



Original article

A computational approach to predict multi-pathway drug-drug interactions: A case study of irinotecan, a colon cancer medication

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ABSTRACT

Drug-drug interactions (DDIs) are a potentially distressing corollary of drug interventions, and may result in discomfort, debilitating illness, or even death. Existing research predominantly considers only a single level of interaction; however, serious health complications may result from multi-pathway DDIs, and so new methods are needed to enable predicting and preventing complex DDIs. This article introduces a novel method for the prediction of DDIs at two pharmacological levels (metabolic and transporter interactions) by means of a rule-based model implemented with Semantic Web technologies. The chemotherapy agent irinotecan is used as a case study for demonstrating the validity of this approach. Mechanistic and interaction data were mined from available sources and then used to predict interactors of irinotecan, including potential DDIs mediated by previously unidentified mechanisms. The findings also draw attention to the profound variation between DDI resources, indicating that clinical practice would see significant value from the development of an evidence-based resource to support DDI identification.

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1. Introduction

Polypharmacy which is having simultaneous prescriptions for at least five medications, has become increasingly prevalent in recent years, as has the concomitant risk of patients experiencing major drug-drug interactions (DDIs) (Létinier et al., 2019). In addition to increased risk of death, DDIs have been implicated in 0.12% of re-hospitalizations (Andersson et al., 2018 May). As the number of prescriptions per patient increases, DDIs are expected to have even greater impact (Létinier et al., 2019), yet the study and identification of potential DDIs will also become increasingly difficult. Early identification of DDIs is hindered by several factors, most particularly the lack of DDI information available before a drug enters the market (LePendou et al., 2013; Reis and Cassiani, 2010). The clinical trials carried out ahead of a new drug's approval are

typically insufficient to test DDIs, most notably because the patients enrolled in the study may not have been prescribed with the interacting drugs. Individual patients may also be predisposed to DDIs on account of idiosyncratic factors such as diet, dosage, and age-related changes in physiology (Patel et al., 2014). To address these issues and minimize the risk of interactions, researchers have begun investigating DDIs through leveraging published resources and using diverse informatics approaches (Percha and Altman, 2013). In particular, informatics approaches offer promising opportunities to identify DDIs before they are encountered clinically. To date, these approaches have been used with extensive biomedical data from published literature, the FDA's Adverse Event Reporting System (FAERS), patient electronic health records (EHRs), and drug information sources (Percha et al., 2012; Tatonetti et al., 2012; 4: 125ra31–125ra31.; Zhang et al., 2014; Herrero-Zazo et al., 2015).

While informatics studies have made significant headway on identifying DDIs, they only capture a portion of the available DDI data (Paczynski et al., 2012) and have predominantly focused on single interaction pathways, mainly metabolism-based interaction (Tari et al., 2010; Preissner et al., 2010). Consequently, the mechanisms of other interactions have not been investigated and described, which increases the difficulty of detecting potential DDIs. Researchers have therefore placed significant effort into the development of informatics approaches that are able to identify and illustrate different mechanisms of interaction in the context

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of DDIs (Berger and Iyengar, 2011). For instance, measures of drug similarity have been developed and mechanistic information have been successfully applied not only to predict DDIs, but also to predict the ways in which drugs interact (Ferdousi, 2017). Additional features used to identify and better understand DDIs and mechanisms of interaction include Semantic Web Technologies and Linked Data (Noor et al., 2017 May 1), molecular structures (Vilar, 2012), interaction profile fingerprints (Vilar, 2013), and drug and protein properties (Kamdar and Musen, 2017).

