MIND Center for Interdisciplinary Informatics

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Semantic Web Applications in Neuromedicine: Problems and Prospects

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Neurodegenerative diseases impose huge social and personal costs

- Alzheimer Disease (5M people in US, 30M world)
- Parkinson's (1.5M US, 6.3 M world)
- Huntington's Disease (30K US, 150K US at risk)
- ALS (30K US)
- …others (CJD, etc)

AD : progressive, widespread loss of neurons …and consequently, brain function

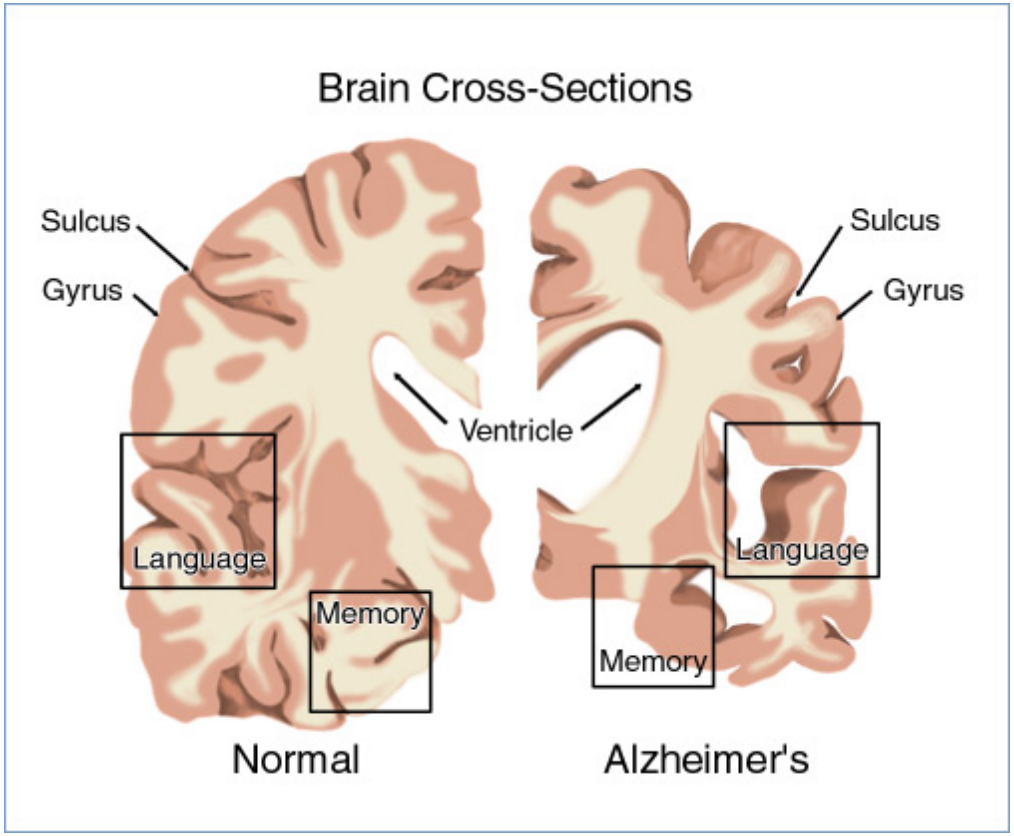

Illustration: American Health Assistance Foundation

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Histopathology: NFTs and senile plaques

