A Semantic Assistant (SA) for Lipidomics Researchers

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Motivation

- Semantic data integration is necessary for lipid research yet this is poorly achievable due to an absence of a single *unified*, *consistent*, and *universally accepted* lipid classification system.

- Lipid nomenclature is highly heterogeneous.
  - Not semantically explicit
  - Many conflicting nomenclatures and multiple synonyms
  - Graphically dependent definitions
  - Lack of universal systematic nomenclature

LIPID Nomenclature

IUPAC

- Open to erroneous interpretation by scientists
- Too bulky for adoption
- No informatics implementation
- Re-interpretations and implementations not scientifically robust.

LIPIDMAPS

- Class names inconsistent with instances
- Classes with no instances
- Lack semantic & textual definitions
- Use of “dumping ground” classes to hold lipid instances that do not “fit in”
- Not all instances classified by structure; some by functions & biosynthetic origin (lack of consistency in classification)

Upto (2009)

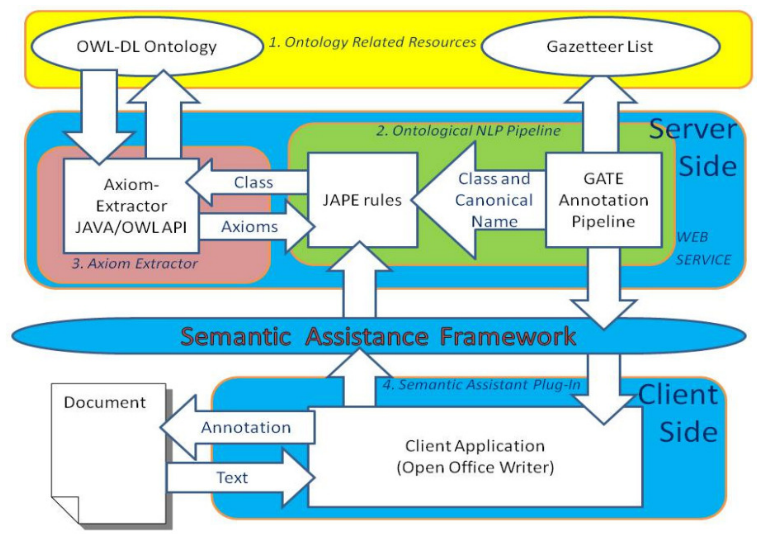
Objectives

- Formalize and represent lipid nomenclature & classification hierarchy in the web ontology language(OWL-DL)
- Provide access to lipid definitions that are:
  - Independent of graphical descriptions
  - Semantically explicit
  - Amenable to inference / classification based reasoning
- To make available:
  - a systematic and formalized OWL-DL definitions of lipids for testing appropriateness of existing nomenclature to lipid structures.
  - serve as a reusable standard for lipid researchers and the lipid bioinformatics community
  - **Formal annotations to users doing Knowledge discovery tasks**

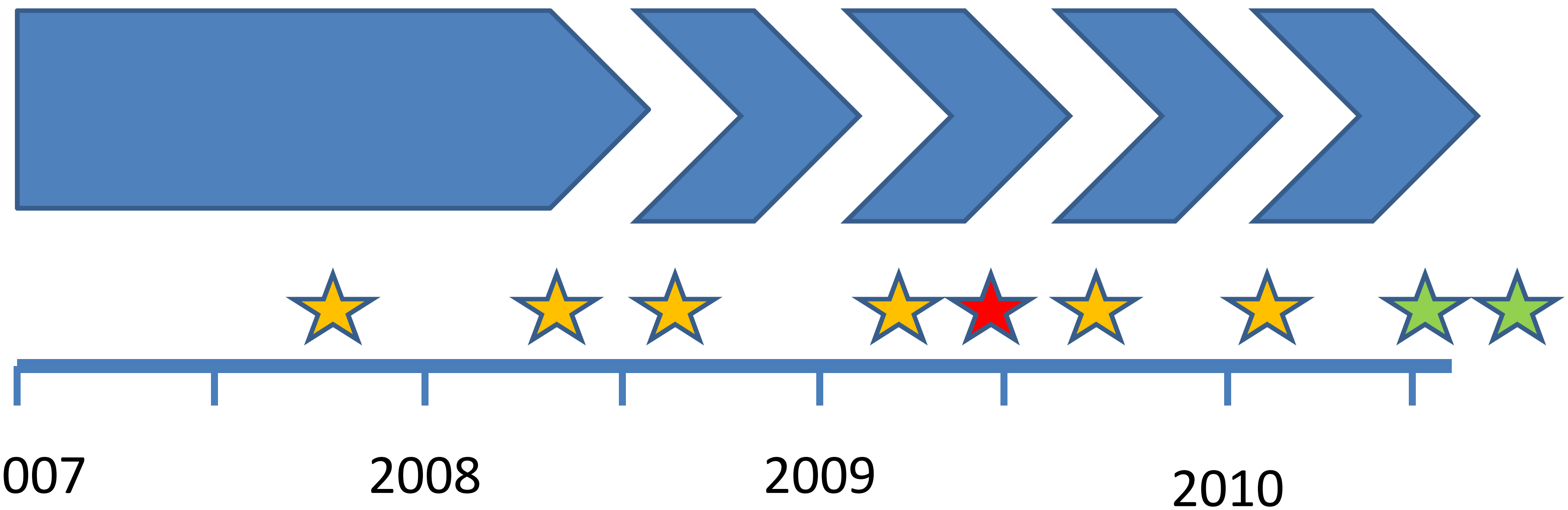
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health

SA: Core System Components

- OWL-DL Lipid Ontology
- Natural Language Processing (GATE/JAPE)
- Semantic Assistant Framework
- Ontology Axiom-Extractor



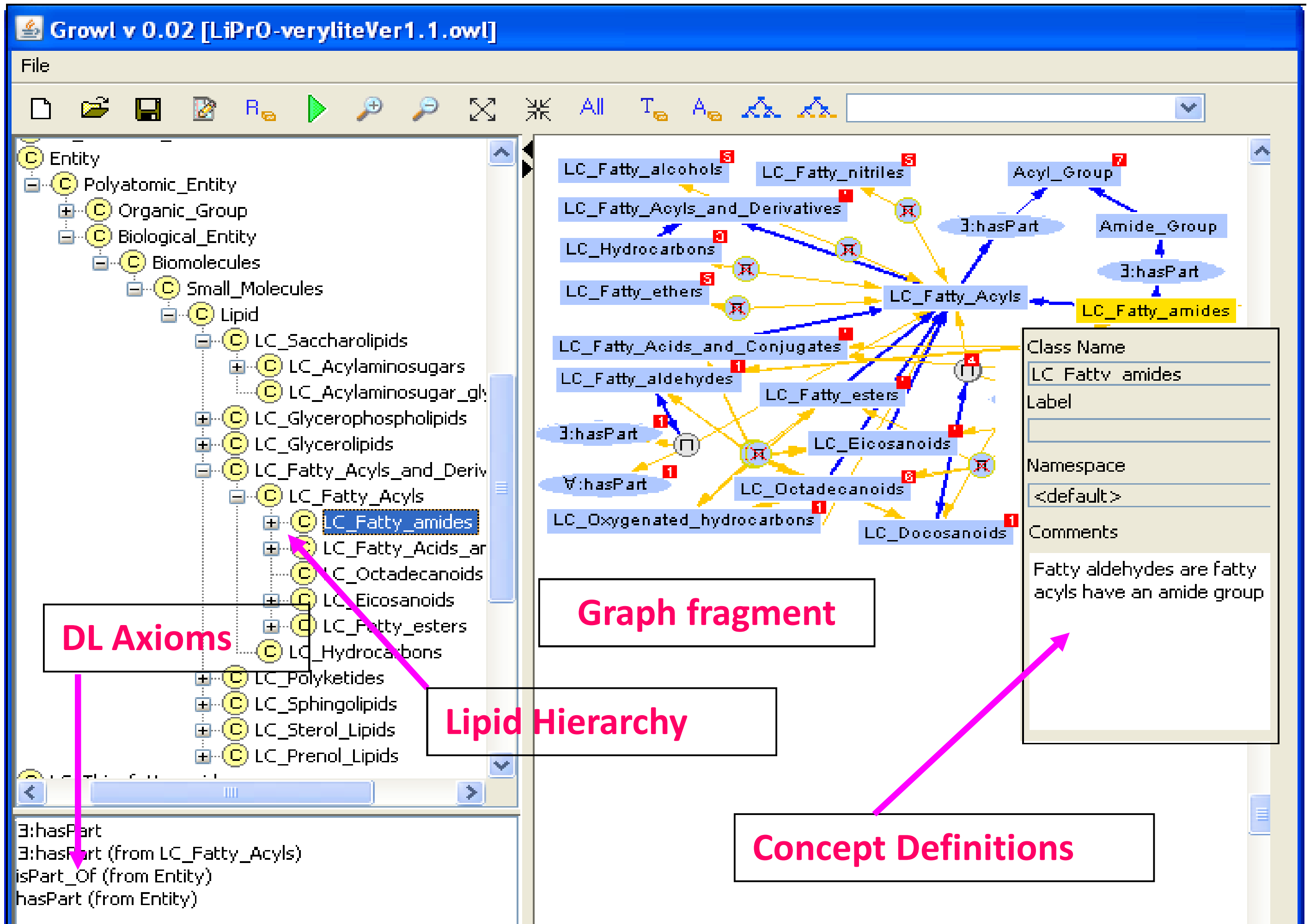
Lipid Ontology: a history



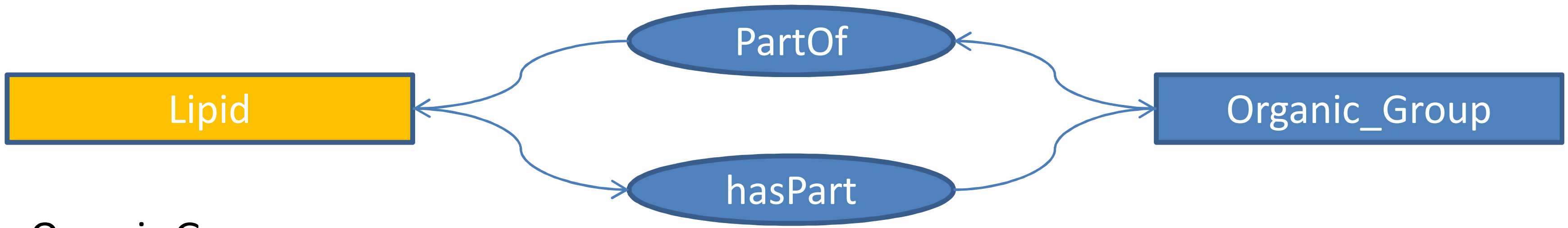
FIRST-ISWC 2007 - Early Text Mining / Simple Ontology / modeling lipid nomenclature
BMC Bioinf. 2008 - Baseline Ontology / Text Mining / Visual Query
ISMB 2008 - Text Mining / Apoptosis / Data Mining for Transitive Relations
OBO 2009 - Online Listing
AMIA 2009 - Text Mining / Ovarian Cancer
HS Low MSc 2009 - Formal Lipid Ontology
ICBO 2009 - OWL-DL Ontology for classification of Lipids
IntOnt 2010 - Lipid Ontologies
ACS 2010 - Semantic Chemistry - Corpus Annotation with Lipid Ontology Axioms