Despite these advances, existing approaches employed to predict and identify DDIs still face several limitations, including the validation process and mechanistic coverage. The validation process refers to the gold standard DDI source used when developing and testing the method. At present, there is neither a single comprehensive database of DDIs nor an integrative technique that incorporates all extant data in order to predict DDIs before they manifest in patients (Roblek et al., 2015; Banda et al., 2015; Scheife et al., 2015; Lewis, 2010). Meanwhile, mechanistic studies have focused predominantly on using pharmacokinetics and pharmacodynamics to predict and demystify DDIs. This focus leads to neglect of other possible interaction pathways, and therefore misses effects that result from two or more interactive mechanisms, termed multi-pathway DDIs. An example drug with multi-pathway DDIs is cyclosporine, which interacts with many cholesterol-lowering HMG-CoA reductase inhibitors (statins) by simultaneously inhibiting CYP3A4-mediated drug metabolism and also the polypeptide-mediated transport of drugs into hepatocytes, which is required for therapeutic activity of statins (Asberg, 2003).

Here we describe a computational method that utilizes Semantic Web technologies to identify and predict potential DDIs at two pharmacological levels. Semantic Web technologies provide “a rigorous mechanism for defining and linking data using web proto-

cols in such a way that the data can be used by machines not just for display, but also for automation, integration, and reuse across various applications” (Pathak et al., 2013). Our method integrates mechanistic and DDI information from multiple drug information sources: DrugBank (Wishart et al., 2008), the National Drug File – Reference Terminology (NDF-RT) (Brown et al., 2004), the National Cancer Institute thesaurus (NCIt) (de Coronado et al., 2004), the Pharmacogenomics Knowledge Base (PharmGKB) (Klein et al., 2001), and the Unified Medical Language System (UMLS) (Bodenreider, 2004). Subsequently, it uses a semantic rule-based model to identify potential multi-pathway DDIs resulting from metabolic and transporter interactions. To illustrate the utility and validity of this approach, a case study was performed on the chemotherapy drug irinotecan, whose pharmacokinetics profile is well documented (Mathijssen et al., 2001).

2. Methods

To ensure accurate discovery of multi-pathway DDIs, it is necessary to have a knowledge framework that incorporates information on both metabolism and transport. As no extant knowledge base supplies both levels of information, it was necessary in this study to develop one that did. Entries in the knowledge base were created and stored using the Java framework Jena (Carroll et al., 2004; Owens et al., 2008). Fig. 1 shows the overall workflow of the multi-pathway DDIs prediction method.

2.1. Data sources

Five key sources were used to develop the DDI knowledge base: DrugBank (which contains detailed information on drugs and their