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Normal brain at autopsy

Trafford, A. (2000) American Alzheimer Association, www.alzwa.org

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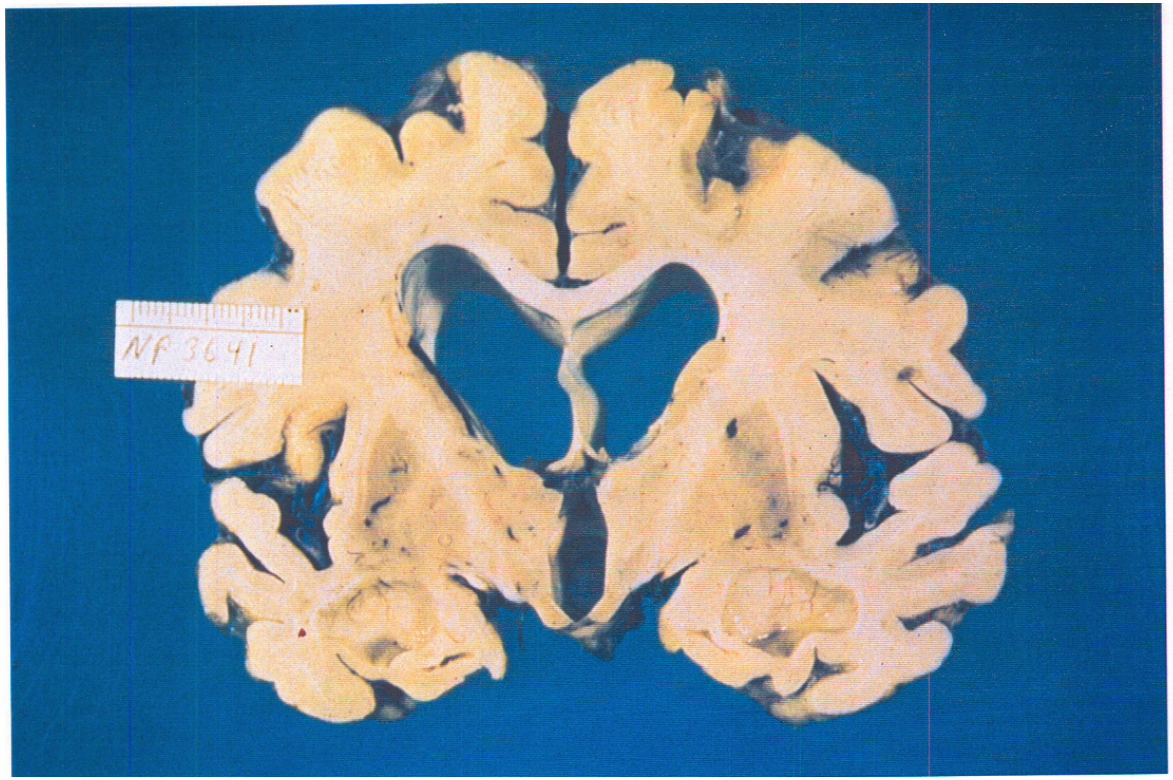
Source: Trafford, Abigail. "Alzheimer's: No Cure Yet, But Reasons For Hope."
Alzheimer's Association, November 7, 2000.
Accessed 16 Sept 2005 at http://www.alzwa.org/ArticlesOnLine/ Research/reseach_article.htm

AD brain at autopsy



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Alzheimer Disease research implicates diverse biological mechanisms

- genes (over 200 candidate genes published)
- environmental risk factors
- changes in cell function
- DNA damage
- misfolded proteins
- immune responses
- changes related to aging
- reduced regenerative capacity
- and others...

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AD therapy development is highly interdisciplinary …

- etiological understanding
  - Genetics, genomics, proteomics, bioimaging, neuropathology, psychiatry, neurophysiology, cell biology…
- intersecting with
  - pharmacology, medicinal chemistry, animal studies and clinical trials

…and rather controversial

- A few current hypotheses on causation of AD
  - Aβ protein direct toxicity to neurons
  - Aβ protein indirect toxicity ("amyloid cascade")
  - Defective cholesterol metabolism
  - Oxidative stress
  - Oxidative stress + abnormal mitotic signalling ("two-hit")
  - Aluminum toxicity
  - Calcium signalling deficit
  - Disruption of white matter (oligodendrocytes and astrocytes)
  - NMDA receptor dysfunction
- "the truth is out there…" in the natural world

Can we build a useful knowledge base of research findings in AD?

