Formal Representation and Reasoning for Microscopic Medical Image-Based Prognosis. Application to Breast Cancer Grading.

Représentation et Raisonnement Formels pour le Pronostic basé sur l'Imagerie Médicale Microscopique. Application à la Graduation du Cancer du Sein.

PhD Thesis

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Timisoara, 22 October 2010

Outline

1. Context

- **What is Knowledge representation?**
- **Types of Knowledge Representation**
- **Knowledge Representation in Medical Applications. Breast cancer Grading (BCG)**

2. My research directions

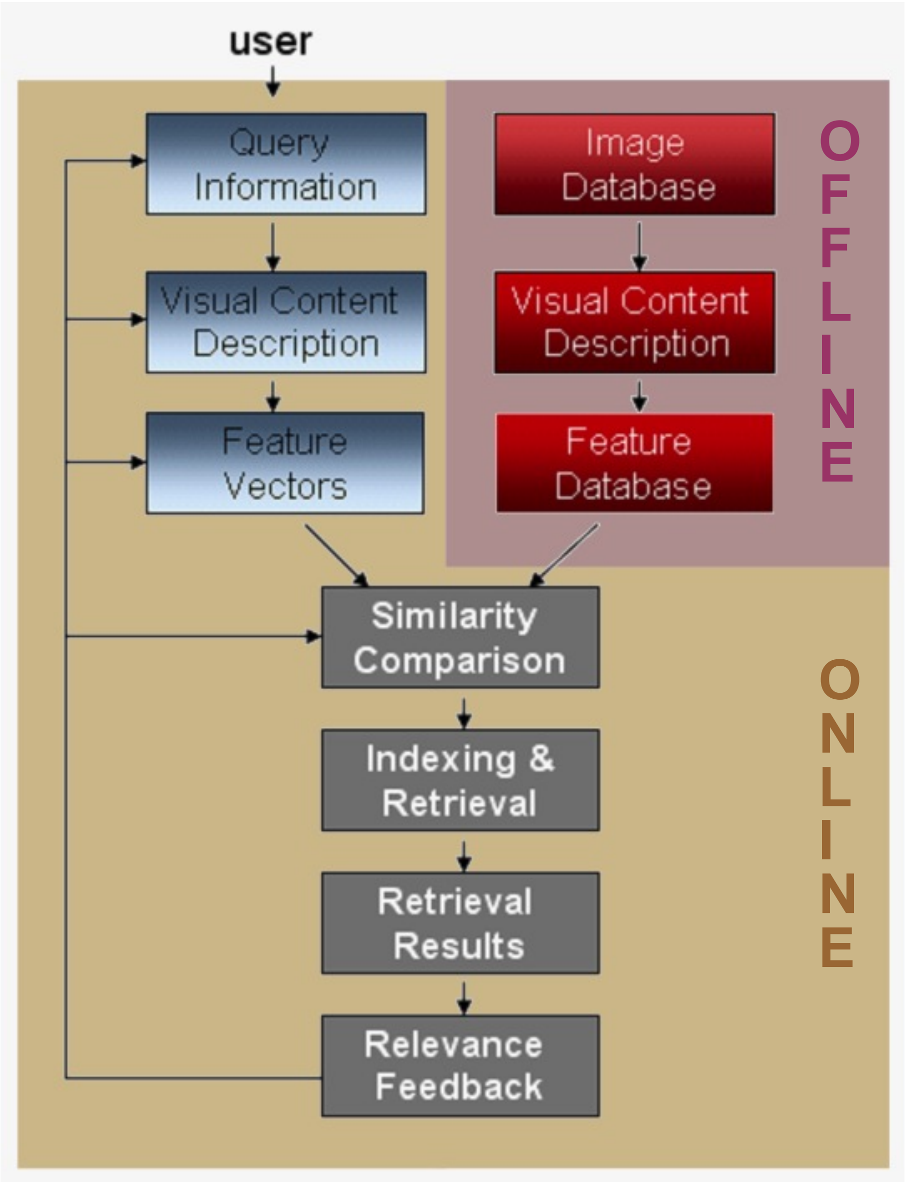
- **Define a Methodology for Knowledge Representation in BCG**
- **Model a Breast Cancer Grading Ontology (BCGO)**
- **Integrate BCGO into Cognitive Microscope Framework**

3. Conclusions and Future Work

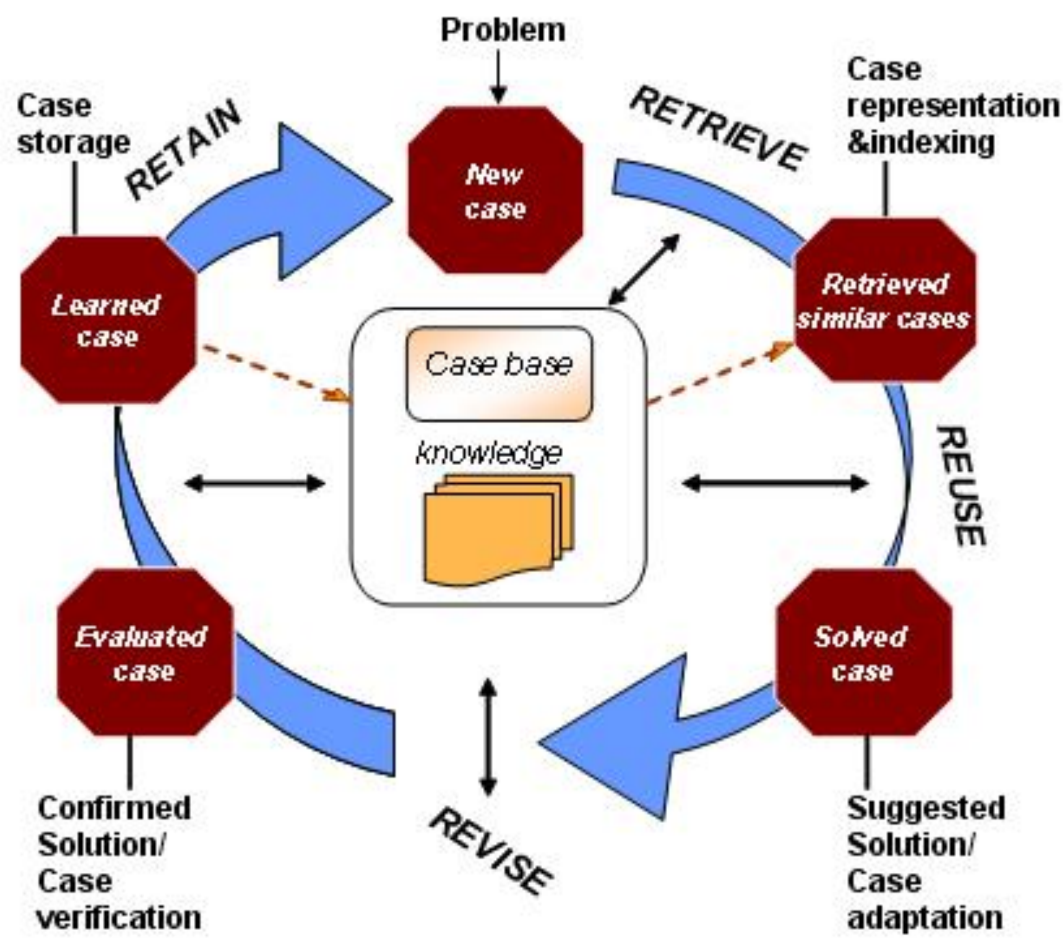
- Knowledge Representation [Davis et al., 1993] –cognition & perception
  - **1. A substitute for the thing itself by which an entity *thinks* instead of *acting*- determine consequences**
  - **2. A set of *ontological commitment***
  - **3. A fragmentary theory of *intelligent reasoning* : *conception, set of inferences***
  - **4. A medium for pragmatically *efficient computation***
  - ***5. A language* in which we say things about the world**

- Qualitative representation versus quantitative representation
  “the aquarium metaphor” [Freksa, 1991]

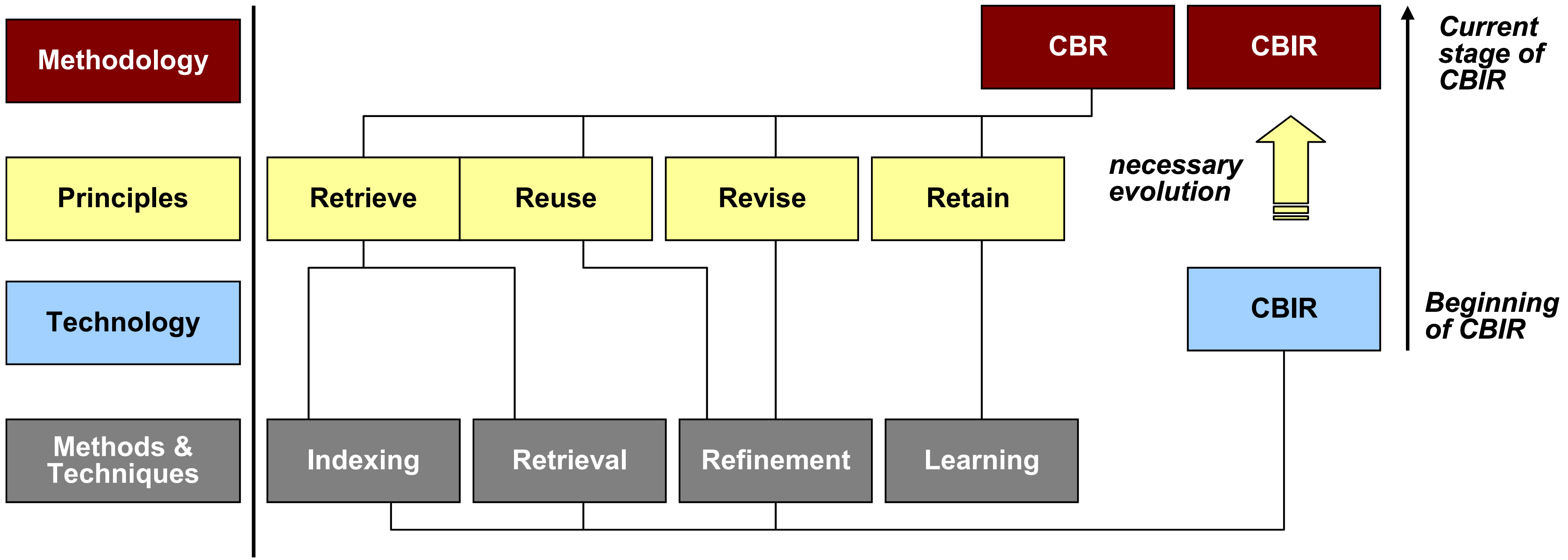
- Content-Based Image Retrieval (CBIR)
  - *image similarity-based retrieval* [Long et al., 2003] (4-5)
  - image-based *reasoning* [Sciacio et al., 2002] (3)

