"Large-Scale Information Extraction for Biomedical Modelling and Simulation"



Martin Hofmann-Apitius

Head of the Department of Bioinformatics Fraunhofer Institute for Algorithms and Scientific Computing (SCAI)

Fraunhofer Society



- Founded 1949
- Europe's largest applied research organisation
- 60 Research Institutes
- 17.000 Employees
- Annual Budget about 1,5 Billion Euro
- Financial model: 40 % industry collaborations 40 % public funding 20 % institutional funding

Seite 2

*Joseph von Fraunhofer (1787 – 1826) Scientist, Inventor and Entrepreneur



Fraunhofer-Campus Schloss Birlinghoven

Institutes

- Algorithms and Scientific Computing SCAI
- Intelligent Analysis and Information Systems IAIS
- Applied Information Technology FIT

600 Scientists, 200 Students Linked to Universities Bonn, Aachen and Cologne







Fraunhofer: Applied Research for Industrial Applications

Fraunhofer stands for:

- sustainable (applied) research
- focus on contract research and innovation
- bridging between excellent academic research and industrial application
- clear mission towards improving and fostering innovation
- research done with the idea in mind to generate added value in a commercial sense

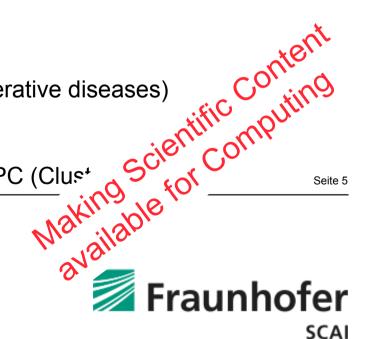
Seite 4



SCAI Department of Bioinformatics: R&D in a nutshell

Fraunhofer SCAI Department of Bioinformatics R&D activities:

- Information extraction in the life sciences: 1
 - Text Mining Recognition of named entities & relationships in text Ι.
 - Image Mining Reconstruction of chemical information from chemical Ш. structure depictions
- Disease modelling (focus on neurodegenerative diseases) 2.
- eScience, Grid-/Cloud- Computing and HPC (Clust 3.



People

Fraunhofer SCAI Department of Bioinformatics currently comprises:

- 10 scientists
- 2 scientific software developers
- 6 PhD students
- > 6 Master students
- predominantly computer scientists & biologists
- additional scientists and PhD students via University of Bonn



The History of High Performance Computing in BioMedicine at SCAI: Once upon a time

Seite 7







- WISDOM stands for Wide In Silico Docking on Malaria
 - Goals
 - Computational goals
 - To show the relevance of computational grids in biomedical applications
 - Biological goals
 - Risk of Malaria, Post genomic era, number of targets, Finding new compounds in a cost effective way
 - Method establishment
 - Establishing virtual screening technology on computational grids



- WISDOM-I: First large scale docking against plasmepsin on computational grids
 - Achievements:
 - 80 CPU years in 45 days (Computational side)
 - Identified three novel scaffolds (biological side)
 - Docking on grids (Method establishment)
- WISDOM-II: Second assault on 4 different proteins (DHFR; Tubulin; two different Plasmepsins) implicated in malaria
 - Achievements:
 - 413 CPU years in 90 days (Computational side)
 - Result analysis is in progress (biological side)
 - Docking on grids (Method improved)

Strategies in result analysis

Results based on Scoring

BioinfoGRID

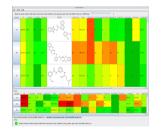
Bioinformatics Grid Application for life science

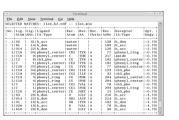
Results based on match information

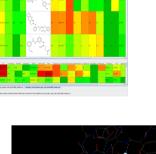
Results based on consensus scoring

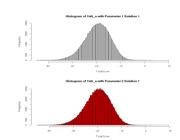
Results based on different parameter settings

Results based on knowledge on binding site

















VS Explorer: a Tool for Analyzing "Grid Scale" Ranking Lists

ile <u>T</u> able <u>I</u>				400.5	mainWindov		144				=)=)×)						
	/groupshare/dcp				mainWindow =												
Number	SMILES	name	scenario1 s	scenarioz	Eile Iable Help												
					/home/bi	o/groupshare/d	prep/dcprep_res	ilts/paran	n.csv: 400 R	ows			4				
					Number	SMILES	name	scenario:	l scenario2	scenario3	scenario4	scenario5	scenario	6 scenario	7 scenario	8 scenarios	9 scenario10
					25		ZINC00603011	-28.92	-29.88	-28.66	-28.08	-27.14	-28.66	-28.08	-28.91	-28.92	-29.88
					26	и и и и и и и и и и и и и и и и и и и	ZINC00605829	-19.20	-17.29	-19.49	-24.32	-20.74	-19.49	-24.32	-19.20	-18.66	-17.29
					27		ZINC00606383	-9.60	-8.35	-10.59	-12.48	-10.59	-10.45	-12.19	-10.45	-10.45	-8.35
Focus: Number 62	SMILES na		01 scenario2	2 scenario	28		ZINC00607811	+00.01	+00.01	+00.01	+00.01	+00.01	+00.01	+00.01	+00.01	+00.01	+00.01
02	Ja. ZINCO		2.02.1	100.01	Focus:												
63		062 +00.01	-15.52	+00.01	Number	SMILES r	ame scenario	l scenar	io2 scena	rio3 scena	rio4 scena	urio5 scer	nario6 so	cenario7	scenario8	scenario	9 scenario:
	0.0				398	1ab	e_ara -13.80	-13.64	-13.55	-14.66	-13.55	5 -13.5	55 -14	4.63 -	13.80	-13.80	-13.64
64		0 <mark>62</mark> -35.64	-37.31	-37.16	399		o_min -6.48	-6.55	-6.27	-6.55	-7.04	-7.04	4 -6.	.34 -	7.04	-7.04	-6.51
_	idgeE_97654_sol	l.csv param.o	sv		400	ر مرکب 1tm	n -18.78	-18.10	-17.50	-19.67	' -16.91	L -16.9	91 -1	9.67 -	19.34	-20.34	-17.95
load	led /home/bio/g	roupshare/dcr	rep/dcpren_r	esults/para	•												
	,, .			, pur	1lee_chem Info:	bridgeE_97654_s aded /home/bio	ol.csv param.cs /groupshare/dcpi) results/na	iram.csv							



