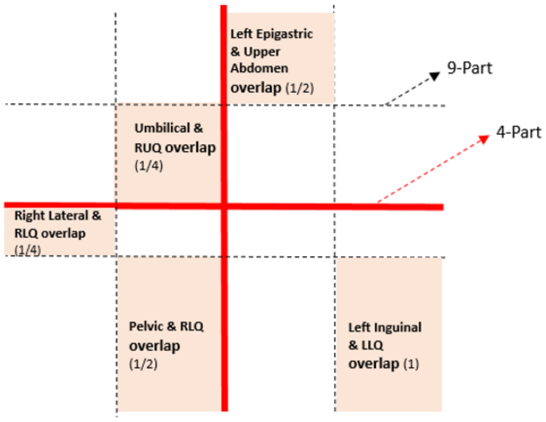


Figure 3. The 4-part and 9-part standards of abdominal pain areas and some overlaps

The Algorithmic Internals of the Semantic Reasoning Processes based on Spreading Activation Techniques

Even though general semantic reasoners are able to infer some standard defined relations, in contrast, they are too rigid to tackle domain-specific heuristics. One of the complement solutions is the weight spreading method in the graph [30] by which new facts are heuristically discovered in the knowledge base. Some past semantic recommenders successfully applied this method in the fields of digital television and tourism [31,32]. In this research, the weight spreading method was used in *Disease-Location* links due to considering the pain-only constraint. In addition, it was performed in the forms of downward and upward in the hierarchy of the ontology.

In downward reasoning, the weight of the parent was considered with a reductive factor of K in each level toward lower levels of hierarchy (Figure 4 and Table 3). Obviously, according to Table 2, the factor of K was used for *hasParent* relationships, whereas in the *hasHalfParent* and *hasQuarterParent*, it was considered as 0.5*K and 0.25 *K respectively due to less certainty (relations 1 and 2, Figure 4). As previously mentioned, these features were applied to implement pseudo-fuzzy association for the machine perception of the pain areas.

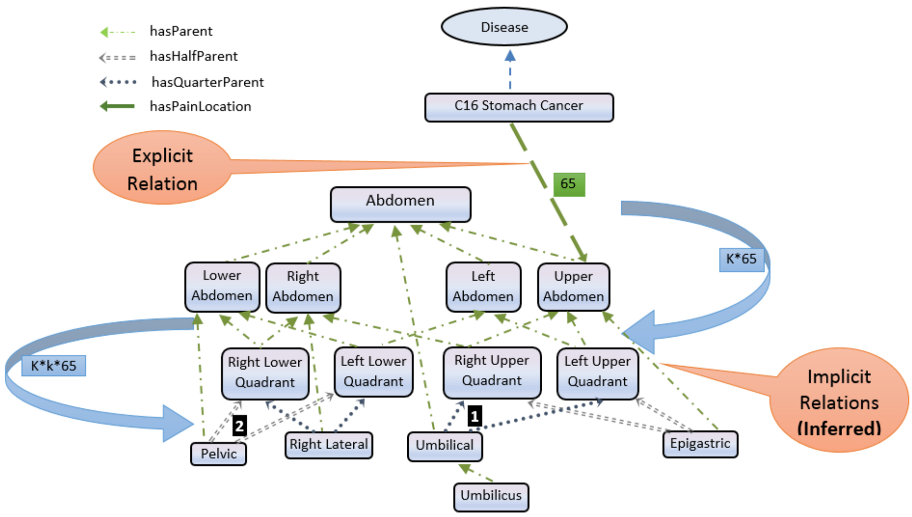


Figure 4. The downward reasoning process by weight spreading toward the children

The upward reasoning means weight spreading from children toward parents in the hierarchy (Figure 5, Table 4). To assign weight of new relations, we should not forget the reductive factor for decreasing confidence level.

Table 3. A sample of inferred triples after downward reasoning

Explicit Relations	Weight	Implicit Relations (inferred)	Weight (inferred)
Stomach Cancer *hasPainLocation* Upper Abdomen	65	Stomach Cancer *hasPainLocation* Epigastric Stomach Cancer *hasPainLocation* Left Upper Quadrant Stomach Cancer *hasPainLocation* Right Upper Quadrant Stomach Cancer *hasPainLocation* Umbilical(region) Stomach Cancer *hasPainLocation* Umbilicus(point)	k * 65 k * 65 k * 65 **0.25*k*** k*65 **k*** 0.25*k*k*65