- Classical knowledge bases resolve all internal contradiction
  - Tractable for reasoning from premises to conclusions
  - Composite of expert knowledge in a domain
  - Monotonic logic, “truth maintenance”
- What if the experts don’t agree?
  - The domain’s natural mode of reasoning is inductive
  - …and results of research are insufficient for rigorous proof
  - I.e., the domain is “underdetermined”

Core goals

- Contains useful current research results
- Can find “surprise” connections to other results
- Curation by true domain experts
- Computability & linkability of all statements
- Keep database current with the science
- Promote and incorporate active discussion

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Technology

- Semantic Web (SW) technology is highly appropriate for this application
- This application is also an excellent demonstration platform for SW technology

Target: core pathways in AD

- Zero in on pathways of central relevance
- Proposed initial focus
  - genetics relevance (presenilin pathway)
  - therapeutics relevance (cholesterol pathway)
- Expansion of focus
  - multiple-disease relevance (protein misfolding)
  - Others as proposed by advisors

Curation by true domain experts

- We want real, leading researchers to curate
  - Experts must not become fulltime curators
  - Implies limitation of scope for each curator
- The toys in the cereal box (motivation)
  - Credit for ideas
  - Private whiteboard space in KB
  - Active collaboration space
- Ability to disagree & challenge statements
  - Part of the KB design

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Web-deployed via AlzForum

- AlzForum is a global platform on AD
  - 70,000+ sessions per month
  - 32,000 visitors view 150,000 pages per month
  - Referenced by 7,700+ web sites
  - 2,000+ registered members
  - 3,000+ subscribers to newsletter
- The very top scientists in AD research serve each year on the AlzForum Editorial Board
- There is an active participant community
  - Online scientific dialogues and discussions

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AlzForum scientific web community

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See http://www.alzforum.org/home.asp.

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Semantic Web technology

- Vision outlined ~ 1998 (Berners-Lee)
- Next generation of WWW technology
- Major development milestones 2004
- can now begin to support large scale Semantic Integration of research results
- numerous life science applications

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SWAN: Semantic Web Applications in Neuromedicine

- Pilot project in Alzheimer Disease
- Construct a broadly integrated KB of research results
- Curation by leading researchers
- Collaboration of researchers, computer scientists, industry and scientific web publishers
  - under auspices of W3C Semantic Web Activity

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The SW-LS Technology stack (2005)

- LSID (Life Science Identifier)
- XML / XMLS
- RDF / RDFS
- OWL (Web Ontology Language)

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Some challenges of Semantic Web application to neuromedicine

- Distributed identifier resolution
- Truth maintenance
- Computability
- Core ontological model
- Publication model / public-private ontology resolution
- Hypothesis representation
- Data provenance
- Socialization…

