Part I Introduction to argumentation

Part II Argumentation theory in the medical context

Part III Argumentation technology for explaining medical hypotheses and anomalous patient responses to treatments

Part IV On the need of aggregating evidence across multiple clinical studies

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Part IV

On the need of aggregating evidence across multiple clinical studies
Part V
Aggregating evidence using argumentation

(Based on the work “Aggregating evidence about the positive and negative effects of treatments” by Hunter and Williams (2012))
Aggregation technologies are needed for:

• Making evidence-based recommendations based on large repositories of complex, rapidly expanding, incomplete and inconsistent evidence.

• Overcoming limitations such as:
  • out-dated guidelines/systematic reviews
  • dealing with huge amounts of existing and new evidence
  • conflicting guidelines

• Considering particular cases: guideline recommendations often interprets general populations, but not cases with specific features (e.g. patients from a particular ethnic group, age, precondition, etc.).

• Offering tools to support evidence-based decisions, to draft systematic reviews and guidelines, and to help resolving conflicts in the available evidence.
Aggregation of CT evidence

• When evidence is aggregated in guideline/systematic reviews development, the aim is to determine whether one treatment is better than another.

• There are two main dimensions to be considered:
  
  • *Outcomes*:  
    • e.g. is one treatment more efficacious than another, does one treatment have more side-effects than the other?

  • *Quality of the evidence*:  
    • e.g. is the evidence supporting the superiority of a treatment over another, based on non-statistically significant studies?
Each row is a meta-analysis from the NICE glaucoma GL for patients with raised IOP (i.e. at risk of glaucoma and thus, irreversible damage to the optic nerve and retina).

<table>
<thead>
<tr>
<th>Left</th>
<th>Right</th>
<th>Outcome indicator</th>
<th>Value</th>
<th>Net</th>
<th>Sig</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>e_{01} BB     NT</td>
<td>visual field prog</td>
<td>0.77</td>
<td>&gt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{02} BB     NT</td>
<td>change in IOP</td>
<td>-2.88</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{03} BB     NT</td>
<td>respiratory prob</td>
<td>3.06</td>
<td>&lt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{04} BB     NT</td>
<td>cardio prob</td>
<td>9.17</td>
<td>&lt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{05} PG     BB</td>
<td>change in IOP</td>
<td>-1.32</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{06} PG     BB</td>
<td>acceptable IOP</td>
<td>1.54</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{07} PG     BB</td>
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<td>0.59</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{08} PG     BB</td>
<td>cardio prob</td>
<td>0.87</td>
<td>&gt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
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<td>&lt;</td>
<td>no</td>
<td>MA</td>
<td></td>
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<td>MA</td>
<td></td>
</tr>
<tr>
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<td>change in IOP</td>
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<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{12} PG     SY</td>
<td>allergic prob</td>
<td>0.03</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{13} PG     SY</td>
<td>hyperaemia</td>
<td>1.01</td>
<td>&lt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{14} CA     NT</td>
<td>convert to COAG</td>
<td>0.77</td>
<td>&gt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{15} CA     NT</td>
<td>visual field prog</td>
<td>0.69</td>
<td>&gt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{16} CA     NT</td>
<td>IOP &gt; 35mmHg</td>
<td>0.08</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
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<td>e_{17} CA     BB</td>
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<td>no</td>
<td>MA</td>
<td></td>
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<td>change in IOP</td>
<td>-0.25</td>
<td>&gt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{20} SY     BB</td>
<td>allergic prob</td>
<td>41.00</td>
<td>&lt;</td>
<td>yes</td>
<td>MA</td>
<td></td>
</tr>
<tr>
<td>e_{21} SY     BB</td>
<td>drowsiness</td>
<td>1.21</td>
<td>&lt;</td>
<td>no</td>
<td>MA</td>
<td></td>
</tr>
</tbody>
</table>
Outcome indicators interpretations

• The outcome indicator is what is being measured, and the value is the value of that measure determined by:
  • *Relative Risk*: proportion of patients who presented an outcome indicator (i.e. “mortality”, “stroke”) in the left arm divided by the proportion of patients presenting it in the right arm.

• Other value Interpretations (e.g. for the glaucoma case):
  • Change in IOP: if $value < 0$, the left arm is superior, otherwise it is inferior.
  • Acceptable IOP: is a desirable outcome. If $value > 1$, then the left arm is superior, otherwise it is inferior.
  • Other outcome indicators (i.e. for respiratory problems, cardiovascular problems, etc.), which are undesirable. If $value < 1$, then the left arm is superior, otherwise it is inferior.
Inductive arguments

• Set of evidence $EVIDENCE = \{e_1, ..., e_n\}$ concerning a pair of treatments $\{\tau_1, \tau_2\}$

• Interpretations:
  
  • $\tau_1 > \tau_2$: the evidence supports the claim that treatment $\tau_1$ is *superior* to $\tau_2$
  
  • $\tau_1 \sim \tau_2$: the evidence supports the claim that treatment $\tau_1$ is *equivalent* to $\tau_2$
  
  • $\tau_1 < \tau_2$: the evidence supports the claim that treatment $\tau_1$ is *inferior* to $\tau_2$
**Definitions**

**Inference rules**, where $X \subseteq \text{evidence}$ and $X \neq \emptyset$:

- If $X \subseteq \text{SUPERIOR}$, then $\tau_1 > \tau_2$
- If $X \subseteq \text{EQUITABLE}$, then $\tau_1 \sim \tau_2$
- If $X \subseteq \text{INFERIOR}$, then $\tau_1 < \tau_2$

**Inductive argument** is a tuple $<X, \epsilon>$, such that $\epsilon$ follows from using one of the inference rules. $X$ is called the support and $\epsilon$ the claim of the argument.

