

ADO: A disease ontology representing the domain knowledge specific to Alzheimer's disease

Ashutosh Malhotra^{a,b}, Erfan Younesi^{a,b}, Michaela Gündel^a, Bernd Müller^a, Michael T. Heneka^c,
Martin Hofmann-Apitius^{a,b,*}

^aDepartment of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing, Sankt Augustin, Germany

^bRheinische Friedrich-Wilhelms-Universität Bonn, Bonn-Aachen International Center for IT, Bonn, Germany

^cDepartment of Neurology, Clinical Neurosciences Unit, University of Bonn, Bonn, Germany

Abstract

Background: Biomedical ontologies offer the capability to structure and represent domain-specific knowledge semantically. Disease-specific ontologies can facilitate knowledge exchange across multiple disciplines, and ontology-driven mining approaches can generate great value for modeling disease mechanisms. However, in the case of neurodegenerative diseases such as Alzheimer's disease, there is a lack of formal representation of the relevant knowledge domain.

Methods: Alzheimer's disease ontology (ADO) is constructed in accordance to the ontology building life cycle. The Protégé OWL editor was used as a tool for building ADO in Ontology Web Language format.

Results: ADO was developed with the purpose of containing information relevant to four main biological views—preclinical, clinical, etiological, and molecular/cellular mechanisms—and was enriched by adding synonyms and references. Validation of the lexicalized ontology by means of named entity recognition-based methods showed a satisfactory performance (F score = 72%). In addition to structural and functional evaluation, a clinical expert in the field performed a manual evaluation and curation of ADO. Through integration of ADO into an information retrieval environment, we show that the ontology supports semantic search in scientific text. The usefulness of ADO is authenticated by dedicated use case scenarios.

Conclusions: Development of ADO as an open ADO is a first attempt to organize information related to Alzheimer's disease in a formalized, structured manner. We demonstrate that ADO is able to capture both established and scattered knowledge existing in scientific text.

© 2014 The Alzheimer's Association. Open access under [CC BY-NC-ND license](#).

Keywords:

Alzheimer's disease; Alzheimer's disease ontology; Neurodegeneration; Ontology; Semantic Web; Neurodegenerative diseases

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the brain that leads to irreversible loss of neurons with age, resulting in severe memory loss and

cognitive dysfunction. Currently, AD can neither be prevented nor cured and is predicted to become a global threat by 2050 [1]. Hence, exigency of action and promotion of research activities becomes even more important. The Internet and other knowledge resources are replete with information on AD generated by the scientific community. A simple search with the term "Alzheimer's disease" using the PubMed search engine produced 72,371 articles on June 21, 2012, and this number is steadily increasing. However, the gap between data generated and the knowledge derived from it is apparently not closing. One of the cardinal reasons accountable for

ADO is made freely available to the research community at <http://www.scai.fraunhofer.de/en/business-research-areas/bioinformatics/downloads.html>. ADO integrated into SCAIView for information retrieval application can be accessed at www.scaiview.com.

*Corresponding author. Tel.: +492241142802; Fax: +492241142656.

E-mail address: martin.hofmann-apitius@scai.fraunhofer.de

this divide is the lack of a strategy for engineering and representing relevant knowledge specific to AD. For research activities focusing on AD treatment to be ultimately successful, there is a vital need for knowledge aggregation from different resources (e.g., literature, experimental results, and databases). No single system is currently capable of covering the complete domain of AD by itself, and manual effort is insufficient to retrieve and comprehend all relevant information in this domain, which makes it necessary to develop an interoperable and standardized semantic framework that enables the scientific community to contribute equally to the representation of the AD knowledge domain.

Formal ontologies with their potential to engineer specific knowledge domains can be beneficial to overcome this hurdle. For instance, gene ontology [2] and SNOMED (Systematized Nomenclature of Medicine–Clinical Terms) [3] have facilitated the procedure of annotation and effective clinical recording of data. Knowledge engineering via application of ontologies to different knowledge domains has been used extensively as a basis for information retrieval and information integration as well [4].

Engineering knowledge using ontologies involves the specification of concepts and relations that exist in the domain, as well as their definitions, properties, and constraints. Currently, the main online repository of ontologies, BioPortal (<http://bioportal.bioontology.org/>), contains only one generalized disease ontology—namely, human disease ontology (<http://bioportal.bioontology.org/ontologies/1009>; last accessed April 22, 2012) that has been designed to link distant data sets through disease concepts. This ontology tries to combine epidemiological concepts, genetic information, symptoms, and findings into a disease scenario. However, the broad coverage and the lack of depth in this ontology restrict its usage for specific disease domains such as AD. Extensive efforts have been undertaken to organize published knowledge related to AD in the form of the AlzSWAN knowledge base (<http://www.alzforum.org/>), which is supposed to be the reference repository for AD-based information available on the Web. Still, information density or scalability remains a challenge for AlzSWAN.

