Modeling Drug Mechanism Knowledge Using Evidence and Truth Maintenance

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***Abstract*—To protect the safety of patients, it is vital that researchers find methods for representing drug mechanism knowledge that support making clinically relevant drug–drug interaction (DDI) predictions. Our research aims to identify the challenges of representing and reasoning with drug mechanism knowledge and to evaluate potential informatics solutions to these challenges through the process of developing a knowledge-based system capable of predicting clinically relevant DDIs that occur via metabolic mechanisms. In previous work, we designed a simple, rule-based, model of metabolic inhibition and induction and applied it to a database containing assertions about 267 drugs. This pilot system taught us that drug mechanism knowledge is often dynamic, missing, or uncertain. In this paper, we propose methods to address these properties of mechanism knowledge and describe a new prototype system, the Drug Interaction Knowledge-base (DIKB), that implements our proposed methods so that we can explore their strengths and limitations. A novel feature of the DIKB is its use of a truth maintenance system to link changes in the evidence support for assertions about drug properties to the set of interactions and non-interactions the system predicts.**

***Index Terms*—Drug interactions, drug mechanisms, knowledge representation, Truth Maintenance Systems.**

I. Introduction

MECHANISM-BASED drug–drug interaction (DDI) prediction is important during drug development to predict interactions between a potential new drug and drugs currently on the market. Systems that model drug mechanisms are being applied in this "premarket" setting to identify optimal drug candidates, predict drug properties, assess the efficacy and safety of new drugs, and estimate dose to concentration relationships [1]. Premarket modeling efforts aim to identify interactions between a new drug and drugs with which it might be coadministered early on, before much time and money is invested [2], [3]. Predictions made using drug mechanisms generally offer a qualitative, rather than quantitative, estimate of the magnitude of the interaction. Scientists can use these qualitative predictions to select the set of clinical trials necessary to establish a new drug's safety profile [4].

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An important fact is that the same knowledge that is useful for predicting DDIs in the premarket setting can help clinicians in the postmarket setting assess the possibility of a DDI occurring between two drugs that have never been studied together in clinical trials [5]. In spite of this fact, and the position of the Food and Drug Administration (FDA) that all relevant information on mechanisms from premarket investigations be included in drug product labeling [6], little research has been done on how to best represent, utilize, and maintain pharmacokinetic and pharmacodynamic drug mechanism knowledge for the purpose of making DDI predictions in the postmarket setting. Our research is beginning to fill this knowledge gap through the process of developing a knowledge-based system capable of predicting clinically relevant DDIs that occur via metabolic mechanisms. The purpose of developing the system is to identify the challenges of representing and reasoning with postmarket drug mechanism knowledge and to evaluate potential informatics solutions to these challenges.

In the next section, we describe our previous research in mechanisms-based DDI prediction and the specific challenges to representing drug mechanism knowledge this early work helped us identify. We then propose informatics methods to address each challenge while discussing related work. Then follows a detailed description of a new prototype system, the Drug Interaction Knowledge-base (DIKB), that implements our proposed methods and employs a novel use of a non-monotonic logic system called a truth maintenance system to link changes in the evidence support for assertions about drug properties to the set of DDIs and non-interactions the system predicts. Finally, we conclude by relating some early research findings and proposing future research aims.

II. Previous Work

Previously, in order to better understand the issues of formally representing DDI knowledge, we constructed a First Order Logic model of the mechanisms underlying DDIs from the lectures and class notes of a graduate class on drug interactions. Several categories of DDIs were covered in the class including DDIs involving changes to liver or kidney function, gastrointestinal motility and absorption, transport protein function, and metabolism. For further experimentation, we selected rules from this representation that model the jointly sufficient conditions for metabolic inhibition or induction DDIs. These rules were interesting because a large number of DDIs can be explained by metabolic mechanisms, especially for drugs metabolized by the cytochrome-P450 (CYP450) enzymes, and considerable research data exist on the metabolic properties of many drugs.

TABLE I
PREDICTED INHIBITION INTERACTIONS FROM OUR PILOT DDI KB NOT DOCUMENTED IN ANY OF FOUR ONLINE REFERENCES

Precipitant	*PCE*	*Object*
amiodarone	CYP2C9	phenobarbital
disulfiram	CYP2C9	phenobarbital
fluorouracil	CYP2C9	phenobarbital
fluconazole	CYP2C9	phenobarbital
gemfibrozil	CYP3A4	carbamazepine
gemfibrozil	CYP2C9	phenobarbital
gemfibrozil	CYP2C9	phenytoin
leflunomide	CYP2C9	phenobarbital
miconazole	CYP3A4	carbamazepine
sulfamethizole	CYP2C9	phenobarbital
sulfamethoxazole	CYP2C9	phenobarbital
sulfinpyrazone	CYP2C9	phenobarbital
sulphaphenazole	CYP2C9	phenobarbital
zafirlukast	CYP3A4	carbamazepine
zafirlukast	CYP2C9	phenytoin
zafirlukast	CYP2C9	phenobarbital

In each row, the precipitant drug inhibits the primary clearance enzyme of the object drug based on information in our pilot system.

We constructed a small database containing the necessary drug facts for inference with the selected rules. Facts on the important metabolic enzymes for 267 currently prescribed drugs were input into the knowledge base (KB) from two references ([7] and [8]). Our methods for combining information from these two references are described in [9]. Since our system could provide no quantitative estimates of its DDI predictions, we modified the rules to apply only to drugs with a *narrow therapeutic index* (NTI), meaning that there is a small gap between the toxic dose of a drug and the dose at which the drug is ineffective. Since any interaction involving a NTI drug could potentially result in harm to a patient, this change ensured that all predictions would be clinically relevant.

We applied the selected rules by performing two queries against the drug KB for any drugs that inhibit or induce the primary clearance enzyme of another NTI drug whose clearance is primarily metabolism. The queries returned a total of 90 predicted DDIs out of 71 022 possible pairwise combinations. We then checked the 90 predictions against four online drug reference databases.[1] A predicted DDI was considered clinically viable if it was reported in any of the four sources.