**Arg(Evidence)**

Given a set $\text{Evidence}$, $\text{Arg(Evidence)}$ is the set of inductive arguments that can be generated from the evidence according to the previous definition.
Example of inductive arguments

<table>
<thead>
<tr>
<th>Left</th>
<th>Right</th>
<th>Outcome indicator</th>
<th>Value</th>
<th>Net</th>
<th>Sig</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_1$</td>
<td>ACE</td>
<td>CCB</td>
<td>1.04</td>
<td>&lt;</td>
<td>no</td>
<td>MA</td>
</tr>
<tr>
<td>$e_2$</td>
<td>ACE</td>
<td>CCB</td>
<td>1.15</td>
<td>&lt;</td>
<td>yes</td>
<td>MA</td>
</tr>
<tr>
<td>$e_3$</td>
<td>ACE</td>
<td>CCB</td>
<td>0.84</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
</tr>
<tr>
<td>$e_4$</td>
<td>ACE</td>
<td>CCB</td>
<td>0.85</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
</tr>
</tbody>
</table>

\[
\langle \{ e_3 \}, \text{ACE > CCB} \rangle \quad \langle \{ e_1 \}, \text{ACE < CCB} \rangle \\
\langle \{ e_4 \}, \text{ACE > CCB} \rangle \quad \langle \{ e_2 \}, \text{ACE < CCB} \rangle \\
\langle \{ e_3, e_4 \}, \text{ACE > CCB} \rangle \quad \langle \{ e_1, e_2 \}, \text{ACE < CCB} \rangle
\]

Results from the NICE Hypertension Guideline concerning angiotensin-converting inhibitors (ACE) and calcium channel blockers (CCB).
For an item of evidence e, the result of the evidence is the pair: \((\text{OutcomeIndicator}, \text{Value})\)

<table>
<thead>
<tr>
<th>e_81</th>
<th>CP</th>
<th>NC</th>
<th>breast cancer</th>
<th>1.04</th>
<th>&lt;</th>
<th>yes</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>e_82</td>
<td>CP</td>
<td>NC</td>
<td>ovarian cancer</td>
<td>0.99</td>
<td>&gt;</td>
<td>yes</td>
<td>MA</td>
</tr>
<tr>
<td>e_83</td>
<td>CP</td>
<td>NC</td>
<td>pregnancy</td>
<td>0.05</td>
<td>&gt;</td>
<td>yes</td>
<td>RCT</td>
</tr>
<tr>
<td>e_84</td>
<td>CP</td>
<td>NC</td>
<td>thrombosis</td>
<td>1.02</td>
<td>&lt;</td>
<td>yes</td>
<td>MA</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
A_1 & = \langle \{e_82, e_83\}, \text{CP} > \text{NC} \rangle \\
A_2 & = \langle \{e_82\}, \text{CP} > \text{NC} \rangle \\
A_3 & = \langle \{e_83\}, \text{CP} > \text{NC} \rangle \\
A_4 & = \langle \{e_81, e_84\}, \text{CP} < \text{NC} \rangle \\
A_5 & = \langle \{e_81\}, \text{CP} < \text{NC} \rangle \\
A_6 & = \langle \{e_84\}, \text{CP} < \text{NC} \rangle \\
\end{align*}
\]

Results(A_1) = \{(ovarian cancer, 0.99), (pregnancy, 0.05)\}
Results(A_2) = \{(ovarian cancer, 0.99)\}
Results(A_3) = \{(pregnancy, 0.05)\}
Results(A_4) = \{(breast cancer, 1.04), (thrombosis, 1.02)\}
Results(A_5) = \{(breast cancer, 1.04)\}
Results(A_6) = \{(thrombosis, 1.02)\}
Let A be an inductive argument where Claim(A) is $\tau_1 > \tau_2$, $\tau_1 \sim \tau_2$, or $\tau_1 < \tau_2$. The **Benefits** function is defined as:

$$
\text{Benefits}(A) = \begin{cases} 
\text{Results}(A) & \text{when Claim}(A) \neq \tau_1 < \tau_2 \\
\text{Normalize}(A) & \text{when Claim}(A) = \tau_1 < \tau_2
\end{cases}
$$

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>$e_{81}$</td>
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<td>breast cancer</td>
<td>1.04</td>
<td>&lt;</td>
<td>yes</td>
</tr>
<tr>
<td>$e_{82}$</td>
<td>CP</td>
<td>NC</td>
<td>ovarian cancer</td>
<td>0.99</td>
<td>&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>$e_{83}$</td>
<td>CP</td>
<td>NC</td>
<td>pregnancy</td>
<td>0.05</td>
<td>&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>$e_{84}$</td>
<td>CP</td>
<td>NC</td>
<td>thrombosis</td>
<td>1.02</td>
<td>&lt;</td>
<td>yes</td>
</tr>
</tbody>
</table>