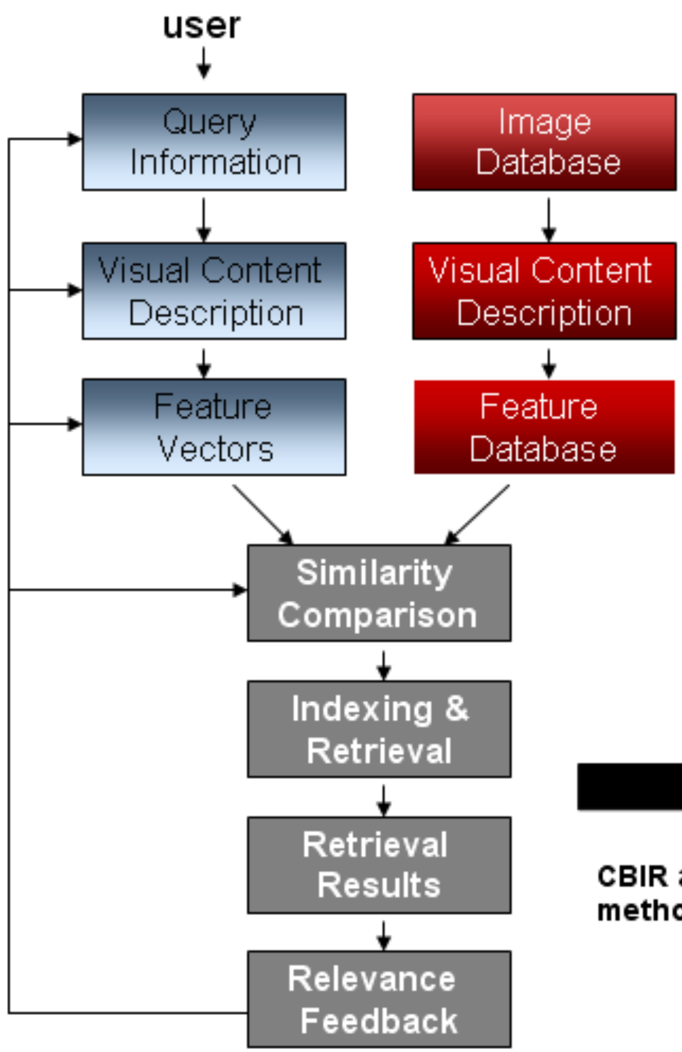


- Case-Based Reasoning (CBR)
  - similar past problems solutions to
    solve new problems
    [Aamodt and Plaza, 2004] (3-5)
  - experience-based approach (medicine)



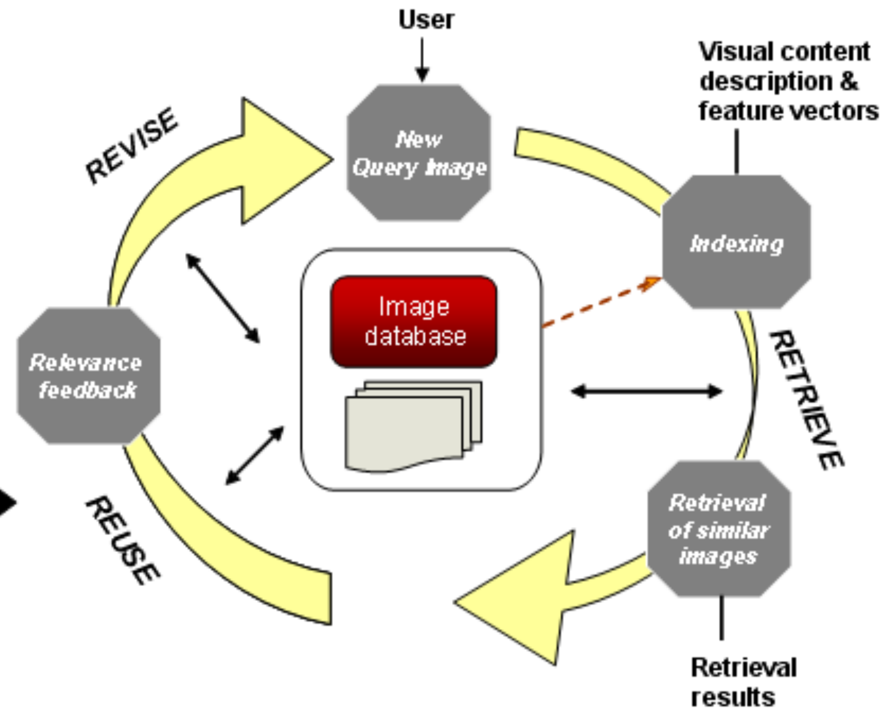
Methodology or Technology ? [Tutac, 2009a]





CBIR functional diagram

CBIR as methodology



CBIR Res cycle

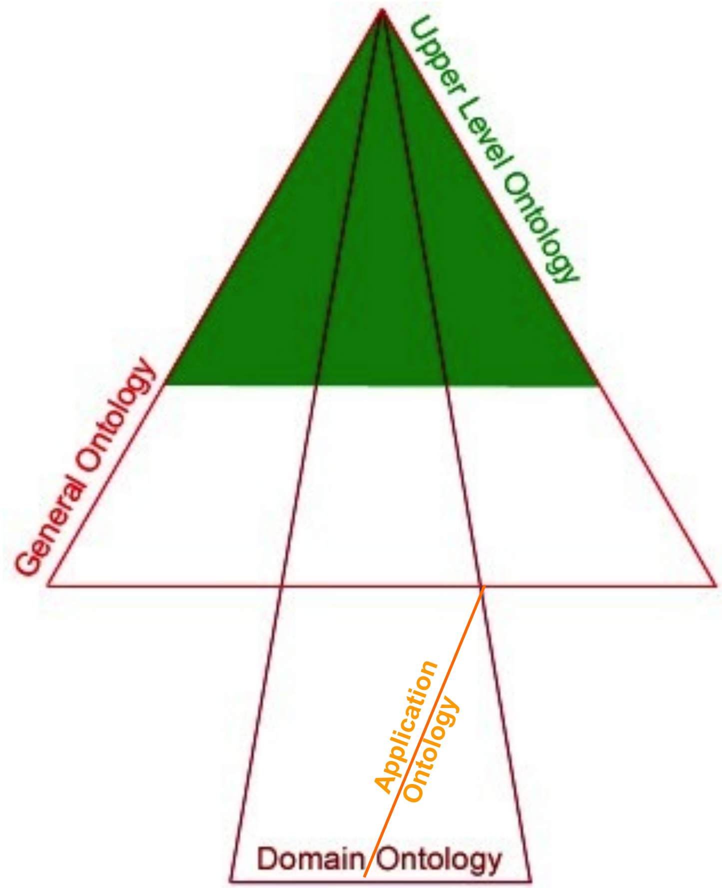
- What is Description Logics (DL) ? [Baader07]
  - **a family of first order logics knowledge representation formalism (e.g. $\mathcal{ALC}$, SHOIN(D), SHIQ (D))**
  - **offers capability of decidability & automated reasoning (3,4)**

- Ontology Web Language (OWL) [McGuiness09]
  - **a language to structure the knowledge from real domain of the world (1,2)**
  - **based on the SH logic family and RDF(S)**
  - **variants : OWL Lite, OWL DL, OWL Full**

- OWL-DL (SHOIN (D))
  - **computational completeness**
  - **high expressivity & decidability power**

Types of ontologies

- **upper-level ontologies** –theories of time space
- **general ontologies** – intermediate level, task-independent
- ***domain (reference) ontologies*** – a particular type of the world (medicine)
- ***application ontologies*** – a specific task



• Semantic Web Rule Language (SWRL)

- **OWL-DL and RuleML in the same framework** [Karimi, 2008]

- **trade-off : expressivity and decidability**

$$Atom \leftarrow C(a) \mid D(v) \mid R(a,b) U(a,v) \mid builtIn(p, v_1, \ldots, v_n) \mid a = b \mid a \neq b$$

Medical CBIR [Müller et al., 2004] [Quellec et al., 2010]	**Advantages**	**Drawbacks**
	➢increasing rate of image production ➢diagnosis, teaching & research	➢gaps (semantic, context) ➢relevance feedback ➢page zero problem ➢user interfaces
Medical CBR [Nillson & Sollenborn, 2004] [Schmidt and Gierl, 2001] [Holt et al., 2006]	➢cognitive adequateness ➢explicit experience ➢duality of knowledge ➢diagnosis, teaching & research	➢adaptation ➢unreliability ➢concentration on reference

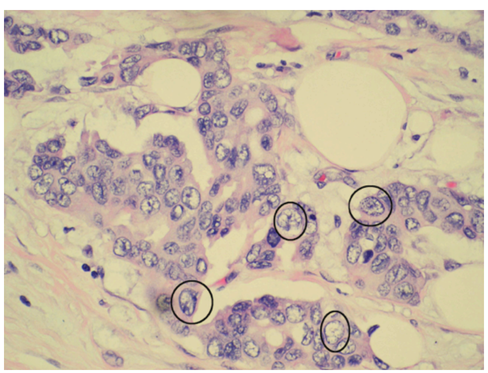
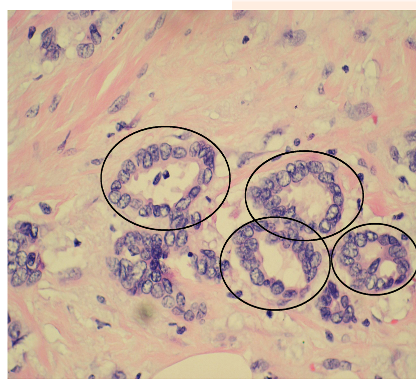
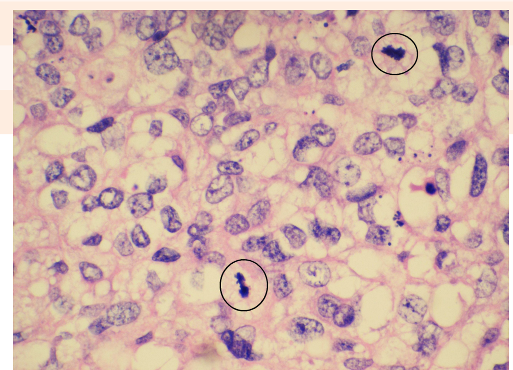
KR approaches	Advantages	Drawbacks	Breast pathology
non-logic-based formalism [Steichen, 2006]	human mind task-solving resemblance	lack of logical inference	semantic networks • large vocabularies (UMLS, SNOMED-CT)
logic-based formalism [Baader et al., 2007]	high expressivity computational power	undecidability in complex representation	Description Logics (DL) •reference ontologies (NCI, GALEN)

Spatial approaches	Biomedical ontologies	Advantages	Drawbacks
mereology [Donnelli et al., 2005], [Mechouche et al., 2009]	➢ FMA ➢ SNOMED-CT ➢ GALEN	➢ reduces ambiguities ➢symbolic &numerical ➢ image processing link	➢decidability (large vocabularies)
topology [Hudelot et al., 2006] geometry [Mezaris et al., 2004]	➢ FMA (brain MRI images) ➢general purpose	➢ image interpretation ➢ reasoning	➢decidability (large vocabularies)

