WHOLE SLIDE ANALYSIS USING A COGNITIVE APPROACH TOWARDS COGNITIVE VIRTUAL MICROSCOPY IN BREAST CANCER HISTOPATHOLOGY

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AGENCE NATIONALE DE LA RECHERCHE ANR

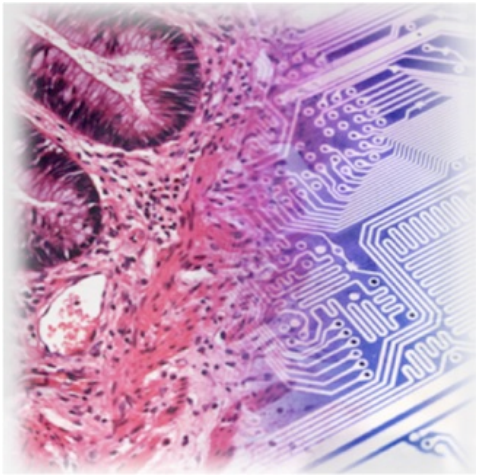
TecSan EDITION 2010
TECHNOLOGIES POUR LA SANTÉ ET L'AUTONOMIE

MICO (ANR TecSan 2011-2014)
COgnitive virtual MIcroscopy for digital pathology

ipal Image & Pervasive Access Lab
UNIVERSITE JOSEPH FOURIER SCIENCES, TECHNOLOGIE, MEDECINE
TRIBVN
THALES
UPMC SORBONNE UNIVERSITÉS
AGFA HealthCare

Challenge of the digital pathology

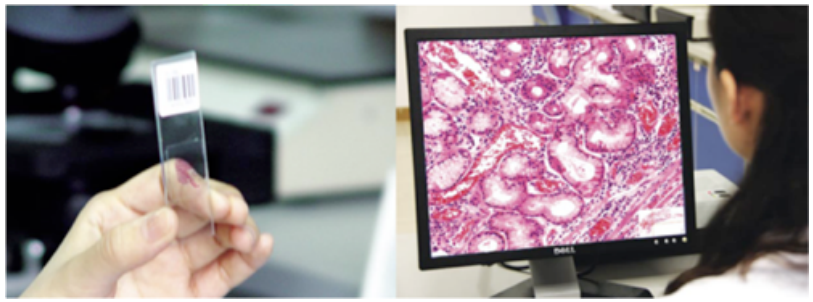
- The future of the pathology will need to be
  - Ethical: traceability / reference / validation
  - Dynamic: predictability / morphogenesis



- Towards digital pathology
  - The pathology is fundamentally cognitive
    (slides / signs reading / interpretation)
  - We need cognitive tools for digital pathology
  - New laws on the telemedecine / telepathology
  - Evolution of the DICOM standard
    (supplements 122, 145)
  - New generation of PACS

Objectives of the MICO project

- Accompany the evolution towards the numerical pathology
  - Augmented Microscopy: cognitive exploration, traceability
- By the breast cancer, towards the cancer grading in histopathology
  - Acquire a methodology
  - Define a formalism
  - Effective efficient cognitive approach
  - Test, validate and integrate the technologies in clinical environment



- Augmented microscopy for high-content imaging
  - A generic challenge in biomedical imaging

Symbolic Cognitive Vision

- Cognitive vision
  - Symbolic / Semantic approach (ANR TecSan MICO project)
    - Close to the medical interpretation of the pathologist
    - Ontological references (SNOMED-CT / ADICAP *)
      - Impact and thesaurus maintenance
  - Connexionnist approach

* ADICAP: Association for the Development of Informatics in Cytology and Anatomo-Pathology

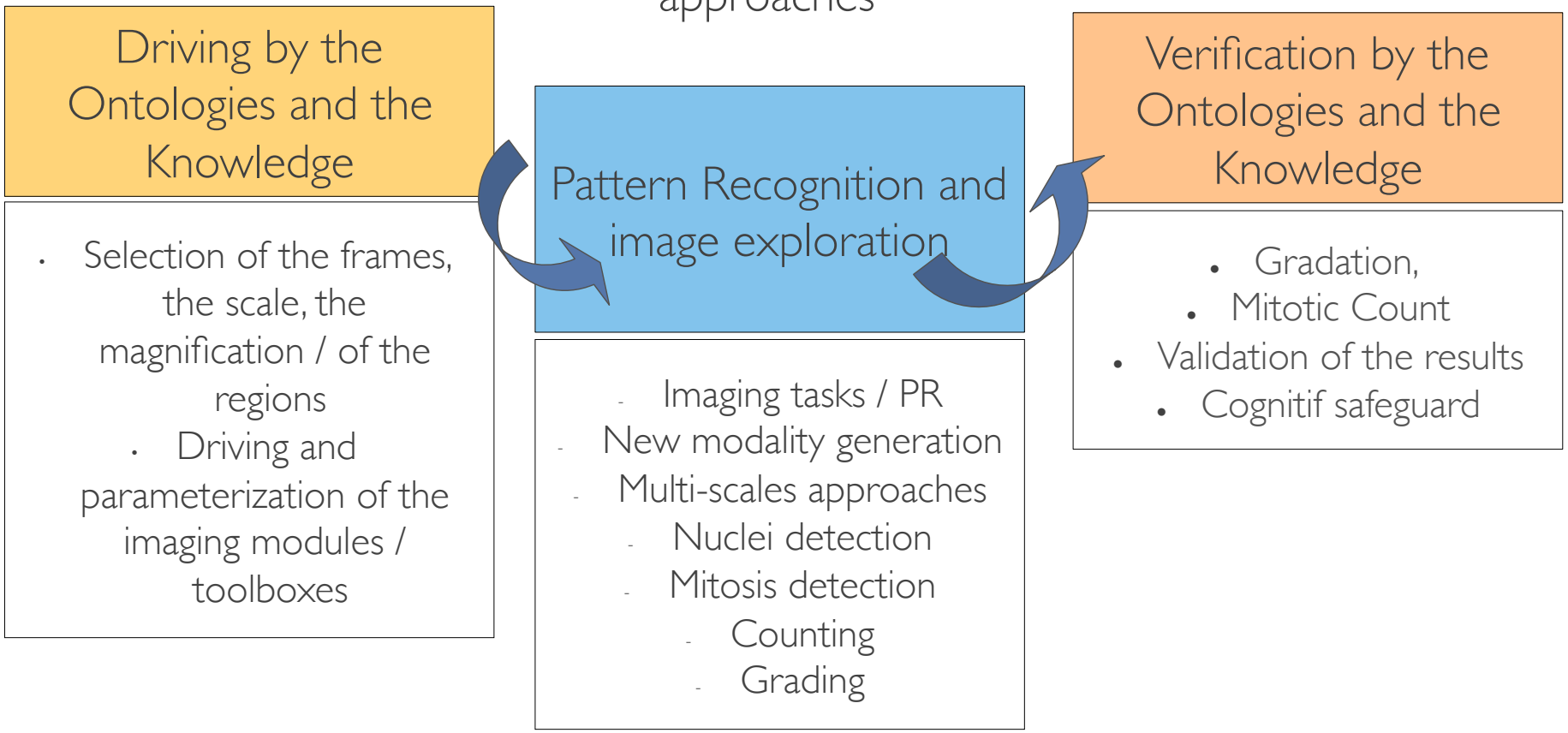
MICO Platform : A semantic approach

- Traceability
  - MICO platform is aimed to help histopathologists to take decisions by providing statements about medical cases, its decisions should obviously provide traceability. Semantic reasoning takes place in a formal world, each inference is proven: each decision is proven.
- System understanding & Decision support
  - Tedious and time consuming tasks. User in the loop.
- Flexibility and maintenance
  - With a full semantic approach, all the facts and processes are expressed in an open manner. They are also fully described and therefore easily understood. Compared to "hard coded" systems, semantic systems are more flexible and easier to maintain.
- Technology acceptance
  - Semantic web technologies helps the user to understand what the system truly does, and therefore increase its perceived ease of use. By increasing the system perceived ease of use and its perceived usefulness, this approach will probably help the user to accept technology.
- Improved image processing
  - Expert knowledge used to guide image processing algorithms, target interesting spots in order to spare as much processing power as possible and to make the overall gradation faster. ONTOLOGY AT THE HELM.

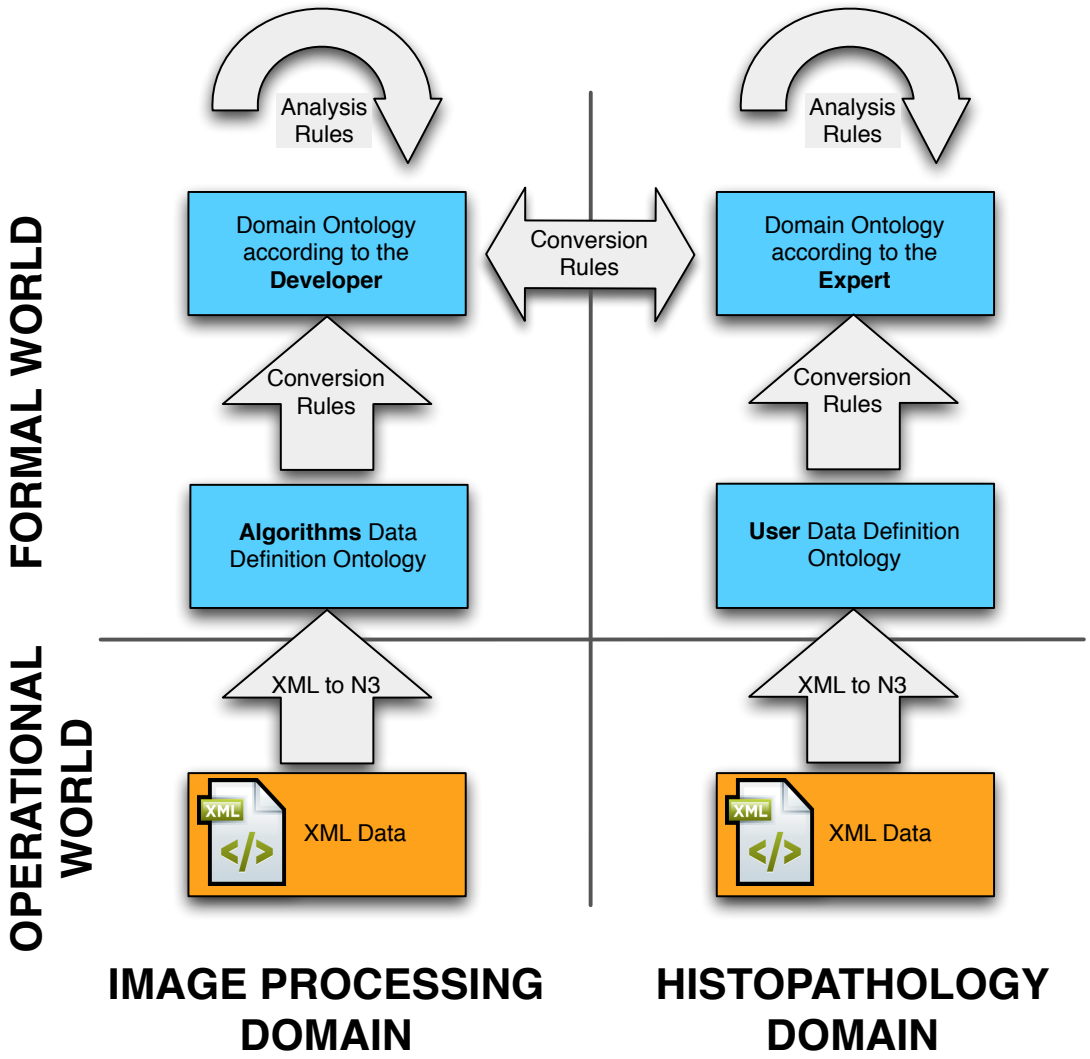
Interaction between ontologies and images