Table 4. A sample of inferred triples after upward reasoning

Explicit Relations	Weight	Implicit Relations (inferred)	Weight (inferred)
Stomach Cancer *hasPainLocation* Epigastric	65	Stomach Cancer *hasPainLocation* Upper Abdomen Stomach Cancer *hasPainLocation* Left Upper Quadrant Stomach Cancer *hasPainLocation* Right Upper Quadrant Stomach Cancer *hasPainLocation* Right Abdomen Stomach Cancer *hasPainLocation* Left Abdomen	k * 65 **0.5*** k*65 **0.5*** k*65 **k*** 0.5*k*65 **k*** 0.5*k*65

Implementing the reasoning strategies, we needed two kinds of reasoners, a generic OWL DL reasoner and the inference engine performing weight spreading technique. With respect to relatively limited ontology of SEPHYRES and simply accessible embedded reasoner in Protégé, the Pellet reasoner was used as a generic DL reasoner practically. Additionally, we divided the application in two phases: pre-processing and run time phases, so that the lazy reasoning of Pellet was performed in the preprocessing phase and did not affect the run time queries. To implement the weight spreading, the Jena library for the Java programming language was used due to its semantic rule expressivity.

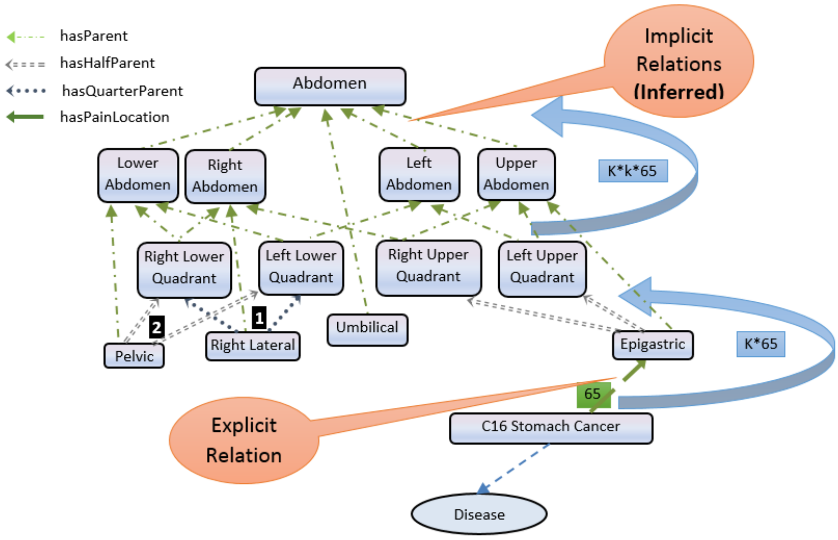


Figure 5. The upward reasoning process by weight spreading toward parent

For the SEPHYRES ontology to be more portable, we have performed the weight spreading methods using semantic rules rather than PHP codes. In Figure 6, an example of SWRL rules in Jena has been shown that performed upward and downward reasoning (k=0.2 and k=0.3 respectively) based on weight spreading techniques. Finally, these inferences developed triples up to 15 times, which provided an extended knowledge base for performing SPARQL queries that is

SPARQL Protocol and RDF Query Language (Figure 7). Here, a simplified sample query extracting diseases related to two pain features has been shown in Figure 8. Accordingly, a list of related diseases is extracted that has been ordered in terms of total weight.

```
[ParentLocation Upward:
(?bn sana:Location ?child),
(?bn rdf:type sana:DiseaseToProblemToBodyPart),
(?bn sana:hasWeight ?weight),
(?problem sana:hasProblemBN ?bn),
(?child sana:hasParent ?parent),
regex2(getName(?bn),    '(.*)(\\!+)(.*)', ?x1, ?x2,?x3),
notEqual(?x2,'!'),
regex2(getName(?bn),    '(.*)(\\$+)(.*)', ?z1, ?z2,?z3),
notEqual(?z2,'$'),
regex2(getName(?parent), '(.*)(\\#+)(.*)', ?m1, ?m2,?m3),
uriConcat(?bn,'~1',?m3,?newNode),
product(?weight,0.2,?newWeight),
noValue(?newNode rdf:type owl:NamedIndividual)
->  (?newNode rdf:type owl:NamedIndividual),(?newNode rdf:type sana:DiseaseToProblemToBodyPart),
    (?newNode sana:Location ?parent),(?newNode sana:hasWeight ?newWeight),(?problem sana:hasProblemBN ?newNode)]
-----------------------------------------------------------------------------------------------------------
[ParentLocation Downward:
(?bn sana:Location ?parent),
(?bn rdf:type sana:DiseaseToProblemToBodyPart),
(?bn sana:hasWeight ?weight),
(?child sana:hasParent ?parent),
(?problem sana:hasProblemBN ?bn),
regex2(getName(?bn),    '(.*)(\\~+)(.*)', ?x1, ?x2,?x3),
notEqual(?x2,'~'),
regex2(getName(?bn),    '(.*)(\\$+)(.*)', ?z1, ?z2,?z3),
notEqual(?z2,'$'),
regex2(getName(?child), '(.*)(\\#+)(.*)', ?m1, ?m2,?m3),
uriConcat(?bn,'!1',?m3,?newNode),
product(?weight,0.3,?newWeight),
noValue(?newNode rdf:type owl:NamedIndividual)
->  (?newNode rdf:type owl:NamedIndividual),(?newNode rdf:type sana:DiseaseToProblemToBodyPart)
    (?newNode sana:Location ?child),(?newNode sana:hasWeight ?newWeight),(?problem sana:hasProblemBN ?newNode)]
```

