Adding Value to Translational Informatics through the Semantic Management of Drug to Drug Interaction

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Abstract: Translational informatics, aimed at bridging the gap between biomedical scientific knowledge and clinical practice has changed the way we use rapidly growing information from biomedical research and bring it closer to clinical practice. Software technologies play an important role in this process, particularly if they help in understanding and manipulating the meaning of data and information generated in biomedical research and translate it into semantic suitable for clinical practice. In this paper, we propose software architectural and conceptual computational models, which use semantic technologies in order to explore the meaning of the relationships between drugs when they interact in clinical practice. The data about drug to drug interactions, available from biomedical research, is reusable in instances where they are decisive factors in drug administration in clinical practice. We explore the power of semantic web technologies and SWRL enabled OWL ontologies to demonstrate the applicability and feasibility of our proposal in translational informatics.

1 INTRODUCTION

This research explores the personalization of patient medication lists in terms of finding potential drug interactions, because of the combination of prescribed drugs. We are interested in *drug to drug interactions* (DDI) which may appear if the therapeutic effect of one drug changes because of the presence of another. This problem is not easy to resolve for many reasons. One of them is that the solution might require a synergy of knowledge and expertise across the disciplines of biomedical science, clinical practice and computer science. Modern medicine strives for personalization, hoping to include gender differences and the clinical physiological effect drugs may have on an individual patient, because every patient is different. However, we still do not perform clinical trials which take this personalization into account. Furthermore, the advances of knowledge discoveries in biomedical science, are not fast-forwarded to clinical practice and the gap between the two is widening. There are examples where translational bioinformatics (Tsafnat et al., 2013) may address the problem, but a long-term solution which addresses a) data sharing between biomedical science and clinical practice and b) personalization of patient medication lists to avoid potential DDI, might be the only way forward. However, a) and b) above are interwoven. If we share the data between biomedical research and clinical practice, we will find more about DDI. In order to align personalized medication lists, for the purpose of eliminating potential DDI between the drugs in the list, we would need more than just data sharing. We would need to understand the semantic relationship between clinical recommendations, i.e. prescribed drugs, drug therapeutic targets (protein/genes) and related biological functions, in the context relevant to a patient. If there is another drug, which shares the same or similar therapeutic target, intentionally or un-intentionally, then these two drugs could have a variety of interactions, which should be semantically explained. DDI would depend on the exact involvement of each drug in their therapeutic targets/biological functions of the patient.

Software engineering solutions, with data sharing across disciplines, and reasoning upon the collected data, in order to find potential DDI for the patient's medication list, would require a software architectural (SA) model first, which specifies sources of shared data and computational models for identifying relevant DDI. A software application, created from

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the SA would work for patient/clinicians and secure the best possible medication lists, personalized in a particular context. The same application should allow updating the semantics of the ***drug$_1$-target-drug$_2$*** relationship from biomedical research and thus fast forward biomedical knowledge, on discovered DDI, towards creating a personalized medication list.

Our proposal uses Semantic Web Technology (SWT) and its languages OWL/SWRL (OWL/SWRL) for defining the reasoning process upon data shared from biomedical experiments, with ***drug$_1$-target-drug$_2$*** pathways and patent clinical data, i.e. medication lists. We infer DDI relationships between the two drugs, from the patient medication list, through semantic reasoning upon the data which originate in biomedical research and clinical practice.

The paper is organized as follows. Related Work lists examples of finding DDI, using software solutions with Natural Language Processing (NLP), semantic technologies and reasoning. Our proposal, described in the sections, which follow, gives a reusable SA model which hosts computations based on reasoning upon shared biomedical and clinical data. We illustrate the reasoning process and debate the proposal in the Implementation and Conclusions.

2 RELATED WORK

Biomedical research has advanced significantly and it is almost impossible to systemize results of research advances and create an overall picture of new knowledge which is emerging as we speak. In the DDI field, we can go back through decades and find a variety of research publications which highlighted the problem. In this section we chose a selection of interesting papers which either influenced us, or illustrate new ideas to finding DDI.

