Managing Microarray Knowledge with the Semantic Web
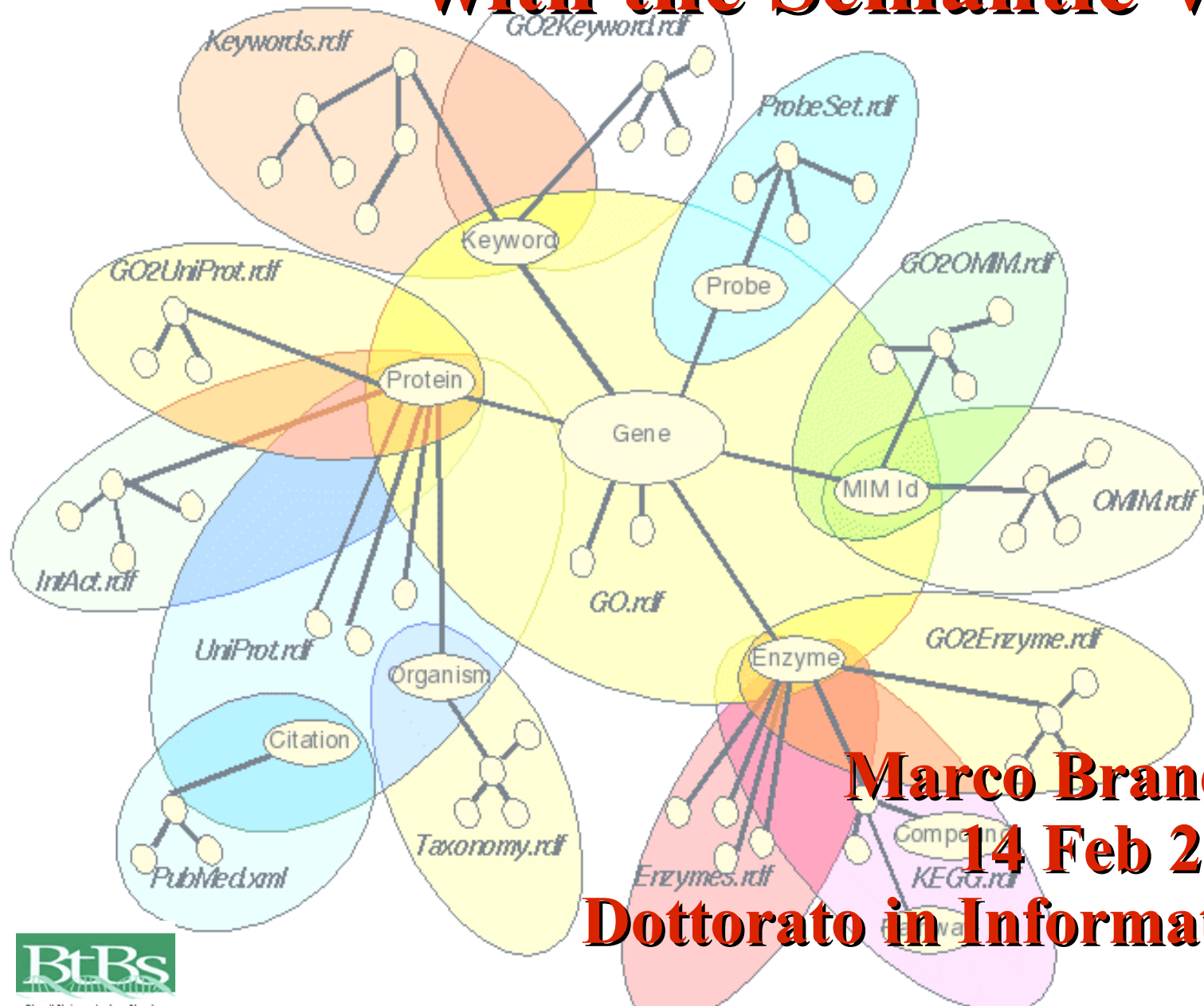
Marco Brandizi
14 Feb 2008
Dottorato in Informatica