Motivated by the participation of Fraunhofer Institute SCAI as a bioinformatics partner in the Neuroallianz Consortium (a part of the BioPharma initiative of the German Ministry of Education and Research) and the lack of an efficient computer readable system to represent the structure of knowledge in the AD domain, we developed a first draft of an ontology representing clinical features, treatment, risk factors, and other aspects of the current knowledge in the domain of AD. It is noteworthy that, although Alzheimer's disease ontology (ADO) has been designed in a way to comply with standard upper ontologies, our attempt was concentrated on keeping the concept definitions close to the expressions in natural language. The hierarchical structure of the ontology thus can serve as a robust

navigation tree for terminology integration and text-mining applications.

2. Methods

ADO is constructed in accordance with the ontology building life cycle [5]. To be compliant with the construction of formal ontologies, we followed the principle criteria of top-level ontologies applying the basic formal ontology upper level concepts [6]. The Protégé OWL editor (Version 4.2.0) was used as a tool for building ADO in Ontology Web Language (OWL) format (<http://protege.stanford.edu/>). Scope and domain coverage of ADO were evaluated by answering three competency questions, which were defined by two experts in clinical/molecular and pharmaceutical AD research.

2.1. Knowledge acquisition and conceptualization

A first collection of terms and concepts related to AD was generated by scanning various knowledge sources, including review articles, content of online books, standard knowledge bases, encyclopedias, glossaries, and informative online sources and websites. Most of the disease-specific knowledge was acquired by performing Web-based searches on resources that focus on various aspects of the disease, such as treatment aspects (<http://www.alzheimerstreatment.org/>), research overviews (<http://www.alzinfo.org/>), neurological perspectives (<http://neurology.health-cares.net/>), diagnostic criteria (<http://alzheimers.about.com/>), research proceedings (<http://www.Omnimedicalsearch.com>), and so forth. Concepts were also extracted from compendiums such as the *Encyclopedia of Alzheimer's Disease* [7] and the *Atlas of Alzheimer's Disease* [8]. Another glossary of terms representing AD was collected from the *Bibliography and Dictionary of Alzheimer' Disease* [9]. Whenever possible, any available hierarchical organization (structure) of the concepts was also extracted along with the concepts themselves. Corresponding definitions and synonyms were also taken into consideration as additional annotation of the concepts.

2.2. Formal representation and concept analysis

Basic formal ontology compliance of ADO as shown in Fig. 1 ensures its interoperability with existing and future biomedical ontologies [10]. To be able to generate the biological views on root subdomains of the ontology, axiomatic class definitions were added. By this means, a reasoner can be run to classify automatically other classes as subclasses of these “views,” which are neither a subclass of “occurrent” nor of “continuant.”

2.2.1. Reasoner run

ADO was tested with regard to formal consistency and absence of cycles using the Fast Classification of Terminologies FaCT++ description logic reasoner [11].

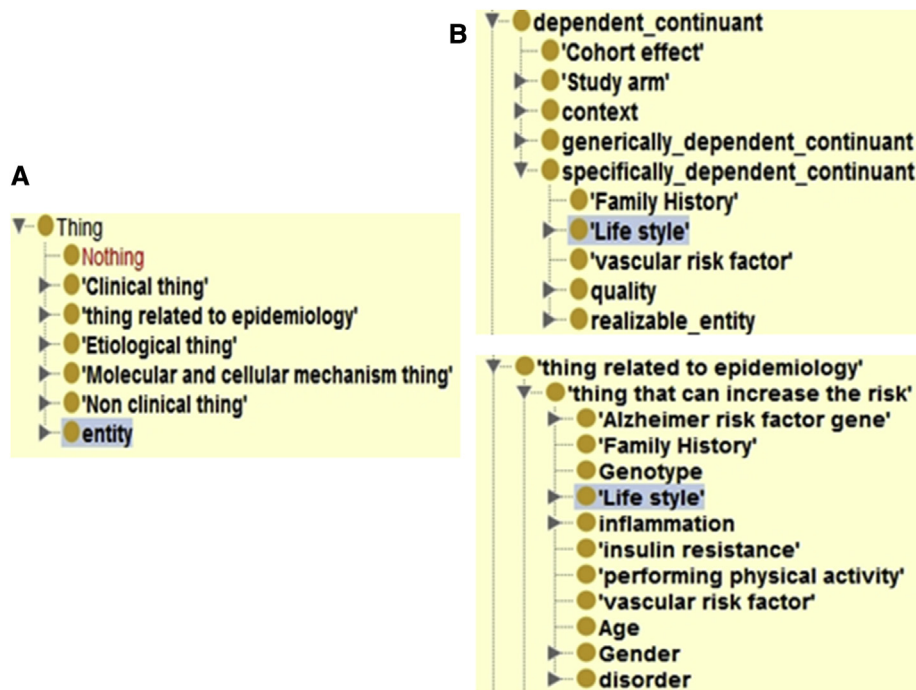


Fig. 1. (A) Alzheimer's disease ontology (ADO) contextual view classes alongside basic formal ontology (BFO). (B) Example class (Life style) in its BFO position (top) and in its inherited ADO view position (bottom).