Out of 90 predicted DDIs, 74 were found in at least one drug reference while 16 could not be found in any online reference (see Table I). We recognized that the 16 predicted interactions not found in any drug reference were not necessarily false predictions. It is not possible to test every possible drug combination in a clinical trial, and the effects of drug interactions can be very hard to recognize so that some drug interactions escape notice in the scientific literature until years after a drug comes to market. The pilot system's predictions were based on pharmacokinetic principles that are considered valid indicators of potential interactions in FDA guidelines [6]. The clinical relevance of these predictions was based on the assumption that any change in the exposure of a patient to an NTI drug is of clinical interest. Thus, it is possible that some of these predictions are valid interactions that have not been studied.

We looked carefully at the evidence behind each fact in our database that supported any of the 16 novel interaction predictions and found that several facts in the drug KB had varying degrees of support from the scientific literature. For example, we found that, based on evidence, the clinical relevance of the three interaction predictions involving zafirlukast inhibition of CYP3A4 were less certain than the two predictions involving gemfibrozil inhibition of CYP2C9 (Table I). Evidence for zafirlukast inhibition of CYP3A4 consisted of a single *in vitro* study mentioned in the drug's product label [10]. We could find no clinical studies where patient exposure to a drug primarily cleared by CYP3A4 was monitored before and after patients were given zafirlukast. This evidence formed relatively weak support for clinically relevant inhibition of CYP3A4 by zafirlukast because, even with very solid *in vitro* evidence, a pharmacokinetic drug property might not have much clinical relevance at the doses in which drugs are prescribed [11], [12]. In comparison, the evidence that gemfibrozil inhibits CYP2C9 was more substantial as it included both an *in vitro* study [13] and a case report [14] showing a significant increase in the exposure of a patient to warfarin, a drug primarily cleared from the body by CYP2C9 metabolism, when the patient was given gemfibrozil.

Examination of the evidence for other drug properties in this pilot system revealed that important drug mechanism knowledge is sometimes missing. For example, all 11 of the interactions involving phenobarbital in Table I are predicted to occur by inhibition of phenobarbital's primary metabolic clearance pathway that we listed as CYP2C9 based on one source [8]. We could only indirectly support the hypothesis that phenobarbital is a CYP2C9 substrate with two studies from the early 1980s [15], [16], that identified an apparent metabolic interaction between sodium valproate and phenobarbital and an *in vitro* study conducted years later [17] showing that sodium valproate is a CYP2C9 inhibitor. This pattern of inference is weak since it assumes that the interaction could only occur by means of CYP2C9 inhibition while pharmacology research has exposed other means by which apparent metabolic interactions can occur including inhibition of transport proteins. We could find no studies, such as an *in vitro* assay, designed specifically to examine whether the phenobarbital is metabolized by CYP2C9. Without this missing information, there remains considerable uncertainty behind this assertion.

We identified three major challenges to representing drug mechanism knowledge from this initial experiment. First, there is often considerable uncertainty behind claims about a drug's properties and this uncertainty affects the confidence that someone knowledgeable about drugs places on mechanisms-based DDI predictions. Another challenge is that mechanism knowledge is sometimes missing; a fact that can make it difficult to assess the validity of some claims about a drug's mechanisms. Finally, mechanism knowledge is dynamic and any repository for drug mechanism knowledge is faced with the nontrivial task of staying up to date with science's rapid advance.

[1]First Data Bank's Micromedex, WebMD's Medscape, Discovery's health.discovery.com, and Cerner Multum's drugs.com

III. Related Work

A. Work Addressing Uncertain Mechanism Knowledge

Perhaps the most significant challenge we identified is that knowledge about drug mechanisms is often *uncertain*. Our pilot database had no way to represent uncertainty or determine how much confidence one should have in predictions made by using uncertain drug facts. There are many methods to support computational reasoning with uncertain knowledge including symbolic methods such as incidence calculus [18], purely numerical approaches such as Bayesian networks [19], and hybrid approaches such as certainty factors attached to rules in MYCIN [20] and similar expert system shells. Parsons and Hunter have written a concise conceptual review of several formalisms [21] as have Russel and Norvig [22].

An interesting informatics research project would be to build a drug mechanism knowledge system using one of these methods. In fact, various models of drug pharmacokinetics and pharmacodynamics employing some of these methods are being used during early drug development for reasons that include helping to assess the efficacy and safety of new drugs, estimating dose to concentration relationships, and more recently, identifying optimal drug candidates [1]. However, our prior work suggests a more immediate, and perhaps more important research question—what are the strengths and weaknesses of explicitly linking evidence support for drug mechanism assertions and how is evidence support best modeled?

When we looked at other knowledge-based systems that link evidence to their drug facts, including DRUGDEX,[2] Q-DIPS [23], and PharmGKB,[3] we identified limitations to the approaches they use. For example, one limitation of these systems is that they tend to collect evidence only in support of assertions. This bias toward collecting only supporting evidence could undermine attempts to evaluate how believable an assertion is. Psychological studies have shown that people tend to search for evidence that confirm their hypotheses, and that this can sometimes lead them to overestimate the likelihood that a hypothesis is true. When subjects were asked to think of situations where their hypotheses would not be true, their confidence estimations were more accurate [24]. The evidence component of the second drug interaction KB that we discuss in Section IV accumulates evidence both for and against object property assertions allowing us to explore the possible benefits and drawbacks of this approach.

Another limitation of the systems we looked at is that they rarely or never provide their criteria for selecting or excluding evidence. The quality of scientific research varies greatly, and busy clinicians and researchers do not have lots of time to evaluate whether the evidence supporting some drug fact meets the proper criteria. A more efficient approach might be for KB maintainer's to explicitly state the inclusion criteria for every evidence type and ensure that the criteria are met by every piece of evidence they link to drug mechanism assertions. We use this approach to collect evidence for the second drug interaction KB that we discuss in Section IV.