Achievements

Completed the screening of 4.3 million compounds against four different targets

- Identified more than 200 new "interesting chemical scaffolds" that have been tested in "wet lab assays"
- Validated biological activity of 13 novel "virtual screening hits"
- Submitted patents for 4 new compounds / scaffolds

Lessons Learned from WISDOM and other Workflows

- 1. Infrastructures such as EGEE (EGI) can be productively used for *in silico experimentation* in biomedicine
- Post-Processing (searching where the data have been stored; which jobs have been successfully finished) of generated data (docking results) took much more time than simulating the ligand-target interaction
- 3. Support of complex workflow design and workflow optimisation in compute infrastructures is still a challenge

Seite 13





Scientific Workflow Optimization on the Grid

Sonja Holl

Jülich Supercomputing Centre (JSC) Institute for Advanced Simulation (IAS) Forschungszentrum Jülich, Germany





Motivation

- Scientific workflows have many parameters
- Optimal settings not known a priori and data dependent
- Often several methods for the same task are available
- Parameters have constraints and non-linear dependencies
- Testing many parameter settings requires HPC
- Currently try and error based optimization, lack of tools
- Our primary goal: Optimizing the *quality* of a scientific workflow



Workflow Optimization

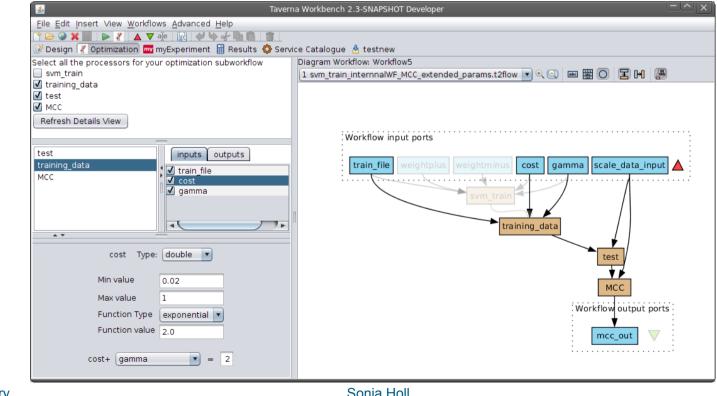
Find workflow settings that optimize the output quality

- Identify user requirements (Parameter, Constraints)
- Optimize relevant parts of a workflow
- Parameter optimization, Component set optimization
- Measure output quality (Fitness Function, User Feedback)
- Use the Grid to speed up optimization (UNICORE Grid middleware)



The UNICORE Taverna Optimization Plugin

- Easy, GUI-based setup of WF and optimization tasks
- Plugin enables optimization within Taverna WFMS
- Parallel execution of WF optimization runs via UNICORE
- Link to major biomedical in silico labs (caBIG; myExperiment)





Workflow Optimization – Techniques 1/2

Find optimal input parameters for WF applications

- Varying free application parameters
- Realized via evolutionary algorithm (JGAP-Framework)

Advanced Parameter Optimization

- Dependent parameters
 - Discrete set of parameter values (files, flags, integer)
 - Dependencies: Fixed combinations, Mathematical dependency, Logical dependency



Workflow Optimization – Techniques 2/2

Component Set Optimization:

- Replace tool or algorithm with an equivalent one
- What is "equivalent"?
- Ontologies for tasks, inputs, and outputs required

Future work

- Workflow structure optimization
- Adaptive optimization learning from community runs
- Supervised optimization User feedback as fitness function

Linking Methods and Algorithms to Scientific

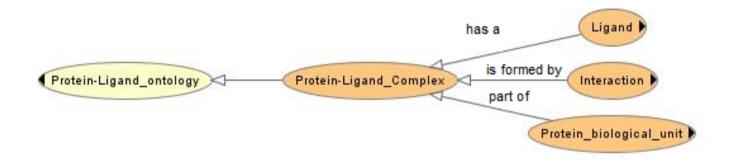
Objectives and Knowledge

The PLIO Ontology

Seite 20



PLIO root concepts (total concepts: 371)



- PLIO concept coverage
 - **<u>Biophysical forces</u>**, e.g. Van der Waals, electrostatics, etc.
 - **Interaction descriptors** e.g. pharmacophore, interaction fingerprint, etc.
 - **Experimental techniques,** e.g. NMR, X-ray, etc.
 - **Prediction and simulation methods,** e.g. MD, docking, etc.
 - **<u>Classification of ligand activities</u>**, e.g. biological activity, binding activity, etc.
 - **Classification of ligand modes of action**, e.g. agonist, inhibitor, etc.
 - **<u>Classification of binding sites</u>**, e.g. allosteric site, orthosteric site, etc.
 - Structure-Activity-Relationships, e.g. QSAR, COMFA, etc.