2.2.2. N-gram analysis and noun phrase chunking

A text corpus of approximately 54,000 abstracts specific for AD was used to generate a list of n-grams ($n = 2 \dots 5$) that occur frequently in scientific text related to the disease. N-grams were ranked according to the frequency of their occurrence and, if found suitable, were included in the ontology either as concepts or synonyms. In search of frequently recurring noun phrases (NPs) in the same text corpus, an NP chunking tool (<http://opennlp.sourceforge.net/projects.html>) was used. Ranked NPs were evaluated manually and used to complement the ontology.

2.2.3. Synonym enrichment

Classes were annotated with synonyms, both manually and in an automated way, making use of mappings to external ontologies. For this purpose, services provided by the National Center for Biomedical Ontology were used to retrieve synonym information [12].

2.3. Terminology analysis and concept enrichment

Transformation of the ontology OWL format into a dictionary file was achieved using a Java program that extracts the concept names and the corresponding synonyms from the ontology OWL structure and assigns unique identifiers to each concept that can be stored in form of a dictionary. This dictionary was incorporated into ProMiner, a named entity recognition software program [13]. In a subsequent step, various class concepts were used as keywords for search in PubMed to build a corpus

that covers domain information related to topics such as AD biomarkers, brain regions, diagnostic procedure, pharmacology, epidemiology, etiology, genetics, pathogenesis, stages, symptoms, clinical trials, risk factors, and many more. From the result list obtained by each concept search, several abstracts were chosen randomly. After compilation of these chosen abstracts, a corpus of 500 abstracts was formed and divided randomly into a training set (250 abstracts), which was used for extracting the terminology manually and building the dictionary, and an annotation set for the development of the gold standard (250 abstracts). From the latter, a test set of 200 abstracts was selected. To create the reference gold standard, suitable annotation guidelines were developed so that the annotator is guided to keep the breadth and depth of the ontology in mind and to consider not only the superclass concepts, but also their corresponding subclass concepts as well as their synonyms for annotation.

Using these annotation guidelines, both training and test sets were annotated manually by means of the Knowtator tool (<http://knowtator.sourceforge.net/>). For enrichment purposes (optimizing the dictionary), the training set was analyzed for false-negative entities, which were added to the ADO terminology after individual expert evaluation. Moreover, an expert in the field cross-checked the whole ontology, and additional knowledge was incorporated. The test set served as the gold standard as well, because the evaluation process requires performance of comparisons between the automatically and manually annotated text from the same set.

To evaluate the quality of the ADO ontology in terms of measuring the boundaries of the knowledge domain that it captures, precision, recall, and *F*-score values were calculated. These values were computed based on the longest string match found between automatically annotated terms by ProMiner and the (human) gold standard annotation for each abstract in the selected corpus. The following equations were used for the computation of recall, precision, and *F*-score values [14].

$$\text{Precision} = \frac{\text{True positives}}{\text{True positives} + \text{False positives}}$$

$$\text{Recall} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}}$$

$$F \text{ score} = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}$$

where true positives are the number of entities that were found by ProMiner and that matched the annotation in the gold standard, false positives are the number of entities that were annotated automatically by ProMiner but could not be matched to annotations in the (expert annotated) gold standard, and false negatives are the number of entities that were not found by ProMiner when compared with the manual gold standard annotation.

2.4. Visualization of concepts through the text

To visualize the named entities embedded in the textual body of PubMed abstracts, the transformed Extensible Markup Language (XML) structure of ADO was integrated into SCAIView [15]. SCAIView is a visualization interface for ProMiner annotations and displays named entities by markup of the text. The key feature of SCAIView is the ability to perform ontological searches in biomedical text using concept hierarchies and synonyms associated with each concept. To adopt ADO in the SCAIView environment, we extracted the inferred views on the ontology and transformed the ontology OWL file into XML format containing the view taxonomy, labels, and synonyms. A ProMiner annotation run with an ADO-derived dictionary generated the meta-information (index) used for searching of ADO terms in SCAIView. Moreover, to reduce the complexity of the hierarchy for better navigation, improve the visualization of the concepts, and increase the specificity, we transferred all the concepts common among general neurodegenerative diseases to a separate hierarchy called neurodegenerative diseases (NDD). This utility, along with the flattened tree structure of ADO, is accessible online at www.scaiview.com.