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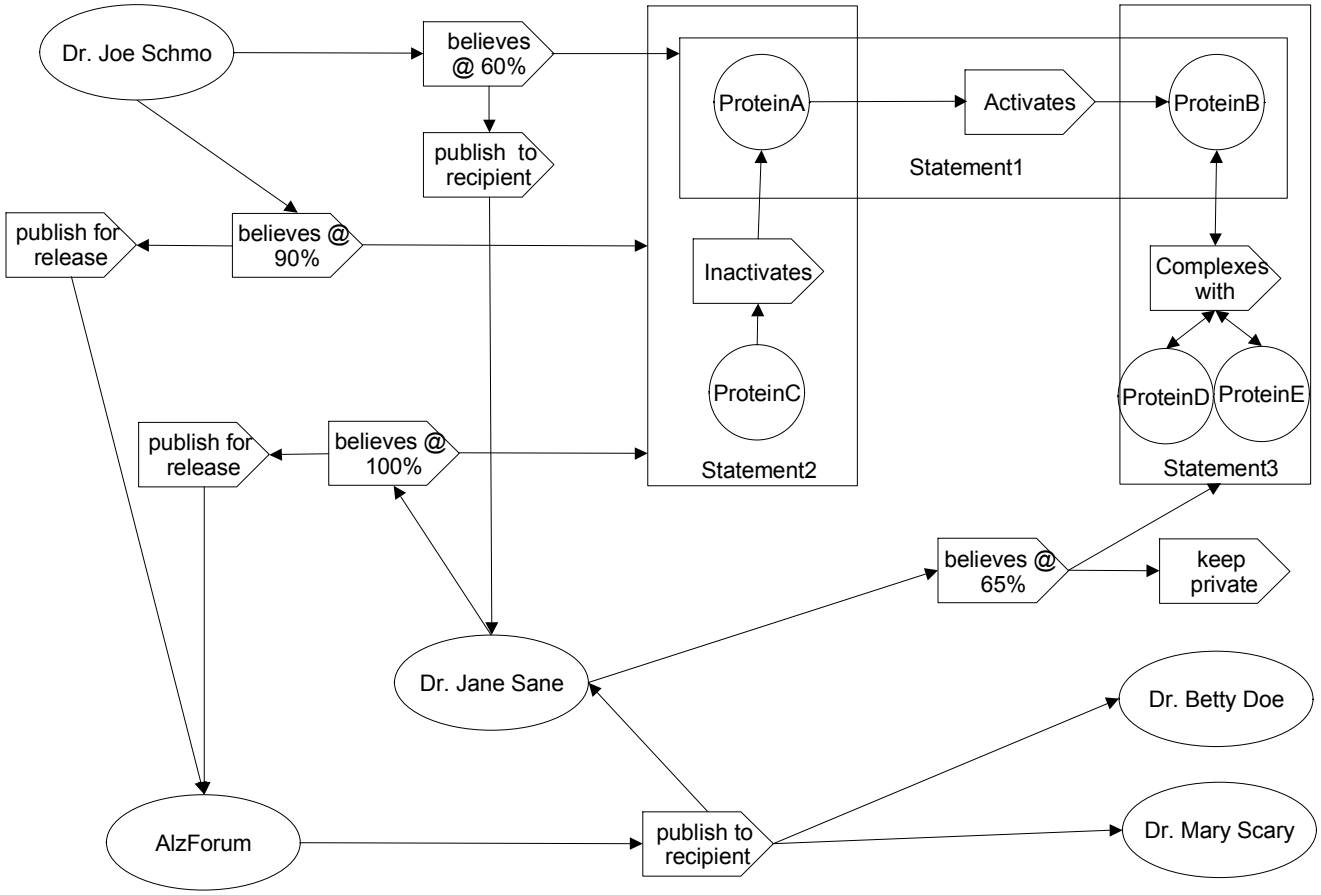
Distributed identifier resolution: LSID

- LSID - Life Science Identifiers (Clark, Martin & Liefeld 2004)
  - Globally resolvable, persistent, locally generated unique web identifiers
- Standardized by W3C & OMG
  - OMG standard issued 2004
  - Specialized W3C URN Namespace
- Increasing adoption in bioinformatics
  - Biopathways Consortium (LSID Authority Service)
  - Broad Institute (GenePattern)
  - UK eScience program (myGrid semantic grid project)
  - National Cancer Institute (caBIG cancer bioinformatics framework)
  - Genome Canada (bioMoby semantic service discovery project)
- Open source resolver software available
  - Lsid.sourceforge.net

Truth maintenance: Absolute or relative?

- Truth maintenance is typically conceived to be about *eliminating contradiction* in the KB
  - Okay on “boutique” scientific KBs
  - Does not scale as a process due to limitations of expertise
- Successful large KBs studiously avoid truth maintenance
  - Medline: correct bibliographic info = correct entry
  - Disregard truth or falsity of the science
  - “Let community process deal with it”, outside the KB
- Our approach: consciously *import contradiction* into the KB
  - “Relativization” (*reification*) of all statements
  - Private “idea incubation” sections of KB (the *Personal Whiteboard*)
  - Explicit statement publication to wide or narrow audience

