# Software Architectures and Efficient Data Sharing for Promoting Continuous Drug Repurposing

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## Abstract

*The proposed layered and component based software architectural style enables data sharing and accessibility of computational software components across Biomedical Science problem domains. It also opens the door to translational informatics, which bridges the gap between knowledge, generated in biomedical science, and clinical practices. Software applications created from the proposed software architectural style, are able to support continuous drug repurposing. They exploit the semantic, which exists, and is available across biomedical problem domains, between drug chemical compounds, their biological targets, particularly unintentional targets and drug therapeutic effects. The excerpt from the proposed software architecture has already been deployed in a computationally light-weight software application, which manages drug repurposing through reasoning upon the available semantic. However a full scale implementation and full deployment of the software architecture, plus data sharing across the spectrum of biomedical research and disciplines, would require some changes in the way therapeutic drugs are discovered, tested and approved.*

## 1. Introduction

Drug repurposing has been in the focus of drug development research for almost 2 decades [1] and it is recognized as an important part of new drug development processes with significant business, technical and scientific challenges and strategies [2]. Reinvestigations of existing, i.e. approved drugs, from various perspectives, including academic, existed in the literature almost 10 years ago [3,4], and drug-disease relationships, for discovering novel uses of drugs [5] have been exploited for triggering research on computational drug repositioning [6] and its prediction in complex diseases [7]. It is interesting that almost 10 years ago a database for network-based drug repositioning was developed and in 2013 an initiative to start open source approaches for the repurposing of existing and failed candidate drugs was proposed in [9]. At the same time we had one of the first attempts to use machine learning for drug repurposing [10], and shortly afterwards interest in applying drug repositioning for discovering cancer drugs took off [11,12]. In the last 5 years, a variety of publications, which address new challenges in drug repurposing, started appearing [13]. Some of them paid attention to the barriers in the process of drug discoveries, such as clinical trials, where their costs may adversely affect drug development [14]. Updated and modernized aspects of drug repositioning were urgently needed [15,16,17] and in the last 2 years we find publications in which trends, resources, repositioning approaches and challenges have been debated again [18-21]. Computational drug repurposing has started [22], their validation strategies have been reviewed [23] and finally there is an initiative to look at various tools which could accelerate the drug discovery process [24,25]. In this year, 2020, we still find new publications which talk about challenges and opportunities with drug repurposing [26,27], but the appearance of the covid-19 pandemic, brought into daylight all existing ideas on drug repurposing, aiming to answer the demand for finding treatment for coronavirus [28-33].

This rather long introduction to the world of drug repurposing indicates that we have two problems here.

a) However we wish to believe that experimental and computational methods, for supporting drug repositioning, have been defined and exercised in the last 2 decades, obviously there is no universal and known computational method for supporting the process and there is no comprehensive drug repositioning strategy.
b) The process of drug discoveries and repositioning is far from being trivial, but it is likely that it faces similar obstacles found in translational informatics [34-36]. Scientific discoveries, data, and information, available from experiments and

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research in biomedical science do not necessarily reach many sub-disciplines across biomedicine, pharmaceutical science and clinical practice. Sharing of data and scientific discoveries is essential for the journey forward and there is no evidence that it is happening at present (in 2020).

It is very difficult to address a) and b) above. However, there is something interesting discovered in all these publications from 2004 onwards. Computer scientists are rarely found in the teams who have led research on drug repurposing. Any novel solution in drug repurposing would have some kind of computations at its core, and would require the expertise of computer scientists to guarantee generic and deployable solutions. This means that now, in 2020, when software technologies and modern computational environments have penetrated almost every aspect of our lives, it would be unreasonable to keep computer science away from research tables and debates on unresolved challenges we still have in drug repurposing. The issue of data sharing, as described in b) above can be addressed and resolved from computer science and software engineering perspectives and consequently, if we exercise a small shift in thinking, we might be in a position to influence existing or find new pathways towards research solutions for problems described in a).

