Semantic Computational Models for Polypharmacology: Applications in Drug Repurposing

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Abstract

This paper proposes a computational model based on the first order logic reasoning, for managing discoveries in polypharmacology for the purpose of efficient drug repositioning. The model uses computational reasoning upon advances documented in the published literature and thus is primarily based on the range of discoveries in biomedical science. The idea behind the model is to exploit drugs multiple intended and particularly unintended therapeutical targets and discover if they can lead us towards drug repurposing. Computational pharmacology is a very complex field, but reasoning upon its concept can bring us closer to the ideal polypharmacological world of finding, developing and approving multitargeted drugs and using them in drug repurposing.

Keywords: Semantic, Computing Polypharmacology, Drug Repurposing

1. Introduction

Polypharmacology in relation to drug discoveries has been in the focus of our interest for more than a decade. It was initially defined as the treatment of diseases by modulating more than one therapeutic target (Boran and Lyengar, 2010). Considering that each approved drug must have its single therapeutic target, we must not forget that the same drug may have adverse mechanisms, because of one or more of its unintended targets. This creates a natural division into therapeutic and adverse polypharmacology. Lately, the therapeutical pharmacology focuses on having *multiple drugs* with *multiple targets*, thus polypharmacology (Readdy and Zhang, 2013). If we add to this problem the complexity of diseases and disorders, then ideas of recognizing and developing multitargeted drugs (Talevi, 2015) forced us to rethink the way we discover, develop new and repurpose approved drugs (Peters, 2013), (Akilesh et al., 2021), (Lavecchia et al., 2016).

The knowledge about intended drug targets is firmly interwoven within biomedical science and the drug discovery and approval process. However, the semantic generated by unintended drug targets, i.e. adverse polypharmacology, when the drug binds to a protein which is not a therapeutic target, is equally powerful, in drug repositioning (Juric and Almami, 2019) (Juric et al., 2021). Side effects and toxicity affect drug discoveries and since 2013 we kept looking at polypharmacology as a future of drug discoveries (Ready and Zhang, 2013). Are we ready to move from ***one-drug-one-target*** to Polypharmacology on a unique disease pathway? Shall we extend polypharmacology and allow it to penetrate multiple disease pathways? These two very important questions from 2013 have not yet been answered.

The initial idea in computational polypharmacology was to integrate data and knowledge from disciplines which affect drug discoveries and then use computational models which could predict the polypharmacology journey far beyond target families (Anighoro et al., 2014), (Chaudhari et al., 2017). In 2015 (Rastelli and Pinzi, 2015) talked about computational polypharmacology which could discover early multi targeted drug activities in drug iterative design, with statistical data analysis and bioinformatics. A similar study appeared in 2021 during the covid pandemic (Pinzi et al., 2021). In (Lavecchia and Cerchia, 2015) the authors focus on structure-and-ligand-based strategies to address polypharmacology and reiterated the importance of finding or predicting off-target toxicities in drug repurposing and the design of multitargeted drugs. The following question is imminent: Could computational polypharmacology predict (or find?) all drug effects, results of knowing intended and non-intended therapeutical and adverse targets and as such provide a better picture of targeting diseases? We still do not have a computational model which would give us better approaches to targeting diseases.

It appears that weaknesses and challenges in computational polypharmacology described in 2017 in (Chaudry et al., 2017) are the same today. We have

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not moved forward. We hoped that predictive and learning technologies and machine learning (ML) may give answers in modern drug discoveries with polypharmacology. There is on example (Zitnik et al., 2018) which uses graph convolutional networks in modelling polypharmacology side effects by exploiting drug to drug interactions, due to drug combinations. However, at the time of writing this paper, we could not find publications which carried on with advances in computational polypharmacology and made an impact on the process of drug discoveries and their repurposing.

Unintended drug targets proved to be powerful knowledge even during the time of the covid pandemic (Akilesh et al., 2021), (Pinzi et al., 2021) and it is disappointing that we have not exploited the semantic stored within drug non-intended targets and drug to drug interactions in order to move towards knowledge systemization and discoveries of complex relationship between diseases, drugs and their targets. This is essential if we wished to create modern computational models for polypharmacology. However, the interests in drug combinations (Ianveski et al., 2019) and drug combination therapies (Paltun et al., 2017), which are based on predictions on the best possible drug combination for a particular disease, do not directly answer the problem of computational Polypharmacology. We can predict effective drug combinations by looking at all possible interactions: chemical, proteins and targeted pathways as suggested in (Madani-Tonekaboni, 2018), but the essence of Polypharmacology should be in the using non-intended targets and side effects to understand potentials of discovering multitargeted drugs. Looking at drug combinations does not guarantee that we will discovered a new and repurposed multitargeted drug. Finally, our long standing and successful drug approval process is based solely on approving drug's ***single intended target***.

This paper illustrates the idea of creating a computing Polypharmacology model, based on reasoning and first order logic, interwoven in Semantic Web Technologies (SWT), for discovering either new or repurposing existing drugs. This computation should use all relevant knowledge on drug targets, intended, i.e. approved, and unintended targets, to drug to drug interactions, in order to create inference which would result in various outcomes: defining a new drug, repurposing of existing drugs and even detecting Polypharmacology side effects.

The paper is organized as follows. Section 2 describes the background of the problem and proposes the potential way forward. Section 3 introduces conceptual ontological model for computational Polypharmacology and sections 4 shows the proposal: the OWL model and the reasoning process which infers potential drug repurposing. The explanation of the implementation of the proposal is in section 5, related work is in 6 and conclusions in section 7.

2. The Background

There are various pathways for enhancing research in computational Polypharmacology.