**Result**(Ai)

- Results(A1) = {(ovarian cancer, 0.99), (pregnancy, 0.05)}
- Results(A2) = {(ovarian cancer, 0.99)}
- Results(A3) = {(pregnancy, 0.05)}
- Results(A4) = {(breast cancer, 1.04), (thrombosis, 1.02)}
- Results(A5) = {(breast cancer, 1.04)}
- Results(A6) = {(thrombosis, 1.02)}

**Benefit**(Ai)

- Benefits(A1) = {(ovarian cancer, 0.99), (pregnancy, 0.05)}
- Benefits(A2) = {(ovarian cancer, 0.99)}
- Benefits(A3) = {(pregnancy, 0.05)}
- Benefits(A4) = {(breast cancer, 0.96), (thrombosis, 0.98)}
- Benefits(A5) = {(breast cancer, 0.96)}
- Benefits(A6) = {(thrombosis, 0.98)}
Benefits: interpretation

• A result (OutcomeIndicator, Value) is a benefit when:
  • The OutcomeIndicator is for something good (e.g. survival rate, etc.) and Value means that the left arm is better than the right arm:
    • e.g. for an outcome indicator measured in RR, value > 1), then (OutcomeIndicator, Value) is a benefit.
  • The OutcomeIndicator is for something bad (e.g. death rate, etc.) and Value means that the left arm is better than the right arm:
    • e.g. for an outcome indicator measured in RR, value < 1), then (OutcomeIndicator, Value) is a benefit.
Benefits preference relations

For arguments $A_i, A_j$:

- $\text{Benefits}(A_i) \succeq \text{Benefits}(A_j)$ means that the results of $A_i$ are preferred to the results of $A_j$

- The user would give the benefits preference relation

- Benefits graph:
  - Each node is the benefits for an argument
  - Each arc denotes that the benefits for the first node are preferred to the benefits of the second node
Benefits graph

Benefits($A_1$) $\succ$ Benefits($A_4$)  
Benefits($A_1$) $\succ$ Benefits($A_5$)  
Benefits($A_1$) $\succ$ Benefits($A_6$)  

Benefits($A_4$) $\succ$ Benefits($A_2$)  
Benefits($A_2$) $\sim$ Benefits($A_5$)  
Benefits($A_2$) $\succ$ Benefits($A_6$)  

Benefits($A_3$) $\succ$ Benefits($A_4$)  
Benefits($A_3$) $\succ$ Benefits($A_5$)  
Benefits($A_3$) $\succ$ Benefits($A_6$)
If the claim of argument $A_i$ is $\varepsilon_i$ and the claim of argument $A_j$ is $\varepsilon_j$ then $A_i$ conflicts with $A_j$ when:

- $\varepsilon_i = \tau_1 > \tau_2$, and ($\varepsilon_j = \tau_1 \sim \tau_2$ or $\varepsilon_j = \tau_1 < \tau_2$)
- $\varepsilon_i = \tau_1 \sim \tau_2$, and ($\varepsilon_j = \tau_1 > \tau_2$ or $\varepsilon_j = \tau_1 < \tau_2$)
- $\varepsilon_i = \tau_1 < \tau_2$, and ($\varepsilon_j = \tau_1 > \tau_2$ or $\varepsilon_j = \tau_1 \sim \tau_2$)

For any pair of arguments $A_i$ and $A_j$, and a preference relation $R$, $A_i$ attacks $A_j$ with respect to $R$ if $A_i$ conflicts with $A_j$ and $A_j$ is not strictly preferred to $A_i$, according to $R$. 
Inductive argument graph

Given a Topic = \{\tau_1, \tau_2\} and a set EVIDENCE, a inductive argument graph Arg(Evidence,Topic) in which:

- the set of nodes is the subset of Arg(Evidence) containing arguments with a claim in \{\tau_1 > \tau_2, \tau_1 \sim \tau_2, \tau_1 < \tau_2\}

- the set of arcs is the attack relation given in the previous definition.
Example of an inductive argument graph

<table>
<thead>
<tr>
<th>Left</th>
<th>Right</th>
<th>Outcome indicator</th>
<th>Value</th>
<th>Net</th>
<th>Sig</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>$e_{81}$</td>
<td>CP</td>
<td>NC</td>
<td>breast cancer</td>
<td>1.04</td>
<td>&lt;</td>
<td>yes</td>
</tr>
<tr>
<td>$e_{82}$</td>
<td>CP</td>
<td>NC</td>
<td>ovarian cancer</td>
<td>0.99</td>
<td>&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>$e_{83}$</td>
<td>CP</td>
<td>NC</td>
<td>pregnancy</td>
<td>0.05</td>
<td>&gt;</td>
<td>yes</td>
</tr>
<tr>
<td>$e_{84}$</td>
<td>CP</td>
<td>NC</td>
<td>thrombosis</td>
<td>1.02</td>
<td>&lt;</td>
<td>yes</td>
</tr>
</tbody>
</table>
Meta-arguments

• Arguments against the quality of the evidence.