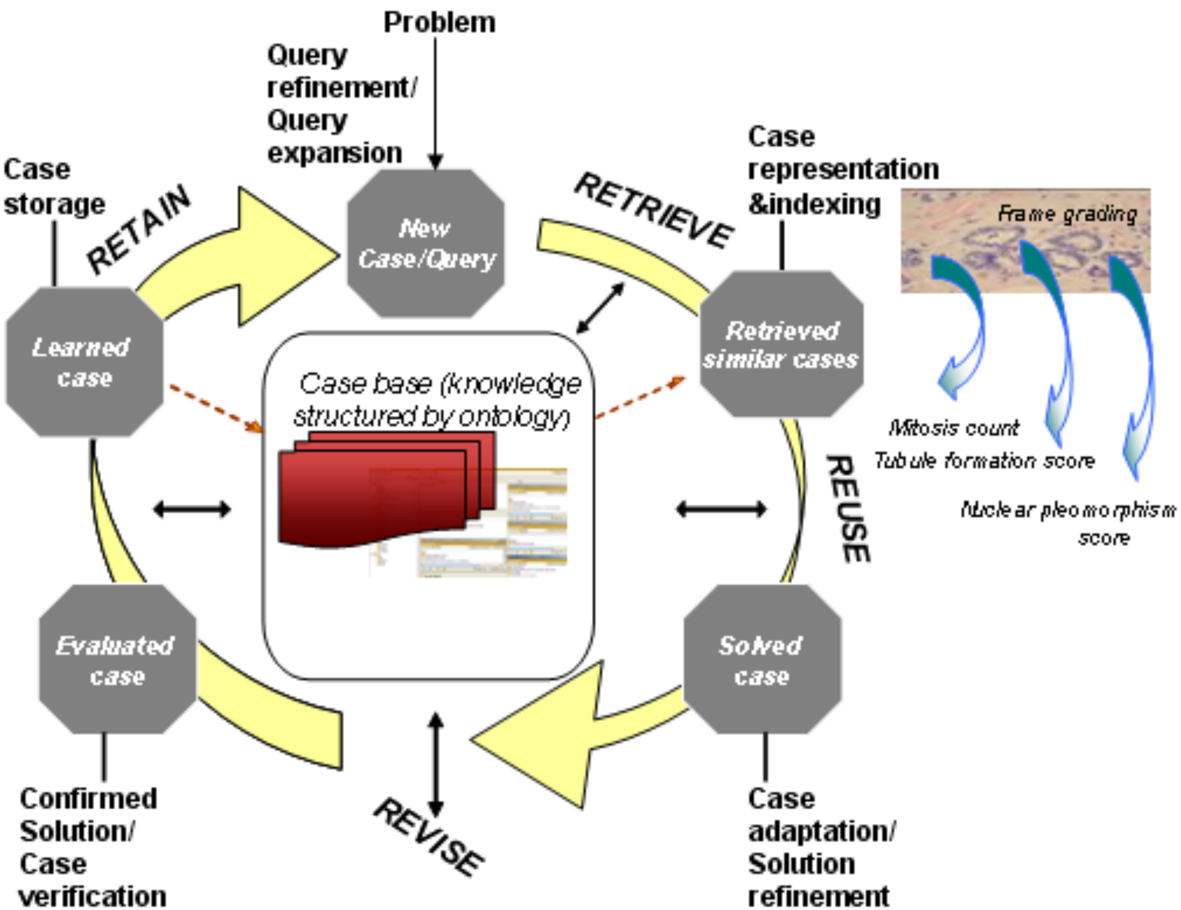
- Breast Cancer Grading

  - **prognosis assessment tool in modern pathology practice [Steichen et al., 2006]**
  - **a semiological approach**
  - **Nottingham Grading System**

		SCORE
NUCLEAR PLEOMORPHISM	Small Regular Uniform Cells	1
	Moderate Nuclear Size And Variation	2
	Marked Nuclear Variation	3
TUBULE FORMATION	Majority of Tumor (>75%)	1
	Moderate Degree (10-75%)	2
	Little or None (<10%)	3
MITOTIC COUNT	0-9 Mitoses/10 hpf	1
	10-19 Mitoses/10 hpf	2
	20 or > Mitoses/10 hpf	3
		3-5
C		6-7
		8-9

- Breast Cancer Grading problems
  - *time consuming (200 case patients in NUH, Singapore/900 cases in PSH, Paris daily)*
  - *automated image analysis algorithms treat only individual criterion*
    - nuclear pleomorphism score [Adawi et al., 2006]
    - tubule formation score [Petushi et al., 2006]
    - mitosis count [Beliën et al., 1997]
  - *lack of formal knowledge representation (agreement inconsistencies)*
  - *semantic gap*



- *concept of similarity*
- *visual content processing & analysis (CBIR)*
- *semantics, ontologies (CBIR)*
- *case-based structure of data (CBR)*
- *duality of medical knowledge (CBR)*
- *incremental learning (CBR)*
- *hybrid reasoning : image-based reasoning & case based reasoning*

➢ nature of formal representation : qualitative or quantitative?

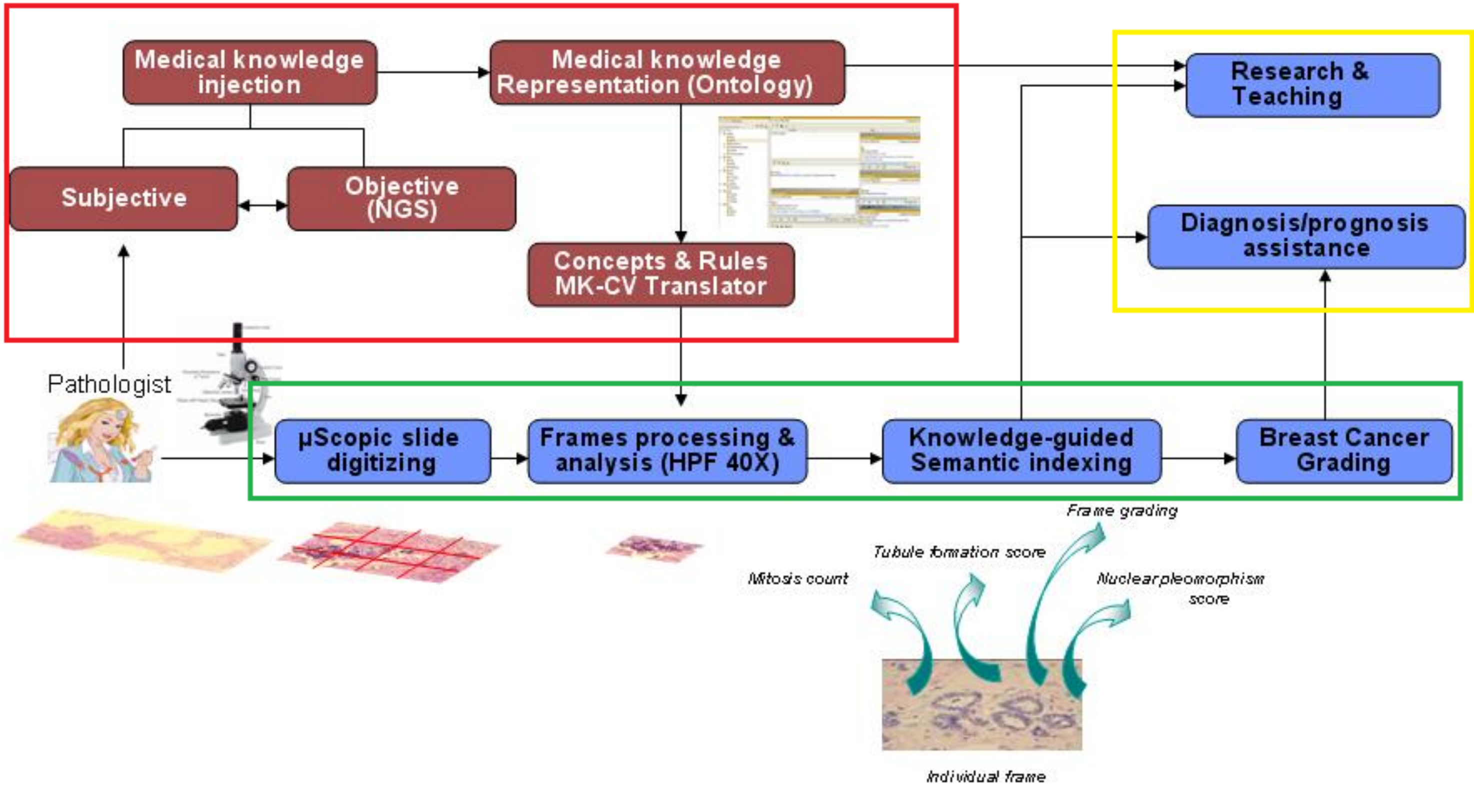
- quantitative approaches force the use of quantities to express qualitative facts [Brageul and Guesgen, 2007]
- OWL formalism supports logical qualitative definitions not quantitative definitions
- in BCG : “close to neoplasm periphery”, “dividing cell nuclei”, “score 3”

Quantitative definitions are confined to the qualitative representation as numerical values allowed by semantic languages.

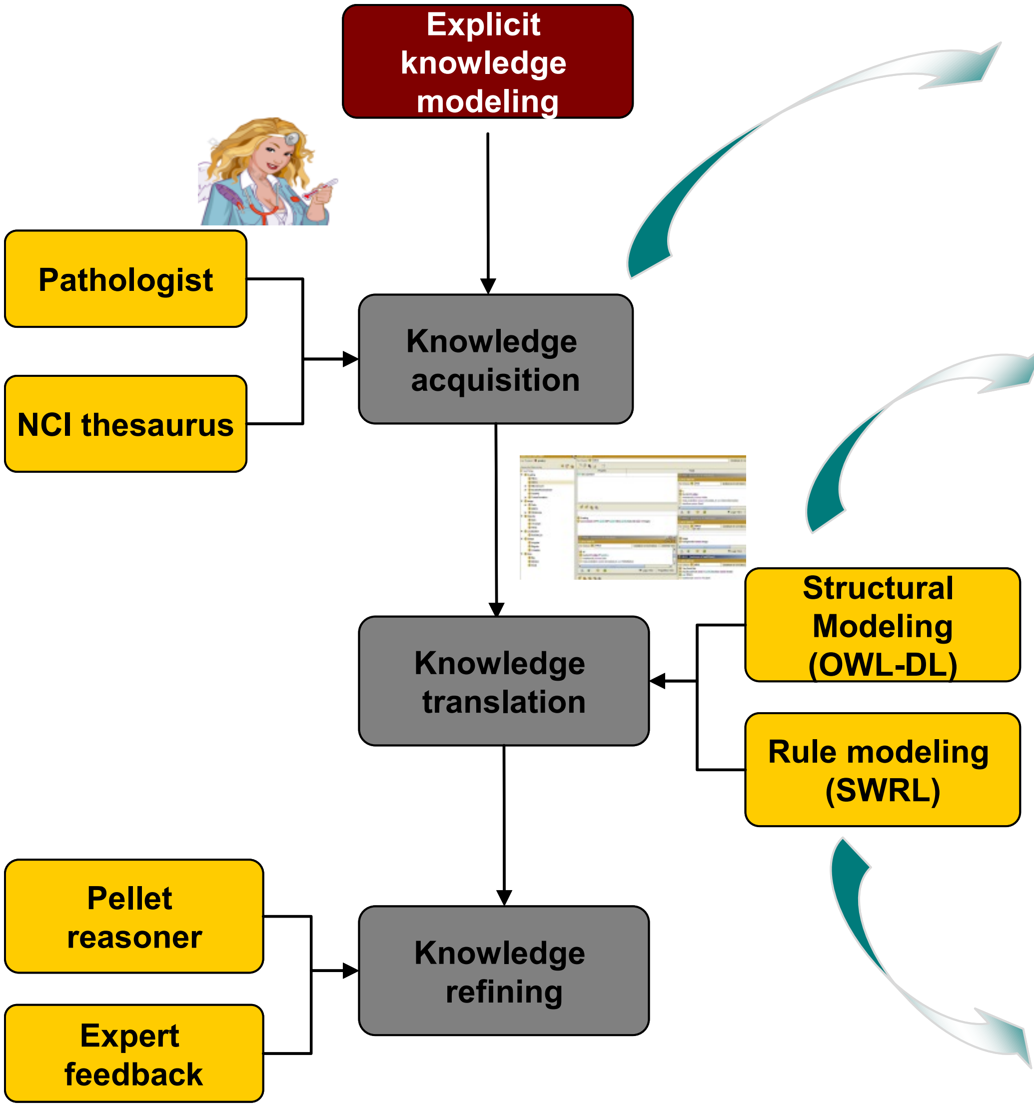
- **target of representation**
  - **endurants** (objects), not perdurants (event, processes)
  - **time-independent spatial representation**
  - **application ontology BCGO (1-5)**
  - **spatial theory support** to eliminate ambiguities and inconsistencies