Image from: http://www.w3.org/2007/Talks/0130-sb-W3CTechSemWeb

Microarrays and Gene Expression Analysis

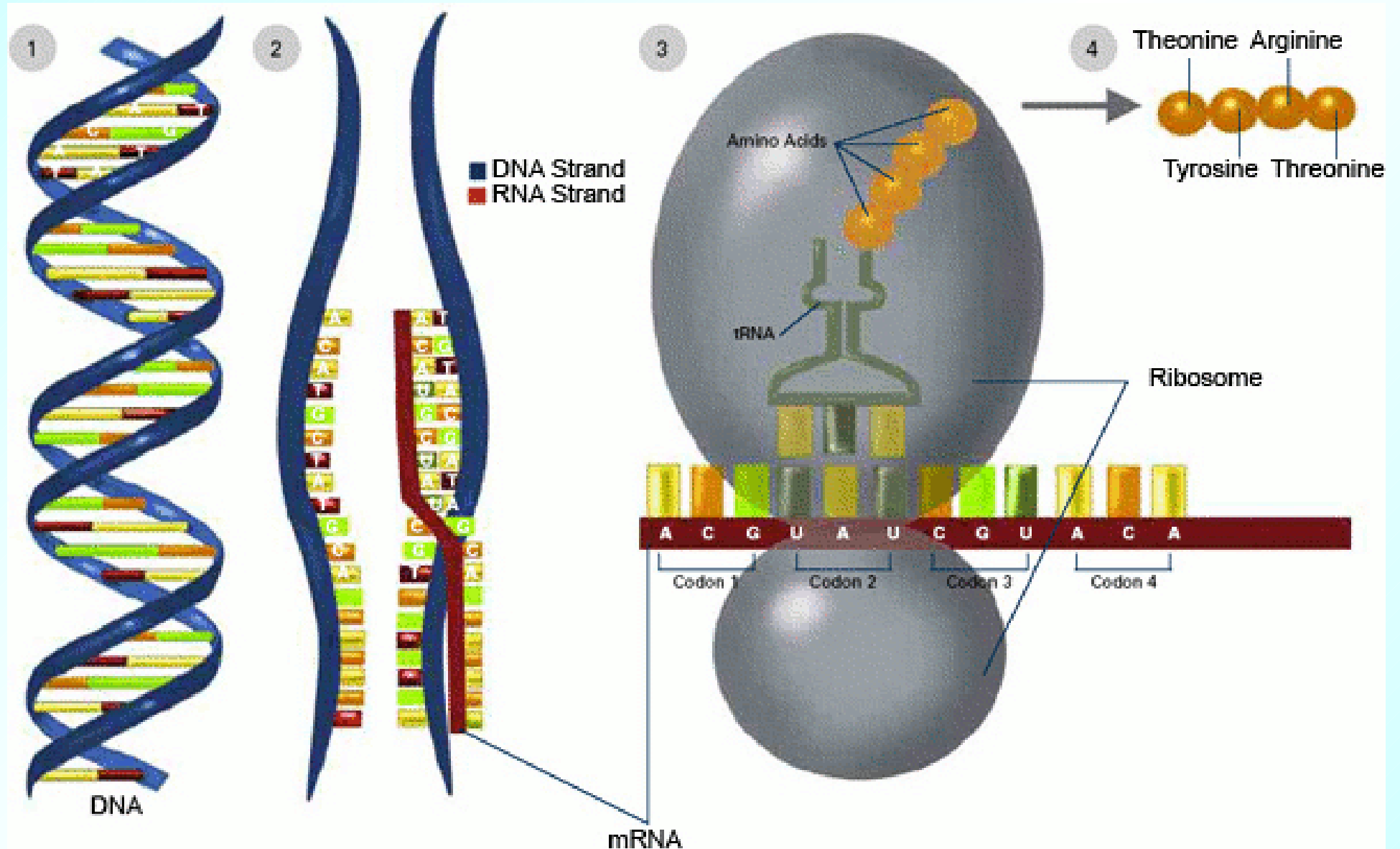**Formal models in Microarray Knowledge**
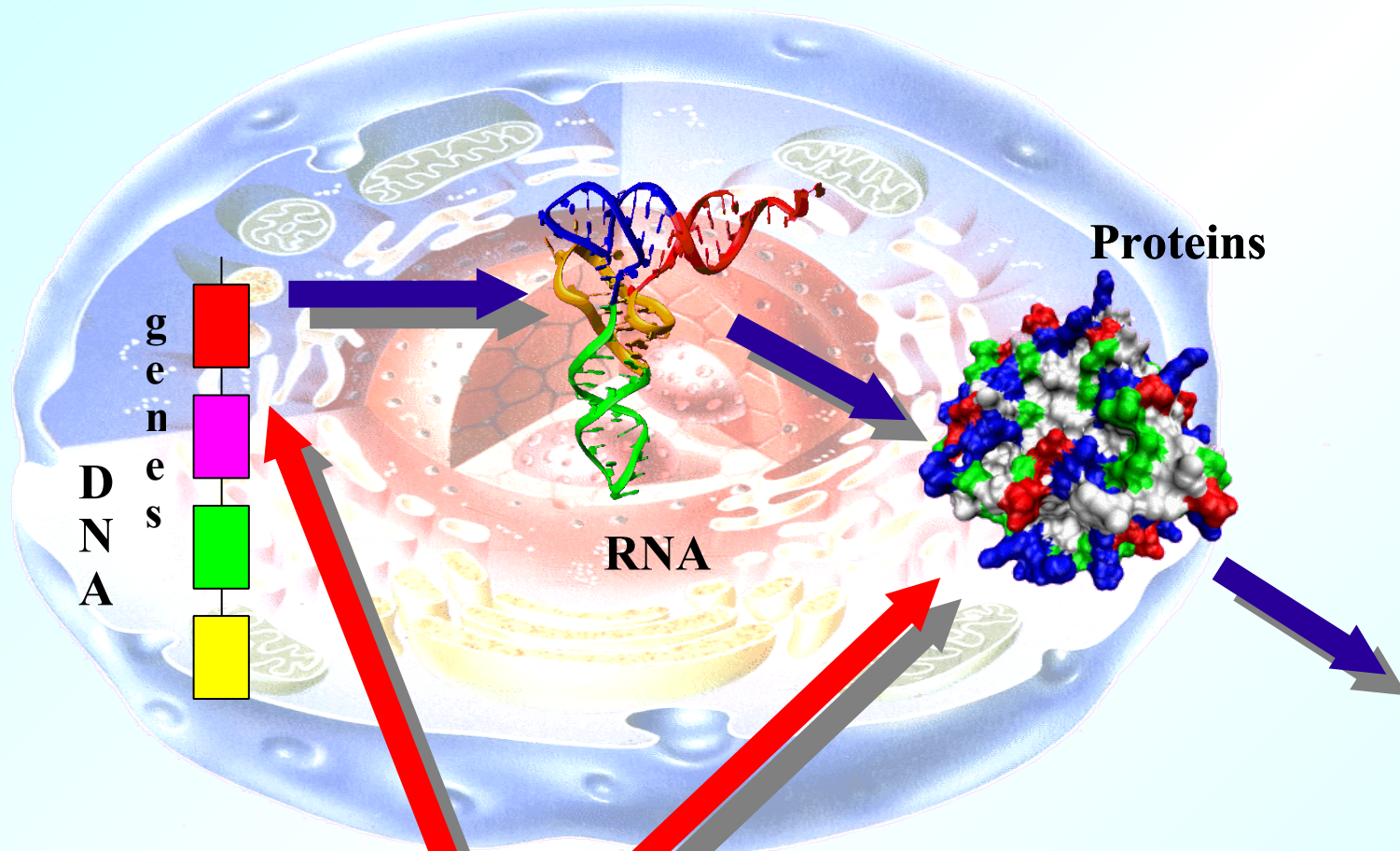
Our Semantic Web based proposal

A demo application

A proposal for Knowledge Ranking

Conclusions/Future

Gene Expression

Gene Expression

genes

DNA

Proteins

RNA

Gene Expression

Life

by Alessandro C...ci(Studio Stalio) - copyright 2000 Andrea dué

Why studying Gene Expression?

- **Functional Genomics**:
  - What is the **function of these genes** (similar expression profiles)?
  - Which genes are involved in Immune response?
- **Genetics studies**
  - Which **gene mutations** characterise this disease?
- **System Biology**
  - Which **pathways** are activated in during cell cycle stages?
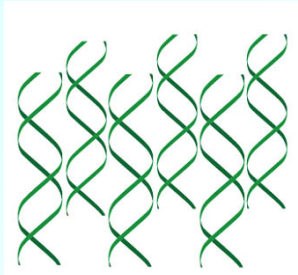 - Which network **modules** explain gene-gene correlation?
- **Diagnostics**
  - A given expression profile may characterise cancer cells, early diagnosis possible
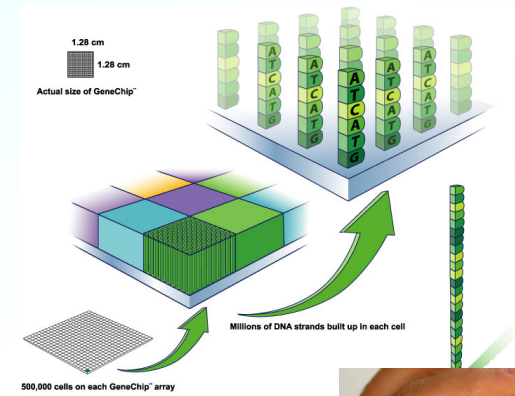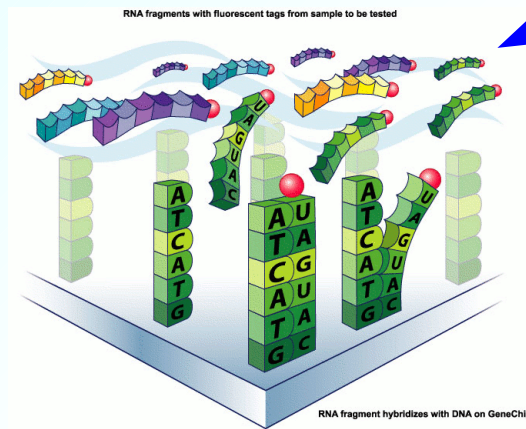
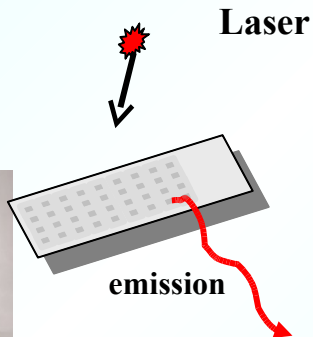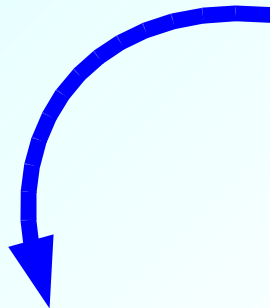# Microarray Technology

Organism (control+treated)

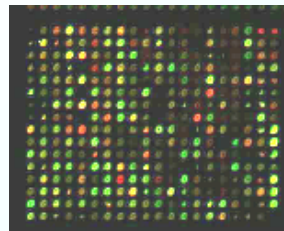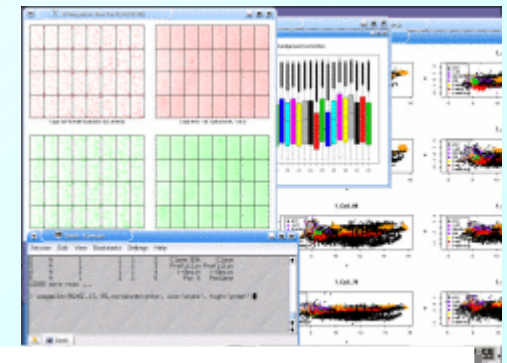RNA fragments, labelling

Microarray Chip

Hybridization

Laser

emission

Scanning/Measurement

Data, Analysis,
New biological knowledge

Why Microarrays?