3. Results

3.1. ADO structure and contents

ADO covers a wide range of key concepts and aims to engineer knowledge specific to AD. Modeled heterogeneity

in this semantic framework tries to touch all relevant concepts, but the range varies from very general (main ontology classes) to more specific concepts (concepts located at the ontology bottom “leaves”). The main views (root concepts) in ADO covering aspects of AD knowledge domain include Clinical, Nonclinical, Etiological, and Molecular and cellular mechanism. Each of these superclasses has its own subclasses, as shown in Fig. 2. Subclasses mentioned under “Clinical thing” cover concepts that have contributed significantly to our understanding of the pathology, diagnosis, and possible treatment options. Concepts defined under each subclass tend to be more domain specific.

Currently, much of the focus of AD research is devoted to preclinical studies that are conducted typically on animals, and it has the potential to play a vital role in drug discovery and development processes. Concepts mapping all aspects of Nonclinical studies (ex vivo, in silico, in vitro, and in vivo) have also been incorporated into ADO, hence elaborating the knowledge related to animal models and bioassays used to understand more completely the biological processes underlying Alzheimer’s disease.

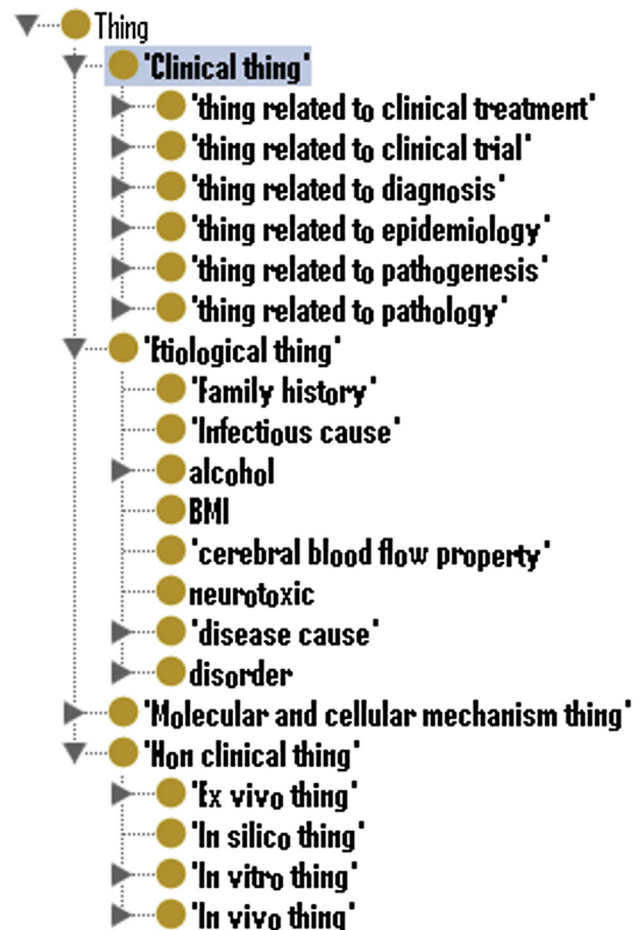


Fig. 2. Extracted Views on Alzheimer’s disease ontology.

The Etiological view forms the third root in ADO and it covers all aspects that might be responsible for the initiation of AD, ranging from genetic factors and environmental influences to morphological changes with effects that vary from individual to individual. Clinical appearance of AD is also marked by anatomic changes as well as cellular and molecular cascades, which together manifest the neuropathological alterations observed in AD.

Furthermore, in ADO, the Molecular and cellular mechanism view is designed to cover all entities and biological mechanisms that find a possible role in AD. Studying the behavior of neurons and other brain cells at the cellular and molecular levels during AD can provide insights into the processes that mark its progression. The semantic relationships “is a,” “has a,” and “part of” were used to define relation types between pairs of concepts.

3.2. ADO evaluation

3.2.1. Structural aspects

The structural features of the ontology reflecting topological and logical properties were measured by means of context-free metrics including depth and breadth (related to the cardinality of paths in a graph), tangledness (related to multihierarchical nodes), and fan-outness (related to the dispersion of nodes). [Supplementary Table 1](#) shows various parameters that were considered in the structural evaluation of ADO.

3.2.2. Functional aspects

The functional dimension of the ontology reflects the main purpose of that ontology by specifying a set of contextual assumptions about an area of interest. Functional evaluation measures how widely and precisely ontological concepts represent the semantic space for the indicated knowledge domain. The boundary of the knowledge domain addressed by ADO was estimated by calculating its fitness to an existing knowledge repository (i.e., PubMed). Using our state-of-the-art text-mining environment, which takes ADO hierarchical structure and corresponding dictionary as input, we were able to evaluate ADO functionally on the prepared test set (see Methods) and report an *F* score of 72%. The result of this evaluation shows that the ontology in its current form can capture a wide range of AD concepts in the

knowledge domain of AD scattered throughout scientific publications.