Lipid Ontology

Total No. of Classes	715
No. of Lipid Classes	**492**
Primitive Lipid Classes	**107**
Defined Lipid Classes	**268**
Total No. Restrictions	901
Total No. Properties	41
DL Expressivity	ALCHIQ(D)

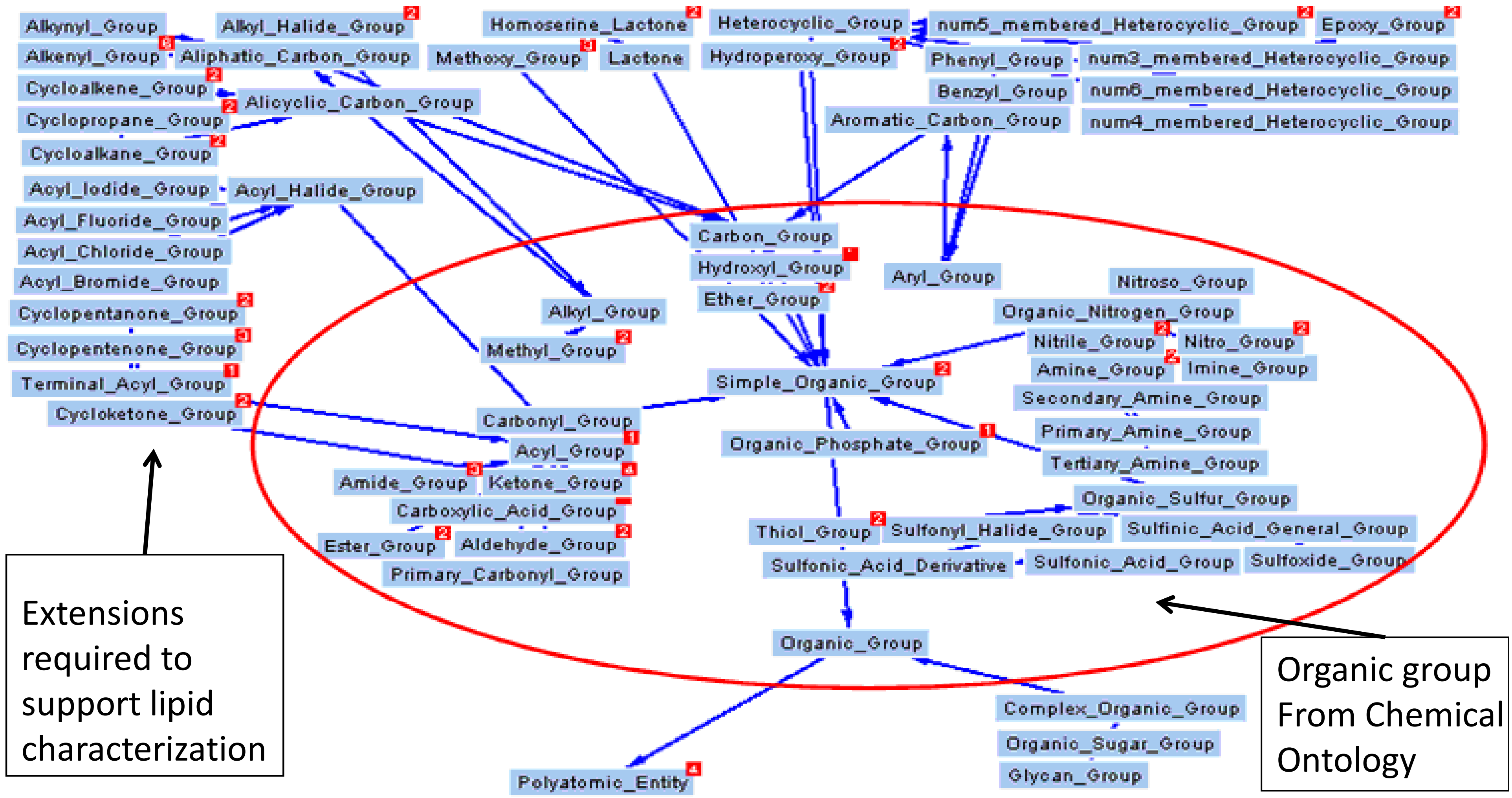


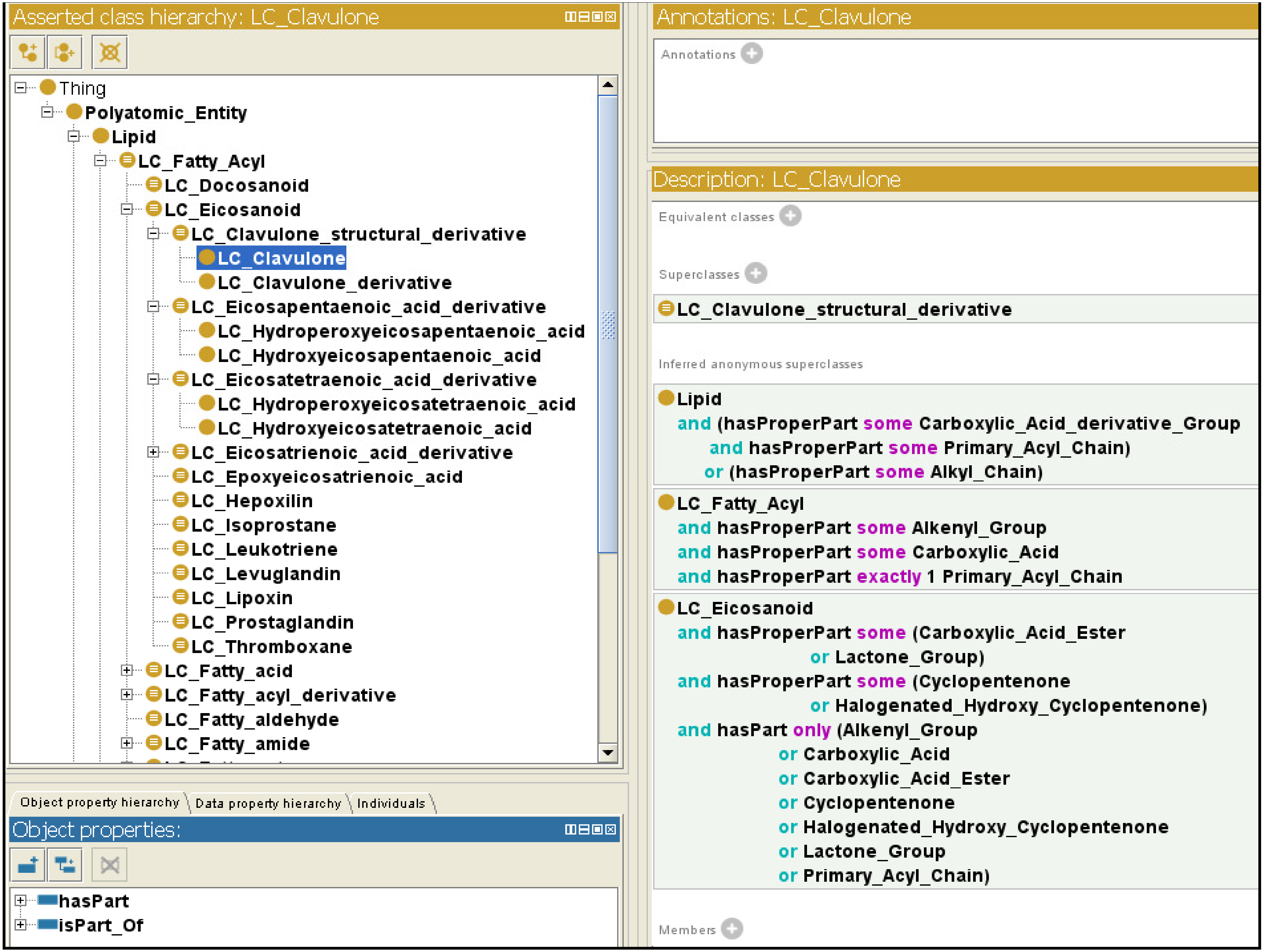
http://www.lipidprofiles.com/LipidOntology/LiPrO-02042009.owl



<u>Organic Group</u>

Total no. of simple organic group = 95 (2009)




