A proposal for determining the evidence types of biomedical documents using a drug-drug interaction ontology and machine learning

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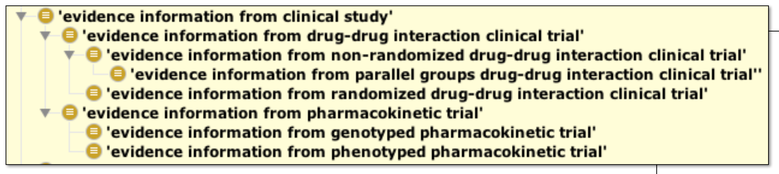
Background

- Knowledge of potential drug-drug interactions (PDDIs) is important for clinicians to make safe treatment decisions.
- It is challenging for clinicians to keep track of new knowledge about PDDIs due to a large amount of new research about PDDIs from a variety of resources including journal articles and drug labels e.g., 4171 new papers about DDIs in PubMed published in 2017 [1].
- PDDI knowledge tends to exist in silos requiring search and synthesis by drug experts. However, experts disagree about how to search and evaluate PDDI evidence.
- We propose to combine **machine learning** with a **formal representation of the DDI knowledge** in order to assist humans in the process of searching, assessing, and summarizing PDDI evidence for clinical use.

The DIDEO Ontology: a formal representation of DDI knowledge

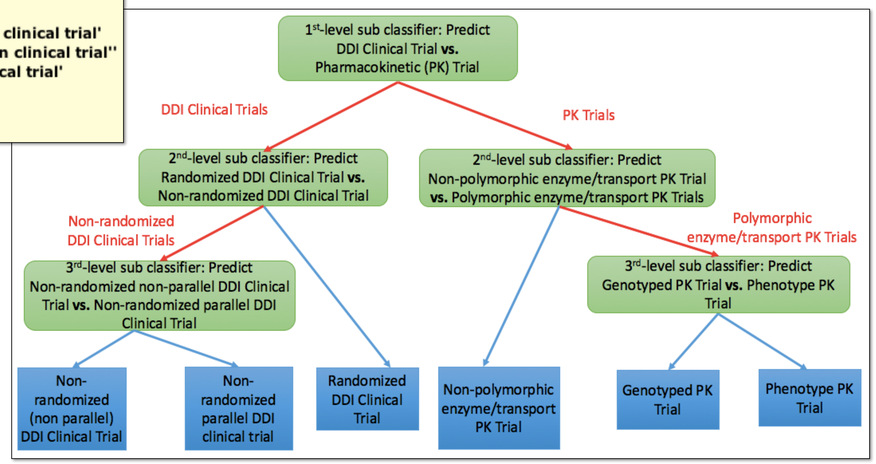
- A rigorous domain representation that allows tracing the evidence underlying potential PDDI knowledge [2].
- Contains 44 evidence types, divided into 4 levels, that were created based on evidence items returned from a systematic search for PDDI knowledge [3].
- Specifies the necessary and sufficient conditions for each evidence type using terms either defined within the ontology, or imported from other ontologies.

Approach



DIDEO Ontology (viewed in Protégé)

We are building a ***hierarchical classifier***, which is a combination of multiple sub-classifiers that automatically predict the specific type of DDI evidence provided in scientific documents, based on a set of 44 evidence types formally defined in the DIDEO ontology.



Hierarchical Classification Design

Implementation

Stage 1: Data Preparation

- *Collect and annotate data*: An existing dataset which contains 189 PDDI evidence items that were partially annotated with the evidence types in a previous study. We had an expert further annotate papers, resulting in a manual gold standard of labels.
- *Preprocess data*: Automatically collected the papers' metadata (title, abstract, publication type) through the PubMed API. Manually collected full-text PDFs and programmatically converted them to plain text.

