Semantic Overlapping in Translational Bioinformatics Applied to the Matching between Clinical Trial Eligibility Criteria and Patient Needs

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Keywords: Clinical Trials, Eligibility Criteria, OWL/SWR.

Abstract: Software technologies play an important role in defining clinical trials, their eligibility criteria and recruitment process, in which patient enrol to a trial if they satisfy eligibility criteria. In this research we address the problem of semantic overlapping between eligibility criteria and patient needs through a software architectural model which houses a specific computational model based on reasoning upon the overlapping semantics. The architectural model is deployed using semantic technologies in order to explore the meaning of the relationships between trials, eligibility criteria and patient needs. The novelty is in the reusability and thus converting of the existing conceptual models on deriving eligibility criteria, available in literature, into the proposed OWL model, which can serve any clinical trial and requirements patients may have. This paper is written by computer scientists interested in manipulating semantics of data through computational models using modern software technologies. It serves as an invitation to researchers from the biomedical and translational informatics to debate the future of software support in managing clinical trials.

1 INTRODUCTION

The complex problem of designing Clinical Trials (CT) and systemizing patient eligibility, using software technologies, has been in the focus of research interest for more than a decade (Kopcke and Prokosch, 2014), (Ross et al., 2010) (Cimino et al., 2007) (Shankar et al., 2006). The work in this field is vast and has resulted in numerous solutions, which address the complexity in defining the purpose of CT and patents clinical and personal needs. Unfortunately, in the third decade of the 21st century, we still do not have a powerful software solution, which could bring us closer to resolving the problem and creating an universal environment for pharmaceuticals, medical professionals and patients, to address the problem in its entirety. The reasons are numerous, but we would like to draw the reader's attention to the following three facts.

First, creating CT and matching their eligibility criteria (ET) to patient needs, through software technologies, is a transdisciplinary work. It would require a high level of collaboration across many disciplines. However, if we expect that software technologies, which constantly offer innovations in the way we collect and process data, can help in resolving this problem, then we should put computer scientists in charge of a new computational model for one important reason. We should avoid using old-fashioned software solutions, which proved to have success in the past and think that they will bring progress in future and in this particular problem domain. Computer science, software engineering and computational modelling are fast moving disciplines, which require constant engagement if we wish to use them properly and successfully in any problem domain. We believe that processing the data generated form bioscience research needs new computational models created by computer scientists and thus it is worthwhile to investigate if this could help to create an universal solution for matching the semantic between CT and their ET and patent needs.

Second, the research on creating and running CT, using software technologies, is dispersed and scattered. After 10 years, we may say that it is confined to the existence of numerous repositories, including ontologies and vocabulary of terms, generated through natural language processing (NLP) (Elkin et al., 2016), for the purpose of storing knowledge and manipulating it, mostly through

Juric, R., Williams, E. and Kim, I.
Semantic Overlapping in Translational Bioinformatics Applied to the Matching between Clinical Trial Eligibility Criteria and Patient Needs.
DOI: 10.5220/0009406503150322
In *Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2020) - Volume 3: BIOINFORMATICS*, pages 315-322
ISBN: 978-989-758-398-8; ISSN: 2184-4305

queries (Baader t al., 2018). This is far from expectations we have in software engineering, where software application manage relevant data and computations, based on a specifically designed computational model for this problem domain. None of them exist in published work.

Third, the vast knowledge generated from biomedical and pharmacological sciences is expanding fast and it is almost impossible to bridge the gap between these fields and clinical practices. In spite of talking about translational informatics, since the late 2000s (Payne et al., 2015), (Butte, 2008), (Tsafnat et al., 2013) and pushing software technologies into this field to help to bridge the gap between biomedicine and clinical practices, we have not even started thinking on how these new advances in biomedical science may have an impact on CT. We can not resolve this problem by keeping on creating new knowledge-bases, new ontologies, new database or similar repositories, and performing queries upon them. This will not take us forward. What we need are new computational models, which would assist in collecting and managing ***the semantic*** of relevant and shared data across these complex research fields (Almami et al., 2016), (Juric et al., 2018), (Juric, 2019). New computational models can perform a miracle in collecting and managing the semantic of data and their matching in order to answer any question we may have across this complex, but semantically rich research field.

In order to understand our contribution, it is important to note that we do NOT wish to

- propose a new “software” for dealing with the problem of creating CT and finding eligible patients,
- address a fraction or a slice of this problem by going into details on how we would implement it using software technologies and
- create a new repository of knowledge (called a knowledge-base in the past), controlled vocabularies often associated with ontologies, and add them to the existing pool of sources available in this problem domain.