Coupling between knowledge and pattern recognition

- Role sharing and interaction between the AI and Pattern Recognition approaches

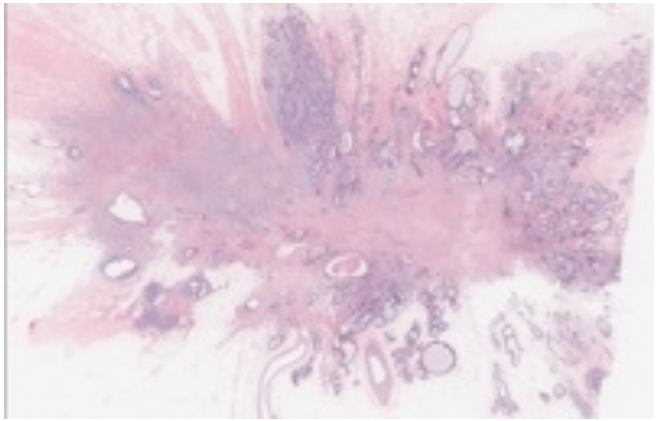


MICO Ontologies

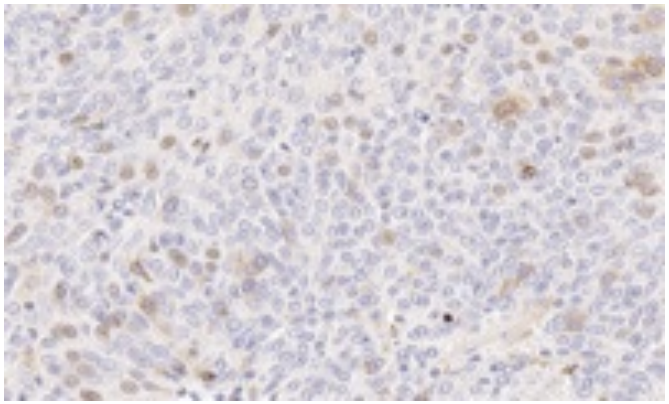


Grading Process
Breast Cancer – Canalar Carcinoma (80%)

- H&E staining - Hematoxylin-eosin staining
  - Architecture evaluation
  - Mitotic count
  - Nuclear polymorphism / atypia



- IHC – Immunohistochemistry – Analysis of Hormone Receptors
  - Nuclear labeling
    - KI-67 Proliferation Index
    - ER, Estrogen Receptor
    - PR, Progesterone Receptor
  - Cytoplasm and cellular membrane
    - HER2/neu, Epidermal Growth Factor Receptor



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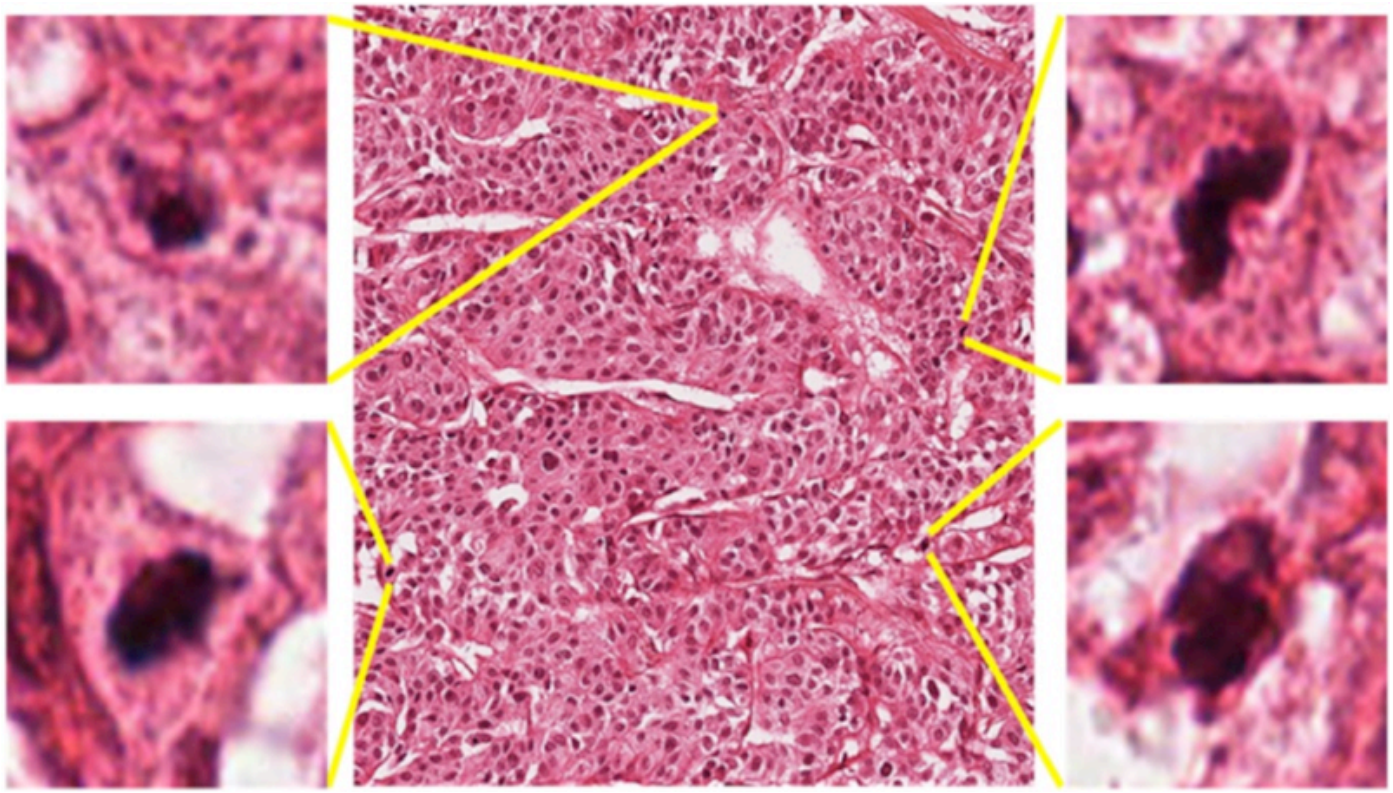
MITOTIC COUNT

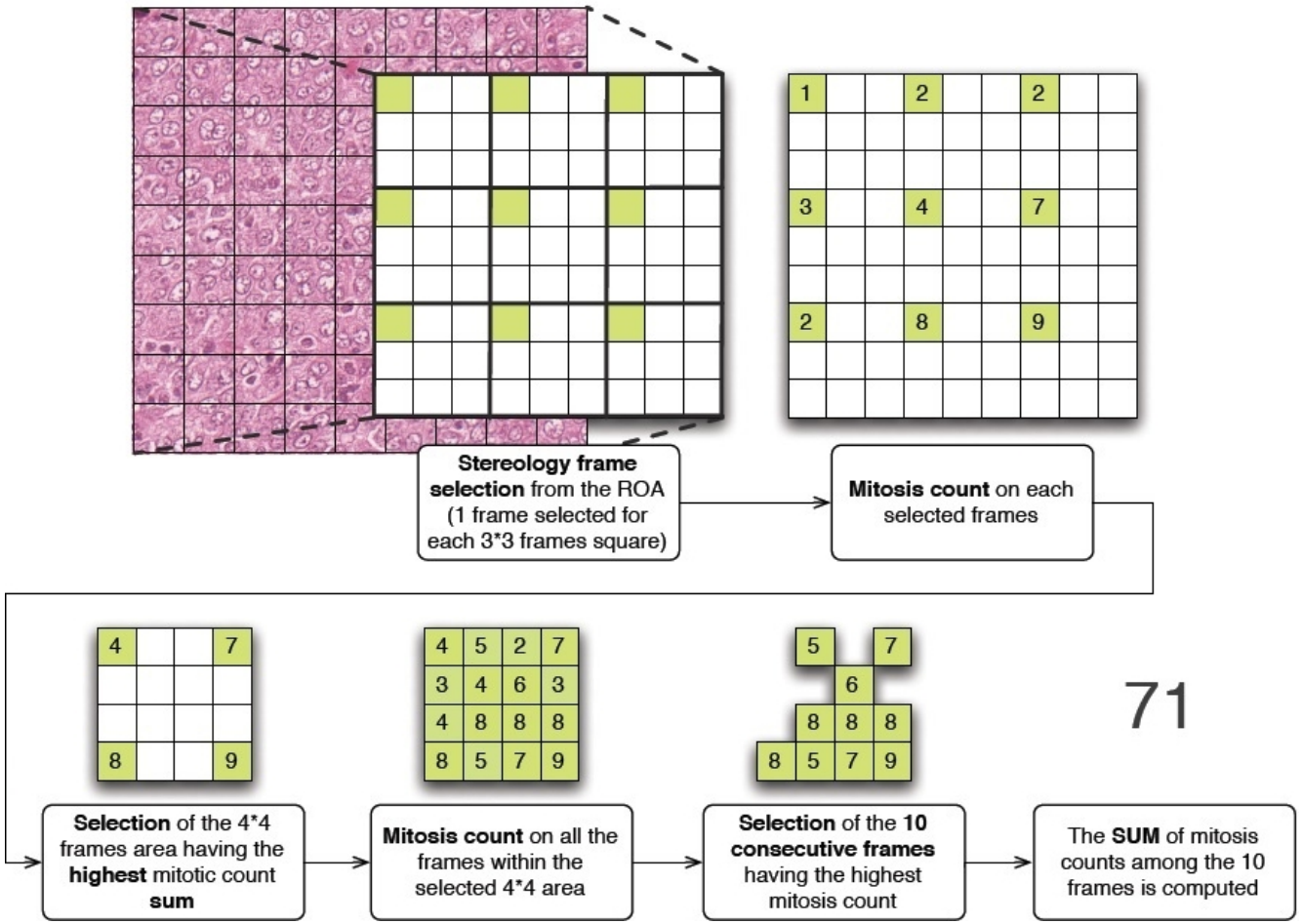
Challenge of the Automatic Mitotic Detection