[2][Online]. Available: http://www.micromedex.com/products/drugdex/

[3][Online]. Available: http://www.pharmgkb.org/

B. Work Addressing Missing Mechanism Knowledge

Missing drug mechanism knowledge includes facts that are unavailable or require tests that are impossible or impractical to perform. We found in the pilot study how the absence of studies specifically examining whether phenobarbital is metabolized by CYP2C9 caused the clinical relevance of 11 of the pilot systems DDI predictions to be uncertain. Other examples of missing drug mechanism knowledge are not hard to find; for example, it is well known that certain individuals carry poorly functioning forms of one or more of the drug-metabolizing enzymes CYP2C9, CYP2C19, and CYP2D6. Knowledge of which form a patient carries can help clinicians plan a drug therapy involving drugs metabolized by one of these enzymes. Unfortunately, it is not practical to genotype every patient, so the knowledge of whether the patient possesses a mutant enzyme will often be missing.

One way to handle missing knowledge when it is important for reasoning is to assume some truth state for the knowledge until proven otherwise. This is a form of *default reasoning* whose various forms include inheritance in semantic networks, circumscription, default logic, and several advanced methods reviewed by Goldszmidt and Pearl [25]. Implementing default reasoning in a system that performs logical inference requires that the system be *non-monotonic*. Conceptually, this means that the system can retract or reinstate inferences as the belief state of assertions change. Continuing with the aforementioned example, a conservative knowledge-based system might, by default, assert that all patients potentially posses the poorly functioning form of each polymorphic enzyme. The system's reasoning engine might then make DDI predictions that assume this assertion to be valid. If clinicians decide that their patients carry the normal functioning form of the enzyme, then it is feasible for a non-monotonic reasoning system to retract all DDI predictions that depend on the patients having the poorly functioning enzyme.

One type of non-monotonic logic system is a justification-based truth maintenance system (JTMS) [26]. Typically, a JTMS system works in conjunction with a rule engine to manage assumptions and their effects on inference. We discuss in Section IV how we use a JTMS in our second drug interaction KB; the remainder of this section describes how a JTMS works.

In formal logic, the *antecedent*, or `IF` portion of an `IF-THEN` rule, must be true for the *consequent*, or the `THEN` portion of the rule, to be true. Many rule engines, including our second knowledge-based system, model theories as Horn clauses; rules consisting of one or more clauses forming an *antecedent* and zero or one clauses forming a *consequent*. In traditional predicate calculus, the consequent of a Horn clause is always true if all clauses in its antecedent are true. This is not the case in a system using a JTMS. Rather, a consequent can depend on other clauses in addition to the ones in its antecedent. The set of clauses a consequent depends on is called its *justifications*. In order for a consequent to hold true, all of its justifications must hold true.

The JTMS represents every clause in the rule engine as a node possessing a *label* reflecting its current belief state. Every rule

in the rule engine specifies a set of justifications its consequent depends on for belief. The JTMS labels a consequent `IN` when all of its justifications are `IN`. If any of a consequent's justifications are `OUT`, then the consequent is `OUT`. Justifications can include clauses or *assumptions*. *Assumptions* are clauses that can be `IN` or `OUT` by assignment; they do not require any supporting justifications. The JTMS labels an assumption node `IN`, or *enabled*, when the rule engine *asserts* belief in it, and `OUT` when the rule engine *retracts* that belief. In this way, the JTMS maintains a dependency network of clauses and justifications. A change in belief in any clause or assumption node recursively propagates through the dependency network, changing the belief state of any other node that contains the changed node in its set of justifications.

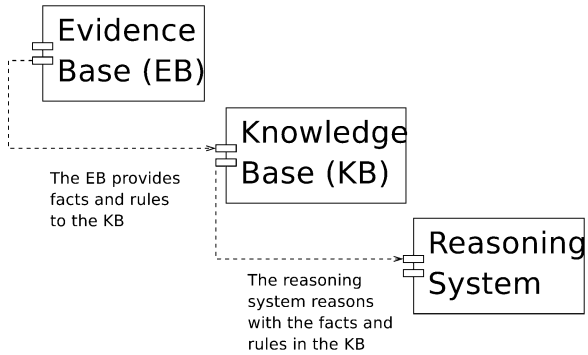

Fig. 1. A knowledge-based system that links assertions about object properties to the evidence for and against those properties.

C. Work Addressing the Dynamic Nature of Mechanism Knowledge

Any repository for drug mechanism knowledge is faced with the nontrivial task of staying up to date with science's rapid advances. Widely used systems like DRUGDEX and Facts and Comparisons use drug product labels as their primary source of drug mechanism knowledge. Unfortunately, drug labels fail to stay up to date with emerging drug mechanism knowledge. For example, since the late 1990s regulatory agencies have recommended detailed investigations into the pharmacokinetic, and especially metabolic, mechanisms during the early stages of a drug's development. However, labeling for older drugs is not current with this emerging knowledge—as of 2002, only 10% of the drugs approved between 1992 and 1997 include *in vitro* metabolic findings and very few labels for drugs approved in the early 1980s even have pharmacokinetic information [27].

A more effective approach is to track and evaluate both drug label and primary research evidence using editorial boards consisting of domain experts. Interestingly, while labeling is the primary source of drug mechanism knowledge for DRUGDEX, Facts and Comparisons, and other comparable systems, these systems stay current with drug efficacy and interaction knowledge by using editorial boards to identify and critically examine clinical trials and case reports. This approach has proven scalable to the thousands of drug products listed in these sources.

Q-DIPS [23], a system designed to help clinicians identify and manage DDIs that occur by metabolic mechanisms, demonstrates that the editorial board approach is feasible for drug mechanism knowledge. The system's maintainers curate a database of *in vitro* and *in vivo* studies that support assertions about the enzymes a drug is a substrate of or modulates. Users of Q-DIPS can identify DDIs by viewing tables showing the metabolic properties of the set of drugs they are interested in. The tables in Q-DIPS are *dynamic* meaning that their content changes as knowledge about each drug's metabolic profile is updated in the study database.

IV. Modeling with Evidence and Truth Maintenance

Building from the lessons of our initial experiment and our review of related work, we have designed a new evidence-based drug mechanism knowledge-base called the Drug Interaction Knowledge-base (DIKB). Fig. 1 shows an architectural model of the system. The DIKB enables users to link each assertion about a drug property to both supporting and refuting evidence. DIKB maintainers place evidence for or against each assertion about a drug's mechanistic properties in an *evidence base* that is kept current through an editorial board approach. Maintainers attach metadata describing the source and study type of each piece of evidence in the *evidence base*, and users of the system can define specific belief criteria for each assertion in the *evidence base* using combinations of evidence metadata.