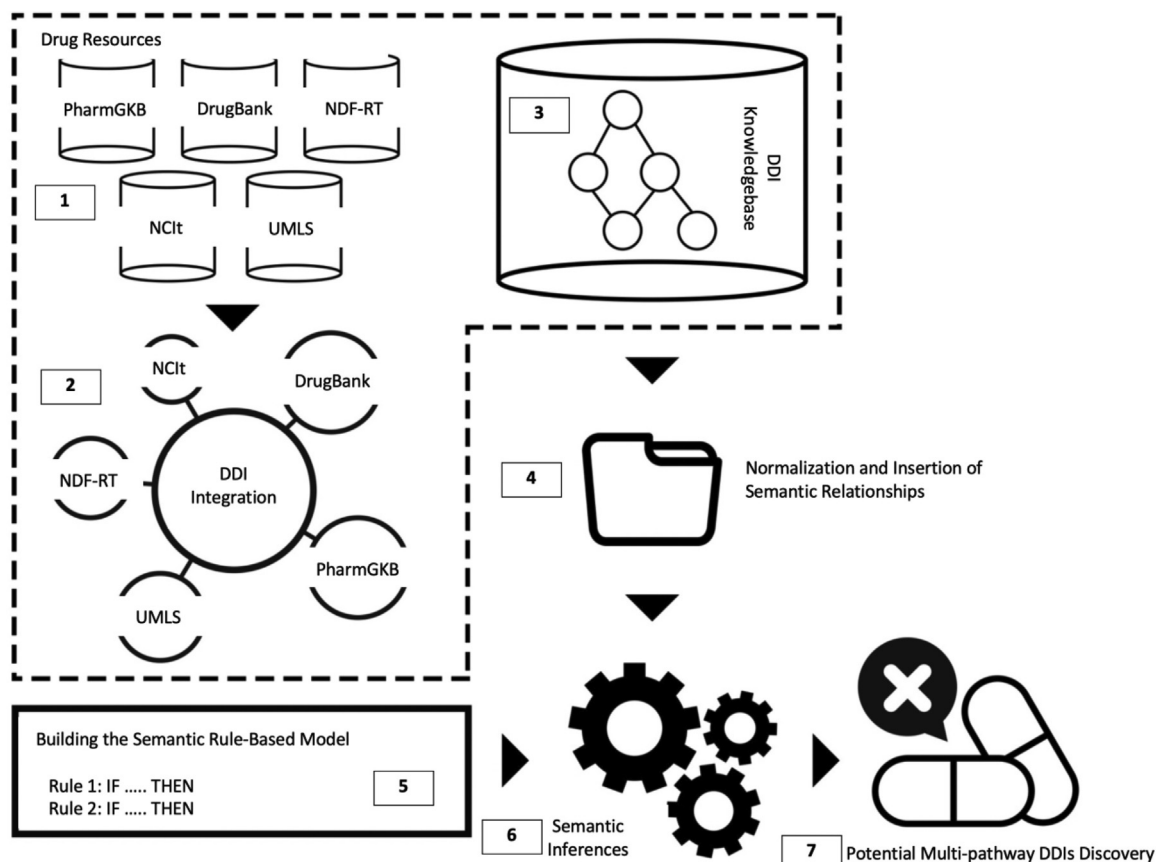


Fig. 1. Multi-pathway DDIs workflow. Starting with five different drug resources, a DDI knowledge base was developed through semantic integration. Multi-pathway DDI prediction was performed by the rule engine.

targets), PharmGKB (which documents significant drug-gene relationships), NDF-RT (an ontology that describes and models drugs within pharmacokinetic, pharmacodynamic, physiological, and related disease domains), NCI (an ontology for medical and translational research vocabulary, focused on cancer), and the UMLS Metathesaurus. The semantic representation, integration, and storage of these sources in the DDI knowledge base fills in critical knowledge gaps in drug information. The backbone of the knowledge base was the UMLS terminology integration system (Version 2020) provided by the National Library of Medicine (NLM), which has been stable for more than 20 years. The information imported from each source was as follows: drugs and their associated transporters from DrugBank, drug pharmacokinetics from NDF-RT, drug metabolic properties from NCI, and specific associations of drugs with enzymes/transporters from PharmGKB. Data from the UMLS, NCI, and NDF-RT were stored in a local MySQL database, while data from DrugBank (<https://www.drugbank.ca/releases/5-1-2/downloads/target-approved-polypeptide-sequences>) and PharmGKB (<https://www.pharmgkb.org/downloads>) were downloaded on November 2019.

2.2. Adding resources into the DDI knowledge base

The reference set of concepts in the knowledge base consisted of Concept Unique Identifiers (CUIs) from ULSM that had been converted to DDI Unique Resource Identifiers (URIs). Information from other data sources was mapped to these reference concepts. The knowledge base was built on four selected UMLS Metathesaurus tables: *MRCONSO* to standardize drug names, *MRREL* to add semantic relationships, *MRSAT* to map external sources, and *MRSTY* to check semantic groups and assure the quality of the mapping process between sources (Bodenreider and McCray, 2003). All knowledge base resources, including external sources, were represented as UMLS CUIs in order to avoid any extra linking between URIs or need for complicated inference syntaxes. Due to being already included in the UMLS, NDF-RT, and NCI data were added to the knowledge base directly during UMLS processing. Subsequently, DrugBank and PharmGKB data were integrated through cross-referencing properties and using the SPARQL/update technique to harmonize identifiers.