• They are atomic arguments (i.e. there is no internal structure to them).

• They are used as counterarguments to inductive arguments.

• Examples:
  • The evidence contains flawed RCTs.
  • The evidence contains results that are not statistically significant.
  • The evidence is from trials that are for a very narrow patient class.
  • The evidence has inconsistent outcomes.
Evidential argument graph

- An evidential argument graph is a directed graph where:
  - each node is either an inductive argument or a meta-argument.
  - each arc is either an attack by a preferred inductive argument or an attack by a meta-argument.
Evidencial argument graph
### Evidence Table

Each row is a meta-analysis from the NICE glaucoma GL for patients with raised IOP (i.e. at risk of glaucoma and thus, irreversible damage to the optic nerve and retina).

Where:
- **NT**: no treatment
- **BB**: beta-blocker
- **PG**: prostaglandin analogue
- **SY**: sympathomimetic
- **CA**: carbonic anhydrase inhibitor

| $e_{01}$ | BB | NT | visual field prog | 0.77 | > | no | MA |
| $e_{02}$ | BB | NT | change in IOP | -2.88 | > | yes | MA |
| $e_{03}$ | BB | NT | respiratory prob | 3.06 | < | no | MA |
| $e_{04}$ | BB | NT | cardio prob | 9.17 | < | no | MA |
| $e_{05}$ | PG | BB | change in IOP | -1.32 | > | yes | MA |
| $e_{06}$ | PG | BB | acceptable IOP | 1.54 | > | yes | MA |
| $e_{07}$ | PG | BB | respiratory prob | 0.59 | > | yes | MA |
| $e_{08}$ | PG | BB | cardio prob | 0.87 | > | no | MA |
| $e_{09}$ | PG | BB | allergy prob | 1.25 | < | no | MA |
| $e_{10}$ | PG | BB | hyperaemia | 3.59 | < | yes | MA |
| $e_{11}$ | PG | SY | change in IOP | -2.21 | > | yes | MA |
| $e_{12}$ | PG | SY | allergic prob | 0.03 | > | yes | MA |
| $e_{13}$ | PG | SY | hyperaemia | 1.01 | < | no | MA |
| $e_{14}$ | CA | NT | convert to COAG | 0.77 | > | no | MA |
| $e_{15}$ | CA | NT | visual field prog | 0.69 | > | no | MA |
| $e_{16}$ | CA | NT | IOP > 35mmHg | 0.08 | > | yes | MA |
| $e_{17}$ | CA | BB | hyperaemia | 6.42 | < | no | MA |
| $e_{18}$ | SY | BB | visual field prog | 0.92 | > | no | MA |
| $e_{19}$ | SY | BB | change in IOP | -0.25 | > | no | MA |
| $e_{20}$ | SY | BB | allergic prob | 41.00 | < | yes | MA |
| $e_{21}$ | SY | BB | drowsiness | 1.21 | < | no | MA |
Evidence aggregation

• If there is a non-empty grounded extension, and \( \epsilon \) is the claim of the arguments in the extension, the result of the aggregation is \( \epsilon \).

• If there is an empty grounded extension, then there are multiple preferred extensions (e.g. \( E_1, ..., E_n \)), so the result of the aggregation are \( \epsilon_1, ..., \epsilon_n \), where \( \epsilon_1 \) is the claim of the arguments in \( E_1 \) and ... and \( \epsilon_n \) is the claim of the arguments in \( E_n \).
Result from the argumentation with the glaucoma case, where a directed arc from $\tau_1$ to $\tau_2$ denotes $\tau_1$ is superior to $\tau_2$ and an undirected arc from $\tau_1$ to $\tau_2$ denotes $\tau_2$ is superior or equivalent or inferior to $\tau_2$. 
Summary of the approach for aggregation through argumentation

Evidence table

Inductive arguments

Inductive argument graphs

Evidential argument graphs

Superiority graph

Benefits preference relation

Meta-arguments
Part VI
Framework for rationalising clinical recommendations
Framework for rationalising clinical recommendations
Recommendations

- Information Retrieval
- Information Extraction
- Knowledge Base
- Argument Generation
- Argument Verbalization
- "I recommend therapy X"
- Rationalizing Summary
- Receiving Expert
- Recommending Expert
The semantic model
# Database models

<table>
<thead>
<tr>
<th>Model</th>
<th>Example format</th>
<th>Data</th>
<th>Metadata</th>
<th>Identifier</th>
<th>Query Syntax</th>
<th>Semantics (meaning)</th>
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<tbody>
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<td>.NET CLR Object Serialization</td>
<td>Object Property Values</td>
<td>Object Property Names</td>
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<td>LINQ</td>
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<td>XML</td>
<td>Tag/Attribute Values</td>
<td>XSD/DTD</td>
<td>e.g. Unique Attribute Key Value</td>
<td>XPath</td>
<td>N/A</td>
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<td>Graph</td>
<td>RDF/XML, Turtle</td>
<td>RDF</td>
<td>RDFS/OWL</td>
<td>URI</td>
<td>SPARQL</td>
<td>Yes, using RDFS and OWL</td>
</tr>
</tbody>
</table>

http://www.linkeddatatools.com/semantic-modeling
The Resource Description Framework (RDF)