What we wish to promote in this paper is a generic computational model, based on the reasoning upon the semantic of requirements in CT and patient’s eligibility criteria. The ultimate goal would be to exploit the semantic overlapping between the two and define, through the reasoning process, either a CT, or ET or patient’s best possible match with the two in particular circumstances.

Software engineering solutions, which would support data sharing across disciplines of pharmaceuticals, biomedical sciences and clinical practices, including patient clinical data, in order to create and manage CT, would require a generic software architectural model (Tarabi and Juric, 2018) ((Juric, 2020). 13,14). It is essential in specifying sources of shared data and computational models for identifying the best matching between a CT and patient needs.

For proving the concept, we illustrate our proposal by using Semantic Web Technology (SWT) and its languages OWL/SWRL for defining the reasoning process in which data is shared from biomedical research published in the literature.

The paper is organized as follows. In section 2 we specify why and how the SWT and its languages can be used in this problem domain. In section 3 we highlight similar work which influenced this research. The proposal of the software architectural model is in section 4 and section 5 illustrates an example of an ad-hoc creation of an OWL model using existing knowledge from conceptual modelling of Ct and ET available in the literature. In section 6 we outline the deployment of the proposal and in the last section we debate results of this research and comment on future steps in the last section.

2 WHY SWT

SWT and its layered cake has widely been used, since its standardisation in 2004, for interpreting the meaning of data available on the Internet. In biomedical science OWL has been used for building common ontologies and controlled vocabularies across domains, enriched with reasoning rules in SWRL for bringing inference and more semantics to biomedical repositories. Knowledge presentation with SWRL enabled OWL ontologies is extremely powerful. It is description logic which allows definition OWL classes and their constraints, in the form of object and data properties, which enable the definition of all concept and relationships between them. This leads to numerous possibilities of

(i) using and exploiting SWRL enabled OWL ontologies in many problem domains, and outside the web (Juric, 2016)
(ii) creating OWL ontologies which are not controlled *vocabularies.* They may still represent relevant knowledge, but they will never become knowledge-bases
(iii) reasoning upon the content of oWL ontologies using SWRL rule for either strengthening its knowledge or adding inference to it.

If we wished to avoid building knowledge bases and still use SWRL enabled OWL ontologies for manipulating the semantic of data we process, then computational models, which house SWRL enabled reasoning upon OWL concepts can bring inference without having complex knowledge systems in the background or using AI algorithms for creating and manipulating inference. In this paper we talk about software engineering applications of the SWT technology which is OUTSIDE formal ontologies and knowledge-bases and as such, might be a promisingfstart for addressing the problem of CT /ET and paitent needs.

We would like to use SWRL enabled OWL ontologies in order to define

a) the semantic specific for defining and manipulating EC for CT,
b) the way of converting the semantic of existing solutions, which use different method/technologies for defining EC into an OWL model and
c) semantic overlapping between CT and their EC and patient needs.

This semantic overlapping would create a cradle for reasoning upon OWL concepts, which gives a semantically rich pool of all possible combinations of ET and patient needs. The power of reasoning, secured through semantics overlapping between relevant OWL concepts, infers either new individuals or constraints in OWL through SWRL rules.

For readers interested in exploring the ways SWT helps in the creation and manipulation of semantic overlapping in biomedicine, we suggest reading our previous publications (Almami et al., 2017), (Juric et al., 2018), (Juric, 2019), (Juric 2016).

3 RELATED WORK

The section illustrates how scattered the research on CT is and how it is impossible to find a thread between the publications.

(Shankar et al., 2006) propose a knowledge-based framework, named Epoch, and tailored it to the Immune Tolerance Network research consortium in order to cover a spectrum of clinical trials management activities, by tracking study participants and biological specimens processed in trial laboratories. The role of developed ontologies in their software architectural model is to conceptualize knowledge in the relevant CT domain. In (Mucke et al., 2009) a semantic model for representing items in CT is proposed. Its purpose is to move away from known database technologies and model the semantic of the problem domain differently. However, their semantic model does not feed any software application and reasoning is not introduced for decision making relevant for CT. In (Besana et al., 2010) the SWT is used for CT recruitment and their ontology contains data from patient heath records in order to verify eligibility of patients for CT. A consumer centric tool from (Pate et al., 2015), named TrailX, which matches patients to CT uses numerous sources of data, such as patient health records, Google health and Microsoft Health Vault. However, the matching of patient information and CT is done using Columbus Matching technology, which relies on NLP with the assistance of the Unified Medical Language System. In (Damen et al., 2013) we can read about the PASTEL platform which assists in CT recruitment, by using the semantic generated through topic maps and in (Dameron, 2013) the authors show an OWL model which systemizes the ET with partially known information. The authors of (Lee et al., 2010) introduce the MindTrial system which facilitates specific matches between clinical trial criteria and patient volunteers, using a set of ontologies and semantic queries. In (Elkin et al., 2016) we can read how local clinical trials can be enhanced with ontologies and Internet of Things, with assistance of technologies such as natural language processing.