First, the environment where drugs and their biological targets interact is a complex portion of biomedical science. It ranges from network analysis of the relationships between drugs and drug targets, the power of therapeutic Polypharmacology in designing combination therapy and off-target binding in non-target tissue, to application of Polypharmacology to underlying diseases, the treatment of diseases through the analysis of signaling networks of the disease state, multiple disease pathways, and multifaceted etiology of diseases, to mention just a few. Therefore, chemical and biological space for understanding and improving Polypharmacology is complex and vast. It is extremely difficult to place all these components of Polypharmacology into one special computational model, hoping that it will address the main goal: efficient drug discoveries and repurposing. Also, the data we have now and will collect in future, relevant to Polypharmacology, is not necessarily directly computable. A new way of thinking on how to "store and manipulate the data semantic" to serve computational polypharmacology, is needed.

Second, outcomes of experiments and research in biomedical science are very often buried in published research papers and as such they are not directly available for any type of computations. However, there are many repositories, mostly databases, created in the last decade, which store data on intended and unintended drug targets. There are non-commercial software tools claiming to predict drug-target interaction networks (DINES). There are repositories where, for example, structural and ligand-based strategies in Polypharmacology and the processes of in-silico methods, which address them, are freely available, (Lavecchia and Cerchia, 2015), Chopra, G., & Samudrala, R. (2016), (Proschak et al., 2019). However, we are in the same boat here, as in the paragraph above: the data available need additional restructuring for running computing programs upon them to either PREDICT or REASON upon the facts which would take us to drug discoveries and their repurposing. This means that we cannot place all these repositories in one "basket" and assume that semantics stored in them would be computable (Juric et al., 2021). Creating centralized repositories for excessive

amounts of data, with complex semantics, is a *no-go* area for efficient computational models today (Juric, 2022). The time of complex and centralized software solutions are long gone.

There is one sentence which appears too often in the latest biomedical literature: "*We tend to produce a huge amount of unstructured data which creates terminological problems regarding semantic transparency, and humpers their re-use and parsing by computers*" (Vogt, 2019). Therefore, it is difficult to talk about centralization/ integration of data or/and computations and we must find a new way forward.

2.1. Potential Way Forward

The first step would be to perform systemizations and create taxonomies of the knowledge in polypharmacological data, and categorize computing models, where only excerpts from these taxonomies are used. The purpose of a particular drug discovery process and the environment in which we perform it are important. Therefore, we need both: taxonomies and categorization of data and computations.

The good news is that in the last decade, we have had successes with taxonomies in biomedical science in the format of formal ontologies (Hoehndorf et al., 2015) which systemize knowledge and outcomes of biomedical and chemical experiments. The phenotype ontologies (Gkoutos et al, 2017) are very powerful and popular in translational research (Robinson and Weber, 2014). There are also ontologies which address a particular disease and drug discoveries related to them (Vaszuez-Naya et al., 2010). Ontologies are instruments to (i) reducing the complexity of polypharmacology (Farish and Grando 2013), (ii) organizing phenotypic data by creating a semantic data model for anatomy (Vogt, 2019) (iii) enhancing computational polypharmacology with text mining and ontologies (Plake and Shroeder, 2011) and creating phenotype ontologies (Gkoutos et al., 2018).

Considering that the road for using ontologies in the biomedical science was paved almost 10 years ago, formal ontologies may help in this research by supplying either data (ontological individuals) or ontological concepts. However formal ontological are not suitable to be a core of computational models because they are collection of knowledge and controlled vocabulary. They are very useful but not effective for computations. We would rather use reasoning upon SWRL enabled OWL ontologies to create new computational models, which means that we do not wish to be directly dependent on formal ontologies. They may potentially contribute towards data sharing and possibly updating our computational model with new advances in biomedical research. They are very important, but they shouldn't become a backbone of computational polypharamcology. (Juric, 2016) (Almami et al., 2016a).

It is important to note that the idea of reasoning when using SWT and the first order logic, within computational models, does NOT include predictions with ML. We accept that predictions are derived from statistical models, available within learning technologies, known as ML algorithms, which shape current AI. However, reasoning and predicting are two different types of computations, and they cannot be mixed and matched without having a specific software architectural solution (Juric and Ronchieri, 2022), (Juric and Kim, 2017). Therefore, advances in predictions of drug combination based on clinical side-effects (Huang, et al., 2014) and ML in drug discoveries (Talevi et al., 2020), predictions of synergistic drug combinations (Gayvert et al., 2017), and selective combinations of druggable targets (Tang et al., 2013) are examples of "predictions". They are popular and powerful in drug discoveries, but they are just complementary computations to the first order logic computational reasoning (with SWRL enabled OWL ontologies). They may enhance each other's efficacy in computational polypharmacology. Ontologies do not calculate and do not predict. They systemize, classify, manage the semantic of data for computing and enable logic reasoning upon them, which is impossible to do with ML predictions.

3. Conceptual Ontological Model for Computational Polypharmacology

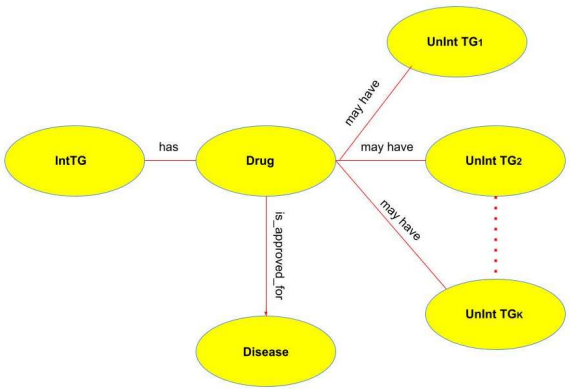

Figure 1. One-drug-one-target OWL model

Figure 1 is a model of ontological concepts which describe our current approach to drug discoveries, development, and approval: ***one drug for one intended target*** (*InTTG*). However, each approved drug, for a particular disease, may have numerous

unintended targets: {$UnIntTG_1$, $UnIntTG_2$, …, $UnIntTG_k$}. Concepts like Drug, Disease, *InTTGI and* {$UnIntTG_1$, $UnIntTG_2$, …, $UnIntTG_k$} are related through ontological properties (red lines in Figure 1), named according to their role or the meaning they may have in relationships between the concepts. They are self-explanatory in Figure 1.