As a test case, DrugBank data on irinotecan was added to the knowledge base by means of cross-referencing the Anatomical Therapeutic Chemical (ATC) system, in which drugs are categorized by their therapeutic, pharmacological, chemical properties, active ingredients, and the systems or organs affected (WHOCC, 2020). As this system is incorporated in the UMLS Metathesaurus, CUIs associated with ATC identifiers can be obtained by querying UMLS. In the ATC system, irinotecan is given the unique identifier L01XX19, which maps to CUI C0123931. The corresponding DrugBank identifier, DB00762, was accordingly replaced with C0123931, and PharmGKB information was similarly integrated.

2.3. Normalization and insertion of DDI semantic relationships

In the Resource Description Framework graph of the DDI knowledge base, resources were linked by way of semantic relationships (predicates) from the UMLS *MRREL* table. During the process of mapping data sources, additional relationships were inherited from PharmGKB and DrugBank. All semantic relationships were reviewed manually, and relationships were grouped when possible in order to simplify and remove redundancies. For example, irinotecan was linked to CYP3A4 in NCI with the *chemical_or_drug_is_metabolized_by_enzyme* relationship, while in DrugBank the two were connected with *substrate_of*. As the same resources were

involved (irinotecan to CYP3A4), we grouped the two relationships and stored them under *drug_is_metabolized_by_enzyme*.

2.4. Description of a semantic rule-based model

Among the most powerful tools of the Semantic Web is inference, the process of arriving at conclusions by reasoning from evidence and conditions. We performed inference using Jena's generic rule engines (Jena and Reasoners, 2015), particularly the forward chaining technique. Using irinotecan as a test case, we identified potential interaction candidates based on similarities at two pharmacological levels (metabolic and transport). That is, drugs were assumed to be potential interactors of irinotecan if they and irinotecan shared metabolic pathways (i.e. CYP3A4 processing) and transporters (i.e. P-glycoprotein [P-gp]). These inferences were made using a semantic rule-based model with the PharmGKB knowledge base as the source of evidence to ensure that only drugs sharing a metabolic and transporter pathway with irinotecan were considered. The inference model is graphically represented in Fig. 2, including the forward chaining rule used to identify potential DDIs.

2.5. Analysis of DDI source variation

Eighty DDIs were reported for irinotecan. A conformity sample was constructed for these DDIs, in which a value of 1 indicated the presence of a reporting source and a value of -1 the absence of a reporting source. Where two reports had opposing scores, the mean of 0 would indicate absolute disagreement. Similarly, two sources in agreement would have a mean of either 1 or -1, both indicating absolute agreement. Agreement was evaluated regardless of whether a DDI was reported or not reported by any two sources, thus only the magnitude of the mean need be considered.

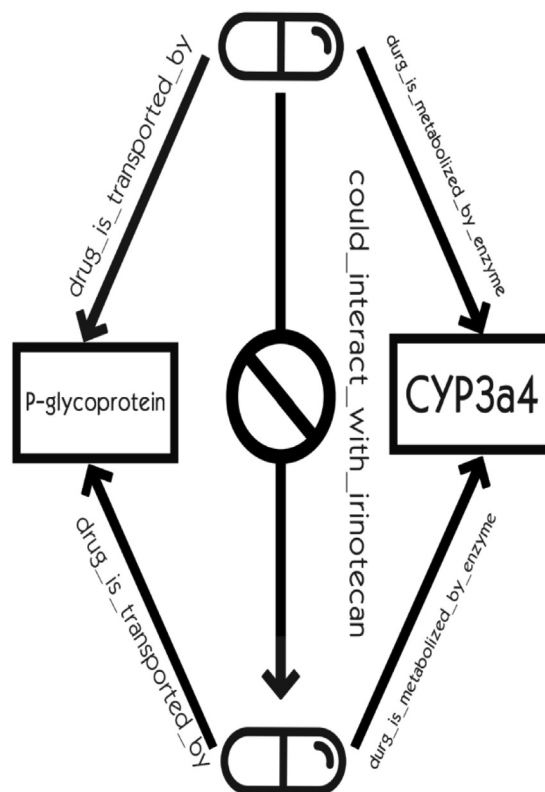


Fig. 2. Model schematic for multi-pathway inference discovery of irinotecan interactors.