Figure 6. The semantic SWRL rules in Jena library related to upward and downward reasoning

Figure 7. The Preprocessing steps

```
SELECT distinct ?disease ?predicate ?weight
WHERE {
      ?disease <rdf:type> <sana:Disease>.
      ?disease <sana:hasProblemBN> ?bn.
      ?disease <sana:hasPrevalenceWeight> ?prevalence.
      ?bn <sana:hasWeight> ?weight.
      ?bn ?predicate ?object.Filter(?object=<sana:Pain> || ?object=<sana:Epigastric> ... )
      }
```

Figure 8. The simplified SPARQL query extracting diseases related to signs and symptoms

The Evaluation Method of SEPHYRES

The SEPHYRES evaluation was carried out using two methods. Firstly, it has been evaluated based on the differential diagnosis pattern in medical science. The differential diagnoses is likely the recall metric in the system-oriented evaluation of the information retrieval systems [33] so that the accurate functionality of SEPHYRES engine means that there is the correct diagnosis among the results, as has been done in research Semigran et al. (2015) [34]. Furthermore, to calculate precision and recall, the test were performed in 14 steps (step1: 1 top results, …, step 14: 14 top results), like the study of Semigran et al. (2015) [34]. Also, the average of results of twenty test cases is considered for each precision and recall at each step.

Secondly, the SEPHYRES engine was comparatively evaluated against the other symptom checkers. In this regard, the study of Semigran et al. (2015) has investigated 23 online symptom checkers and has demonstrated that the best symptom checkers has an accuracy level about 84% of top 20 results related to Isabel engine [34]. Hence, we comparatively evaluated the semantic pseudo-diagnostic engine of SEPHYRES against the Isabel powerful engine. Exactly, we used the online system patient.info, the trusted source of health information for both patients and professionals with more than 18 million visits a month that has been powered by Isabel engine [35].

To collect test cases as sample size, after searching term "Abdominal Pain", we randomly selected top twenty cases provided that their correct diagnoses were in our domain of interest, mostly from MEDSCAPE and PubMed databases (Appendix 1). After that, the concepts associated with pain descriptors were extracted from each test case and entered in both SEPHYRES and Isabel user interfaces (Figure 9).

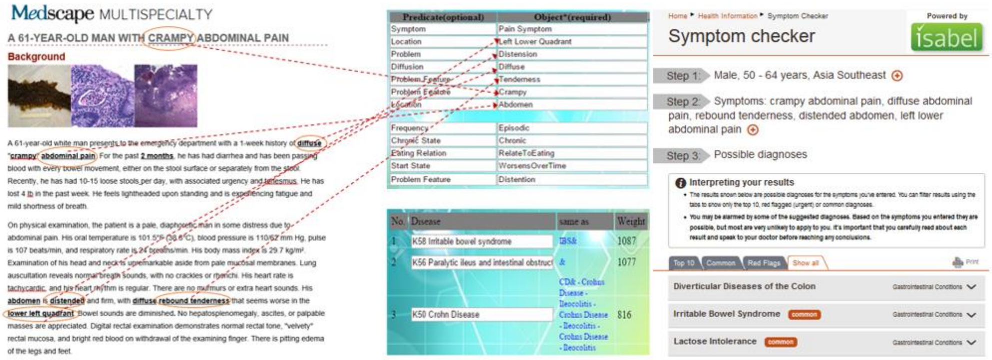


Figure 9. The comparative evaluation process

Furthermore, to perform significance test of results, respecting to ordinal parameters and dependent twenty samples, the Wilcoxon signed-rank test was applied in SPSS.