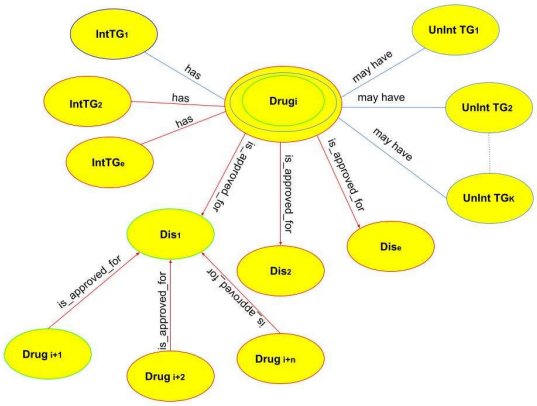

Figure 2. Multiple drugs - multiple targets OWL model.

Figure 2 is a conceptual OWL model for computational polypharmacology, where each drug:

a) may have any number of intended {$InTTG_1$, $InTTG_2$, $InTTG_l$}, and international targets {$UnIntTG_1$, $UnIntTG_2$, ..., $UnIntTG_k$ },
b) has been approved for a number of diseases {Dis_1, Dis_2, ... Dis_l} and
c) a particular disease Dis_1 may have a set of drugs {$Drug_1$, $Drug_2$, ... $Drug_n$} approved for treating Dis_1

The model from Figure 2 allows for our visionary world of computational polypharmacology: ***multiple drugs for multiple targets*** (and diseases). Ontological properties in this figure (red lines) have the same role as object properties in Figure 1.

The philosophy of polypharmacology, from Figure 2, shows how complex it could become. From the computer science point of view, it would be extremely difficult to create a computational model which would create structures to do exactly what the figure shows. It is feasible to implement the model from Figure 2, but its software application might exhibit performance and efficiency issues (Juric, 2017). However, if we consider only excepts from the semantic shown in Figure 2, we can run reasoning according to a particular situation/circumstance where only a fraction of the semantic from Fig. 2 is relevant.

Figures 3 and 4 are such examples. We use the generic model from Figure 2 and explore two different situations. One shows the problem of one intended target *IntTG* being found for two drugs and the other shows a potential chain of relating drugs through intended *IntTG* and unintended *UnIntTG* targets.

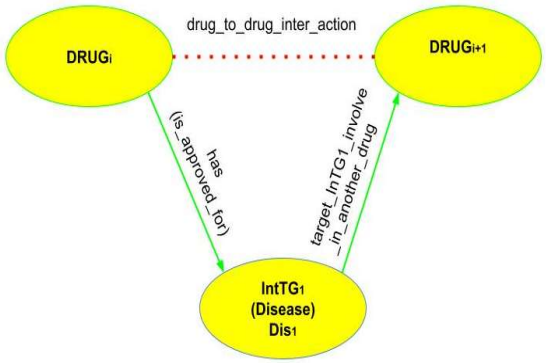

Figure 3. Potential drug-to-drug interaction OWL model.

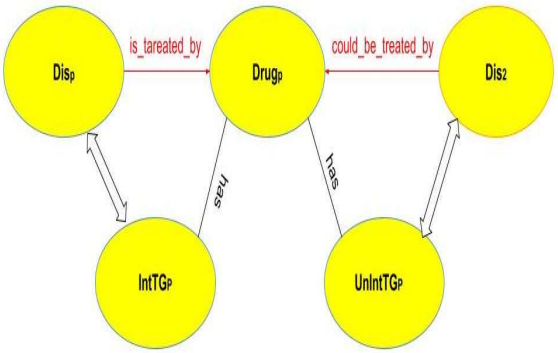

Figure 4. Potential drug repurposing.

Therefore, ***drug-to-drug interaction*** in Figure 3 exists because the intended target *IntTG* for $Drug_i$ (approved for Dis_1) is involved in another drug $Drug_{i+1}$, as an international target *UnIntTG*, probably as having indications for treating a different disease Dis_2. Thus $Drug_i$ and $Drug_{i+1}$ may not be administered together because of their possible interaction.

Figure 4 shows something else, closer to drug repurposing. If disease Dis_p is treated by $Drug_p$ and $Drug_p$ has intended $IntTG_p$ and unintended targets $UnIntTG_p$ and if we can find a disease Dis_q which can be treated by a drug with intended target *IntTG* equal to the same one as in $UnIntTG_p$ then it is likely that Dis_q could be treated by $Drug_p$.

These two examples are two of many derived from Figure 2. We should be able to derive ontological models from Figure 2 according to the task

we have: repurposing the drug, discovering a new drug, finding a disease for a drug's unintended target *UnIntTG*, harmonizing disease potential multiple drug-to-drug interactions and many more.

