Self-Organizing Ontology of Biochemically Relevant Small Molecules

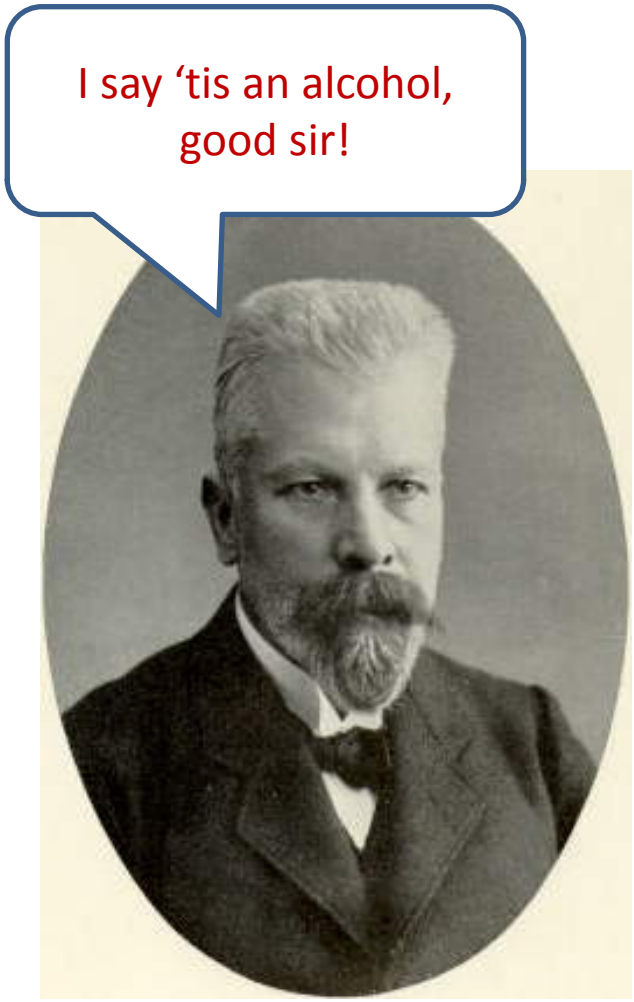
Leonid Chepelev, Michel Dumontier

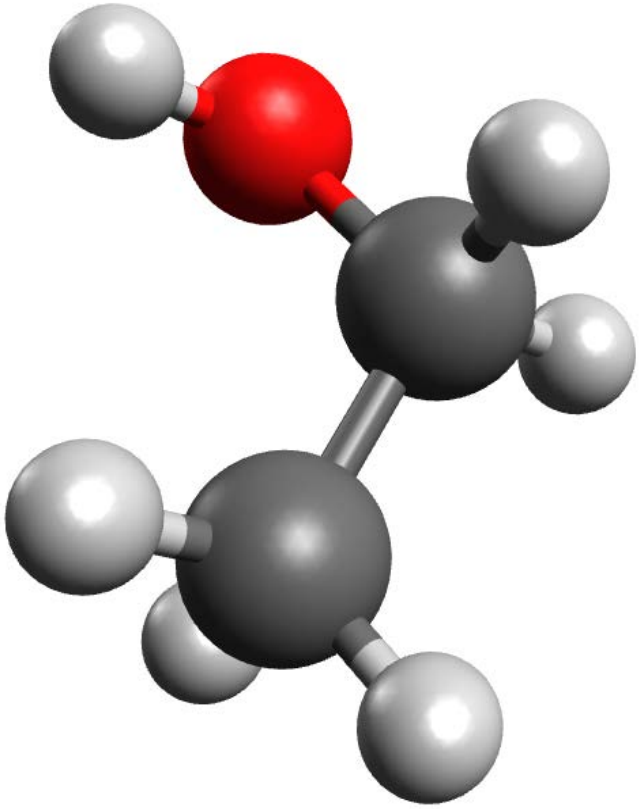
Department of Biology, School of Computer Science, Institute of Biochemistry, Carleton University

Chemical Classification

- Structure dictates function.
- If represent chemical knowledge in terms of structure and function, then we can reason about the composition of biochemical networks.
  - By characterizing metabolic substrates, we will **automatically identify** *potential enzyme substrates*.
  - By characterizing biochemical roles, we will **automatically identify** *toxic compounds*, and explain their toxicity.