Each Concept has:

Reference

"http://www.shodor.org/chemviz/glossary.html"

Synonym

"activation energy Energy of activation Arrhenius activation energy activation barrier activation barriers E(a)"

formula

"k=Aexp(-Ea/RT)

- Ea activation energy (Arrhenius activation energy)
- k rate constant
- A the pre-exponential factor or simply the prefactor
- R the gas constant
- T tempreture"

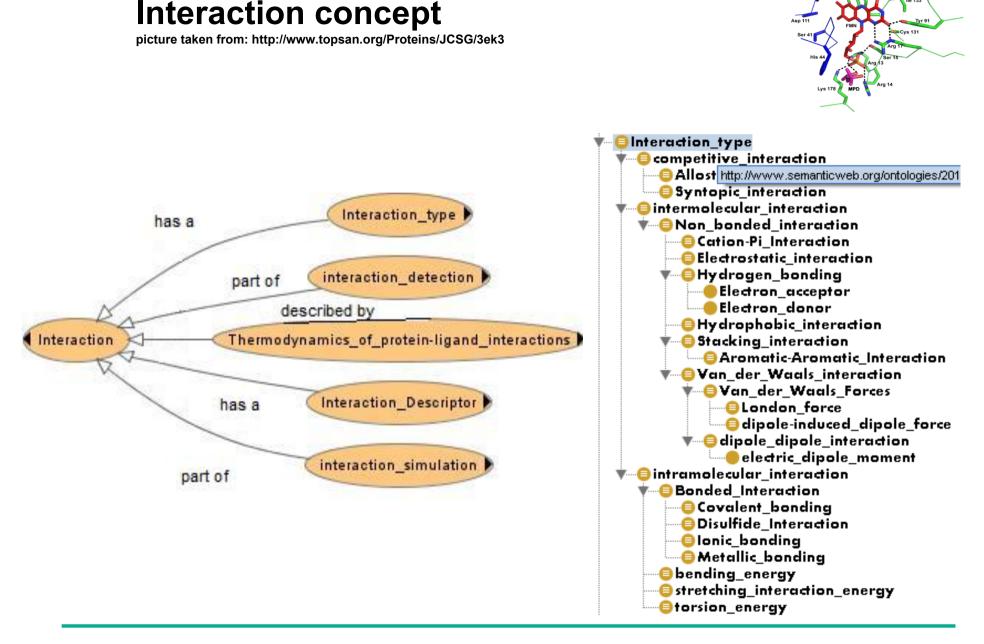
software

"Activation energy Arrhenius calculation from two temperatures. http://www.calctool.org/CALC/chem/kinetics/act_en

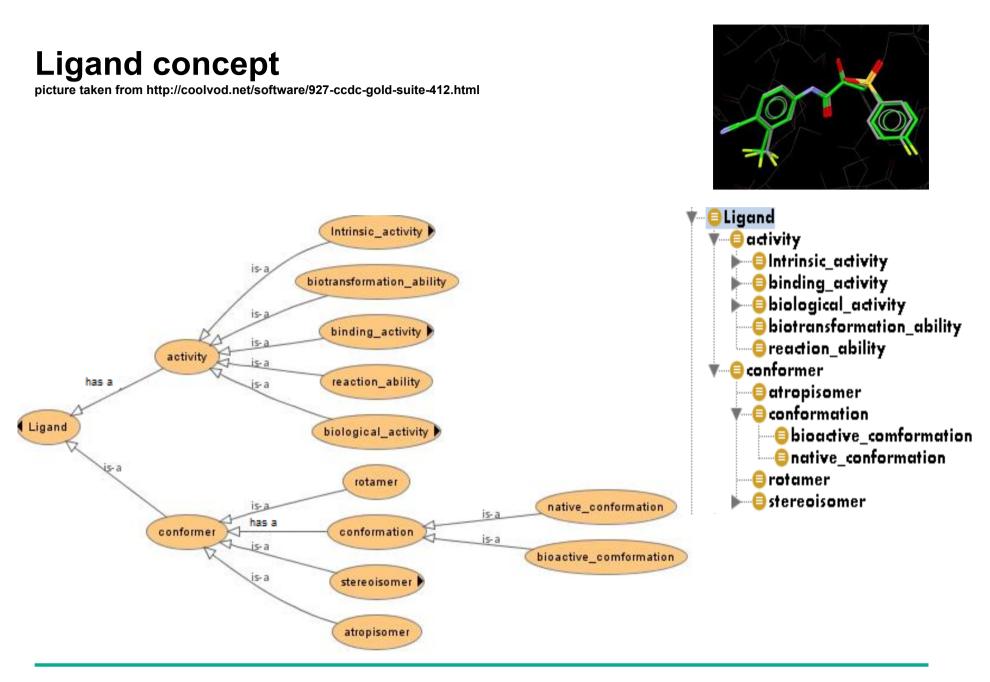
isDefinedBy

"Activation energy can be thought of as the height of the potential barrier separating two minima of potential energy (of the reactants and products of a reaction). For a chemical reaction to proceed at a reasonable rate, there should exist an appreciable number of molecules with energy equal to or greater than the activation energy.

