Towards Using Literature-based Discovery to Explain Drug Adverse Effects

Dimitar HRISTOVSKI\textsuperscript{a}, Anita BURGUN-PARENTHOINE\textsuperscript{b}, Paul AVILLACH\textsuperscript{b} and Thomas C RINDFLESCH\textsuperscript{c}

\textsuperscript{a} Institute for Biostatistics and Medical Informatics, Medical faculty, University of Ljubljana, Slovenia
\textsuperscript{b} University of Rennes, France
\textsuperscript{c} National Library of Medicine, NIH, Bethesda, USA

e-mail: dimitar.hristovski@mf.uni-lj.si
Introduction / Motivation

- Pharmacovigilance:
  - detection, and prevention of drug adverse effects

Goal of our research:
- Find pharmacogenomic explanation of
Related Work

- Pharmacovigilance
- Literature-based Discovery
- Natural Language Processing:
  - Semantic relation extraction
Proposed Solution

• Find genes that link drugs to adverse effects

• Basic assumption:
  – drugs affect genes,
  – genes affect adverse effects

• Literature-based Discovery:
  – SemBT tool (http://sembt.mf.uni-lj.si)
  – Based on SemRep extracted semantic relations
Literature-based Discovery

- Generates novel hypotheses by analyzing the literature and (optionally) other resources

- Two modes of operation:
  - Open discovery: generates novel hypotheses
  - Closed discovery: provides explanation
Using LBD to Explain a (Known) [Drug X, Adv.Eff. Z] Pair

Drug X e.g. Lithium

Gene (or protein) Y1 e.g. Sodium Channel

Gene (or protein) Y2 e.g. Insulin

Gene (or protein) Y... e.g. ...

Gene (or protein) YN e.g. INS

Adverse effect(s) Z e.g. Brugada Syndrome

Causes(?)

ReX\text{Y}\phantom{Z}

ReY\text{Z}
SemRep

• Extracts semantic relations from biomedical text
• Based on UMLS Metathesaurus and Semantic Network (extended)
  – <MetaConc> SEMNET RELATION <MetaConc>
• Relations extracted:
  associated_with, predisposes, causes, interacts_with, inhibits, stimulates, affects, disrupts, augments, administered_to, manifestation_of, treats, location_of, part_of, process_of, co-exists_with
SemRep Examples

• “... lithium is a potent blocker of cardiac sodium channels...”
• Relation: Lithium inhibits Sodium Channel

• “... a mutation in the human cardiac sodium channel contributes to... Brugada syndrome ...”
• Relation: Sodium Channel predisposes Brugada syndrome
Example: Lithium-Brugada Syndrome

SemBT Closed Discovery

XY Relations found: 477, YZ Relations found: 23, Common Ys found = 3

Semantic relation search
Query XY: sub_name:lithium AND obj_semtype (aapp OR gnmg) Expand XY: none
Microarray Filter XY:
Experiment: none Limit arguments any to top N 100 all genes at p <= 0.0001
Query YZ: sub_semtype (aapp OR gnmg) AND obj_name:"brugada syndon" Expand YZ: none
Microarray Filter YZ:
Experiment: none Limit arguments any to top N 100 all genes at p <= 0.0001

Common Ys:

<table>
<thead>
<tr>
<th>Value</th>
<th>Count XY</th>
<th>Count YZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Channel</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>INS</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
• X = Lithium, Z = Brugada Syndrome
• Y = unknown?
• Query XY:
  – sub_name:lithium AND obj_semtype:(aapp OR gngm)
  – meaning: Lithium related to any genes or proteins
• Query YZ:
  – sub_semtype:(aapp OR gngm) AND obj_name:"brugada syndrome"
  – meaning: (the same) genes or proteins related to Brugada syndrome
Example: Intermediate Concepts

<table>
<thead>
<tr>
<th>Value</th>
<th>Count XY</th>
<th>Count YZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Channel</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>INS</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Example: Providing Explanation through an Intermediate Concept

Aligned relations for Sodium Channel:

<table>
<thead>
<tr>
<th>X-Relation-Y</th>
<th>Y-Relation-Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>INHIBITS</td>
</tr>
</tbody>
</table>

Lithium can unmask Brugada syndrome through its ability to block sodium channels, even at subtherapeutic concentrations. (PMID: 20016437)

CONCLUSIONS: The widely used drug lithium is a potent blocker of cardiac sodium channels and may unmask patients with the Brugada syndrome. (PMID: 16144991)

Because lithium is a potent blocker of cardiac sodium channels, and given the critical importance of sodium channels in pacemaker activity, lithium-induced sodium channel blockade is likely an important mechanism in sinus node dysfunction. (PMID: 17347696)

SCN5A, the gene encoding the alpha subunit of the sodium channel, is the only gene thus far linked to Brugada syndrome ...(PMID: 16415541)

Mutations in SCN5A, a cardiac sodium channel gene, have been recently associated with Brugada syndrome. (PMID: 11960580)

Loss of function mutations in SCN5A, encoding the cardiac sodium channel, are one cause of the Brugada syndrome ... (PMID: 16415376)

Changes in the sodium channel are responsible for long QT syndrome, Brugada syndrome and conduction defects. (PMID: 17497250)

A mutation in the human cardiac sodium channel (E161K) contributes to sick sinus syndrome, conduction disease and Brugada syndrome in two families. (PMID: 15910881)
Summary