The authors of (Herrero-Zazo et al., 2013) use NLP, which is still very popular for retrieving textual information from biomedical sources and finding DDI. In order to improve NLP they created an annotated corpus of pharmacological substances and DDI, sourced at DrugBank database (Knox, 20|11) and 233 Medline abstracts. The authors from (Aywaz et al. 2015) created a complete data set of DDI information from 14 public sources and merged them, but found that there are inconsistencies and overlapping between sources which disseminate information on DDI. In (Segura-Bedmar et al.m 2010) linguistic extraction techniques and a hybrid linguistic approach to DDI detection are used, that combine shallow parsing, provided by UMLS (UMLS, 2009) tools, and syntactic simplification with pattern matching. Lexical patterns achieved reasonable precision. In (Liu et al., 2019) the detection of adverse drug events (ADE) from social media is shown. This is not exactly DDI, but it is a refreshing way of getting information fast and exploring social media for learning differently about DDI. Because of the type of sources used in this work, a semi-supervised learning method, with weighted features is used to distinguish between ADE and non-ADE. (Kim et al., 2015) use text mining techniques to identify DDI in the body of unstructured medical text and consequently, a support vector machine with a linear kernel is a good option for the task. The authors of (Xhoua, et al., 2018) use a position aware and multi-task deep learning to extract DDI from unstructured medical texts. Deep neural networks, which use words and their positions in the unstructured text, for defining latent features and thus avoiding explicit feature engineering, for finding DDIs are in (Sahu and Anand, 2018).

All these examples show that NLP, information extraction, text mining and statistical classifications, with learning technologies, dominate the research scene for one important reason. The Semantic of the DDI from biomedical research is often buried in unstructured biomedical texts.

Ontologies are not often used for detecting DDIs. If they appear in research, they are mostly controlled vocabularies for cumulating knowledge as results of reasoning. Data retrievals are carried out with SPARQL. Drug Interaction Ontology from (Yoshikawa, 2004) is a very old, but formal ontology, which accumulates reusable knowledge in molecular pharmacology. Its information model is based on fundamental concepts of biological interactions. The paper was published before the standardization of the SWT and its languages and therefore it can not be compared with modern SWT solutions. Potential DDI are results of retrievals upon ontological concepts. The authors of (Alhaj et al., 2019) created the ontology identifying DDI, but reasoning classifies only DDI effects: reduction, synergism and toxicity. In (Saleha et al, 2017) the DDI ontology helps in drug discovery investigations, in (Sara et al., 2018) a drug interaction ontology contains information about ADE, and in (Grando et al., 2012) ontology is used for safe and effective generic prescription principles.

DINTO ontology, which contains formal representation of different types of DDI is available in (Herrero-Zazo, 2015). It is very complex and models DDIs as classes and properties. This may have an impact on the OWL model's efficiency and reusability. It is interesting that they created a set of inference rules for a variety of DDIs. They are

inferred on the basis of their pharmacological mechanisms, which in turn depend on the biological process leading to their occurrence. These interwoven facts must be presented within the ontology, possibly through chaining of object properties. This can lead to inefficiency in the reasoning process, if the object properties chaining were to be a part of any stand-alone software application. If DINTO were used as a formal vocabulary, then its efficiency in real life will depend on the way SPARQL performs, and not on the constraints, imposed by OWL object properties.

We could not find any solutions, which would infer DDI from prescribed medication lists. However, DINTO ontology could be used in our proposal as a supporting source of information for understanding the context within which we infer DDI for a particular patient and his/her medication list.