The system has a separate *knowledge-base* that contains only those assertions in the *evidence base* that meet belief criteria. The DIKB's reasoning system uses assertions in this *knowledge-base*, and so, only makes DDI predictions using those facts considered current by the system's maintainers and believable by users. The DIKB uses a JTMS to handle both default reasoning and the effects on inference of changes in the *knowledge-base* as new evidence causes assertions in the *evidence base* to meet, or fail to meet, belief criteria. To the best of our knowledge, this latter application is a novel use of a JTMS within biomedical informatics.

The DIKB contains the same model for predicting metabolic inhibition interactions validated in our pilot system, but focuses on a family of cholesterol lowering drugs called "statins" and drugs that they are sometimes co-prescribed with. While statins have a relatively wide therapeutic index, adverse events, including myopathy and rhabdomyolysis, have been reported due to extreme overexposure [28]. In addition to six statins, the DIKB currently contains knowledge about 11 drugs that are sometimes coprescribed with statins, have been the subject of numerous pharmacokinetic studies (both *in vivo* and *in vitro*), and are thought to be substrates or inhibitors of the same enzyme responsible for metabolizing many of the statins (CYP3A4).

The DIKB implements the three modules shown in the Fig. 1 using two components: one called the `ddi-theory` and the other called the `evidence-model`. The `ddi-theory` consists of a JTMS, a rule-based theory about DDIs, and assertions about the mechanistic properties of the 17 drugs. The `evidence-model` consists of a database that stores the evidence for and against each assertion in the `ddi-theory` and communicates to the `ddi-theory` which assertions it

```
(rule
  ((:IN (inhibits ?x ?y))
   (:IN (substrate-of ?z ?y)))
  (rassert!
   (inhibit-metabolic-clearance ?x ?z ?y)
   (nil
    (inhibits ?x ?y)
    (substrate-of ?z ?y)
    (inhibitory-concentration ?x ?y)
  )))
```

Fig. 2. Rule in the `ddi-theory` for when a precipitant inhibits the metabolic clearance of an object drug.

can use for inference. The `ddi-theory` implements both the *knowledge-base* and the *reasoning system* components of the model in Fig. 1. Inference over facts and rules in the `ddi-theory` occurs when a user, or the system, calls an explicit function that executes a forward chaining inference algorithm over the rules and adds any inferred assertions to the *knowledge-base*. At anytime, users can pose queries against the *knowledge-base* and the system will return any assertions about drugs, including DDI predictions, that match a user's query. It will also return links to the evidence for and against each fact used to satisfy the query. We set forth each component of this system in greater detail in the next two sections.

A. The `ddi-Theory`

The `ddi-theory` component of the DIKB consists of two parts—a rule engine and a JTMS that maintains the belief state of clauses in the rule engine. Section III-B relates how a JTMS works, we now show how the JTMS is used in the `ddi-theory` to handle both default reasoning and the effects on inference of changes in the *knowledge-base* as new evidence causes assertions in the *evidence base* to meet, or fail to meet, belief criteria.

Fig. 2 shows a `ddi-theory` rule applicable when a precipitant drug inhibits the metabolic clearance of an object drug. The first line declares that this is a `rule`, the next line specifies a pattern for when one object inhibits another. The `:IN` before the pattern declares that this clause must be believed in order to evaluate as true. For example, when we assert that clarithromycin (CMYN) inhibits CYP3A4 in the following listing, the JTMS creates a node for the assertion and assigns it an `IN` label.

```
(assert!
  '(inhibits 'CMYN 'CYP3A4)
  'dikb-assertion)
```

The next line in our rule is a clause for when one object is a substrate of another object. To assert that CYP3A4 metabolizes carbamazepine (CARB) we input

```
(assert!
  '(substrate-of 'CARB 'CYP3A4)
  'dikb-assertion)
```

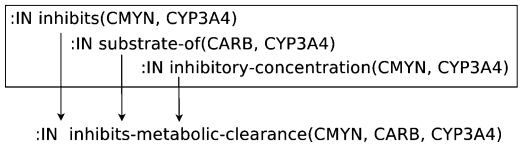

Fig. 3. A small dependency network; justifications are shown in the box.

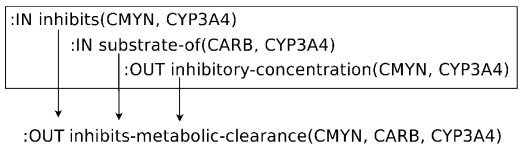

Fig. 4. A change in the belief state in one of the justifications propagates to dependent consequents.

The consequent in Fig. 2 says to assert that `?x` inhibits the metabolic clearance of `?z` by inhibiting the catalytic function of `?y` when the antecedents evaluate true. Then follows a list containing an *informant*, and a series of justifications for the consequent. The *informant* is a variable that further explains the inference; in this case, it is set to `nil`. The justifications represent clauses or assumptions that must be `IN` in order for the consequent to be `IN`. When the rule engine makes an assertion, the JTMS creates a node for it, and then, looks to see if the consequent's justifications are `IN`. If so, the JTMS labels the node `IN`.

