
KING'S
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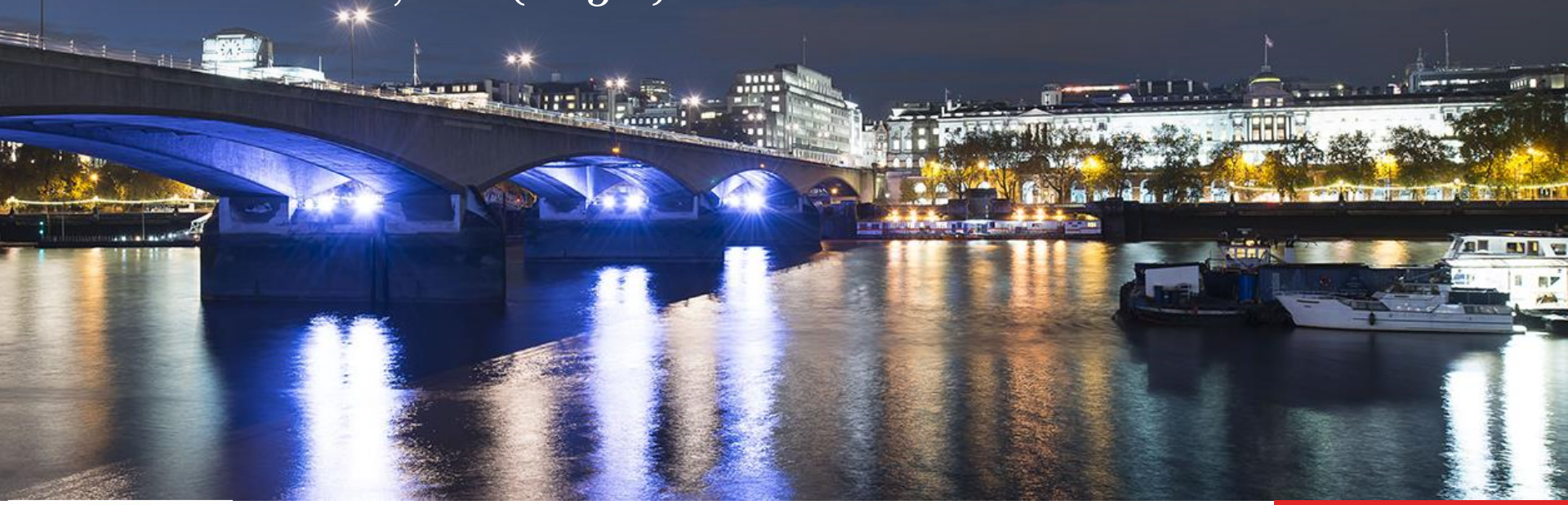
Pharmacological Data Integration for Drug-Drug Interactions

Recent Developments and Future Challenges

María Herrero-Zazo, PhD (KCL)
Isabel Segura-Bedmar, PhD (UC3M)
Paloma Martínez, PhD (UC3M)



The 5th UK Ontology Network Meeting
April 14th 2016 (Newcastle)

Drug-Drug Interactions (DDIs)

DDIs are serious adverse drug reactions (ADR) occurring when one drug affects to the **levels** or **effects** of another drug, leading to unexpected and undesirable consequences (toxic effects, therapeutic failure…)

DDIs information resources

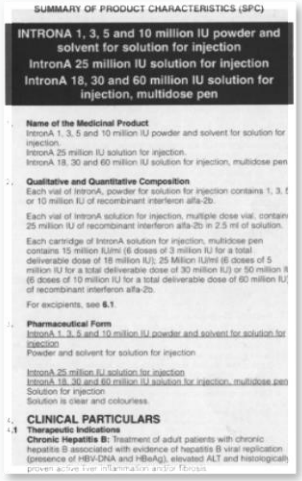
Databases

HIV InSite

KEGG

DRUGBANK
Open Data Drug & Drug Target Database

SPCs


SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

INTRONA 1, 3, 5 and 10 million IU powder and solvent for solution for injection
IntronA 25 million IU solution for injection
IntronA 18, 30 and 60 million IU solution for injection, multidose pen

1. Name of the Medicinal Product
IntronA 1, 3, 5 and 10 million IU powder and solvent for solution for injection.
IntronA 25 million IU solution for injection.
IntronA 18, 30 and 60 million IU solution for injection, multidose pen

2. Qualitative and Quantitative Composition
Each vial of IntronA, powder for solution for injection contains 1, 3, 5 or 10 million IU of recombinant interferon alfa-2b.

Each vial of IntronA solution for injection, multiple dose vial, contains 25 million IU of recombinant interferon alfa-2b in 2.5 ml of solution.

Each cartridge of IntronA solution for injection, multidose pen contains 15 million IU/ml (6 doses of 3 million IU for a total deliverable dose of 18 million IU); 25 Million IU/ml (6 doses of 5 million IU for a total deliverable dose of 30 million IU) or 50 million IU (6 doses of 10 million IU for a total deliverable dose of 60 million IU of recombinant interferon alfa-2b.