There is only one publication which comes closer to this research than any other. It uses GalenOWL ontology for drug recommendation discovery (Doluaverakis et al., 2003). It is an online-service, based on queries aimed at ***drug-to-drug*** and ***drug-to-disease*** discoveries. It offers conceptual reasoning rules upon a set of domain ontologies for inferring OWL properties and thus recommends a particular drug to a patient. Its rule base engine evaluates conflicts between drug therapeutic indications and contraindications and thus indicates implicitly, but not explicitly the problem of DDI.

3 THE PROPOSAL

The proposal consist of two parts. In the first part we introduce the SA model which specifies the main software components of the layered and component based architectural style. The model is a prescription on how to build software applications for delivering the inference of potential DDIs.

In the second part, we look at the specificity of the computational model from the software application perspective and define OWL classes, with their individuals and properties, and the reasoning process.

However, before we define the proposal, we briefly debate the role of SWT in this problem domain. This is important because we do NOT create another formal ontology in biomedical science. SWRL enabled OWL ontologies are here to (i) become a part of a software engineering application (ii) exploit the semantic relevant for the task of discovering DDI and (iii) contribute towards a computational model, which detects a potential DDI and change the proposed medication list, if necessary.

3.1 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 Web. It is perfect for building common ontologies and controlled vocabularies across domains, enriched with reasoning rules in SWRL, and thus bringing inference and more semantics to the Web. We can represent knowledge with OWL/SWRL because of its powerful representation through description logic.

There are numerous possibilities of using and exploiting SWRL enabled OWL ontologies, but we would like to emphasise its use *outside the Web and controlled vocabularies, i.e. knowledge-bases* for many reasons. The most important reason is that computational models, which house SWRL enabled reasoning upon OWL concepts, bring inference without either having complex knowledge systems in the background or using Artificial Intelligence (AI) algorithms for creating inference. Therefore we talk about software engineering applications of the SWT technology. We can also create SWRL/OWL inference on an ad-hoc basis and address constant changes in environments we model. If we add that SWRL reasoning upon OWL concepts can be teamed-up with filtering, ranking, tagging, semantic annotations, transactional and big data processing, and performing prediction analytics (Juric 2016), (Juric and Kim 2017) then our proposed software engineering solution, outside formal ontologies and knowledge-bases, is a promising start.

3.2 Software Architectural Model

The SA model is proposed in Figure 1. Its middle vertical content houses a computational model which performs reasoning upon SWRL enabled OWL ontologies. This repository contains semantics of both: drug(s) specifications, their therapeutic targets (genes/proteins), and biological functions and clinical-level of physiological effects, relevant to the prescribed medication list (for a particular patient). Therefore prescribed medication list originates in the software application which ***Manipulates Clinical Data*** (right vertical part of Fig 1.)

The left part of Fig. 1 illustrates repositories from the biomedical (BM) field and may include BM Databases $\{BMDB_1, BMDB_2, ...BMDBn\}$, existing BM ontologies $\{BMOnt_1, BMOnt_2, ...BMOnt_m\}$ containing results of BM research. Drug specifications, explanations on their therapeutic targets, and knowledge of existing DDI are all

available within BM software applications, which ***Manipulates Biomedical Data***, and their repositories.

The right side of Figure 1 (***Manipulate Clinical Data)*** contains data/software applications specific to clinical data and patients Electronic Health Records (EHR). Patient medication lists may be generated there (not compulsory) and therefore the clinical level of physiological effects of prescribed drugs to the patient, might also be known within this environment.

The proposed ***computational model*** sits between the two environments (left and right part of Figure 1) and ***Creates Personal DDI***. It bridges the gap between the knowledge available from BM research and data related to clinical practices. The data sharing between these two environments, which are in reality two separated worlds, is essential if we wish to bridge the gap. *DDI OWL Ontology with SWRL*, can be populated with the semantic of data from both sides (Juric, 2016). This is the only way we can perform inference where the reasoning creates a DDI on an ad-hoc basis.