The `ddi-theory` models dynamic and default knowledge as JTMS assumptions. Belief in the truth of dynamic or default information causes the assumption representing that information to be *enabled*. Currently, the DDI theory assumes by default that all precipitants reach a concentration sufficient to cause a clinically significant effect on the enzymes they are known to inhibit. In our previous example, the `ddi-theory` would create an enabled assumption declaring CMYN to be at a concentration sufficient to inhibit CYP3A4. The symbol `'default-inference-assumption` is an informant, tracing this assumption to default reasoning

```
(assume!
  '(inhibitory-concentration 'CMYN 'CYP3A4)
  'default-inference-assumption)
```

Fig. 3 shows how the JTMS dependency network would look at this point in our example. If further data cause the belief state of our default assumption to change to false, then the program can retract belief

```
(retract!
  '(inhibitory-concentration 'CMYN 'CYP3A4)
  'default-inference-assumption)
```

The effect of changing this belief is shown in Fig. 4. The JTMS changes the node labels for both the assumption `(inhibitory-concentration 'CMYN 'CYP3A4)`

```
(rule
 ((:IN
   (inhibit-metabolic-clearance ?x ?z ?y)
                  :TEST (not (equal ?x ?z)))
  (:IN
   (primary-clearance-mechanism
                          ?z 'METABOLISM)))
 (rassert!
  (increase-drug-exposure ?x ?z ?y)
  (nil
   ;;justifications
   (inhibit-metabolic-clearance ?x ?z ?y)
   (primary-clearance-mechanism
                          ?z 'METABOLISM)
   )))

(rule
 ((:IN (narrow-therapeutic-range ?z)))
 (rassert!
  (nti-or-sensitive-substrate ?z)
  ;;justifications
  (nil
   (narrow-therapeutic-range ?z))
  ))

(rule
 ((:IN (sensitive-substrate ?z)))
 (rassert!
  (nti-or-sensitive-substrate ?z)
  ;;justifications
  (nil
   (sensitive-substrate ?z))
  ))

(rule
 ((:IN (increase-drug-exposure ?x ?z ?y))
  (:IN (primary-clearance-enzyme ?z ?y))
  (:IN (nti-or-sensitive-substrate ?z)))
 (rassert!
  (metabolic-inhibition-interaction ?x ?z ?y)
  ;;justifications
  (nil
   (increase-drug-exposure ?x ?z ?y)
   (primary-clearance-enzyme ?z ?y)
   (nti-or-sensitive-substrate ?z)
   )))
```

Fig. 5. The `ddi-theory` consists of these rules plus the one shown in Fig. 2.

and the assertion `(inhibit-metabolic-clearance CMYN CARB CYP3A4)` to `OUT` meaning that this assertion is no longer believed true. It is important to note that *any other assertions or inferences* that depend directly, or indirectly, on either of these assertions will now also be labeled `OUT`.

Figs. 2 and 5 show the rules represented in the `ddi-theory` at this time. The rule in Fig. 2 and the first rule in Fig. 5 capture inhibition of a clearance enzyme of a drug that is primarily cleared by metabolism. The third and fourth rule serve to capture a disjunctive state when a drug has an NTI and/or is considered a *sensitive substrate*.[4] These rules are necessary because our JTMS implementation can only accept single literal positives and cannot directly assert disjunctive clauses. The final rule in Fig. 5 specifies conditions that, if present, greatly increase the likelihood of a clinically significant inhibition interaction.

B. The Evidence Model

The `evidence-model` component of the DIKB stores instances of objects that the `ddi-theory` reasons about, currently limited to drugs. The purpose of the `evidence-model` is to manage knowledge about the properties of the objects it stores and to communicate their current state of belief to the `ddi-theory`. Both the set of assertions in `ddi-theory` and their belief state changes as the `evidence-model` accumulates evidence for and against object property assertions. To satisfy its purpose, the `evidence-model`:

1) stores evidence for and against each property and its metadata;
2) tests the evidence for each property against user-defined criteria for belief;
3) tells the `ddi-theory` to retract and assert *enabled assumptions* about the properties of its objects.

1) Storing Evidence and Evidence Metadata: The `evidence-model` represents objects of interest to the `ddi-theory` and assertions about their properties as instances of classes derived from an abstract `Frame` class. A simple class, called `KB`, performs storage and retrieval functions for these class instances. This class has two subclasses or children: `DrugKB` for objects whose properties are important for inference and `EvidenceBase` for assertions about the properties of these objects.

As of this writing, the singleton `DrugKB` only contains instances of type `Drug`, a class that models knowledge about a drug and its properties (Table II). The class `Drug` contains two types of slots: *categorical* slots that store plainly factual knowledge about a drug such as its generic and trade names and *evidence* slots that model knowledge about a drug property that rests on conclusions from research. The singleton `EvidenceBase` stores instances of class `Assertion` (Table III), a class that models the evidence both for and against an property belonging to some instance in `DrugKB`. When users find evidence for or against the property represented by an *evidence* slot, they create a new instance of the `Evidence` class shown in Table IV and enter values for its slots. These instances are then placed in either the `evidence-for` or `evidence-against` slot of the `Assertion` instance associated with the property's *evidence* slot.

2) User-Defined Criteria for Belief and Disbelief: We relate in our description of pilot work (Section II) how we looked at evidence support for the facts in the pilot database to assess the validity of the system's predictions. The reader might recall that when we looked at the evidence support for zafirlukast inhibition of CYP3A4 and gemfibrozil inhibition CYP2C9, we were able to say that the clinical relevance of the interaction prediction involving zafirlukast was less certain than the two interactions involving gemfibrozil inhibition of CYP2C9. This case and others from our early work suggest that the confidence someone knowledgeable about drugs has in the clinical validity of a DDI prediction varies with depending on the *type* of evidence that support or refute each of the facts that led to the prediction. To explore this idea further, the DIKB supports using evidence types to track the level of certainty users have in the system's drug mechanism assertions.

The types of evidence that can support drug mechanism facts include, among others, labeling statements, results from *in vitro* studies, expert interpretation of case reports, and various

[4]The FDA defines a sensitive substrate as a substrate that exhibits a fivefold or greater increase in exposure with the addition of an inhibitor. There are currently several drugs on the FDA's published list including buspirone, eletriptan, felodipine, lovastatin, midazolam, sildenafil, simvastatin, and triazolam [6].