3.2.3. Expert evaluation

The expert panel’s revision of the ontological view structure is considered to be genuine evaluation for disease ontologies [16]. Following this revision, our ontology was curated manually by a team of clinician experts in the field (also coauthor in manuscript) who added certain clinically relevant concepts to ADO, increasing its pragmatic usability.

Two competency queries defined by the expert clinician and one from a pharmaceutical expert were selected to evaluate the semantic performance of ADO and its capability to return appropriate information:

1. Return references linking amyloid beta to synaptic dysfunction in the mild stage of AD.
2. Return references that associate the total tau protein to frontotemporal dementia and AD.
3. Return references containing clinical evidence that correlate cerebrospinal fluid levels of phosphorylated tau with cerebrospinal fluid amyloid beta 42 and cognitive decline.

To evaluate these queries, we compared manually documents returned by ADO in SCAIView with documents returned by PubMed advanced search using the same queries. The results of this evaluation are summarized in [Table 1](#) and details of query formulations are reported in [Supplementary Table 2](#).

As shown in [Table 1](#), querying SCAIView with the support of ADO in comparison with querying PubMed using comparable query formulations for all competency queries returns better results in terms of both sensitivity and specificity. These results indicate that ADO-supported information retrieval improves the chances for gaining better coverage with focused results in the same time compared with naive PubMed-based searches. Also, the knowledge gain in terms of concept recognition and enrichment is better when performing ontology-based semantic searches. To -validate this supposition, we used the third competency query and executed it in SCAIView under two conditions: using the MeSH (medical subject heading) dictionary (without using ADO) and using ADO in conjunction with NDD terminology. Our reason is that the same corpus is indexed behind SCAIView so

Table 1

Results of competency questions evaluation using ADO within SCAIView compared with nonontological search of PubMed

Question no.	Total SCAIView hits, n	Relevant SCAIView hits, n	Total PubMed hits, n	Relevant PubMed hits, n
1	23 documents	20 documents	1 document	1 document
2	130 documents	14 documents out of top 20	20 documents	7 documents
3	12 documents	7 documents	0 document	0 document

Abbreviation: ADO, Alzheimer’s disease ontology.