Asserted class hierarchy: LC_Clavulone
Thing
Polyatomic_Entity
Lipid
LC_Fatty_Acyl
LC_Docosanoid
LC_Eicosanoid
LC_Clavulone_structural_derivative
LC_Clavulone
LC_Clavulone_derivative
LC_Eicosapentaenoic_acid_derivative
LC_Hydroperoxyeicosapentaenoic_acid
LC_Hydroxyeicosapentaenoic_acid
LC_Eicosatetraenoic_acid_derivative
LC_Hydroperoxyeicosatetraenoic_acid
LC_Hydroxyeicosatetraenoic_acid
LC_Eicosatrienoic_acid_derivative
LC_Epoxyeicosatrienoic_acid
LC_Hepoxilin
LC_Isoprostane
LC_Leukotriene
LC_Levuglandin
LC_Lipoxin
LC_Prostaglandin
LC_Thromboxane
LC_Fatty_acid
LC_Fatty_acyl_derivative
LC_Fatty_aldehyde
LC_Fatty_amide
Object property hierarchy
Data property hierarchy
Individuals
Object properties:
hasPart
isPart_Of
Annotations: LC_Clavulone
Annotations
Description: LC_Clavulone
Equivalent classes
Superclasses
LC_Clavulone_structural_derivative
Inferred anonymous superclasses
Lipid
and (hasProperPart some Carboxylic_Acid_derivative_Group
and hasProperPart some Primary_Acyl_Chain)
or (hasProperPart some Alkyl_Chain)
LC_Fatty_Acyl
and hasProperPart some Alkenyl_Group
and hasProperPart some Carboxylic_Acid
and hasProperPart exactly 1 Primary_Acyl_Chain
LC_Eicosanoid
and hasProperPart some (Carboxylic_Acid_Ester
or Lactone_Group)
and hasProperPart some (Cyclopentenone
or Halogenated_Hydroxy_Cyclopentenone)
and hasPart only (Alkenyl_Group
or Carboxylic_Acid
or Carboxylic_Acid_Ester
or Cyclopentenone
or Halogenated_Hydroxy_Cyclopentenone
or Lactone_Group
or Primary_Acyl_Chain)
Members

SA: Core System Components

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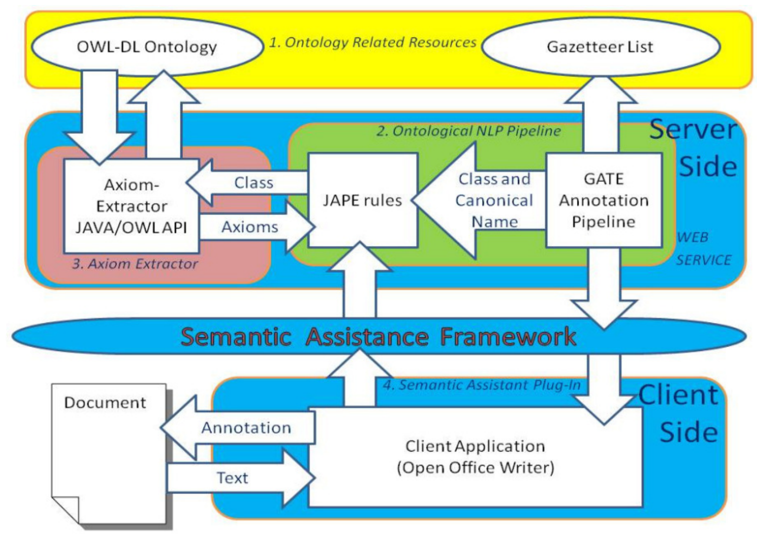
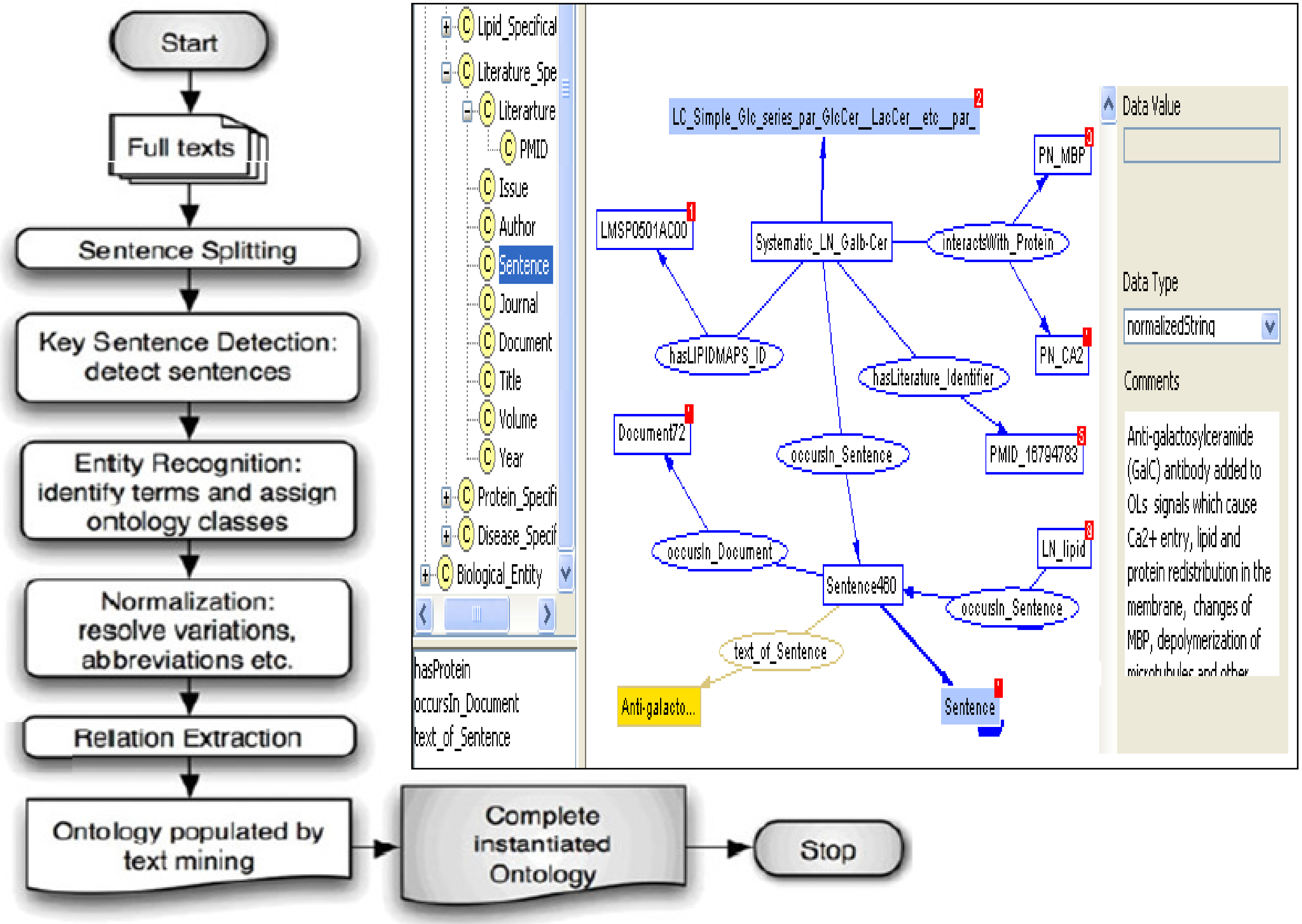
- Natural Language Processing (GATE/JAPE)
- Semantic Assistant Framework
- Ontology Axiom-Extractor