TABLE II
THE CLASS drug CONTAINS TWO TYPES OF SLOTS, *categorical* SLOTS THAT STORE PLAINLY FACTUAL KNOWLEDGE ABOUT A DRUG SUCH AS ITS GENERIC AND TRADE NAMES AND *evidence* SLOTS THAT MODEL KNOWLEDGE THAT RESTS ON CONCLUSIONS FROM RESEARCH

Slot	*Type*	*Description*
generic-name	*categorical*	FDA generic name
trade-name	*categorical*	manufacturer's name
drug-class	*categorical*	therapeutic class of the drug
form	*categorical*	default form of administration
ingredients	*categorical*	active and inactive ingredients
prodrug	*categorical*	is the drug a prodrug? true or false
substrate-of	*evidence*	enzymes that metabolize this drug
inhibits	*evidence*	enzymes this drug inhibits
induces	*evidence*	enzymes this drug induces
level-of-first-pass	*evidence*	level of first pass metabolism
primary-clearance-enzyme	*evidence*	the enzyme that accounts for the greatest amount of metabolic clearance
primary-clearance-mechanism	*evidence*	primary route clearance - metabolism, renal or exhalation
narrow-therapeutic-index	*evidence*	does the drug have a narrow therapeutic range - true or false
sensitive-substrate	*evidence*	enzymes for which this drug meets the FDAs definition of a sensitive substrate

TABLE III
SLOTS IN CLASS Assertion

Slot	*Description*
object	the object's name in DrugKB
slot	name of the slot
value	an allowable value for this slot
evidence-for	a list of Evidence types
evidence-against	a list of Evidence types
ready-to-classify	True if this assertion is ready to classify
evidence-rating	The current classification state of the assertion

TABLE IV
SLOTS IN CLASS Evidence

Slot	*Description*
evidence-type	a meta-data label describing the evidence's type (Table V)
doc-pointer	a pointer to the evidence document
quote	a short summary of the evidence
reviewer	person entering this evidence

pharmacokinetic clinical trials. A novel feature of the DIKB is that expert users can define combinations of evidence that they believe lend different degrees of certainty to the assertion types that the DIKB uses to predict DDIs. Different combinations of evidence types might confer different levels of certainty in an assertion and these can be rank ordered to produce "levels of evidence" (LOEs).

The DIKB distinguishes between assertion *instances* and assertion *types*. An assertion instance is a specific fact about a particular object such as a drug or protein. For example, (substrate-of 'CARB 'CYP3A4) is an instance of the generic (substrate-of X Y) assertion type. DIKB users define one or more LOEs for each generic assertion type by creating logical statements listing the level's required evidence types and their multiplicity. The LOEs for an assertion type apply to any instance of that type. Users can also place evidence types that they feel have similar levels of validity into a group called a *ranking category*. They can then use the ranking category just like other evidence types to define LOEs.

For every assertion type, users select one LOE as the *belief criteria*. The evidence-model will tell the ddi-theory to use a particular assertion instance in inference if, and only if, there exists a body of evidence for the assertion that satisfies the *belief criteria* for the assertion's type and there is no evidence against the object property. Table V shows some of the evidence types and ranking categories we are currently experimenting with and Fig. 6 shows some example LOEs.

3) Asserting and Retracting Enabled Assumptions: There are two situations where the evidence-model will reassess the evidence for an assertion about one of its objects—when an assertion's evidence support changes or DIKB users change the LOE that they have selected as the belief criteria for the assertion's type. In either case, the evidence-model compares the evidence for and against the assertion. If the evidence for the assertion satisfies the belief criteria currently assigned to the assertion's type, and there is no evidence against the assertion, then the evidence-model will cause the assertion to be enabled (labeled IN) in the ddi-theory. The evidence-model will retract (label OUT) the same assertion when either: 1) evidence against the assertion is found or 2) the belief criteria changes and the evidence for an assertion is no longer sufficient. Since object properties might already be asserted or retracted in the ddi-theory, the evidence-model keeps track of state. For example, if the evidence-model has already enabled an assertion and the assertion's evidence continues to meet belief criteria, then the system will make no change.

V. IMPLEMENTATION AND EXAMPLES

Users can enter and view evidence for drug property assertions into the evidence-model from a Web interface. This same interface allows users to select belief criteria and reassess evidence. Both the Web interface and the evidence-model

TABLE V
SET OF EVIDENCE TYPES THAT WE ARE EXPERIMENTING WITH ORGANIZED BY AN EXPERIMENTAL RANKING SCHEME

Ranking Category	*Evidence Type*
• **RCT**	• a randomized, controlled, pharmacokinetic study
• **Non-random**	• a cohort study • a case-control study • a non-randomized trial with concurrent or historical controls • a retrospective study looking a clinical records over time • a fixed order study with non-randomized healthy volunteers
• **Case Reports**	• a single case report • a case series
• **FDA Guidances**	• a statement in an FDA guidance to industry
• ***in vitro***	• *in vitro* evidence from human tissue, microsomal • *in vitro* evidence from human tissue, recombinant
• **Drug Labeling**	• Non-cited information in a drug label • Non-cited in vitro information in a drug label • Non-cited in vivo information in a drug label

Users assign one of these evidence types to each evidence item they enter into the DIKB evidence-base.

are implemented in Python.[5] The latter is implemented as a set of Python classes and shell scripts while the former uses the HTMLGen library[6] for creating Web pages and the Twisted networking framework[7] for serving them.

The `ddi-theory` uses Forbus and De Kleer's ANSI Common Lisp rule engine (JTRE) and JTMS from [26] with no

[5][Online]. Available: http://www.python.org

[6][Online]. Available: http://starship.python.net/crew/friedrich/HTMLgen/html/main.html

[7][Online]. Available: http://twistedmatrix.com/

```
LOE-1 ::=  RCT+ |
           FDA Guidances+
LOE-2 ::=  LOE-1 |
           Drug Labeling+
LOE-3 ::=  LOE-2 |
           Drug Labeling+ |
           (in vitro+ and Non-random+)
LOE-4 ::=  LOE-2 |
           in vitro+ |
           Non-random+
```

Fig. 6. Set of LOEs we are testing. The symbol "::=" means the term to the left "is defined as" the term to the right, "|" means "or," and "+" means that "one or more occurrences of" of the symbol to the left are allowed. So, item one reads "LOE-1 is defined as one or more **RCT** OR one or more **FDA Guidance** evidence types."

modification. The rules shown in Figs. 2 and 5 are enclosed in a Lisp function that initializes globally accessible JTRE and JTMS objects. The `evidence-model` writes asserted and retracted assumptions to a file stored on disk. This file is manually loaded by the user from an interactive Lisp session each time the `evidence-model` reassesses its evidence.