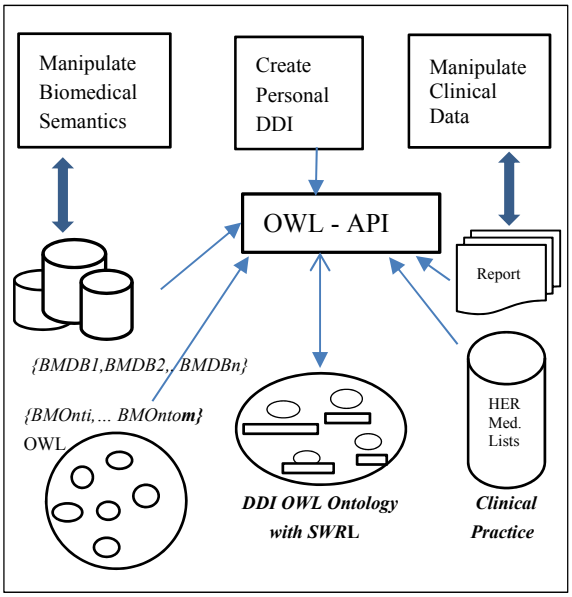

Figure 1: Software Architectural Model.

3.3 Semantic of DDI Relationship

The section on Related Work shows various ways of describing the semantics of potential DDI. One publication proved to be extremely beneficial for performing reasoning upon biomedical concepts in general. The relationship between drugs and their therapeutic targets, described through semantic predications, related to all medications, available in Sem-MedDB (Kilicogly et al., 2012) is almost ideal for being converted into OWL ontologies.

Semantic PREDICATES are defined in the UMLS Manual (UMLS) (Ahlers et al., 2007), and the authors of (Zhang et al., 2014) also use them as an input into their own method of finding DDIs. These predications are very attractive to software engineers because they are TRIPLETS:

$$\textbf{\textit{subject-PREDICATE-object}}$$

where ***subject*** is a particular ***drug*** and ***object*** is its ***target (genes/enzymes)***. DDI between two drugs can be identified, if we have the following logic:

$$\textbf{\textit{subject}}_i\textbf{\textit{-PREDICATE}}_j\textbf{\textit{-object}}_k\textbf{\textit{-PREDCATE}}_l\textbf{\textit{-subject}}_m$$

where $\textbf{\textit{subject}}_i$ is NOT the same as $\textbf{\textit{subject}}_m$ (these are two different drugs) and therefore

$$\textbf{\textit{subject}}_i \neq \textbf{\textit{subject}}_m \rightarrow \textbf{\textit{DDI}}_{i,j}$$

This means that if we have two drugs, both involved in the same target (genes / enzymes / biological function) through different predicates, and thus would interfere with each other. The types and number of PREDICATES, which can be extracted from the SemMedDB and UMLS Manual are ideal for logic reasoning. We can transfer scientifically agreed predications directly into OWL (object properties). This is one of the most important task when creating a reasoning process using OWL/SWRL: semantically rich object properties. There are many predicates in SemMedDB, such as TREATS, AFFECTS, INTERACTS_WITH, STIMULATES, INHIBITS, which can be object properties in OWL. They can connect individuals between drug and target concepts in ***drug-tehrapeutic target*** pathways.

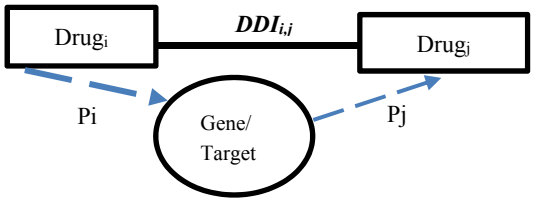

Figure 2: $DDI_{i,j}$ is defined between any pair of drugs.