There is another outcome from Figures 3 and 4. In the both cases we can use semantic predication (Juric et al., 2021) (Zhang et al., 2014) which has been prevalent in translational semantics and use its "subject-predicate-object" structures when creating our ontological models. Figure 5 shows predication elements converted from Figure 3. Therefore, all our ontological models from Figures 1,2,3 and 4 can be expressed using biomedical semantic predication

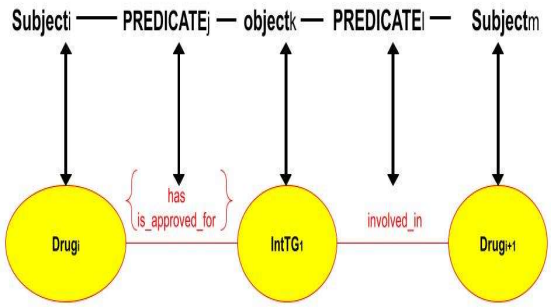

Figure 5. Semantic predications for Figure 3

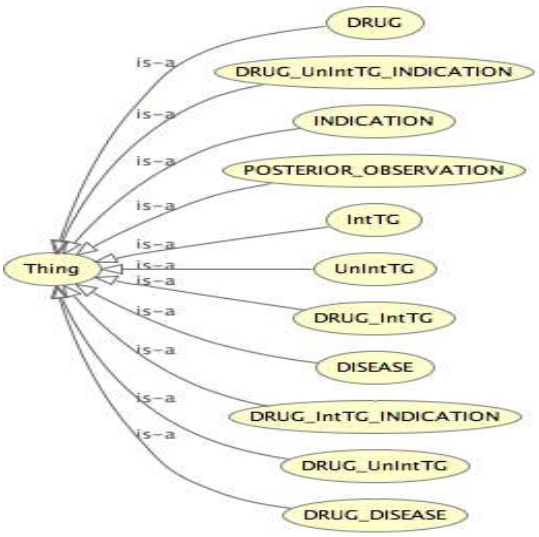

Figure 6. Working ontology

4. The Proposal: OWL Model and the Reasoning process

Figure 6 shows a set of basic ontological OWL: classes which can be a starting point of creating computational models for polypharmacology. The choice of classes is self-explanatory and follow what was shown in Figures 1 and 2, but some of the OWL classes are explained below.

Posterior Observation class may store any data on any drug, created after the drug has been approved and in use. This is an opportunity to monitor the behavior of approved drugs and discover unintended targets which were not know before.

Indication class expands the semantic stored in *Drug* and *Disease* classes, by containing individuals which would list the indications for taking drugs, as approved for a disease (or many diseases, as desired in polypharmacology). This means that we are able to use *Indication* class, if we wish, if there will be a need to elaborate on drug indications, because they are related to intended targets *IntTG*.

There are a few more classes in Figure 6 which are needed for preparing OWL concepts for the process or reasoning. Considering that we might need to keep (temporarily) the results of reasoning, because of ontological matching between individuals of OWL classes, which in turn will infer individuals of OWL classes (Kataria et al., 2015), (Saaidi et al., 2009) we would like to store inferred individuals in *DRUG_UnIntTG_INDICATION*, *DRUG_DISEASE, DRUG_IntTG_INDICATION, DRUG_UnIntTG,* classes which will be used as placeholders for storing inference if necessary.

It is important to note that the power of SWRL enabled OWL ontologies is not in the number of OWL classes and individuals they have (Juric et al., 2018), (Koay et al., 2010), (Shojanoori and Juric, 2013). It is a set of object properties and a selection of OWL classes which define the power of OWL models and NOT the complexity and size of OWL classes. Therefore, we need to create OWL model first which would secure definitions of SWRL rules for reasoning. OWL ontologies, which are not prepared for reasoning in a particular situation cannot be used for creating inference, even with a pedantic, elaborative and long selection of OWL classes and their individuals.

Figure 7 selects OWL classes of interest from Figure 6 and adds potential object (i.e. ontological) properties. This is still not a reasoning process, but it shows how object properties could be defined in the ontology from Figure 5, and thus make provisions for reasoning. Figure 7 is one of many possibilities of creating conceptual OWL model, based on Figure 2, having base classes from Figure 6 in mind.

There is one interesting object property "repurposed_for" in Figure 7. It is denoted with thick red line. This property has not been defined. The red line denotes that we would like to create a reasoning

process which would infer "repurposed_for" between ontological individuals.

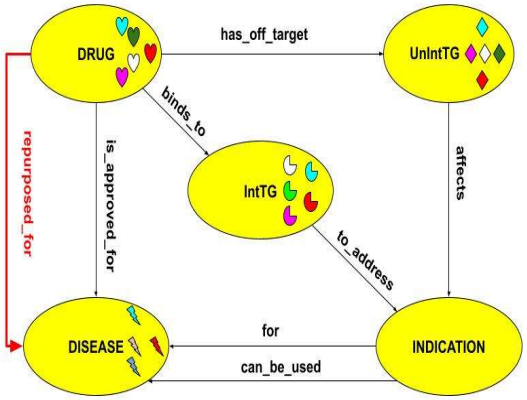

Figure 7. OWL model description.

Figure 7 is a deliberately simple OWL model which could be sufficient for a particular drug repurposing, because it uses an unintended target to learn that this target could be intended for another drug/disease. The model does not impose that we will always repurpose a drug. We could do this only if we have enough information in the model (individuals and object properties). For example:

A) If the drug has no unintended target, we can not repurpose it (according to this model)

B) If the unintended target $UnIntTG_g$ is NOT an intended target for any disease, we can not repurpose the drug in question.

4. 1. The reasoning Process

The reasoning process given in Figure 8 is the most important part of this computation. It is tailored for information given in Figure 7, but by no means is the only reasoning process we may have. However, its simplicity would allow for creating a very short SWRL rule which would infer exactly what we wanted in Figure 7: object property ***repurposed_for***.

The reasoning process in Figure 8 shows ontological matching between the classes which secure inference and thus the colored shapes placed within the symbol of OWL classes. These small colored symbols indicate which types of individuals are being stored and then possibly inferred (i.e. moved after the ontological matching) and when the individuals of *DISEASE* class are ready to be connected through ***repurposed_for*** object property (as the final inference which gives the result of the reasoning).