Ontology Population Workflow

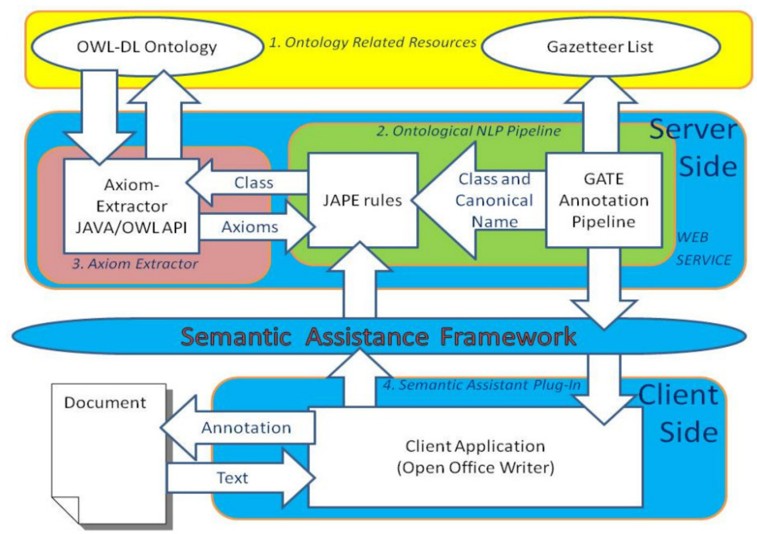


Mapping Named Entities to Axioms

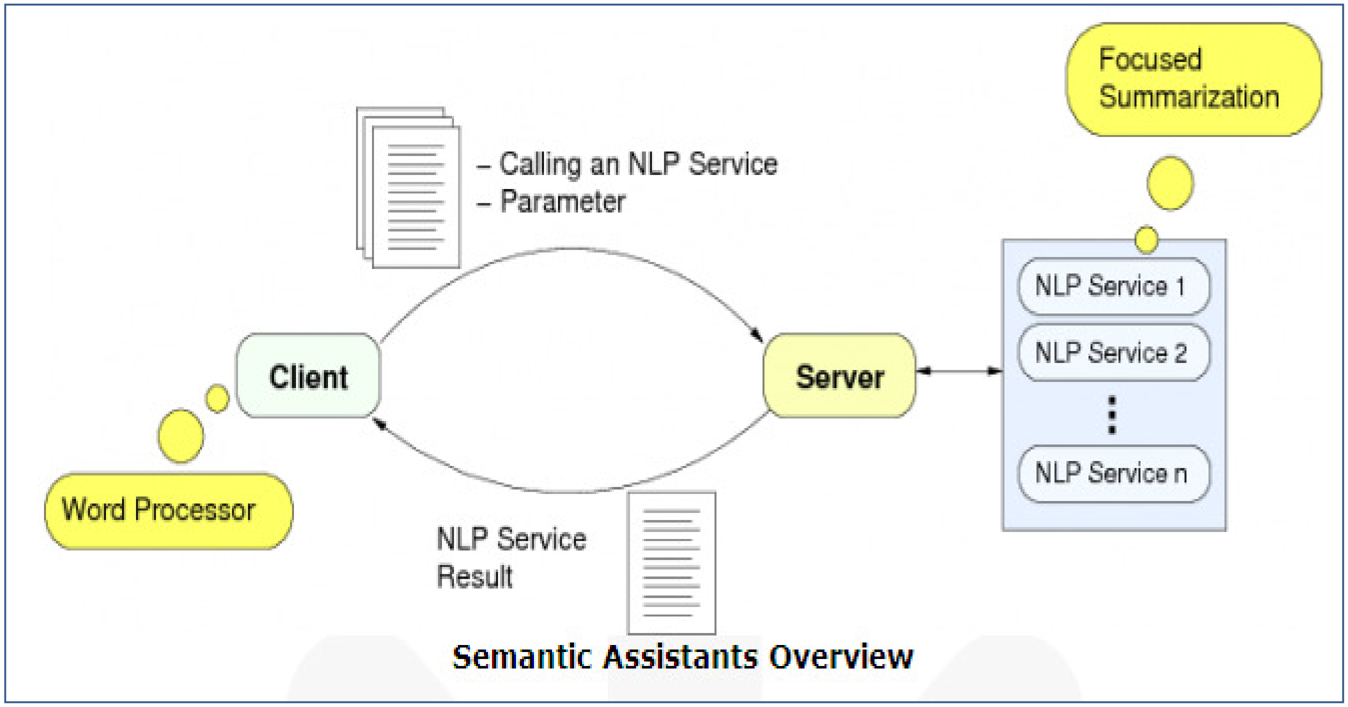
	A	B	C	D	E	G	H
1	LMID	Common name	Systematic name	Iupac name	Pubchem_ID	LipidMaps Class	Lipid Ontology Class
1421	LMFA01060161	5-oxopentanoic acid	5-oxo-pentanoic acid	5-oxopentanoic acid	7982783	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1422	LMFA01060160	9-oxononanoic acid	9-oxo-nonanoic acid	9-oxononanoic acid	7982782	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1423	LMFA01060159	8-oxononanoic acid	8-oxo-nonanoic acid	8-oxononanoic acid	7982781	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1424	LMFA01060158	3-oxononanoic acid	3-oxo-nonanoic acid	3-oxononanoic acid	7982780	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1425	LMFA01060157	7-methyl-6-oxo-octanoic acid	7-methyl-6-oxo-octanoic acid	7-methyl-6-oxo-octanoic acid	7982779	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1426	LMFA01060156	4,7-dioxooctanoic acid	4,7-dioxo-octanoic acid	4,7-dioxooctanoic acid	7982778	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1427	LMFA01060150	(Z)-19-oxooctacos-22-enoic acid	19-oxo-22Z-octacosenoic acid	(Z)-19-oxooctacos-22-enoic acid	7982776	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1428	LMFA01060149	(Z)-17-oxohexacos-20-enoic acid	17-oxo-20Z-hexacosenoic acid	(Z)-17-oxohexacos-20-enoic acid	7982775	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1429	LMFA01060148	(Z)-15-oxotetracos-18-enoic acid	15-oxo-18Z-tetracosenoic acid	(Z)-15-oxotetracos-18-enoic acid	7982774	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1430	LMFA01060147	3-oxotetracosanoic acid	3-oxo-tetracosanoic acid	3-oxotetracosanoic acid	7982773	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1431	LMFA01060146	3-oxotricosanoic acid	3-oxo-tricosanoic acid	3-oxotricosanoic acid	7982772	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1432	LMFA01060155	7-methyl-4-oxo-octanoic acid	7-methyl-4-oxo-octanoic acid	7-methyl-4-oxo-octanoic acid	7982777	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1433	LMFA01060136	20-oxohenicosanoic acid	20-oxo-heneicosanoic acid	20-oxohenicosanoic acid	7982762	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1434	LMFA01060135	2-oxohenicosanoic acid	2-oxo-heneicosanoic acid	2-oxohenicosanoic acid	7982761	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1435	LMFA01060134	3-oxoicosanoic acid	3-oxo-eicosanoic acid	3-oxoicosanoic acid	7982760	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1436	LMFA01060133	2-oxoicosanoic acid	2-oxo-eicosanoic acid	2-oxoicosanoic acid	7982759	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1437	LMFA01060132	19-oxoicosanoic acid	19-oxo-eicosanoic acid	19-oxoicosanoic acid	7982758	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1438	LMFA01060131	3-oxononadecanoic acid	3-oxo-nonadecanoic acid	3-oxononadecanoic acid	7982757	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1439	LMFA01060130	2-oxononadecanoic acid	2-oxo-nonadecanoic acid	2-oxononadecanoic acid	7982756	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1440	LMFA01060120	8-oxooctadecanoic acid	8-oxo-octadecanoic acid	8-oxooctadecanoic acid	7982746	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1441	LMFA01060119	2-oxooctadecanoic acid	2-oxo-octadecanoic acid	2-oxooctadecanoic acid	7982745	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1442	LMFA01060118	17-oxooctadecanoic acid	17-oxo-octadecanoic acid	17-oxooctadecanoic acid	7982744	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1443	LMFA01060117	16-oxooctadecanoic acid	16-oxo-octadecanoic acid	16-oxooctadecanoic acid	7982743	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1444	LMFA01060116	15-oxooctadecanoic acid	15-oxo-octadecanoic acid	15-oxooctadecanoic acid	7982742	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1445	LMFA01060115	14-oxooctadecanoic acid	14-oxo-octadecanoic acid	14-oxooctadecanoic acid	7982741	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1446	LMFA01060114	13-oxooctadecanoic acid	13-oxo-octadecanoic acid	13-oxooctadecanoic acid	7982740	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1447	LMFA01060113	12-oxooctadecanoic acid	12-oxo-octadecanoic acid	12-oxooctadecanoic acid	7982739	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1448	LMFA01060084	(E)-5-oxodec-7-enoic acid	5-oxo-7E-decenoic acid	(E)-5-oxodec-7-enoic acid	7982710	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1449	LMFA01060082	(E)-9-oxodec-2-enoic acid	9-oxo-2E-decenoic acid	(E)-9-oxodec-2-enoic acid	7982708	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1450	LMFA01060080	6,9-dioxodecanoic acid	6,9-dioxo-decanoic acid	6,9-dioxodecanoic acid	7982706	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1451	LMFA01060079	3,6-dioxodecanoic acid	3,6-dioxo-decanoic acid	3,6-dioxodecanoic acid	7982705	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1452	LMFA01060110	2-methyl-4-oxo-heptadecanoic acid	2-methyl-4-oxo-heptadecanoic acid	2-methyl-4-oxo-heptadecanoic acid	7982736	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1453	LMFA01060167	-	12-oxo-9(Z)-dodecenoic acid	-	-	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1454	LMFA01060176	xodecanoic acid##(2S)-2-amino-8-(oxiran-2	2-amino-8-oxo-9,10-epoxy-decanoic acid	-	14184	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1455	LMFA01060175	cid##4-Oxo-cis-9,trans-11,trans-13-octadec	4-oxo-9Z,11E,13E-octadecatrienoic acid	-	10517	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1456	LMFA01060174	ic acid##2-Oxohex-trans-4-enoate##(E)-2-o:	2-Oxo-4E-hexenoic acid	-	8981	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1457	LMFA01060171	acid##2-Amino-4-oxopentanoate##(2R)-2-an	2-amino-4-oxo-pentanoic acid	-	6184	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1458	LMFA01060177	ODE##9-KODE##(10E,12Z)-9-Oxooctadeca	9-oxo-10E,12Z-octadecadienoic acid	-	-	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1459	LMFA01060170	cid##4-Methylthio-2-oxobutanoate##4-meth	2-oxo-4-methylthio-butanoic acid	-	4407	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1460	LMFA01060169	oate##2-Oxo-5-aminopentanoate##alpha-Ke	2-oxo-5-amino-pentanoic acid	-	4342	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1461	LMFA01060168	ate##8-Amino-7-oxononanoic acid##8-amin	7-oxo-8-amino-nonanoic acid	-	4327	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1462	LMFA01060173	acid##(S)-5-Amino-3-oxohexanoate##(5S)-5	3-oxo-5S-amino-hexanoic acid	-	6434	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl
1463	LMFA01060172	ate##L-2-Amino-acetoacetate##(S)-2-Aminc	2S-amino-3-oxo-butanoic acid	-	6318	Fatty Acids and Conjugates <<FA01>>	LC_Fatty_Acyl

SA: Core System Components

- OWL-DL Lipid Ontology
- Natural Language Processing (GATE/JAPE)
- Semantic Assistant Framework
- Ontology Axiom-Extractor

