Predicting Drug-drug Interactions That Occur by Metabolic Inhibition Using Evidence and Truth Maintenance

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Motivation

- Drug safety dilemma
  - too many drug-combinations to study
  - the coverage and accuracy of DDI knowledge sources is often less than optimal
- Knowledge of drug mechanism can help…
- …but presents informatics challenges
  - knowledge is sometimes missing
  - scientific advance changes the body of knowledge
  - uncertainty
Interactions by metabolic inhibition

- Our system predicts:
  - reductions in clearance
  - changes in metabolite formation
  - non-ambiguous effects at four levels
Knowledge-representation system

- Evidence Base (EB)
  - The EB provides facts and rules to the KB

- Knowledge Base (KB)
  - The reasoning system reasons with the facts and rules in the KB

- Novel features
  - evidence for and against each assertion
  - meta-data tags for each evidence item
  - expert-defined belief criteria
  - non-monotonic and default reasoning
Validation and exploration

- **Focus**
  - 16 drugs and their known active metabolites

- **Validation**
  - Pharmacokinetic interactions from clinical trials, labeling, and vetted case-reports

- **Exploration**
  - What belief criteria does the validation set suggest?
  - Is there a correlation with signals from spontaneous reporting?
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