The authors' interest in drug repurposing, translational informatics and knowledge sharing in biomedicine is not new [37,38,39]. However, the research was mainly focused on computational models which could bring solutions to problems in biomedical informatics, through the manipulation of semantics stored in such environments. What is currently needed is to collate all proposed computations into a conceptual software architectural model, which can show exactly how information and data are possible to share in the biomedical field and relevant computations built across shared data. These conceptual software architectures are applicable in many biomedical problem domains [40] and it is just a small step forward to apply them in drug repositioning.

This paper proposes a generic, layered and component based software architectural style [41,42] for creating software applications which could initiate addressing a) and b) above. However, the most important role of the software architecture (SA) is to focus on sharing of data and knowledge across wider problem domains in biomedicine and pharmacology, and reusing existing computational models, with their data repositories for enabling more efficient discoveries of data for drug repurposing. A working prototype from [43] proves that there are still opportunities to create new computations, which would find a way towards drug repurposing. This is particularly true if we employ software technologies which could interpret the meaning of biomedical data in data-sharing, and secure reasoning upon its semantic, for the purpose of finding relevant semantic in data which could take us toward drug repurposing. Therefore Semantic Web Technologies (SWT) [44,45] and their languages, OWL and SWRL [46,47] could still be used for retrieving existing knowledge in formal medical and biomedical ontologies. The SWT can also be used for reasoning upon SWRL enabled OWL ontologies, in order to create new computations which would be specific for drug repurposing, as illustrated in [43].

Finally, the proposed SA should not be interpreted as another attempt to create a new platform or framework under which we can create a miracle solution for drug repurposing. It should be the opposite: a new light-weight software application, built according to the architectural style, easily deployable and not creating enormous computational burdens on anyone who wishes to run such computations. Obviously, the issue of data sharing is essential and could trigger further thinking in the manipulation of data from different sources or created by different parties, which might not be directly involved in drug repurposing. However, these are the questions which could be answered by corporations and laboratories which generate biomedical data and would depend on their readiness to contribute towards achieving a joint goal by sharing them. Consequently, this research can not answer such questions, but could prove that the proposed SA is feasible, and can be deployed if data sharing culture is in place.

The paper is organized as follows. Section 2 overviews related work in which we look at specific computational solutions, using the SWT for drug-repurposing. Section 3 elaborates on the proposed SA for addressing the problem and in Section 4 we illustrate the proposal and in section 5 give a generic ontological model which would infer drug repositioning according to the semantic relationships between drugs and their (un)intended targets. We conclude in section 6.

## 2. Related Work

At the time of writing the paper there were no publications which propose a software architectural model for long term solutions in drug repurposing, which would include data sharing and reusability of existing computations. In this section, a review of papers which come close to the excerpts from this proposal are outlined. Attention is also paid to computational solutions, which use reasoning, SWT and formal ontologies to aid the drug repurposing process.

There is one publication, which helps in promoting the feasibility of our proposal and, at the same time, influences the implementation of the prototype from [43]. The idea of exploiting the drug-target identification, using side-effect similarity, as described in [48], may have an impact on the process of discovering new purposes of existing drugs. It enables focusing on phenotypic side-effect similarities in order to infer if two drugs share the same target. The power of side effects could add more semantics to any OWL model used for knowledge presentation and strengthen the reasoning process needed in drug re-positioning. However, this is not the only way of reasoning/inference for drug repositioning, but it remains a powerful mechanism for computational analysis of the semantic of drugs and their unintentional biological targets. If these ideas could be fully converted into a computational model as in [43] then there is an opportunity to find more overlapping semantic between drugs and their intended and non-intended biological targets.

A new wave of innovations, which use SWT tools for drug discoveries from [49] would fit within the main structure of the proposed SA model. However, none of the papers referenced in [49] come close to the proposed SWRL enabled OWL model from [43] for one important reason. Our proposal includes building a software engineering solution with a software application in mind, and creating a computational model based on SWRL enabled reasoning. This is rather different to the traditional use of ontologies for semantic annotations in drug discoveries.