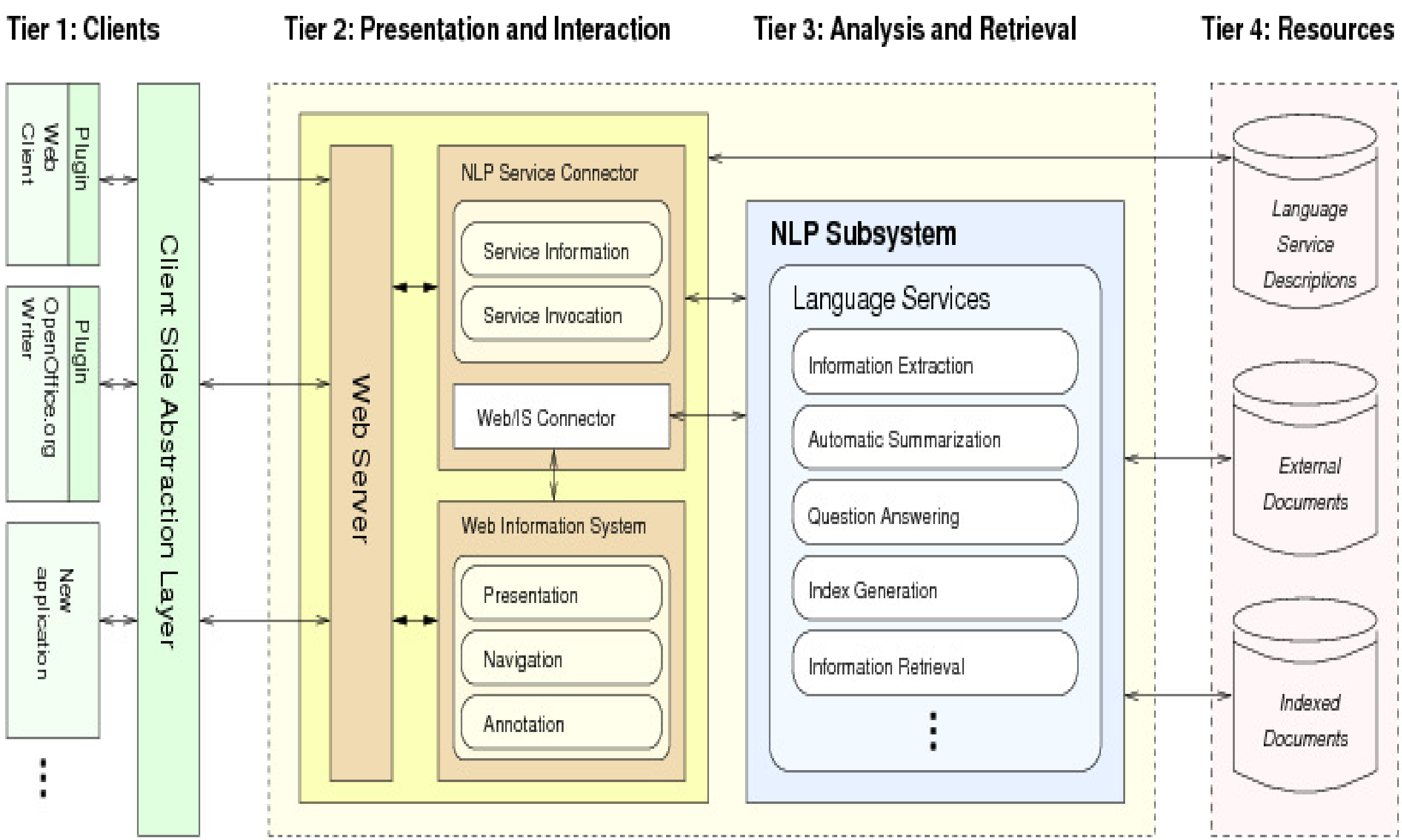


Semantic Desktop Assistant



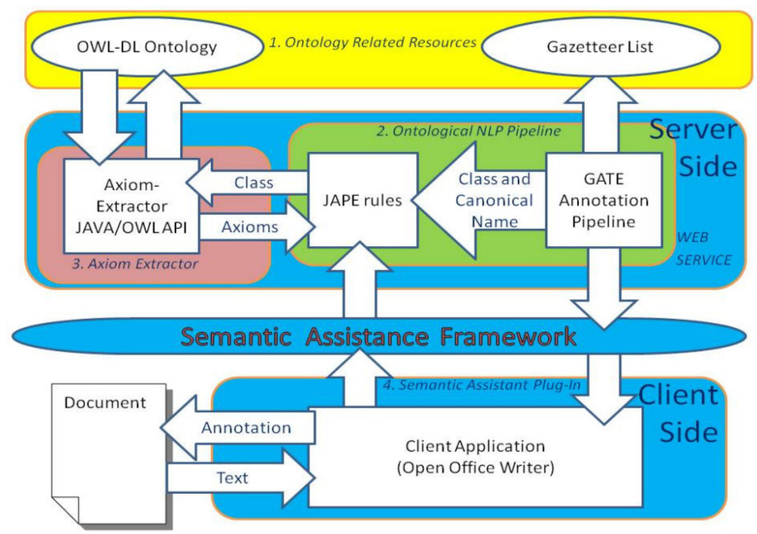
René Witte and Thomas Gitzinger.
Semantic Assistants – User-Centric Natural Language Processing Services for Desktop Clients.
3rd Asian Semantic Web Conference (ASWC 2008), February 2–5, 2009, Bangkog, Thailand.
Springer LNCS 5367, pp. 360–374. *(Acceptance rate: 31%)*

Semantic Assistant Framework

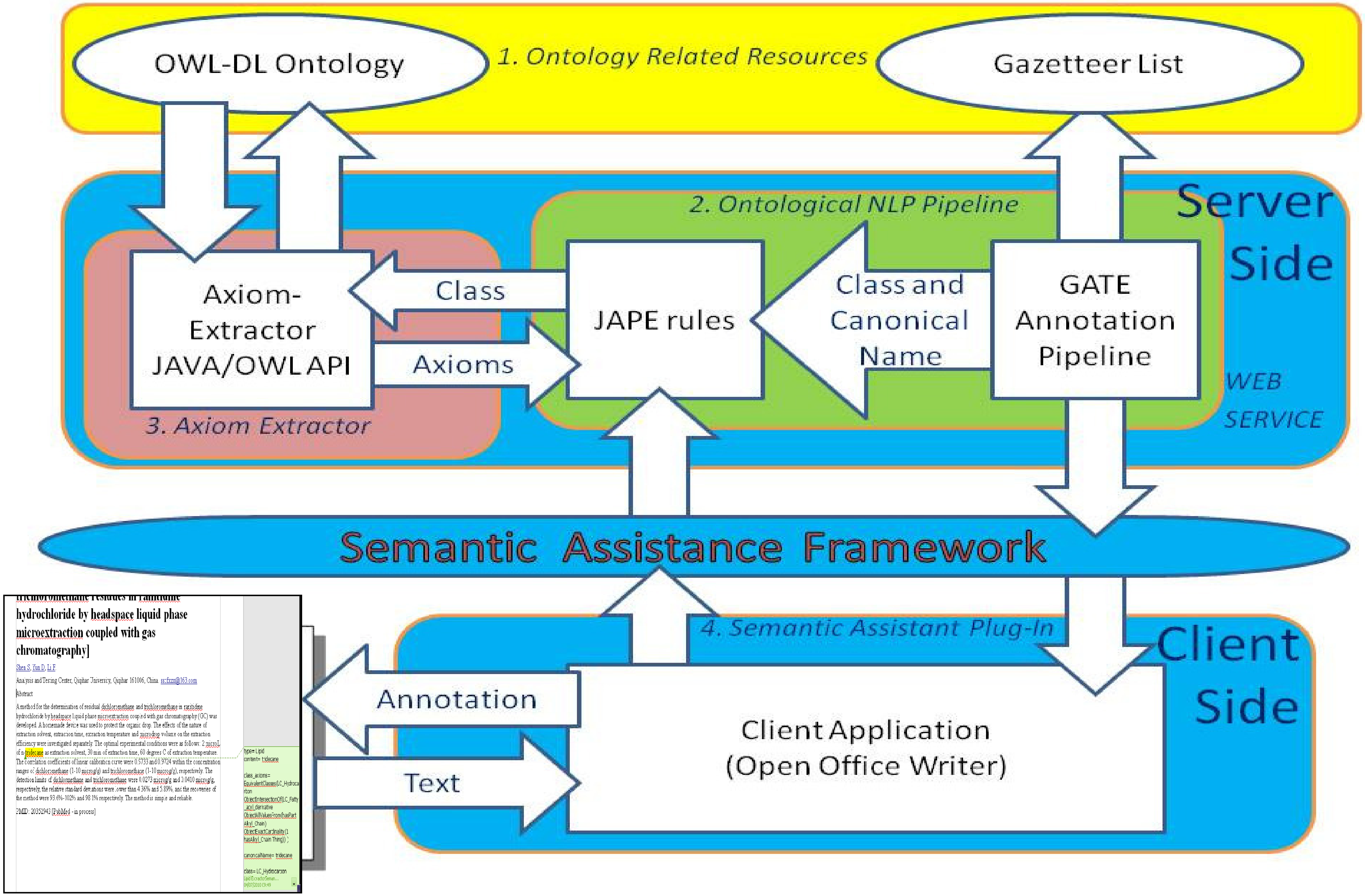


Core System Components

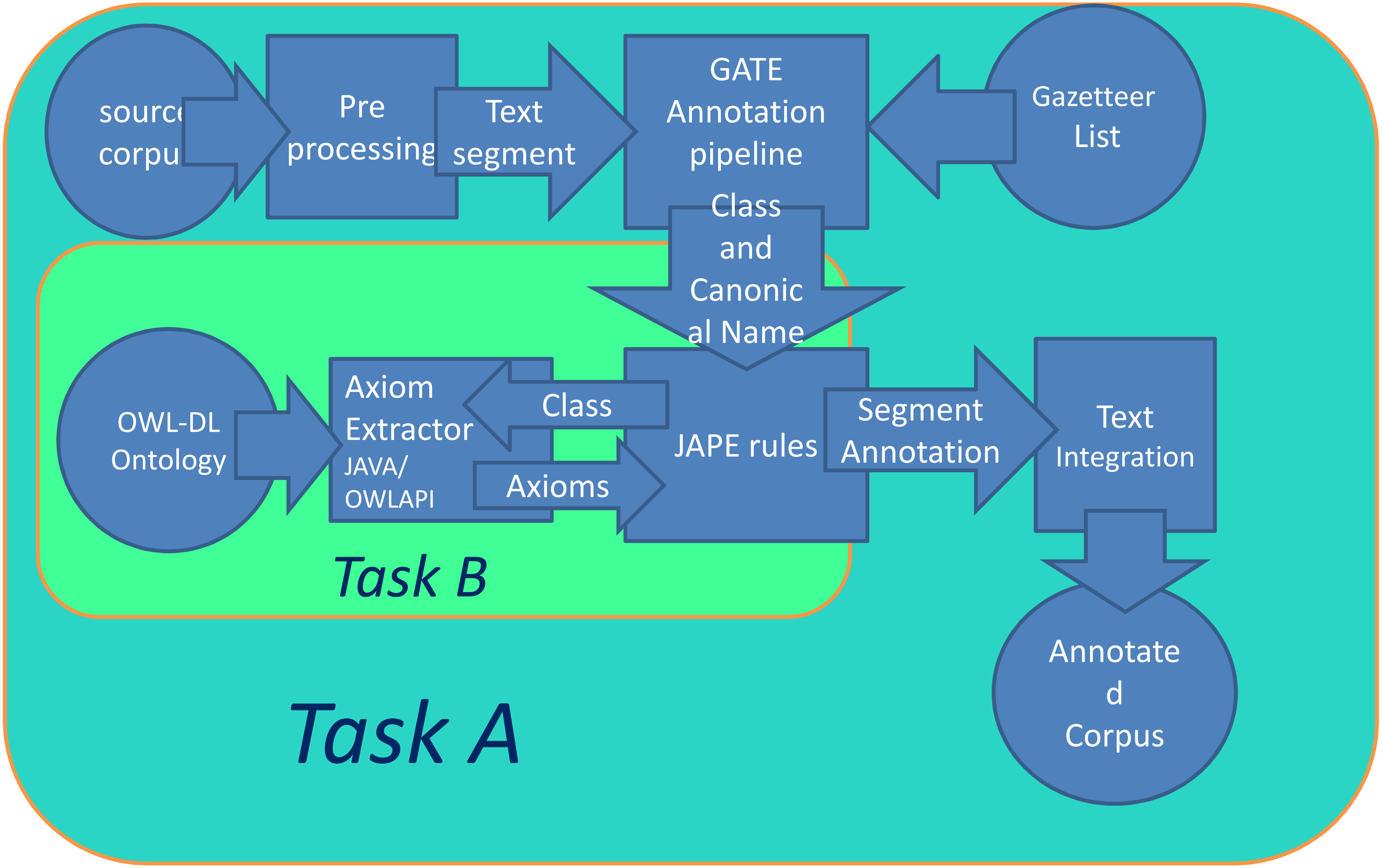
- OWL-DL Lipid Ontology
- Natural Language Processing (GATE/JAPE)
- Semantic Assistant Framework
- Ontology Axiom-Extractor