➢ **Two approaches**

- **image driven : semi-automated breast cancer grading**



- **limitations: no benefit of DL, to close to image level**



Mitosis – very dark diving cell nuclei, which are not located in tubule formation area and are close to neoplasm periphery

Formal representation for Mitosis in OWL

Class(Mitosis complete NucleusDivision
restriction(hasIntensity someValuesFrom VeryLow)
restriction(hasIntensity allValuesFrom VeryLow)
restriction(isCloseTo someValuesFrom NeoplasmPeriphery)
restriction(isCloseTo allValuesFrom NeoplasmPeriphery)
complementOf(restriction(isLocatedIn someValuesFrom Tubule))
complementOf(restriction(isLocatedIn allValuesFrom Tubule))
restriction(hasEccentricity hasValue hasEccentricityValue))
c

Formal representation for Mitosis in OWL - DL

$Mitosis \equiv NucleusDivision \sqcap$
$\exists hasIntensity.VeryLow \sqcap$
$\forall hasIntensity.VeryLow \sqcap$
$\exists isCloseTo.NeoplasmPeriphery \sqcap$
$\forall isCloseTo.NeoplasmPeriphery \sqcap$
$\neg \exists isLocatedIn.Tubule \sqcap$
$\neg \forall isLocatedIn.Tubule \sqcap$
$\ni hasEccentricity\ has\ hasEccentricityValue$

Formal representation for hasEccentricityValue in SWRL

$Nucleus(?y) \wedge hasEccentricity(?x,?value) \wedge$
$swrlb: lessThan(?value, 1) \wedge$
$swrlb: greaterThan(?value, 0) \rightarrow hasEccentricityValue(?x,?value)$

•semantic-driven

[Uschold and Grüninger, 1996]

1. Knowledge acquisition

- **ontology semi-automated segmentation (PROMPT)**
- **a knowledge base KA =(NCI, NGS)**

NCI → National Cancer Institute thesaurus (e.g. *Disease*, *Patient*, *Assessment*, *Specimen*)

NGS → Nottingham Grading System & 20 patients cases NUH (e.g. *NottinghamGrading, Tubule, Mitosis)*

- **Why NCI and not SNOMED-CT or UMLS?**

  - **NCI is homogenous, dedicated to cancer information representation**
  - **semantic mapping and concept alignment**
  - **NCI is freely available**

2. Knowledge translation [Tutac, 2009b]

- **structural modeling with OWL-DL (high expressivity)**

$\mathcal{TB}$ox

definitions of concepts
$Nucleus = MicroscopicEntity \sqcap ..$

statement of constraints
$\exists hasSize.Size \subseteq Size$

$\mathcal{AB}$ox

concept assertions
Nucleus (Nucleus_1)

roles assertions
hasSize(Nucleus_1, SmallSize)

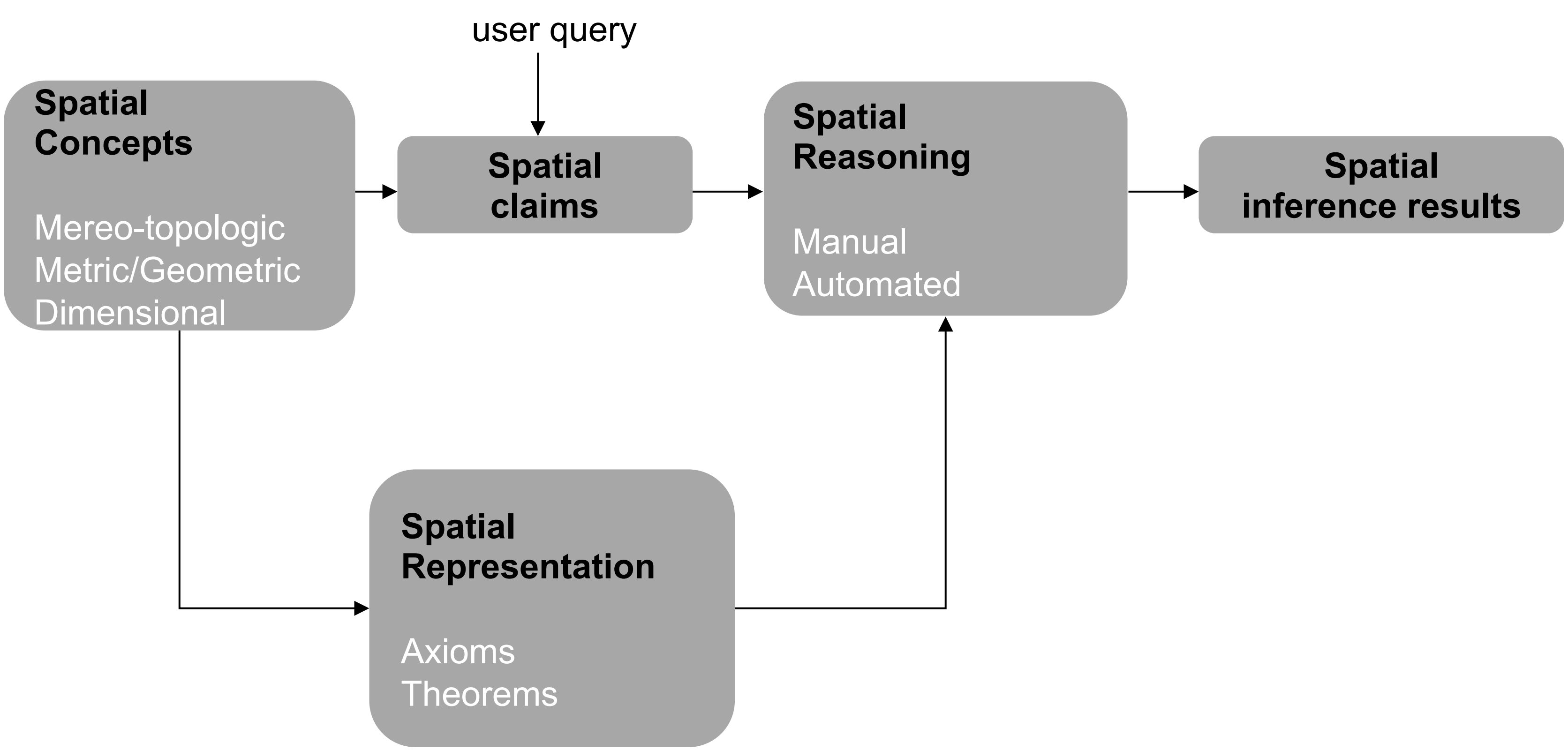
- **rule modeling with SWRL - DL safe rules (decidability)**

3. Knowledge refining

- **Pellet reasoner**
  - **based on the DL tableau algorithm**
  - **verifies ontology consistency**
  - **computes inferred knowledge**

- **Medical feedback**

Spatial Reasoning. Formal theory



Spatial Reasoning. *Mereo-topological axioms & theorems*

Definition. Surrounded By (***SurrBy***) [Tutac et al., 2010]

$$(SA1) SurrBy(x,y) \text{ B } \Pr(x)r(y) \wedge \sim PCoin(x,y))$$

or

$$(SA2)\ SurrBy(x,y) \text{ B } Loc\text{ - }In(x,y) \wedge \sim O(x,y)$$

Applied to classes:

$$(ST1)\ SurrBy_1(A,B) \text{ B } \forall x(Inst(x,A) \rightarrow \exists y(Inst(y,B) \wedge SurrBy(x,y))$$

$$(ST2)\ SurrBy_2(A,B) \text{ B } \forall y(Inst(y,B) \rightarrow \exists x(Inst(x,A) \wedge SurrBy(x,y))$$

$$(ST3)\ SurrBy_{12}(A,B) \text{ B } Loc\text{ - }In_1(A,B) \wedge Loc\text{ - }In_2(A,B)$$

Spatial Reasoning. *Mereo-topological axioms & theorems*

How to eliminate ambiguities or redundant definitions ?

Definition. *Inclusion* (*Included-In*)

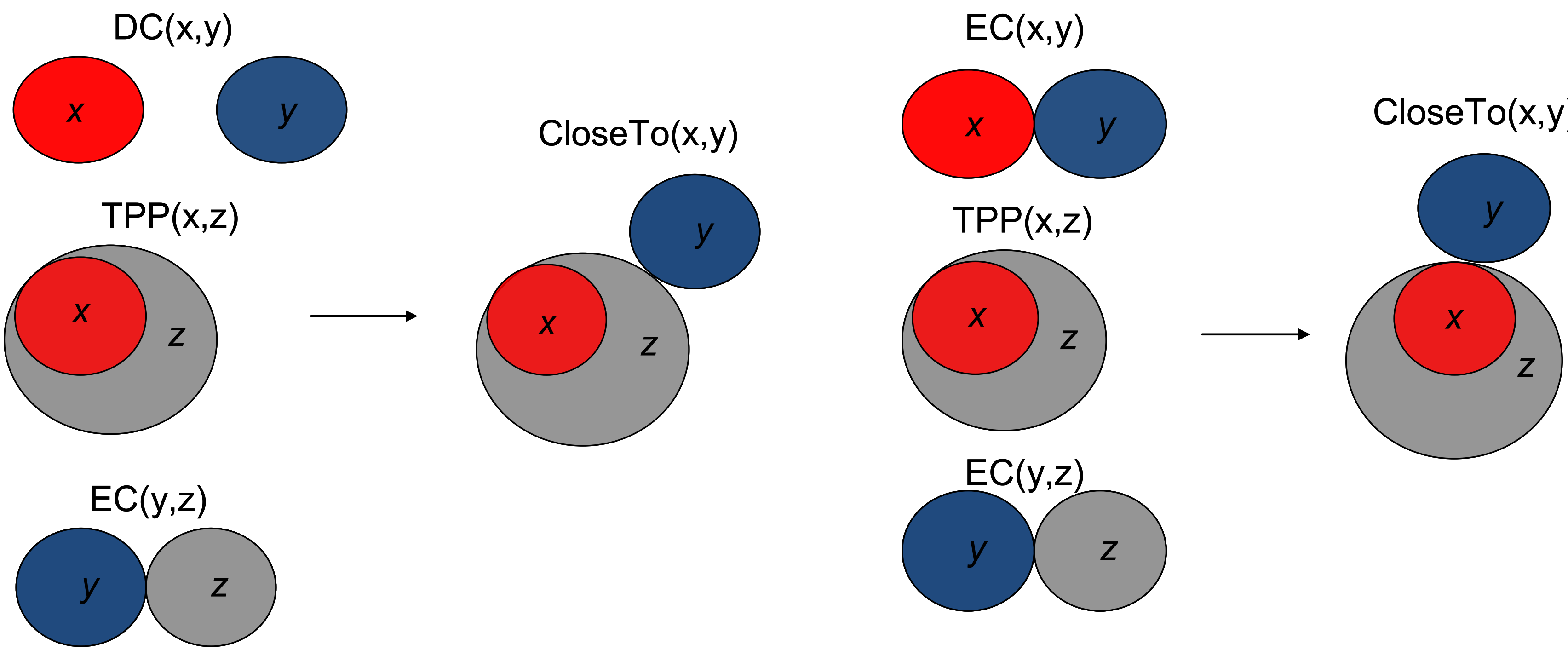
$$(IA1)\ Included - In(x,y)\ \mathrm{B}\ \exists z Loc - In(x,z) \wedge Loc - In(y,z) \wedge \sim PCoin(x,y))$$