5. The implementation

Table 1. Object Properties with Individuals

DRUG	Object Property	Intentional target (IntTG)	Object Property	INDICATION	Object Property	DISEASE
Valproic Acid	binds_to	ALDH5A1 ABAT	to_address	seizures bipolar dis.	for	Mental disorders
Zidovudine		NRTI		progress of HIV		HIV
Doxycycline		rpsD, rpsI		bacteria growth		Bacterial infection
Imatinib		BCR-ALB		first line treatment		CML
DRUG	**Object Property**	**UnIntentional target (UnIntTG)**	**Object Property**	**INDICATION**	**Object Property**	**DISEASE**
Valproic Acid	has_off_target	HDAC2	affects	cell growth cell cycle arrest	can_be_used_for	Cancer
Zidovudine		Human DNA polymerase		DNA replication		immune system disorder
Doxycycline		MMP1/7/8/13		periodontitis		Stomatognathic disease
Imatinib		KIT,PFG-FRA		metastatic GST		cPotential drug repurposing

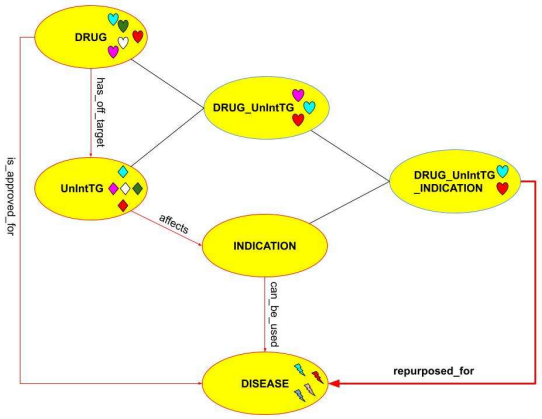

Figure 8. The reasoning process.

We have implemented a prototype to prove the proposed concept and illustrate our ideas. The first step was to define object properties which connect individuals of the main ontological classes. Table 1 gives an illustrative explanation of drugs, their intended and unintended targets, and object properties defined between the individuals of domain and range classes. The data has been taken from the published literature (this is where published formal biomedical ontologies can become handy). Therefore, individuals and object properties are not there arbitrary placed: they are results of the dissemination of results of experiments in biomedical science.

Readers should note by looking at Table 1, that we show only excerpts of individuals from our working ontology, with drugs we know that can be repurposed. This helps to illustrate the reasoning. If the drug cannot be repurposed, according to the

individuals and object properties from the reasoning process, then it will not appear in result of reasoning.

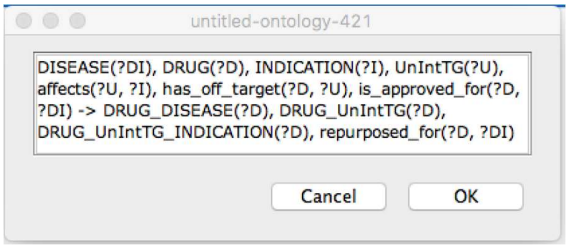

Figure 9. SWRL rule (in Protégé).

Figure 9 shows SWRL rule for reasoning as indicated in Figure 8. It is not difficult to follow the semantic of the rule. Its result is the inference of ***repurposed_for*** object property between the individuals of D (drug) and DI (disease) classes.

This is not the only inference in the rule. We infer individuals of *DRUG* class into *DRUG_UnIntTG* class and individuals of *DRUG_UnIntTG* class in the *DRUG_UnIntTG_INDICATION* class. This is essential if we wish to find out if there is any chance of repurposing a particular individual(s) from class *DRUG*. The rule above runs all these inferences in one go, which is extremely important when creating a software engineering solution and software application which hosts this rule. Computations behind the rule are efficient and fast and it is unlikely that the same result could be achieved more efficiently with any other software technology. SWRL enabled OWL ontologies can perform computational reasoning in any component based integrated development environment, including Java technologies, and its efficiency is based on simplicity of definition of object properties and number of classes in our OWL model (Saaidi et al., 2011), (Tarrabi and Juric, 2018) (Almami et al., 2016). Number of individuals (the size of data sets) does not significantly affect the performance of the rule. Therefore, our OWL model may have millions of individuals in classes from Figure 8, but SWRL rule efficiency will not be affected. The efficiency of any software application which hosts the proposed SWRL reasoning will always depend on the semantic from Table 1 (object properties) and the way we wish to reason, which is given in Figure 8 (Kataria and Juric, 2011), (Koay et al., 2011).

Figure 10 gives a screenshot of the result of reasoning with SWRL rule from Figure 9: ***Valproic_Acid, initially approved for mental disorders could be repurposed as a cancer treatment.***

The reasoning process from Figure 8 has multiple purpose and gives more options for reasoning *about drugs and their intended and unintended targets*.

It could be a very simple listing of drugs approved for a particular disease, as shown in SWRL Rule 2a in Figure 11 and its results in Figure 12.

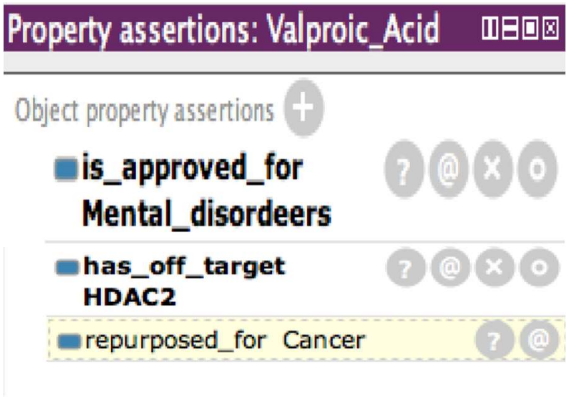

Figure 10. Results of SWRL Rule in Protégé.