…to a formal "computable" model



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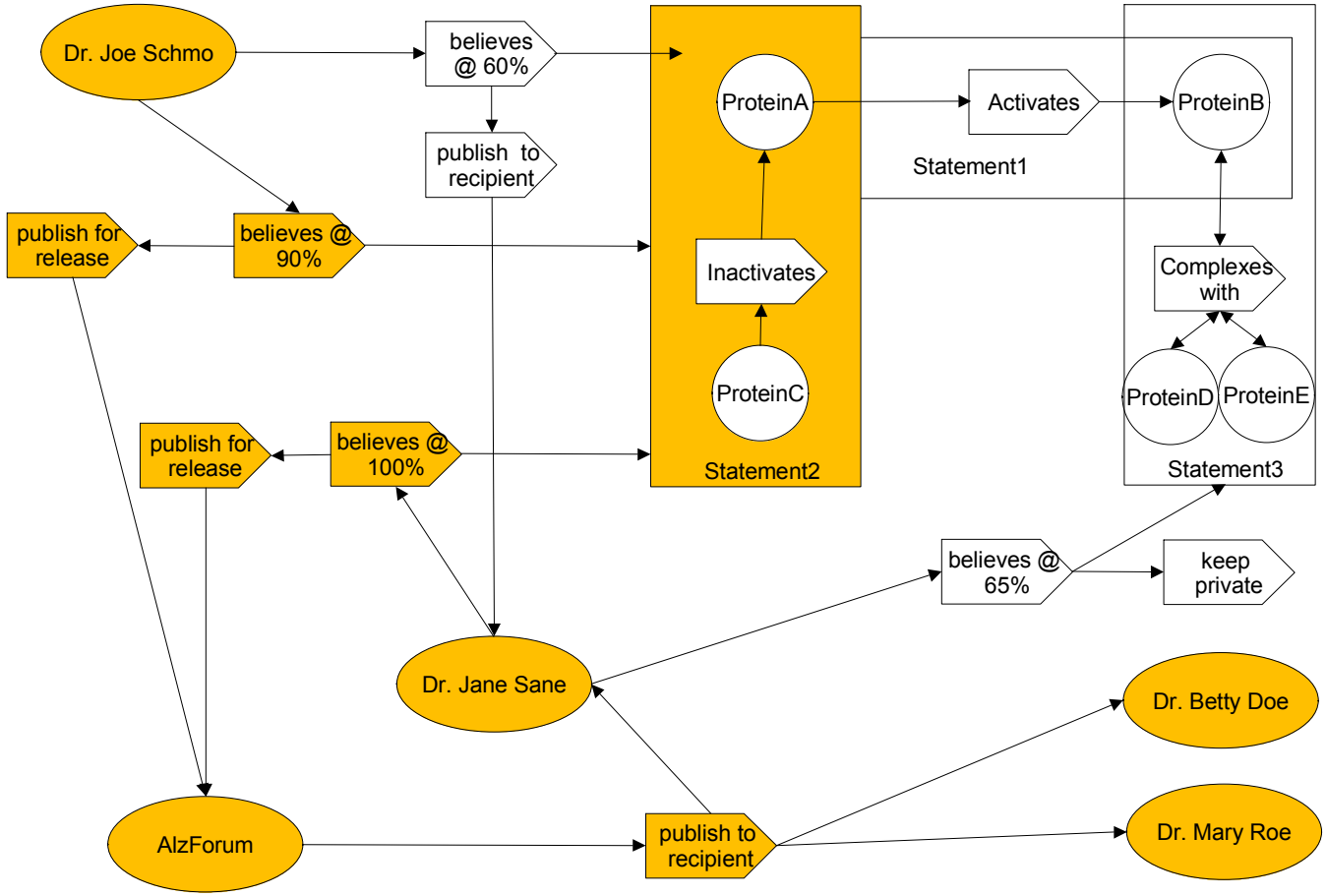
AlzForum public view of KB



<u>Drs. Sane, Doe & Roe see these statements (public KB):</u>

"Dr. Sane believes (100%) Protein C inactivates Protein A"

"Dr. Schmo believes (90%) Protein C inactivates Protein A"