- Framework for representing information in the Web
- Graph-based model for recording data that is internationally interchangable

**URI (Uniform Resource Identifier)**
http://www.linkeddata.com/fruits#apple
Semantic Web model

- This model allows sharing data from different sites across the web, by using:
  - Common *vocabulary*: terms given a well-defined meaning that is consistent across contexts.
  - *Ontology*: allows to define contextual relationships behind a defined vocabulary.
  - A formal syntax for defining ontologies such as OWL (Web Ontology Language), which is an extension of RDFS (RDF Schema).
Web Ontology Language (OWL)

- Goal of ontology: classifying things in terms of semantics or meaning.
- OWL does this through classes, subclasses and instances (individuals).
- A class is a classification of individuals into groups which share common characteristics.
- An individual is under the semantic classification given by the corresponding class.
OWL properties

- Individuals are related by properties:
  - *Object* properties (owl:ObjectProperty) relates individuals (instances) of two classes.
  - *Datatype* properties (owl:DatatypeProperty) relates individuals (instances) of classes to literal values.
RDFS and OWL are the main syntaxes for annotating RDF data.

RDFS and OWL are W3C specifications.

```xml
<?xml version="1.0"?>
    xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#"
    xmlns:owl="http://www.w3.org/2002/07/owl#"
    xmlns:xsd="http://www.w3.org/2001/XMLSchema#"
    xmlns:rdfs="http://www.w3.org/2000/01/rdf-schema#"


</rdf:RDF>
Why to use web ontologies?

- Knowledge integration across different domains in automatic way (use of URIs).
- No need for transformation, mapping, or contracts among different sites.
- Communications among sites through semantics.
- Query a semantic database (knowledge base).
- Perform machine inference on that knowledge base.
SPARQL

• Is a protocol and an RDF query language.

• SELECT: selects data from a dataset.

• FROM: indicates the site where the dataset to be queried is located.

• WHERE clause: defines graph patterns to find a match for it in the dataset.

• Graph pattern: consists of the subject, predicate and object triple.
### SPARQL: General form

<table>
<thead>
<tr>
<th>Component</th>
<th>Example Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREFIX</td>
<td><code>PREFIX plant: &lt;http://www.linkeddatatools.com/plants&gt;</code></td>
</tr>
<tr>
<td>SELECT</td>
<td><code>SELECT ?name</code></td>
</tr>
<tr>
<td>FROM</td>
<td><code>FROM &lt;http://www.linkeddatatools.com/plantsdata/plants.rdf&gt;</code></td>
</tr>
<tr>
<td>WHERE</td>
<td><code>WHERE { ?planttype plant:planttype ?name }</code></td>
</tr>
<tr>
<td>ORDER BY, DISTINCT</td>
<td><code>ORDER BY ?name</code></td>
</tr>
</tbody>
</table>

http://www.linkeddatatools.com/querying-semantic-data
The C-TrO Ontology for aggregation of clinical studies
C-TrO: main goals

• provide the structure for a KB that stores CT information and related information.

• provide the logical structure for summarising and aggregating evidence from multiple trials.

• support an annotation scheme of CT publications.
C-TrO: requirements

• Describe any type of clinical trial (e.g. randomized, crossover, parallel, etc.)

• Any health condition (e.g. disease, disorder, etc.)

• Consider important evidence for superiority of interventions:
  • risk of bias, results according to a given aggregation method
  • relative or absolute risk
  • size of effect of the interventions
<table>
<thead>
<tr>
<th>P</th>
<th>I</th>
<th>C</th>
<th>O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population / Problem</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Outcome</td>
</tr>
<tr>
<td>What are the characteristics of the Population or Patient?</td>
<td>Which interventions are applied to the patients?</td>
<td>What is the Comparison or alternative to the intervention: placebo, a different drug, surgery, etc.?</td>
<td>What are the possible Outcomes of the study: reduce morbidity, death, complications, etc.?</td>
</tr>
</tbody>
</table>
Patients with elevated intraocular pressure (IOP), male and female, mean age 61.9 years.

- latanoprost

- compared with timolol maleate

- effective in reducing mean diurnal (IOP)

- low rate in allergic response
## Related CT ontologies

<table>
<thead>
<tr>
<th>RCT Schema</th>
<th>PICO Ontology</th>
<th>OCRe</th>
<th>C-TrO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation of reports and analysis of randomized clinical trials.</td>