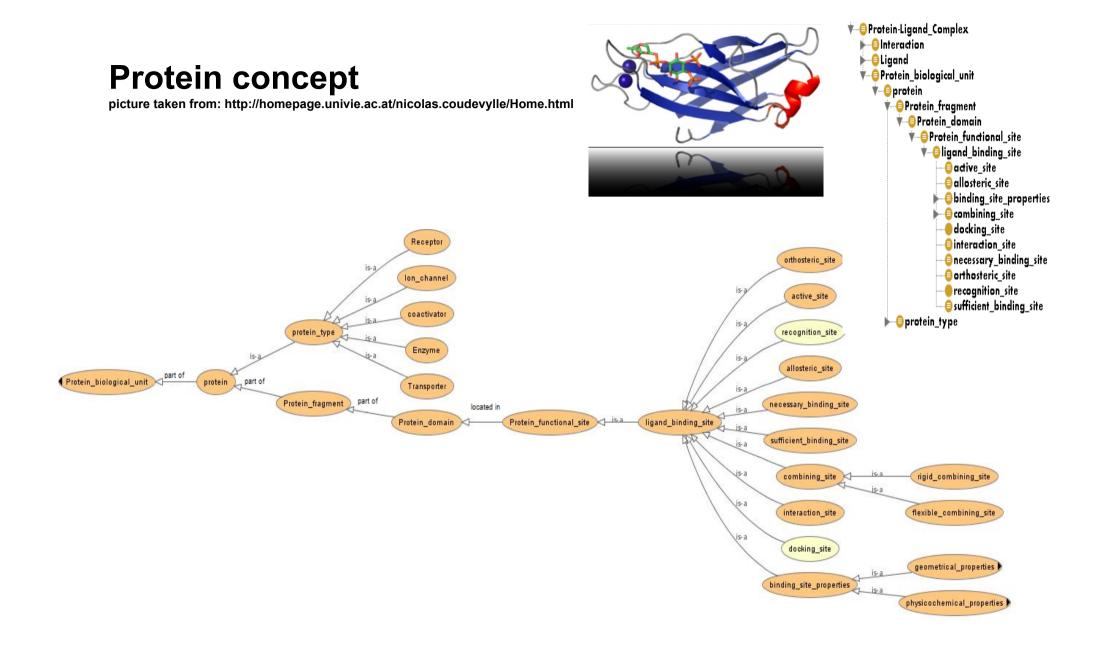














Productive Use of Large Compute Infrastructures

High Throughput Extraction of Scientific Information from Full Text Sources:

The UIMA-HPC Project

Seite 26



GEFÖRDERT VOM



Bundesministerium für Bildung und Forschung



Efficient Information Extraction Workflows in many-core environments











Vision

Scientific Challenge:

The knowledge in Chemistry, Biology and Pharmaceutical Sciences growths with impressive speed. As a result, the number of publications in these areas is reaching unparalleled dimensions. However, knowledge is being communicated in non-standardised ways.

Relevant knowledge sources are not well standardized, let alone is the knowledge structured. This limits the ability to query knowledge sources.

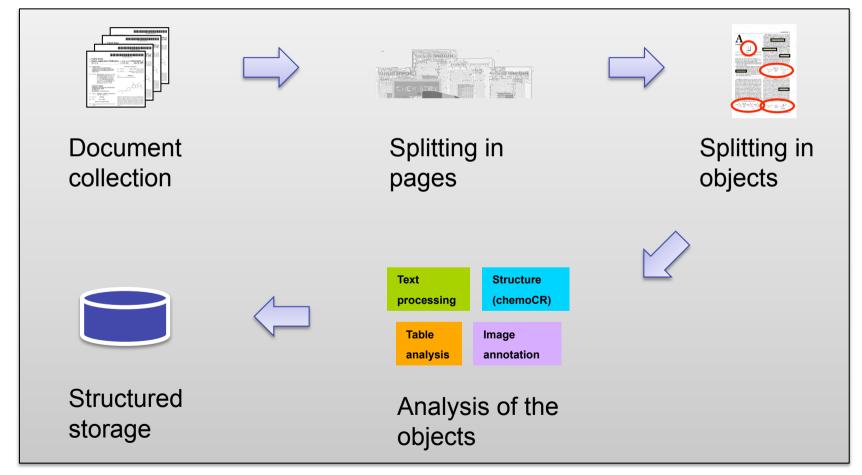
Problem-solving approach:

Development of technology that – based on HPC – allows for high throughput extraction of structured information from unstructured knowledge sources

Structured Knowledge

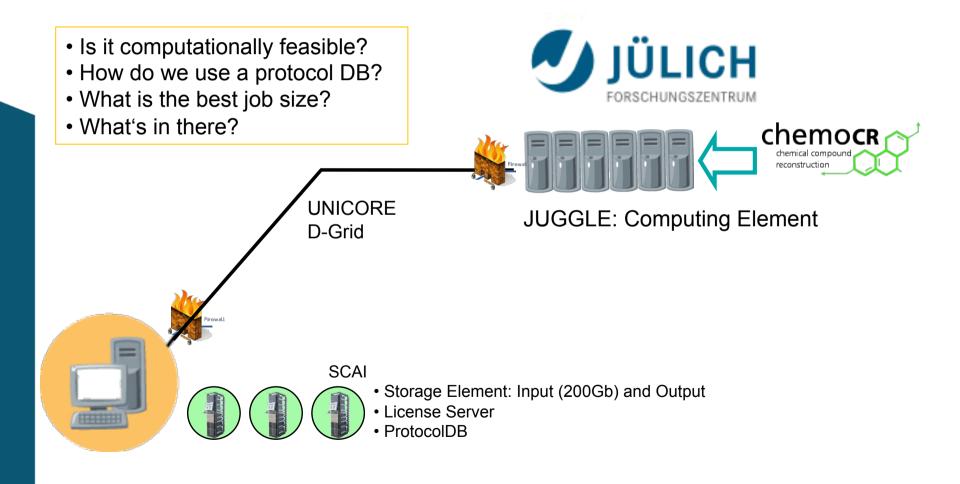


Use case scenario: automatic patent structuring





Previous study: The grand patent challenge 2009





Technical Issues and Pitfalls

- User accession rights (files, scheduler, installed tools and libs, ...)
- Firewall (ports: MySQL, denial of service attack, time outs, ...)
- Missing files (NFS down, package lost, not installed, ...)
- Too many requests on license server
- Too many connections in database
- Ressources (reservation, priorities, ...)