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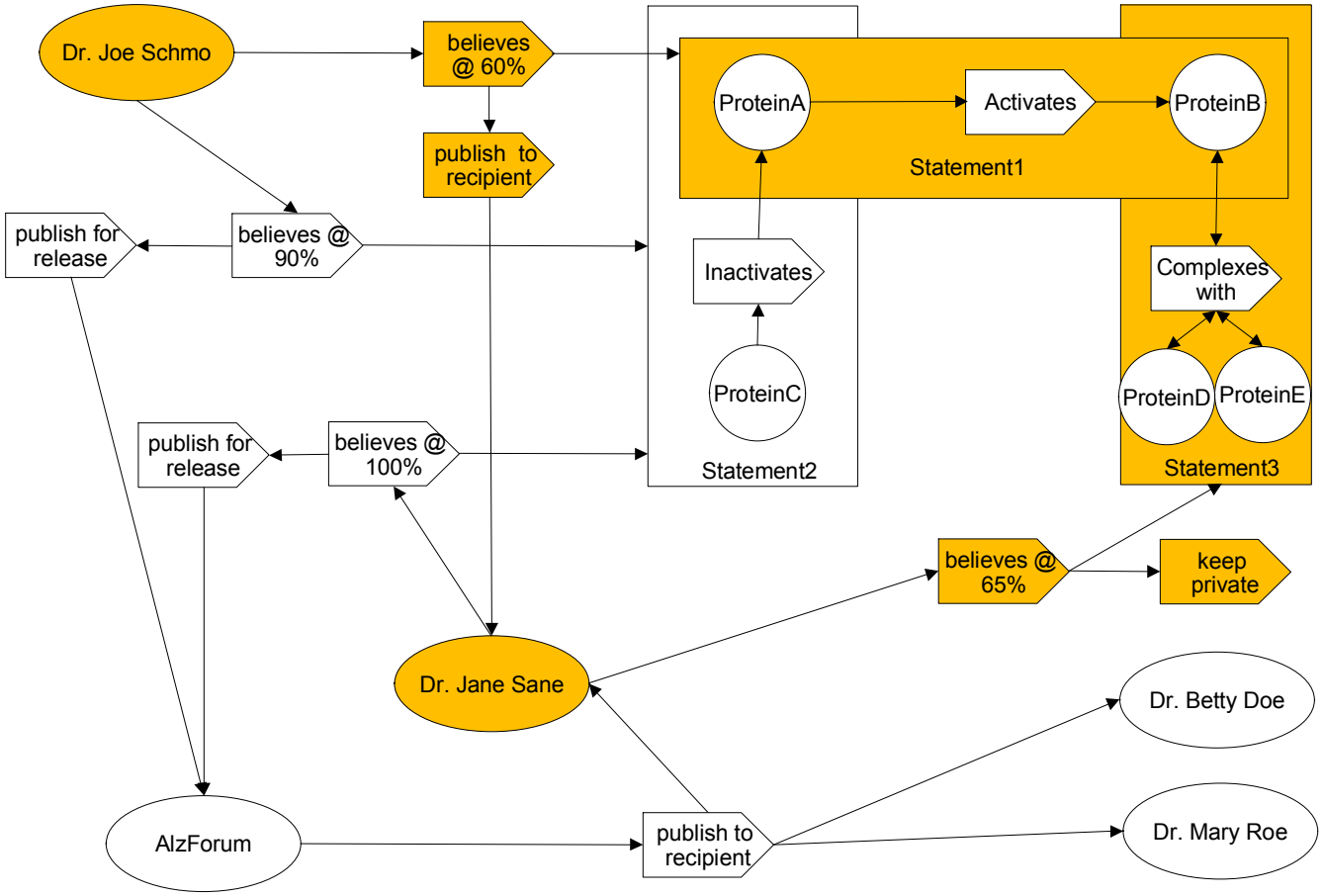
Individual private view of KB



<u>Dr. Sane also sees these "private" statements:</u>

"Dr. Sane believes (65%) that B complexes with D and E"

"Dr. Schmo believes (60%) that A activates B"