Stage 2: Classifier Development

- *Features*: Stemmed TF-IDF of unigrams taken from the titles, from abstracts and from the Methods sections; drug entities from the titles and abstracts as detected by MetaMap.
- *Machine learning model:* All sub-classifiers are trained and tested using Support vector machine (SVM), cross validation (5 folds), class weighting mechanism. All papers are used to train and test the top-level sub-classifier. A subset of the dataset from the top-level classifier are used to train and test the next level sub-classifiers.
- *Evaluation metrics*: ROC AUC, precision, recall and F1-score.

Error Analysis

Examples of the most informative unigrams for each evidence type

Non randomized (non parallel) DDI Clinical Trial	Non randomized parallel DDI Clinical Trial	Randomized DDI Clinical Trial	Non-polymorphic enzyme/Transport PK Trial	Genotyped PK Trial	Phenotype PK Trial
confidence	outreach	crossover	accumulation	carriers	undetectable
concentration	output	randomized	fitted	genotype	hydroxylators
clozapin	team	placebo	eaten	polymorphisms	interpreted
from	anaesthesia	blind	hydroxyclarithromycin	primer	mesoridazine
significant	coinciding	double	elderly	genetic	luoxetine

Examples of wrong predictions

Article 13 predicted as Genotyped; should be Phenotype

Title: Change from the CYP2D6 extensive metabolizer to the poor metabolizer **phenotype** during treatment with bupropion

Abstract: Some data indicate that bupropion inhibits the cytochrome P-450 enzyme CYP2D6, but very little published data is available on the extent of this inhibition. The objective of the present study was to quantify this inhibition in a subject treated with bupropion for smoking cessation.

Genotypically, the patient was a CYP2D6 homozygous extensive metabolizer (EM). His CYP2D6 **phenotype** was assessed using the test drug dextromethorphan before, during, and after treatment with bupropion. During treatment with bupropion, he clearly changed from the EM to the poor metabolizer (PM) phenotype. Although the results from a single patient should be interpreted with great caution, the extent of the interaction indicates that bupropion might be a CYP2D6 inhibitor as potent as the most powerful CYP2D6 inhibitors known, such as quinidine and paroxetine.

Article 17 is predicted as "Non RCT non parallel DDI Clinical Trial"; should be "Non RCT Parallel DDI Clinical Trial"

Title: Coadministration of nefazodone and desipramine: a pharmacokinetic interaction study.

Abstract: To determine the potential for pharmacokinetic interaction between nefazodone (NFZ), and desipramine (DMI). A single center, open-label, multiple-dose, **parallel-group pharmacokinetic trial** conducted in 28 healthy male and female subjects. Group A received DMI 50 mg/day for 2 days followed by DMI 75 mg/day for the next 17 days. On Days 10-14, subjects also received 100 mg NFZ twice daily, and during Days 15-19, the NFZ dose was increased to 150 mg twice daily. Group B received 100 mg NFZ twice daily for 5 days followed by 150 mg NFZ twice daily for the next 14 days. On Days 11-12, subjects also received 50 mg DMI and during Days 13-19, the DMI dose was increased to 75 mg daily.

Classification Results

Sub-classifiers' prediction performance:

Classifier	ROC AUC	Precision	Recall	F1
Level 1 – Clinical vs. PK trials	0.74	0.88	0.87	0.85
Level 2 – Randomized vs. non-randomized trials	0.96	0.97	0.97	0.97
Level 2 – Polymorphic vs. non-polymorphic enzyme/transport	0.95	0.96	0.95	0.95
Level 3 – Parallel vs. non-parallel group	0.95	0.87	0.93	0.90
Level 3 – Genotyped vs Phenotype	0.95	0.81	0.82	0.79

Future Work

- Expand the existing classifiers to other evidence types in the DIDEO ontology.
- Run the classifiers on new articles (e.g. from PubMed Central) to get predictions of PDDI evidence types as well as to identify potentially new evidence types.
- Run the model with different features: MeSH terms, drug entity recognizer.

References

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