Reports were also scaled by a trust score (weight) for each source; however, for the purpose of the case study, all sources were considered to have equal weight, preserving fairness and objectivity. In hypothesis testing, means and standard deviations were first calculated for the sample comprised of mean magnitudes (conformity values). Potential population means were then assumed so that 95% confidence intervals could be determined.

3. Results

3.1. Identification of potential Multi-pathway DDIs using Semantic inference

After applying the semantic rule-based model, a total of 215 FDA-approved drugs were identified as potential interactors of irinotecan. These drugs were all inferred as being metabolized by CYP3A4 and transported by P-gp, and those associations were validated with evidence from PharmGKB. Out of the 215 candidate interactors, only 116 had validating evidence in PharmGKB.

Of the 116 drugs with validated inferences, 28 had potential metabolism-based interactions with irinotecan (either inhibition or induction), another 28 had potential transporter-based interactions (either inhibition or induction), and 8 drugs did not inhibit or induce CYP3A4 or P-gp, but were considered co-substrates for both (similar disposition). The remaining 52 drugs were inferred to potentially interact with irinotecan through both transporter and metabolic mechanisms (Fig. 3).

3.2. Validation of predicted potential Multi-pathway DDIs

As no single comprehensive database of DDIs exists (Ayvaz et al., 2015), the 116 predicted interactions were compared against five different commercial and free license DDI information sources: Drugs.com (Drugs.com | Prescription Drug Information, Interactions Side Effects [Internet]. [cited, 2020]), Lexi-Comp (Lexicomp® Online | Clinical Drug Information [Internet]. [cited, 2020]); Micromedex Solutions (Micromedex® Healthcare Series. [Internet]. Thomson Micromedex, 2020), Medscape (News and Trials, 2020), and finally the Potential Drug-Drug Interactions (PDDIs) source by Ayvaz et al. (Ayvaz et al., 2015), which combines five clinical sources, four natural language corpora, and five pharmacovigilance sources. Notably, Zhang et al. (Zhang et al., 2014) suggest that when using extant curated data sources for validation, as here, the incompleteness of those sources could lead to many false positives and impaired precision. Tari et al. (2010) also reported limitations of using DrugBank as a gold standard for validation, in that only 11.0% of their results were represented in the database, while 77% were detected via literature search; therefore, poor recall is also an issue with curated databases. In this study, 80 of the predicted DDIs were found to be reported in the collected

sources, while 36 were not represented in any curated source. Of those 36, supporting evidence for 12 was obtained from published literature and other clinical websites (Table 1) (Supplementary Tables 1, 2, and 3). The remaining 24 interactions have never been studied or discussed in either the medical literature or in commercial and free DDI sources.

3.3. Statistical significance of predicted potential Multi-pathway DDIs

The gold standard for this study was the PDDIs source from Ayvaz et al., as it is comprised of 14 publically available sources of DDI information. The significance of the overlap between model results and documented PDDIs was evaluated by Fisher's exact test on a two-by-two contingency table (Table 2).

3.4. Precision and recall of predicted potential Multi-pathway DDIs

The recall and precision were additionally calculated for evaluation of the predicted interaction candidates. As described above, of the 116 potential interactors, 80 were validated with support in curated databases (true positives, TP) and 36 were not (false positives, FP). As a count of false negatives (documented interactions not predicted by the model) is required to determine recall, all irinotecan interactions were individually retrieved from PDDIs, Lexi-Comp, Drugs.com, Micromedex Solutions, and Medscape sources, then combined and cleaned of duplicate reports to produce a total of 547 interacting drugs. Subtracting the 80 true positives gave 467 as the number of false negatives (FN). The recall then was computed as:

$$\left(\frac{Tp(80)}{TP(80) + FN(467)}\right) \times 100\% = 14\%$$

and the precision as:

$$\left(\frac{Tp(80)}{TP(80) + FP(37)}\right) \times 100\% = 68\%$$

The poor recall of the inference model can be attributed to the strict restrictions used to define interactors (i.e. metabolism by CYP3A4 or transport by P-gp). Notably, in the context of DDIs, the relevance and precision of information is key; that is to say, for the purpose of this case study, precision is more important than recall. The recall can also be improved in future by modifying the model to account for enzyme-transporter co-interactions.