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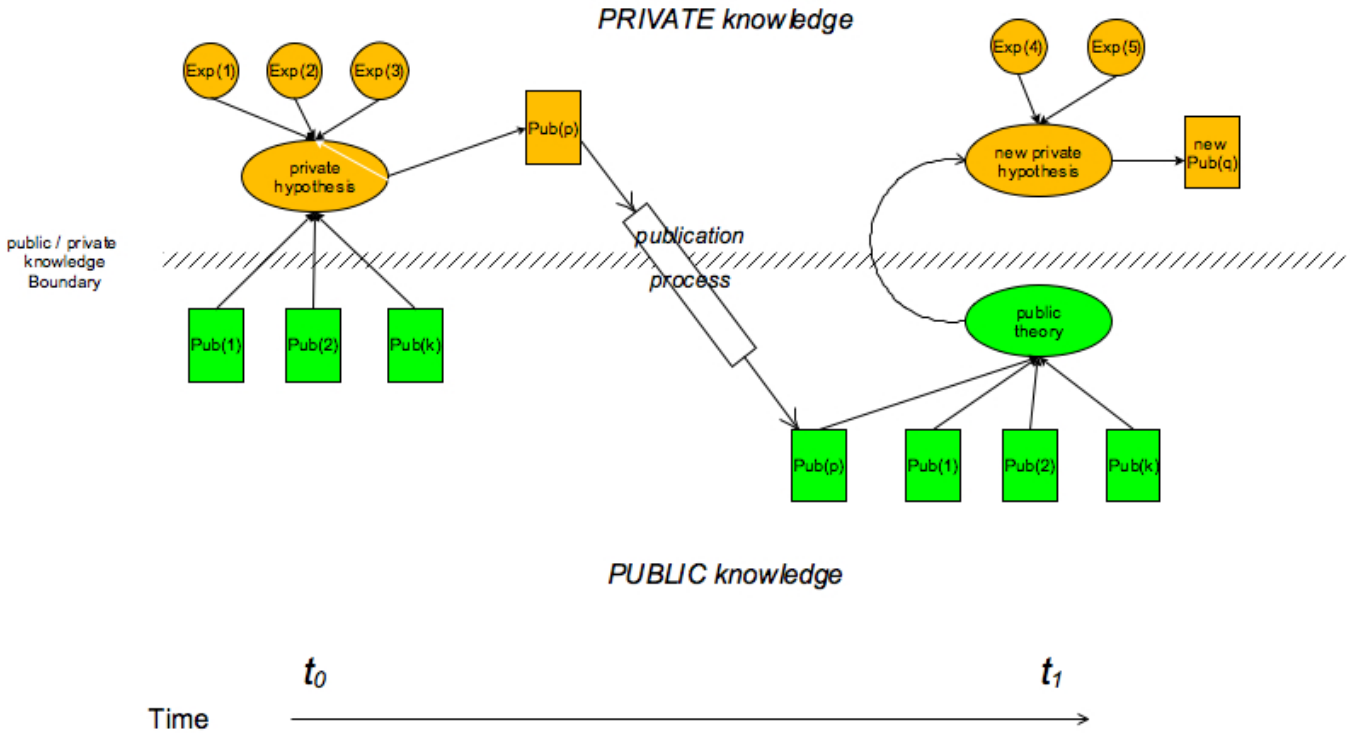
Core ontological model

- ***[–constructive] models*** (Hausser 2000)
  - Spekar-hearer is part of the model structure
    - goal is “to characterize truth”
    - previously seen as associated with science and mathematics
- ***[+constructive] models*** (Hausser 2000)
  - model-structure is part of the speaker-hearer
    - cognition seated in individuals and circumstances
    - previously seen as characteristic of language interpretation
- ***explicit treatment of the hearer***
  - allows a collaboration network to be established
  - externalizes truth maintenance