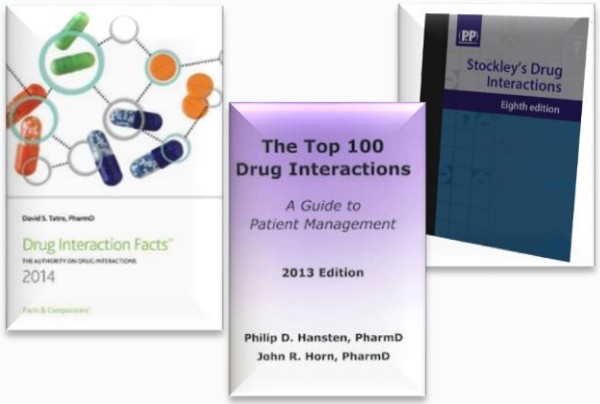
For excipients, see 6.1.

3. Pharmaceutical Form
IntronA 1, 3, 5 and 10 million IU powder and solvent for solution for injection
Powder and solvent for solution for injection

IntronA 25 million IU solution for injection
IntronA 18, 30 and 60 million IU solution for injection, multidose pen
Solution for injection
Solution is clear and colourless.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Chronic Hepatitis B: Treatment of adult patients with chronic hepatitis B associated with evidence of hepatitis B viral replication (presence of HBV-DNA and HBeAg), elevated ALT and histologically proven active liver inflammation and/or fibrosis

Compendia



Scientific literature

PubMed

National Library of Medicine NLM

Suspected ADR

EudraVigilance

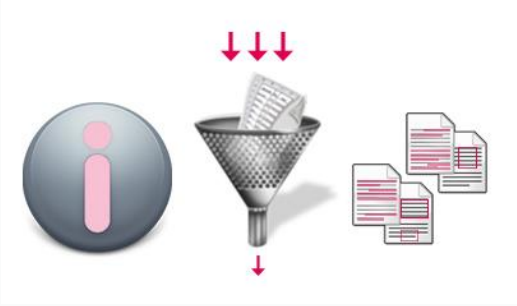
FDA

PROBLEM

Large volume of information

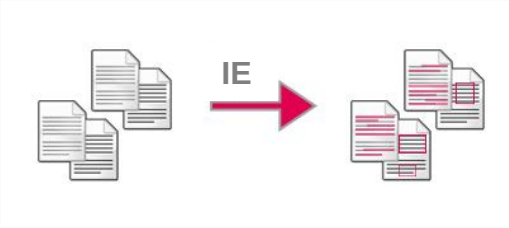
SOLUTION

Tools to filter and find the desired information

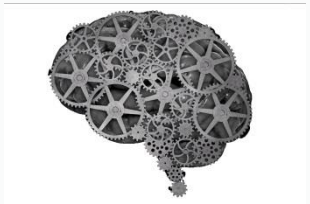


Tools to predict unknown DDIs

Information Extraction systems



Inference systems



```
inhibits(?othery, ?z),
metabolizes(?z, ?y), -> 'may
interact with'(?othery, ?y)
```

LIMITATION

Knowledge representation of the domain

The Drug-Drug Interactions Ontology – DINTO

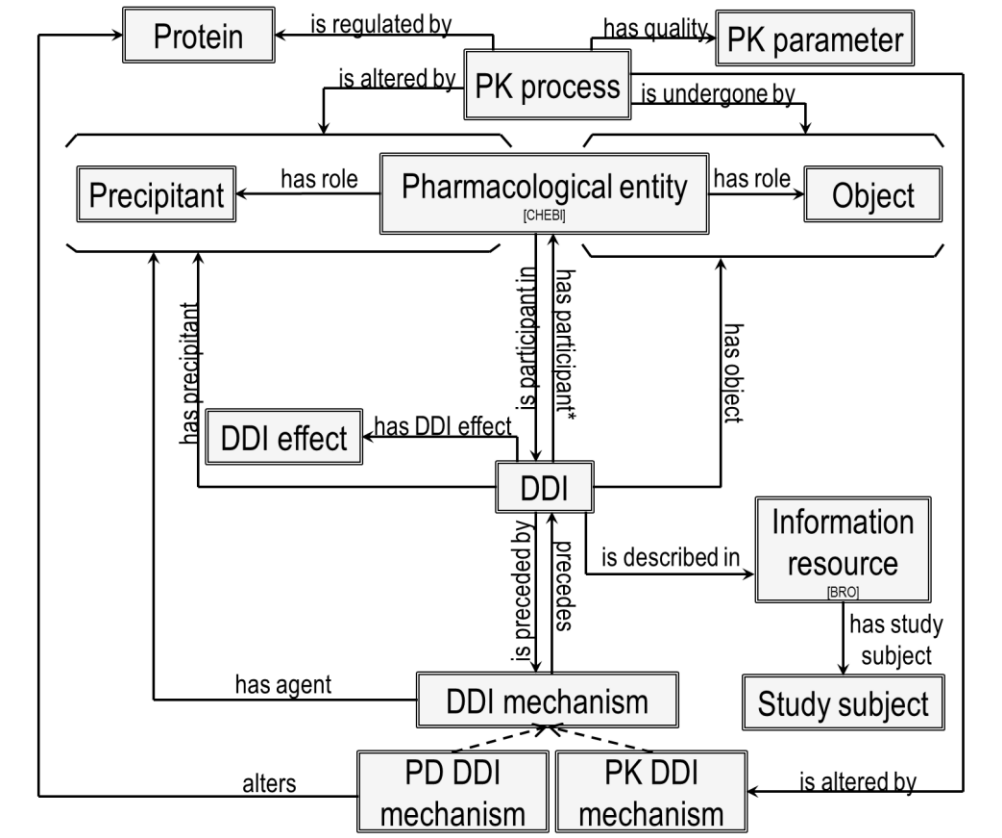
Our aim:

- **Global** and **detailed** representation of the DDI domain.
- **Different applications**
  - Information Extraction
  - Inference of DDIs and their mechanisms
- **Great visibility**, **maintenance** and **updates**

The Drug-Drug Interactions Ontology – DINTO

Neon Methodology[*]:

Iterative process for the creation of ontologies from scratch and reusing information from ontological and non-ontological sources.



Conceptual Model in DINTO: represents the general concepts of the domain and the relationships between them.

*Suárez-Figueroa et al. *Ontology Engineering in a Networked World*. Springer Berlin Heidelberg; 2012. p. 9–34

The Drug-Drug Interactions Ontology – DINTO

Integration of information sources

Ontologies (concepts)

ChEBI Ontology
- **Drugs and roles**

Pharmacokinetics Ontology (PKO)
- **PK parameters**

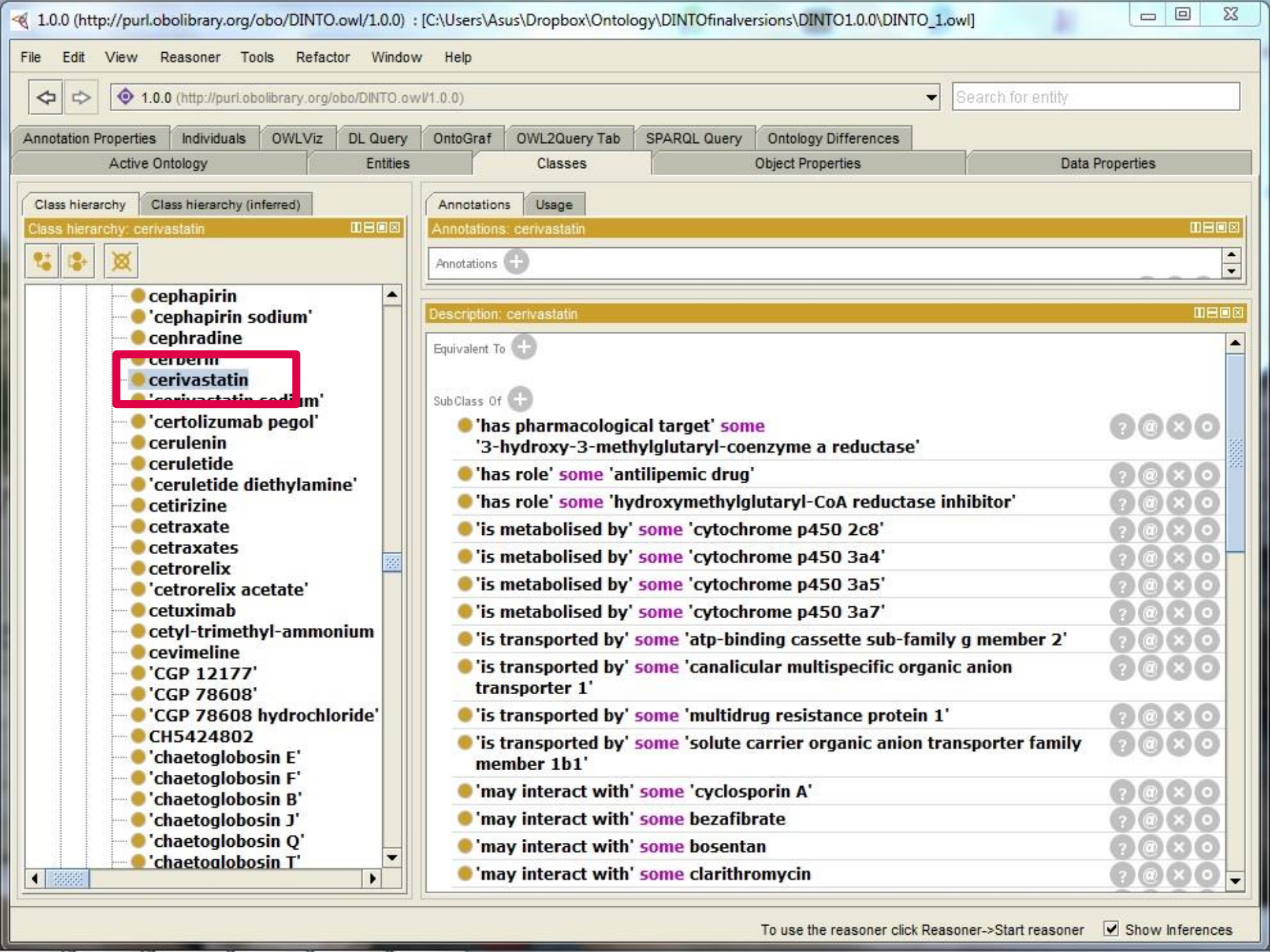
Biomedical Resource Ontology (BRO)
- **Information sources**