If *PCoin(x,y)* denotes overlapping, and

SurrBy is already defined as previously

Included-In is redundant

Spatial reasoning, Metric axioms/theorems RCC-8 & composition table



$$(CA1)\,CloseTo(x,y)\ \mathrm{B}\ DC(x,y) \vee EC(x,y) \wedge TPP(x,z) \wedge EC(y,z),$$

where z<threshold

Spatial Reasoning. *Mereo-topological axioms and theorems*

e.g. verifying transitivity axiom on classes

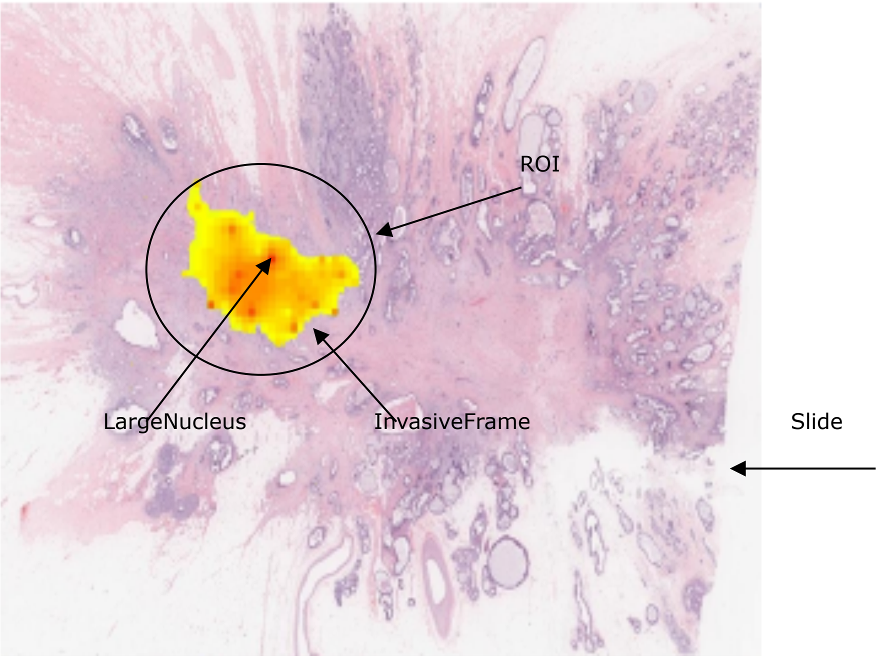
Loc-In1 (LargeNucleus, InvasiveFrame)
(Every large nucleus is located in some invasive frame)

and

Loc-In1 (InvasiveFrame, ROI)
(Every invasive frame is located in some ROI)

It follows logically that:
Loc-In1 (LargeNucleus, ROI)

(Every large nucleus is located in some ROI)



e.g. Loc-In12(A, B) not holding

Loc-In1 (ROI, Slide) holds, but we cannot apply

Loc-In2 (ROI, Slide)

Spatial Reasoning. *Mereo-topological axioms and theorems*

e.g. SurrBy12(A, B) holding

SurrBy1 (Lumina, StringNuclei)
Every *Lumina* is surrounded by some String*Nuclei*

SurrBy2 (Lumina, StringNuclei)
Every String*Nuclei* has some *Lumina* surrounding it
SurrBy12 (*Lumina*, *Tubule*)

e.g. complex relations

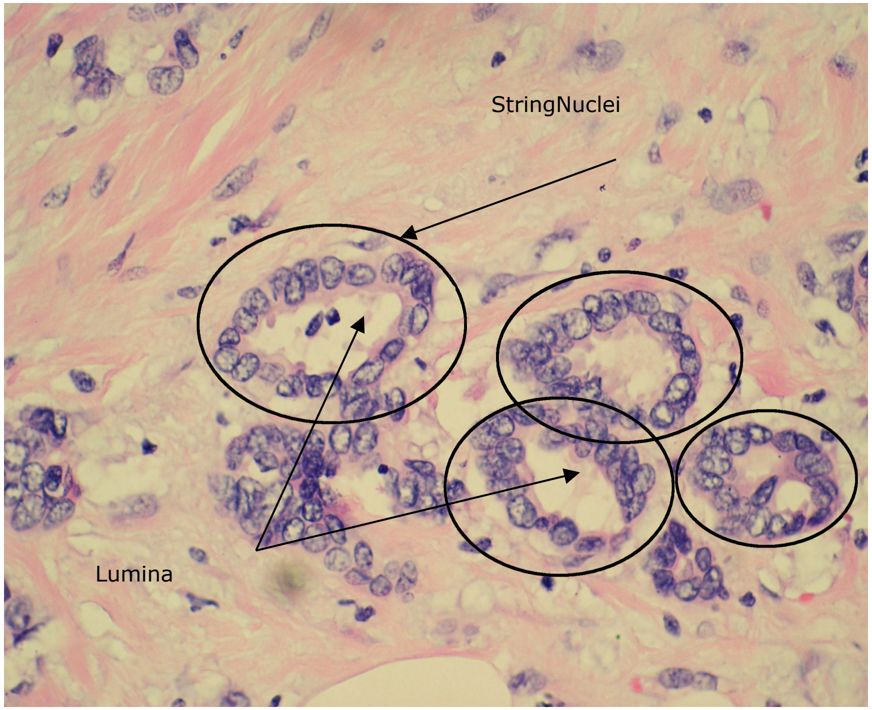
SurrBy1 (Lumina, StringNuclei)
Every *Lumina* is surrounded by some *Nuclei* and

P2 (StringNuclei, Tubule)
Every *Tubule* has some *StringNuclei* as a part

we can infer:

P1 (Lumina, Tubule)
Every *Lumina* is part of some *Tubule*

P2 (*Lumina*, *Tubule*)
Every Tubule has some Lumina as a part



DL reasoning. Tableau-based algorithm

- ***Concept subsumption is reduced to concept satisfiability***

$$Nucleus \text{ Ù } MicroscopicEntity$$

$$NucleusDivision \text{ Ù } Nucleus$$

$$Mitosis \text{ Ù } NucleusDivision \Pi \neg \forall isLocatedIn.Tubule$$

$$Mitosis\_1 \text{ Ù } Mitosis$$

Is Mitosis_1 subsumed by MicroscopicEntity?

DL reasoning. Tableau-based algorithm

1. Unfolding or TBox elimination

$$Mitosis\_1 \cup Mitosis \equiv NucleusDivision \sqcap \neg \forall isLocatedIn.Tubule$$

$$Mitosis\_1' \sqcap NucleusDivision \sqcap \neg \forall isLocatedIn.Tubule$$

$$Mitosis\_1' \sqcap NucleusDivision' \sqcap Nucleus \sqcap \neg \forall isLocatedIn.Tubule$$

$$Mitosis\_1' \sqcap NucleusDivision' \sqcap Nucleus' \sqcap MicroscopicEntity \sqcap \neg \forall isLocatedIn.Tubule$$