The deployment of learning and mining technologies for drug re-positioning was initiated in this decade [50,10, 7] because of an excessive amount of data and information we have been generating in Biomedical science and research. Consequently, we talk about databases for network based drug repositioning [8], the changed landscape of academic drug discoveries [15] and pathway analysis based on Public Database mining as in [13], as mentioned in the introduction. However, this we should not pursue a uniform computational model for this problem domain. It is sufficient that all current results of biomedical research, including predicting drug side effects from Drug – Target relationships as in explained [51] and relating proteins to drug side effects as described in [52], and finding their space in computational models from the proposed SA, which was emphasized in [43]. It goes without saying that work from [53-55] would find its space in the proposed SA model.

It was mentioned in the Introduction that a very rich, published literature, focusing on drug repositioning, has been sourced from papers which do not involve enough (if any?) computer scientists. Therefore all their work remains in the field of knowledge building and classifications. This is far away from any universal and long term solutions which could enable a constant process of drug repositioning. Hopefully, this proposal might change the picture of the this problem domain landscape.

## 3. The Proposal: SA Model

The proposed SA model is in Figure 1. As a layered and component based architectural style it has specific characteristics which resemble the MVC pattern, typical for software modelling, where separation of concerns is essential. For readers not familiar with principles of software architectures and patterns, it is important to pay attention to layering of software components which secure the separation of user interfaces, computational components and software components which house data and data repositories, in general. Therefore each layer of the SA model in Figure 1 contains software components of the same type.

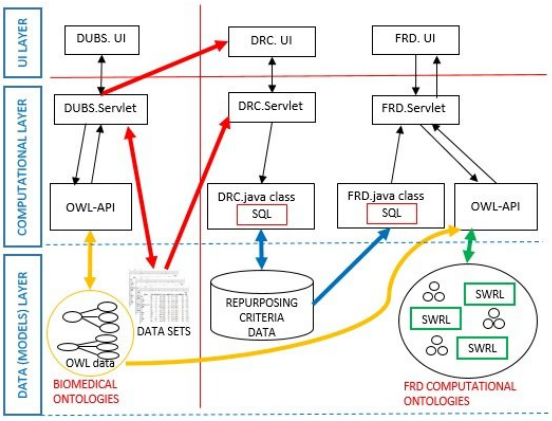


**Figure 1: The Proposed Software Architecture for FRD (Finding Repurposed Drug)**

The computational layer is very important because it can house a variety of computational models and thus the SA ensures that these computations are fed by relevant data repositories. Very often in computational components we recognize a variety of functionalities which are supposed to be delivered by software applications generated from the SA. Therefore the Data layer must contain all possible data repositories which might be needed by any of the computational components from the middle layer.

One of the most important aspects of software component layering is that its deployment is managed by Integrated Development Environments (IDE) and thus these tools secure communication between layers. Also the proposal strictly follows an architectural style

which allows communication between software components by utilizing the role of each layer. The separation of concerns allows adding more software components in each layer if needed. Therefore more computations are welcome, as long as we have data repositories available for running such computations. Distribution of these software components is feasible and thus they may not in reality always belong to the same software applications. In other words data repositories may be shared across various computations as long as there is agreement between different parties, who are the owners of these data repositions that data could be shared.

In summary, data sharing across computations is not feasible i) if the rules of software component layering are not followed and ii) if we do not keep separation of concerns in mind. Bearing in mind that today, we often compute with data which do not originate in our computational environment, then it is of the upmost importance that the SA defines which computations will be dependent on which data repository(ies).

### 3.1. Description of Computational Software Components

The SA from Figure 1 is generic, but software components within it are technology specific. When defining and proposing any SA style, we must ensure that it is deployable within an IDE. In this particular case, NetBeans IDE and J2E technology are used for the deployment of the proposal and components carry technology specific tags. Therefore the computational components in Figure 1 are deployed as either servlets, or java beans, which in turn means that we can include Java level of programming, SQL types of code together with potential database definitions and retrievals plus any other type of computing we may need, within the middle layer of Figure 1. OWL-API is a software component which contains an API in order to take us towards software components deployed with different technologies: SWT and its languages. In these cases, computations within SWRL enabled OWL ontologies happen with a rule language, which performs reasoning upon data stored in OWL concepts. This means that reasoning is performed using an unusual, but often used data repository denoted in Figure 1 as green and yellow circles (left and rightmost parts of the data layer in Figure 1). SWT is a different technology compared to our traditional database management and programming with procedural languages and thus this computational part has 2 pathways: either retrieval of data through OWL-API using SPARQL or reasoning upon data using SWRL. Obviously data stored in OWL ontologies could be accessed through OWL-API only, but these plug-ins are available across many IDE and work very well within Android operating environments. In summary, a green bidirectional arrow denotes initiation of SPARQL retrievals or reasoning with SWRL, plus any other type of defining essential OWL concepts or defining SWRL rules in advance. The yellow bidirectional arrow means that the model supports retrievals with SPARQL and definition of OWL classes and their semantics. A one-directional yellow arrow supports SPARQL retrievals only. Blue arrows refer to database definitions, retrievals and updates.