Results and Discussion

To perform the first system-oriented evaluation method of SEPHYRES, the averaged results of precision and recall in 14 steps has been shown in Table 5 and Figure 10. As mentioned before, in first step, the 1 top result of outputs was considered and as the same way, in step 14, the 14 top results were considered as SEPHYRES outputs.

Table 5. The system-oriented measures of SEPHYRES

Considered Results / Step	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Precision	0.3	0.175	0.15	0.1125	0.1	.0833	0.786	0.0813	0.0778	0.075	0.0682	0.0625	0.0577	0.0607
Recall	**0.3**	**0.35**	**0.45**	**0.45**	**0.5**	**0.5**	**0.55**	**0.65**	**0.7**	**0.75**	**0.75**	**0.75**	**0.75**	**0.85**

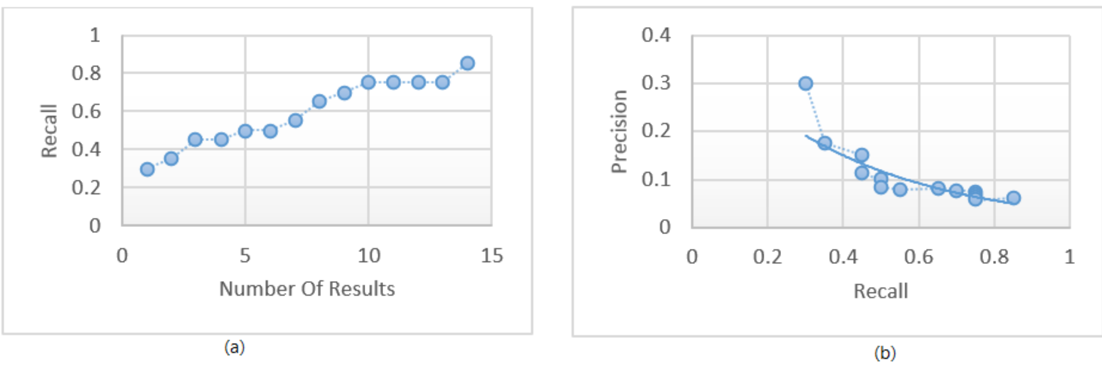
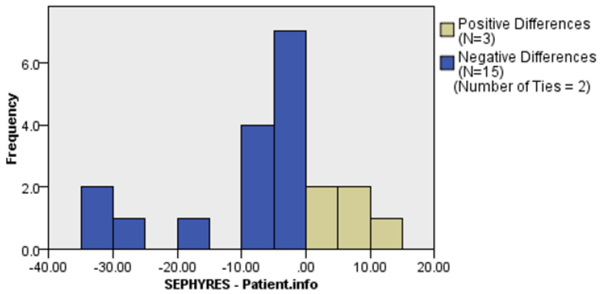


Figure 10. (a) The recall values in terms of differential diagnoses. **(b)** The precision/recall chart

Furthermore, the results of comparing SEPHYRES against Isabel engine (Patient.info) have been noted in Table 6. After that, the Wilcoxon signed-rank test in SPSS was applied with significance level and confidence level equal 0.05 and 0.95 respectively. Consequently, the null hypothesis was rejected, so the difference between ranks was highly significant (P= 0.016) (Figure 11).

Table 6. The ranks of accurate diagnoses in both systems(the max. rank of 38 for failed queries)

Test Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Patient.info (Isabel)	13	9	38	38	38	1	38	10	2	3	3	2	22	1	15	28	5	38	3	12
SEPHYRES	3	9	18	36	5	14	37	3	1	8	1	1	14	1	10	1	1	7	8	2



Total N	20
Test Statistic	30.000
Standard Error	22.935
Standardized Test Statistic	-2.420
Asymptotic Sig. (2-sided test)	.016

Figure 11. The related-samples wilcoxon signed-rank test

Above all, the results presented in the recall graph (Figure 10) showed that if the system was adjusted to only ten results as differential diagnoses, the accuracy level was equal to 75%. Even though all signs and symptoms have not been applied yet, the result was satisfactory for this study. Nevertheless, the fact that the number of triples increased up to 15 times after reasoning stages, was a key challenge for SEPHYRES development, as it has been in other semantic-enabled applications. Of course, all the reasoning strategies were done in pre-processing phase, so that there was no run-time and real-time requirements and this could help with concerns related to time execution.