Ontology of Adverse Events (OAE)
- **Adverse Drug Reactions (ADR)**

Databases (relations)

DrugBank
- **Drugs**
- **Proteins**
- **Drug-protein interactions**
- **Drug-drug interactions**

SIDER
- **Drug-ADR relations**


1.0.0 (http://purl.obolibrary.org/obo/DINTO.owl/1.0.0) : [C:\Users\Asus\Dropbox\Ontology\DINTOfinalversions\DINTO1.0.0\DINTO_1.owl]
File Edit View Reasoner Tools Refactor Window Help
1.0.0 (http://purl.obolibrary.org/obo/DINTO.owl/1.0.0)
Search for entity
Annotation Properties Individuals OWLViz DL Query OntoGraf OWL2Query Tab SPARQL Query Ontology Differences
Active Ontology Entities Classes Object Properties Data Properties
Class hierarchy Class hierarchy (inferred)
Class hierarchy: cerivastatin
cephapirin
'cephapirin sodium'
cephradine
cerivastatin
'certolizumab pegol'
cerulenin
ceruletide
'ceruletide diethylamine'
cetirizine
cetraxate
cetraxates
cetrorelix
'cetrorelix acetate'
cetuximab
cetyl-trimethyl-ammonium
cevimeline
'CGP 12177'
'CGP 78608'
'CGP 78608 hydrochloride'
CH5424802
'chaetoglobosin E'
'chaetoglobosin F'
'chaetoglobosin B'
'chaetoglobosin J'
'chaetoglobosin Q'
Annotations Usage
Annotations: cerivastatin
Annotations
Description: cerivastatin
Equivalent To
SubClass Of
'has pharmacological target' some '3-hydroxy-3-methylglutaryl-coenzyme a reductase'
'has role' some 'antilipemic drug'
'has role' some 'hydroxymethylglutaryl-CoA reductase inhibitor'
'is metabolised by' some 'cytochrome p450 2c8'
'is metabolised by' some 'cytochrome p450 3a4'
'is metabolised by' some 'cytochrome p450 3a5'
'is metabolised by' some 'cytochrome p450 3a7'
'is transported by' some 'atp-binding cassette sub-family g member 2'
'is transported by' some 'canalicular multispecific organic anion transporter 1'
'is transported by' some 'multidrug resistance protein 1'
'is transported by' some 'solute carrier organic anion transporter family member 1b1'
'may interact with' some 'cyclosporin A'
'may interact with' some bezafibrate
'may interact with' some bosentan
'may interact with' some clarithromycin
To use the reasoner click Reasoner->Start reasoner
Show Inferences

The Drug-Drug Interactions Ontology – DINTO

Integration of information sources

Ontologies (concepts)