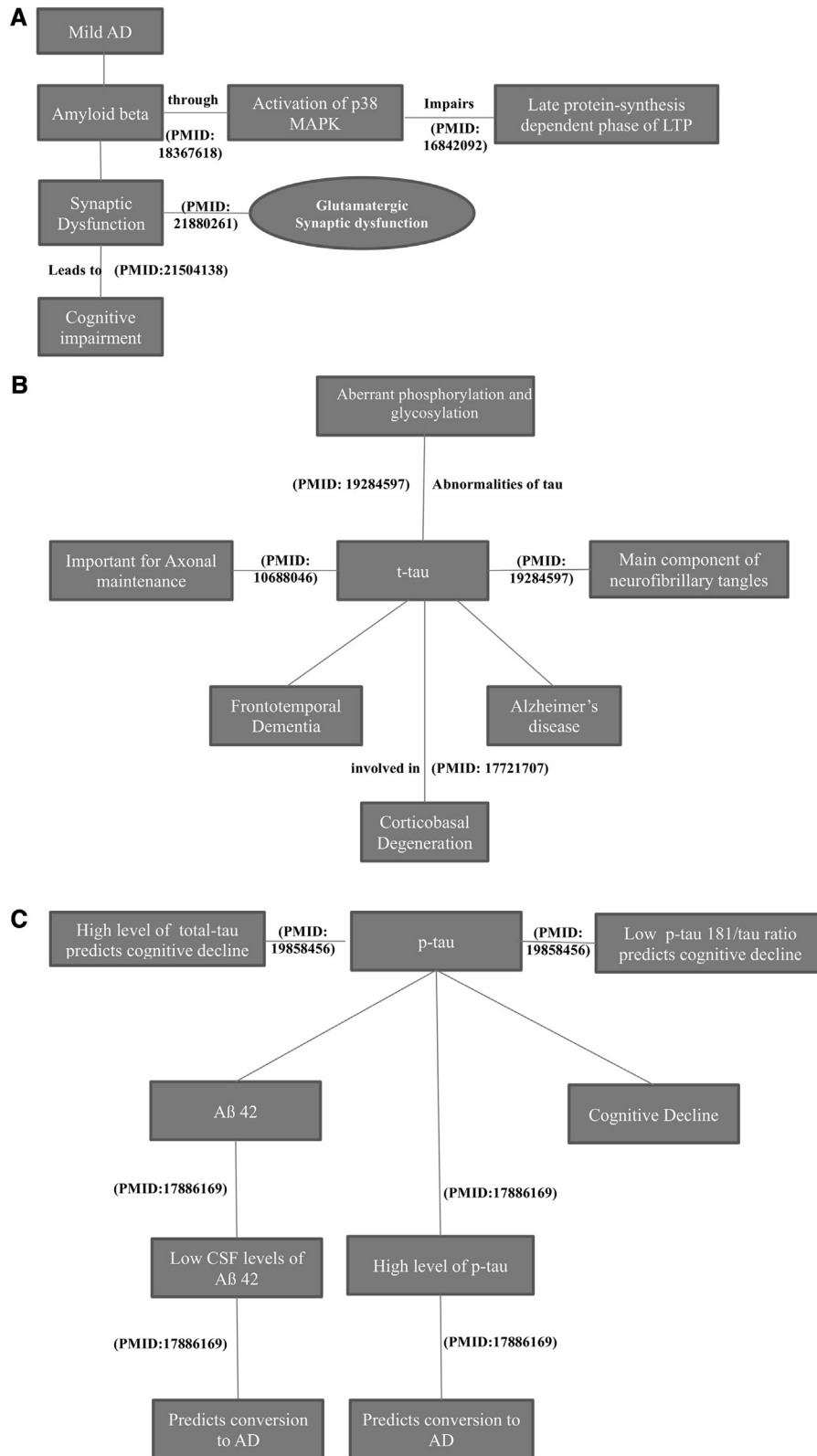


Fig. 3. (A–C) Entities expressed in the competency questions that are annotated by Alzheimer's disease ontology (ADO) and further identified to be linked to other ADO concepts such as the ones associated with amyloid beta (A β), synaptic dysfunction (A), total tau (t-tau) and frontotemporal dementia (B), and phosphorylated tau (p-tau) and A β 42 (C). AD, Alzheimer's disease; MAPK, mitogen-activated protein kinase; LTP, long-term potentiation; CSF, cerebrospinal fluid.

PATIENT NAME: **NAME[AAA, <2> BBB M]ACCOUNT #: **ID-NUM DATE OF SERVICE: **DATE[Feb 02 07] PRIMARY CARE PHYSICIAN: **NAME[TTT SSS RRR]

CHIEF COMPLAINT:
<3> Agitation.

HISTORY OF PRESENT ILLNESS:
Ms. **NAME[AAA] is a <4> AGE in 70s)-year-old woman with a past medical history significant for <5> Alzheimer's disease, <6> diabetes, recently admitted one and a half weeks ago for mental status <8> depression. They believe that it was related to a urinary tract <9> infection. According to her son, initially the patient was doing better than she had been. She was awake, alert, eating and drinking well. However, over the 1 and down the steps, as well as going after pots and pans. They are concerned that she may injure herself because of this <12> agitation. Her so needed for control of <13> agitation. She has been on 1 mg p.o. t.i.d. p.r.n. <14> Symptoms of <15> agitation. However, they have been told the 1 mg t.i.d. The patient was also anxious and agitated this morning, did receive 1 mg of p.o. Haldol prior to arrival in the Emergency Department.

REVIEW OF SYSTEMS:
As in HPI according to family. Otherwise, unable to obtain from the patient given her significant <17> dementia.

Fig. 4. Comorbidity captured in electronic health records using Alzheimer's disease ontology.

that the condition for queries remains fairly comparable. We then checked the document retrieval under both conditions; it turns out that the ontology-based search using SCAIView (along with all MeSH concepts included as a subset) was able to highlight approximately five times more entities than was possible using the MeSH dictionary alone. With this in mind, we tried to derive inferences about the enrichment of the knowledge space surrounding the basic answer to the query with the help of ADO concepts—for example, how entities addressed in the competency queries are linked to other biological entities and processes (highlighted in the abstracts using ADO) in an AD context.

Fig. 3 shows that additional knowledge gained by means of ontological concept enrichment adds greater value to the original answer found by ADO. Although ontology-based context modeling has long been acknowledged to be a key aspect in a wide variety of problem domains, the full power of semantic search using a disease ontology comes with using a combination of the ontology with entity recognition, as shown by the strategies discussed previously.

3.3. Application scenario: Mining electronic health records of AD patients for comorbidity analysis

Our motivation for the development of ADO was to extract automatically domain-specific knowledge related to AD that can be used to gain further insights into the disease mechanism. To demonstrate further the utility of ADO, we aimed at capturing knowledge beyond Medline abstracts. In an evaluation experiment independent from Medline, we used ADO to mine 650 AD-related electronic patient health records to screen systematically for other diseases or disorders that may exist simultaneously but independently in patients with AD. In medical, terms this concept is described as a comorbidity analysis [17]. An example of the annotation of relevant terms in electronic patient records using the ADO dictionary is shown in Fig. 4.