<td>Annotation of Cochrane Reviews according to its PICO models.</td>
<td>Indexing of research data across different clinical data resources.</td>
<td>Knowledge base and annotation schema for the aggregation of the level of evidence of clinical trials.</td>
</tr>
</tbody>
</table>
C-TrO: Knowledge base

:CT_3 rdf:type ctro:ClinicalTrial ;
  :hasObjectiveDescription "Latanoprost, a new prostaglandin..." ;
  :hasConclusionComment "Latanoprost has the potential..." ;
  :hasAnalysisApproach PreProtocol ;
  :hasArm Arm_31, Arm_32 ;
  :hasPopulation :CT3_Population ;
  :hasCTDesign :DoubleBlind, :Randomized .

:Arm_31 rdf:type ctro:Arm ;
  :hasNumberPatients 134 ;
  :hasIntervention :CT3_Intervention1 .

:CT3_Population rdf:type ctro:Population ;
  :hasGender "Mixed" ;
  :hasMinAge 30 ;
  :hasMaxAge 90 ;
  :hasCountry :USA ;
  :hasPreconditionDescription "Ocular hypertension and glaucoma" .

:CT3_Intervention1 rdf:type ctro:Intervention ;
  :hasDuration "3 months" ;
  :hasAnalysisMetric "ChangeFromBaseLine" ;
  :hasDesiredEffectDirection "Reduction" ;
  :hasPrimaryOutcome :CT3_I1_OC1 ;
  :hasAdverseEffect :CT3_I1_OC2 ;
  :hasMedication :CT3_I1_M1 .

:CT3_I1_OC3 rdf:type ctro:Outcome ;
  :hasEndpoint :EndPoint_CT3_I1_OC3 ;
  :hasAggregationMethod "Mean" ;
  :hasBaselineValue 25.3 ;
  :hasBioAndMedUnit :mmHg ;
  :hasResult :Result_CT3_I1_OC3 .

:EndPoint_CT3_I1_OC3 rdf:type ctro:EndPoint ;
  :hasEndpoint Description :Diurnal_IOP .

:Result_CT3_I1_OC3 rdf:type ctro:Result ;
  :hasResultValue 6.7 .

:CT3_I1_M1 rdf:type ctro:Medication ;
  :hasDrug :Timolol ;
  :hasDoseValue 005 ;
  :hasBioAndMedUnit "Percent" ;
  :hasDeliveryMethod "Eyedrops".
C-TrO: Knowledge base

CT_3:ClinicalTrial
:hasObjectiveDescription
"Latanoprost, a new prostaglandin..."
:hasArm Arm_31, Arm_32
:hasCTDesign:DoubleBlind, Randomized

Arm_31
:hasNumberPatients 134;
:hasIntervention :CT3_Intervention1

Arm_32

CT3_Intervention1
:hasFrequency
"Once_per_night";
:hasInterval "Daily";
:hasDuration "3 months";
:hasAnalysisMetric
"ChangeFromBaseline";
:hasDesiredEffectDirection "Reduction"

CT3_Population
:hasGender "Mixed";
:hasCountry :USA;
:hasMinAge 30;
:hasMaxAge 90;
:hasPreconditionDescription
"Ocular hypertension and glaucoma"

CT3_11_OC1
(Primary Outcome)
:hasEndpointDescription
"Diurnal IOP";
:hasAggregationMethod
"Mean"
:hasBaselineValue 25.3
:hasResultValue 6.7
:hasBioAndMedUnit mmHg

CT3_11_OC2
(Adverse Effect)

CT3_11_M1
(Medication)
:hasDrug :Timolol;
:hasDoseValue 005;
:hasBioAndMedUnit "Percent";
:hasDeliveryMethod "Eyedrops"
A 12-month, randomized, double-masked study comparing latanoprost with timolol in pigmentary glaucoma.

Objective Description:

To compare the efficacy and side effects and the effect on aqueous humor dynamics of 0.005% latanoprost applied topically once daily.

Participants:

Thirty-six patients affected with bilateral pigmentary glaucoma controlled with no more than a single glaucoma medication.

Intervention:
The sample population was randomly divided into 2 age- and gender-matched groups each of 18.

Group 1 received

0.005% latanoprost eyedrops twice daily.

Main outcome measures:

Diurnal curves of intraocular pressure (IOP) were performed on the baseline day and after 0.5 Frequency

The IOP measurements were performed at 8:00 AM, 12:00 noon, 4:00 PM, and 8:00 PM.

Outflow facility ("C") was measured on the baseline day and on the last day of the study with a Schiotz electronic tonometer.

Diurnal IOP measurements were compared hour by hour.

Mean values of the two eyes IOP and "C" were used for analysis.
<table>
<thead>
<tr>
<th>#AnnotationID, ClassType, DocCharOnset(incl), DocCharOffset(excl), Text, Meta, Instances</th>
</tr>
</thead>
<tbody>
<tr>
<td>2, PublicationYear, 18, 22, &quot;1994&quot;, &quot;&quot;, &quot;<a href="http://ctro/data/Publication_1">http://ctro/data/Publication_1</a> <a href="http://ratio.de/ctro/hasPublicationYear">http://ratio.de/ctro/hasPublicationYear</a>&quot;1994&quot;.&quot;</td>
</tr>
<tr>
<td>3, Title, 50, 177, &quot;Additive effect of latanoprost, a prostaglandin F2 alpha analogue, and timolol in patients with elevated intraocular pressure&quot;, &quot;&quot;, &quot;<a href="http://ctro/data/Publication_1">http://ctro/data/Publication_1</a> <a href="http://ratio.de/ctro/hasTitle">http://ratio.de/ctro/hasTitle</a>&quot;Additive effect of latanoprost, a prostaglandin F2 alpha analogue, and timolol in patients with elevated intraocular pressure&quot;.&quot;</td>
</tr>
<tr>