Red arrows denote access to unstructured data and data sets, often used for processing big data and running various types of predictions, such as machine learning classifications (to mention just the most popular way of performing predictive inference in modern computing). These software components, reserved for ML algorithms, are tagged as servlets, but they could have their own API which could take the computations towards software tools to run predictions upon available data sets. This part of the SA model open doors to running predictions with ML algorithms, together with SQL retrievals from traditional transactional processing and reasoning upon OWL concepts, all under one umbrella of software applications which uses a variety of software technologies.

### 3.2. Description of Functionalities Defined in the SA

Figure 1 introduces three different types of functionalities. They are visible through its vertical lines, which cross the layers of the SA.

On the right part of the figure, we define FRD which stands for **F**inding **R**epositioning for a **D**rug. A possible reposition is a result of reasoning upon SWRL enabled OWL ontology, denoted in the green circle which is a software component containing OWL concepts and reasoning rules associated to them. However the reasoning depends on the OWL model, and the OWL model in turn depends on the knowledge extracted from Biomedical data repositories. They can range from formal ontologies (the left bottom part of the SA) and various unstructured (e.g. data sets) and structured repositories available across biomedical research. Therefore, Figure 1 signals that we have to have a structured repository for defining drug repurposing criteria, which can be generated for a particular drug after retrieving the existing formalized knowledge and data from biomedical experiments. The SQL retrievals through FRD java class brings semantics for creating ontological concepts and reasoning rules in FRD computational ontologies.

The middle part of Figure 1 accommodates the functionality of **D**efining **R**epurposing **C**riteria (DRC).

This computation is likely to operate in SQL like environments where various database retrievals from biomedicine could bring enough knowledge to define criteria. The data component of this functionality is represented by only one database symbol, but in reality, there should be numerous structured repositories which can contain semantic relevant for defining the criteria. Whether these repositories should belong to the middle functional column (DRC) or to the left one, could be debated, but the layered SA could accommodate any changes we may have when associating computations from the middle layer with data repositories.

The left part of Figure 1 is likely to be found outside the software applications which exactly compute drug repositioning (right part of Figure 1). This means that the world of biomedical knowledge is responsible for creating and storing their knowledge. It may contain its own computations in order to process biomedical data as part of their own research; it may run ML algorithms for the purpose of running biomedical experiments and research and may create formal ontologies (yellow oval symbol) for accumulating biomedical knowledge. **DUBS** stands for **D**efining and **U**pdating **Bi**omedical **S**ources, and thus it is likely that the DUBS.Sservelet will operate outside the environment where FRD computes. However, their "connection" is in sharing of data (possibilities are a yellow one-directional line and red arrows).

## 4. Illustration of the Proposed SA

Figure 2 denotes which part of the proposed SA was deployed and which data repositories we used in the deployment, for creating a software application. The software application is circled with a green broken line.

The FRD Servlet and Java classes were programmed, but we did not have the Repurposing Criteria Data repository explicitly available and thus had to create it. The deployment of the FRD functionality has been published in [43] with ontological concept and reasoning upon them. Figures 3 and 4 show its OWL model and the reasoning process, both taken from [43]. The most important part was the repurposing criteria, which was deployed as OWL constraints but extracted from the literature, i.e. published papers because there is no formal source which stores semantics relevant to drug repurposing.