- Variation in shape and size,
- Variation in pixel intensity,
- Few mitosis per frame,
- Similarity with other types of objects (e.g., apoptosis, necrosis, dust particles, lymphocytes, etc)

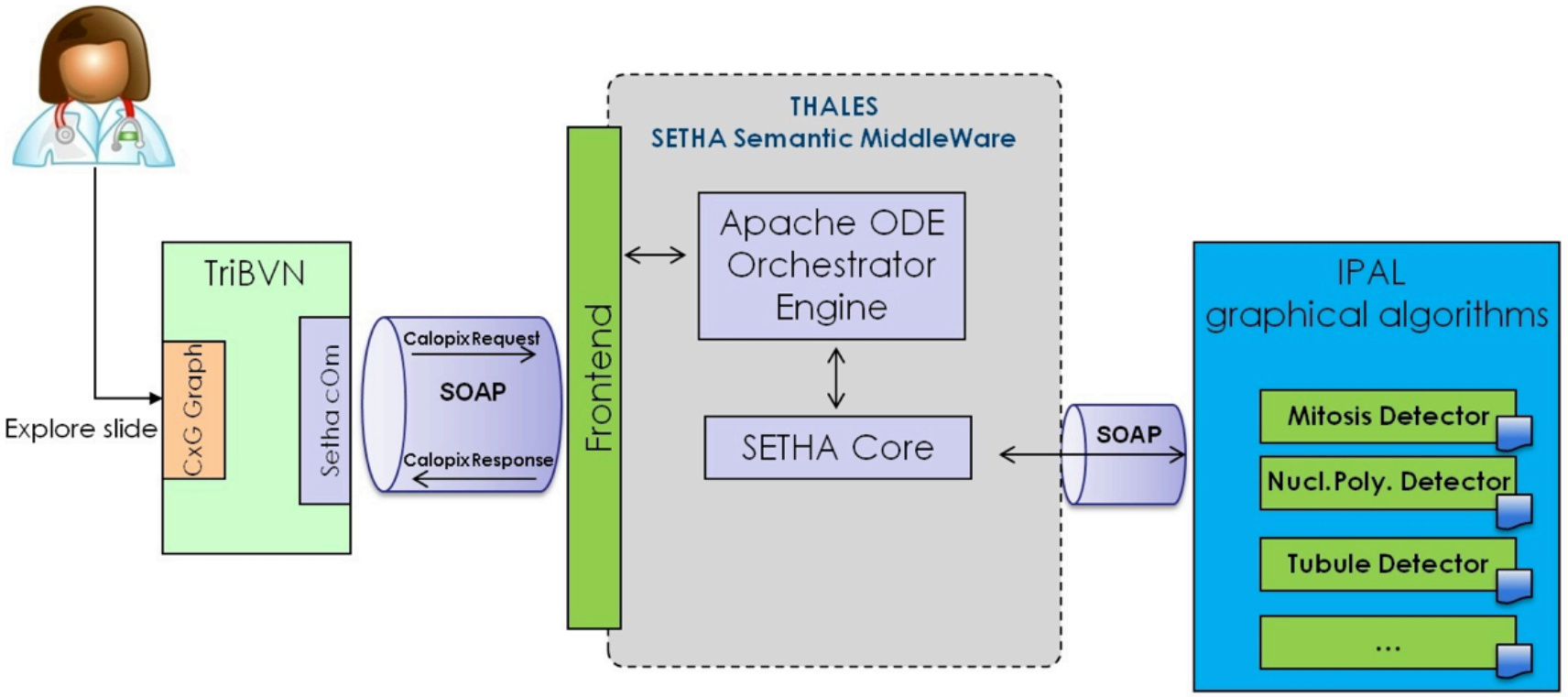


Digital Pathology Protocol

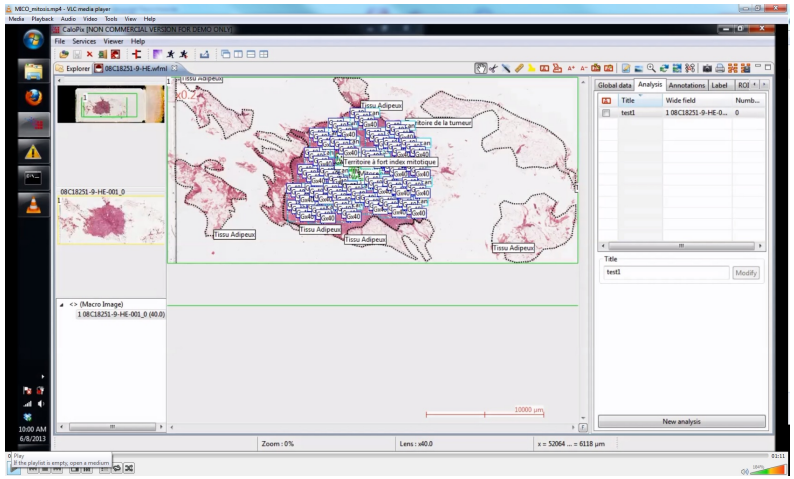
- Mitotic count algorithm



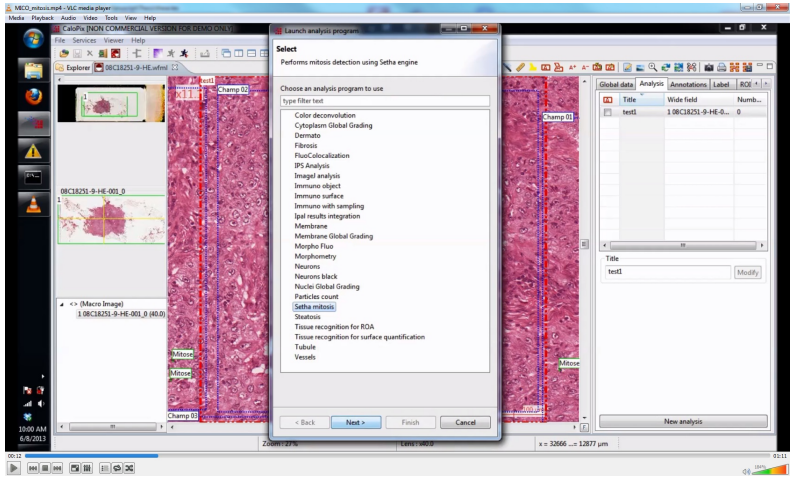
MICO 2.0 around a semantic middleware



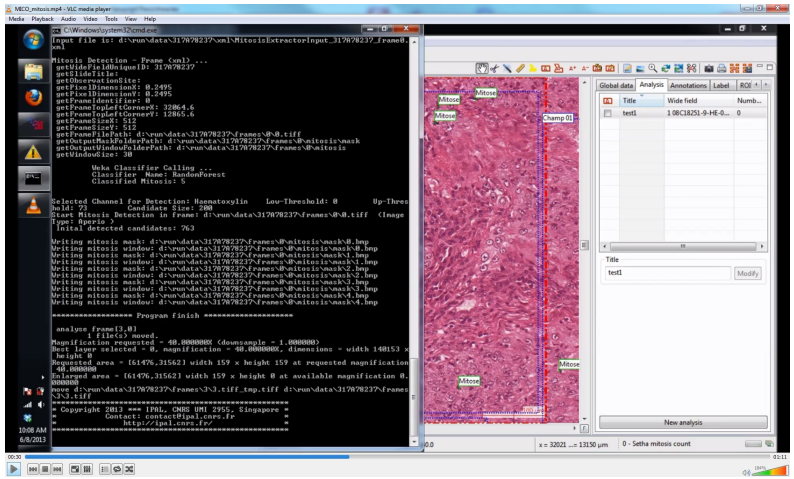
MICO 2.0 prototype POC



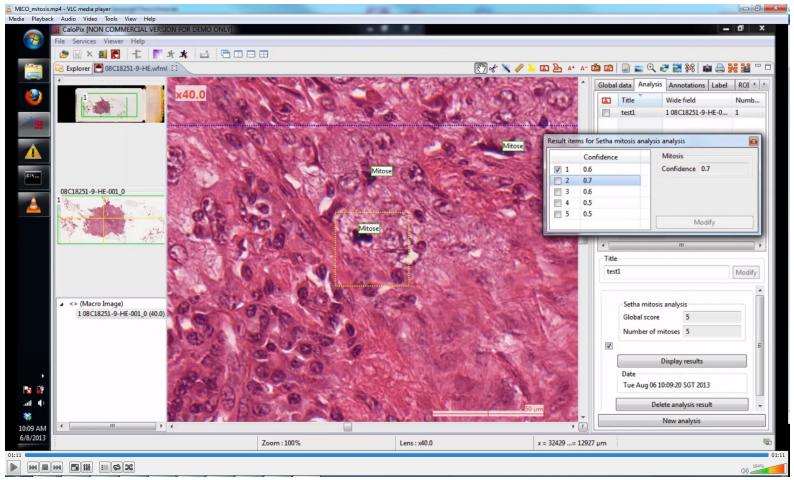
(a) Calopix user interface



(b) Calling Mitosis Detection from Calopix

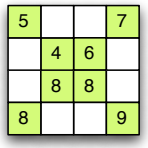


(c) Mitosis Detection execution