$$Mitosis\_1 \sqcap MicroscopicEntity \sqcap \neg \forall isLocatedIn.Tubule$$

DL reasoning. Tableau-based algorithm

2. Normalization - Negation Normal Form of De Morgan

$$\neg \exists R.C \equiv \forall R.\neg C$$

$$\neg \forall R.C \equiv \exists R.\neg C$$

$$\neg \leq nR.C \equiv \geq (n+1)R.C$$

$$\neg \geq (n+1)R.C \equiv \leq n.R.C$$

$$\neg \geq OR.C \equiv \mathrm{C} \prod \neg \mathrm{C}$$

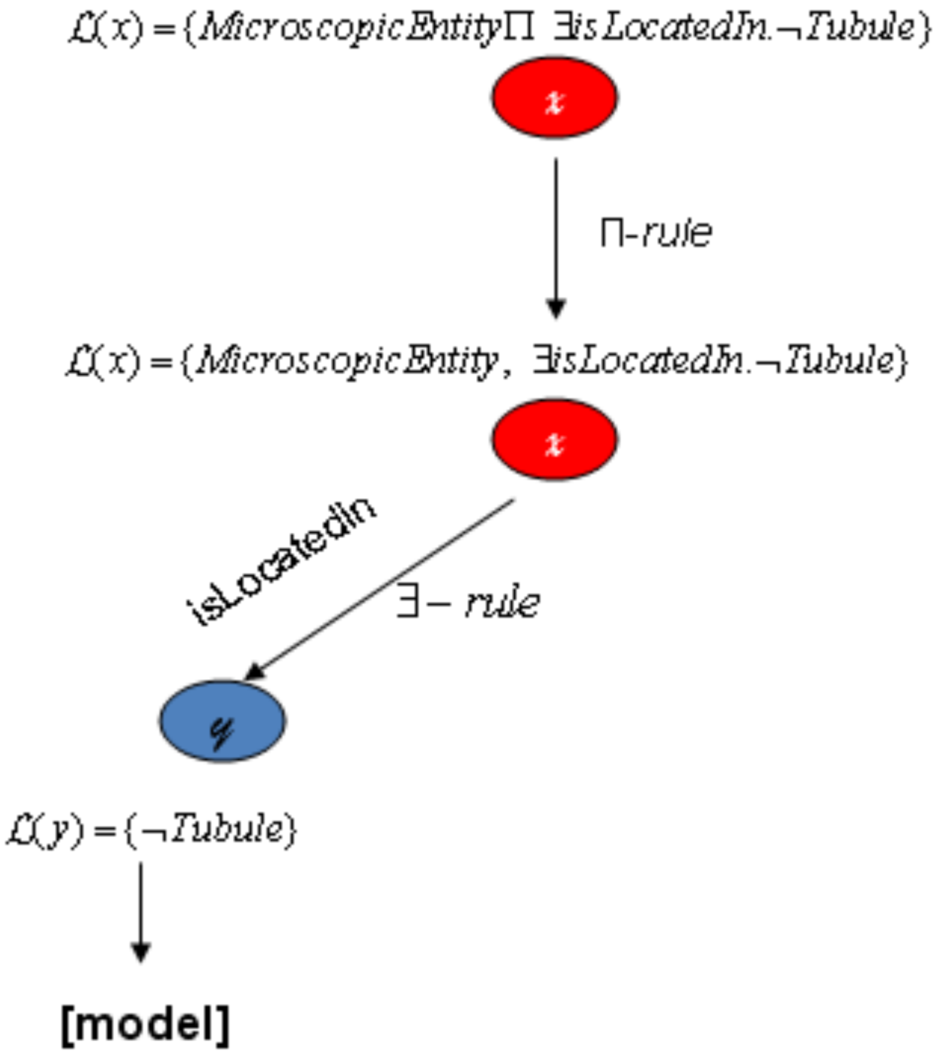
⬇

$$Mitosis\_1' \Pi MicroscopicEntity \Pi \exists isLocatedIn.\neg Tubule$$

DL reasoning. Tableau-based algorithm

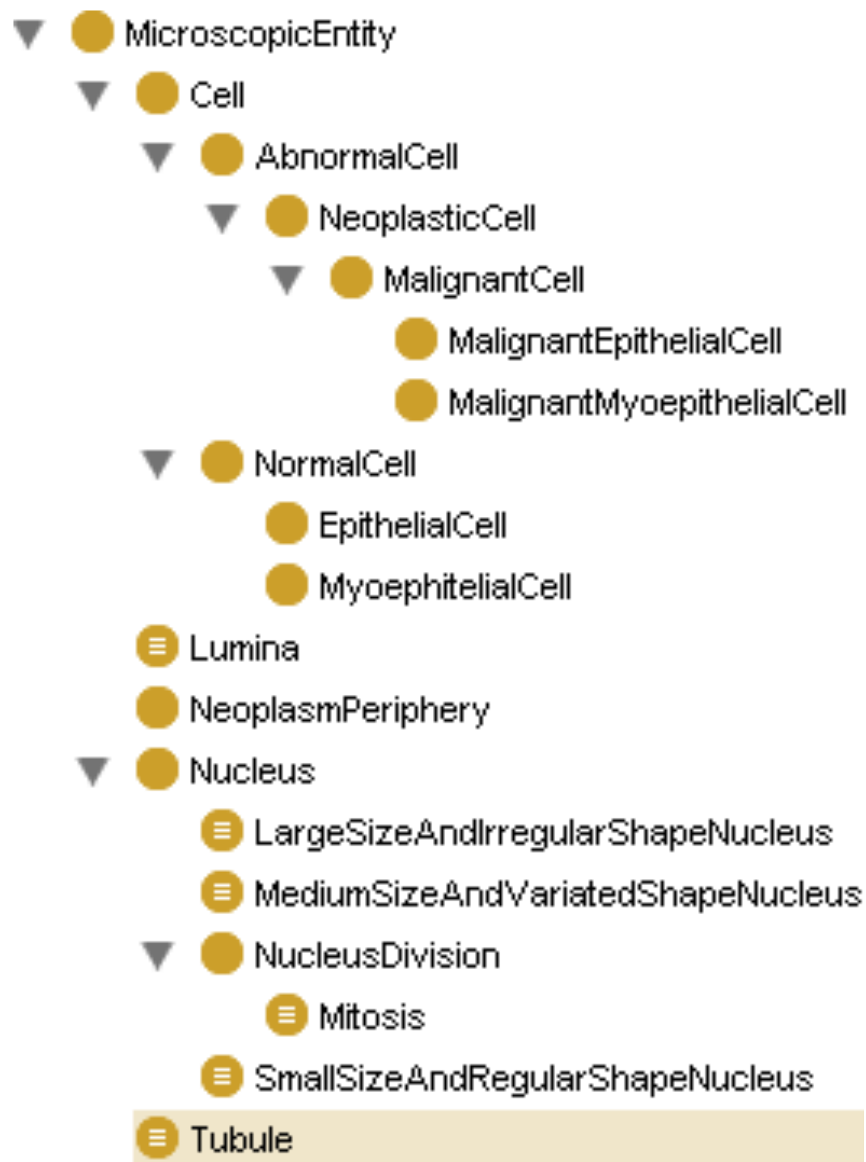
3. Proving with Tableau - expansion r

$$L(x) = \{MicroscopicEntity \sqcap \exists isLocatedIn.\neg Tubule\}$$

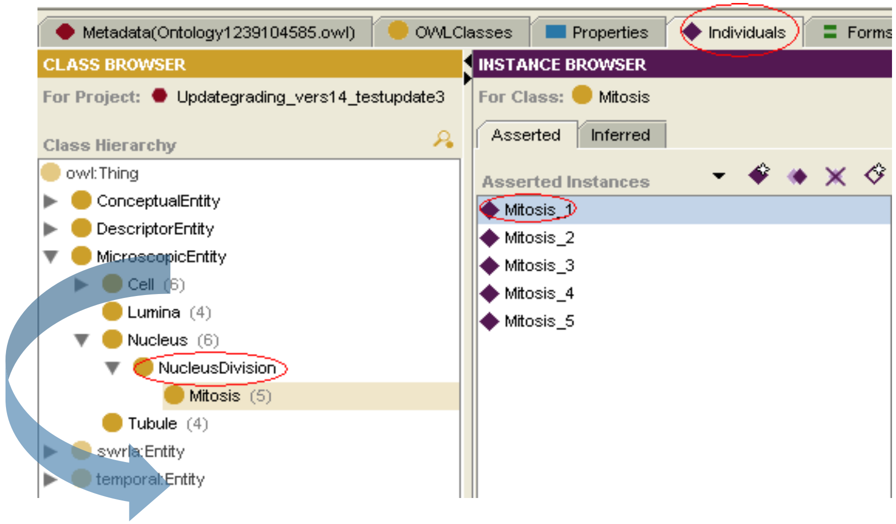


Model Implementation. Protégé

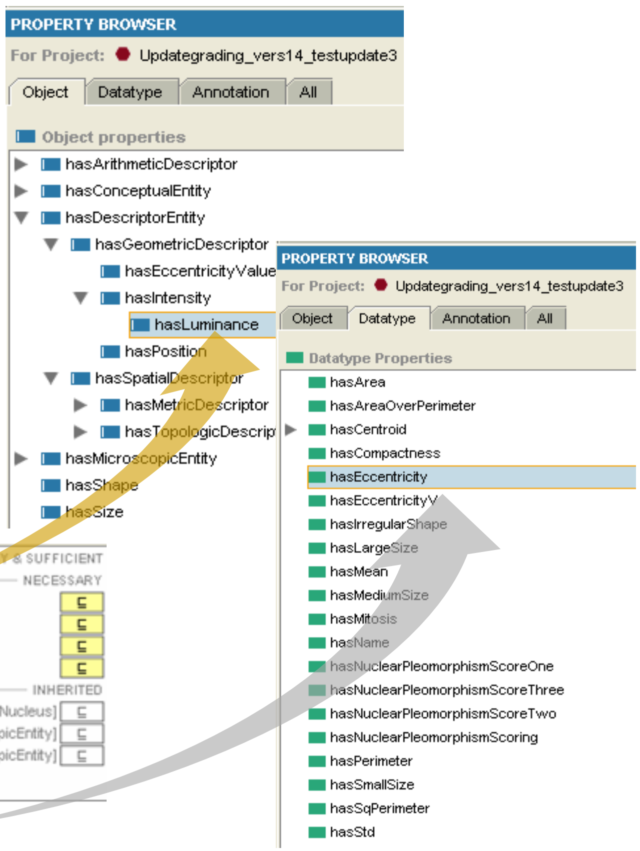
- ***AnatomicalEntity***
- ***ConceptualEntity***
- ***MicroscopicEntity***
- ***DescriptorEntity***



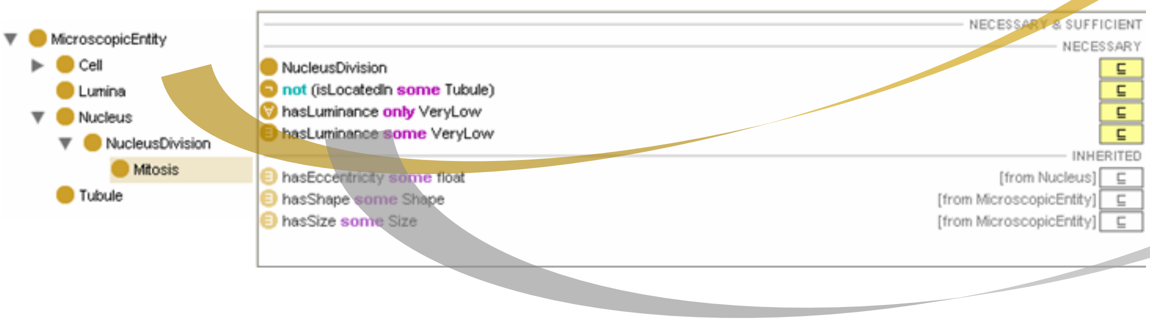
1. Structural modeling- OWL classes, individuals & properties



e.g. *Mitosis_1* is an instance of the *Mitosis class*



Definition of the *Mitosis class*



1. Structural modeling -DL TBox. Defined (complete) classes

OWL:

Class (NuclearPleomorphismScoreOne complete NuclearPleomorphismScoring
restriction (hasNucleus someValuesFrom SmallSizeAndRegularShapeNucleus)
restriction (hasNucleus allValuesFrom SmallSizeAndRegularShapeNucleus))

OWL-DL:

$$NuclearPleomorphismScoreOne \equiv NuclearPleomorphismScoring \sqcap \exists hasNucleus.SmallSizeAndRegularShapeNucleus \sqcap \forall hasNucleus.SmallSizeAndRegularShapeNucleus$$

Paraphrase: A NuclearPleomorphismScoreOne is any NuclearPleomorphismScoring that, amongst other things, has only SmallSizeAndRegularShapeNucleus

1.Structural modeling - DL TBox. Open World Assumption (OWA) ?

OWL:

Class (Mitosis complete NucleusDivision
restriction (hasIntensity someValuesFrom VeryLow)
restriction (hasIntensity allValuesFrom VeryLow)
restriction (isCloseTo someValuesFrom NeoplasmPeriphery)
complementOf (restriction (isLocatedIn someValuesFrom Tubule)))

Paraphrase: Mitosis is any NucleusDivision that has, amongst other things, some VeryLow intensity and is close to some NeoplasmPeriphery and is not located in some Tubule

1. Structural modeling- DL TBox. OWA and closure axiom

OWL:

Class (Mitosis complete NuclearDivision
restriction (hasIntensity someValuesFrom VeryLow)
restriction (hasIntensity allValuesFrom VeryLow)
restriction (isCloseTo someValuesFrom NeoplasmPeriphery)
restriction (isCloseTo allValuesFrom NeoplasmPeriphery))
complementOf (restriction (isLocatedIn someValuesFrom Tubule))
complementOf (restriction (isLocatedIn allValuesFrom Tubule)))

OWL-DL:

$$Mitosis \equiv NuclearDivision \sqcap$$
$$\exists hasIntensity.VeryLow \sqcap \forall hasIntensity.VeryLow \sqcap$$
$$\exists isCloseTo.NeoplasmPeriphery \sqcap$$
$$\forall isCloseTo.NeoplasmPeriphery \sqcap$$
$$\neg \exists isLocatedIn.Tubule \sqcap \neg \forall isLocatedIn.Tubule$$

1. Structural modeling- DL ABox. Object & datatype properties

OWL:
Class (Frame complete VirtualSpecimen
restriction (hasNottinghamScoring someValuesFrom NottinghamScoring)
restriction (hasNottinghamScoring allValuesFrom NottinghamScoring))

or

OWL:
Class (Frame complete VirtualSpecimen
restriction (hasNottinghamScoring someValuesFrom int))

2. Rule modeling

- SWRL rules alternative to OWL

ScoreBetween3and5(?x) ∧ hasScoreBetween3and5(?x, ?value) ∧ swrlb: greaterThan(?value, 3) ∧ swrlb: lessThan(?value, 5) → hasScoreBetween3and5(?x, ?value)

- SWRL DL safe rules
  - **enforce DL safety by restricting rules to individuals**

e.g. DL safe rule BreastCancerPatient(?p)

hasDisease(?x, ?value) ∧ hasAssessment(?x, ?value) ∧ Patient (?x) ∧ NotthinghamGrading(?value) → BreastCancerPatient(?x)