Online Annotation workflow

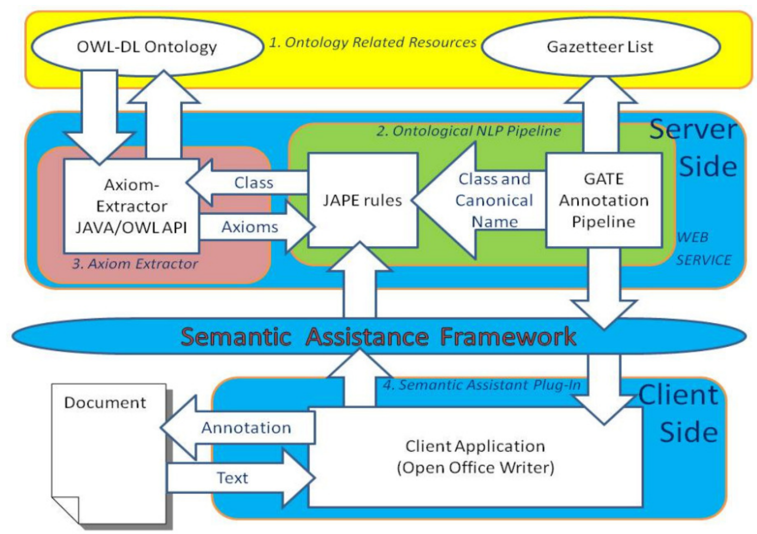


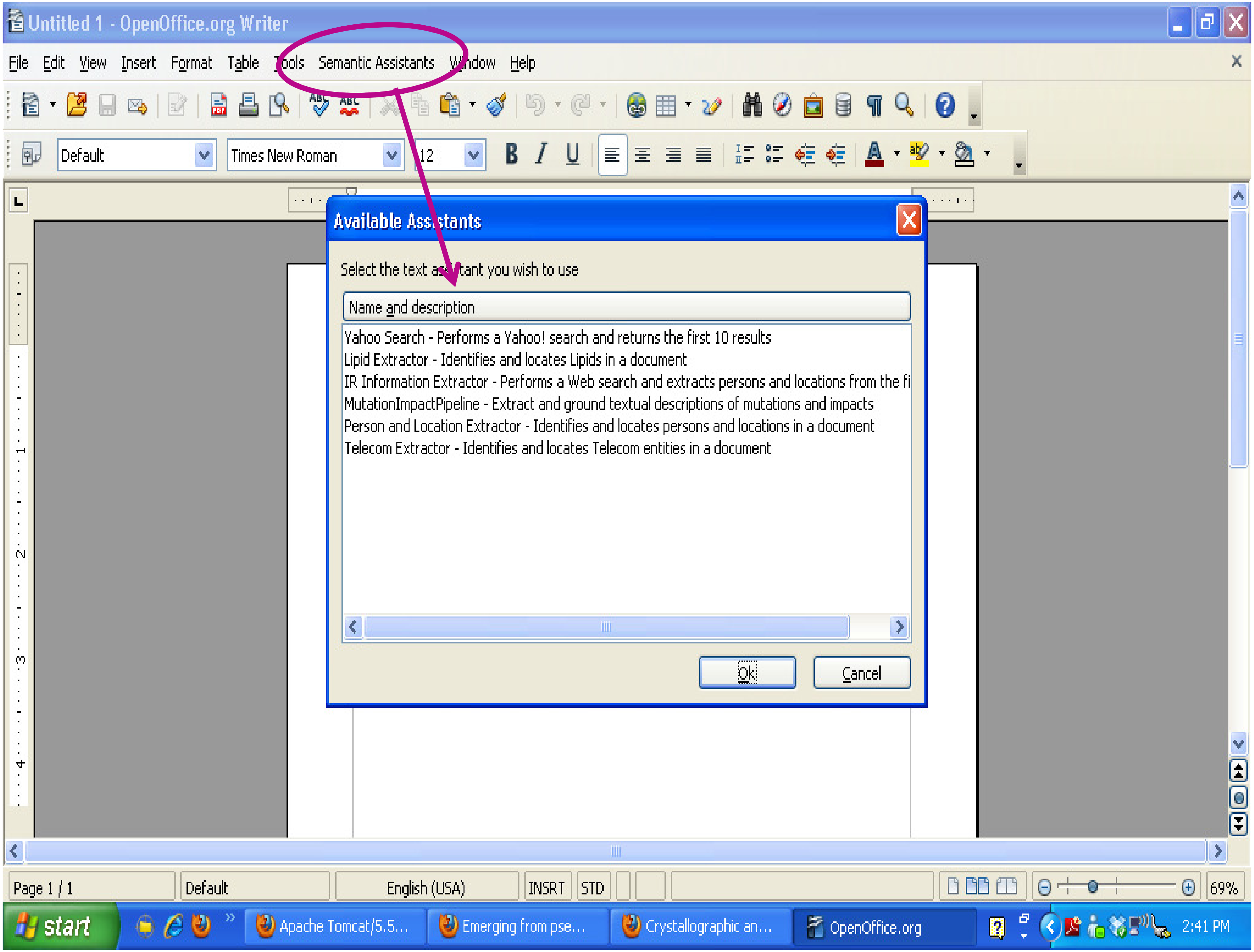
Offline Annotation Workflow

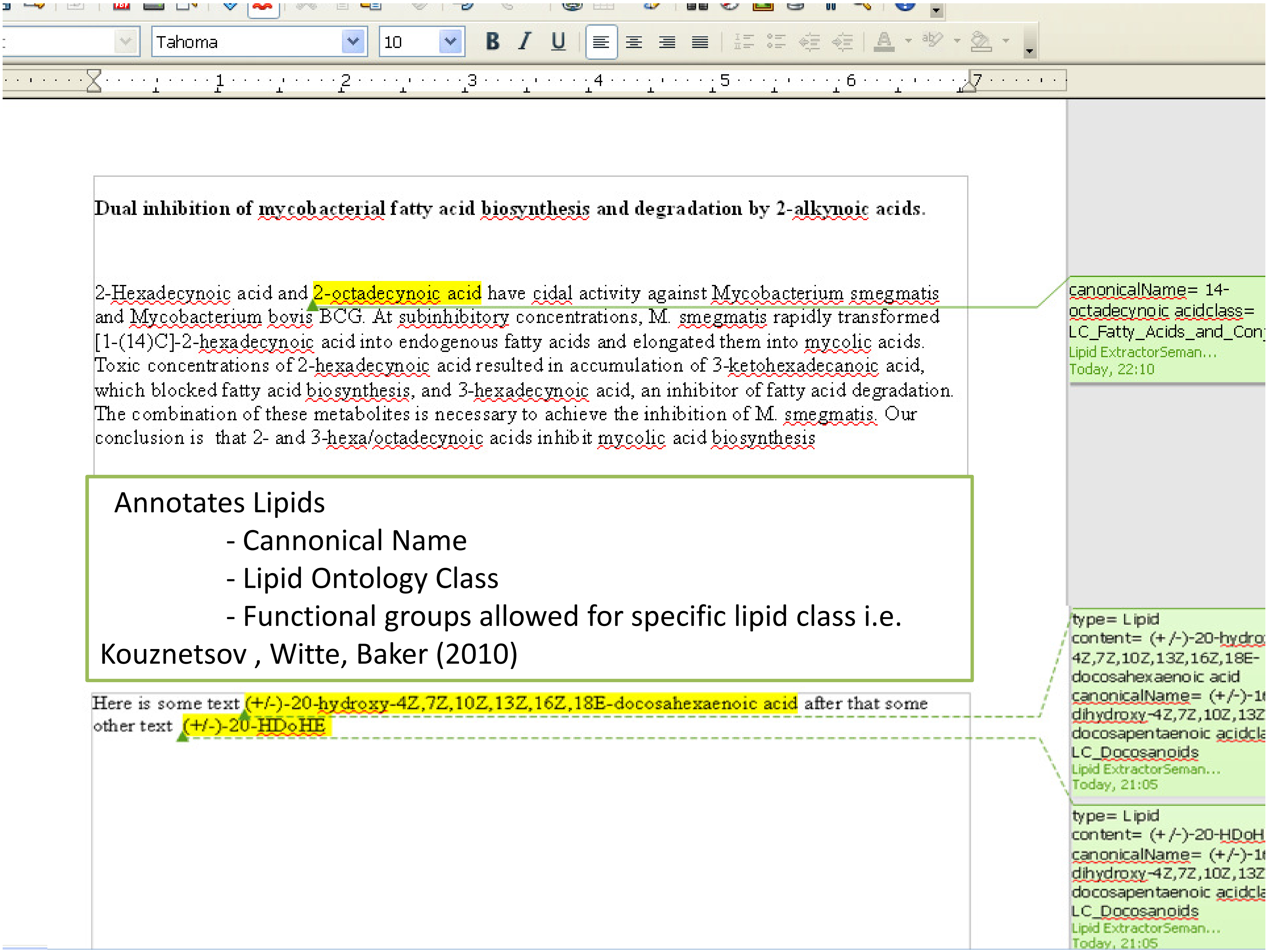


Core System Components

- OWL-DL Lipid Ontology
- Natural Language Processing (GATE/JAPE)
- Semantic Assistant Framework
- Ontology Axiom-Extractor
- Clients:
  - Open Office
  - Firefox




Untitled 1 - OpenOffice.org Writer
File Edit View Insert Format Table Tools Semantic Assistants Window Help
Available Assistants
Select the text assistant you wish to use
Name and description
Yahoo Search - Performs a Yahoo! search and returns the first 10 results
Lipid Extractor - Identifies and locates Lipids in a document
IR Information Extractor - Performs a Web search and extracts persons and locations from the fi
MutationImpactPipeline - Extract and ground textual descriptions of mutations and impacts
Person and Location Extractor - Identifies and locates persons and locations in a document
Telecom Extractor - Identifies and locates Telecom entities in a document
Ok
Cancel
Page 1 / 1
Default
English (USA)
INSRT
STD
69%
start
Apache Tomcat/5.5...
Emerging from pse...
Crystallographic an...
OpenOffice.org
2:41 PM



Annotates Lipids

- Cannonical Name
- Lipid Ontology Class
- Functional groups allowed for specific lipid class i.e.