(d) Result of Mitosis detection with confidence

FrameSelector 8+2

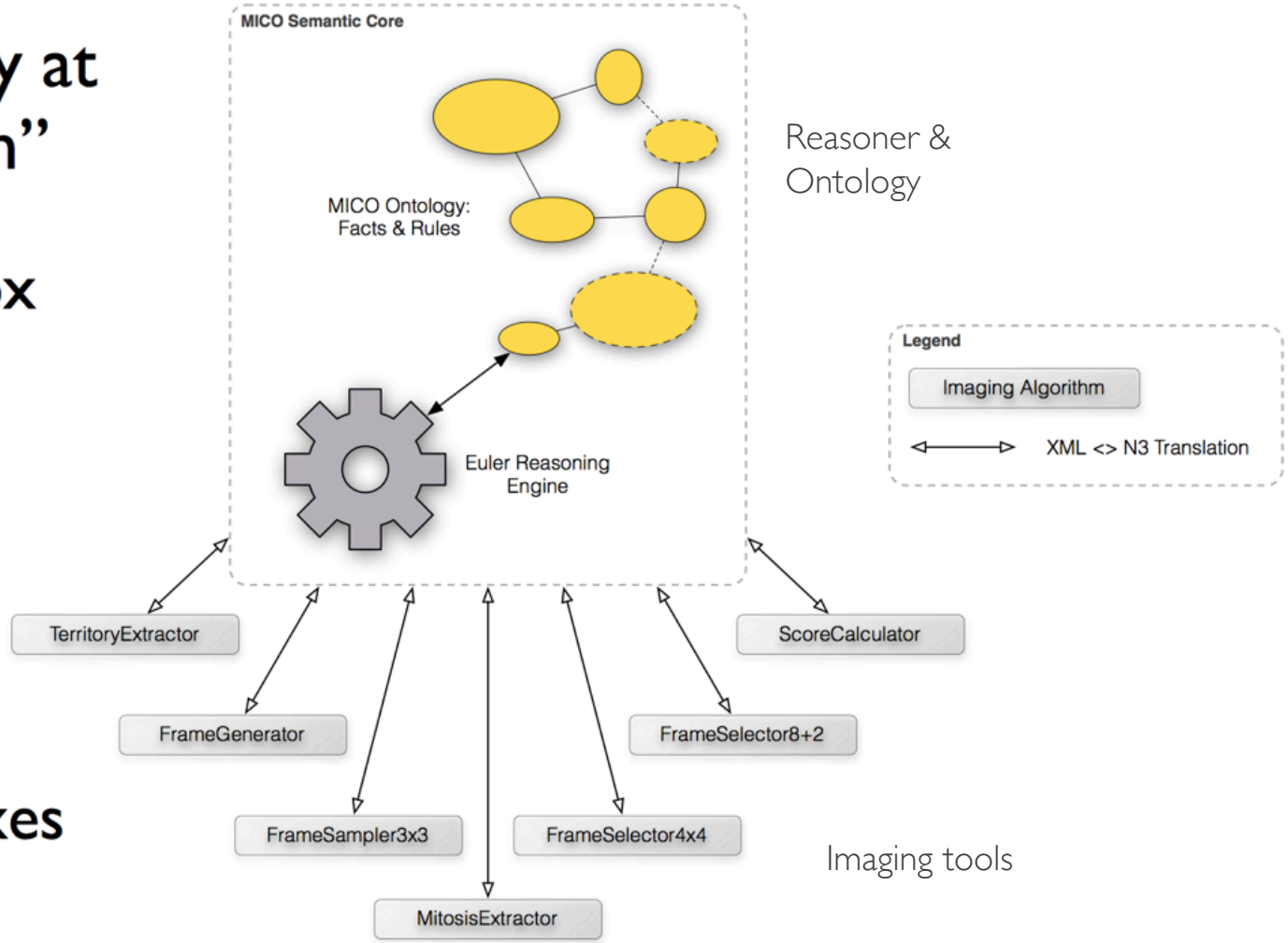


Cognitive-visual whole slide image exploration
MICO 3.0 POC

"Ontology at the helm"

Glass box

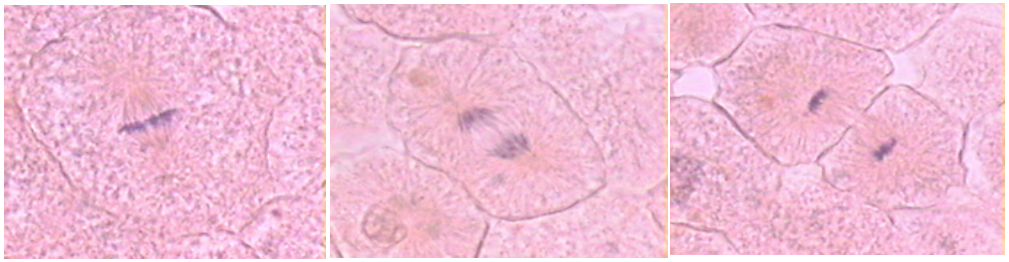
Black boxes



MITOSIS DETECTION INTERNATIONAL BENCHMARKING @ ICPR 2012

initiative leaded by IPAL

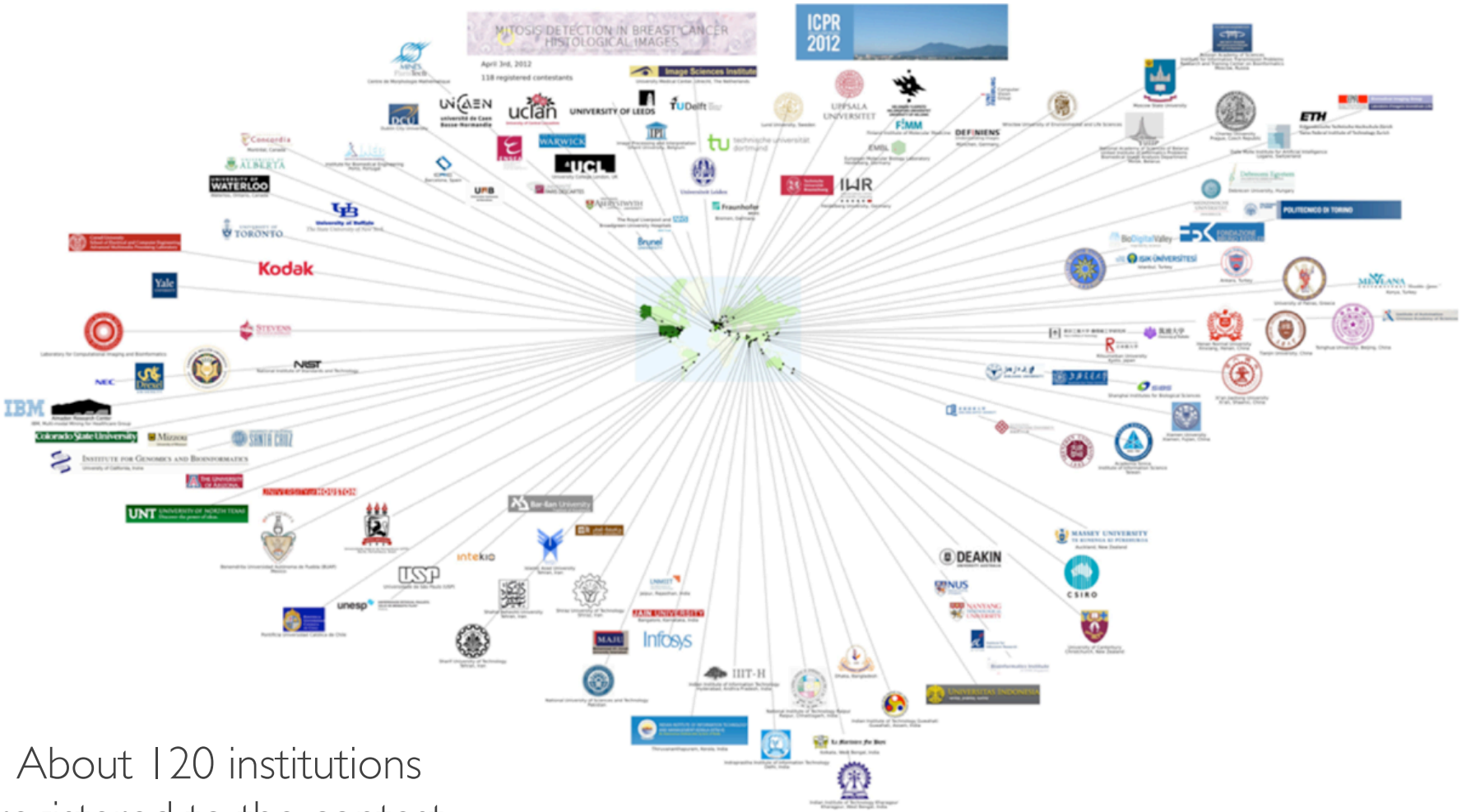
- Organized by IPAL/UJF/UPMC, La Pitié Hospital, TRIBVN, Ohio Univ
  - ICPR 2012, November 11, 2012, Tsukuba, Japan
  - URL: http://ipal.cnrs.fr/ICPR2012/



  - Multimodal data :
    - Fast scanners (Aperio & Hamamatsu)
    - Multispectral Multifocal Microscopy
  - Special issue in JPI - Journal Pathology Informatics – March 2013