It is obvious from the paragraph above that ontologies are used for a variety of purposes and no ontological model, generated in one study/project has been used in another. Furthermore, the power of logic reasoning with SWRL, suitable for ontology matching, has not been exploited at all, and therefore if there were a need for matching the semantic of CT to patient eligibilities, some other technologies are used. Finally, emantic overlapping, which is essential in logic inference, enabled with SWT, is also not used. This shows that the SWT has not been completely utilized in this problem domain, except for creating or retrieving knowledge-bases.

The inference, secured by the semantic overlapping between OWL concepts, are not to be confused with the term “reuse and overlapping” in biomedical science, as described in (Maulik et al., 2017). In the SWT world, the semantic overlapping is a computational mechanism which secures reasoning and inference as in (Almami et al., 2016), (Juric et al., 2018), (Juric, 2019), and therefore its use might be associated to semantic mapping evolution known in biomedical ontologies, as described in (Dos Res et al., 2014).

4 SOFTWARE ARCHITECTURE

If we wish to propose a solution which would address problems with CT as described in the introduction, and use the SWT which would infer the matching between CT/EC and patient needs, Figure 1 shows the essential software architectural (SA) model. Software components in Figure 1 are technology specific, i.e. we can use Java Servlet and Enterprise Java beans technology in order to create a computational model from the proposed architecture.

Therefore the applications generated from the SA in Figure 1 would have a computational model consisting of two types of computations:

a) typical transactional processing with SQL databases in the background (left part in Fig. 1)
b) reasoning with OWL concepts through SWRL in order to perform matching of CL/EC and patients needs (right part in Fig. 1).

These types of computations are not very common, but they are feasible and they do have applications across many problem domains (Juric, 2016). For readers interested in software engineering aspects of the implementations of applications from the software architecture in Figure 1, we suggest sources similar to (Patadia et al., 2011), (Shojanoori, 2013) (Tarabi and Juric, 2018).

SA In Figure 1 is component based and layered, and allows a synergy between computations with SQL in Java environments and reasoning with SWRL in the OWL environment though OWL-API. Obviously, UI.EC+CT interface (left part of the SA model) would lead us towards the categorization of EC and CT, which could be converted into ontological concepts to secure reasoning with SWRL for the matching with patient needs. (right part of the SA model) Semantic Overlapping between CT/EC and patient needs.

There is one important aspect of the proposed SA. It will generate a software application suitable for patients. The ***CATEGORISATION EC+CT*** computations (servlet, left side of Figure 1)) would collect relevant information from Biomedical Sources and perform the categorisation of EC for each CT in order to create an environment for ontological matching. However, patient requests and needs have already been categorised through the ***PERFORM CTM*** computations (servlet, right side of Figure 1) and asserted in the application though ***UI.CTM*** interface (Kataria and Juric, 2014). However, we could have turned the SA around and start with categorisation of PATIENTS requests (left side of Figure 1) and create an environment for matching with EC for all CT, which have already been categorised and enter into the ***PERFORM CTM*** computations (right part of Figure 1.) The SA and computations remain the same, only data and entry mechanisms with UI change. To summarise, the SA form Figure 1 creates software application, for pharmaceutics/ clinicians/ patients, in order to secure the best possible definition of eligibility criteria and patient needs.