3.5. Consensus of DDIs among data sources

The various data sources demonstrated significant differences in terms of the number and coverage of DDIs. For instance, NDF-RT listed seven drug interactions for irinotecan, while Drugs.com reported 329 and DrugBank reported only 11 interactions. Of greater concern was the lack of consensus among the various sources; that is, it was common for one source to report a particular interaction while others did not. For instance, only in Lexi-Comp reported irinotecan to interact with beta-blocker drugs. Upon noting these inconsistencies, we investigated the level of agreement among the curated sources. As a preliminary null hypothesis, it was proposed that the sources would have neither

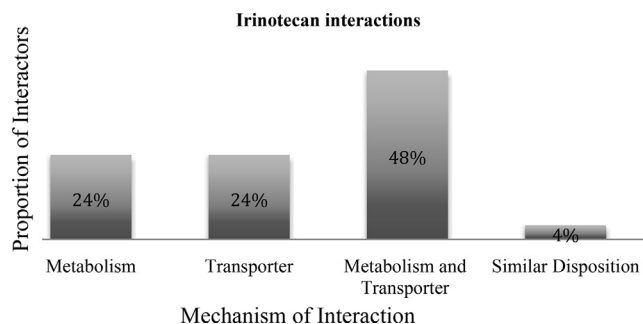


Fig. 3. Classification by mechanism of 116 drugs predicted to interact with irinotecan.

Table 1

Validation results for the 116 predicted irinotecan interactions.

| Validation Source | Predicted Interactions |
|---------------------|------------------------|
| Curated DDI sources | 80 (69%) |
| Literature | 12 (10%) |
| Never studied | 24 (21%) |

Table 2
Contingency table and Fisher's exact test two-tailed *p*-value for predicted interactors of irinotecan.

| | True | False | <i>P</i> -value |
|--------------------|------|-------|-----------------|
| Predicted | 55 | 37 | <0.05 |
| Unpredicted | 166 | 1356 | |

consistent agreement nor consistent disagreement. Then, an agreement/disagreement scale was constructed in which a value of zero represented absolute disagreement and one absolute agreement. The null hypothesis thus corresponded to the middle of the scale ($H_0 = 0.5$). This scale and structure was chosen with the goal of exploring various forms of hypothesis testing in order to collectively analyze the overall relative reporting behaviors of the sources. Such hypothesis testing would also allow the approximate determination of source independence in terms of reporting behavior to be approximately determined. For testing, a sample set was prepared from the sources based on the reporting behaviors of the 80 validated irinotecan DDIs. Those samples were used to construct a conformity sample consisting of the mean reporting behaviors determined for all pairwise combinations of the five sources and for the sources as an overall whole. The collective sample had a 95% confidence interval of 0.49 to 0.58, overlapping the null hypothesis score (0.5). Based on this interval and the constructed conformity, it was strongly evident that no level of statistical agreement existed for the DDI sources used in this study. The

dependence and independence of the sources was further investigated by analyzing pairwise confidence intervals (Fig. 4).