- It's an **High Throughput Technology**
  - **Thousands of measures**, about thousands of gene, in one single measurement operation (hybridization)
  - **Olistic** approach: we may find insights analysing many factors (genes) at the same time, not gene-by-gene
    - Systems biology: we may model the whole system
  - **Bioinformatics and Statistics methods**
    - Statistical analysis
    - simulation and modelling (e.g. Systems Theory)
    - Data may be publicly distributable and analysed many times, by many people
  - May be **integrated with other HT technologies** (e.g.: Mass Spectrometry)
- May be integrated with **wet lab approaches**

How to represent Microarray Data: MIAME/MAGE Standards

Samples are grouped into **experiments**
- Exeriment meta-data (title, date, objective)
- Experimental **Factors** (indipendent variables)
- **Authors** and Derived **Publications**

- **Organism** and **characteristics** (age, sex...)
- **Treatments** (compound, infection, dose...)
- Preparation and methods (**protocols**, **labelling** substance...)

(Mostly Pub Sources)
- **Gene** Names
- Gene Products
(**Proteins**)
- Gene/Proteins
Biological **Pathways**
and interactions
- Gene/Protein
Sequence
- Other kind of
RNA/DNA sequences
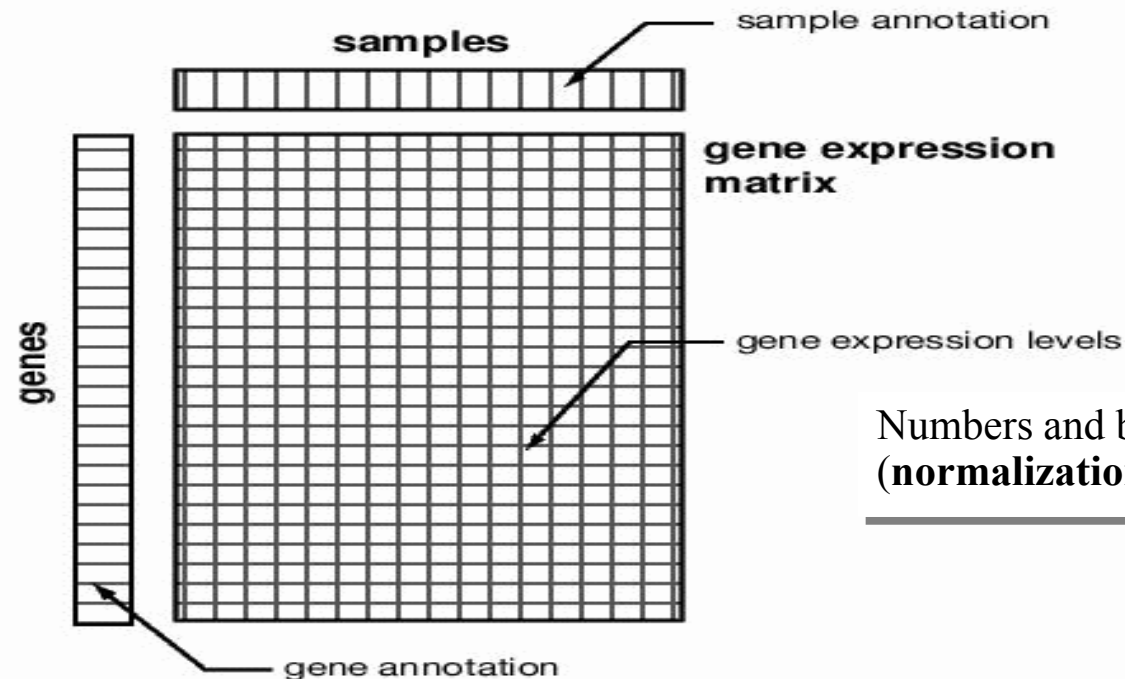
Numbers and basic processing
(**normalization**, **scaling**)

Array Design (which sequences are in the
device, where, grouping of probes)

Why Standard formats?

- **Basically**: experimental activity has to be **understandable** by the whole scientific community and **reproducible**
  - **Comparable** results is also very valuable
- For instance:
  - we may want to compare the expression of a set of known genes, under different conditions, using data from different laboratories
  - **genes** = standards for gene representation (e.g.: Unigene) and annotations (e.g. GeneOntology)
  - compare the **expression** = description of data processing and data production process
  - different **conditions** = terminology for factor types, experimental design
  - different labs = standard **meta-data for experiments**.
- We want redo an experiment to check its reproducibility
  - precise description of **experimental design**, **biological materials**, laboratory **protocols** and the **pipeline** that has lead from the organisms to the final data.
  - description/reference of the **arrays** that have been employed

Microarrays and Gene Expression Analysis

Formal models in Microarray Knowledge

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Conclusions/Future

How is the Transcriptomics Analysis Output?

- **Set of Genes**
  - List of **Differentially Expressed Genes** (Control vs. Conditions)
- **Set of Clusters** (Hierarchical Gene Sets)
  - Bi-Clusters (Both genes and conditions are grouped into clusters
- **Enriched Set of Genes**
  - Sets are classified according to Experimental Factors and/or to biological categories (e.g.: to Gene Ontology or to KEGG pathways)
    - Experimental factor = independent variable that is varied to study the effect of its variation on the gene expression
- More abstract Knowledge
  - **Biological Conclusions or insights**
  - **Papers, Books**
  - Knowledge about materials and methods (often tacit)

  And behind all above: Biological Knowledge

Examples of Microarray Knowledge

- **Genes, Gene products**
  - Under which conditions (exp. factors) is this gene expressed?
  - Which data/experiments do support a transcription profile?
  - Are the genes related to a function expressed under X?
- **Conditions, Experiments**
  - Which genes are expressed on diabetic patients?
  - Which experiments are about dendritic cells and which genes are mostly expressed?
- **Data, Protocols, Methods**
  - For which organism does this protocol perform best?
  - Is this data set, leading to a given conclusion, reliable? Did the experts noted any problem?
  - Is a given platform/array more used with certain experimental designs?
- **People, knowledge authoritativeness**
  - Who is studying these genes?
  - How many times a claim has been concluded by an analysis? By who? What is his/her role? Does he/she have important publications on the topic?

How to represent Results from Microarray Analysis

Natural Language

LOOPED DNA STRUCTURE

More formally

?