Believe it or not, the current approach to structural classification is manual assignment





- Medical Subject Headings
- Hierarchically organized Controlled Vocabulary developed by the US National Library of Medicine (NLM)
  - Used primarily for indexing of documents, MEDLINE abstracts from over 5400 journals

1. + Anatomy [A]
2. + Organisms [B]
3. + Diseases [C]
4. − Chemicals and Drugs [D]
   - Inorganic Chemicals [D01] +
   - Organic Chemicals [D02] +
   - Heterocyclic Compounds [D03] +
   - Polycyclic Compounds [D04] +
   - Macromolecular Substances [D05] +
   - Hormones, Hormone Substitutes, and Hormone Antagonists [D06] +
   - Enzymes and Coenzymes [D08] +
   - Carbohydrates [D09] +
   - Lipids [D10] +
   - Amino Acids, Peptides, and Proteins [D12] +
   - Nucleic Acids, Nucleotides, and Nucleosides [D13] +
   - Complex Mixtures [D20] +
   - Biological Factors [D23] +
   - Biomedical and Dental Materials [D25] +
   - Pharmaceutical Preparations [D26] +
   - Chemical Actions and Uses [D27] +
5. + Analytical, Diagnostic and Therapeutic Techniques and Equipment [E]
6. + Psychiatry and Psychology [F]
7. + Phenomena and Processes [G]
8. + Disciplines and Occupations [H]
9. + Anthropology, Education, Sociology and Social Phenomena [I]
10. + Technology, Industry, Agriculture [J]
11. + Humanities [K]

- Freely available database of curated chemicals, focused on those of interest to biology
  - To replace proprietary sources
  - Contains constitutionally or isotopically distinct atom, molecule, ion, ion pair, radical, radical ion, complex, conformer, etc
  - Draws chemicals from IntEnz, KEGG compound, PDBeCHEM, ChEMBL
  - Stores attributes: formula, mass, charge, synonyms
- ChEBI Ontology
  - Manually constructed ontology of chemical types

Objectives and Approach

- Objectives
  - To uncover the chemical signature of compound classes from annotated data
  - To automatically generate an integrated MeSH + ChEBI ontology

- Approach:
  - Formalize consensus fragments as OWL ontologies amenable to automated reasoning

Web Ontology Language (OWL)

Classes and class axioms

- **a class** is a set of individuals that share one or more characteristics
  - a protein
- classes can be organized in a hierarchy using subClassOf axioms
  - i.e. every member of C2 is a member of C1
  - subClassOf (protein molecule)

- special classes
  - **owl:Thing** is the superclass of all things
  - **owl:Nothing** is the subclass of all things, denotes an empty set

- classes can be made **disjoint** from one another
  - i.e. there is no member of C1 that is also a member of C2
  - disjointClasses (protein DNA)

- classes can be said to be **equivalent**
  - i.e. all members of C1 are members of C2 and all members of C2 are members of C1
  - *EquivalentClass (Peptide Polypeptide)*

Class Expressions

Class expressions are rich descriptions of classes through the logical combination of ontological primitives (classes, object properties, datatype properties, individuals)

Protein subClassOf
molecule and ‘has direct part’ min 2 ‘amino acid residue’

Combinations specified using logical operators

- conjunction (and), disjunction (or), negation (not)

Object or data property expressions provide a qualified cardinality over the relation

- minimum: *rel* min # Y
- maximum: *rel* max # Y
- exact: *rel* exactly # Y (minimum + maximum)
- **some**: *rel* min 1 Y

Class Expressions

- The quantifications can qualified by the object type
  - *rel* only Y – the only values allowed are of type Y