4. Discussion and conclusions

To aid patients in avoiding serious health complications, it is key to detect DDIs early and effectively. A number of studies have applied *in vitro*, *in vivo*, or informatics approaches to identify potential DDIs, including mining scientific literature, AERS, and EHRs. While these approaches have seen success, the most common approaches also feature significant limitations that can contribute to neglect of potentially important DDI pathways and to delayed detection. First, although *in vitro* and *in vivo* investigative processes are useful for alerting researchers to interactions (Wienkers and Heath, 2005), these studies are slow and often involve limited numbers of drugs and targets (Hutzler et al., 2011). Consequently, researchers are not able to use these methods to evaluate new drugs for DDIs as rapidly as those drugs are added to the market (Tatonetti et al., 2012). Second, informatics benefits from a rich data source in the form of medical literature, but the extracted data is error-prone and must undergo substantial manual curation and cleanup before use. Ultimately, the currently available resources are disparate and disconnected, and so create challenges for researchers attempting to discover potential hazards for medical patients, such as DDIs.

The Semantic Web technologies employed here provide a viable approach for the identification and investigation of potential DDIs.

Expected DDI Source Agreement Levels for Irinotecan DDIs (with 95% Statistical Confidence)

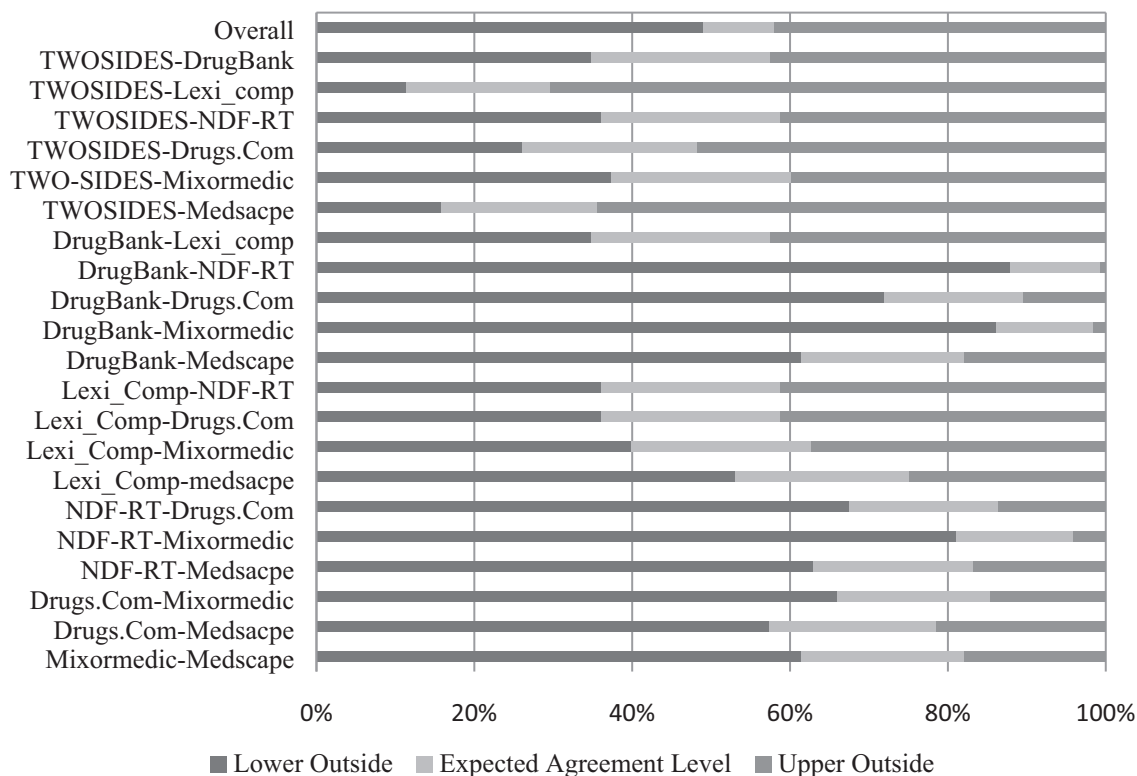


Fig. 4. Depiction of the degree of independence (95% confidence) among five DDI sources based on 80 degrees of freedom (true positive predictions for irinotecan interactions). Values below 40% indicate disagreement of sources, those above 60% indicate agreement, and intermediate values a level of variation. All five sources combined (Overall) have an expected agreement level in the middle bound, thus are often independent. Other rows represent pairwise comparisons for all combinations of sources, indicating their dependence on and independence from one another.

