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Model and Strategy for Predicting and Discovering Drug-Drug Interactions

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Abstract. Taking several medications at the same time is an increasingly common phenomenon in our society. The combination of drugs is certainly not without risk of potentially dangerous interactions. Taking into account all possible interactions is a very complex task as it is not yet known what all possible interactions between drugs and their types are. Machine learning based models have been developed to help with this task. However, the output of these models is not structured enough to be integrated in a clinical reasoning process on interactions. In this work, we propose a clinically relevant and technically feasible model and strategy for drug interactions.

Keywords. Drug Drug interaction, Modeling, Machine learning, Decision support Systems

1. Introduction

The aging of the population, the onset of many chronic diseases, and the resistance to treatment often necessitate the use of multiple medications. Drug combinations can be beneficial and interesting, but they can also lead to problematic situations for the patient. Indeed, if we take into account the different interactions, we can take advantage of the synergistic effects between several molecules to propose an effective treatment, on the other hand, if we do not take into account all the interactions, this can lead the patient to dangerous or fatal iatrogenic accidents. To take into account drug interactions, clinicians usually rely on manually structured databases based on data from the literature. However, the absence of an interaction in the databases does not mean that it does not really exist. In fact, the absence of evidence does not mean the evidence of absence. A search on PubMed with the query "drug interactions" returns 336,256 results without counting the interactions and articles duplication. On DrugBank [1], we can count 15,229 substances[2]. The number of possible interactions

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[2] DrugBank: https://go.drugbank.com/about

between all these substances is the set of combinations C (2, 15229) which gives a total of 115,953,606. In addition, there can be several interactions between the same pair of substances.

To address the challenge of conducting clinical trials on all possible interactions, alternative solutions based on machine learning algorithms have emerged. To predict unknown drug interactions [2]. However, most existing machine learning models predict only whether two drugs may interact, without specifying the type of interaction. While there are proposed models that predict the description of the interactions [3,4], the output data is often in the form of unstructured text.

To overcome this limitation, we propose a structured and simplified output data model for drug interaction prediction that is both machine-feasible and contains sufficient information to compare automatically the predictions with structured databases. This will enable us to confront the predictions with real-life data and use them in a decision support system for prescription analysis.

2. Methods

2.1. Formal model proposal

To define and create the model proposed in this work, we relied on the recommendations of the minimal clinically relevant information to be filled in for each interaction in clinical practice [5], the model of interactions generally found in databases on drugs (Drugbank for example), as well as the output formats of some machine learning models that predict the type of interactions [3,4].

It was also deemed necessary to distinguish between pharmacodynamic (PD) interactions that have consequences on the effects of the drug on the body and pharmacokinetic (PK) interactions that have consequences on the effect of the body on the drugs.

2.2. Strategy and reasoning

The strategy used in this work consists in linking the different interactions that may exist in a set of substances in order to detect interactions between more than 2 drugs that may contribute to the same effects according to the following:

- A PD interaction between n drug: includes all drugs that are involved in the set of 2 by 2 interactions that share the same effect.
- A PK interaction between n drug: includes all drugs that are involved in the set of 2 by 2 interactions that modify the Bio-availability of a given substance.

2.3. Proof of concept

To show the feasibility and usefulness of our model and strategy, we have taken up the work of Yan *et al* [4] who developed a model and a database of interaction types obtained by machine learning techniques. This data is freely accessible on github[3]. The

[3]https://github.com/YifanDengWHU/DDIMDL/

predicted interaction types are in unstructured text format. It contains information on the action of the interaction (increase or decrease) but no information about the "victim drug" and the "perpetrator drug". There is also no distinction between PD & PK interactions. We developed a program that reclassifies the interactions present in this database in the proposed data format. We then manually validated the automatic classification.
Finally, we applied the strategy described above to generate two tables summarizing all the interactions present in a set of arbitrarily chosen drugs.

