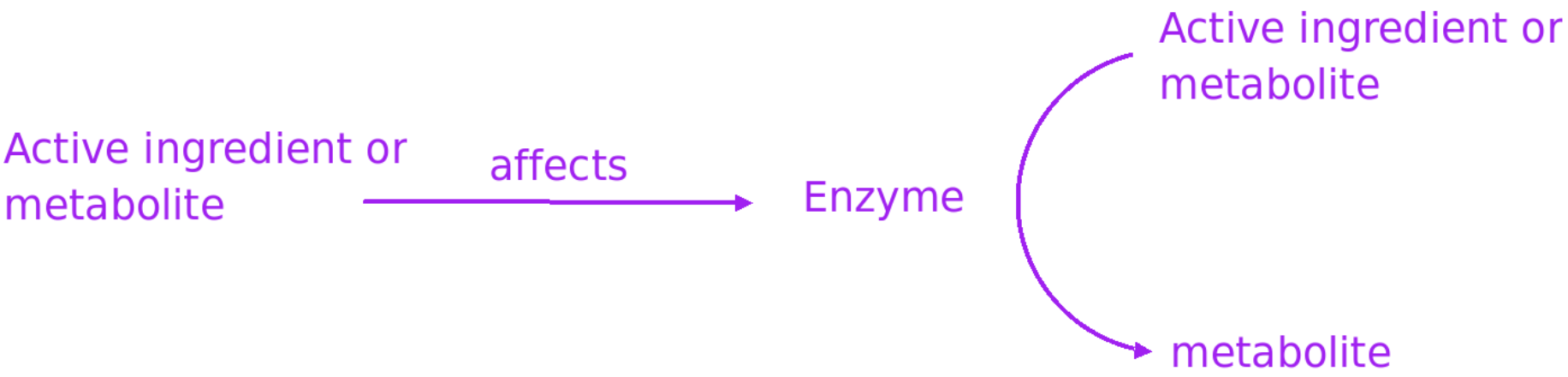
Predicting Drug-drug Interactions That Occur by Metabolic Inhibition Using Evidence and Truth Maintenance

Richard Boyce, Carol Collins, John Horn, Ira Kalet
University of Washington,
Biomedical and Health Informatics

Motivation

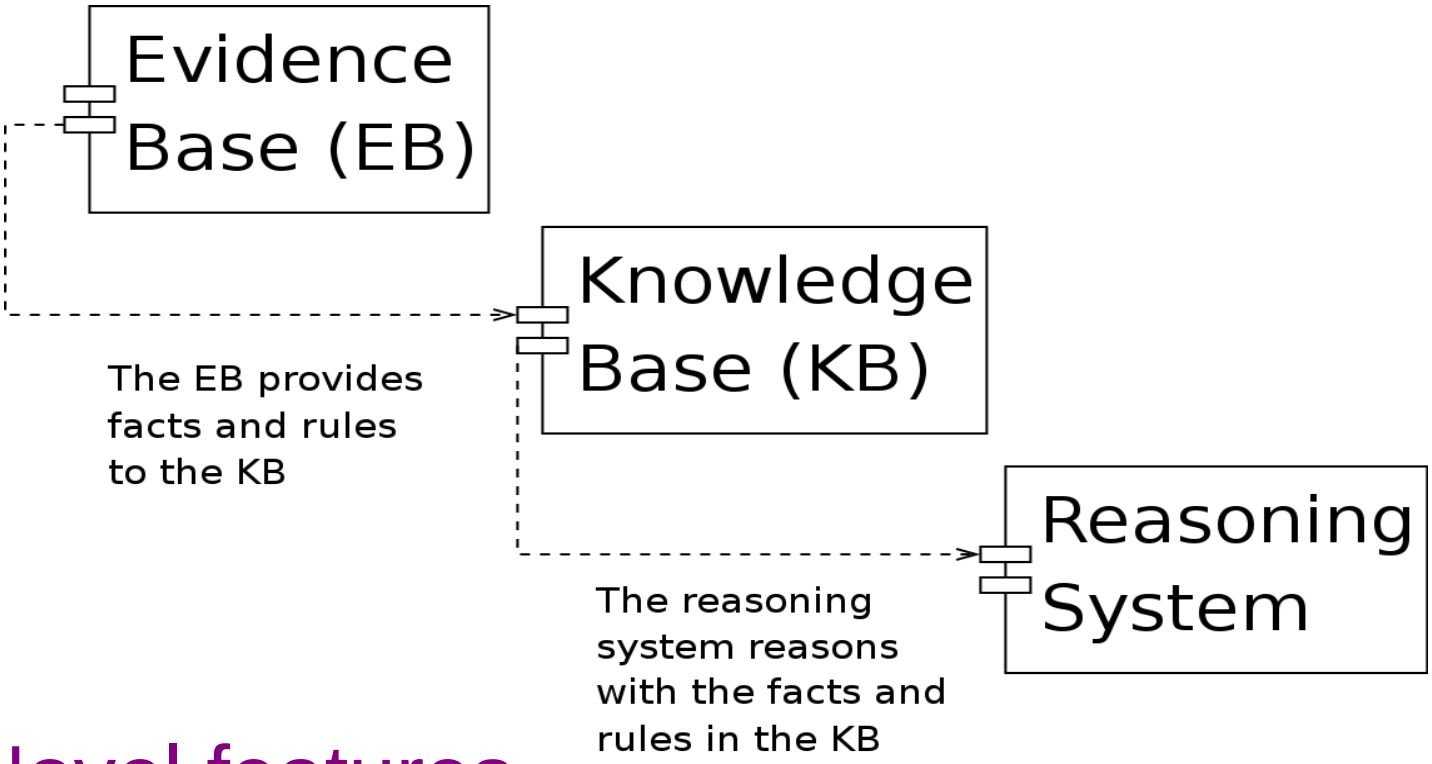
- Drug safety dilemma
  - too many drug-combinations to study
  - the coverage and accuracy of DDI knowledge sources is often less than optimal
- Knowledge of drug mechanism can help…
- …but presents informatics challenges
  - knowledge is sometimes missing
  - scientific advance changes the body of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



- 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?

Acknowledgments:

This work was partially supported by NIH grant T15 LM07442 from the National Library of Medicine and a grant from the UW School of Pharmacy Elmer M. Plein Endowment Research Fund

Thanks to Tom Hazlet, John Gennari, Eric Webster, Greg S., Alan A., and Brent L. for discussion and ideas