Figure 2 shows a possible DDI between two drugs $Drug_i$ and $Drug_j$ from the set of ***n*** drugs D= $\{Drug_1, Drug_2, .. Drug_n\}$, where we allow up to ***n-1*** potential DDI between them. Some of $DDI_{j,k}$ might be imported from repositories of the BM research (left part of Fig. 1) and some might be known to clinicians (right part of Fig 1). If there is no knowledge about

potential ***DDIi,j*** we have an opportunity to infer it through reasoning if the semantics of ***subject$_i$-PREDICATE$_j$-object$_k$-PREDCATE$_l$-subject$_m$*** allows. Broken one directional lines in Fig. 2 indicate therapeutic pathways for a drug, and the solid line denotes (potential DDI). Abbreviation Pj and P_l is for two particular PREDICATES.

3.4 Semantic Relationship between Drugs and Their Targets

We identify examples of predicates which can be used for illustrating the semantic between Drugs and their targets in order to define an OWL model.
Let us assume that the relationship between *Drug$_i$,* and *gene* is defined as a triplet

(*Drug$_i$*-PREDICATE$_j$-*Gene)*

where ***Drug$_i$*** affects a particular ***Gene.*** However, the same ***Gene*** might be involved, as a target, with ***Drug$_m$***. This would require the definition of another PREDICATE, between the same Gene and ***Drug$_m$***. If we put these two triplets together,

Drug$_i$-PREDICATE$_j$-Gene-PREDCATE$_l$-Drug$_m$ then the above construct can create Fig. 3, which reads: *Drug$_i$* AFFECTS a particular gene, but this gene might be INVOLVED IN another *Drug$_m$*.

Fig. 3 sends two messages. If there is a predicate AFFECTS for an approved target for ***Drug$_i$*** (black arrow) we investigate if there is a potential predicate INVOLVED-IN for the same target, but for a known or approved ***Drug$_m$*** (red arrow) The semantic of predications is read in both directions. We may know that a particular gene is involved in ***Drug$_m$*** which might require investigating is there is a drug ***Drug$_i$*** which affects the same gene. From the computer science perspective, we may allow multiple instances of ***Drugi*** and ***Drugj***, to appear in Fig. 3.

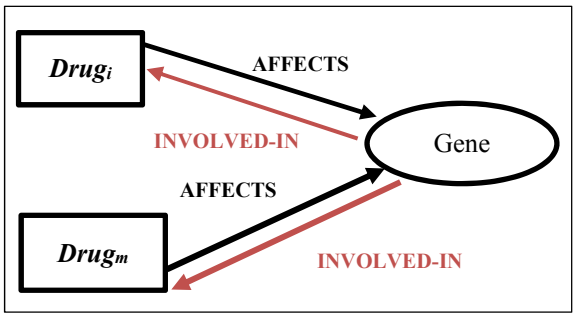

Figure 3: AFFECTS/INVOLVED-IN Predicates may be used both ways.

3.5 Owl Model

One of the most important use of semantic predication is in grasping semantic important for the discovery of DDIs. From Figure 3, all PREDICATIONS can be easily converted into OWL constraints in ontological modelling. This means that when building an ontological model we will be in a position to use some PREDICATIONS as either asserted OWL object properties or inferred.

In order to infer potential DDI between the two drugs ***Drugi*** and ***Drugm***, the most convenient way would be to conceptualise them into two separate OWL classes, which may change their role from domain to range, to allow both way of reading form Figure 3 (red and black arrows).

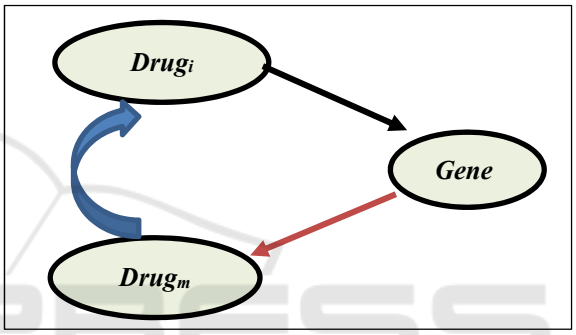

Figure 4: OWL Model derived from Figure 3.