UIMA AS in the context of HPC

Support of many-core architecture

- several instances of a service
- eff. usage of shared memory (JVM)
- asynchronous execution

Support of clusters

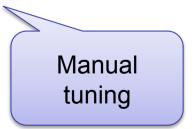
- several remote services (eg SOAP)
- communication via JMX and http





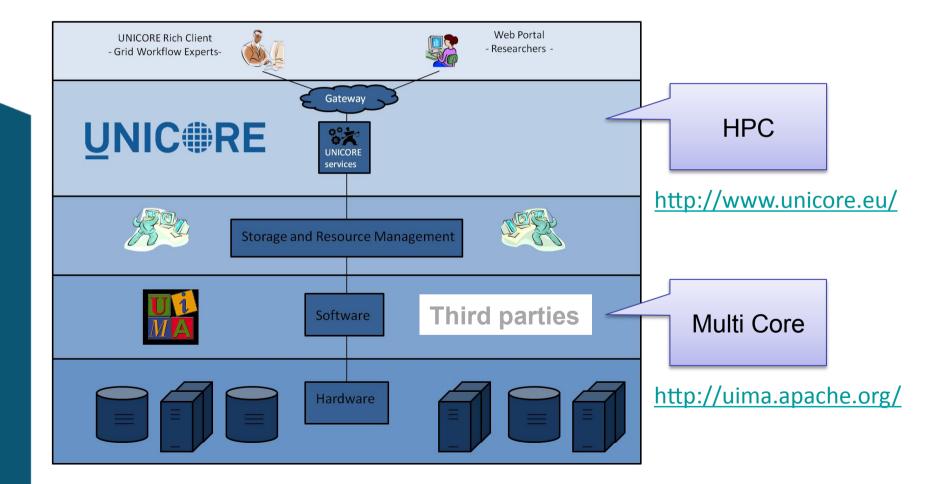
Control via pre-configured parameters

- CAS pool size
- casMultiplier poolSize
- . . .



