Semantic Insights using Agile NLP-based Text Mining

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ICIC
Sitges, Spain
October 18-21, 2009
Overview

◆ Agile Text Mining

◆ Extraction from large documents
  – Case study on extracting quantitative information from compound safety reports

◆ Semantic Insights via
  – Linking information extracted from different documents
  – Linking structured and unstructured knowledge
  – Linking chemical and biological knowledge
Knowledge Discovery Challenges

- Need to use available information to make better decisions

- Integrate knowledge from different sources
  - External
    - literature
    - news
    - web
  - Internal
    - experimental data
    - reports
    - databases
  - Automatically derive insight
  - Get to weak signals
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Search, Information Extraction and Agile Text Mining

- **Document search**
  - Provides the most relevant documents for a query

- **Information Extraction**
  - Finds specific assertions using Natural Language Processing

- **Agile Text Mining**
  - Provides answers to ad-hoc questions
“Which, What, Who?”

- Go directly to answers, e.g. find all the genes associated with a specific disease
- “Which gene” searches for >10,000s genes and all their synonyms
- Provides highlighted evidence and link to the document:
  - Read a sentence or a single document to convince you that the gene is relevant (or not)
“Which, What, Who?”

- Find which gene mutations are mentioned specifically related to the disease, e.g. breast cancer

<table>
<thead>
<tr>
<th>Entrez Genes</th>
<th>Mutation</th>
<th>Doc</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERBB2</td>
<td>Ile655Val</td>
<td>15970791</td>
</tr>
<tr>
<td></td>
<td>Ile654Val</td>
<td>15550452</td>
</tr>
<tr>
<td>BRCA1</td>
<td>4153delA</td>
<td>15960987</td>
</tr>
<tr>
<td></td>
<td>C61G</td>
<td>15960987</td>
</tr>
<tr>
<td>BRCA2</td>
<td>C5972T</td>
<td>16280055</td>
</tr>
<tr>
<td></td>
<td>999del5</td>
<td>16418514</td>
</tr>
</tbody>
</table>
“Tell me about X”

- Search would provide documents most about X
- Here, profiling X by summarising information from millions of docs

<table>
<thead>
<tr>
<th>Pharmacologic Substance</th>
<th>Relation</th>
<th>Entity</th>
<th>Doc</th>
<th>Hit</th>
<th>qID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>treats</td>
<td>Psoriasis</td>
<td>81</td>
<td>3 Cyclosporine therapy for psoriasis: a cell cycle-derived dosing schedule.</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>dosage</td>
<td>5 mg/kg/day</td>
<td>15</td>
<td>3 Alterations in renal function in psoriasis patients treated with cyclosporine, 5 mg/kg/day.</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>causes</td>
<td>nephrotoxic</td>
<td>2</td>
<td>1 Methotrexate treatment can lead to bone marrow suppression and hepatotoxicity, and cyclosporine can cause nephrotoxicity.</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>inhibit</td>
<td>Growth factor</td>
<td>2</td>
<td>1 FK506 and cyclosporin A inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the G0/G1 phases of the cell cycle.</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>affect</td>
<td>PGP</td>
<td>1</td>
<td>1 CONCLUSIONS: Cyclosporin A modulates Pgp, MRP-1, BCRP, and LRP, and this broad-spectrum activity may contribute to its clinical efficacy.</td>
<td>1</td>
</tr>
<tr>
<td>IC50</td>
<td></td>
<td>3.0 ng/ml</td>
<td>1</td>
<td>1 We classified these patients into two groups on the basis of their PBMC sensitivity to cyclosporine with use of the median cyclosporine IC50 (3.0 ng/ml) of these patients as the cutoff point.</td>
<td>12</td>
</tr>
</tbody>
</table>
Interactive Information Extraction (I2E)

- **Natural Language Processing (NLP):** using linguistics to interpret the meaning of unstructured text sources.

- **Structured Output:** presenting extracted information with drill-down to supporting evidence.

- **Search Engine Approach:** returning results in real time.

- **Domain Knowledge Plug-in:** ability to provide semantic search capabilities with domain knowledge such as thesauri and taxonomies.

- **Graphical User Interface:** users can define, share, and adapt queries.
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Extracting Data from Safety Reports

Extracting toxicity data for structure-activity modeling

- Reports in PDF format, up to 1000 pages, often as scanned electronic images
- Complex sentence construction
- Necessary data may be within text or within tables
- Inconsistent identifiers, e.g. for compounds, both in format and over time

**Semi-Automated Approach**

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>FQPA SF* and Endpoint for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short- and Intermediate-Term Incidental Oral (1 to 30 days and 1 month to 6 months)</td>
<td>NOAEL = 15 mg/kg/day</td>
<td>LOC for MOE = 300 (Residential)</td>
<td>Co-critical studies: subchronic oral (rat); subchronic neurotoxicity (rat) developmental toxicity (rat); LOAEL = 50 mg/kg/day based on reductions in body weight, body weight gain and food consumption.</td>
</tr>
</tbody>
</table>

**OCR/PDF conversion**
Example PDF from EPA

**I2E Text Mining**

**Results Curation**
Extracting Quantitative Information

- Clinical chemistry, e.g. serum chemistry, hematology, urinalysis
- Clinical signs, observations
- Complex, precise patterns used to extract from “respectively” constructions, e.g. for exposure