<td>4, Author, 180, 187, &quot;Rulo AH&quot;, &quot;&quot;, &quot;<a href="http://ctro/data/Publication_1">http://ctro/data/Publication_1</a> <a href="http://ratio.de/ctro/hasAuthor">http://ratio.de/ctro/hasAuthor</a>&quot;Rulo AH&quot;.&quot;</td>
</tr>
<tr>
<td>5, Author, 196, 204, &quot;Greve EL&quot;, &quot;&quot;, &quot;<a href="http://ctro/data/Publication_1">http://ctro/data/Publication_1</a> <a href="http://ratio.de/ctro/hasAuthor">http://ratio.de/ctro/hasAuthor</a>&quot;Greve EL&quot;.&quot;</td>
</tr>
<tr>
<td>8, Country, 289, 304, &quot;The Netherlands&quot;, &quot;&quot;,</td>
</tr>
</tbody>
</table>

**RDF File**

Argument Schemes for reasoning about evidence in clinical trials
AS for superiority in terms of efficacy

Major premise: For people who suffer a given disease/health-disorder, it is desirable that a certain outcome indicator (or measurement) related to that disease/health-disorder changes, that is either increasing or decreasing.

Minor premise: It has been shown in a number of comparable clinical trials that T1 changes (either increasing or decreasing) a given disease/health-disorder indicator from the baseline in terms of an aggregation method in greater magnitude than T2.

Conclusion: T1 is a more effective medication treatment compared to T2 for changing the given disease/health-disorder indicator in the desired direction.

Critical Questions:

CQ1: Is the change (either increasing or decreasing) of the given disease/health-disorder indicator statistically significant (p-value)?

CQ2: Is the size of effect of T1 bigger than the one of T2?

CQ3: Are T1 and T2 applied to a comparable number of patients across the different studies?
AS for superiority in terms of safety

**Major premise:** For people who suffer a given disease/health-disorder and who are under a medication treatment, it is desirable not to suffer any adverse effect.

**Minor premise:** It has been shown in a number of comparable clinical trials that administration of $T1$ leads to less incidence of adverse effects compared to the administration of $T2$.

**Conclusion:** Therefore, $T1$ is superior to $T2$ in terms of its safety profile.

**Critical Questions:**

*CQ1:* Is the adverse effect statistical significant?

*CQ2:* Is the size of effect of the adverse effect bigger for $T2$ than for $T1$?
Critical Questions

**CQ3**: How reliable and trustable is the evidence from these studies?

- **CQ3.1** Is there a risk of bias?
- **CQ3.2** Is the study randomized?
- **CQ3.3** Is the study blind?
- **CQ3.4** Is the study multi-center?
- **CQ3.5** Is the study intention-to-treat?
Use case of glaucoma: efficacy

**Major premise:** For people who suffer glaucoma it is desirable that the *diurnal mean IOP* is reduced.

**Minor premise:** It has been shown in eleven comparable clinical trials that *latanoprost* treatments reduced the *diurnal mean IOP* from baseline in greater magnitude than *timolol* treatments.

<table>
<thead>
<tr>
<th>CT_Id</th>
<th>Reference</th>
<th>Mean IOP reduction by Latanoprost (mmHg)</th>
<th>Mean IOP reduction by Timolol (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT.1</td>
<td>Alm A et al,1995</td>
<td>7.8</td>
<td>6.7</td>
</tr>
<tr>
<td>CT.1</td>
<td>Alm A et al,1995</td>
<td>8.6</td>
<td>6.7</td>
</tr>
<tr>
<td>CT.10</td>
<td>Nicolela MT et al.,1996</td>
<td>6.8</td>
<td>5.3</td>
</tr>
<tr>
<td>CT.11</td>
<td>Drance SM et al.,1998</td>
<td>3.6</td>
<td>3.1</td>
</tr>
<tr>
<td>CT.2</td>
<td>Aquino MV et al.,1999</td>
<td>11.1</td>
<td>9.1</td>
</tr>
<tr>
<td>CT.3</td>
<td>Camras CB et al.,1996</td>
<td>6.7</td>
<td>4.9</td>
</tr>
<tr>
<td>CT.4</td>
<td>Diestelhorst M et al.,1998</td>
<td>4.9</td>
<td>2.1</td>
</tr>
<tr>
<td>CT.5</td>
<td>Mastropasqua L et al,1999</td>
<td>4.8</td>
<td>4.6</td>
</tr>
<tr>
<td>CT.6</td>
<td>Mishima HK et al.,1996</td>
<td>6.2</td>
<td>4.4</td>
</tr>
<tr>
<td>CT.7</td>
<td>Rulo AH et al.,1994</td>
<td>8.9</td>
<td>5.9</td>
</tr>
<tr>
<td>CT.8</td>
<td>Watson P et al,1996</td>
<td>8.5</td>
<td>8.3</td>
</tr>
<tr>
<td>CT.9</td>
<td>Diestelhorst M et al.,1997</td>
<td>9.8</td>
<td>6.7</td>
</tr>
</tbody>
</table>

**Conclusion:** *latanoprost* treatment is a more effective medication treatment compared to *timolol* treatment for reducing the *diurnal mean IOP*. 
Use case of glaucoma: efficacy

**CQ1:** Is the reduction of the diurnal mean IOP statistically significant?

<table>
<thead>
<tr>
<th>CT_Id</th>
<th>Intervention_Id</th>
<th>p-value</th>
<th>CT_Id</th>
<th>Intervention_Id</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT_1</td>
<td></td>
<td>N/A</td>
<td>CT_1</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_1</td>