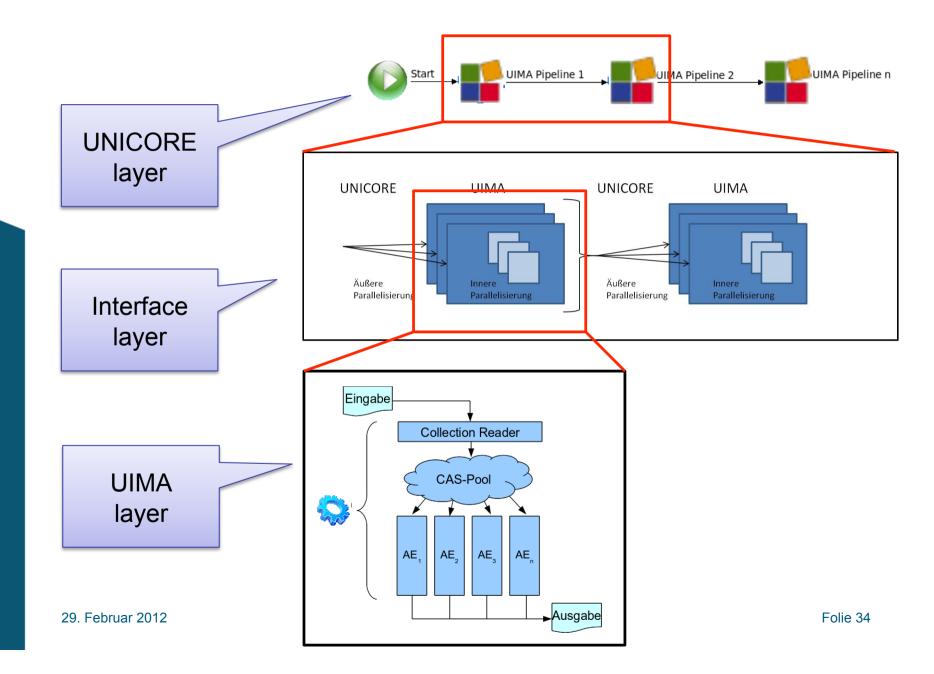


Problem-Solving Approach



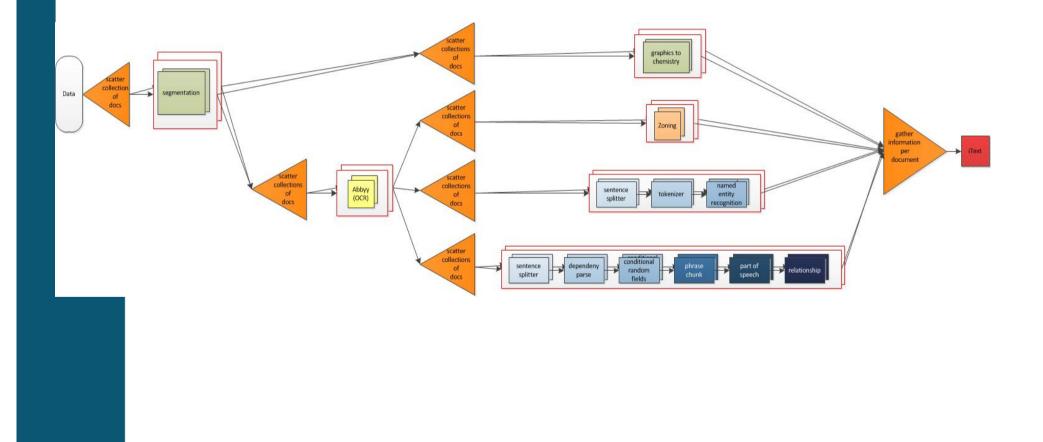
System Architecture

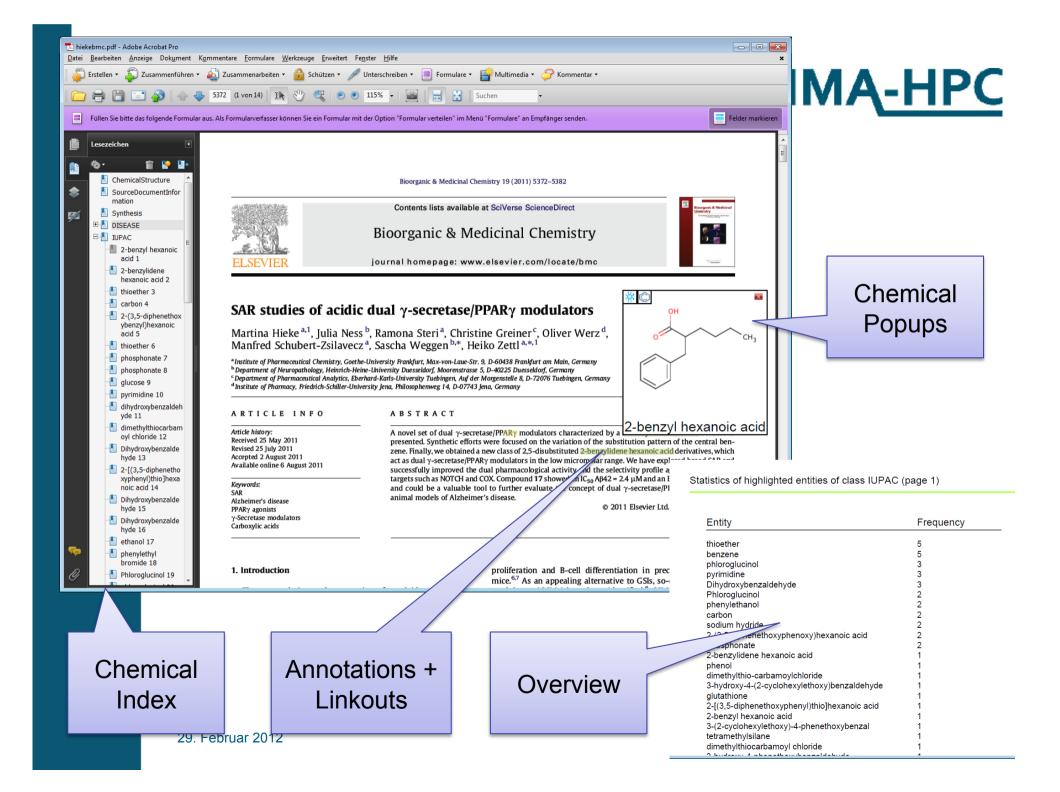
UIMA-HPC





First Prototype: PDF Annotation of Patents





Direct Usage of Unstructured Information

Sources for Disease Modelling

From Medline Mining

to

Modelling Neurodegenerative Diseases



Why Modelling of Neurodegeneration?

- In 2009 the Federal Government of Germany decided to start a new research centre that focuses on translational research on neurodegenerative diseases. In fact, neurodegenerative diseases (Alzheimer, Parkinson, Multiple Sclerosis; Epilepsy; "rare" NDDs)
- The total costs of Alzheimer is estimated to exceed 20 trillion US\$ in the US in the years between 2020 2050. (source: Alzheimer.org). Current costs / year in the US (according to Alzheimer.org): **183 billion US\$**
- The incidence rate of Alzheimer and other dementias is almost 50% in the population older than 85 years. Next generation will regularly have a life span of >100 years.



The Starting Conditions

What we have:

- An ontology capturing relevant knowledge on Alzheimer's Disease (ADO)
- An ontology representing and integrating brain regions and cell types (BRCO)
- A method for the automated identification of hypotheses in text based on regular expressions
- An excellent machinery for biomedical text mining (ProMiner) with top performing gene and protein name recognition



Alzheimer's Disease Ontology (ADO)

Alzheimer's ontology:

- Captures more than 700 classes/ concepts
- □ BFO already implemented



Brain Region and Cell-type Ontology (BRCO)