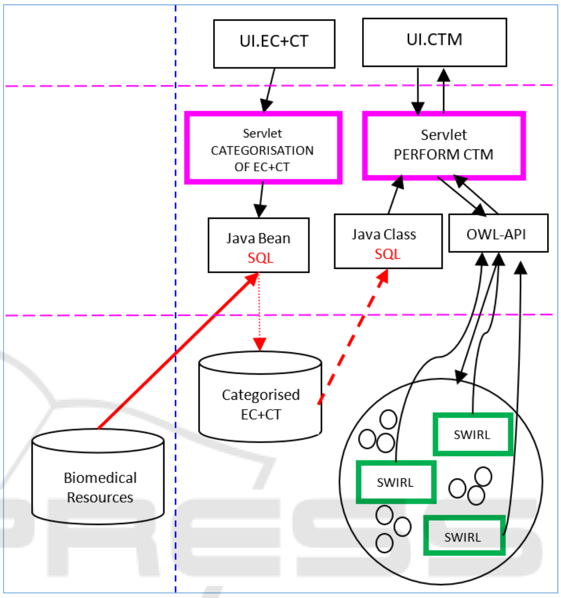

Figure 1: Software Architecture for enabling ontological matching (CTM stands for Clinical Trial Matching).

4.1 Semantics of Biomedical Resources

Repository named ***Biomedical Resources*** from Figure 1 is an abstract repository illustrated in Figure 2. There exists a vast biomedical knowledge in various formats, available through a variety of software solutions such as

(i) Public databases which exist across Biomedical Informatics, including potential repositories where various CT and their EC are advertised. We should also look at sources such as UMLS (UMLS) and SemDB (Kilicoglu, 2012) which describe biomedical semantics and co-relation between therapeutic drugs and diseases.
(ii) Numerous data sets which are generated from biomedical experiments, and some of them might be publically available. They are often associated with the computational analytics and could be used with popular leaning and predictive technologies;
(iii) Biomedical data which available on the web / social media / dedicated web applications, for the

purpose of disseminating advances in biomedical research through either publications or social media means (blogs, twitter, Facebook).

(i)-(iii) are collated in the red box in Figure 2. It is important to note that ***Extraction of Biom. DATA*** does not mean pure data retrieval. It should include both: extraction of relevant data and their semantics at the same time (Kataria and Juric, 2010), (Saaidi et al., 2010).

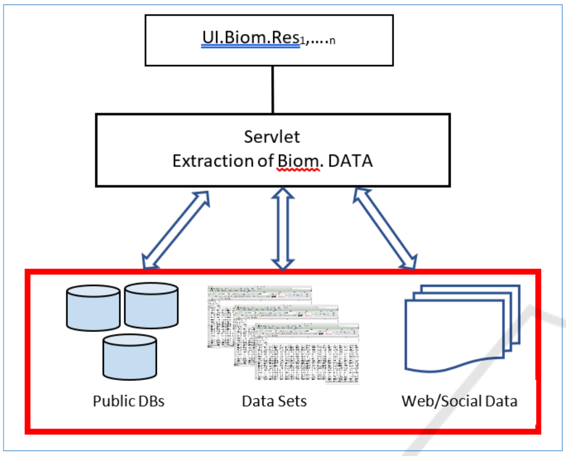

Figure 2: Resources of Biomedical Data.

Figure 2 can also be implemented as a software application using java technologies (Kataria and Juric, 2010), but the creation of Biomedical Resources repository from Figure 1, outlined in Figure 2, is outside the scope of this work. It would depend on each particular CT, and would vary between suitable sources. The options on reusing biomedical knowledge across a variety of repositories must be open for future work.

In the study we show an example of using public databases focusing on CT, but we do not exclude data collected from publications in which categorisation of EC for a particular CT is debated.

4.2 OWL Model for CT/ET

Figure 3 shows a potential benefit of using the semantic from UMLS in order to categorise biomedical knowledge relevant to CT and convert it into OWL concepts. Sematic Predications (Ahlers et al., 20107), (Zhang, 2014), (Machado, 2015) have already been exploited in biomedical science and could be an excellent starting point for categorizing semantic of CT/EC and patient needs.

In Figure 3 we show the pathway from the predications in the form of triplets:

(subject, predication, object)

where we can define the relationships between subjects and objects through predications. It is important to note, that a set of triplets: **(s,p,o)** could be directly converted into RDF triplets and consequently create an ontological model according to the SWT stack.