In Fig 4. red and black arrows denote asserted object properties (AFFECTS and INVOLVED-IN) and the blue arrow is a new object property which is inferred: It denotes a potential ***DDI$_{i,j}$***.

Fig. 4 also shows a basic principle of conceptual modelling of the OWL ontology: potential ***DDI$_{i,j}$*** can be inferred between *Drug$_i$* and *Drug$_m$* through reasoning, if there existed a triplet D***rug$_i$-AFFECTS-Gene-INVOLVED_IN-Drug$_m$*** where ***Drug$_i$*** is not the same as ***Drug$_m$***. Fig. 5 shows a conceptual SWRL rule with asserted PREDICATES are asserted from SemMedDB for performing the reasoning.

Drug$_i$(?x) ∧ affects (?x, Gene) ∧ Gene(?y) ∧ involved_in (?y,Drug$_m$) ∧ differentFrom (?x,?y)
➔
Drug_Interaction (?x, ?,y)

Figure 5: Conceptual SWRL rule for Fig. 3 and 4.

The rule in Fig. 5 would work as long as semantic predication is correct. Object properties *affects (?x, Gene* and *involved_in (?y,Drug$_m$)* may be replaced with any other type of predicates available in SemMedDB or UMLS and inferred using SWRL.

4 IMPLEMENTATION

The implementation of the middle part of the SA model in Fig. 1 for ***Creating Personal DDI*** is based on the reasoning process which conforms to Figures 3,4 and 5. The prototype was implemented as a Java application, adopted from the research on biomedical discoveries (Almami et al., 2016), (Almami et al., 2017) and the modelling of semantic software applications (Patadia et al., 2011), (Shojanoori, 203).

Due to space restrictions we show two important aspects of the implementation.

Firstly, Fig. 6 illustrates a set of PREDICATES extracted from public databases in order to test our reasoning and the implementation.

Aspirin –INHIBITS -EGF-INTERACTS_WITH-Ascorbic Acid
Lisinopril-INHIBITS-VIP-STIMULATES -Thyroxine
Metformin -STIMULATES-Glu-INTERACTS_WITH-Aspirin
Metformin-STIMULATES-THI-INTERACTS_WITH -Pioglitazoone
Trastuzumab-INHIBITS-ld HER2 INHIBITS-Pertuzumab
Ibuprofen-INHIBITS- COX-INTERACTS_WITH-Warfarin
Nacfillin-INDUCES-CYP3A4-AFFECTS-Warfarin
Ibuprofen-INHIBITS-PTGS52-INTERACTS-

Figure 6: Selection of Semantic Predications for the Implementation.

We ran experiments for populating OWL classes with individuals, extracted from the peer reviewed papers on DDI discoveries. Figure 6 has data extracted from Table 1 of (Zhang et al., 2014) and thus we were able to define numerous triplets. We also added a few other predicates available in some of the sources described in the related work, which shows that we can use any other set of biomedical data (from the left part of the SA in Figure 1.) and create more suitable triplets for our OWL model. In cases where biomedical research results do not generate knowledge in the format of predications, it would not be difficult to create them either through the software application from Figure 1 or by exploring the nature of OWL object properties defined Fig.4.

Secondly, an example of user interface for the prototype is in Figure 1. From the patient medication list, which initially contained Aspirin, Ibuprofen, Warfarin, Diazepam, Lysinopril, Thyroxine, two drugs have potentially known DDI: Ibuprofen and Warfarin. However, our reasoning with SWRL detected a new inferred DDI between Lisinopril, Thyroxine.