Table VI shows the output of our system using the rules in Figs. 2 and 5, a subset of the drug properties and evidence in `evidence-model`, and three of the LOEs shown in Fig. 6. The table illustrates one advantage of using evidence metadata to specify belief criteria for assertions in the KB—the system can provide different views of its knowledge and inferences to users who might not agree about what combination of evidence makes an assertion believable. LOE-1 accepts only one or more evidence items from either the **RCT** or **FDA Guidance** categories as evidence. LOE-2 adds to this a very significant source of evidence **labeling**. As is shown, changing the LOE from LOE-1 to LOE-2 has a dramatic effect on the belief state of predicted DDIs. Only one change in the predicted DDIs occurs when moving from LOE-2 to LOE-4: the prediction that fluvastatin will inhibit the metabolic clearance of rosuvastatin. This is because, *at the time of this writing*, `evidence-model` contains only one item of evidence for the claim that fluvastatin inhibits CYP2C9, an *in vitro* type acceptable only at LOE-4.

Table VII demonstrates how the DIKB output changes when maintainers find new evidence that causes an assertion in the *evidence base* to meet a belief criteria where it did not before. As the table shows, the hypothetical addition of an item of **RCT** evidence that fluvastatin inhibits CYP2C9 would cause the system's prediction that fluvastatin will inhibit the metabolic clearance of rosuvastatin via CYP2C9 to be believed at *LOE-2*. It is important to note that *any other assertions or inferences* that depend directly, or indirectly, on this inference will now also be labeled `IN` provided that all of their other justifications are `IN`. This example shows how a JTMS can efficiently handle the effect on inference of changes the *knowledge-base* as new evidence causes assertions in the *evidence base* to meet, or fail to meet, a user's belief criteria.

VI. DISCUSSION

The DIKB implements our proposed methods for handling absent, uncertain, and changing drug mechanism knowledge.

TABLE VI
BELIEF STATE OF A SUBSET OF DRUG PROPERTY ASSERTIONS AND INFERENCES IN THE DIKB WHEN THREE DIFFERENT LOEs FROM FIG. 6 WERE CHOSEN AS BELIEF CRITERIA

Drug property assertions

Drug Property	Evidence for	*LOE-1*	*LOE-2*	*LOE-4*
(INHIBITS 'DILTIAZEM 'CYP3A4)	RCT,Non-random,*in vitro*	IN	IN	IN
(INHIBITS 'FLUVASTATIN 'CYP2C9)	*in vitro*	OUT	OUT	IN
(SUBSTRATE-OF 'SIMVASTATIN 'CYP3A4)	RCT, Non-random, *in vitro*	IN	IN	IN
(SUBSTRATE-OF 'ROSUVASTATIN 'CYP2C9)	label	OUT	IN	IN
(PRIMARY-CLEARANCE-ENZYME 'SIMVASTATIN 'CYP3A4)	label	OUT	IN	IN
(PRIMARY-CLEARANCE-MECHANISM 'SIMVASTATIN 'METABOLISM)	label	OUT	IN	IN
(SENSITIVE-SUBSTRATE 'SIMVASTATIN 'CYP3A4)	FDA Guidance	IN	IN	IN

Predicted Drug-drug interactions

Drug Property	*LOE-1*	*LOE-2*	*LOE-4*
(INHIBIT-METABOLIC-CLEARANCE 'DILTIAZEM 'SIMVASTATIN 'CYP3A4)	OUT	IN	IN
(INCREASE-DRUG-EXPOSURE 'DILTIAZEM 'SIMVASTATIN 'CYP3A4)	OUT	IN	IN
(METABOLIC-INHIBITION-INTERACTION 'DILTIAZEM 'SIMVASTATIN 'CYP3A4)	OUT	IN	IN
(INHIBIT-METABOLIC-CLEARANCE 'FLUVASTATIN 'ROSUVASTATIN 'CYP2C9)	OUT	OUT	IN
(INCREASE-DRUG-EXPOSURE 'FLUVASTATIN 'ROSUVASTATIN 'CYP2C9)	OUT	OUT	OUT

Inferences were made using the rules in Figs. 2 and 5. The evidence *for* each drug property is shown; no drug property shown had evidence *against* it.

TABLE VII
HYPOTHETICAL EXAMPLE SHOWING HOW THE ADDITION OF NEW EVIDENCE TO THE DIKB CAN EFFECT A CHANGE IN WHICH PREDICTIONS ARE CONSIDERED BELIEVABLE DEPENDING ON THE LOE SELECTED AS BELIEF CRITERIA

Drug property assertions

Drug Property	Evidence for	*LOE-1*	*LOE-2*	*LOE-4*
(INHIBITS 'FLUVASTATIN 'CYP2C9)	*in vitro* , RCT†	IN	IN†	IN
(SUBSTRATE-OF 'ROSUVASTATIN 'CYP2C9)	label	OUT	IN	IN

Predicted Drug-drug interactions

Drug Property	*LOE-1*	*LOE-2*	*LOE-4*
(INHIBIT-METABOLIC-CLEARANCE 'FLUVASTATIN 'ROSUVASTATIN 'CYP2C9)	OUT	IN†	IN

Here, an RCT type supporting (INHIBITS 'FLUVASTATIN' CYP2C9) has been added causing one of the system's inferences to be believed at *LOE*-2.
†Items different from Table VI.

We are now beginning to use the system to explore the strengths and limitations of our proposed methods including the DIKB's novel use of a truth maintenance system to link changes in the evidence support for assertions about drug properties to the set of DDIs and non-interactions the system predicts. This section relates some observations and lessons we have learned from implementing the system.

A. The DIKB as a System for Research

The DIKB's reasoning system, like that of our prototype system, is unable to track uncertainty through inference. Rather, the DIKB automatically selects assertions that meet user-defined belief criteria assuming that these assertions are certain from the user's perspective. If the user selects belief criteria that represent full confidence in each assertion type, and each assertion the DIKB uses meets the user's belief criteria, then, so will its DDI predictions. This arrangement is useful for researching how evidence can be used to establish the certainty of drug mechanism knowledge but it does not address how to handle assertions that do not meet belief criteria.

