Effective communication of Drug-drug interaction (DDI) knowledge

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Objectives

1. Present a new approach to representing and making predictions with drug mechanism knowledge

2. Identify core knowledge elements for DDI decision support and suggest the possibility of a common model for representing and sharing DDI knowledge

3. Suggest how further research on clinical trigger systems could lead to reduced DDI alert fatigue while improving patient safety
Objective 1:
Present a new approach to representing and making predictions with drug mechanism knowledge
A large number of potential interactions can be inferred based on mechanisms

- pre-clinical and pre-market
- post-market *in vitro* and *in vivo*

For example, metabolic interactions:
Three informatics challenges to reasoning with drug mechanisms\textsuperscript{1}

Drug mechanism knowledge is dynamic, sometimes missing, and often uncertain

Hypothesis:
A computable model of drug-mechanism evidence will enable powerful methods for addressing these issues.

Case study: The Drug Interaction Knowledge Base (DIKB)

The DIKB:

- infers drug-mechanism knowledge from a computable representation of evidence
- makes interaction and non-interaction predictions with measurable performance characteristics

Current focus:

DDIs that occur by metabolic inhibition
The DIKB architecture

- 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

- Reasoning System
The reasoning system's current DDI prediction model

- Uses facts in the knowledge-base that meet explicit belief criteria
- Provides a "ball-park" magnitude estimate
  - based on the importance of the affected metabolic pathway to the object drug
- Predicts enzyme-specific non-interactions
  - enables the suggestion of alternative drugs

The DIKB is an evidential system

- All assertions are linked to their evidence for or against:

  \[(\text{FLUCONAZOLE inhibits CYP2C9})\]

  Evidence for \hspace{1cm} Evidence against

- helps assess credibility, draw attention to errors, and establish confidence
All assumptions are linked to evidence

- Enables the system to identify when assumptions are no longer valid
- Helps identify poor uses of evidence
All evidence is classified using a study taxonomy

- Oriented toward user confidence assignment
- 36 types over several sub-hierarchies

  A DDI clinical trial
  ...randomized
  ...non-randomized
  ...

  A non-traceable statement
  ...in drug product labelling
  ...

  A metabolic enzyme inhibition experiment
  ...focusing on CYP450 enzymes
  ...done in human liver microsomes
Basic quality standards are defined for every evidence type

- Example: Pharmacokinetic clinical trials
  - adequate duration and magnitude of dosing
  - patient genotype/phenotype is noted if the target enzyme is polymorphic

- Example: in vitro enzyme metabolism identification
  - human hepatocyte or recombinant CYP450
  - 'selective' inhibitors and 'probe' substrates
This DIKB's architecture helps identify evidence use strategies

- What evidence is sufficient to justify that a drug possesses certain mechanistic properties in vivo?

- What evidence-use strategy enables the system to make the best predictions?

- How do these predictions compare with the most rigorous treatment of evidence possible?
An experiment focusing on statins¹

- Study overview:
  - Collect evidence on statins and a sub-set of co-prescribed drugs (16 drugs, 19 metabolites)
  - Make predictions using a “belief criteria strategy” designed by two drug experts
  - Explore computer-generated strategies to find the ones that were “best-performing”
  - Examine the feasibility of novel DDI predictions

An experiment focusing on statins

Study overview:

- Collect evidence
- Explore prediction performance using all evidence-selection criteria
- Assess the feasibility of 'novel' predictions

(16 drugs, 19 metabolites)

36,000 strategies

Metrics

- sensitivity, specificity, positive predictive value (PPV)
- accuracy = (true pos + true neg) / (all predictions)
- kappa
### The validation set

<table>
<thead>
<tr>
<th>Drug Pairs</th>
<th>586</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactions</td>
<td>41  (7%)</td>
</tr>
<tr>
<td>Non-interactions</td>
<td>7  (1.2%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>538  (91.8%)</td>
</tr>
</tbody>
</table>

'unknown': a pair for which no interaction or non-interaction can be confirmed
Test 1 – the DIKB's most rigorous evidence-use strategy possible