MITOS @ ICPR 2012

Participants to the international benchmark



About 120 institutions registered to the contest

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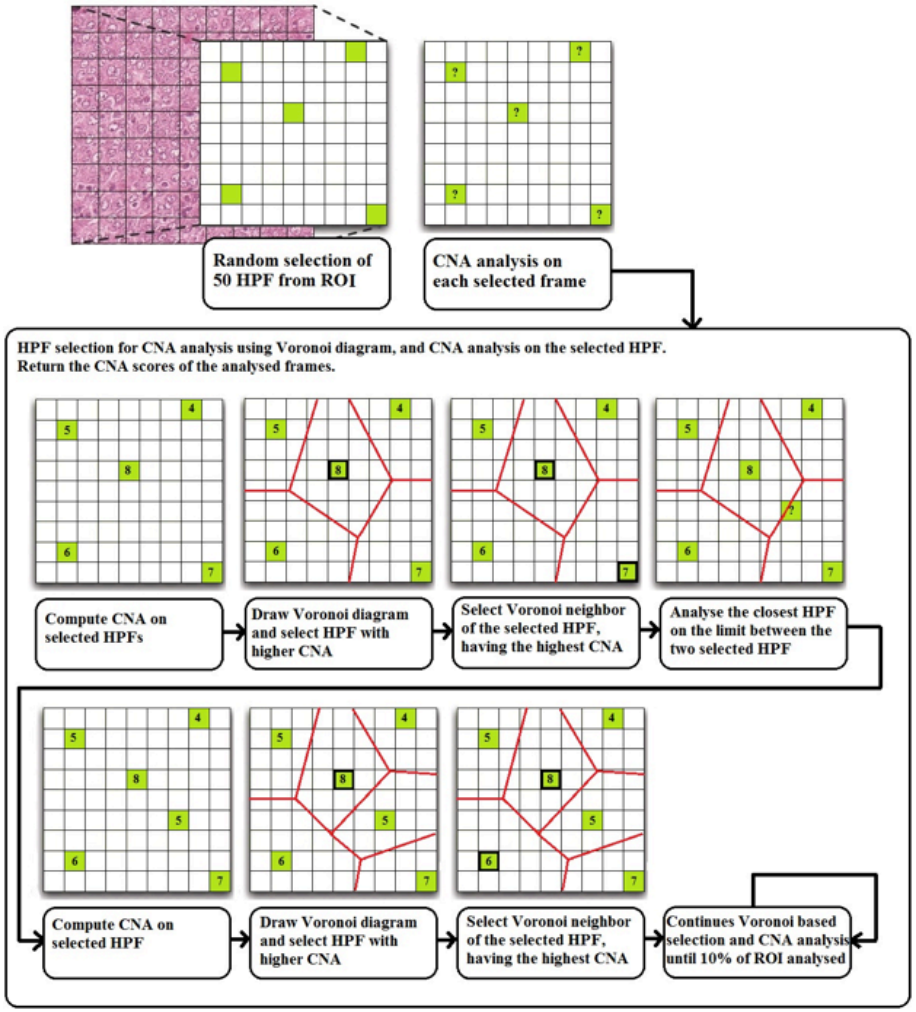
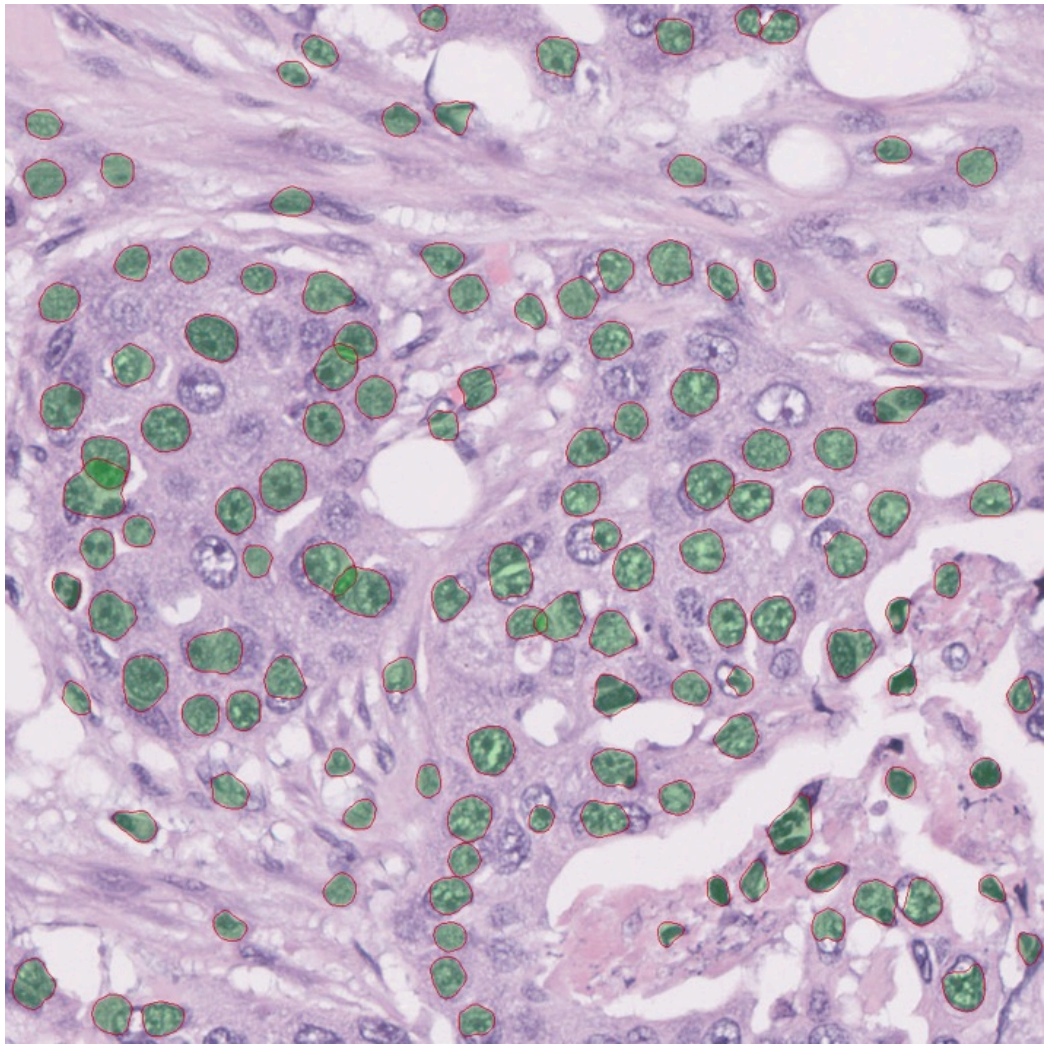
NUCLEAR ATYPIA

Digital Pathology Protocol – Nuclear Atypia

- Nuclear polymorphism analysis algorithm



Nuclei extraction challenges



Score 3

Problems:
- Nuclei non-homogeneity
- Nuclei vary a lot in terms of size, shape and cytoplasm homogeneity

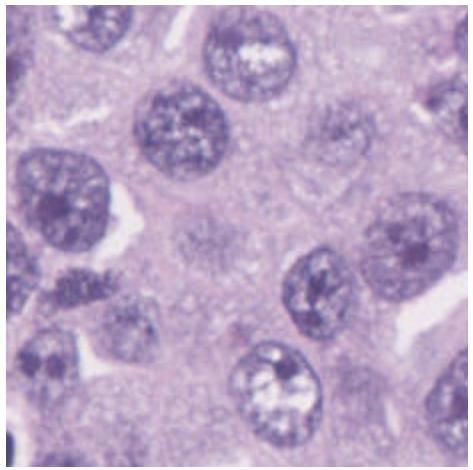
Nuclei non-homogeneity

- Create a new image modality using a machine learning based method using
  - colour
  - texture,
  - scale information,

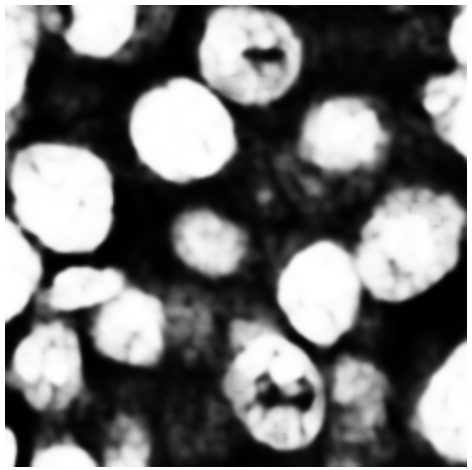
in order to improve the accuracy of nuclei extraction

Probabilistic Image Modality

- Probability Map
- The resulting 180-dimensional feature vector X is used to compute the probability p(X) of each pixel to belong to a cell nuclei

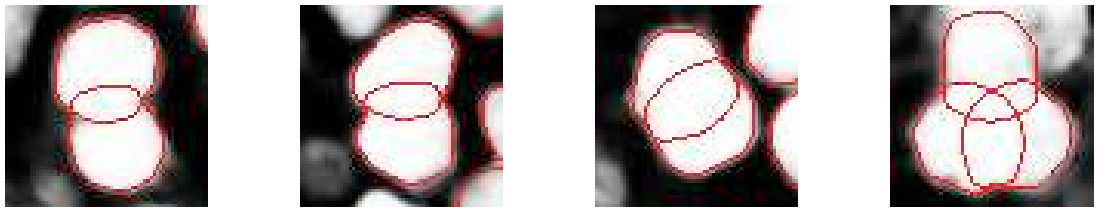


Original H&E image



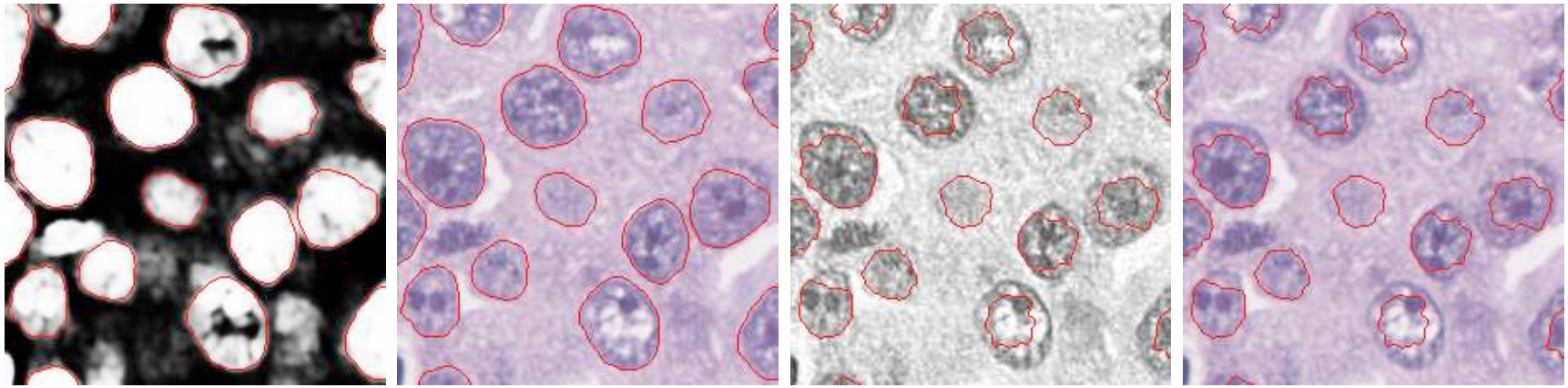
Obtained image modality

Nuclei Segmentation use of the probabilistic modality and of the Marked Point Process



(a) (b) (c) (d)

Figure 4: The shape prior information allows to extract the overlapping nuclei.