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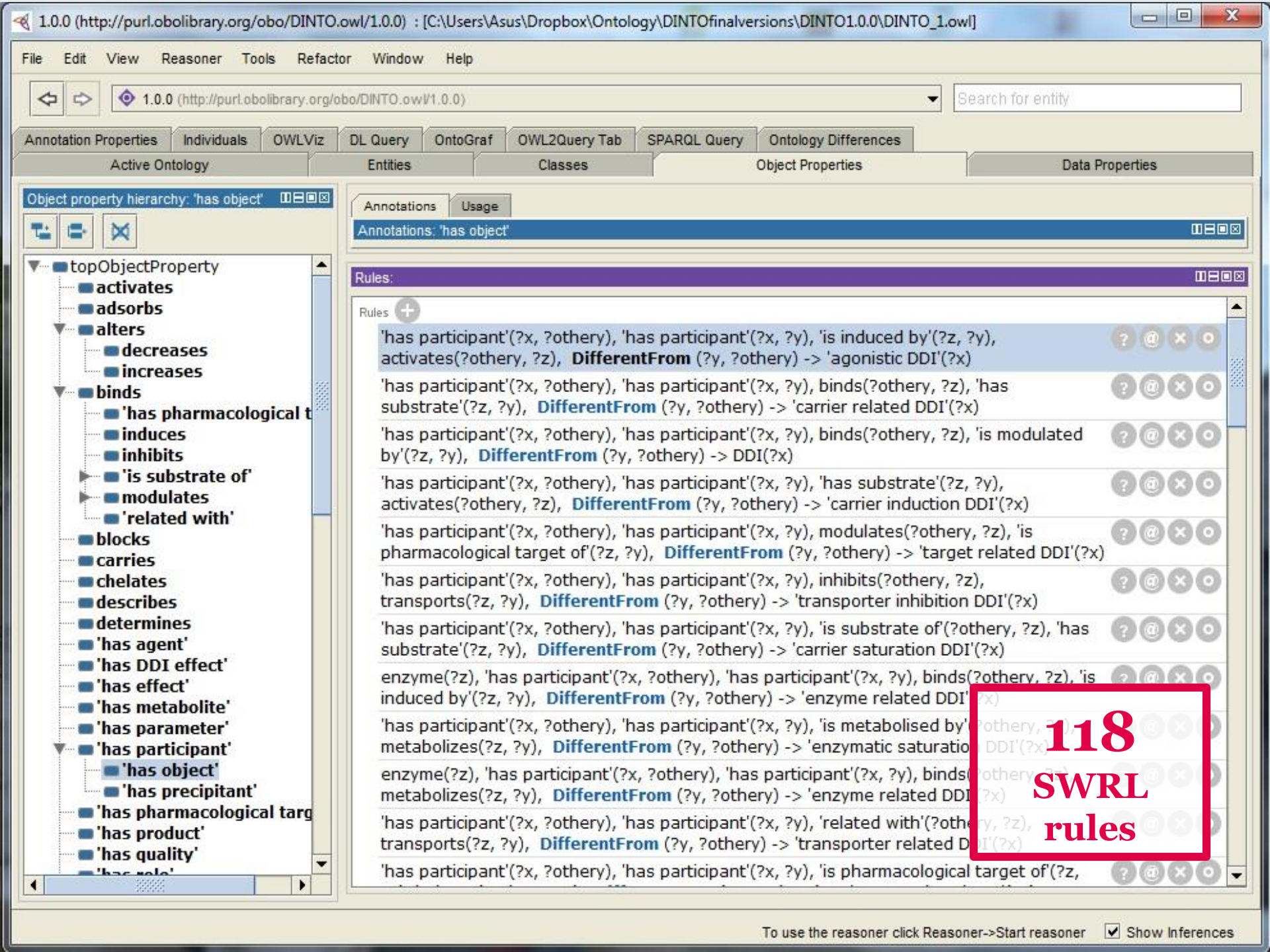
- **Drugs**
- **Proteins**
- **Drug-protein interactions**
- **Drug-drug interactions**

SIDER
- **Drug-ADR relations**

Semantic Web Rule Language (SWRL) rules (DDI mechanisms)

```
'inhibits' (?z, ?x), 'is metabolized by'(?y, ?z)
DifferentFrom (?x, ?y) -> 'may interact with'(?x, ?y)
```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File Edit View Reasoner Tools Refactor Window Help
1.0.0 (http://purl.obolibrary.org/obo/DINTO.owl/1.0.0)
Search for entity
Annotation Properties Individuals OWLViz DL Query OntoGraf OWL2Query Tab SPARQL Query Ontology Differences
Active Ontology Entities Classes Object Properties Data Properties
Object property hierarchy: 'has object'
topObjectProperty
activates
adsorbs
alters
decreases
increases
binds
'has pharmacological t
induces
inhibits
'is substrate of'
modulates
'related with'
blocks
carries
chelates
describes
determines
'has agent'
'has DDI effect'
'has effect'
'has metabolite'
'has parameter'
'has participant'
'has object'
'has precipitant'
'has pharmacological targ
'has product'
'has quality'
Annotations Usage
Annotations: 'has object'
Rules:
Rules
'has participant'(?x, ?othery), 'has participant'(?x, ?y), 'is induced by'(?z, ?y), activates(?othery, ?z), DifferentFrom (?y, ?othery) -> 'agonistic DDI'(?x)
'has participant'(?x, ?othery), 'has participant'(?x, ?y), binds(?othery, ?z), 'has substrate'(?z, ?y), DifferentFrom (?y, ?othery) -> 'carrier related DDI'(?x)