In addition, another limitation of this study was the fact that the disease profiling method was laboratorial so the results shown will not be able to show its applicability in the real world. For example, respect to decision aid systems, when describing pain characteristics, patients fail to use the divisions and official medical terminology method. So, perhaps using an interactive graphical interface and the natural language-based engine could improve the utility of the results of the study as well as the design model quality.

Moreover, improving the quality of medical care, several studies and projects have developed patient information in the form of electronic health record (EHR). Also, semantic representation of EHR was used to integrate health information from the various sources as well as the medical coding system [36,37]. In this way, the SEPHYRES could exploit EHR information, including but not limited to medical history, diagnoses, medications, test results, allergies and symptoms. However, in this version of SEPHYRES, we preferred to manually enter the signs and symptoms in the SEPHYRES interface, as is done in symptom checker systems.

As previously mentioned, the SEPHYRES applied the complement type of reasoners due to tackle general semantic reasoner deficiencies, specially domain-specific heuristics. Obviously, it applied weight spreading techniques in the forms of downward and upward in the hierarchy of the ontology. Additionally, to complete the argument, it should be noted to another type of reasoning called the sibling reasoning in which weights are spread toward sibling concepts in the hierarchy. Conceptually, if a disease is apparent in multiple children of a parent, it would be related to the remaining children [38]. Furthermore, he weights of new inferred nodes were considered as less weights. Some previous studies used a reductive factor for weights of the children in the downward method, considering less confidence level [38] and in upward method, due to relating several children, some papers have used the averaging amount among weights of children for weight of inferred parent node (pointing zero for children which are not linked) [38,39]. Even though, in this research, these techniques were only applied in the *Disease-Location* links due to considering pain-only constraint. However, the weight spreading could be used in *Disease-Problem* links too which is ignored in this research. For example, the relation between *Kidney Stone* and *Dysuria* can be spread to concept *Urinary Tract Symptoms*, a more general concept.

About the reasoner selection, according to some benchmark studies, there was no reasoner performing all kinds of reasoning aspects, even though they found that the Pellet reasoner could be finished on ontologies which been timed out or failed by others such as FaCT++. Consequently, they suggested that the Pellet reasoner is more resilient, practical and popular to non-trivial ontologies due to widely accessible interfaces and extended reasoning services [40-42]. However, despite the advantages, the scalability was not satisfactory, as has been mentioned in some other studies [40,41].

To apply SWRL rules performing spreading techniques, because of the fact that the syntax of the SWRL rules in the Protégé was less expressive, instead, we used the Jena library for the Java programming language. It allowed to define complex SWRL rules in a separate file, similarly, another research also combined Pellet reasoner and SWRL Jena rule reasoner as a new reasoner called DLEJena [43].

Finally, planning to compare SEPHYRES against other similar applications, the study of Semigran et al. (2015) was considered. It had investigated 23 online symptom checkers and had demonstrated that the best symptom checkers has an accuracy level about 84% of top 20 results related to Isabel engine [31], so the SEPHYRES was compared against it practically.

Proceeding with this research, we are going to exploit the SEPHYRES as an intelligent infrastructure to a more comprehensive diagnostic model. In the upper layers of this model other diagnostic modules can be established. For example, a module that receives some pain attributes such as pain location, pain focus location, pain radiation area through a visual fuzzy-enabled user interface and delivers RDF triples to the semantic infrastructure layer due to further semantic inference. Another example can be made of a fuzzy-enabled laboratory finding module that after executing image processing techniques on laboratory textual test, it delivers the laboratory signs in the form of RDF triples to the semantic infrastructure layer due to adding into the diagnostic query. Additionally, it is recommended that future researchers upgrade SEPHYRES engine by turning it into a real diagnostic engine using a limited selection of disease profiles.

Conclusion

In this paper, a clinical decision support solution has been presented in the form of the symptom checker under the title "SEPHYRES". This was achieved using semantic-enabled strategies, evidence-based medical references and weight spreading methods due to applying in either decision aid or professional systems performing medical diagnosis. Using common medical terms with the variant generality level and semantic pain descriptors besides two types of reasoners, we prepared the pseudo-fuzzy modeling as well as high-level semantic expressiveness. The achieved results indicated that this method was capable to tackle complex medical concepts and enhance medical diagnosis models.

Conflict of Interest

The authors declare that they have no conflict of interest.

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