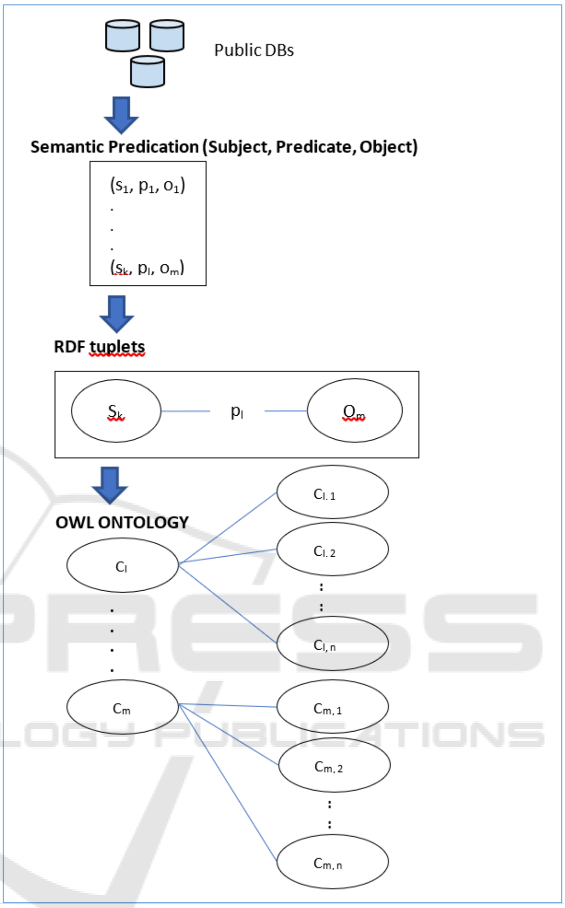

Figure 3: From Triplets to OWL Model.

Set $\{C_1,\ldots C_n\}$ from Figure 3 are OWL classes, converted from subjects and objects of semantic predications. Predicates are converted into OWL constraints, such as object properties. Ontological hierarchies, shown at the bottom part of Figure 3 are the main OWL concepts. Potential object properties might be of either the ***"is-a"*** or **"has"** format or any other type of relationship which may have existed between subject and object in definition of CT. In this particular example, where we need to define a CT through its EC, ***"has"*** object property is more suitable for explaining the semantic of a CT through EC

In Figure 3 C_i denotes a CT and a set of $\{O_{1,1},\ldots O_{1,n}\}$ denote a categorised EC for that C_i .

If we wish to perform semantic matching between CT/ET and patient needs then ontological structures based on triplets (s,p,o) should be available for describing patient requirements for CT. Therefore Fig. 4 mirrors Figure 3: $\boldsymbol{P_1}$ denotes a patient and a set of $\{R_{1,1},\ldots R_{1,n}\}$ denote his/her requirements for a CT.

The similarity between Fig. 3 and 4 means that if we wish to match patient requests with CT/EC then we should use similar categorisation for both: $\boldsymbol{C_i}$ classes are described though $\boldsymbol{\{O_{1,1},\ldots O_{1,n}\}}$ and $\boldsymbol{P_j}$ classes though $\boldsymbol{\{R_{1,1},\ldots R_{1,n}\}}$.

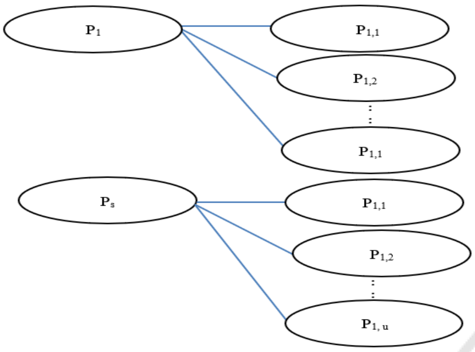

Figure 4: OWL Model for Patient Requirements.

5 REASONING PROCESS

We illustrate the way of identifying semantic triplets for categorizing the complexity of EC in CL as described in (Ross et al., 2010). They have a specific categorization of criteria (EC), affected by complex relationships between disease diagnosis, clinical phenotypes, which in turn are refined by their severity, associated complications or response to a specific treatment. We use a data sample from (Ross et al., 2010) in order to illustrate that existing knowledge (publication) is reusable, i.e. their categorisation of EC could b entered into our OWL model as individuals and properties, as long as we can find semantic triplets (s,p,o).

(p1, diagnosed, disease1)
(p1,exludes, disease2)
(lab-tests, contains-normal-values, p1)
(disease2, treated-by, antibiotics)
(treatment2, unsuccessful-for, p1)
(visits-repeated, required-for, tretament1)
(p1, refuses, repeated visits)

Figure 5: A selection of triplets for OWL model.

A set of triplets could relate symptoms and disease, treatment/intervention for the disease, behaviour of a patient, clinical content related to the disease, temporal criteria and similar. Predications are available and range from "caused-by", "described-with" and "diagnosed-by", to "without", "at least n times per week", "at hospital discharge" and "contains-normal-values".