'has participant'(?x, ?othery), 'has participant'(?x, ?y), binds(?othery, ?z), 'is modulated by'(?z, ?y), DifferentFrom (?y, ?othery) -> DDI(?x)
'has participant'(?x, ?othery), 'has participant'(?x, ?y), 'has substrate'(?z, ?y), activates(?othery, ?z), DifferentFrom (?y, ?othery) -> 'carrier induction DDI'(?x)
'has participant'(?x, ?othery), 'has participant'(?x, ?y), modulates(?othery, ?z), 'is pharmacological target of'(?z, ?y), DifferentFrom (?y, ?othery) -> 'target related DDI'(?x)
'has participant'(?x, ?othery), 'has participant'(?x, ?y), inhibits(?othery, ?z), transports(?z, ?y), DifferentFrom (?y, ?othery) -> 'transporter inhibition DDI'(?x)
'has participant'(?x, ?othery), 'has participant'(?x, ?y), 'is substrate of'(?othery, ?z), 'has substrate'(?z, ?y), DifferentFrom (?y, ?othery) -> 'carrier saturation DDI'(?x)
enzyme(?z), 'has participant'(?x, ?othery), 'has participant'(?x, ?y), binds(?othery, ?z), 'is induced by'(?z, ?y), DifferentFrom (?y, ?othery) -> 'enzyme related DDI'
'has participant'(?x, ?othery), 'has participant'(?x, ?y), 'is metabolised by'
metabolizes(?z, ?y), DifferentFrom (?y, ?othery) -> 'enzymatic saturatio
enzyme(?z), 'has participant'(?x, ?othery), 'has participant'(?x, ?y), binds
metabolizes(?z, ?y), DifferentFrom (?y, ?othery) -> 'enzyme related DDI
'has participant'(?x, ?othery), 'has participant'(?x, ?y), 'related with'(?oth
transports(?z, ?y), DifferentFrom (?y, ?othery) -> 'transporter related D
'has participant'(?x, ?othery), 'has participant'(?x, ?y), 'is pharmacological target of'(?z,
118 SWRL rules
To use the reasoner click Reasoner->Start reasoner
Show Inferences