On this occasion, we looked at side effects of drugs approved for a specific target (gene, biological manifestation) and reason upon the semantic overlapping between

***Disease-drug-approved target-side effects-drug unintentional target-disease***

This was easy to collect and use as our repurposing criteria, because some of the publications available online do follow predication semantics [56, 57] in which relationships between drugs and their targets can be presented as the ***subject-predicate-object*** triples [58,59]. Considering that OWL concepts are based on RDF triples and they do support semantically ***subject-predicate-object*** notion, it was extremely easy to create OWL concepts, find their constraints and write SWRL rules for the example above.

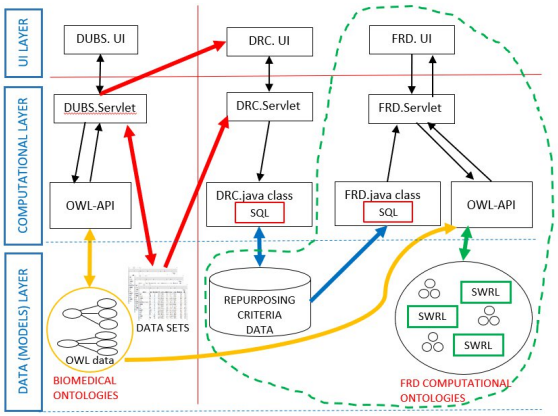


**Figure 2 Excerpts from the Implementation**

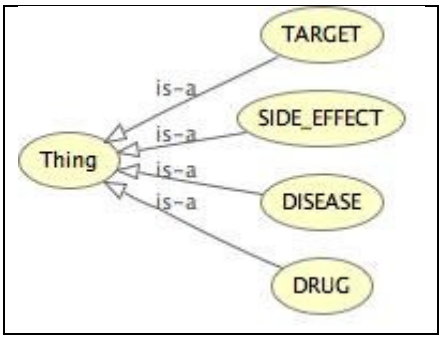


**Fig. 3 Ontological Classes for DRUG Ontology [43]**

The reasoning rules have "found" that ***"Amantadine could be repositioned for Parkinson's disease"***.

It is important to note that the implemented model and reasoning from [43] proved the concept: we could infer drug repositioning through reasoning. However, our criteria for repurposing is one of many possibilities to represent a complex relationship between drugs and their biological targets, which can be formalized though OWL concepts and used in reasoning.

## 5. Formal Ontological Model for FRD Computations

The OWL model from Figure 3, is repurposing criteria specific in terms of using ***side effects*** for finding possibilities of drug repurposing. However, this paper offers a generic OWL model, for any other type of repurposing criteria. For example, it could use semantic relationship between drugs intentional and non-international targets. Figure 5 shows a generic OWL model with the reasoning processes interwoven. This is probably one of many possibilities of using description logic in managing overlapping semantics between OWL terms for drug repurposing, and thus more debate is needed to find out which repurposing criteria could be seen as the most generic.