Related Work

- Repositories and LIMS
  - Parkinson et al., *ArrayExpress—a public database of microarray experiments and gene expression profiles.* (2007). Ranks genes according to experiments and conditions of expression. Limited overall analysis, no collaboration features.
  - Kapushesky et al., *Expression Profiler: next generation-an online platform for analysis of microarray data.* Allows for management of DEG/clustering lists. Limited collaboration.
  - (More modestly...) Brandizi, Splendiani et. al., *The Genopolis Database*. Allows data sharing among collaborators groups. Gene lists. Focused on Affymetrix/DCs. Limited inference.
- Collaboration Systems
  - **Array Management Manager** by Biodiscovery. Basic analysis features and results sharing. Non standard (web) interface.
  - **Synapsia** by Agilent. Narrative, hypothesis driven discovery and collaboration system. Non standard (web) interface.
- Knowledge-based systems
  - Massar et al., *BioLingua: a programmable knowledge environment for biologists* (2004). Frame-based system for data integration, non microarray-specific, limited user feedback & collaboration.
  - Racunas et al., *HyBrow: a prototype system for computer-aided hypothesis evaluation*. Frame-based system for pathway-based investigation. Limited user feedback and collaboration.

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Our approach: Microarray-specific modelling with the Semantic Web

- **MANN: an OWL model** for representing experiments, results, people, hypothesis/conclusions (more later)
  - **A Web Demo**, based on the Makna Semantic Wiki
    - that shows some real cases
- Examples of pre-crafted **SPARQL queries**, that have biological significance
- A proposal for **ranking OWL-modelled knowledge**

Why The Semantic Web for Biology?

- **Public knowledge** ("resources") that is **highly interrelated**
- Wide **use of WWW** and growing interest for **RDF integration**
  - LSID project
  - HCLS group
- Very **heterogeneous** models, data types, etc.
- **Ontologies** (or similar models) are much needed in Biology and already extensively used
  - Need to conceptualise
  - Need to standardise the conceptualisations and available information
  - Even basic inference may be useful (and still not much used)
  - Increasing use of OWL and DL
- **Similar projects** already existing that make use of OWL and/or SW in general
  - HCLS Demo
  - ART Ontology, Soldatova et al., 2007
  - Ontology for Biological Investigations (OBI), http://obi.sourceforge.net/

The MicroAnnOnto (MANN) OWL Model

- Informally: an Ontology

- Tries to reuse existing models/ontologies (MGED-Ontology, GeneOntology, SKOS, SWRC/COIN)

- Models **Assertions** (e.g.: hypotheses and conclusions) which are supported by Microarray Data, have authors, and more

- Models **Microarray Experiments**, with the aim of linking assertions and data

- Models **Data Evaluation and Ranking**, allowing for user feedback and data quality management (e.g.: precision, significance, likelihood)

- Promotes collaboration: comments, people and roles, papers, conferences

The MANN Model: Basic Classes
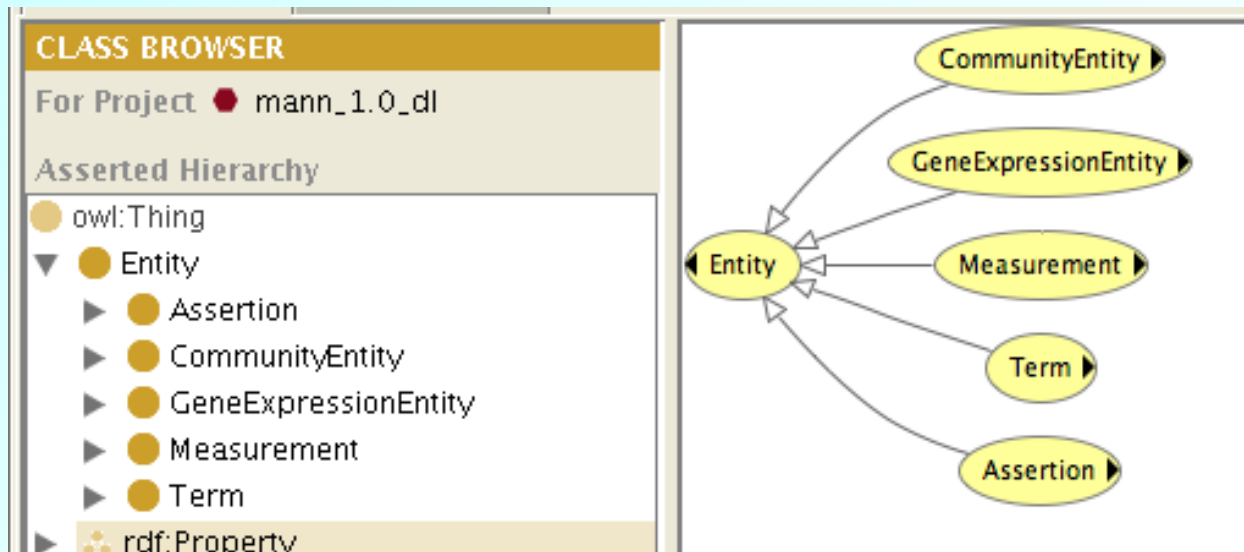
- Basic Properties
  - entityName (short name), entityTitle, entityDescription
  - entityOwner(Entity->PeopleEntity)
  - **evaluation** (Entity->Literal, typically numbers)
  - termAnnotation(Entity->Term)
  - entitySupports(Entity->Entity) more in the follow
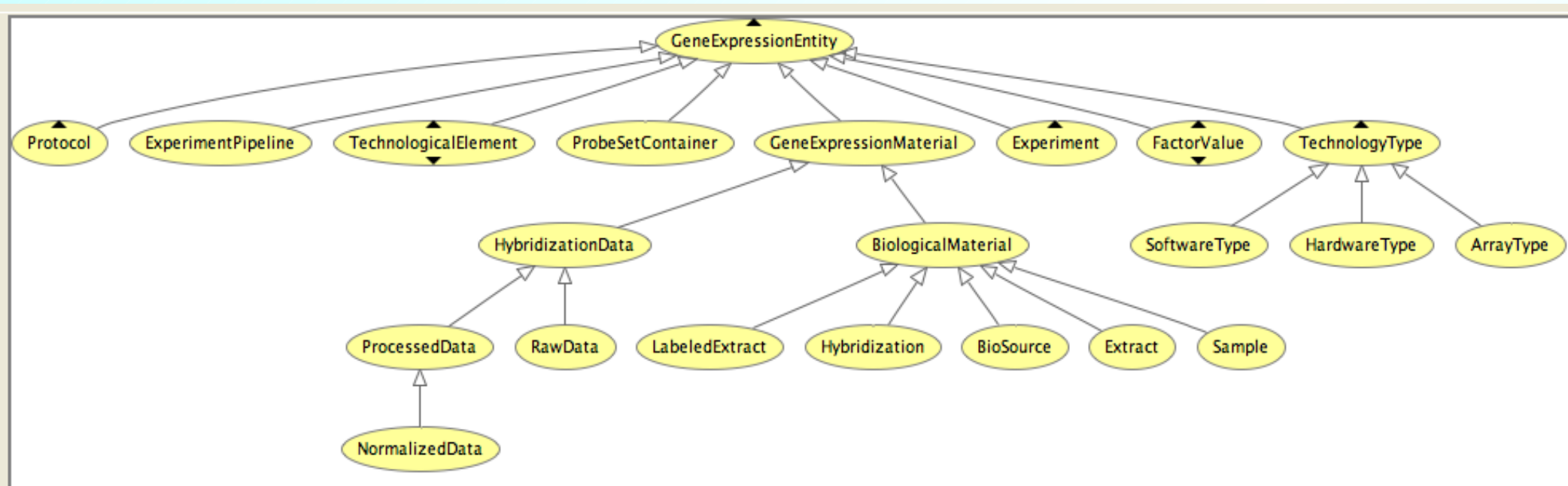
- GE Properties
  - usesGentity(GeneExpressionEntity->GeneExpressionEntity)
  - Specific usage (arrayProbes, arrayHasType)