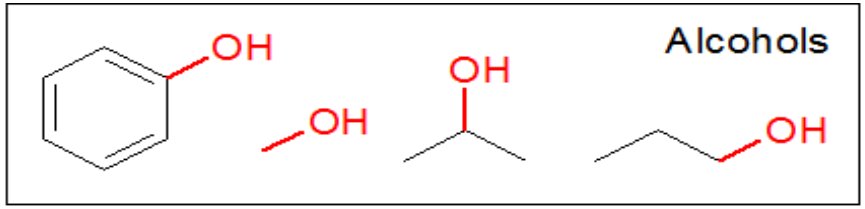
- To form complex class expressions like
  - 'molecule' and not 'dna'
  - 'has direct part' min 2 'amino acid'
  - 'is located in' only ('nucleus' or 'cytoplasm')

- and be expressed as axioms in the ontology

Protein subClassOf
molecule and ‘has direct part’ min 2 ‘amino acid residue’

Transcription Factor equivalentTo
‘protein’
and ‘has disposition’ some ‘to bind to DNA’
and ‘has function’ some ‘to regulate gene expression’

Methods



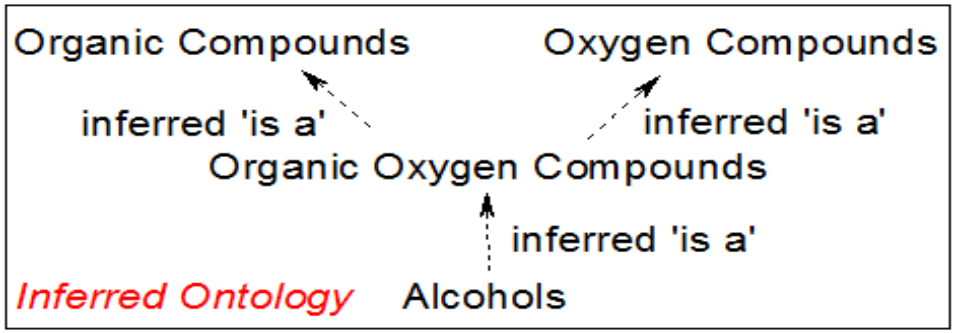
Consensus Features

[#6] [#8] [OX2H] [#6][#8] [#6][OX2H]

Formalize Definition

EquivalentTo
'Molecular entity'
and 'has part' some '[#6]'
and 'has part' some '[#8]'
and 'has part' some '[#6][#8]'
and 'has part' some '[#6][OX2H]'

Infer Hierarchy



Data:
60 MeSH classes + 766 PubChem compounds
40 ChEBI classes + 606 3 star ChEBI compounds

Fragmentation:
up to 4 bonds
SMILES/SMARTS canonicalization (OpenBabel)

Consensus:
maximal common substructures
using binary combinations
of five smallest class members
Chemistry Development Kit (CDK)

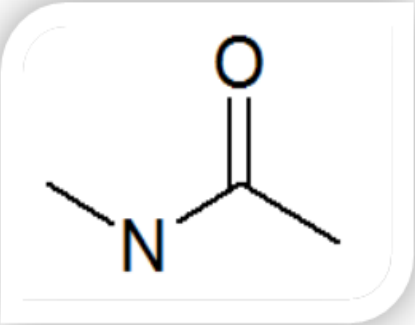
Formalization:
URIs generated from SHA1 Hash
Semanticscience Integrated Ontology (SIO)
Axioms generated with the OWL API

Reasoning:
Pellet

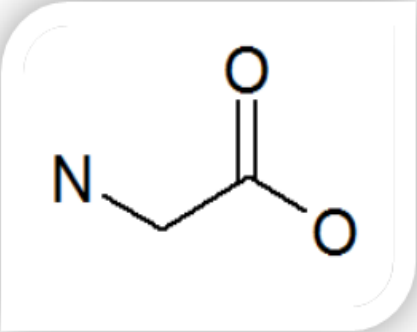
Getting Consensus
Significantly easier with chemicals ☺