3. Results

3.1. Structured and simplified interactions model

We propose the following attributes to describe an interaction:
Substance: The active ingredients involved in the interactions.
Description: Narrative text explaining the interaction in a textual way.
Type: Description of the meaning of the interaction. Is it "Drug1" that acts on "Drug2", the reverse or the addition of the effects of the two substances. It is a question of determining the "victim drug" and the "perpetrator drug".
Action: Qualifies the nature of the interaction in relation to the target property. Is it an increase or a decrease of this property.
Property: We classify the properties of drugs targeted by an interaction with a pharmacological logic. We thus suggest two main types of interactions:
Pharmacodynamic interaction: In this type of interaction, the nature of the target property is a modification of an effect of the drug on the body. This effect can be the therapeutic effect or an adverse effect. This interaction therefore targets a single effect.
Pharmacokinetic interaction: In this type of interaction, the nature of the target property is a modification of the bio-availability of the active ingredient. This interaction can occur in several phases of the pharmaceutical active substances, namely: Absorption, Distribution, Metabolism, Elimination. Depending on the phase of occurrence of the interaction, the consequence on the bio-availability differs. For example, a decrease in absorption decreases bio-availability. On the contrary, a decrease in elimination increases bio-availability. Finally, this interaction can concern all the effects of the "victim-drug". Indeed, if the bio-availability of an active ingredient is decreased, there is a decrease in adverse effects but also a risk of therapeutic failure. Conversely, there is a risk of toxicity and of the appearance and accentuation of undesirable effects.
Finally, in this model, we consider that the same pair of substances can be the object of several interactions (Figure 1).

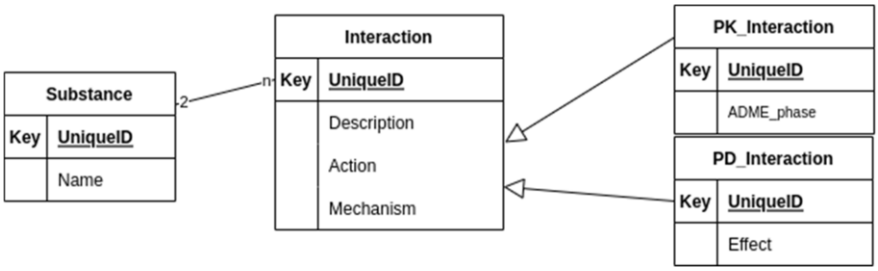

Figure 1. Structured and simplified model for the prediction of drug-drug interactions and their type ADME_phase : Acronym for (Absorption, Distribution, Metabolism or Elimination phases); PK = pharmacokinetic, PD: pharmacodynamic, Key : Primary key.

3.2. Application on machine learning predictions

In Yan *et al* [4] study, the authors developed a method to predict and classify interactions. We built upon their work by incorporating our proposed model (Figure 1) to structure the various types of interactions. The original work contains 37264 interactions divided into 65 types. Each interaction was manually annotated and assigned a structured type based on our proposed model. This step took 5 hours since the number of distinct types were small. This resulted in a comprehensive map that we used to automate the process of re-structuring the interactions.
Using this map, we classified the 37,264 interactions into 19,022 PK, which consisted of 30 A, 0 D, 10799 M, 161 E, and 8032 bio-availability interactions, without specifying the ADME phase. Additionally, we classified 18242 PD interactions, which included 1477 therapeutic effects (without specifying the effect), 9496 adverse effects (without specifying the effect), and 7269 particular effects.

3.3. Database and proposal for decision support

The database generated in this work is available in a freely accessible github repository[4]. A python program that can be found in the same repository makes it possible to generate decision support tables for researchers or developers of decision support systems.

4. Discussion

With the proposed output data model for drug interaction prediction, it becomes possible to take into account all the interactions involved in a set of substances. This allows us to consider interactions between multiple drugs, including 2-to-2 interactions that share the same effect or PK interactions that modify the bio-availability of a drug that fits or does not fit into PD interactions. We believe that this method can be integrated into a comprehensive process of monitoring and discovering new clinically significant drug interactions.
By aligning the model with MEDDRA terminology, we can query pharmacovigilance databases and health data warehouses to attribute adverse events to one or more drug interactions. This may lead to the discovery of new interactions based on real-life data

[4]https://github.com/MalikMouazer/ddireasoninglite

or raise the need to conduct clinical trials to support the evidence of a predicted interaction with machine learning algorithms.
Our proposed model does not take into account certain variables that are relevant in clinical practice, such as the severity of the interaction and recommended actions. Although this information may be of interest, we have not found data based on machine learning predictions that incorporate these variables.

5. Conclusions

The data model we propose is a compromise between the models of structured databases, which are often too complex, and the models obtained by machine learning techniques which are not structured enough. This work demonstrates the technical feasibility and clinical utility of our approach.
Our proposed model for drug-drug interactions (DDIs) provides a simple and structured way of representing interactions, which can be beneficial for training machine learning (ML) algorithms.
In perspective, we plan to fully automate the process of predicting and structuring interactions to adapt to the proposed model.

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