The MANN Model: Assertions
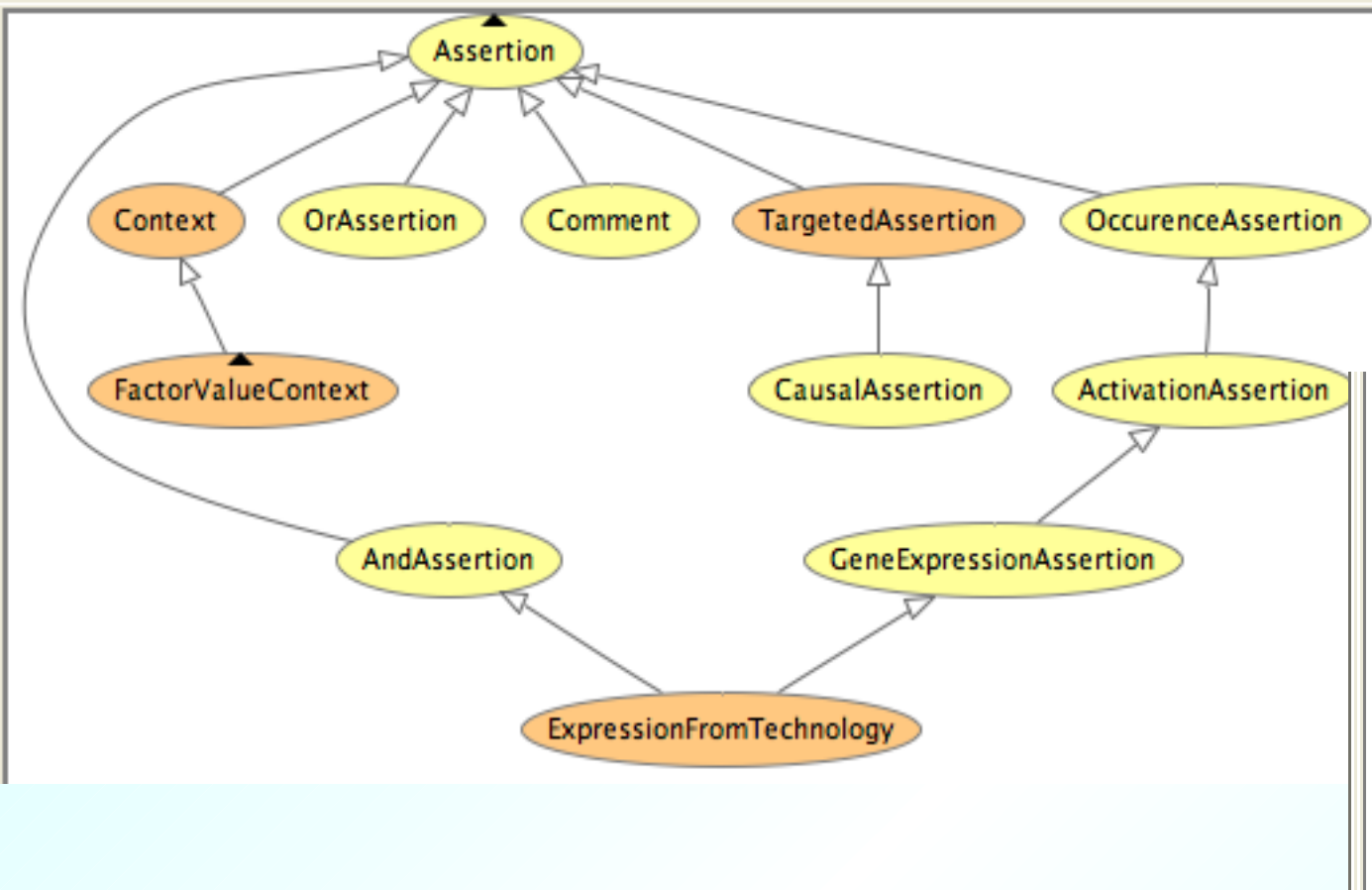
- Assertions have subjects, which are intended in And combination (e.g.: all true at the same time) or in Or combination
- An assertion may have a context to be referred to (e.g.: Gene X is expressSued in leukaemia cells)
- A set of assertion-assertion properties is available
- Supporting data, authors, terms and other attributes may be added

The MANN Model: Community Entities

- Inspired by SWRC+COIN
  - To be integrated
- Roles for CommunityEntity(s) may be important in searching and ranking
  - e.g.: an assertion stated by a professor could be ranked more than one stated by a PhD student
- For the same reason a set of role-role properties is defined
- Applicability of this part is currently limited by data availability
  - Co-citation is one of the available things

- cooperatesWith ↔ cooperatesWith
  - organizationHasManager ↔ isManagerOfOrg
  - studiesAtOrganization ↔ organizationHasStu
- isLeaderOf ↔ hasLeader
  - isHeadOf ↔ hasHead
  - isSupervisorOf ↔ isSupervisedBy
  - isCoordinatorOf ↔ coordinatedBy
  - isManagerOfPerson ↔ personHasManag
  - isManagerOfOrganization ↔ organizatior
- hasHead ↔ isHeadOf
- organizationHasStudent ↔ studiesAtOrganiz
- isEmployeeOfOrganization ↔ organizationH
  - isManagerOfOrganization ↔ organizatior
- organizationHasEmployee ↔ isEmployeeOfC
- personHasManager ↔ isManagerOfPerson
- teachesAtOrganization ↔ organizationHasTe
- hasLeader ↔ isLeaderOf
- organizationHasTeacher ↔ teachesAtOrgani
- coordinatedBy ↔ isCoordinatorOf
- hasCollegue