This study illustrates the utility of a semantically integrated knowledge base for the identification of multi-pathway interactions, specifically at the metabolism and transporter levels. We hypothesized that the sharing of important factors across multiple biomedical levels could be informative for the prediction of potential DDIs. The model we developed identified 116 FDA-approved medications as potential irinotecan interactors. The observed tendency for drugs to interact with irinotecan through multiple mechanisms highlights the essential import of a rule-based model that can accurately and simultaneously infer all potential interaction mechanisms. For example, the model successfully detailed the interaction of nefazodone with irinotecan in terms of both transporter and metabolism mechanisms. In contrast, decision support tools such as Micromedex, Lexicomp, and Facts and Comparisons identified only the metabolic interaction via CYP3A4. As interaction via one mechanism may enhance or mitigate another interaction that occurs through a distinct mechanism, perhaps with clinically meaningful impact, comprehensive identification of all DDI mechanisms is critical (Hinton et al., 2008). The complex case of irinotecan thus illustrates inadequacies in conventional systems for DDI identification, and equally demonstrates the value and capability of integrated the Semantic Web technology as a means of modeling potential DDIs and ultimately developing tools that better support clinical decisions.

Although our method achieved 79% correct detection of irinotecan interactors (69% from DDI sources +10% from literature and clinical websites [Table 1]), there are nonetheless several limitations of this study that merit addressing in future work. First, the rule-based model only investigated potential interactions; it did not consider whether those interactions had clinical significance. In fact, assessing interaction severity from mechanistic information alone is complex, and best aided by using clinical pharmacokinetic/pharmacodynamic studies to (1) determine the effect of identified interactions on the concentrations of interacting drugs and (2) assess how altered drug concentration will impact therapeutic efficacy and the potential for adverse effects (i.e. therapeutic index). A benefit of our model is that it can provide scientists and clinicians with potential interaction candidates for further evaluation through clinical studies. Second, due to limited available data source for other events such as absorption and excretion, the method in this paper and the determination of metabolism and transport as the main pharmacokinetic events were based on the available well-known, reliable, and validated data sources. With the expansion of and increased attention paid to the world of big data (Noor, 2019), we expect to have available in future years more sources with reliable data that can be used to build more comprehensive and thorough programs that will precisely identify DDIs across multiple pathways. Lastly, this study is also limited by examining interactions only for the drug irinotecan. While the complex pharmacokinetic profile of irinotecan enabled testing of the full range of our model, additional examples would provide more definitive proof of the value of the developed DDI knowledge base.

In conclusion, while this study was limited in scope, the results give clear illustration of the benefits of Semantic Web technologies in identifying potential DDIs across multiple pharmacological levels, and of the capability of a comprehensive DDI knowledge base to yield novel candidate interactions for further clinical study. It remains necessary to conduct further prospective and retrospective studies in order to determine the clinical significance of the findings and to propose recommendations for future clinical use.

Key points

- Present state-of-the-art drug-drug interaction (DDI) research largely focuses on fairly simple linear interactions and neglects effects arising from more complicated scenarios, including multi-pathway interactions.

- It is feasible to use Semantic Web technologies to predict novel DDIs that involve multiple pathway interactions. Using the chemotherapy agent irinotecan as an exemplar, we show that our model can identify previously unreported multi-pathway (metabolic and transporter) interactions.
- This study might inform clinicians in the selection of medications that do not interact with a patient's existing prescriptions. It also suggests that the establishment of a single evidence-based resource for DDI identification would offer significant value for clinical practice.

Author contributions

AA and AN wrote the manuscript, designed the research, performed the research and analyzed the data, and prepared the manuscript.

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Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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