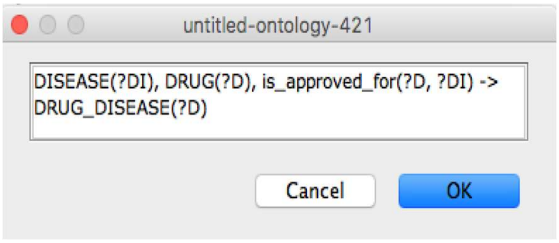

Figure 11. SWRL rule 2a (in Protégé).

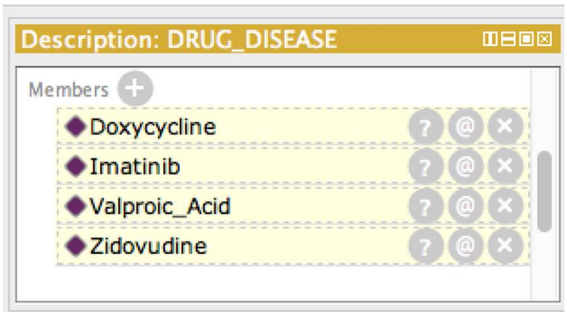

Figure 12. Results of SWRL Rule 2a in Protégé.

If we want to find out if the approved drug ***D*** has unintended target(s), known as indication ***I*** for treating a known disease, there is a possibility of repurposing the approved drug ***D*** for that disease (Fig. 13 and 14).

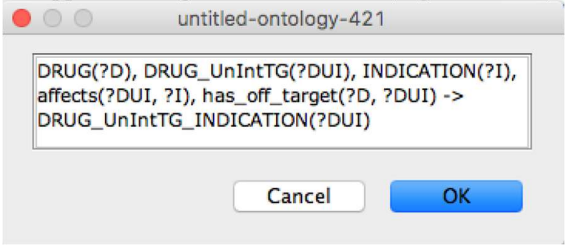

Figure 13. SWRL rule 2b (in Protégé).

These SWRL rules have been implemented in Java applications using OWL-API and Java technologies, with similar software architectural models as in (Almami et al., 2016), (Tarabi and Juric, 2019), (Juric at al., 2021).

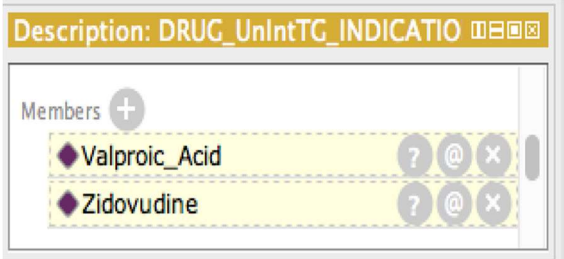

Figure 14. Results of SWRL rule 2b in Protégé.

6. Related Work

It is difficult to find related work because we do NOT create knowledge-based ontologies and we do not use ontologies as controlled vocabulary. Our ontologies are software engineering artefacts solely created for computing. Therefore, this paper cannot be compared with (Kanza and Frey, 2019), (Machado et al., 2015), (Bokrum and Frey, 2014). However, if readers have interests in using ontologies to add to knowledge classification in biomedicine and translational informatics, then these publications above give a good overview of the impact of SWT and tools on drug discoveries, based on knowledge discoveries. Also, in these papers there are interesting examples of OWL modelling and SPRQL query retrievals for OWL ontologies. Readers may read about the availability of platforms for drug discovery ontology (Clark et al., 2016), developing a consensus knowledge base for drug-target interactions (Tang et al., 2018) and ontologies for drug discoveries in neurology (Vazquez-Naya et al., 2010).

The papers which motivated us to push forward reasoning with SWRL enabled OWL ontologies to represent complex semantics of drugs intended and unintended targets in polypharmacology, are (Zhang et al., 2014) and (Parisi et al., 2020). Readers might not find a connection of the structural perspective of polypharmacology, debated in these papers, and our OWL proposed model, but their deployment of unintended drug targets is very similar to this work. Both publications collected interesting examples of repurposed drugs from biomedical publications.

The predecessor of this research can be found at (Juric and Almami, 2019), (Juric et al., 2021) (Juric et al., 2018), (Almami et al., 2016). In these publications readers can find further comparison of related work and computations with SWRL in terms of their computational efficiency. The discussion and evaluation of the implementation of the proposal, i.e., proving that the proposal is computable can be found in (Almami et al., 2016), (Juric et al., 2021), (Tarabi and Juric, 2018).

7. Conclusions

This research is a continuation of long-term interest in applying the SWT in biomedical science and developing new models for computational polypharmacology. The problem has been examined from the computer science perspective. It has been assessed if we can carry on with the SWT and ontological models to define and manipulate complex semantics of the polypharmacological paradigm and look at their impact on the current practices of drug discoveries and their approval processes. The prototype from this work is deployable in Android environments and computing based on Java technologies. It creates efficient software applications as debated in (Almami et al., 2016), (Juric et al., 2021), (Shojanoori and Juric, 2013), (Juric, 2016).

Considering that we propose first order logic and ontological models for reasoning, we could extend the work by adding other technologies for manipulating meanings of words, which may include natural language processing (NLP) and text mining. We do not see any urgent need for using them, but they should not be excluded in future. In terms of data availability and quality, when populating ontology and defining object properties (Table 1) we would NOT recommend straight forward automation of moving data available in bioscience literature into the model from Figures 7 or 8. Human intervention is essential in populating Table 1, to have a correct interpretation of the semantic within the model. Object properties, which secure a correct relationship between ontological individuals, should be inspected and changed by humans. We do not exclude full-scale automation in future, but at this stage there is no silver bullet in computer science which guarantees automatic and semantically correct interpretation of the meaning of "words" in biomedical discoveries using any of the available NLP algorithms. The flexibility of the proposal is in choosing excerpts of the model from Figures 6,7, 8 and making changes by humans in Table 1, dictated by the exact problem in polypharmacology. We may be in a position to use an extremely simple OWL model in some cases, or explore the semantic of a pathway ***disease-approved drug-intended target-unintended target–disease*** with the full OWL model and the most complex set of relationships between its ontological classes (Table 1). The process of reasoning will then depend on what we need to define

and discover in polypharmacology. Ultimately the goal is to move away from ***one-drug-one-target*** philosophy.