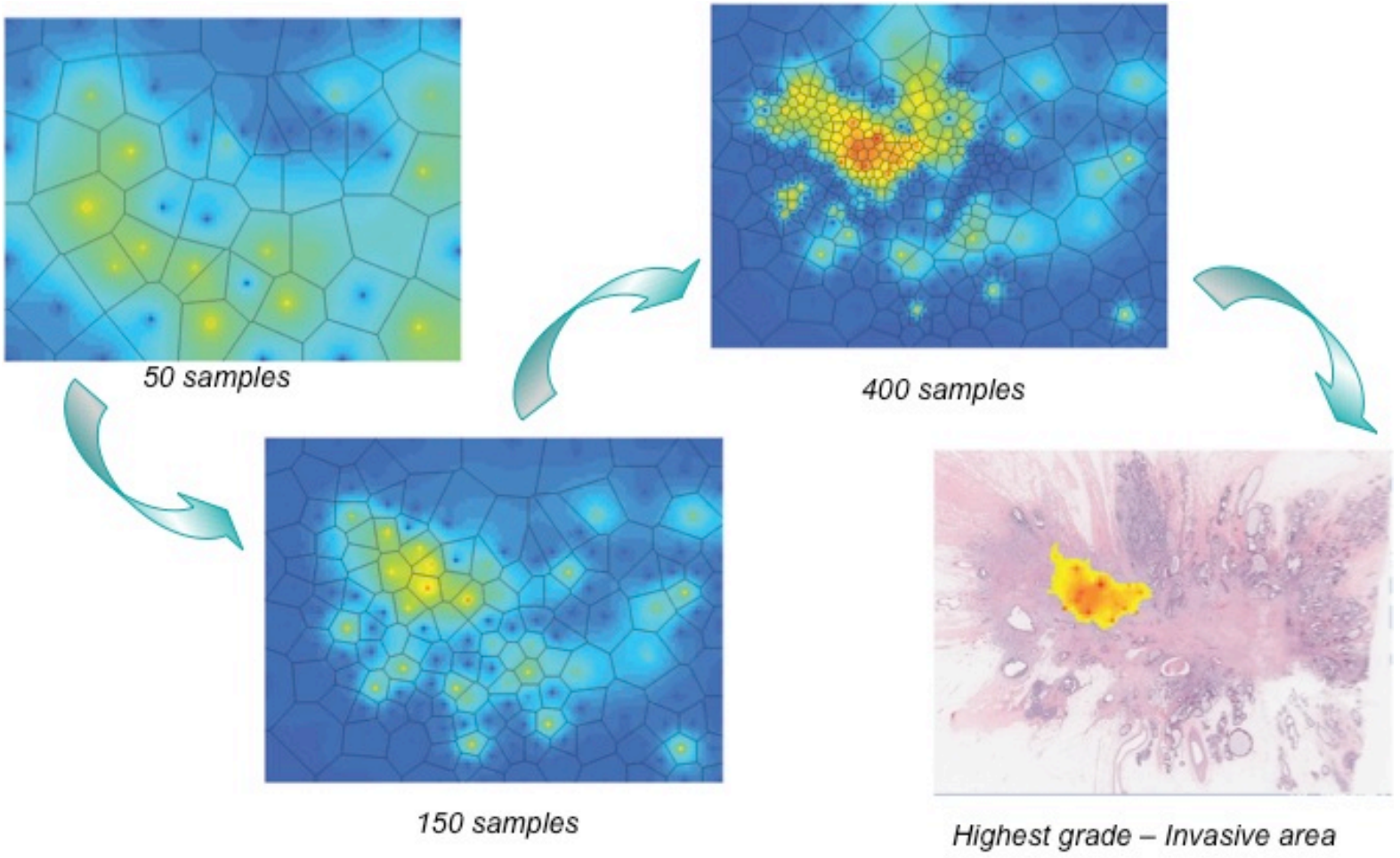


(a) Probability map (b) Corresponding H&E stained image (c) Haematoxilin image (d) Corresponding H&E stained image

Figure 5: Illustration of the extraction results : (a-b) is obtained using the probability map and (c-d) is obtained using the haematoxilin channel after the image color deconvolution.

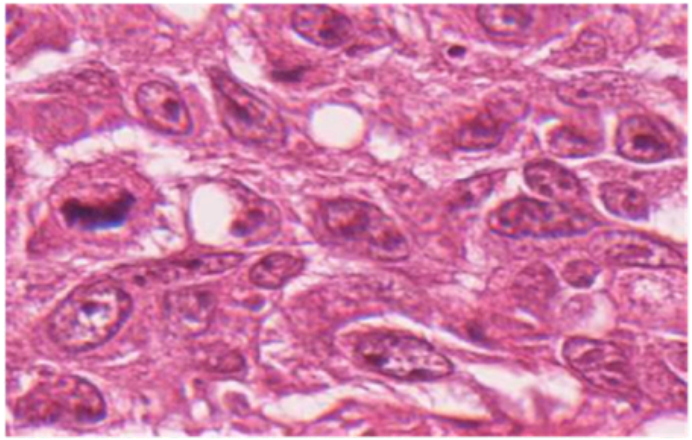
Cell Nuclei Extraction from Breast Cancer Histopathology Images Using Color, Texture, Scale and Shape Information, European Congress on Telepathology and 5th International Congress on Virtual Microscopy, June 2012.

WSI efficient BCG using dynamic sampling involving Voronoi Diagrams

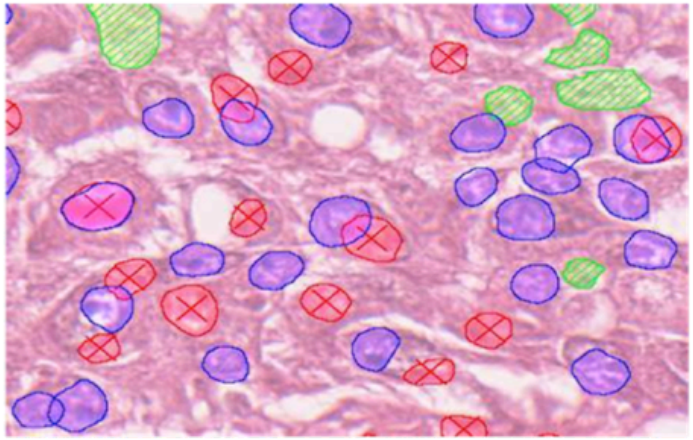


An Exploration Scheme for Large Images: application to Breast Cancer Grading, ICPR 2010

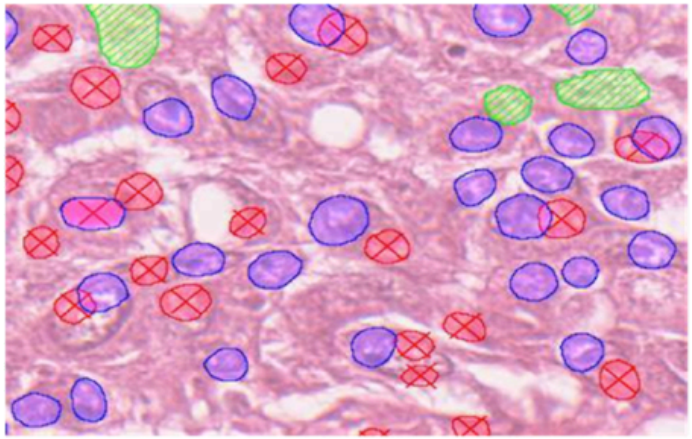
Various MPP versions



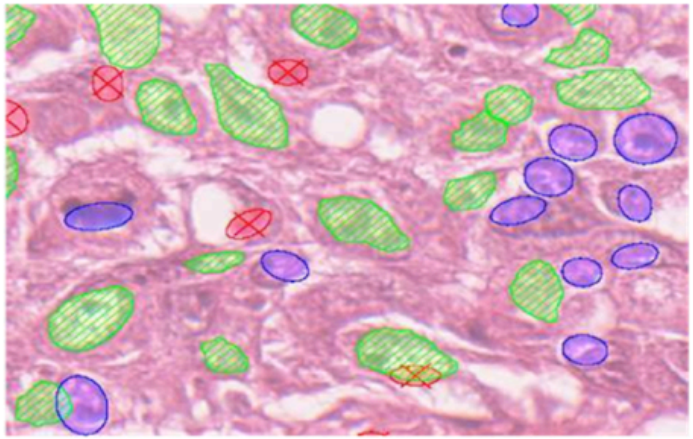
(a) H&E breast cancer surgical slide



(b) Results of Arbitrarily-Shaped Object MPP with a large radius range



(c) Results of Arbitrarily-Shaped Object MPP with a small radius range

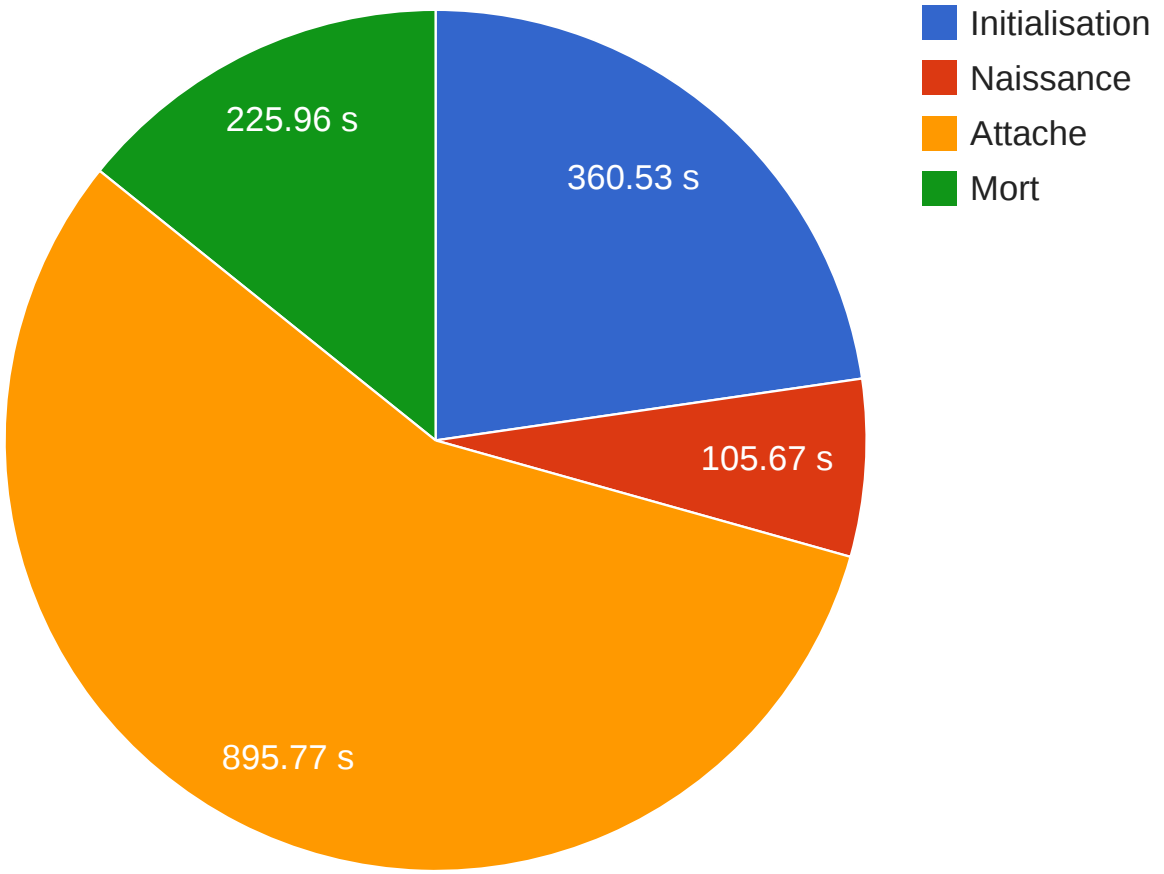


(d) Results of Elliptically-Shaped Object MPP

Figure 3: Comparing results on a single H&E image of high grade

Sequential algorithm: computation time

- Processing time ratio



Performances of the Parallel Algorithm

Computation time in seconds on 3326x2971 pixel image:

[s]	Initialization	Birth	Energy	Death	Total
Sequential	360.53	105.67	895.77	225.96	1583.02
Multi-core	37.34	19.96	156.73	31.23	244.17
GPU	2.52	2.41	94.98	36.36	136.37

Acceleration ratio:

	Initialization	Birth	Energy	Death	Total
Multi-core	9.65	5.25	5.67	7.18	6.48
GPU	142.95	44.19	9.49	6.25	11.61

CALL FOR PARTICIPATION
MITOS & ATYPIA CONTEST

ICPR 22nd INTERNATIONAL CONFERENCE ON PATTERN RECOGNITION

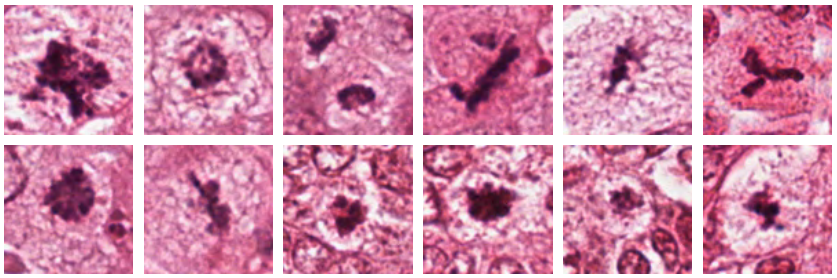
IAPR Linköpings universitet LUNDS UNIVERSITET UPPSALA UNIVERSITET

24-28 August 2014 Stockholm, Sweden

Detection of Mitosis and Evaluation of Nuclear Atypia Score in Breast Cancer Histological Images

Detection of Mitosis

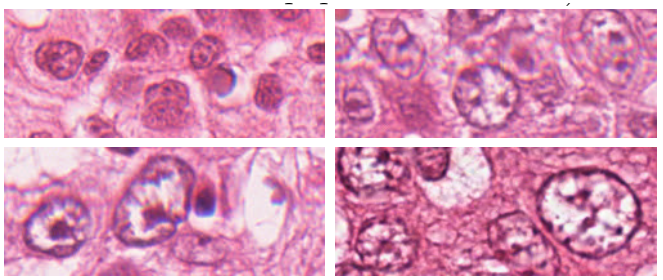
Mitotic count gives an evaluation of the aggressivity of the tumour. Detection of mitosis is a challenging task since mitosis have a large variety of shape configurations. There is a very low density of mitosis in one image. Other objects like apoptotic cells (process of programmed cell death) can look very similar to mitotic cells.