After analyzing the results obtained by calculation of term frequencies, we found that hypertension, diabetes

mellitus, and stroke are disorders that are reported to occur frequently in patients who already have AD. This observation is in good agreement with the scientific literature [18]. Furthermore, using our named entity recognition-driven literature mining machinery, we extracted a list of the top 300 genes associated with these three diseases in the literature and compared the list with that of the top 300 AD genes extracted from the literature using the same methodology. After curation for their relevance to the indication area, we found 19 common genes between AD and diabetes mellitus, 14 between AD and hypertension, and 46 between AD and stroke, as shown in Fig. 5.

4. Discussion

In recent years, the realization of the benefits of ontologies for data management, integration, and processing in biology—and in the neuroscience domain in particular—has resulted in a surge of interest in developing disease-specific, high-resolution ontologies such as the epilepsy ontology [19]. In addition to other controlled vocabularies in the field, such as BrainML [20], the epilepsy ontology is the only formal ontology representing NDDs so far. However, the coverage of this ontology is limited to the representation of the current diagnostic scheme proposed by the International League Against Epilepsy (<http://www.ilae.org/>), which includes epileptic syndromes, seizures, electroencephalogram terminology, and a limited number of general concepts. Such limitations suggest that there is

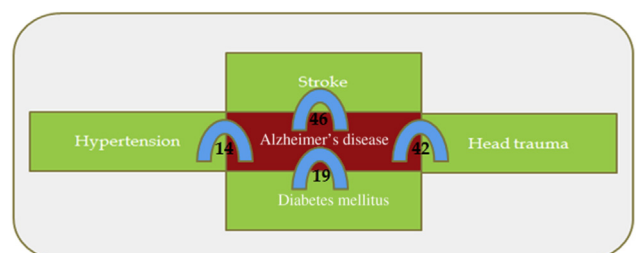


Fig. 5. Number of genes reported in the literature to be commonly involved in Alzheimer's disease and four comorbid diseases.

a need to delve deeper into the NDD domain and build a stronger semantic basis for this indication area with new ontologies capable of capturing and representing disease-specific knowledge.

ADO has been designed to provide maximum coverage, keeping all aspects of AD in mind. It provides different “views” on AD in a structured and formalized manner. During the course of construction of ADO, special emphasis was applied to aspects of usability of the ontology. ADO has been designed to be useful for and applied by end users via ontology-driven searching of the literature. One particular scenario for the application of ADO is the capturing of AD stage-specific knowledge related to genes and proteins; cross-sectioning of the AD knowledge space using ADO in combination with human gene/protein terminologies enables extraction of highly specific pieces of information from the AD knowledge space. Such specific and complex information extracted from scientific text can be used to develop models reflecting the progression of AD per stage at the molecular level (data not shown). Moreover, new disease-associated genes can be identified and may serve as candidates for experimental studies. In addition, the application scenario on electronic patient health record mining presented earlier demonstrates what can be done with ADO in the area of reusing routine clinical data for scientific purposes. When integrated into our information retrieval system, ADO leveraged the efficiency of semantic information retrieval and knowledge representation by providing the ability to perform ontological searches in two directions: in-depth use of concept hierarchies and in-breadth use of synonyms associated with concepts. In addition, enrichment of the retrieved knowledge with ADO concepts could contribute to the gain of useful information linked implicitly to the main query.

5. Conclusion

Despite the fast growth of knowledge domains describing neurological disorders, the number of existing ontologies representing these domains in a formalized and structured manner is not proportional to the large volume of generated knowledge. Development of ADO as an open ADO was a first attempt in this direction, which is by no means complete and needs constant enrichment by contributions from the scientific community and experts in the field of neuroscience.

Acknowledgments

We thank Dr. Michael Krams at Johnson & Johnson for his contribution to the provision of the competency queries, Theo Mevissen, Harsha Gurulingappa for technical support, and Stephan Springstube for fruitful discussions and motivational support during the project. This work was supported by the Bonn-Aachen International

Center for Information Technology foundation and a scholarship to A. M. (ScholarShip PLUS program of the State of NorthRhineWestfalen).

RESEARCH IN CONTEXT

1. Systematic review: ADO is constructed in accordance with the ontology-building life cycle and state-of-the-art ontology evaluation techniques were used to test and to validate the ontology.
2. Interpretation: ADO provides a first draft version of a semantic framework that is supposed to support research on Alzheimer's Disease. ADO can be used to add meta-information to existing AD data, it provides the basis for efficient information retrieval and knowledge representation. It can automatically extract domain-specific knowledge related to AD, which can be used to gain further insights into disease mechanisms.
3. Future directions: ADO is a first attempt to develop an open, public ontology representing relevant knowledge on Alzheimer's disease. We do not claim that ADO covers the entire knowledge related to the AD knowledge domain. Thus, like other ontologies, ADO needs continuous improvement and we encourage members of the scientific community to apply the ontology in order to further enhance and improve it.