Applications

1. Information Extraction

- Drug Named Entity Recognition (NER)
- Relation Extraction (RE)
- Combination with current IE systems

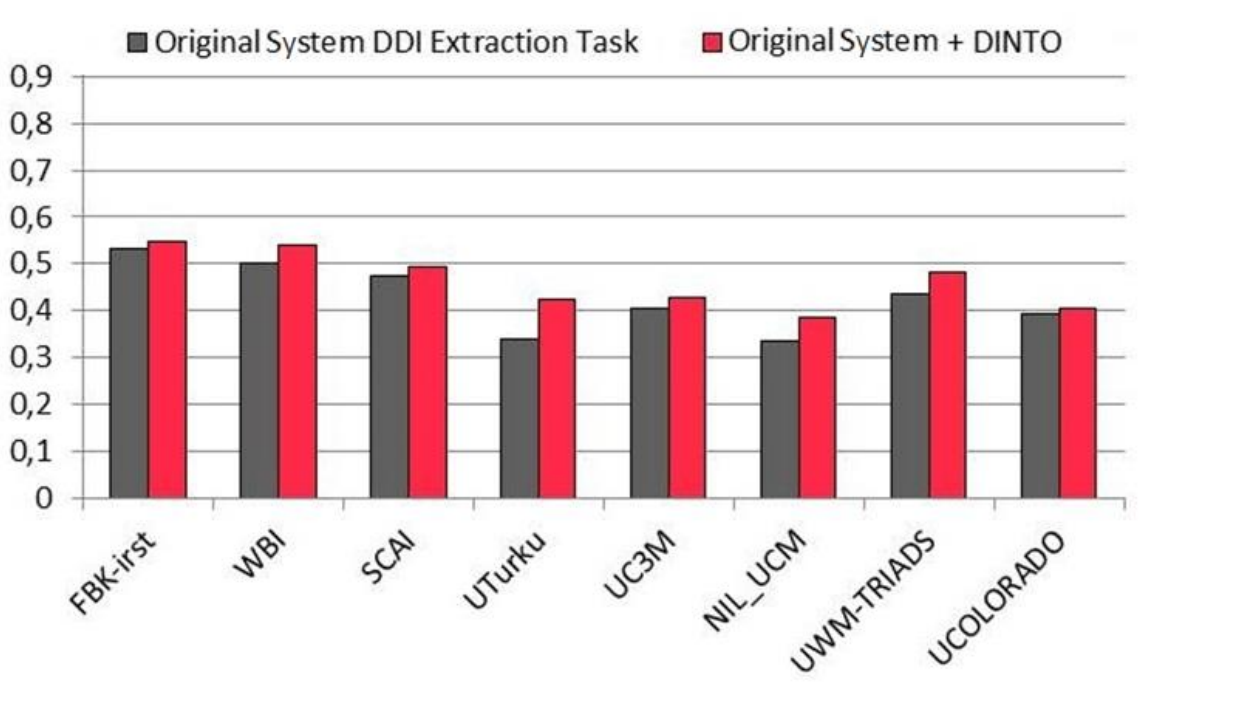
2. Prediction of DDIs

- Inference of a possible DDI
- Inference of the DDI mechanism

1. Information Extraction[*]

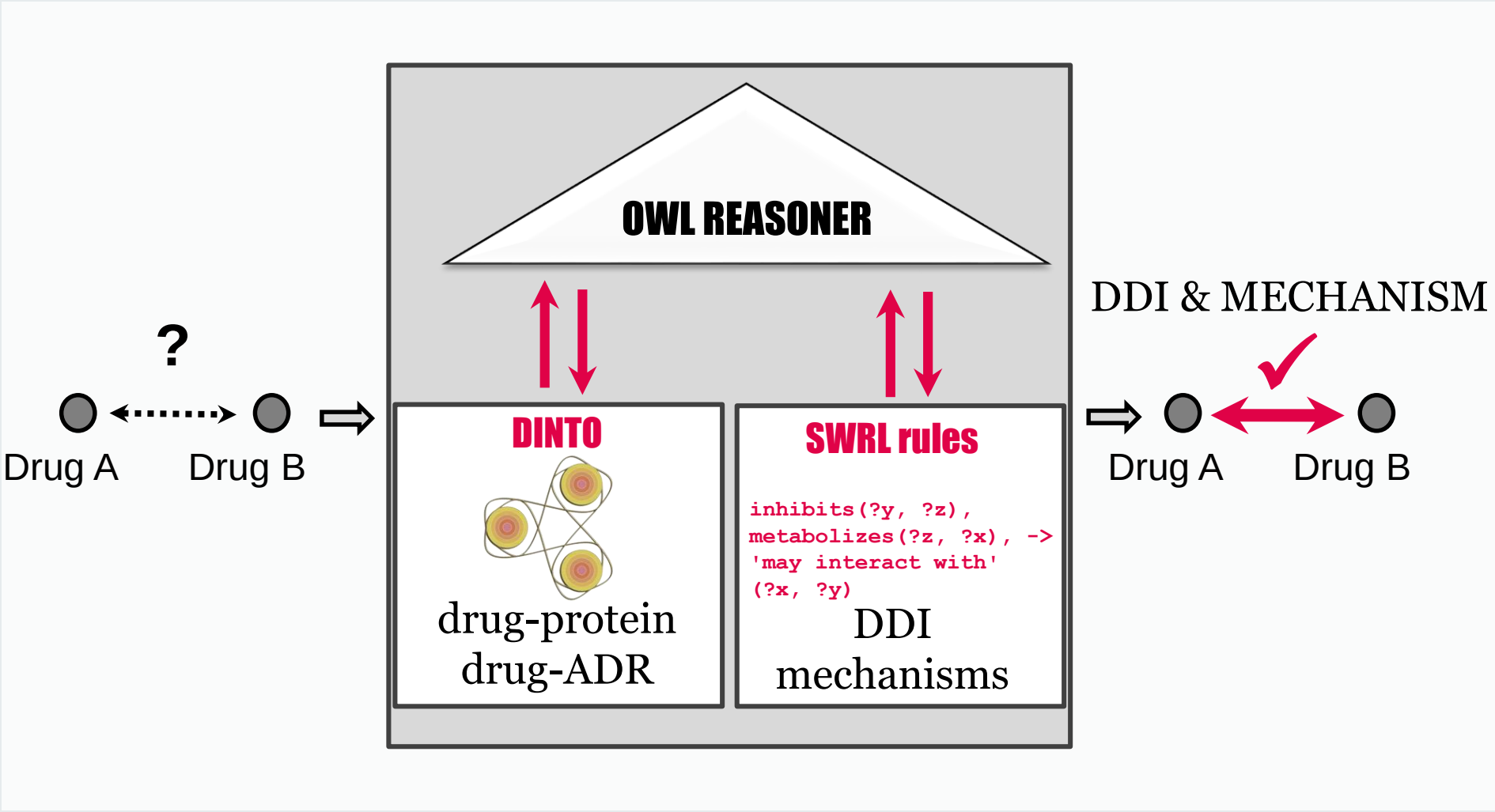
Ensemble with current IE systems:

- **DDI corpus** as a gold standard
- Comparison with participants at the ***2013 SemEval DDI Extraction task***.
- DINTO increased performance of DDI relation extraction in **scientific papers**.