Example of Mitotic Cells

Evaluation of Nuclear Atypia

Nuclear pleomorphism refers to nuclei shape variations as compared to normal epithelial nuclei. The more advanced is the cancer, the more nuclei become atypical in their shape, size, internal organisation…
Nuclear atypia score can be estimated from criteria computed on nuclei such as size of nuclei, size of nucleoli, density of chromatin, thickness of nuclear membrane, regularity of nuclear contour, anisonucleosis (size variation within a population of nuclei)…



Examples of different degrees of nuclear atypia

MITOS & ATYPIA @ ICPR 2014

- Dataset

- The training dataset is made up of frames at X20 and X40 magnification extracted from 10 slides of breast cancer. Each frame is a RGB image corresponding to a surface of about 379 × 338 μm2 on the slide.
  Slide have been scanned at 40X magnification by two slide scanners: Aperio Scanscope XT and Hamamatsu NanoZoomer 2.0-HT. Images have a size of 1539 × 1376 pixels for Aperio scanner, and of 1663 × 1485 pixels for Hamamatsu scanner.

- Mitosis are annotated on images at X40 magnification.
  Nuclear atypia score is provided for images at X20 magnification, and values for six criteria related to nuclear atypia are given for images at X40 magnification.
  Selection of images, nuclear atypia scores and mitosis annotations have been provided by two senior pathologists and three junior pathologists of PitiéSalpêtrière Hospital and of Institut Curie, Paris France.

- Website: http://mitos-atypia-14.comicframework.org/

- Important Dates
  - December 2nd, 2013: Training data set available.
  - July 1st, 2014: Evaluation data set available.
  - Participants send an abstract (one page) describing their method.
  - July 27th, 2014: Deadline for participants to send their results.
  - August 24th, 2014: Contest meeting will take place during ICPR 2014 in Stockholm, Sweden. Acknowledgement

- This proposal is supported by the French National Research Agency ANR, project MICO under reference ANR-10-TECS-015.

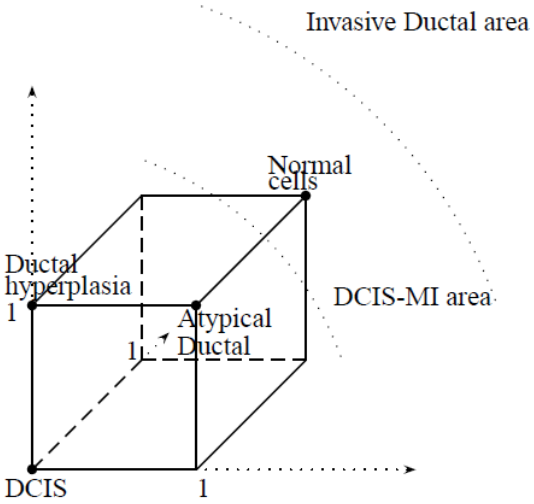
Preliminarily results

ARCHITECTURE & SPATIAL POSITIONNING

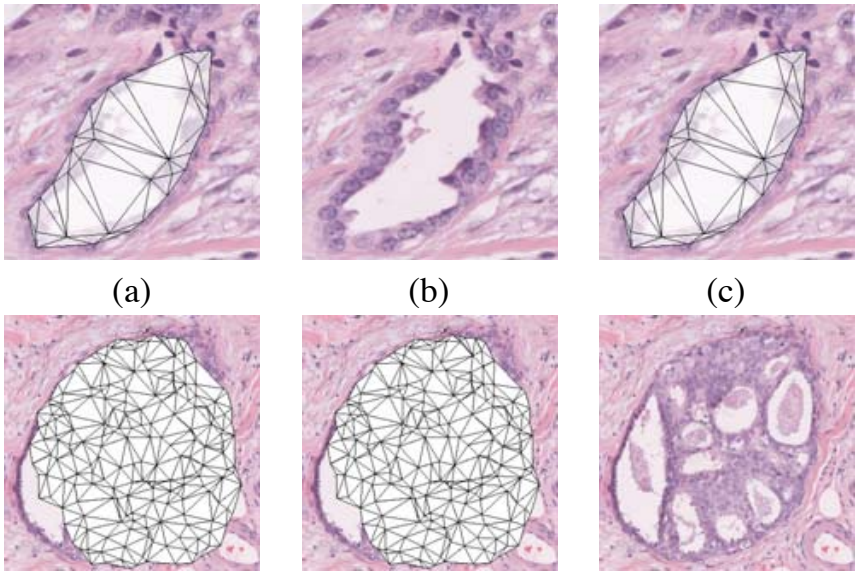
Morphological Operators on sparse WSI structures

Geometric criteria to discriminate between various cancer types computed on $M_1 - o^2(M_1)$ Median Size of 0 refers to small size and 1 to large size. EN, CC and MS stands respectively for Euler Number, number of Connected Components and σ^2-simplex Median Size whose concatenation provide a digital structural coding of the observed bio-structure.

Cancer type	EN	CC	MS
Normal cells	1	1	1
Ductal hyperplasia	0	1	0
Atypical ductal	1	1	0
DCIS	0	0	0
DCIS-MI	2	2	0
Invasive	5	5	0



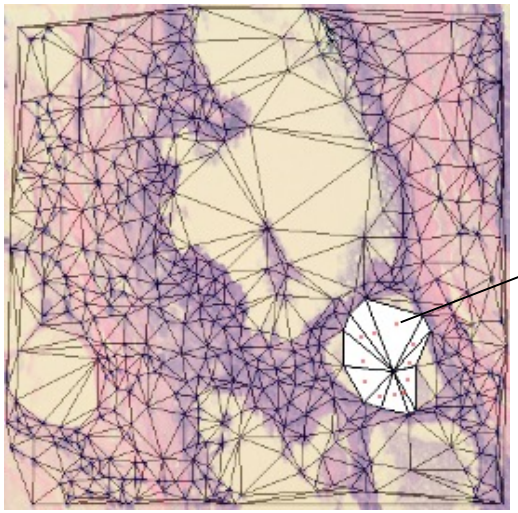
Repartition of the six various breast cancer cases of Fig. 18 over the three dimensional bio-code cube.



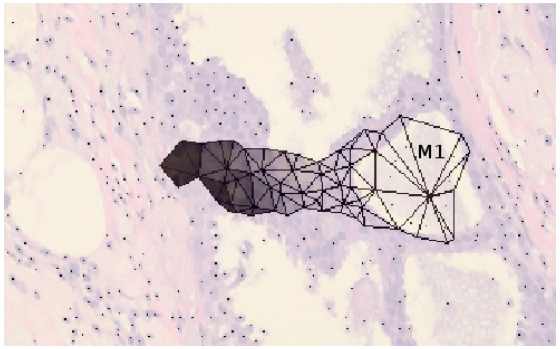
On the left (a) $Del_{\alpha_{opt}}$ representation of a tubular bio-structure; (d) of a DCIS bio-structure. In the middle, opening of order two $o^2(Del_{\alpha_{opt}})$ as an opening based morphological filtering of (b) the tubular formation; (e) the DCIS formation. At right, the difference between $Del_{\alpha_{opt}}$ and $o^2(Del_{\alpha_{opt}})$ for the (c) tubular formation and (d) the DCIS formation.

Nicolas Loménie, Daniel Racoceanu, Point set morphological filtering and semantic spatial configuration modeling: applications to microscopic image and bio-structure analysis, Pattern Recognition, vol. 45, Issue 8, Feb 2012

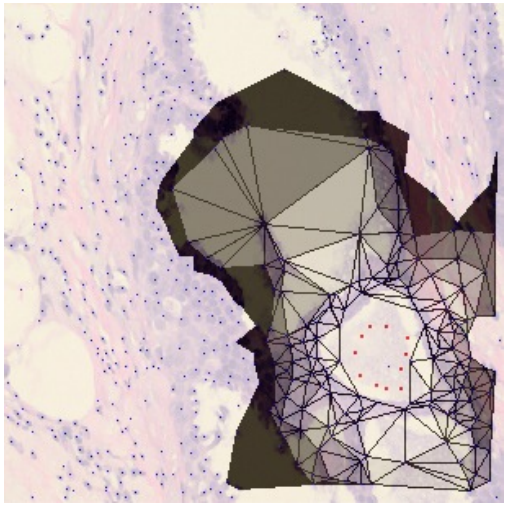
Extension to spatial relationship handling