The MANN Model: Terms

- Inspired by SKOS (to be integrated)
- Annotation with terms is a semiformal way to semantically characterise entities, exp. when no further formalisation is available
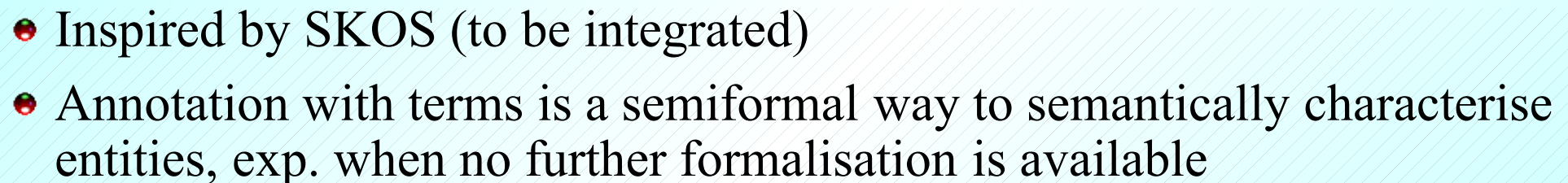
The MANN Model: Application example
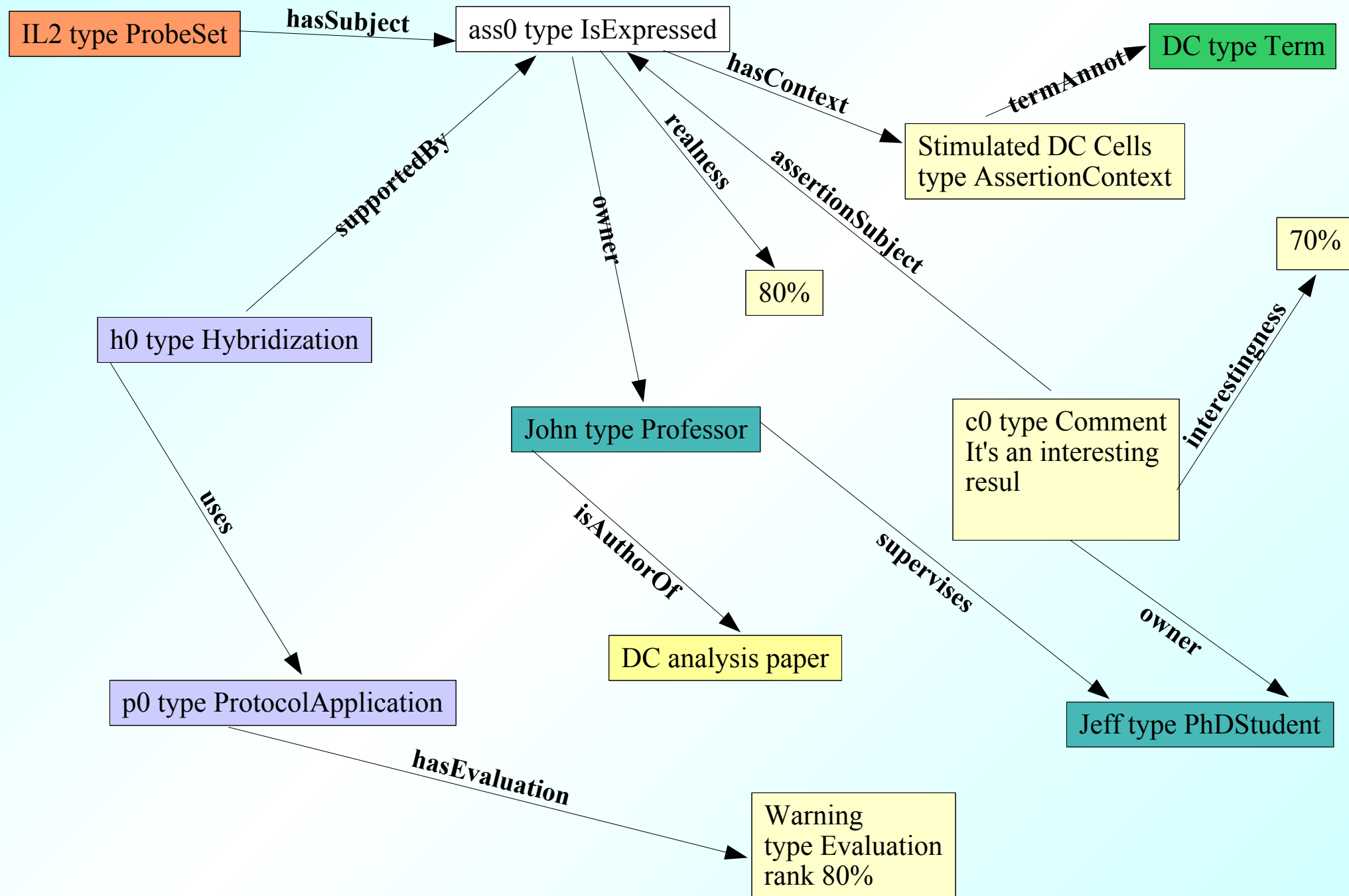
IL2 type ProbeSet

hasSubject

ass0 type IsExpressed

DC type Term

hasContext

termAnnot

Stimulated DC Cells type AssertionContext

supportedBy

owner

realness

assertionSubject

h0 type Hybridization

80%

70%

interestingness

uses

John type Professor

c0 type Comment It's an interesting resul

isAuthorOf

supervises

owner

p0 type ProtocolApplication

DC analysis paper

Jeff type PhDStudent

hasEvaluation

Warning type Evaluation rank 80%

The Gene Expression

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A Demo Application: MannMakna Wiki

[http://ikewiki.salzburgresearch.at/]

[http://www.aifb.uni-karlsruhe.de/WBS/hha/papers/SemanticWikipedia.pdf]

Makna and Jena

- Makna: a Semantic Wiki, based on JSPWiki
  - Has a **simple syntax** for editing contents
  - Has a **simple interface**, where the semantic structure of a page/resource is clearly shown
  - It's based on Jena
- Jena: a comprehensive framework for the Semantic Web, including features like:
  - Persistance with DBMS back-ends (we use MySQL)
  - OWL support, OWL reasoning, either via DIG or with built-in reasoners
  - **Rule system** that allows for adding custom inference
  - SPARQL
- Pro and Cons
  - Makna has limited support for pages with **many statements** (ranking and filtering being developed)
  - Makna badly supports **some SW features** (e.g.: URIs that are not wiki URLs, namespaces, labels, typed literals)
  - **Jena performance** (esp. in reasoning) is not great (optimizations being developed)

An real case stored in MannMakna

A Type I IFN-Dependent Pathway Induced by *Schistosoma mansoni* Eggs in Mouse Myeloid Dendritic Cells Generates an Inflammatory Signature[1]

François Trottein,[2]* Norman Pavelka,[2]† Caterina Vizzardelli,† Veronique Angeli,* Claudia S. Zouain,* Mattia Pelizzola,† Monica Capozzoli,† Matteo Urbano,† Monique Capron,* Filippo Belardelli,‡ Francesca Granucci,† and Paola Ricciardi-Castagnoli[3]†

- 2 experiments with design: Stimulation of DCs with Schistosoma + several time points + 2 biological replicas per time point
- Main results was:
  - A set of 283 DEGs
  - Functional classification of the first 98 DEGs
  - *"Taken as a whole, our data provide molecular insights into the immune evasion mechanism of schistosomula and suggest an unexpected role for type I IFN in the innate response to **helminth eggs**"*
    - **CausalAssertion**, **subject**:Helminthiasis(UMLS_ST:T047), **target**: IFN I response (GO:0032606)

An real case stored in MannMakna

An real case stored in MannMakna

A Demo Application: MannMakna Wiki

Try a Semantic Search   Add a statement about SchistosomaConclusions   Delete a statement   Edit this page   More info   Attach file

SchistosomaConclusions

GeneExpressionAssertion^type

The role of IFN/I in the innate response to helminth eggs

The following conclusion has been given in the Schistosoma paper⏩.

taken as a whole, our data provide molecular insights into the immune evasion mechanism of schistosomula and suggest an unexpected role for type I IFN⭐ in the innate response to helminth eggs⭐

The assertion is supported by EGNPS1⭐ and EGNPS2⭐ experiments.

Go to top   Edit this page   More info...   Attach file...
This page last changed on 10-Nov-2007 18:54:46 GMT by 127.0.0.1.

Properties of this page:

Predicate	Object
seeAlso	Schistosoma
entityIsPositivelySupportedBy	EGNPS1
entityIsPositivelySupportedBy	EGNPS2
type	GeneExpress
assertionSubject	GO_003260
assertionContext	NCI_C35002

Statements about this page:

no matching statements found. Why don't you add one?