- Sample of the two most critical assertions:
  - D inhibits ENZ:
    - FOR: clinical trials with D and another drug known to selectively inhibit ENZ \textit{in vivo}
    - AGAINST: metabolic inhibition studies with probe substrates
  - D substrate-of ENZ
    - FOR/AGAINST: drug metabolism studies involving participants with known CYP450 phenotypes or genotypes
**Test 1 – results using the most rigorous criteria**

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>number of predictions</td>
<td>17</td>
</tr>
<tr>
<td>True positive</td>
<td>14</td>
</tr>
<tr>
<td>True negative</td>
<td>0</td>
</tr>
<tr>
<td>novel</td>
<td>3</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>1.00</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>1.00</td>
</tr>
<tr>
<td>Specificity</td>
<td>undefined</td>
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<td>Coverage of validation set</td>
<td>14/49 = 29%</td>
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## Test 2 – computer-derived 'best' strategy

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<tr>
<th>LOE</th>
<th>inhibits</th>
<th>substrate-of</th>
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<td>High</td>
<td>in vitro study AND PK</td>
<td>authoritative</td>
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<tr>
<td>Med</td>
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<td></td>
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<tr>
<td>Low</td>
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**Diagram:**
- **Evidence Base (EB):**
  - The EB provides facts and rules to the KB
- **Knowledge Base (KB):**
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- **Reasoning System:**
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Test 2 – better-performing strategies

- 8,351 (23%) of 36,000 tested strategies
- Equal or better sensitivity, positive predictive value, and agreement than the expert-designed strategy
- 1,152 (3%) performed at the top level

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<tr>
<td>true positives</td>
<td>34</td>
<td>false positives</td>
<td>0</td>
</tr>
<tr>
<td>true negatives</td>
<td>0</td>
<td>false negatives</td>
<td>0</td>
</tr>
<tr>
<td>sensitivity</td>
<td>1.00</td>
<td>specificity</td>
<td>n/a</td>
</tr>
<tr>
<td>PPV</td>
<td>1.00</td>
<td>kappa</td>
<td>0.52</td>
</tr>
</tbody>
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Test 2 – relaxing belief criteria often improved performance
Test 2 – relaxing belief criteria often improved performance
### Test 2 Novel Predictions

- 31 novel interaction predictions
- 13 matched to 15 published case reports
- 18 other non-refuted interaction predictions
- Two interaction predictions supported by case reports that were not present in product labelling:

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<tr>
<th>Interaction prediction</th>
<th>Level</th>
<th>Evidence</th>
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</thead>
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<td>diltiazem – atorvastatin</td>
<td>&gt; 2-fold</td>
<td>2 case reports – possible</td>
</tr>
<tr>
<td>fluconazole – simvastatin</td>
<td>&gt; 2-fold</td>
<td>1 case report – possible</td>
</tr>
</tbody>
</table>
Conclusions from the pilot experiment

The new approach to representing drug mechanism knowledge

- can suggest the best use of available evidence for metabolic DDI prediction
- is less subjective than ranking evidence and selecting the most rigorous

This is interesting because

- drug mechanism evidence base varies dramatically across marketed drugs
Objective 2:
Identify core knowledge elements for DDI decision support and suggest the possibility of a common model for representing and sharing DDI knowledge
**Example - A possible observed DDI**

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<th>Evidence</th>
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<td>&gt; 2-fold</td>
<td>2 case reports – <em>possible</em></td>
</tr>
</tbody>
</table>

- Two case reports reporting on five individuals who developed symptoms of myopathy or rhabdomyolysis\(^1,2\)
- All cases provide some evidence that an adverse event (AE) was caused by this DDI


Assessing the example DDI

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<th>Level</th>
<th>Evidence</th>
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<tbody>
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</tr>
</tbody>
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The DDI:
- is reasonable
- could lead to a serious or fatal adverse event

...but, we don't know:
- patient-specific risk factors
- prevalence of co-prescribing and various outcomes
Structured DDI assessment

- A structured assessment scores evidence and potential severity\(^1\)

Evidence for/against a DDI

- pre- and post-market studies
- in vitro experiments
- known or theoretical mechanisms
- case reports and case series
- pharmacovigilance
Risk factors