Kouznetsov , Witte, Baker (2010)

Untitled 2 - OpenOffice.org Writer

[Determination of dichloromethane and trichloromethane residues in ranitidine hydrochloride by headspace liquid phase microextraction coupled with gas chromatography]

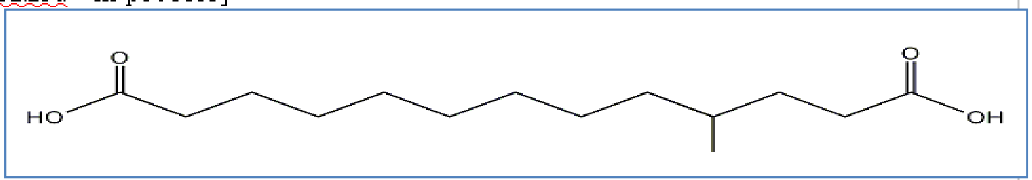
Shen S, Yun D, Li F.

Analysis and Testing Center, Qiqihar University, Qiqihar 161006, China. sscfxzx@163.com

Abstract

A method for the determination of residual dichloromethane and trichloromethane in ranitidine hydrochloride by headspace liquid phase microextraction coupled with gas chromatography (GC) was developed. A homemade device was used to protect the organic drop. The effects of the nature of extraction solvent, extraction time, extraction temperature and microdrop volume on the extraction efficiency were investigated separately. The optimal experimental conditions were as follows: 2 microL of n-tridecane as extraction solvent, 30 min of extraction time, 60 degrees C of extraction temperature. The correlation coefficients of linear calibration curve were 0.9733 and 0.9724 within the concentration ranges of dichloromethane (1-10 microg/g) and trichloromethane (1-10 microg/g), respectively. The detection limits of dichlormethane and trichloromethane were 0.0273 microg/g and 0.0410 microg/g, respectively, the relative standard deviations were lower than 4.36% and 5.89%, and the recoveries of the method were 93.6%-102% and 98.1% respectively. The method is simple and reliable.

PMID: 20352943 [PubMed - in process]



- Canonical Name
- Lipid Class
- Equivalent Class Axioms (Functional groups lipid classes)

type= Lipid
content= tridecane

class_axioms=
EquivalentClasses(LC_Hydrocarbon
ObjectIntersectionOf(LC_Fatty_acyl_derivative
ObjectAllValuesFrom(hasPart Alkyl_Chain)
ObjectExactCardinality(1 hasAlkyl_Chain Thing)))

canonicalName= tridecane
class= LC_Hydrocarbon
Lipid ExtractorSeman...
04/07/2010 09:49

Page 1 / 1 | Default | English (USA) | INSRT | STD | 204%

Migration to Firefox

1) Firefox
2) GreaseMonkey Plugin
3) Install Lipid SA service (Java Script / Tomcat)

Nature. 2009 Oct 29;461(7268):1287-91.

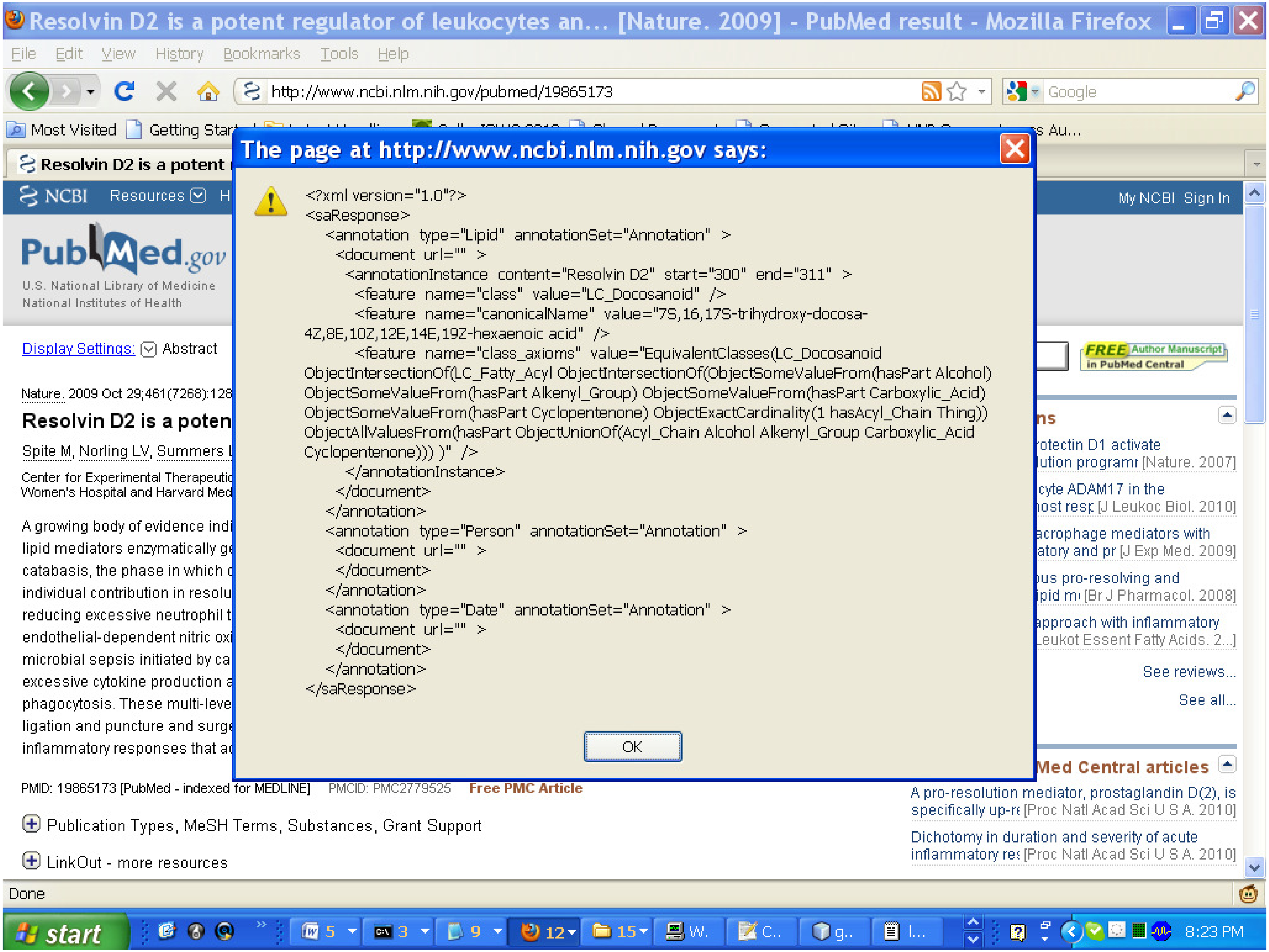
Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis.

Spite M, Norling LV, Summers L, Yang R, Cooper D, Petasis NA, Flower RJ, Perretti M, Serhan CN.

Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.

A growing body of evidence indicates that resolution of acute inflammation is an active process. Resolvins are a new family of lipid mediators enzymatically generated within resolution networks that possess unique and specific functions to orchestrate catabasis, the phase in which disease declines. Resolvin D2 (RvD2) was originally identified in resolving exudates, yet its individual contribution in resolution remained to be elucidated. Here, we establish RvD2's potent stereoselective actions in reducing excessive neutrophil trafficking to inflammatory loci. RvD2 decreased leukocyte-endothelial interactions in vivo by endothelial-dependent nitric oxide production, and by direct modulation of leukocyte adhesion receptor expression. In mice with microbial sepsis initiated by caecal ligation and puncture, RvD2 sharply decreased both local and systemic bacterial burden, excessive cytokine production and neutrophil recruitment, while increasing peritoneal mononuclear cells and macrophage phagocytosis. These multi-level pro-resolving actions of RvD2 translate to increased survival from sepsis induced by caecal ligation and puncture and surgery. Together, these results identify RvD2 as a potent endogenous regulator of excessive inflammatory responses that acts via multiple cellular targets to stimulate resolution and preserve immune vigilance.

PMID: 19865173 [PubMed - indexed for MEDLINE] PMCID: PMC2779525 **Free PMC Article**