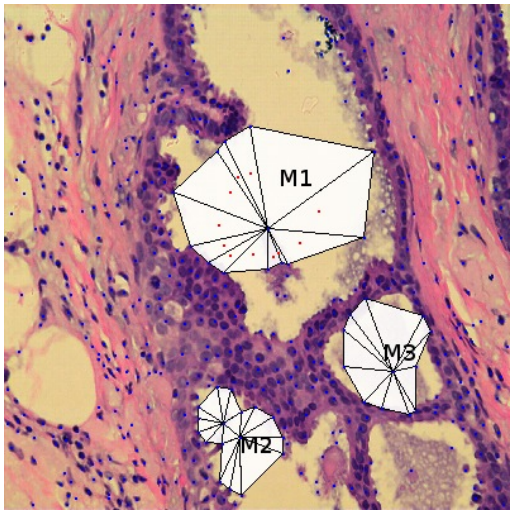


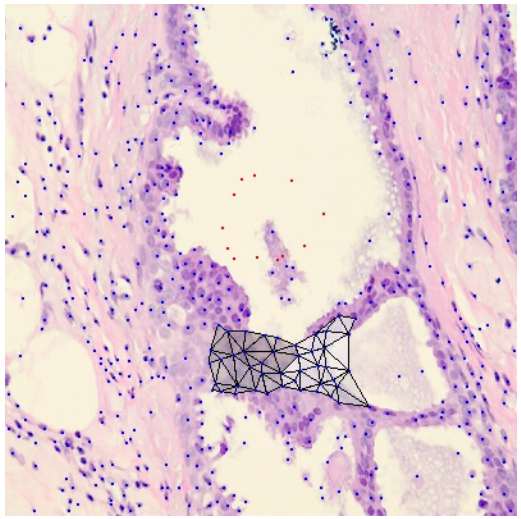
Fuzzy Left Region of M1



Around Region of M1



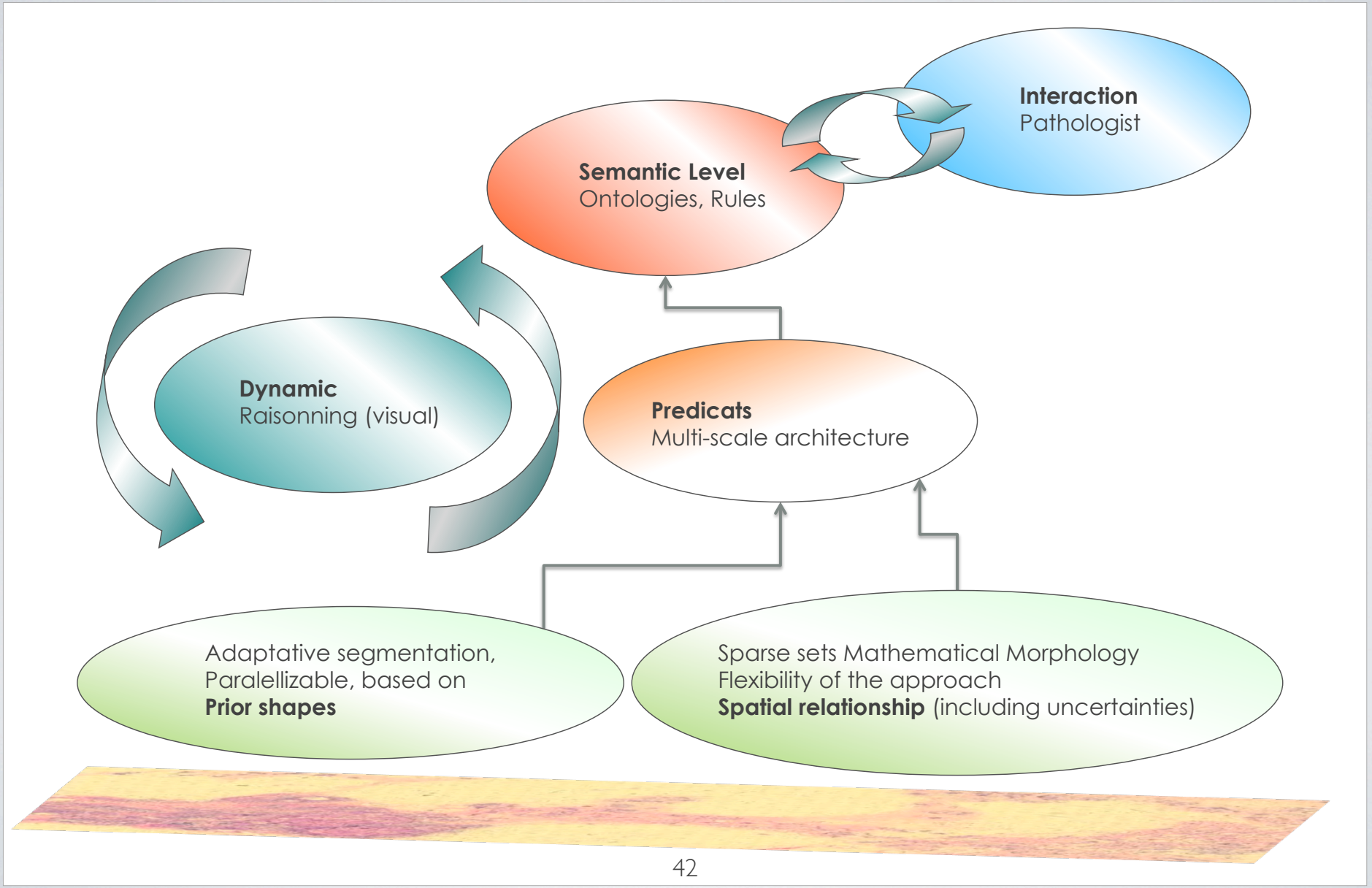




Between
(M1,M2,M3)
Region

Nicolas Loménie, Daniel Racoceanu, Point set morphological filtering and semantic spatial configuration modeling: applications to microscopic image and bio-structure analysis, Pattern Recognition, vol. 45, Issue 8, Feb 2012

Cognitive Integrated Microscopy



SYSTEMATIC

MEDICEN PARIS REGION

FlexMIm (Grand Emprunt, FUI project 2013-2016)

Collaborative Telepathology based on semantic imaging

orange

TRIBVN

pertimm

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

UPMC SORBONNE UNIVERSITÉS

université PARIS DIDEROT

Collaborative digital telepathology

- Treats the user needs, expressed by anatomo-pathologists, in a context of decrease of their demography and increase of the number of medical acts
- Provide the pathologists with tools increasing their cooperative (initial tele-diagnostic, tele-expertise, e-learning) and collaborative capabilities, based on whole slide imaging technologies
- Develop and setup cognitive algorithms, driven by medical knowledge models (image exploration and cancer grading rules, annotation procedures, valid medical ontologies), to identify specific regions of interest for pathological analysis/grading
- Provide innovative, effective solutions to manage and manipulate WSI according to the used devices and networks. Provide intelligent algorithms allowing fluid data sharing and exchange via telecommunication network in the «Télépathologie Ile de France» cluster.
- Annotation and enrichment tools using medical databases and ontologies, by bringing closer the imaging and patient data.
- "Télépathologie Ile de France" evaluates and validates efficient/effective cooperative and collaborative process proposed by FlexMIm, focusing on the anatomopathological imaging, in order to reach concrete clinical use and dissemination, by formalizing a professional reference.

12TH EUROPEAN CONGRESS ON DIGITAL PATHOLOGY

12th European Congress on Digital Pathology

previously European Congress on Telepathology and International Congress on Virtual Microscopy

Worldwide INDUSTRY, RESEARCH and CLINICS participants:

- Business processes in Pathology: hospital integration, telepathology, e-learning
- Imaging technological advances: WSI, molecular imaging, label free technologies...
- Image analysis, knowledge formalization and modeling

Organized under the presidency of *Catherine Guettier* SFP (French Society of Pathology), honorary president, *Etienne Martin* with the contribution of ADICAP (Association for Developing Informatics in Cytology and Anatomic Pathology), *Frédérique Capron* and GFHC (French Group for Cellular Haematology), *Xavier Troussard.*

Paris, France, 18-21 June 2014, collège des Bernardins, close to île Saint-Louis

www.digitalpathology2014.org

12TH EUROPEAN CONGRESS ON DIGITAL PATHOLOGY

Abstracts submission deadline: 20 January 2014 !!

- Contributors are invited to submit an abstract (max. 400 words) for oral and poster presentations on all research fields related to digital pathology, telepathology, image analysis.
- Submission should be done electronically at the following link: www.digitalpathology2014.org
- In addition, contributors who also aim at individually Pubmed indexed articles shall submit an extended abstract (less than 1500 words). Selected articles will be published either in
  - "Diagnostic Pathology"
    - (editor-in-chief Klaus Kayser, co-chairs Catherine Bor, Philippe Camparo, Myriam Oger) or
  - "Computerized Medical Imaging and Graphics" Elsevier journal
    - (editor-in-chief Daniel Racoceanu, co-chair Philippe Belhomme)
  - Pecha kucha: young scientists & creative researchers : thomas.schrader@computer.org

Organizing committee co-chaired by Jacques Klossa and Philippe Bertheau: Philippe Belhomme; Catherine Bor; Philippe Camparo; Odile Crepin; Christel Daniel; Bettina Fabiani; Vincent Leymarie; Daniel Lusina; Michel Manfait; Etienne Martin; Myriam Oger; Daniel Racoceanu; Thomas Schrader; Béatrice Vergier

Scientific advisory board co-chaired by Klaus Kayser, Catherine Bor, Daniel Racoceanu

CALL FOR SUBMISSION
CMIG ELSEVIER - SPECIAL ISSUE

CALL FOR SUBMISSIONS: "BREAKTHROUGH TECHNOLOGIES IN DIGITAL PATHOLOGY"

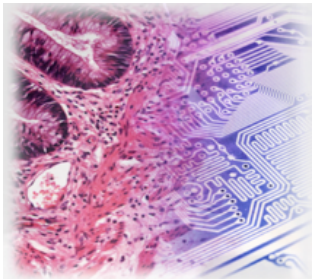
a special issue of CMIG - COMPUTERIZED MEDICAL IMAGING AND GRAPHICS, ELSEVIER

in link with the "EUROPEAN CONGRESS ON DIGITAL PATHOLOGY 2014", 18-21 JUNE 2014, PARIS

Special issue, dedicated to a selection of articles concerning the coming breakthrough technologies in the modern era of the pathology, following its evolution towards (not exclusively):

- Digitisation, Label-free,
- Knowledge-driven (including semantics),
- Data-driven and telepathology,

▸ in symbiosis with recent advances in high-content imaging



▸ The deadline for the submissions will be on the 20th of January 2014 for an extended abstract - 1500 words – to be submitted at: www.digitalpathology2014.org

▸ 28th of March 2014 for the full paper at CMIG (information will follow after the acceptance of the extended abstract)

▸ Editors: Daniel Racoceanu (Univ. Pierre and Marie Curie, Sorbonne Universities, Paris),
Philippe Belhomme (University of Caen)
Contact: daniel.racoceanu@upmc.fr , philippe.belhomme@unicaen.fr

12TH EUROPEAN CONGRESS ON DIGITAL PATHOLOGY

Are you ready for Paris ?

Paris, France, 18-21 June 2014, collège des Bernardins, close to île Saint-Louis

www.digitalpathology2014.org

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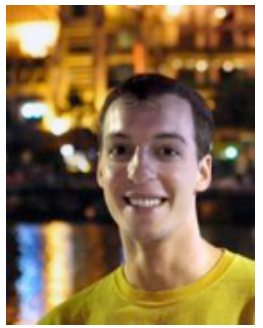

Prof. Frédérique CAPRON, Hospital Pitié -Salpêtrière, Paris

- Dr Jacques KLOSSA, TRIBVN