- patient characteristics X potential adverse event
- patient characteristics X DDI mechanism
- drug characteristics
  - route of administration, dose, timing, sequence
Risk factors depend on evidence

Context for decision support

evidence for/against risk factors
Incidence

- prevalence of co-prescription
- prevalence of AE
- incidence of AE in exposed and non-exposed
Incidence and evidence strengthen each other

evidence for/against

Context for decision support

incidence (exposed & non-exposed)
Seriousness of the AE

- Classified by specific clinical outcome
- ...but, can any seriousness ranking be generally accepted?

no effect ← ? → death
### Re-assessing the example DDI

<table>
<thead>
<tr>
<th>Drug Pair</th>
<th>Diltiazem – Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential AE</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Other HMG-CoA inhibitors, phenotype, ...</td>
</tr>
<tr>
<td>Evidence</td>
<td>Five possible cases, established mechanism</td>
</tr>
<tr>
<td>Prevalance of Pair</td>
<td>Common</td>
</tr>
<tr>
<td>General Incidence of AE</td>
<td>Rare</td>
</tr>
<tr>
<td>Incidence in Exposed</td>
<td>...</td>
</tr>
<tr>
<td>Incidence in Non-Exposed</td>
<td>...</td>
</tr>
</tbody>
</table>
Structured assessments vary

- focus and content
- methods for ranking severity
- across compendia, vendors\(^1\), and implementations\(^2\)


Agreement on common elements might be possible

<table>
<thead>
<tr>
<th>drug pair</th>
<th>potential AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>risk factors</td>
<td>evidence</td>
</tr>
<tr>
<td>prevalance of pair</td>
<td>general incidence of AE</td>
</tr>
<tr>
<td>incidence in exposed</td>
<td>incidence in non-exposed</td>
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...and could form the basis for a sharing DDI knowledge across resources
Objective 3:
Suggest how further research on clinical trigger
systems might lead to reduced DDI alert fatigue while
improving patient safety
Results from a recent review on medication alerting¹

- “Adverse events were observed in 2.3%, 2.5%, and 6% of the overridden alerts, respectively, in studies with override rates of 57%, 90%, and 80%.”
- “The most important reason for overriding was alert fatigue caused by poor signal-to-noise ratio”
- Only one study looked at error reductions for DDI alerts – the results were statistically non-significant

What does the literature suggest?

- find a balance between push vs. pull alerts
- tier DDI alerts by severity
- give users the ability to set preferences for some types of alerts
- provide value e.g. changing meds or correcting the medical record from the alert
- make alert systems more intelligent
A potential complementary approach

Clinical event monitor - a system that identifies and flags clinical data indicative of a potentially risky patient state
Example – UPMC MARS-AiDE

alerts to consultant pharmacist

MARS-AiDE

lab and drug signals

MARS-LTC data repository

Lab data

pharmacy data
## Example triggers from UPMC MARS-AiDE

<table>
<thead>
<tr>
<th>signal</th>
<th>alerts</th>
<th>ADRs</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+) polystyrene given; taking a drug that may cause hyperkalemia</td>
<td>2</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Vitamin K given; taking warfarin</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Clostridium difficile toxin positive; taking a drug that may cause pseudomembranous colitis</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase concentration; taking a drug that may cause/worsen hepatocellular toxicity</td>
<td>5</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

DDI-aware clinical event monitoring

- alerts/notifications
- Rule engine
  - DDI knowledge-base
  - signal/trigger knowledge-base
  - patient-specific clinical data
Potential benefits and risks of DDI-aware clinical event monitoring

- **Benefits**
  - automatic consideration of patient-specific risk factors
  - a possible safety net for some 'potential DDI' alerts
  - may provide implicit management options (e.g. stop/change interacting drug)

- **Risks**
  - potential for additional alert burden
  - is it ethical to not alert prescribers?
  - ...
Conclusions

We've looked briefly at three areas of research that aim to make more effective use of DDI knowledge in clinical care:

- representing and using evidence for predicting DDIs
- DDI knowledge sharing
- integrating DDI knowledge with clinical event monitoring
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