The DIKB does not prevent users from assigning as belief criteria LOEs that do not inspire their full confidence in an assertion. However, the system has no way of establishing the certainty a user should have in a DDI prediction that depends on such assertions. One can imagine scenarios where having knowledge of even uncertain DDI predictions could be valuable. For example, if the perceived risk of death to a patient is high, a clinician might want to be extra cautious while determining a drug therapy and avoid, if possible, every predicted DDI, regardless of the certainty of its occurrence. In such cases, selecting as belief criteria an LOE that does not confer complete confidence in an assertion might be justified if it had the effect of producing more, though possibly less certain, DDI predictions. It might be possible to assign a numerical value to each LOE that represents the user's certainty in any assertion possessing the combination of evidence the LOE models. Then, the system could arrive at a final certainty value for any inference by combining the confidence value for all the assertions it depends on using some theory of reasoning under uncertainty. We are currently designing experiments that will explore the feasibility of this treatment of LOEs by testing the accuracy of the DIKB using many different combinations of belief criteria.

B. Ensuring the Quality of Evidence

The DIKB assumes that it is possible to map a user's confidence in an assertion type to some arrangement of one or more

abstract evidence types. Belief criteria are established based on a prospective arrangement of evidence metadata rather than a specific review of evidence items. Unfortunately, there are many possible problems with studies or other types of evidence that can affect their quality. A poor quality study could provide false support for an assertion, so we need some way to tell users in advance what the quality of an item will be.

To address this issue, we are developing inclusion criteria for each type of evidence in the DIKB. Our inclusion criteria are explicit conditions that each type of evidence must meet to be used in the DIKB. For example, we define a quality pharmacokinetic study as one where the duration and magnitude of dosing is adequate for the drugs involved, patient genotype is noted if target enzyme is polymorphic, and if drug has active metabolites, the duration and magnitude of dosing is adequate to account for their effect on the enzyme pool. Similarly, we define quality labeling information as an unambiguous statement from the most currently available label source. We are defining inclusion criteria for each type of evidence and being careful to only enter evidence into the system that satisfies our inclusion criteria.

C. Incorporating Assumptions Can Help Maintain the system's Knowledge

One significant finding from implementing the DIKB is that incorporating assumptions into the evidence model can facilitate keeping knowledge in the system current. In building the DIKB, we noticed that interpreting the results of a scientific investigation as support for a particular assertion can sometimes require making assumptions that scientific advance might later prove to be invalid. When assumptions are later shown to be false, it is important to reconsider how much support the original investigation lends to any assertion it was once thought to support.

For example, assume that we find a pharmacokinetic study involving healthy patients that shows a significant increase in patient exposure to simvastatin in the presence of diltiazem. If the study meets our inclusion criteria, and if we have knowledge that simvastatin is primarily cleared by CYP3A4, we might apply this evidence as support for the assertion `(inhibits 'DILTIAZEM 'CYP3A4)`. Since our use of diltiazem–simvastatin study as supporting evidence for the assertion `(inhibits 'DILTIAZEM 'CYP3A4)` depends on the assumption that simvastatin is primarily cleared by CYP3A4, we would want to reconsider using this evidence if future work reveals that simvastatin is not primarily cleared by CYP3A4 or that diltiazem increases patient exposure to simvastatin by some other mechanism (e.g., transport protein modulation).

Unlike systems that just cite evidence, a formal model of evidence like the DIKB's `evidence-model` can help flag when an assumption has become invalid and alert maintainers to the need to reassess their original interpretation of what facts a piece of evidence supports. With some simple modifications, the DIKB could inform maintainers that a piece of evidence supporting an assertion should be reassessed if: 1) users make the assumption known to the DIKB by adding it as a new assertion in the `evidence-model` and linking it to any use of evidence that depends on the assumption and 2) we program the DIKB to alert users if there is a change in the belief state of any assumption in the system. This functionality is possible by a small change to the system that we will make in future work.

D. Expanding the DIKB

An important concern is how feasible it would be to expand the system's DDI prediction ability to more drugs and mechanisms. New drugs can be easily added to the system but each addition increases the number of assertions for which system maintainers need to collect evidence for. Adding more mechanisms is more difficult since it requires that we develop and validate new DDI prediction rules. Rules can come from many sources including experts in pharmacology and textbooks [29]. Once the new rules are developed, they can be added to the reasoning system along with any new object properties that the rules require. Maintainers may, then, begin to collect evidence for the new properties; this might require developing new evidence types, LOEs, and belief criteria. In both cases, a major limiting factor is the amount of knowledge that the editorial process can keep up to date. We will collect more data on this issue as we experiment with the system.

VII. Conclusion

This paper has described a working system that links drug property assertions to their supporting evidence and allows users to define and vary the criteria for belief in an assertion. In comparison with other knowledge-based systems that link evidence to their drug facts the DIKB is unique in that: 1) it collects evidence both for and against assertions; 2) it uses explicitly stated inclusion criteria; 3) it enables users to define LOEs and belief criteria for assertions using evidence metadata; and 4) it can provide different views of its knowledge and inferences to users who might not agree about what combination of evidence makes an assertion believable.

We anticipate that this research could lead to improvements in patient's safety by suggesting improvements to the methods commercial drug knowledge-bases use to represent drug mechanism knowledge and its evidence. Our research could also have broad informatics implications outside of modeling drug interactions. For example, the pathway/genome databases in MetaCyc[8] link evidence metadata to many of their assertions [30] but cannot use these evidence metadata to provide different views of its knowledge and inferences to users who might not agree about what combination of evidence makes an assertion believable.

The design of the DIKB addresses several of the issues with modeling drug mechanism knowledge. More research is necessary to determine the strengths and limitation of linking evidence to facts in a computable knowledge-base and to validate the use of evidence metadata to define belief criteria for drug mechanism facts. For future work, we will: 1) ensure that all evidence in the system is current and use the system to predict all metabolic

[8][Online]. Available: http://metacyc.org/

DDIs and non-interactions for the 17 drugs in the system and 2) validate the use of evidence metadata to assign a subjective assessment of the degree of certainty for drug mechanism facts by compiling all known metabolic inhibition interactions and non-interactions between the 17 drugs and the testing of the accuracy of DDI predictions using various, representative, belief criteria.

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