<table>
<thead>
<tr>
<th>AUC</th>
<th>Concentration</th>
<th>Units</th>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2630</td>
<td>ng-h/mL</td>
<td>5 mg/kg</td>
<td>Day 1</td>
<td>Mean AUC 0-24h values were 2630, 98800, and 785000 ng-h/mL on Day 1 and 3190, 116000, and 1340000 ng-h/mL on Day 30 at 5, 50, and 250 mg/kg, respectively.</td>
</tr>
<tr>
<td>98800</td>
<td>ng-h/mL</td>
<td>50 mg/kg</td>
<td>Day 1</td>
<td>Mean AUC 0-24h values were 2630, 98800, and 785000 ng-h/mL on Day 1 and 3190, 116000, and 1340000 ng-h/mL on Day 30 at 5, 50, and 250 mg/kg, respectively.</td>
</tr>
<tr>
<td>785000</td>
<td>ng-h/mL</td>
<td>250 mg/kg</td>
<td>Day 1</td>
<td>Mean AUC 0-24h values were 2630, 98800, and 785000 ng-h/mL on Day 1 and 3190, 116000, and 1340000 ng-h/mL on Day 30 at 5, 50, and 250 mg/kg, respectively.</td>
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### Potential Mechanism of Action of Compound on Disease

<table>
<thead>
<tr>
<th>Compound</th>
<th>Gene</th>
<th>Disease</th>
<th>Doc</th>
<th>Hit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>inhibit</td>
<td>Interferon</td>
<td>affect</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>inhibit</td>
<td>IL8</td>
<td>affect</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>affect</td>
<td>CALM3</td>
<td>affect</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>inhibit</td>
<td>Growth factor</td>
<td>affect</td>
<td>Psoriasis</td>
</tr>
</tbody>
</table>

**Example: How does A relate to B**

1. In addition, cyclosporin blocked the interferon-gamma-induced increase in epidermal 12(S)-HETE binding. (Doc: 1789988)
2. It was found out that CSA inhibits IL-8 production by stimulated THP-1 monocyte cell. (Doc: 9588089)
3. Cyclosporine binds to calmodulin with low affinity, and... (Doc: 2277142)
4. FK506 and cyclosporin A inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the... (Doc: 8884530)
```
<table>
<thead>
<tr>
<th>Disease</th>
<th>Relation</th>
<th>Gene</th>
<th>Location</th>
<th>Serum/Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>associate</td>
<td>ERBB2</td>
<td>plasma</td>
<td>15756435</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>associate</td>
<td>TNF</td>
<td>plasma</td>
<td>15999154</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>associate</td>
<td>IL6</td>
<td>serum</td>
<td>16115909</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>associate</td>
<td>INS</td>
<td>plasma</td>
<td>16393696</td>
</tr>
</tbody>
</table>
```

- However, the effect of TNFA and TNFB gene polymorphisms on the expression of steroid receptors in breast cancer cells is not well documented.
- The IL6 polymorphism was significantly associated with breast cancer.
- Insulin-like growth factor II mediates resveratrol stimulatory effect on cathepsin D in breast cancer cells.
- ... protein in tumor tissue and the HER-2 extracellular domain in plasma were used to show interdiction ...
- ... in a significant rise in plasma TNFAlpha levels(0.05 +/- 0.05 ng ...
- ... in pigs: TNF-alpha, IL-6 expressions in serum and rates of MODS after ...
- ... and a 38.5% increase in plasma insulin at 60 min, compared ...
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Linking Candidate GWAS Genes with Diseases: Case Study with InforSense: Parkinson’s Disease

<GWAS>-<relation>-<Gene>* -<relation>-<Parkinson’s>
Merging Structured and Unstructured: Case Study with GeneGo: Liver Fibrosis

Identifying disease pathways with more confidence by combining information from GeneGo and I2E

Blue: 12 GG genes
Green: 8 LM genes
Black: 2 common in both sets
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Linking Chemical and Biological Knowledge: Integrated Substructure Search from ChemAxon with I2E Text Mining

\[
\text{<Structure>-<is-substructure>-<Chemical>-<relation>-<Target>}
\]

\[
\text{N(C1=CC=CC=C1)C1=*C=*C=N1}
\]

<table>
<thead>
<tr>
<th>Class1</th>
<th>Relation</th>
<th>Class2</th>
<th>Doc</th>
<th>Hit</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib</td>
<td>inhibit</td>
<td>ABL1</td>
<td>216303243</td>
<td>1</td>
</tr>
<tr>
<td>imatinib methanesulfonate</td>
<td>inhibit</td>
<td>ABL1</td>
<td>315803362</td>
<td>1</td>
</tr>
<tr>
<td>gefitinib</td>
<td>inhibit</td>
<td>EGFR</td>
<td>215692759</td>
<td>2</td>
</tr>
<tr>
<td>lapatinib</td>
<td>inhibit</td>
<td>ERBB2</td>
<td>316452223</td>
<td>2</td>
</tr>
</tbody>
</table>

1. Imatinib, an inhibitor of BCR-ABL tyrosine kinase, also inhibits BCRP-mediated drug transport.
2. BACKGROUND: Imatinib mesylate is a potent inhibitor of Abl, KIT, and PDGFR tyrosine kinases.
3. The clinical benefit and safety of the EGFR tyrosine kinase inhibitor gefitinib (‘Iressa’) was evaluated in this Phase II, multicentre study of patients with taxane and anthracycline pretreated, metastatic breast cancer.
Semantic Insights using Agile Text Mining

- Derive structure from unstructured and semi-structured text
- Text treated as a database
  - With dynamic relationships
- Query results are structured, allowing
  - Further analysis
  - Visualisation
  - Gaps to be filled in structured knowledge
- Derive new insights by combining information from multiple
  - Documents
  - Data types
  - Disciplines