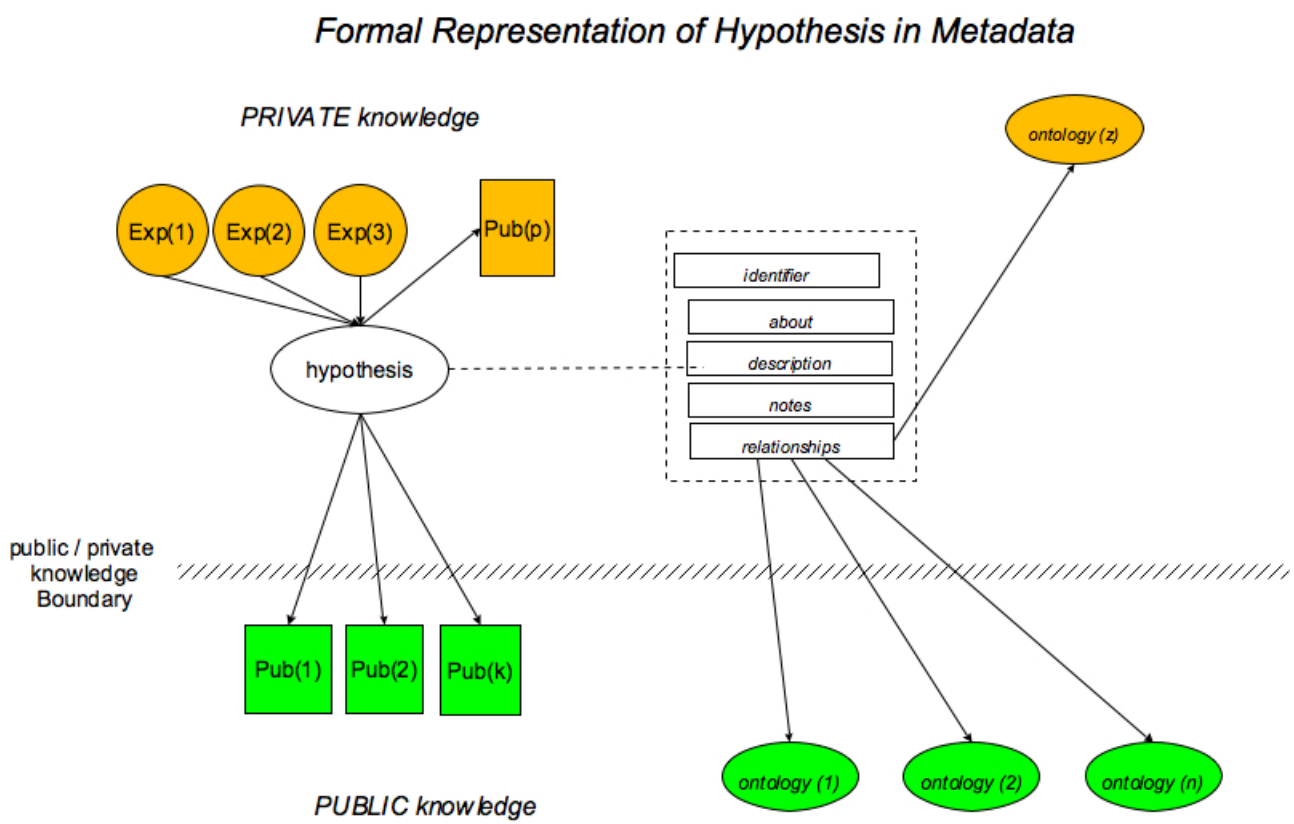
Publication model and ontology alignment

SWAN: Private and Public Concept Spaces

Transition from Private Hypothesis to Public Theory



Hypotheses and ontology alignment



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Data provenance

- Data level:
  - Where did this data come from?
  - Any known corrections/retractions/challenges?
- Information level:
  - What algorithms (and versions) were used?
- Knowledge level:
  - Who made this assertion? Any counter-assertions?
  - What publications /data are referenced?
- Constructive level:
  - Who may see /hear this assertion?
- Trust /security level:
  - Level of trust & security models for content & audience?
  - For the provenance software itself?

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Socialization

- Changing the publication model for science…
- Data & publications = one's career…
- KB curation and scalability…
- Trust model…
- Software development model…

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To Sum Up

- Neurodegenerative diseases are huge problems
- Deep multi-disciplinary understanding required
- Technological basis for deep integration is here
- Potential huge benefit to researchers
- …and most importantly, patients

- We have to think very creatively about how we develop the next generation of Knowledge bases in neuromedicine

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Collaborators

- Alzheimer Research Forum
  - June Kinoshita (co-PI), Elizabeth Wu
- MassGeneral Institute for Neurodegenerative Disease
  - Yong Gao, Georgios Asteris
  - Dora Kovacs, Lars Hernquist, Anne Young
- Brigham and Women's Hospital
  - Dean Hartley
- MIT Computer Science and Artificial Intelligence Laboratory
  - Eric Miller, Ralph Swick
- IBM Advanced Technology Group
  - David Grossman, Sean Martin, Jordy Alboz
- HP Laboratories
  - Andy Seaborne, Steve Cayzer

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