Fragment	Contained
C	y
C=O	y
CC	y
CC(=O)N	y
CC(=O)O	y
CC=O	y
CCN	y
CCO	y
CN	y
CNC	y
CNC(=O)C	n
CNC=O	y
CNCC	y
CO	y
N	y
NC=O	y
NCC(=O)O	n
NCC=O	y
NCCO	y
O	y
OC=O	y

Principal Characteristic Sub-Graph A



Principal Characteristic Sub-Graph B



Self-Assembling Hierarchy

0 000 000 000 001
Organic Molecular Entity

↑ 'is a'

0 000 110 100 101
Carboxylic Acid

↑ 'is a'

0 111 111 111 111
Amino Acid

↑ 'is a'

1 111 111 111 111
Biological Amino Acid

Feature List	
1	NCC(=O)O
2	CC
3	CCO
4	CC=O
5	CO
6	C=O
7	CCN
8	OC=O
9	CN
10	CC(=O)O
11	O
12	N
13	C

‘Flat’ Ontology

Asserted class hierarchy: diolChebi

- molecularentity
  - OrganometallicCompoundChebi
  - acyclicCarboxylicAnhydrideChebi
  - aldoseChebi
  - aminoAcidChebi
  - aralkylAmineChebi
  - areneCarbaldehydeChebi
  - azacycloalkaneChebi
  - benzamidesChebi
  - carboxylicAnhydrideChebi
  - carboxylicEsterChebi
  - chlorocarboxylicacidChebi
  - cholestanoidChebi
  - crownEtherChebi
  - cyanidesChebi
  - cyclicDicarboxylicAnhydrideChebi
  - cyclicKetoneChebi
  - diolChebi
  - esterChebi
  - fattyAcylsChebi
  - ferrocenesChebi
  - hydroperoxideChebi
  - inositolsChebi
  - naphthaldehydeChebi
  - nitrosamineChebi
  - oniumCompoundsChebi
  - organicAminoCompoundChebi
  - organicsulfateChebi
  - organochlorineCompoundChebi
  - organohalogenCompoundChebi
  - oxacycleChebi
  - oximeChebi
  - penicillinsChebi
  - phenylhydrazinesChebi
  - porphyrinogenChebi
  - pyrrolidinesChebi
  - pyrrolidinonesChebi
  - secondaryAmidesChebi
  - tetrasaccharideChebi
  - thiolChebi
  - tripeptideChebi

Annotations: diolChebi

Annotations

Description: diolChebi

Equivalent classes

SIO_000028 some O
and SIO_000028 some [#6][#6][#8]
and SIO_000028 some [#6][#6]
and SIO_000028 some [#8]
and SIO_000028 some [#6]
and SIO_000028 some [#6][#8]
and SIO_000028 some [#6]~[#7,#8,#16]
and SIO_000028 min 2 [#8X2H]