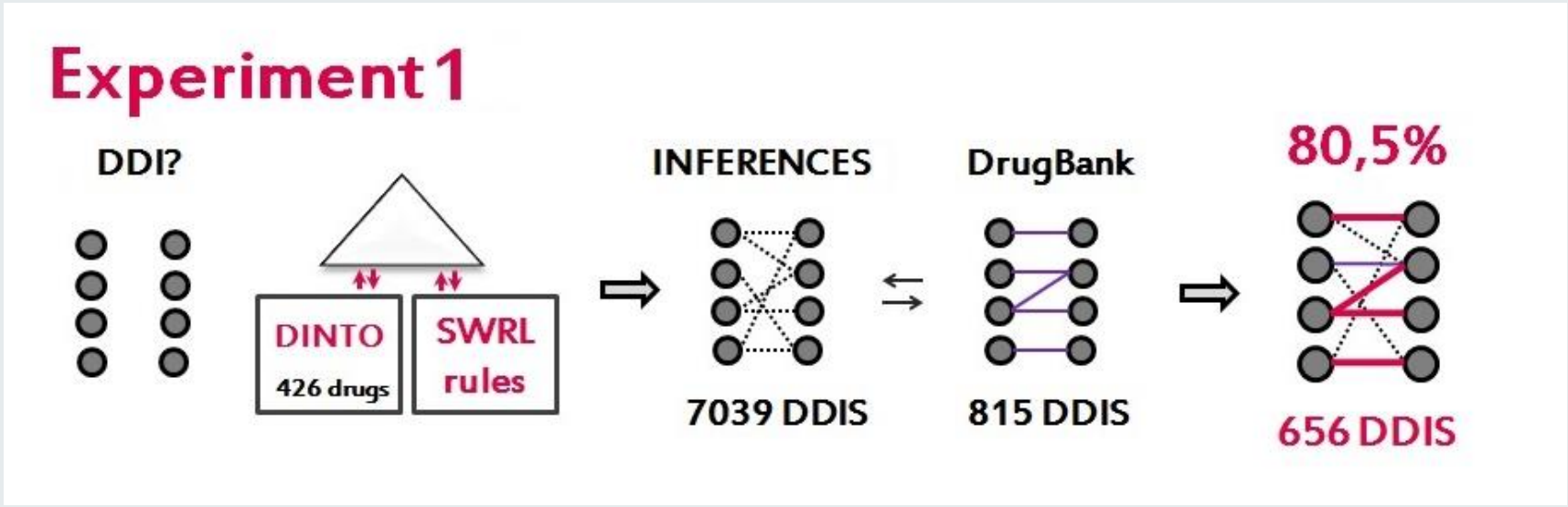


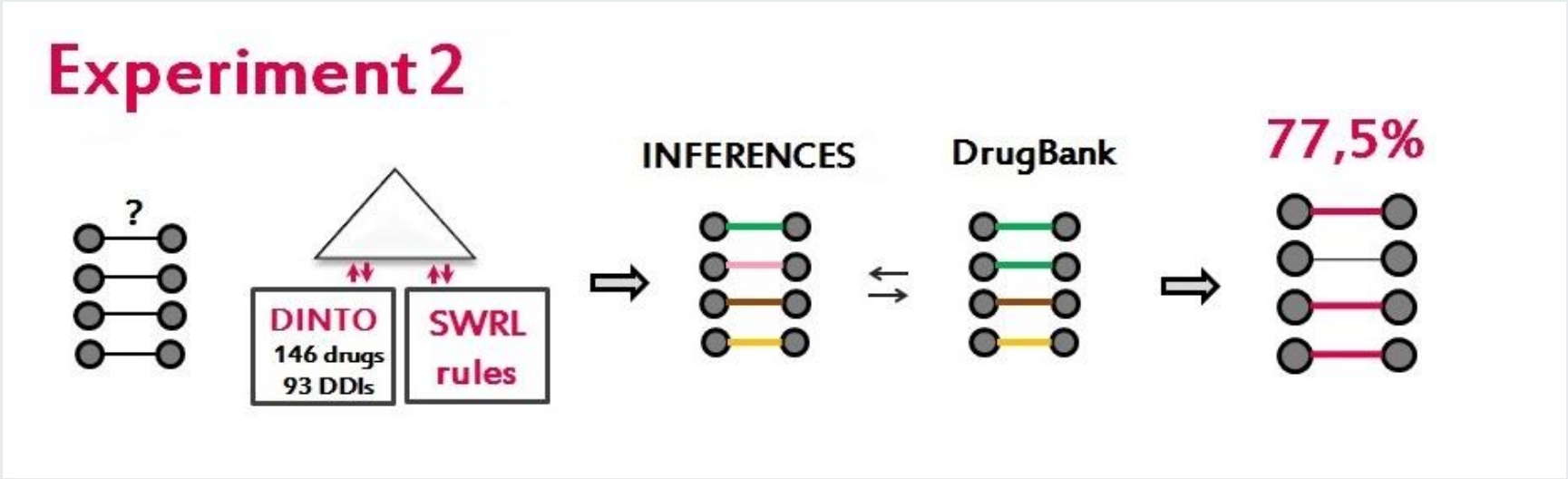
*Herrero-Zazo et al. *Int J Inf Retr Res*. 2015;5(3)

2. Inference of DDIs and their mechanisms



2. Inference of DDIs and their mechanisms[*]





*Herrero-Zazo et al. *J Chem Inf Model*. **2015**, 55(8)

Conclusions & Future Work

DINTO is the largest and most comprehensive ontology in the DDI domain and it has proven to be useful in different applications.

Future work lines:

- To **maintain** and **update** the current version.
- To include more information from **other databases**: physicochemical properties, drug-protein binding affinity, drug therapeutic index, etc.

  Could this knowledge be integrated in the SWRL rules?
- To combine inferences with **machine learning** techniques to identify clinically relevant DDIs.
- To **collaborate** with the current shared effort for the development of a **minimal information model for drug interaction evidence and knowledge**, led at the Department of Biomedical Informatics (University of Pittsburgh)

Thank you

maria.herrero@kcl.ac.uk

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ChEBI team (C. Steinbeck group) at the European Bioinformatics Institute