Resolvin D2 is a potent regulator of leukocytes an... [Nature. 2009] - PubMed result - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://www.ncbi.nlm.nih.gov/pubmed/19865173
Google
Most Visited Getting Started
Resolvin D2 is a potent
NCBI Resources H
My NCBI Sign In
PubMed.gov
U.S. National Library of Medicine
National Institutes of Health
Display Settings: Abstract
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Nature. 2009 Oct 29;461(7268):128
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Spite M, Norling LV, Summers
Center for Experimental Therapeutic
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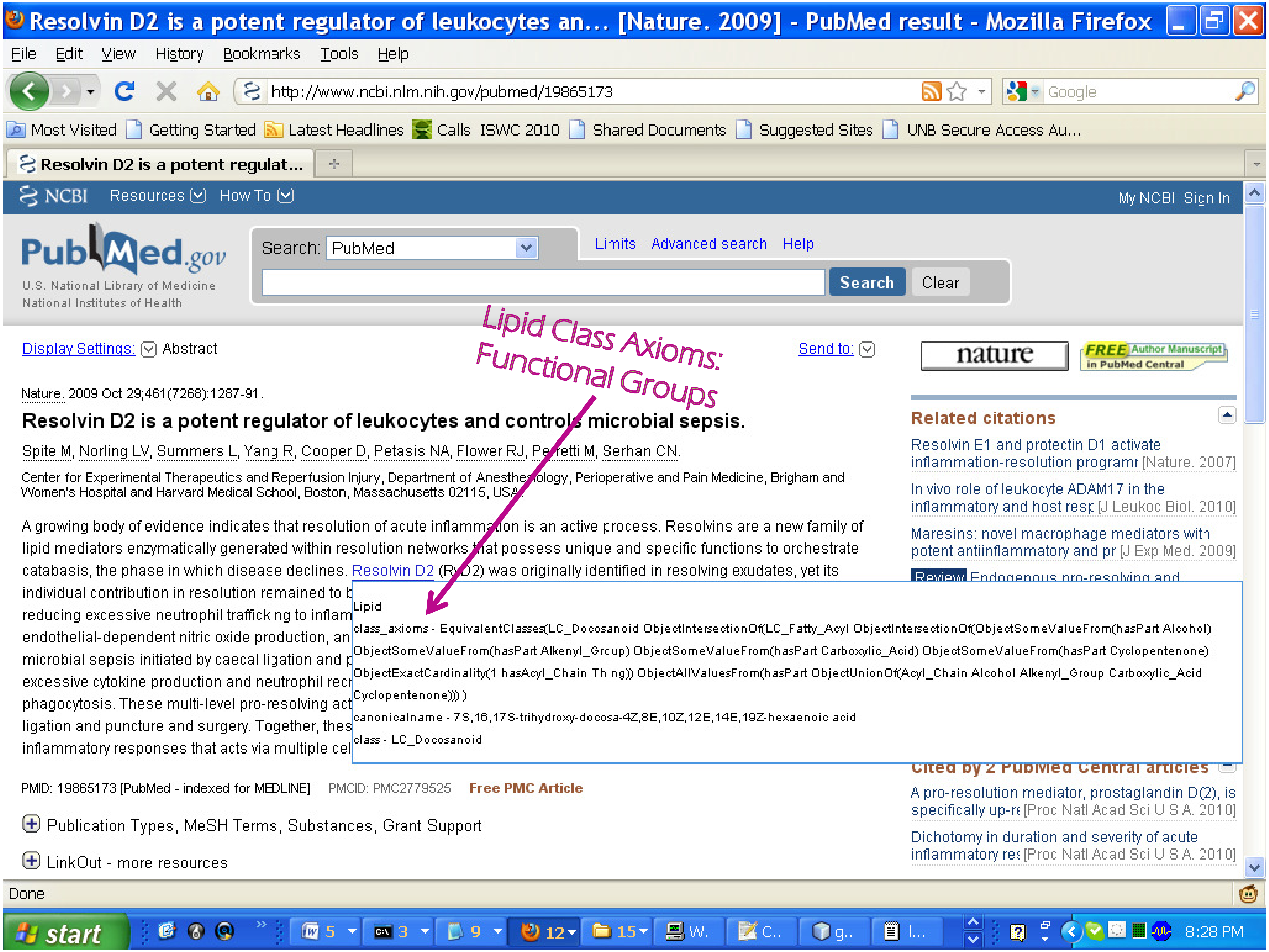
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Nature. 2009 Oct 29;461(7268):1287-91.
Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis.
Spite M, Norling LV, Summers L, Yang R, Cooper D, Petasis NA, Flower RJ, Perretti M, Serhan CN.
Center for Experimental Therapeutics and Reperfusion Injury, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.
A growing body of evidence indicates that resolution of acute inflammation is an active process. Resolvins are a new family of lipid mediators enzymatically generated within resolution networks that possess unique and specific functions to orchestrate catabasis, the phase in which disease declines. Resolvin D2 (RvD2) was originally identified in resolving exudates, yet its
individual contribution in resolution remained to b
reducing excessive neutrophil trafficking to inflam
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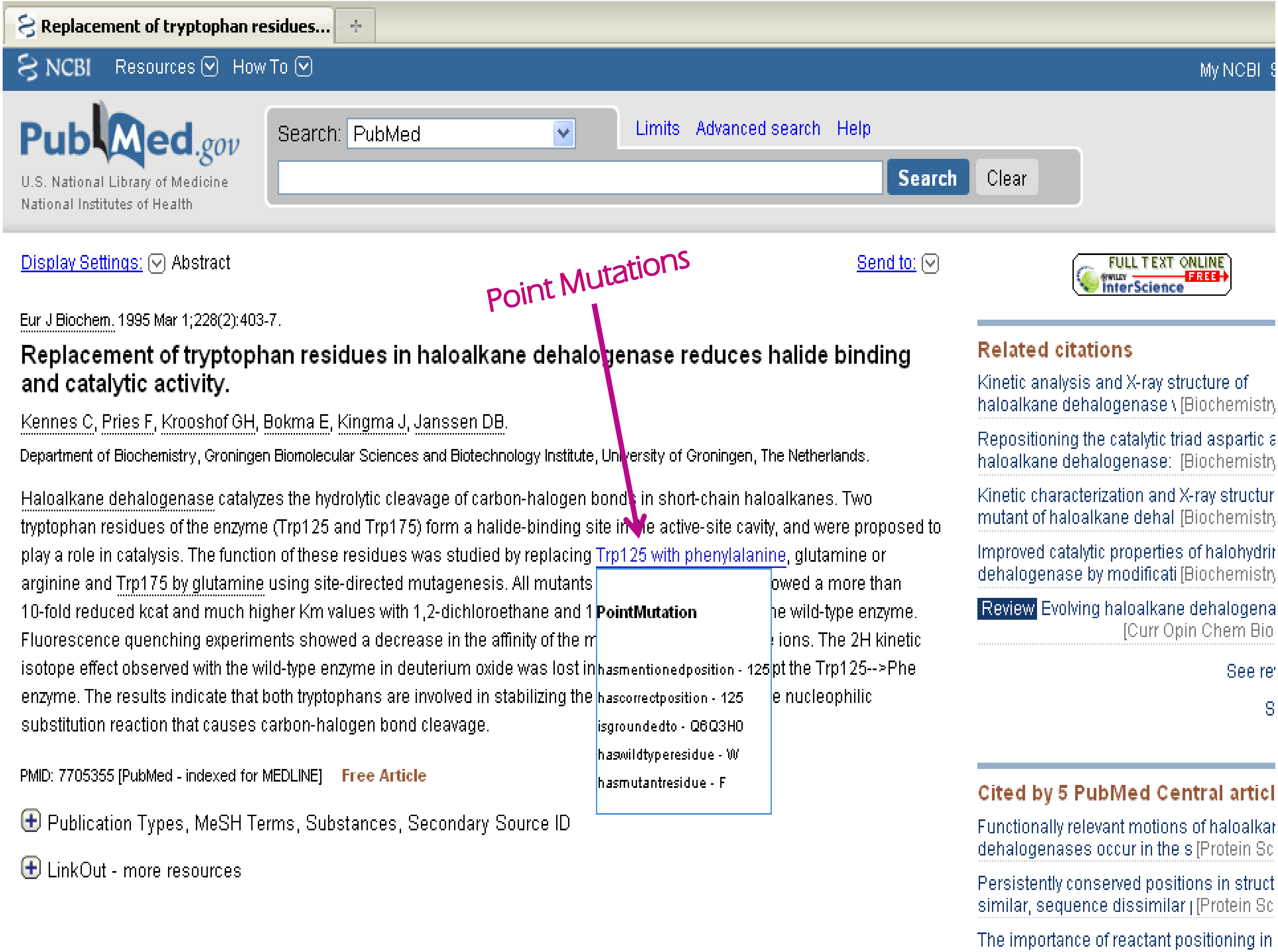

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Eur J Biochem. 1995 Mar 1;228(2):403-7.

Replacement of tryptophan residues in haloalkane dehalogenase reduces halide binding and catalytic activity.

Kennes C, Pries F, Krooshof GH, Bokma E, Kingma J, Janssen DB.

Department of Biochemistry, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, The Netherlands.

Haloalkane dehalogenase catalyzes the hydrolytic cleavage of carbon-halogen bonds in short-chain haloalkanes. Two tryptophan residues of the enzyme (Trp125 and Trp175) form a halide-binding site in the active-site cavity, and were proposed to play a role in catalysis. The function of these residues was studied by replacing Trp125 with phenylalanine, glutamine or arginine and Trp175 by glutamine using site-directed mutagenesis. All mutants ... owed a more than 10-fold reduced kcat and much higher Km values with 1,2-dichloroethane and 1 ... he wild-type enzyme. Fluorescence quenching experiments showed a decrease in the affinity of the m ... ions. The 2H kinetic isotope effect observed with the wild-type enzyme in deuterium oxide was lost in ... pt the Trp125-->Phe enzyme. The results indicate that both tryptophans are involved in stabilizing the ... e nucleophilic substitution reaction that causes carbon-halogen bond cleavage.

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Biochemistry. 1999 Sep 14;38(37):12052-61.

Crystallographic and kinetic evidence of a collision complex formed during halide import in haloalkane dehalogenase.

Pikkemaat MG, Ridder IS, Rozeboom HJ, Kalk KH, Dijkstra BW, Janssen DB.

Laboratory of Biochemistry, BIOSON Research Institute, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, The Netherlands.

Haloalkane dehalogenase (DhlA) converts haloalkanes to their corresponding alcohols and halide ions. The rate-limiting step in the reaction of DhlA is the release of the halide ion. The kinetics of halide release have been analyzed by measuring halide binding with stopped-flow fluorescence experiments. At high halide concentrations, halide import occurs predominantly via the rapid formation of a weak initial collision complex, followed by transport of the ion to the active site. To obtain more insight in this collision complex, we determined the X-ray structure of DhlA in the presence of bromide and investigated the kinetics of mutants that were constructed on the basis of this structure. The X-ray structure revealed one bromide ion firmly bound in the active site and two bromide ions weakly bound on the surface of the enzyme. One of the weakly bound ions is close to Thr197 and Phe294, near the entrance of the earlier proposed tunnel for substrate import. Kinetic analysis of bromide import by the Thr197Ala and Phe294Ala mutants of DhlA at high halide concentration showed that the rate constants for halide binding no longer displayed a ...ncrease with increasing bromide concentrations. This is in agreement with an elimination or a ... surface-located halide-binding site. Likewise, chloride binding kinetics of the mutants indicated ...ith wild-type enzyme. The results indicate that Thr197 and Phe294 are involved in the formation of an ...or halide import in DhlA and provide experimental evidence for the role of the tunnel in substrate and

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- Quebec -New Brunswick University Co-operation in Advanced Education - Research Program, Government of New Brunswick, Canada
- NSERC Discovery Grant, Canada 2009