₩		Synonym	
Thing		"Substantia nigra dopaminergic cell,Nigral dopaminergic cell"	96
Domain_entity			-
lndependent_entity		reference	0
▼ ● Nervous_system		"http://neurolex.org/wiki/Category/Substantia_nigra_pars_compacta_dopaminergic_cell"	
Vervous_System	n_Cell	is DefinedBy	
▶ ● Neural		"Nigral dopaminergic cell is a neuron found in the midbrain of vertebrates. These neurons comprise most of the substantia nigra	
🕨 😑 Non-Neural		and mainly regulate motor and sensorimotor functions within the brain.	
🔻 🤤 Regional_part_c			
Peripheral_n		Description	
	part_of_peripheral_nervous_system	Description:	
Nerve_part_of_peripheral_nervous_system		Soma Location: Substantia nigra pars compacta	
🛌 🛑 autonomatic		Spine density on dendrites: Aspiny Dendrite Quality	
<pre> * central_nervo </pre>	ous_system		
▼ Brain		Axon Specific Properties	
	ry_structures	Axon projection laterality: ipsilateral Location of axon arborization: Neostriatum	
	al_part_of_brain	Cellular synarborization. Neostriatum Cellular synaptic target: Neostriatum	
	regate_regional_part_of_brain	Reurotransmitter: Dopamine	
► ● CA3.		1	
	_stratum_lucidum	Description: Substantia_nigra_pars_compacta_dopaminergic_cell	
	noarchitectural_part posite_part_spanning_multiple_base_regional_parts_of_brain		
Hind		Equivalent classes 💿	
	cortex_laver_4		
	form_cortex_layer_1	Superclasses 💿	
	form_cortex_layer_2	Substantia_nigra_pars_compacta	•
	onal_part_of_forebrain		
	onal_part_of_hindbrain	Inferred anonymous superclasses	
	onal_part_of_midbrain		
	egional_part_of_cerebral_peduncle	Aspart some Substantia_nigra_pars_compacta	
	Regional_part_of_midbrain_tegmentum	has_part some Substantia_nigra_pars_reticulata	e
	Regional_part_of_substantia_nigra	has_part some CA3_alveus	0
	Predominantly_gray_regional_part_of_substantia_nigra	has_part some Piriform_cortex_layer_1	0
	🔻 😑 Substantia_nigra_pars_compacta		
	Substantia_nigra_pars_compacta_dopaminergic_cell	Image: Some Neocortex_layer_4	0
	🔻 😑 Substantia_nigra_pars_reticulata	has_part some Chemoarchitectural_part	0
	Substania_nigra_pars_reticulata_interneuorn_GABA	has_part some CA1_alveus	0
	Substantia_nigra_pars_reticulata_principal_cell	has_part some CA3_stratum_lucidum	0
	cerebral_crus		
	interpeduncular_fossa	As_part some Hindbrain	e
	oculomotor_nerve ventrolateral_fissure_of_midbrain	has_part some Piriform_cortex_layer_2	e
	egional_part_of_midbrain_tectum	has_part some Aggregate_regional_part_of_brain	0
	rior_cerebellar_incisure		e
	brocerebellar_fissure	Image: Some Regional_part_of_forebrain	
	rpeduncular_cistern	• has_part some Molecular_layer_of_dorsal_cochlear_nucleus	0
	erior_cistern	• has_part some Trigeminal_nucleus	0
	erior_pontine_sulcus	has_part_some Regional_part_of_midbrain	0
🕨 😑 Spinal_Co			
🕨 🛑 meninges		Instant some Composite_part_spanning_multiple_base_regional_parts_of_brain	G
		has_part_some_Regional_part_of_hindbrain	•

Current state: more than 3000 concepts; more than 5000 synonyms

Expression of Speculative Statements in Scientific Text

Kallikrein-related peptidase 6 in Alzheimer's disease and vascular dementia.

PubMed 20846516 Authors: Ashby, Emma L; Kehoe, Patrick G; Love, Seth Date: 2010-12- Journal: Brain research Affiliation: Dementia esearch Group, Institute of Clinical Neurosciences, Clinical Science at North Bristol, University of Bristol, UK.

Statistics
Select ID with comment:

Human kallikrein-related peptidase 6 (KLK6) is highly expressed in the central nervous system. Although the physiological roles of this serine protease are unknown, in vitro substrates include amyloid precursor protein and components of the extracellular matrix, which are altered in neurological disease, particularly Alzheimer's disease (AD). We have compared KLK6 expression in post-mortem brain tissue in AD, vascular dementia (VaD) and controls. We studied the distribution of KLK6 in the temporal cortex and white matter by immunohistochemistry, and measured KLK6 mRNA and protein levels in the frontal and temporal cortex from 15 AD, 15 VaD and 15 control brains. Immunohistochemistry showed KLK6 to be restricted to endothelial cells. After adjustment for variations in vessel density by measurement of factor VIII-related antigen, we found KLK6 protein level was significantly decreased in the frontal but not the temporal cortex in AD. In VaD, KLK6 protein level was significantly increased in the frontal cortex. Our findings suggest that an altered KLK6 expression may contribute to vascular abnormalities in AD and VaD.

Hypothesis = KLK6 + may contribute

Seite 42

AD



Hypotheses finder∩ AD ontology ∩Human genes and proteins

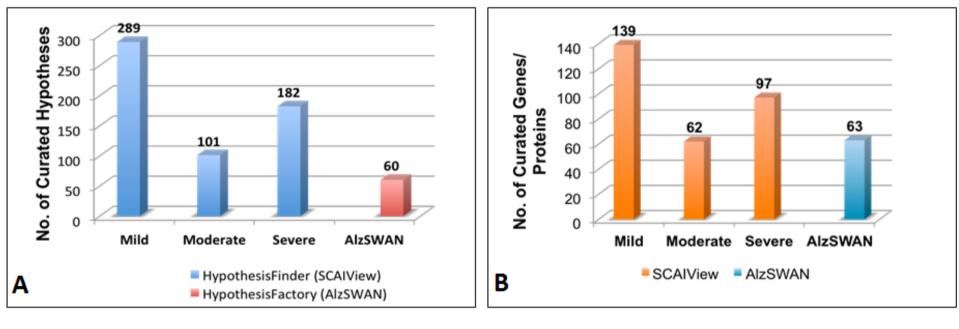
<u>SCAIVIEW</u>	🥠 alzheimer	
pharma	🖉 Search 🛛 🔗 Help 🛛 👼 A	About
Epilepsy Ontology V Alzheimer Ontology	Your Search:	
Molecular and cellular mechanis Etiological thing Non clinical thing – v Clinical thing	 Fulltext query: alzheimer 	
Thing relating to clinical trial Thing relating to diagnosis Thing relating to epidemiolog Thing relating to pathology Thing relating to clinical treat	 Filtering from Entity Tree: v (Boolean OR) ∧ (Boolean AND) E 	
V Thing relating to pathogen Mild cognitive Impairmen Stage Moderate cognitive Declin	Alzheimer Ontology:(((Mild cognitiv Hypothesis Finder AND Human Genes / Proteins	e mpannen jjjano
Alzheimer disease Parkinson Ontology Phypothesis Finder O Prog Names Phyman Genes / Proteins	 Display entities in Entity View of t Human Genes / Proteins 	type:
Evaluation of plas		predictors of conversion to Alzheimer's
Elisabet; Wallin, Anders; Minthon, L	ennart; Blennow, Kaj Date: 2010-03 Journal: Neurob Imō, Lund University, Sweden. oskar.hansson@med.li	len, Eugeen; Vanderstichele, Hugo; Andreasson, Ulf; Londos, biology of aging Affiliation: Clinical Memory Research Unit, lu.se
Alzheimer's disease (AD). Howev controls. Here, we analyzed plasm Abeta(1-42), and Abeta(n-42). Th impairment (MCI) and age-match years. In the second cohort, 14% isoforms differed between MCI pa model did not reveal any difference	na samples using a new multiplex immunoassay for sin e plasma samples were obtained at baseline from two ed controls. In the first cohort, 41% of the 117 MCI ca of the 110 MCI subjects developed AD during a clinica tients that subsequently developed AD and healthy co tes in the probability of progression from MCI to AD re	show very marginal differences between patients and imultaneous analysis of Abeta(1-40), Abeta(n-40),
marked change in CSF(may be)	xplained by the lack of a correlation between the levels are better predictors of progression to AD than plasm	is of Abeta(1-42) in CSF and plasma. In conclusion, the