<td></td>
<td>N/A</td>
<td>CT_1</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_10</td>
<td></td>
<td>N/A</td>
<td>CT_11</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_11</td>
<td></td>
<td>N/A</td>
<td>CT_3</td>
<td>CT3_Intervention1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT_3</td>
<td>CT3_Intervention1</td>
<td>&lt; 0.001</td>
<td>CT_2</td>
<td>CT2_Intervention1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT_2</td>
<td>CT2_Intervention1</td>
<td>&lt; 0.001</td>
<td>CT_3</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_3</td>
<td></td>
<td>N/A</td>
<td>CT_4</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_4</td>
<td></td>
<td>N/A</td>
<td>CT_5</td>
<td>CT5_Intervention1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT_5</td>
<td>CT5_Intervention1</td>
<td>&lt; 0.001</td>
<td>CT_2</td>
<td>CT2_Intervention2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT_6</td>
<td></td>
<td>N/A</td>
<td>CT_5</td>
<td>CT5_Intervention2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT_6</td>
<td></td>
<td>N/A</td>
<td>CT_7</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_7</td>
<td></td>
<td>N/A</td>
<td>CT_8</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>CT_8</td>
<td></td>
<td>N/A</td>
<td>CT_9</td>
<td>CT9_Intervention1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CT_9</td>
<td>CT9_Intervention1</td>
<td>&lt; 0.001</td>
<td>CT_9</td>
<td>CT9_Intervention2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Use case of glaucoma: safety

**Major premise:** For people who suffer glaucoma and who are under a medication treatment it is desirable not to suffer any adverse effect.

**Minor premise:** It has been shown in eleven comparable clinical trials that the administration of the *timolol* treatment leads to less incidence of *Conjunctival_hyperemia* than the *latanoprost* treatment.

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Latanoprost</th>
<th>Timolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse effect</strong></td>
<td><strong>Number</strong></td>
<td><strong>Adverse effect</strong></td>
</tr>
<tr>
<td>Increased Pigmentation</td>
<td>2</td>
<td>Increased Aqueous Humor Protein</td>
</tr>
<tr>
<td>Iris Pigmentation Change</td>
<td>7</td>
<td>Change Blood Velocity</td>
</tr>
<tr>
<td>Conjunctival Hyperemia</td>
<td></td>
<td>Reduced Heart Rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced Blood Pressure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smarting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iris Pigmentation Change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conjunctival Hyperemia</td>
</tr>
</tbody>
</table>

**Conclusion:** The *timolol* treatment is superior to the *latanoprost* treatment in terms of its safety profile, leading to less cases of the adverse effect *Conjunctival_hyperemia*.

**CQ1:** Is the presence of *Conjunctival_hyperemia* statistically significant?

No statistical significance was reported for this adverse effect.
Glaucoma case: Critical Questions

CQ3.1 Is there a risk of bias? No risk of bias was reported for any clinical study.
CQ3.2 Is the study randomized?
CQ3.3 Is the study blind?
CQ3.4 Is the study a multi-center?
CQ3.5 Is the study an intention-to-treat? None study was a ITT-study.

<table>
<thead>
<tr>
<th>CT_Id</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT_1</td>
<td>Randomized Crossover Multicenter DoubleMasked</td>
</tr>
<tr>
<td>CT_10</td>
<td>Crossover DoubleMasked</td>
</tr>
<tr>
<td>CT_11</td>
<td>Randomized DoubleMasked</td>
</tr>
<tr>
<td>CT_2</td>
<td>Parallel Randomized DoubleMasked SingleCenter</td>
</tr>
<tr>
<td>CT_3</td>
<td>Parallel Randomized Multicenter DoubleMasked</td>
</tr>
<tr>
<td>CT_4</td>
<td>Parallel Randomized Multicenter DoubleMasked</td>
</tr>
<tr>
<td>CT_5</td>
<td>Randomized DoubleMasked</td>
</tr>
<tr>
<td>CT_6</td>
<td>Parallel Randomized DoubleMasked</td>
</tr>
<tr>
<td>CT_7</td>
<td>Parallel Masked Randomized</td>
</tr>
<tr>
<td>CT_8</td>
<td>Randomized DoubleMasked</td>
</tr>
<tr>
<td>CT_9</td>
<td>Randomized DoubleMasked</td>
</tr>
</tbody>
</table>
WHERE{
{
{SELECT ?d1 ?d2
WHERE{?d1 rdf:type :Drug.
?d2 rdf:type :Drug. filter(?d1 != ?d2)} limit 1}
?medic1 :hasDrug ?d1.
?medic2 :hasDrug ?d2.
?interv1 :hasPrimaryOutcome ?outcome1.
?interv2 :hasPrimaryOutcome ?outcome2.
?endpoint1 :hasEndpointDescription :Diurnal_IOP.
?endpoint2 :hasEndpointDescription :Diurnal_IOP.
bind(str(?result1) as ?reduction1) bind(str(?result2) as ?reduction2)
FILTER (?result1 > ?result2)
Thanks!