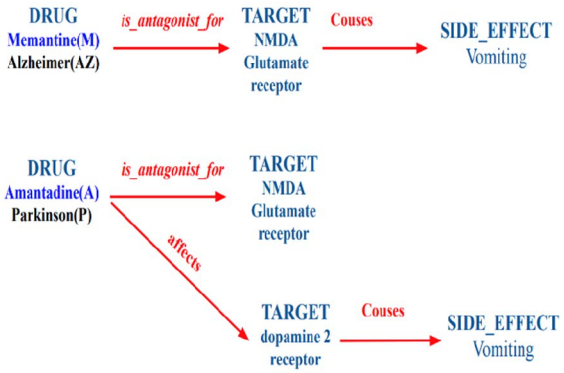


**Figure 4: The Reasoning Process for Inferring Drug Repurposing (with OWL Classes and Constraints) [43]**

The generic OWL model with the reasoning process in Figure 5 is self-explanatory. Drug Drdug$_i$ is described through its intentional $\{t_{i,1}, t_{i,2}, \ldots t_{i,n}\}$ and unintentional targets: $\{t_{i,n+1}, t_{i,n+2}, \ldots t_{i,m}\}$, and the same applies to drug Drug$_j$ with $\{t_{j,1}, t_{j,2}, \ldots t_{j,k}\}$, and $\{t_{j,k+1}, t_{j,k+2}, \ldots t_{j,l.}\}$ where i,j are elements of N. The most powerful part of the model is very difficult to draw and requires a detailed table with object properties defined between the domain and range classes, but the bi-directional black arrow between Drugi and Drugj classes is the place where we define object properties on the diagram. They may contain all possible semantic, including the overlapping semantic between Drugi and Drugj, plus the set of targets: $\{t_{i,1}, t_{i,2}, \ldots t_{i,n}\}$, $\{t_{i,n+1}, t_{i,n+2}, \ldots t_{i,m}\}$, $\{t_{j,1}, t_{j,2}, \ldots t_{j,k}\}$ $\{t_{j,k+1}, t_{j,k+2}, \ldots t_{j,l.}\}$. What is important to read from the diagram is that the result of reasoning is not a particular new drug: it is an object property between existing drug Dj and Disease$_i$, which did not exist before (red arrow shows where the reasoning happens and what is being inferred). From this perspective, the model does not depart from the implementation in [43], where its inference is in the form of the object properties. This means that the individual of Di class (a particular DRUG) has been repurposed to be relevant for Disease$_s$. Therefore the power of the model is in our way of describing drugs through their targets. Targets, from the computer science point of view, can really be ANYTHING which contains the semantic relevant to the drug and thus the model also allow predicate semantic to be used as much as possible and pay more attention to un-intentional targets, which may hide drug effects not visible, or known or even not reported. For readers interesting in the applicability of generic OWL models, as in Figure 5 in computational reasoning, when OWL model and SWRL reasoning become a core part of the main computational model, we suggest reading the authors' earlier publications.

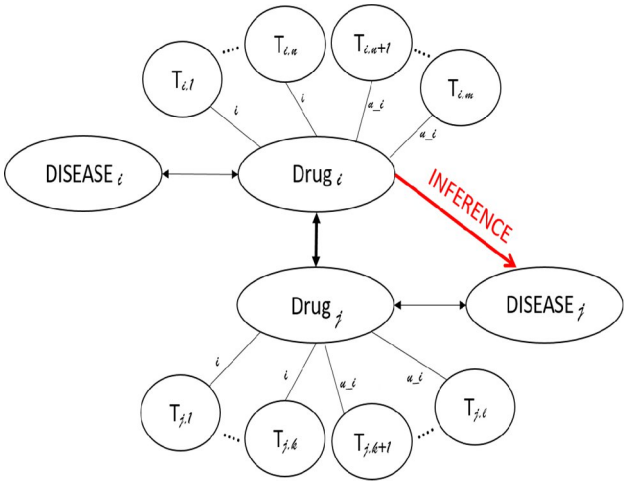


**Figure 5: Generic OWL Model for continues Drug Repurposing**

## 6. Conclusions

This paper touches the tip of the iceberg of the problems we face in the field of sharing and disseminating data and knowledge across Biomedical science and related disciplines [59] and the issue of drug repositioning is not an exception. Since the early 2000s we have not conquered the drug repositioning problem, in spite of reading some very interesting proposals and ideas. To the eyes of computer scientists, the lack of their involvement in the problem solving process is a problem. Also, the absence of a generic SA model which must allow data sharing across disciplines which should enable sharing of data and knowledge, can not take us forward in drug repositioning. The proposal shows how feasible and efficient some software solutions in this field could be. The issues of heterogeneity and interoperability in this field, privacy of medical data and

data in general are very easy to resolve and the model we propose, together with its separation of concern can guarantee almost all of them. These types of SA have been around for almost 2 decades and are probably one of the most successful ways of constructing software in modern computing.

This work would be primarily of interest to pharmaceuticals and research in new drug development. However, there is something else here which should attract the attention of any lab and research group in Biomedical Science or Pharmacology. Their research results sometimes remain completely buried in peer-reviewed publications, which are being generated at enormous speed, as we write this. It has become impossible to have any overall picture of research progress in Biomedical science and interesting details of research results sometimes never get read or evaluated. There should be a joint interest in sharing data and information across all these disciplines through software applications and the message from computer scientists is that this is very feasible and not difficult to design and implement.

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