Performance of Hypotheses finder

S.No	Data type	Source	Precision	Recall	F score
1	200 abstracts related to Alzheimer's	PubMed	0.84	0.86	0.85
2	2 full text articles related to Alzheimer's	Journal of Medical Hypotheses	0.85	0.88	0.86
3	143 abstracts related to Alzheimer's	Alzswan/PubMed	0.90	0.97	0.93
4	100 abstracts related to Epilepsy	PubMed	0.96	0.91	0.94
5	100 abstracts related to Parkinson's	PubMed	0.90	0.93	0.92

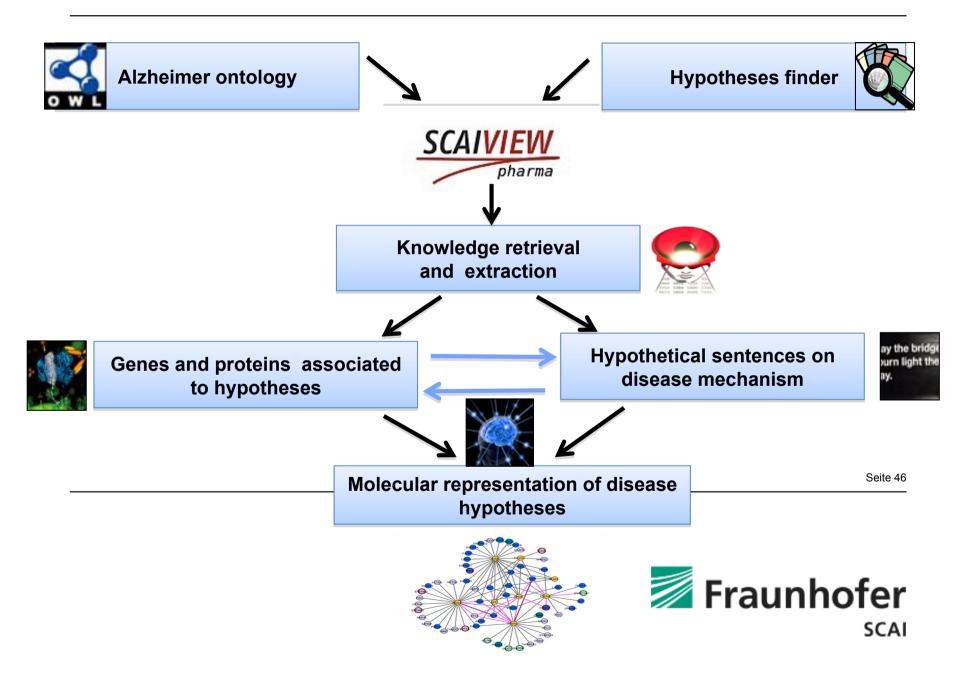


Performance of Hypotheses finder



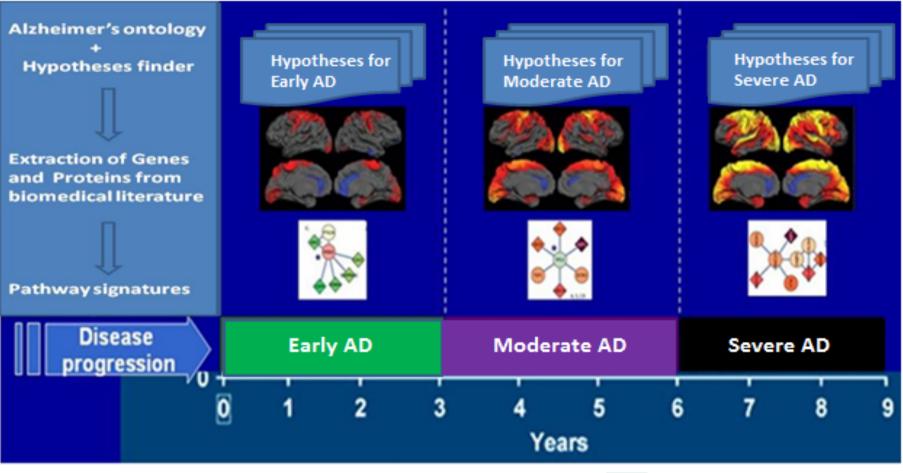


The Knowledge – Discovery Strategy



Analysis of hypotheses patterns across

disease stages





Summary

Fraunhofer SCAI Department of Bioinformatics stands for:

- Advanced technologies in text- and data mining, disease modelling in the area of neurodegeneration and high performance computing
- Trying hard to make the "eScience" paradigm a "living experience"
- Clear dedication towards contract research and sustainable innovation
- Internal usage of technologies (information extraction; distributed and high performance computing) for biomedical application