In 2022 we are confident that there should be some changes in the way we envisage computational polypharmacology for two reasons. Our current drug discoveries, development and approval strategies are based on ***one-drug-one-target*** philosophy. However successful this approach has been in securing drugs safety and efficiency, it limits our progress because all drugs have unintended targets which are not consistently exploited in drug discoveries through any computational model. *UnIntTG* are only widely acknowledged as potential side effect and source of adverse drug reactions for patients, but the nature of *UnIntTG*, for each drug, has never actively led towards systematic understanding of the power the drug multiple targets (and their impact on disease pathways). Research on *UnIntTG* and drug discovery is rather sporadic and scattered across various disciplines, and computer scientists are not necessarily leading team members in computational polypharmacology.

Second, in the last decade, we used predictive and learning technologies in biomedicine, which moved our focus on drug discoveries towards an AI pathway. They offer new possibilities of managing complex data from a pool of chemical, biological, phenotypic and network data (and genomics/proteomics in particular) in drug discovery initiatives, using ML and neural networks. This may deliver the promise of addressing production costs and the burden of complicated and expensive procedures of bringing new drugs to the market. It is premature to say that ML algorithms are sine qua non for a new era of drug discoveries and repurposing with computational polypharmacology (Juric and Ronchieri, 2022), (Juric et al., 2020), (Almami et al., 2016a).

The remarks above have their own merits, but they did not help with creating computational models for polypharmacology. Symbiosis of predictions with ML algorithms, upon an abundance of biomedical data in polypharmacology, and the support of logic and reasoning computed with SWT, as proposed in this paper, may be the answer when addressing this complex problem domain. Also, the time might have arrived for scientists, pharmaceuticals, medical profession and governments, with their drug approval agencies, to rethink the scientific process through which we test and approve drugs. Having ***one-drug-one-target*** approach is not sustainable and polypharmacology is a possible answer. Since 2011 we have not seen serious improvement towards creating computational polypharmacology and it is rather difficult to predict what the future holds.

References

Akilesh, S. M., Palanisamy, D., & Wadhwani, A. (2021). Repositioning of Drugs to Counter COVID-19 Pandemic-An Insight. Current pharmaceutical biotechnology, 22(2), 192-199.

Almami, E., Juric, R., & Ahmed, M. Z. (2016), Software Applications Built Upon SWRL Enabled OWL Ontologies In Proceedings of the 21th International Conference on Society for Design and Process Science, (SDPS '16), Orlando, Florida.

Almami, I., Almami, E., & Juric, R. (2016a) Knowledge Dissemination In Biomedical Science: Using Ontological Reasoning For The Analyses Of Activated Enzymes In Various Diseases In Proceedings of the 21th International Conference on SDPS '16, Florida.

Anighoro, A., Bajorath, J., & Rastelli, G. (2014). Polypharmacology: challenges and opportunities in drug discovery: miniperspective. Journal of medicinal chemistry, 57(19), 7874-7887.

Boran, A. D., & Iyengar, R. (2010). Systems approaches to polypharmacology and drug discovery. Current opinion in drug discovery & development, 13(3), 297.

Borkum, M.I., Frey, J.G. Usage and applications of Semantic Web techniques and technologies to support chemistry research. *J Cheminform* **6,** 18 (2014)

Chaudhari, R., Tan, Z., Huang, B., & Zhang, S. (2017). Computational polypharmacology: a new paradigm for drug discovery. Expert opinion on drug discovery, 12(3), 279-291.

Chopra, G., & Samudrala, R. (2016). Exploring polypharmacology in drug discovery and repurposing using the CANDO platform. Current Pharmaceutical Design, 22(21), 3109-3123.

Clark AM, Litterman NK, Kranz JE, et al. BioAssay templates for the semantic web. PeerJ Comput Sci. 2016;2:e61

Farrish, S., & Grando, A. (2013). Ontological approach to reduce complexity in polypharmacy. AMIA Annual Symposium Proceedings,

Gayvert KM, Aly O, Platt J, Bosenberg MW, Stern DF, Elemento O (2017) A Computational Approach for Identifying Synergistic Drug Combinations. PLoS Comput Biol 13(1)

Gkoutos, G. V., Schofield, P. N., & Hoehndorf, R. (2018). The anatomy of phenotype ontologies: principles, properties and applications. Briefings in bioinformatics, 19(5), 1008-1021.

Hoehndorf, R., Schofield, P. N., & Gkoutos, G. V. (2015). The role of ontologies in biological and biomedical research: a functional perspective. Briefings in bioinformatics, 16(6), 1069-1080.

Huang, H., Zhang, P., Qu, X. A., Sanseau, P., & Yang, L. (2014). Systematic prediction of drug combinations based on clinical side-effects. Sci. reports, 4(1), 1-7

Juric, R. (2016). Could Semantic Web Technologies Create New Computational Models Outside Semantic Web In Proceedings of the 21th Intern. Conf. Society for Design and Process Science, (SDPS '16), Florida.

Juric, R. Kim, I, (2017) Software Architectures for Smart Applications Which Merge Ontological Reasoning

with Big Data Analytics, 22nd SDPSS 2017 conference, Birmingham, AL.

Juric, R., & Almami, E. (2019). Proposing Drug Repositioning through Semantic Reasoning. proceedings of the 24th Conference on SDPS.

Juric, R., Almami, E., & Almami, I. (2018). Semantic Overlapping of OWL Models in Biomedicine. proceedings of the SDPS 2018 Workshop on Accountability in AI.