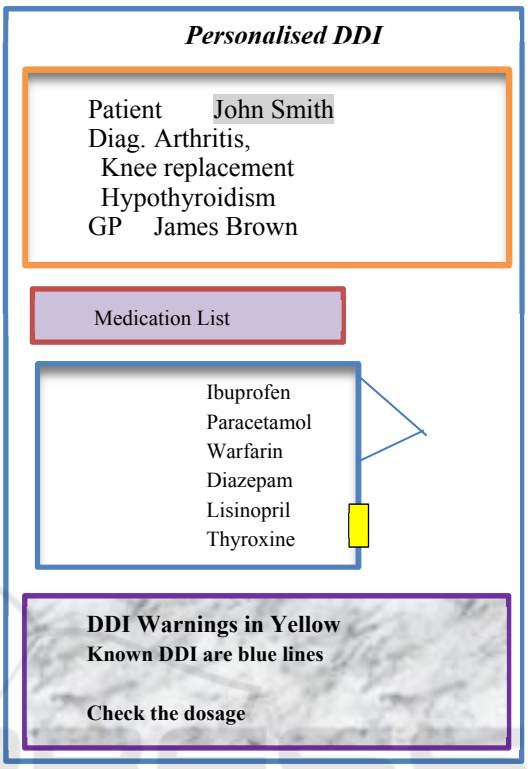

Figure 7: Excerpt from Prototype UI.

However, our prototype, as an illustration of the concept defined in Figure 1, which pushes forward translational informatics, using efficient and light weight software technologies, based on semantic reasoning, shows only an excerpt of the overall research. The comparison of two drugs, based on semantic predications, uses bindings of drug therapeutic compounds to intentional target genes. There is much more semantic in biomedical science which can enrich our OWL model and predications. They include semantic of biological functions from molecular to organism level to pathological function related to diseases, to mention just a few.

5 CONCLUSIONS

Translational bioinformatics has come of age (Butte, 2008), (Machado et al., 2015), (Payne and Embi, 2015), and computational algorithms can be used for assisting in experiments and analyzing results of biomedical research at bio-molecular level. However, we have not resolved all the problems we identified more than a decade ago. The dissemination

of and sharing viomedicla research/data in lcinicla applications is not common therefore translational bioinformatics is still evolving. This research shows that we can enhance it with the manipulation of semantics of and reasoning from the results of biomedical research, which in turn derives new knowledge and tools in/for clinical practice and medicine in general. This is an opportunity for all of us to allow the synergy between biomedical and clinical data and secure that clinical practices encompass results from biomedical science, because the gap between the two has not been closed.

This paper just touches the top of the iceberg of opportunities we may have in the field of adding value to translational informatics. There are opportunities of reusing the conceptual model from this paper for the whole range of problem domains, from predicting side effects from a drug to therapeutic targets relationships, to looking at un-intentional binding of drugs and therapeutic targets, which could help to define drug repositioning, to mention just a few (Juric, 2019) (Juric and Almami, 2019). Therefore this work continues towards the development of software application, from the same proposed SA from Figure 1, with reasoning upon SWRL enabled OWL ontologies as a part of new computational models, but in different parts of biomedical fields. The only prerequisite is that data sharing and dissemination of biomedical research is essential for progressing in medical science.

For readers interested in methods of populating OWL ontologies from databases and structured repositories, which exist in biomedical research, we suggest reading a few publications (Juric, 2019), (Saaidi et al., 2010). For readers interested in understanding how the SA from Fig. 1 can be implemented as a software application, which involves accessing OWL ontologies and computing with SWRL through OWL–API, we suggest reading (Juric, 2016), (Juric and Kim, 2016), (Tarabi and Juric, 2018), (Shojanoori,, 2013).

For the full deployment of the SA from Figure 1, in terms of commercialising the prototype, we face expected obstacles such as

(i) gaining access to a variety of data banks, databases and knowledge repositories from biomedicine and
(ii) the acceptance of this type of applications in clinical practice.

Resolving (i) and (ii) would require changes in the way clinical trials are conducted and biomedical research financed. However, it would also require changes in the way we manage differences between interests of pharmaceuticals and biomedical scientists.

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