Suggested actions:

show explicit+inferenced

Search for Resources with

- seeAlso SchistosomaPaper
  Explicit Inferenced
- entityIsPositivelySupportedBy EGNPS1
  Explicit Inferenced

A Demo Application: MannMakna Wiki

A Demo Application: MannMakna Wiki

Prepared queries: genes -> conditions

```
SELECT
   DISTINCT ?pbset ?name ?title ?geAss ?ctx ?ctxTerm
WHERE
{ ?pbset rdf:type mann:ProbeSetContainer
  .
   {     # _____ Basic Attrs _____

       { ?pbset mann:entityTitle ?title . FILTER regex( ?title, "$keywords", "i" )
           . OPTIONAL { ?pbset mann:entityName ?name }
       } UNION {
           ?pbset mann:entityName ?name . FILTER regex( ?name, "$keywords", "i" )
           . OPTIONAL { ?pbset mann:entityTitle ?title }
       }
       # _____ Term Annotations _____

       UNION {
           ?pbset mann:entityTermAnnotation ?term
           . ?term mann:entityTitle ?termTitle
           . FILTER regex( ?termTitle, "$keywords", "i" )
           . OPTIONAL { ?pbset mann:entityTitle ?title }
           . OPTIONAL { ?pbset mann:entityName ?name }
       }
   }

  # _____ Where they are expressed _____
  .
  OPTIONAL {
      ?geAss rdf:type mann:Assertion;
             mann:assertionSubject ?pbset
           . OPTIONAL {
                   ?geAss mann:assertionContext ?ctx . ?ctx
                   mann:geExperimentalFactorAnnotation ?ctxTerm
               }
   }

}
```

- Parameters coming from user Input (simple code written)
- Works over the inferred model
- Results may be integrated into the Wiki (search function and current page statements)

Prepared queries: conditions->genes

```
SELECT
   DISTINCT ?pbset ?pbsTitle ?geAss ?ctx ?ctxTerm ?ctxTermTitle ?expLevel
WHERE
{
   ?geAss rdf:type mann:GeneExpressionAssertion;
          mann:assertionSubject ?pbset . ?pbset rdf:type mann:ProbeSetContainer

   . OPTIONAL { ?pbset mann:entityTitle ?pbsTitle }

   . OPTIONAL {
     ?geAss  mann:intensity ?expLevel
     . FILTER ( xsd:float ( ?expLevel ) > $level )
   }

   .
   {
     { # ___ Match the URI ___
       ?geAss mann:assertionContext ?ctx
       . ?ctx mann:geExperimentalFactorAnnotation ?ctxTerm
       . FILTER regex ( str ( ?ctxTerm ) , "$keywords", "i" )
       . OPTIONAL { ?ctxTerm mann:entityTitle ?ctxTermTitle }
     }

     UNION
     { __ Or match the Title __
       ?geAss mann:assertionContext ?ctx
       . ?ctx mann:geExperimentalFactorAnnotation ?ctxTerm
       . ?ctxTerm mann:entityTitle ?ctxTermTitle . FILTER regex( ?ctxTermTitle,
   "$keywords", "i" )
     }
   }

}

ORDER BY DESC(xsd:float(?expLevel))
```

Prepared queries

Find Genes expressed under given conditions — MannMakna

http://localhost:8080/mannMaknaExtra/query/condGenes/show.jsp?keyword=Inflammation&level= ▼ → | Google

Find Genes expressed under given conditions, Results:

mkb:92694_at, Chitinase 3-like 3

Involved/Expressed in: mkb:EGNPS1_inflammation_Egg_0h_high, context: mkb:Inflammation condition: mkb:InflammationTerm, level: 1.74

mkb:95597_at, PGG/H

Involved/Expressed in: mkb:EGNPS1_inflammation_Egg_0h_high, context: mkb:Inflammation condition: mkb:InflammationTerm, level: 1.74

mkb:99991_at, Il17r

Involved/Expressed in: mkb:EGNPS1_inflammation_Egg_0h_high, context: mkb:Inflammation condition: mkb:InflammationTerm, level: 1.74

Done

MANN Rules: Reified relations

```
-> (mann:NormalizedData mann:usesMaterialInPipelines mann:RawData).
-> (mann:HybridizationData mann:usesMaterialInPipelines mann:BiologicalMaterial).
-> (mann:Hybridization mann:usesMaterialInPipelines mann:LabeledExtract).
-> (mann:LabeledExtract mann:usesMaterialInPipelines mann:Extract).
...

#
# Inference about Material usage:
#  If x type Class1, y type Class2, Class1 usesMaterialInPipelines Class2,
#    x,y in the same pipeline
#  THEN x uses y
#
# For instance: a sample uses a source that is in the same pipeline
#
[materialPipelineUse:
 (?matx mann:usesGEntity ?maty)
 <-
  (?ep mann:pipelineMaterial ?matx),
  (?ep mann:pipelineMaterial ?maty),
  (?matx rdf:type ?MatTypeX),
  (?maty rdf:type ?MatTypeY),
  (?MatTypeX mann:usesMaterialInPipelines
                 ?MatTypeY)
]
```


Single Pipeline
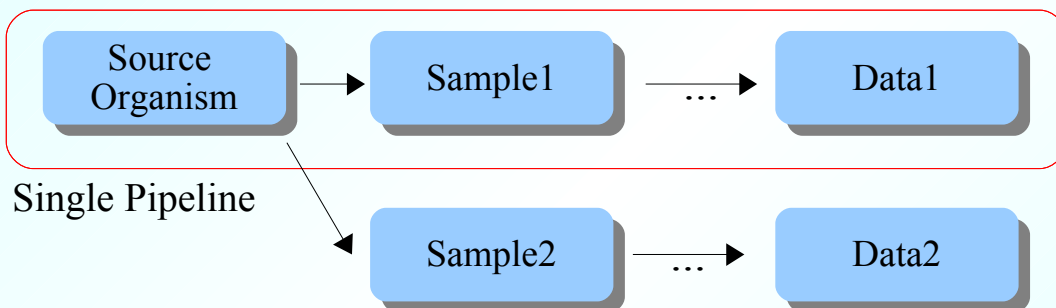
Try a Semantic Search   Add a statement about EGNPS2_Pipeli

EGNPS2_Pipeline4

ExperimentPipeline type for the Experiment E-GNPS-2

Source: SRC-GNPS-E2-1 ⭐
Grow Protocol: P-GNPS-GRWCND-E2-SRC1 ⭐
Sample: SMP-GNPS-E2-2 ⭐
Treatment Protocol: P-GNPS-TRT-E2-SRC1-SMP2 ⭐
Extraction Protocol: P-GNPS-EXT2 ⭐
Extract: XTR-GNPS-E2-2 ⭐
Labeled Extract: LBL-GNPS-E2-2 ⭐
Hybridization Protocol: P-GNPS-HYB6 ⭐
Hybridization: HYB-GNPS-E2-3 ⭐
Scanning Protocol: P-GNPS-SCN7 ⭐
Image Analysis Protocol: P-GNPS-IMG8 ⭐
Raw Data: EGNPS2H3.cel ⭐
Normalization Protocol: P-GNPS-NRM9 ⭐
Final (Normalized) Data: E-GNPS-2_fdm.txt ⭐

Go to top   Edit this page   More info...   Attach file...
This page last changed on 16-Aug-2007 23:00:35 BST by 127.0.0.1.