Juric, R., Che Fuh C., Kim, I. (2021) Software Architectures and Efficient Data Sharing for Promoting Continuous Drug Repurposing, Proceedings of the 54th HICSS conference, January 2021.

Juric, R., & Ronchieri, E. (2022). Semantic Framework for Practicing Data Science in Public Health Organizations during the Covid-19 Pandemics. HICSS 55.

Juric, R. Ronchieri, E, Blagojevic Zagorac, G. Mahmutefendic, H., Lucin, P. (2020) Predictive Technologies and Biomedical Semantics: A Study of Endocytic Trafficking, in Proceedings of The 13th Int. Joint Conference On Biomedical Engineering Systems and Technologies, Volume 3 Malta, February 2020.

Kataria, P., Juric, R. (2011): "Sharing Healthcare Data by Manipulating Ontological Individuals", book chapter, in: Suh, S.C., Tanik, M., Gurupur, V. P. (Eds.) Biomedical Engineering: Healthcare Systems, Technology and Techniques, Springer; 1st Edition (20 Aug 2011), ISBN-10: 1461401151, pp. 117-128.

Koay, N., Kataria, P., & Juric, R. (2010). Semantic management of nonfunctional requirements in an e-health system. Telemedicine and e-Health, 16(4), 461-471.

Lavecchia, A., & Cerchia, C. (2016). In silico methods to address polypharmacology: current status, applications and future perspectives. Drug Discovery Today, 21(2), 288-298.

Machado CM, Rebholz-Schuhmann D, Freitas AT, Couto FM. The semantic web in translational medicine: current applications and future directions. *Brief Bioinform*. 2015;16(1):89-103

Madani Tonekaboni SA, Soltan Ghoraie L, Manem VSK, Haibe-Kains B. (2019) Predictive approaches for drug combination discovery in cancer. *Brief Bioinform*atics19(2):263-276.

Paltun, BT, Kaski, S.m Mamitsuka, H. (2021) Machine learning approaches for drug combination therapies, *Briefings in Bioinformatics*, 22(6) pp 1-16.

Parisi, D., Adasme, MF, Sveshnikova,A., Bolz, SM, Moreau, Y., Schroeder, M. (2020) Drug repositioning or target repositioning: A structural perspective of drug-target-indication relationship for available repurposed drugs, Computational and Structural Biotechnology Journal, 18(2020),1043-1055.

Peters, J.-U. (2013). Polypharmacology–foe or friend? Journal of medicinal chemistry, 56(22), 8955-8971.

Pinzi, L., Tinivella, A., Caporuscio, F., & Rastelli, G. (2021). Drug repurposing and polypharmacology to fight SARS-CoV-2 through inhibition of the main protease. Frontiers in pharmacology, 12, 84.

Plake, C., & Schroeder, M. (2011). Computational polypharmacology with text mining and ontologies. Current pharmaceutical biotechnology, 12(3), 449-457.

Proschak E, Stark H, Merk D (2019) Polypharmacology by design: a medicinal chemist's perspective on multitargeting compounds. J Med Chem 62(2):420–444.

Rastelli, G., & Pinzi, L. (2015). Computational Polypharmacology Comes of Age. Frontiers in pharmacology, 6, 157.

Reddy, A. S., & Zhang, S. (2013). Polypharmacology: drug discovery for the future. Expert review of clinical pharmacology, 6(1), 41-47.

Robinson, P. N., & Webber, C. (2014). Phenotype ontologies and cross-species analysis for translational research. PLoS genetics, 10(4), e1004268.

Saaidi, R., Kataria, P., Juric R. (2011)Semantic Management of Submissions of Applications for Marketing Authorisation of Medicines", book chapter, in: Suh, S.C., Tanik, M., Gurupur, V. P. (Eds.) Biomedical Engineering: Healthcare Systems, Technology and Techniques (,Springer; 1st Edition (20 Aug 2011), ISBN-10: 1461401151, pp.99-116.

Shojanoori, R., & Juric, R. (2013). Semantic remote patient monitoring system. Telemedicine and e-Health, 19(2), 129-136.

Talevi, A. (2015). Multi-target pharmacology: possibilities and limitations of the "skeleton key approach" from a medicinal chemist perspective. Frontiers in pharmacology, 6, 205.

Talevi, A., Morales, J. F., Hather, G., Podichetty, J. T., Kim, S., Bloomingdale, P. C.,Winterstein, A. G. (2020). Machine learning in drug discovery and development part 1: a primer. CPT: pharmacometrics & systems pharmacology, 9(3), 129-142.

Tang J, Tanoli Z-R, Ravikumar B, et al. (2018) Drug target commons: a community effort to build a consensus knowledge base for drug-target interactions. Cell Chem Biol. 2018;25:224–229.

Tarabi, M., & Juric, R. (2018). Software Architectures for Smart Applications in the Management of Chronic Diseases: A Study of Reversibility of Diabetes 2. Proceedings of the 51st HICSS.

Vazquez-Naya M.J. Marcos, MR., Porto-Pazos AP, Novoa F., Valladares-Ayerbes M., Pereira Javier, R. Munteanu C. Dorado J. (2010) Ontologies of Drug Discovery and Design for Neurology, Cardiology and Oncology, Current Pharmaceutical Design, 16(24)

Vogt, L. (2019). Organizing phenotypic data—a semantic data model for anatomy. Journal of Biomedical Semantics, 10(1), 1-14.

Zhang R, Cairelli MJ, Fiszman M, Rosemblat G, Kilicoglu H, Rindflesch TC, Pakhomov SV, Melton GB (2014) Using semantic predications to uncover drug-drug interactions in clinical data, J Biomed Inform. 49(2014),:134-147.

Zitnik, M., Agrawal, M., & Leskovec, J. (2018). Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics, 34(13), 457-i466.