• A method and tool for explaining drug adverse effects presented
• Based on literature-based discovery and semantic relations from the literature
• To be used by a pharmacovigilance expert
• Availability: http://sembt.mf.uni-lj.si
Mbd1 can directly regulate the expression of Htr2c

- MedPost tagger and shallow parser
Semantic Processing

- Identify concepts: MetaMap and ABGene

[ NP[head([… semtype(gngm),entrez(MBD1,4152))], ... ]
  [verb([inputmatch(regulate),lexmatch(regulate),tag(verb)]),... ]
  NP[... head([… semtype(gngm),entrez(HTR2C,3358)])]] ]
• Identify concepts: MetaMap and ABGene

\[ \text{NP}[\text{head}([\ldots \text{semtype}(\text{gngm}), \text{entrez}(\text{MBD1}, 4152)], \ldots \\
\text{verb}([\text{inputmatch}(<\text{regulate}>), \text{lexmatch}(<\text{regulate}>), \text{tag}(\text{verb})])], \ldots \\
\text{NP}[\ldots \text{head}([\ldots \text{semtype}(\text{gngm}), \text{entrez}(\text{HTR2C}, 3358)])] ] \]

• Match semantic type patterns to ontology:

\text{<gngm> INTERACTS_WITH <gngm>
Semantic Processing

• Identify concepts: MetaMap and ABGene

\[ \text{NP[... semtype(gngm),entrez(MBD1,4152)], ...} \]
\[ \text{verb([inputmatch(regulate),lexmatch(regulate),tag(verb)])]},... \]
\[ \text{NP[... head([... semtype(gngm),entrez(HTR2C,3358)]])]} \]

• Match semantic type patterns to ontology:

<gngm> INTERACTS_WITH <gngm>
Semantic Processing

- Identify concepts: MetaMap and ABGene
  
  \[
  \text{NP[head([… semtype(gngm),entrez(MBD1,4152)], ...}
  \text{verb([inputmatch(regulate),lexmatch(regulate),tag(verb)])]],...}
  \text{NP[… head([… semtype(gngm),entrez(HTR2C,3358)])] ]}
  \]

- Match semantic type patterns to ontology:
  \(<\text{gngm}> \text{ INTERACTS\_WITH } <\text{gngm}>\)

- **Apply indicator rule:** \(\text{Verb}(\text{regulate}) \rightarrow \text{INTERACTS\_WITH}\)
Semantic Processing

• Identify concepts: MetaMap and ABGene

\[
\text{NP}[\text{head}(\ldots \text{semtype(gngm)}, \text{entrez(MBD1,4152)})], \ldots
\]

\[
\text{verb}(\text{inputmatch(regulate)}, \text{lexmatch(regulate)}, \text{tag(verb)})], \ldots
\]

\[
\text{NP}[\ldots \text{head}(\ldots \text{semtype(gngm)}, \text{entrez(HTR2C,3358)})] \]

• Match semantic type patterns to ontology:

\text{<gngm> INTERACTS_WITH <gngm>}

• Apply indicator rule: Verb(regulate) \rightarrow \text{INTERACTS_WITH}
Semantic Processing

- Identify concepts: MetaMap and ABGene

\[
\text{NP}\left[\text{head}(\ldots \text{semtype}(\text{gngm}), \text{entrez}(\text{MBD1,4152})), \ldots \right. \\
\ldots \text{verb}(\left[[\text{inputmatch}(\text{regulate}), \text{lexmatch}(\text{regulate}), \text{tag}(\text{verb})]\right]), \ldots \\
\text{NP}\left[\ldots \text{head}(\ldots \text{semtype}(\text{gngm}), \text{entrez}(\text{HTR2C,3358}))\right] \right]
\]

- Match semantic type patterns to ontology:

\(<\text{gngm}> \text{INTERACTS\_WITH} <\text{gngm}>\)

- Apply indicator rule: \(\text{Verb}(\text{regulate}) \rightarrow \text{INTERACTS\_WITH}\)

- **Substitute concepts for semantic types:**
 Semantic Processing

• Identify concepts: MetaMap and ABGene
  \[ \text{NP}[\text{head}(\ldots \text{semtype(gngm)},\text{entrez(MBD1,4152)}), \ldots \]
  \[\text{verb}(\text{inputmatch(regulate)},\text{lexmatch(regulate)},\text{tag(verb)})],\ldots\]
  \[\text{NP}[\ldots \text{head}(\ldots \text{semtype(gngm)},\text{entrez(HTR2C,3358)})]\]

• Match semantic type patterns to ontology:
  \(<\text{gngm}>\text{INTERACTS\_WITH}\ <\text{gngm}>\)

• Apply indicator rule: Verb(regulate) \rightarrow \text{INTERACTS\_WITH}

• Substitute concepts for semantic types:
Semantic Processing

• Identify concepts: MetaMap and ABGene

[\text{NP}[\text{head}([\ldots \text{semtype(gngm)},\text{entrez(MBD1,4152)}], \ldots
\quad \text{verb}([\text{inputmatch(regulate)},\text{lexmatch(regulate)},\text{tag(verb)}])],\ldots
\text{NP}[\ldots \quad \text{head}([\ldots \text{semtype(gngm)},\text{entrez(HTR2C,3358)}])] ]

• Match semantic type patterns to ontology:
<\text{gngm}> \text{INTERACTS\_WITH} <\text{gngm}>

• Apply indicator rule: Verb(regulate) $\rightarrow$ INTERACTS\_WITH

• Substitute concepts for semantic types:
\text{MBD1 \text{INTERACTS\_WITH} HTR2C}