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Spread Activation Search/Ranking

- Basic SA

$$I_j = \sum_i w_{ij} \cdot O_i \cdot \beta$$
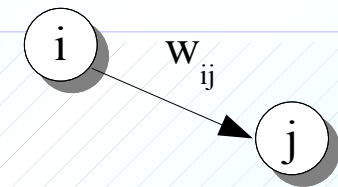
The ranking of node j is a weighted sum of the ranking of incoming nodes. The weight depends on the edges, for instance on the relation type.

$$I_i = f(O_i) \quad \text{in the simplest case} \quad I_i = O_i$$

```
queue = initialQueue(); stopFlag = false;
while ( !queue.empty() && !stopFlag )
  i = queue.pull()
  if ( checkPreRestrictions(i) )
    for each j in (i,j)
      j.in += w(i,j) * i.out * beta
      j.out = f(j.in)
      if ( !j.visited )
        queue.push ( j )
      }
    }
  }
  stopFlag = checkPostRestrictions()
}
```
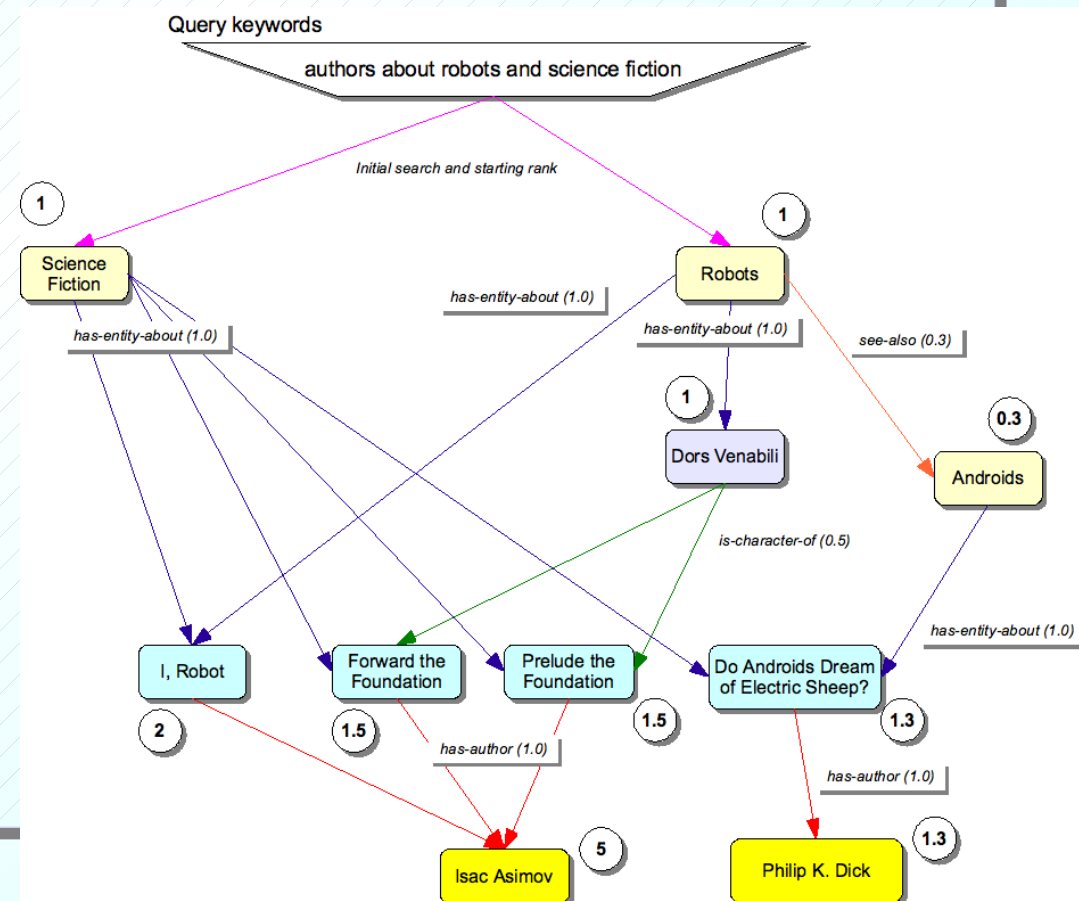
Spread Activation Search/Ranking

- May be generalised to RDF graphs, with an available Query language (SPARQL)
- We may define a set of SPARQL queries, which receive the current node i as parameter and return a set of semantically linked "outgoing" nodes j: {Query$_k$(i)}
- The propagation of activation in the algorithm is done according to:

$$\forall\, j \in Query_k(i): I'_j = I_j + w_k \cdot O_i \cdot \beta$$

- Initial ranking too may be arranged with SPARQL or rules
- Again, it may well work with the inferred graph
- May be flexibly used for either ranking or searching from an initial set of nodes

SW Spread Activation

- Initialisation, evaluated entities

```
For ech x in:
  SELECT ?x WHERE ?x mann:evaluation ?v
do
  x.out += v
```

- Initialisation, evaluated entities

```
For each x in:
  SELECT ?x WHERE ?x rdf:type mann:Assertion
  x.out += 1
```

  - may use inference (sub-classes of Assertion)

- Propagation of evaluations given by comments

```
Starting from c, for each x in:
  SELECT ?x WHERE
    $c rdf:type mann:Comment
    $c mann:assertionSubject ?x
do
  x.out += 0.8 * c.out * beta
```

- Propagation of support

```
Starting from s, for each x in:
  SELECT ?x WHERE $s mann:entityPositivelySupports ?x
do
  x.out += s.out * 0.8 * beta
```

  - may use inference (sub-properties)

  - similar query for negative support (neg. weight)

SW Spread Activation

- Author-based ranking

```
Starting from a, for each x in:
   SELECT ?x WHERE
     $a rdf:type mann:Person
     ?x mann:Experiment
     ?x mann:hasPrincipalInvestigator $a
do
   x.out += $a.out * beta
```

- similar for hasInvestigator (with minor weight)
- may be refined considering Person (student, professor, etc.) or the role played by the person (worksWith etc.)
- Other approaches may be used to provide an initial ranking of persons or their publications (e.g.: co-citation, IF, Social Network Analysis)

SW Spread Activation

- A rule for gene assertion counting

```
[(?ass mann:assertionSubject ?pbset)
 (?ass mann:assertionContext ?ctx)
 (?ctx mann:entityTermAnnotation ?term)
=>
 addSupportToGExpression ( ?pbset, ?term, ?ass )
```

- For each new pair of probeset/term, adds/create the statements:

```
[<id> rdf:type InferredGExpression
      mann:assertionSubject ?pbset
      mann:assertionContext [ <ctx:id> mann:entityTermAnnotation ?term]
      mann:supportedBy ?ass]
```

  - i.e.: sum-up pairs of probeset/term
  - the propagation of support will automatically weight this synthesising assertion, the more it is asserted the more it is ranked
  - if the original assertion is ranked according to several criteria (e.g.: author, evaluation, etc.), then this is propagated too

Microarrays and Gene Expression Analysis

Formal models in Microarray Knowledge

Our Semantic Web based proposal

A demo application

A proposal for Knowledge Ranking

Conclusions/Future

Some words of conclusion

- The **Semantic Web is increasingly being used in Life Sciences**
  - mostly because of heterogeneous information to be integrated

- **Ontologies are common as well, reasoning will hopefully be used** more in the future of Life Sciences
  - Expressive formalization of Biological Knowlegde
  - Even the basic inference is useful
  - Problems to be solved: scalability, performance

- **We have shown an example** of all of the above
  - A simple OWL model that reuse existing ontologies and formalise a piece of knowledge previously not machine-readable
  - A simple demo application that used the model
  - Examples of how to exploit the semantic content provided by the model

Possible future developments

- **Refine** MANN and integrate existing ontologies
  - Try to reduce verbosity (of assertions)
  - More Ontologies Integration
- Experiment with **SW/SA**
- From the demo to a more useable application
  - **Better import** services and **Integration** in other Microarray Management Systems (e.g. BASE)
  - Improve the UI, **AJAX and Visual editors**

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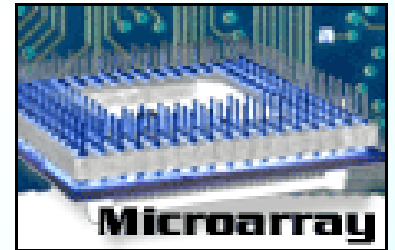
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