References

- [1] Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 2007;3:186–91.
- [2] Ashburner M, Ball CA, Blake JA, Botstein D, Butler H, Cherry JM, et al. Gene ontology: tool for the unification of biology: the Gene Ontology Consortium. *Nat Genet* 2000;25:25–9.
- [3] Donnelly K. SNOMED-CT: the advanced terminology and coding system for eHealth. *Studies Health Technol informatics* 2006; 121:279–90.
- [4] Bodenreider O. Biomedical ontologies in action: role in knowledge management. *Data Integr Decision Supp NIH Public Access* 2008; 3841:67–79.
- [5] Gómez-Pérez A, Fernández-López M, Corcho O. *Ontological engineering*. Berlin: Springer; 2004.
- [6] Grenon P, Smith B, Goldberg L. Biodynamic ontology: applying BFO in the biomedical domain. *Studies Health Technol informatics* 2004; 102:20–38.
- [7] Turkington C, Mitcheli D. *The encyclopedia of Alzheimer's disease: (facts on file library of health and living)*. 2nd ed. New York: Facts on File Inc; 2010.

- [8] Feldman H. Atlas of Alzheimer's disease. London: Informa Healthcare; 2007.
- [9] Icon Health Publications. Alzheimer's disease: a medical dictionary, bibliography and annotated research guide to Internet references. San Diego: Icon Health Publications; 2003.
- [10] Smith B, Kumar A, Bittner T. Basic formal ontology for bioinformatics. *J Inf System* 2005;1–16.
- [11] Tsarkov D, Horrocks I. FaCT++ description logic reasoner: system description. In: Proc. of the Int. Joint Conf. on Automated Reasoning (IJCAR). Lecture Notes in Artificial Intelligence, Vol. 4130. Springer, Berlin;2006:292–297.
- [12] Musen MA, Noy NF, Shah NH, Whetzel PL, Chute CG, Story MA, et al. The National Center for Biomedical Ontology. *J Am Med Inform Assoc* 2011;19:190–5.
- [13] Hanisch D, Fundel K, Mevissen HT, Zimmer R, Fluck J. ProMiner: rule-based protein and gene entity recognition. *BMC Bioinformatics* 2005;6:S14.
- [14] Morgan AA, Lu Z, Wang X, Cohen AM, Fluck J, Ruch P, et al. Overview of BioCreative II gene normalization. *Genome Biol* 2008; 9:S3.
- [15] Friedrich CM, Dach H, Gattermayer T, Engelbrecht G, Benkner S, et al. @neuLink: a service-oriented application for biomedical knowledge discovery. *Stud Health Technol Inform* 2008;138:165–72.
- [16] Obrst L, Ceuster W, Mani I, Ray S, Smith B. The evaluation of ontologies. Springer, Berlin: Semantic Web; 2007;139–58.
- [17] Cornoni-Huntley JC, Foley DJ, Guralnik JM. Co-morbidity analysis: a strategy for understanding mortality, disability and use of health care facilities of older people. *Int J Epidemiol* 1991; 20:S8–17.
- [18] Tsolaki M, Fountoulakis K, Chantzi E, Kazis A. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of a Greek population. *Int Psychogeriatr* 1997;9:327–41.
- [19] Almeida P, Gomes P, Sales F, Nogueira A, Dourado A. Ontology and knowledge management system on epilepsy and epileptic seizures. In: Proceedings of the 3rd International Workshop on Semantic Web Applications and Tools for the Life Sciences. Berlin; 2010.
- [20] Gardner D, Xiao Y, Abato M, Knuth K, Gardner E. BrainML and GENIE: neuroinformatics schemas for neuroscience data sharing. *Soc Neurosci Abstracts* 2002;28.

Did you know?

The screenshot shows the homepage of the journal *Alzheimer's & Dementia*. At the top right, there is a search bar with a dropdown menu set to 'This Periodic'. Below the search bar, there are links for 'Advanced Search', 'MEDLINE', and 'My Saved Searches'. A red circle highlights the 'My Saved Searches' link, with a black arrow pointing to it from the left. The main content area includes a 'Current Issue' section for November 2009, a 'Featured Articles' section with several article titles, and a 'Now Included on MEDLINE' badge. The left sidebar contains navigation links such as 'JOURNAL HOME', 'CURRENT ISSUE', 'ARTICLES IN PRESS', and 'SEARCH THIS JOURNAL'. The bottom of the page features a 'START' button and a 'JOIN' button.

You can save your online searches and get the results by email.

Visit www.alzheimersanddementia.org today!