Qualitative evaluation metrics [Brank et al.,2005], [Tartir et al., 2005]

1. **Granularity** -relations between levels of ontology hierarchy, set theory, mereology and non-scale dependency (NSD).

richness of relationships

$$RR = \frac{\sum P}{\sum P + \sum SC} = \frac{86}{255} = 0.33$$

→ RR more close to 0 than to 1, most relations are class-subclass relationships

attribute richness

$$AR = \frac{\sum P}{\sum C} = \frac{86}{129} = 0.66$$

→ RR more close to 1 than to 0, lot of knowledge is conveyed to our ontology

Qualitative evaluation metrics [Brank et al.,2005], [Tartir et al., 2005]

2. Scope or **degree of reflection**

- **average population**

$$AP = \frac{\sum Inst}{\sum C} = \frac{169}{129} \cong 1$$ → **AP shows a very good population of K**

- **class richness**

$$CR = \frac{\sum C'}{\sum C} = \frac{147}{129} \cong 1$$ → **K has almost all knowledge represented in the ontology**

3. Integration

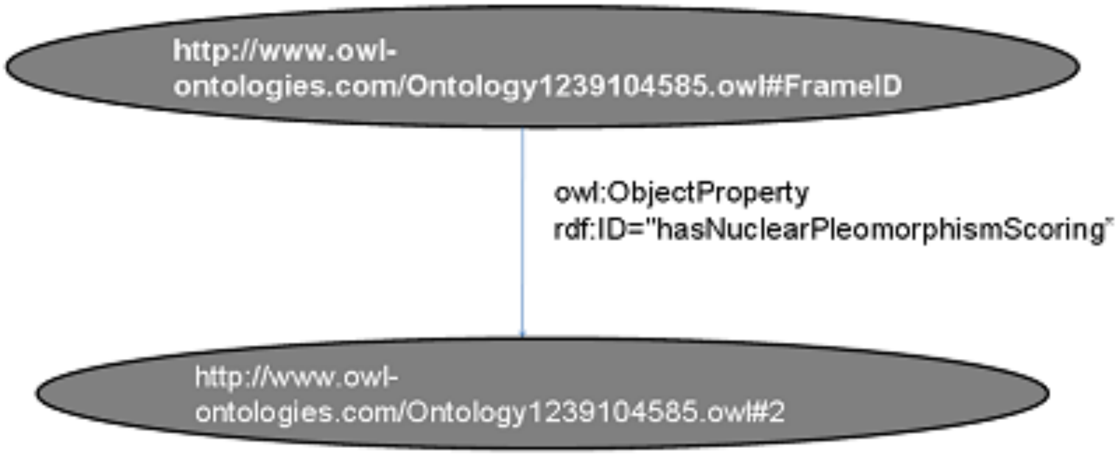
- **ontology integration**

$$OI = \frac{\sum IC}{\sum C} = \frac{35}{129} = 0.27$$ → **the level of connectedness wrt classes is low, yet expected**

Evaluation. Reasoning perspective

- **129 classes, 169 instances, 86 properties, max depth 10 & 4 siblings**
- **termination : 2.48 sec**
- **concept satisfiability**
- **classification of hierarchy (explicit model and inferred model)**

Evaluation. Semantic Retrieval



“Find all Slides which have
NuclearPleomorphism Score 2 and Mitotic Count 3”

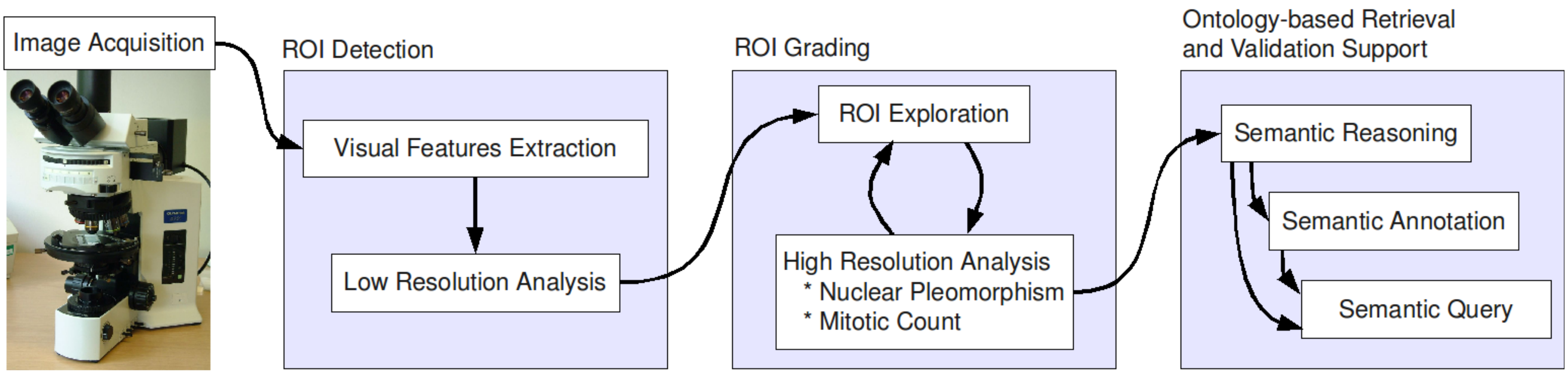
Slide(?x) ∧
hasNuclearPleomorphismScoring(?x,?nuclearscore)
∧ NuclearPleomorphismScoring(?nuclearscore, 2)
∧ hasMitoticCount(?x,?mitoticcore) ∧
MitoticCount(?mitoticscore, 3) → sqwr:select(?x)

Evaluation. Precision & Recall challenges

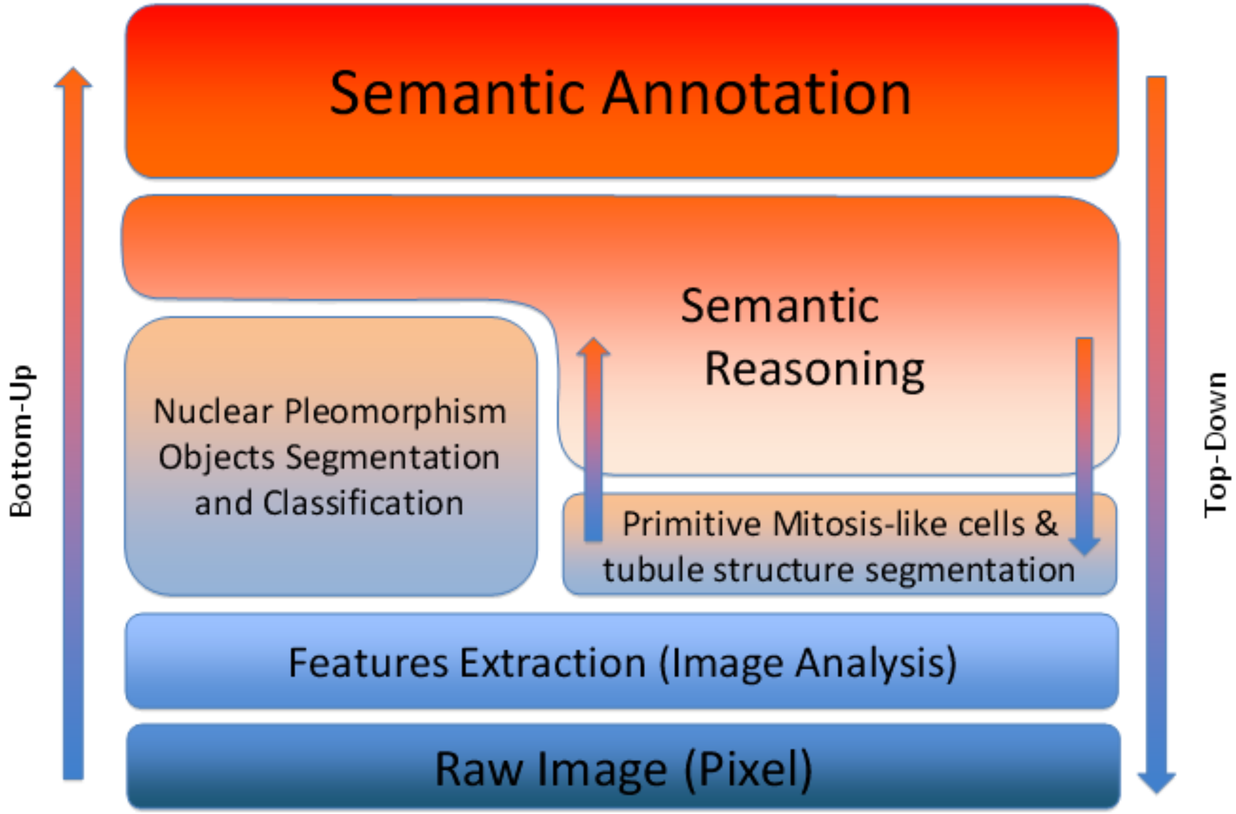
- **our approach does not use a classic CBIR**
- **there is no benchmark for BCG to compare with**
- **the number of histopathology annotation needed is enormous**

  (for 20 cases/slides from NUH, 4000 frames each =>80.000 frames)
- **resolution issue (mitosis are identified on a different scale than tubules) => precision/recall on different scales/ Mean-Average Precision?**
- **the DCIS issue**

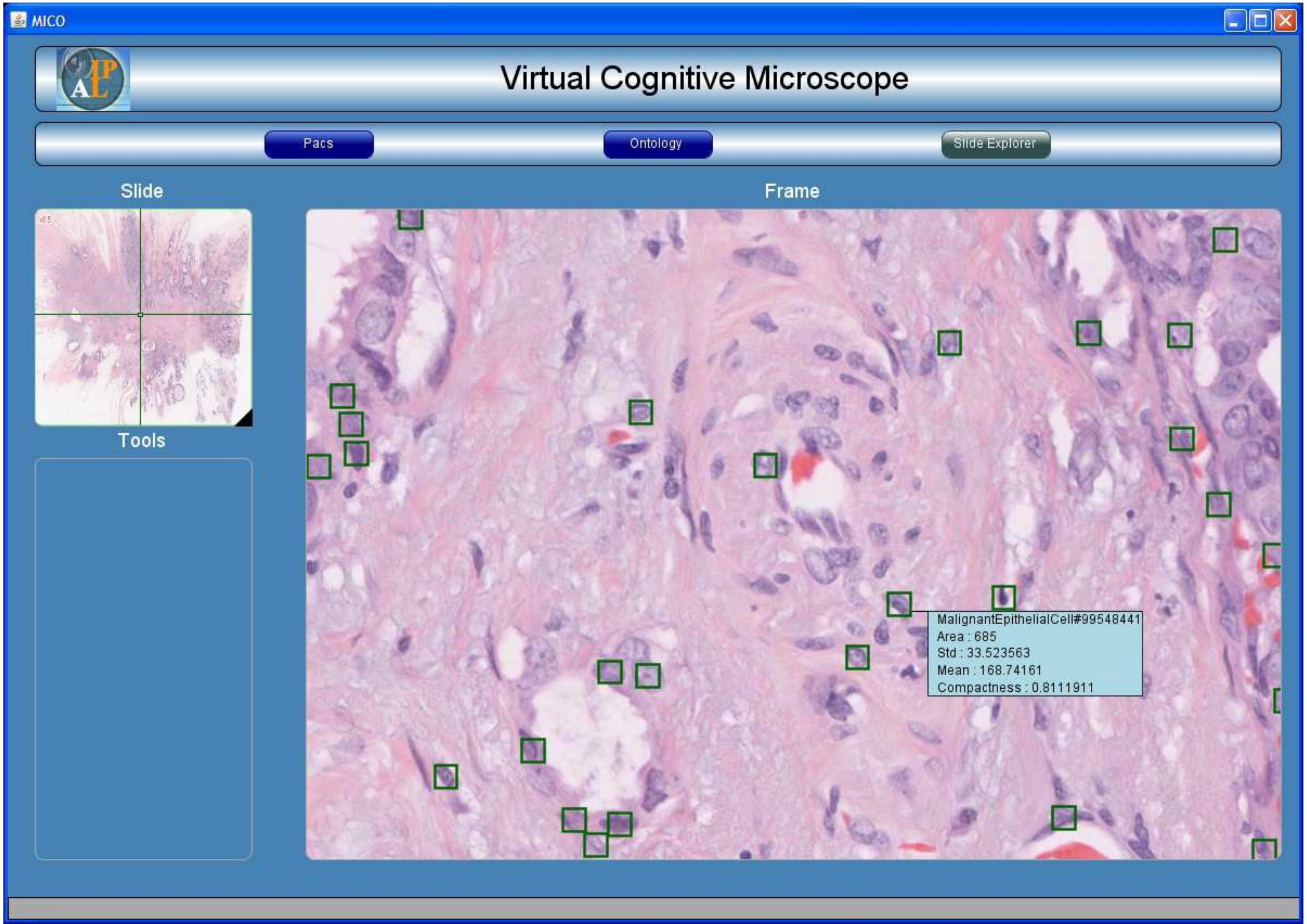
Model applicability. MICO framework [Roux et al., 2009a] MICO – Project funded recently by ANR, TecSan 2010