Figure 5 shows a selection of triplets, where ***p1*** is an object/subject representing a patient. Predicates are defined as object properties between individuals of classes. Individuals of these classes are subject/objects defined in these triplets.

If we connect all individuals of these OWL classes (subject/objects) with appropriate object properties derived from predicates, we could run SWRL reasoning upon such classes and create an answer if a particular patient would be eligible for a CL. The decision will depend on the reasoning process in which individual(s) of the PATIENT class will be eligible for a CT only if the reasoning with SWRL confirms that the particular patient(s) have the same object properties (predicates) defined between him/her (them) and eligibility of a clinical trial (subjects and objects in triplets).

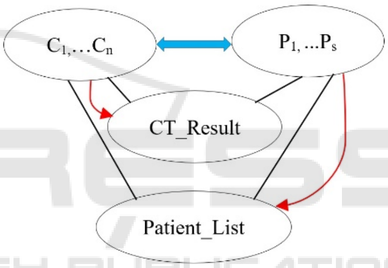

Figure 6: The Reasoning Process.

The reasoning process from Fig 6 is self explanatory. Blue arrow specifies definition of object properties between $\boldsymbol{C_i}$ and $\boldsymbol{P_j}$ classes, black lines indicate classes involved in reasoning and red one-directional arrows show inference: only suitable CT are moved into the CT_Result class for a patient and only patients which satisfy the EC would be moved to Patient_List class. The reasoning process is programed through the following SWRL rules.

CLINICAL_TRIAL (?, D) and has_EC1(?D, EC1) and has_ECn (?D,ECn) - > CT_Result (?D).
PATIENT (?, XXX) and has_Req1(?XXX, Req1) and has_Rwqn (?XXX,Reqn) - > PATIENT_LIST (?XXX).

where EC_1, ... ECn and Req_1, ... Req_s are predicates (object properties) identified in triplets from the above and D/XXX are variable for patient/CT.

The message from the OWL model and reasoning with SWRL, based on semantic overlapping between ET for a CT and patient requirements, is that the semantic overlapping secures an almost instant answers to the questions we may have. We filtered all the patients (?D) which satisfy ET for a CT for SWRL rule 1. SWRL rule 2 answers this question: Which CT are available for a particular patient? The computational model remains the same, and SWRL rule uses the same object properties (predicates). The only difference would be in the format of the rule:

6 CONCLUSIONS

This paper is written from the computer science and software engineering perspectives and therefore should show concepts upon which we can build an application for finding semantic overlapping between CT and patient needs. Data sharing and computations upon biomedical and clinical data will reside within one dedicated light-weight software application. It should be, suitable for running in mobile and wireless environments, where updates and constant changes are welcome and not seen as obstacles. The application will NOT build an excessive new knowledge base, but will reuse existing biomedical knowledge, which has been growing rapidly on a daily basis and add value to the way we conduct CT.

This study is one of many attempts of using the SWT and ontological modelling for the purpose of creating semantic overlapping for matching of CT and their EC with patient needs. The OWL model and its constraints, as introduced in (Juric, 2019) can fit the SA model from Figure 1 and individuals needed for the OWL model, which would secure reasoning, could be taken from any of the available sources which document information on CT. If we could represent this knowledge in the form of semantic predications (triplets), than the implementation of the application, defined by Figures 1,2 and 3 would be straight forward. In cases when we do not have structures of triplets, the categorization of data for CT and EC and patient needs should be performed with OWL principles in mind. SWRL enabled OWL ontologies are very powerful and they can really make a difference in this problem domain, considering that the computational model and the SA allow software solutions which could run on modern environments, including Android. Therefore, from the computational science and software engineering perspectives, there should be no obstacles in commercializing the proposal.

However, this study may send message to researchers from the biomedical field. Repositories which may contribute towards Biomedical Resources in Figure 1 should be available, accessible and shared, but never integrated or changed due to their role in creating semantic matching. We should leave their manipulation to computer scientists who can make this proposal operational and commercial. This implies that variations of possible implementations of the SA from Figure 1 would keep up with advances in software technologies, as long as we can interpret the semantic overlapping between CT and ET with patient needs.

We are currently looking at the possibilities of using biomedical data sets for running predictive analytics with learning technologies in order to predict possible predications between various ranges of subjects and objects, applicable to clinical trials. The proposed computational model remains the same.

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