Superclasses

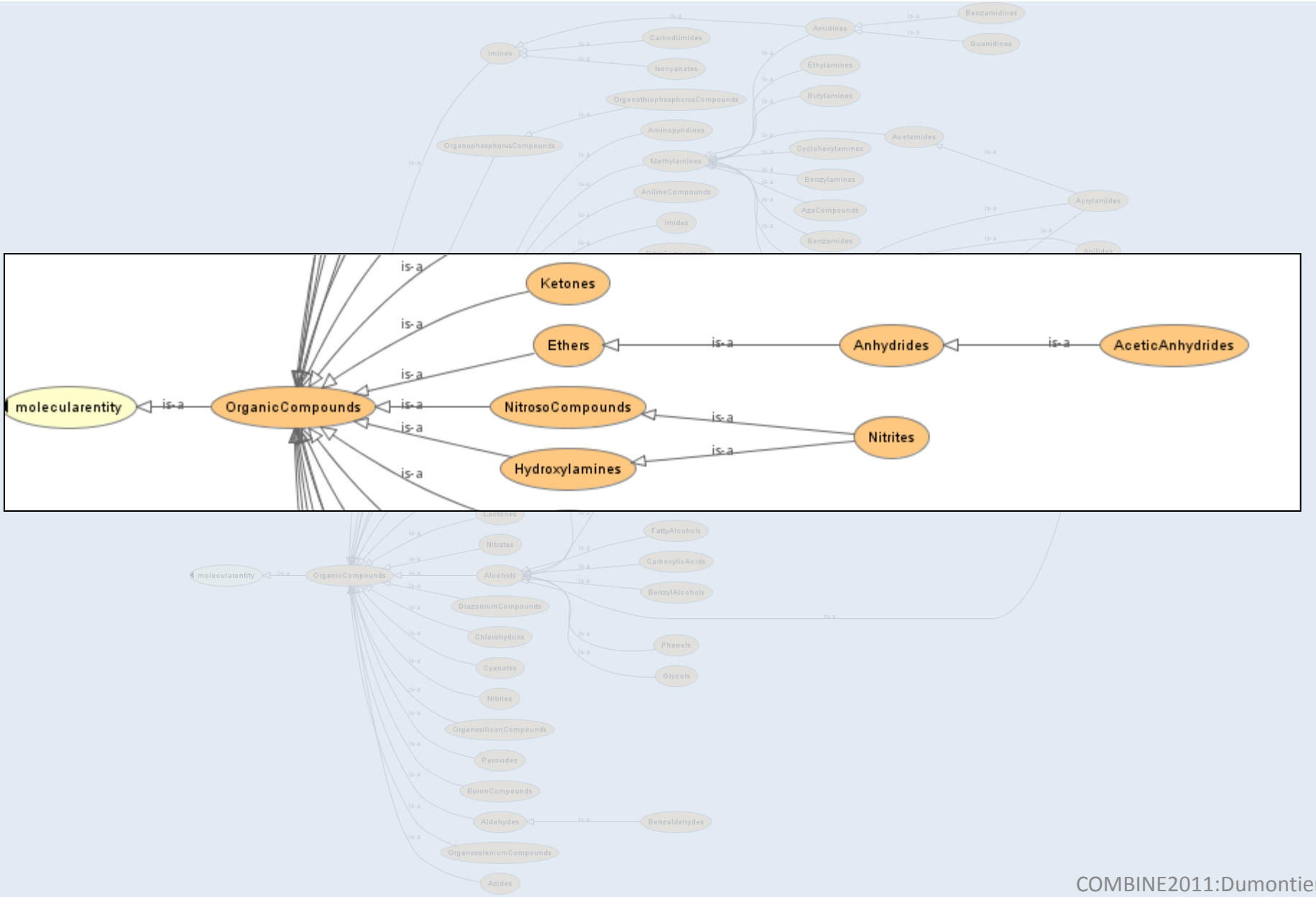
molecularentity

Inferred anonymous superclasses

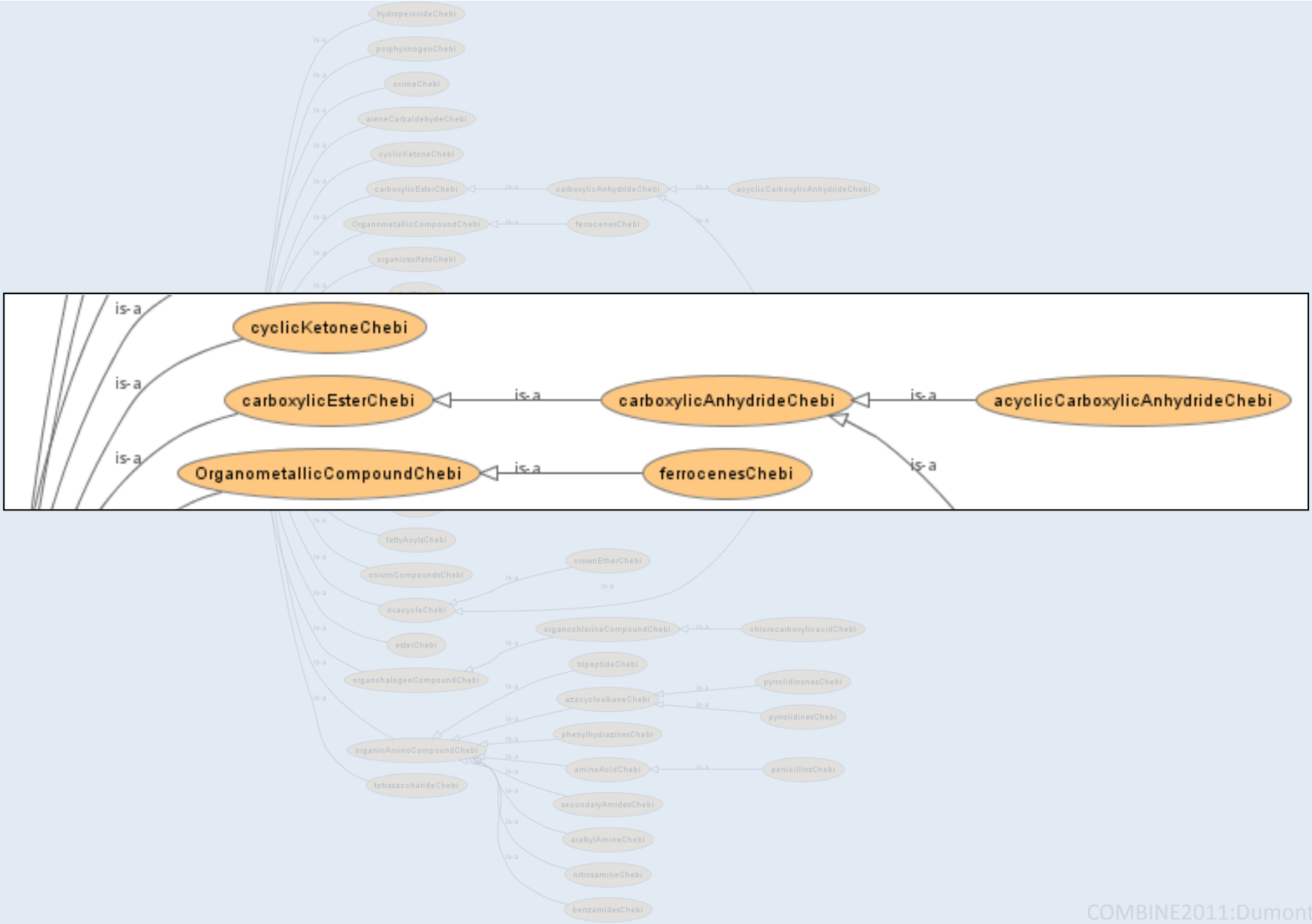
Members

Disjoint classes

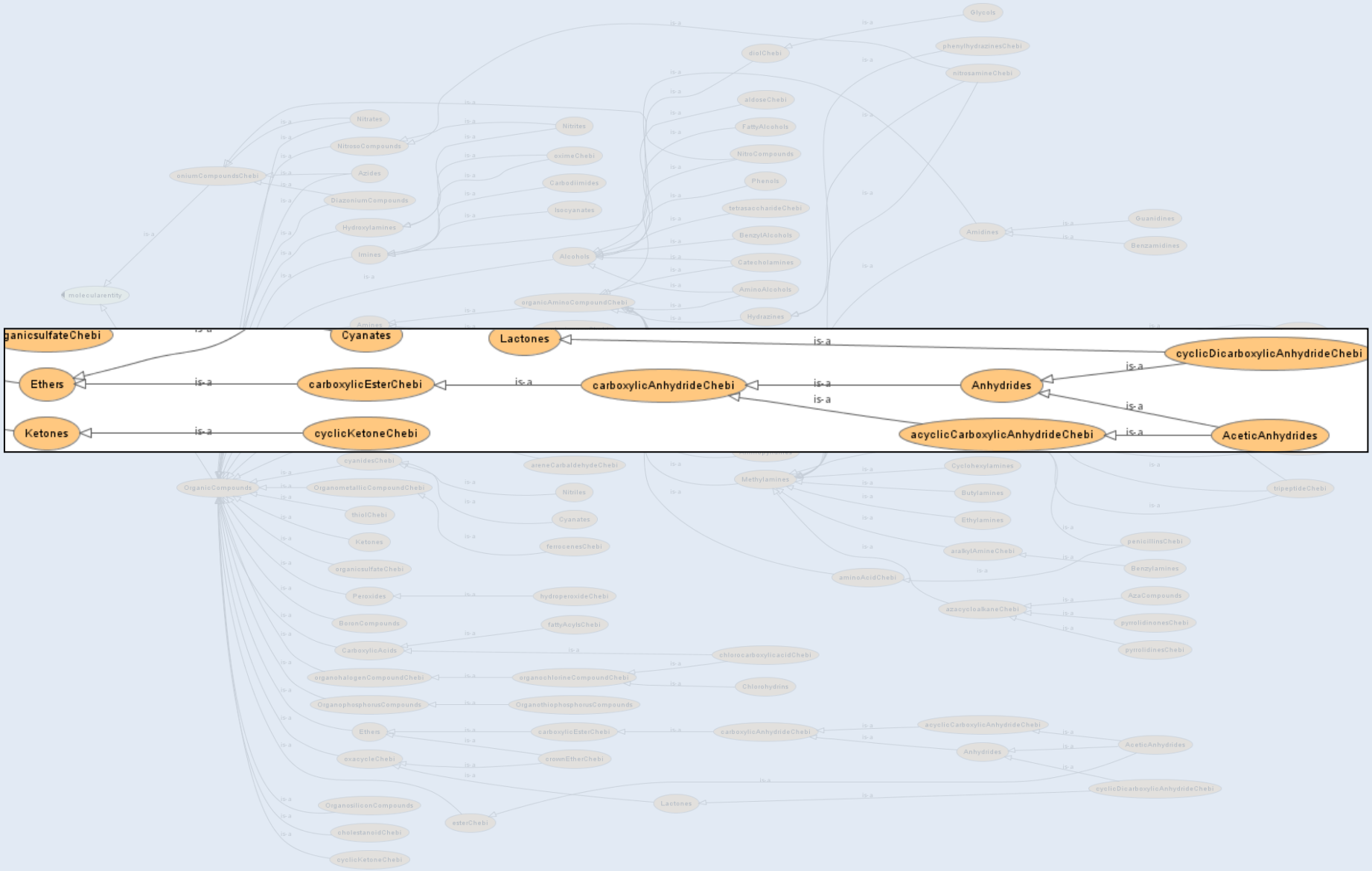
Reasoning unveils the MESH Hierarchy



Reasoning unveils the ChEBI Hierarchy



Automatic Integration: MeSH + ChEBI



Evaluation

- Test: recapitulate the original classification
  - 200 randomly selected molecules
- Results
  - 91% exactly matched assigned annotations
  - 8.5% discovered new, correct annotations
  - 92.7% correct annotations; errors found in those types requiring negation (e.g. in classical chemistry, an alcohol is not a carboxylic acid, although it is structurally correct

Application: Enzyme Substrate Specificity

- BRENDA – database of enzyme kinetics
- 23 substrates for yeast alcohol dehydrogenase
- Obtained the consensus fragment as equivalent to that for alcohols

Structure-Based Classification

- Obtain formal definitions for controlled vocabularies used as entity annotation
- High degree of accuracy in uncovering consensus attributes, provided that the annotations are ***correct***
- Enormous potential for application for biological analysis and understanding
- Attribute-based descriptions reduce manual labour to providing formal definitions.
- Flexible, re-usable, extensible.

Michel Dumontier

michel_dumontier@carleton.ca

Publications: http://dumontierlab.com

Presentations: http://slideshare.com/micheldumontier

MITACS NSERC CRSNG Canada Foundation for Innovation Fondation canadienne pour l'innovation canarie Carleton UNIVERSITY Health Canada Ontario