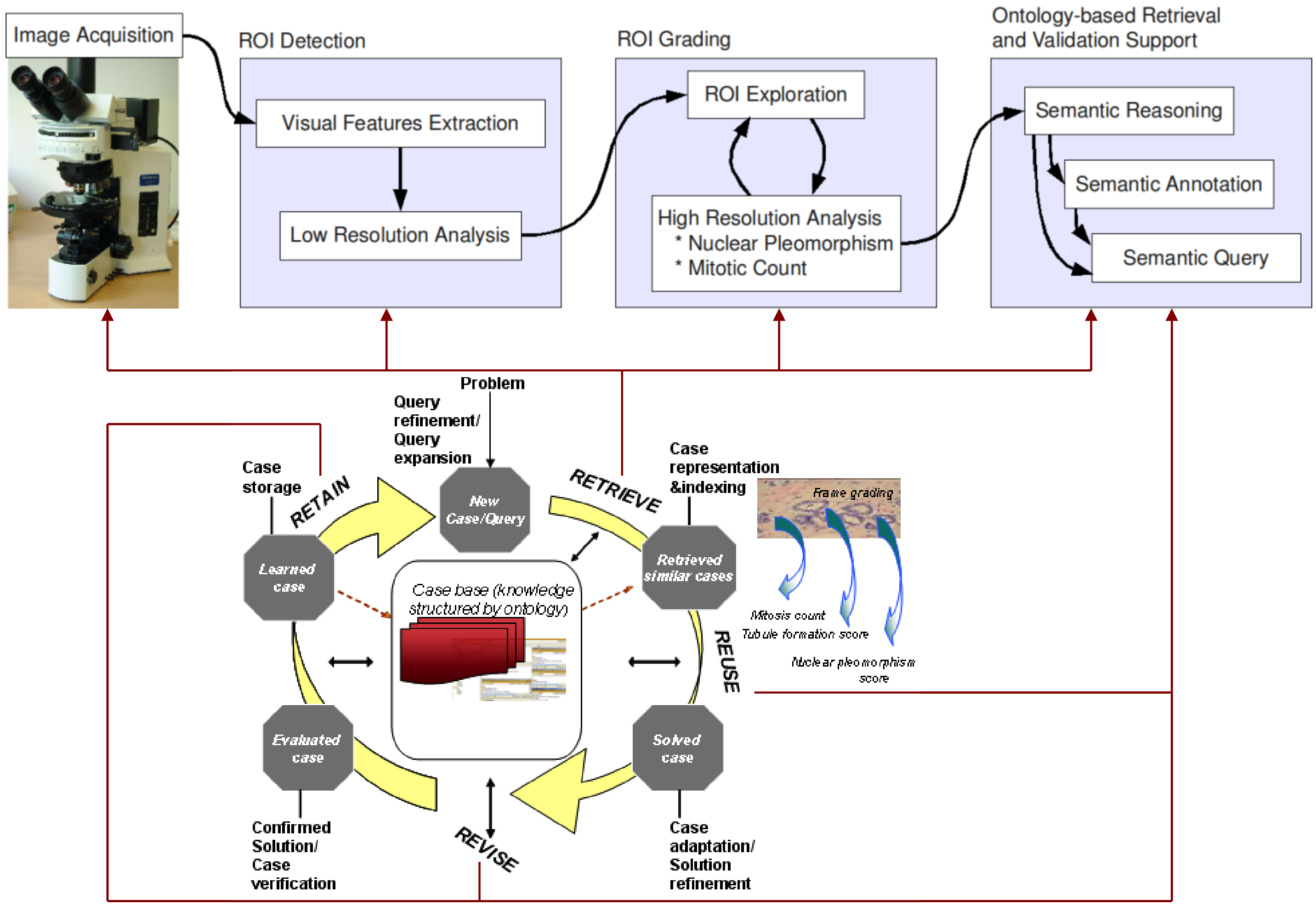
Ontology-driven mitosis and tubule formation scoring



Ontology-based retrieval and validation support



MICO prototype based on CBIR-CBR paradigm



- *CBIR –CBR methodological comparative analysis*
- *approach to bring together image and semantic representation (perception and cognition) :breast cancer grading application ontology, qualitative representation, spatial integration, modeling of perdurants*
  - *bridges semantic and context gap : formal logic semantic indexing techniques*
  - *offers high expressivity and decidability : OWL-DL and SWRL formalisms*
  - *semantic reasoning : DL reasoning extended with spatial reasoning*
  - *semantic retrieval for evaluation and validation of the ontology*
- *integration of ontology in a cognitive virtual microscope framework following the CBIR-CBR methodology*

- *refining of ontology (e.g. scale information, temporal extension)*
- *explanation-based medicine*
- *integration in reference ontologies (NCI thesaurus vs SNOMED-CT, UMLS, MeSH)*
- *evaluation in a clinical setting (intra-observer and inter-observer agreement, k-coefficient)*
  - *define methodology*
  - *define set of metrics*
  - *apply metrics*
- *Integration in complex representation with heterogeneous data-interoperability (VPH)*

Selected Publications

- **[Tutac et al., 2009a] A.E. Tutac,** D. Racoceanu, T.Putti, W-K.Leow, H.Muller, T.Putti, V.Cretu, “Towards Translational Incremental Similarity Based in breast cancer grading”, in Medical Imaging 2009: Computer-Aided Diagnosis, Proc. SPIE (SPIE, Bellingham, WA 2009), Vol. 7260, 72603C (2009), pp.1-12, Nico Karssemeijer, Maryellen L.Giger eds, ISBN : 978-0-8194-7511-4, Orlando, Florida, **SUA**, **7-12 February 2009**, in “Progress in biomedical optics and imaging, ISSN: 1602-1744, SUA (IEEE, CAT-INIST indexed)

- [**Tutac et al., 2008] A.E. Tutac**, D. Racoceanu, T. Putti, W. Xiong, W.K. Leow, and V. Cretu, “Knowledge-Guided Semantic Indexing of Breast Cancer Histopathology Images”, BioMedical Engineering and Informatics: New Development and the Future, in Proc. BMEI, ed.Yonghong Peng and Yufeng Zhang pp. 107-112, China, 2008 (ISI, IEEE indexed)

- **[Roux et al., 2009a]** L. Roux, **A. Tutac**, N. Lomenie, D. Balensi, A. Veillard, D. Racoceanu, W.K. Leow, J. Klossa, T.C. Putti, “A cognitive virtual microscopic framework for knowledge-based exploration of large microscopic image in breast cancer histopathology”, in Proc. EMBC, vol.1, pp.3697-702, **2-6 Sept, Minneapolis, SUA** (IEEE indexed)

- **[Roux et al., 2009b]** Roux L., **Tutac A**., Veillard A., Dalle J., Racoceanu D., Lomenie N., Klossa J, "A cognitive approach to microscopy analysis applied to automatic breast cancer grading" , Virchows Archiv The European Journal of Pathology, Springer-Verlag Berlin Heidelberg, H.Höfler ed, no. 428, vol. 455, suppl 1, pp.34-35, ISSN : 0945-6317 (Print) 1432-2307 (Online), 22nd European Congress of Pathology, Florence, **Italy, Sept 2009** (ISI indexed)

Selected Publications

- **[Tutac et al., 2009b] A. Tutac**, D.Racoceanu, N.Loménie , W.K.Leow., L.Roux, V.I.Cretu, TPutti , "Knowledge Modeling of Breast Cancer Grading using OWL-DL formalism", Virchows Archiv The European Journal of Pathology, Springer-Verlag Berlin Heidelberg, H. Höfler ed, no. 428 vol. 455, suppl 1, pp. 36, ISSN : 0945-6317 (Print) 1432-2307 (Online), 22nd European Congress of Pathology, Florence**, Italy, 4-9 Sept 2009** (SpringerLink indexed)
- **[Tutac et al., 2009c] Adina Tutac,** Daniel Racoceanu, Nicolas Loménie, Ludovic Roux, Thomas C. Putti, Vladimir Cretu, "Breast Cancer Grading Knowledge Modeling and Reasoning for Cognitive Virtual Microscopy", National Institutes of Health NIH Inter-Institute Workshop on Optical Diagnostic and Biophotonic Methods from Bench to Bedside, Bethesda, **USA, 1- 2 Oct 2009**
- **[Tutac et al., 2009d] Adina Tutac**, Daniel Racoceanu, Nicolas Loménie, Ludovic Roux, Didier Balensi and Thomas Putti, "Knowledge Representation and Reasoning for Breast Cancer Grading in Cognitive Virtual Microscope Framework", A*STAR Scientific Conference 2009, Biopolis, **Singapore, 28-29 Oct, 2009**
- **[Lomenie et a., 2009]** N.Loménie, L.Roux, D. Balensi, **A. Tutac**, D. Racoceanu, "MICO: The COgnitive Virtual Microscope project", Cognitive Systems with Interactive Sensors (COGIS) symposium, Paris, **France, 16-18 Nov 2009**
- **[Tutac et al., 2010**] A. Tutac, V.Cretu, D.Racoceanu "Spatial representation for Breast Cancer Grading Ontology", Proc. IEEE International Joint Conferences on Computational Cybernetics and Technical Informatics ICCC-CONTI, pp.89-94, Timisoara, Romania, 27-29 May, 2010 (IEEE indexed)

Research Activity

- Research grants/internships :

  - TD- 65/2008 “Micro-Medical Image Processing”

  - “HISTOGRAD – a virtual microscope for breast cancer grading” Patent - software declaration (inventoried as *DI 2944-01* by the CNRS for the *UMI 2955*. Registered by the CNRS, Daniel Racoceanu, Adina Tutac, Xiong Wei, Jean-Romain Dalle, Chao-Hui Huang, Ludovic Roux, Wee-Kheng Leow)

  - CNRS, France & NUS, Singapore - 3 research stages in Singapore 2007 - 2009