IMAGE AND PERVERSIVE ACCESS LAB

Since 1998 ...

www.ipal.cnrs.fr
History and Evolution

1998-2007

IPAL
Image Processing and Application Lab
EP 1956 & FRE CNRS 2339

Image Processing
Image Indexing and Retrieval
Image and 3D Perception
Video Indexing and Retrieval

BUILDING CONFIDENCE

2007-2011

IPAL
Image Perception, Access & Language
UMI CNRS 2955

Content-Based Image/Information Retrieval
Multilingual Access to Multimodal Images
Mobile Information Access
Medical Image Analysis, Indexing, Retrieval

BENCHMARKING AND INNOVATION

2011-2015

IPAL
Image & Pervasive Access Lab
UMI CNRS 2955

Biomedical Image Understanding
Formal Methods and Model Checking
3D Visual Objects Streaming
Visual Memory Extension
Ambient Assistive Living

EXCELLENCE AND IMPACT
Our supporting Partners

- National University of Singapore (NUS)
- Institute for Infocomm Research (I²R) Agency for Science Research and Technology (A*STAR)
- Centre National de la Recherche Scientifique (CNRS)
- Université Pierre et Marie Curie, Sorbonne Universités
- Institut Mines-Télécom
- Université Joseph Fourier, Grenoble I
Role of IPAL

Scientific bridge between Singapore / ASEAN and France / EU

French & European Research Institutes & Universities

Post Docs / PhDs / Masters

R&D Support to Spin-offs & Companies

East and North Asian Universities & Markets (China, Taiwan, Japan, Korea, etc.)

Southeast Asian Universities & Markets (Philippines, Thailand, Vietnam, Malaysia, etc.)
Role of IPAL

MAJOR IMPACTS

- Inspire **scientific breakthrough** by a new way of thinking: mixing Asian and European scientific research approaches
- **Research Incubation Unit** - future French/ASEAN sc. leaders
- **Research HUB** for French and ASEAN countries
- **Translational research** support for ASEAN emerging economies
- **Accelerate innovative technologies** maturation and deployment in a dynamic Singaporean and ASEAN environment
- Better **understand each-other** philosophy, culture, way of life
Research Themes / Focuses

Wellness
PAWM
Pervasive Access and Wellbeing Management

AAL - Ambient Assistive Living and Mobile Information Access

Healthcare
BMIU
BioMedical Image Understanding

BioMedical Images
Pervasive Exploration and Modeling for Prognosis and Treatment Assistance
Recent Competitive Projects (6 M€ - total research budget since 2010)

BMIU (BioMedical Image Understanding)

- MICO: COgnitive Microscope for breast cancer grading.
  ANR TecSan (Feb. 2011 – Jan 2014)

- VS4NSC: Intelligent Vision System Quantit Microscopy Neural Stem Cells Progenitor Growth Differentiation
  A*STAR JCO (Joint Council Office)
  (Dec. 2009 - July 2013)

- AMUPADH: Activity Monitoring and UI Plasticity for supporting Ageing with Mild Dementia at Home
  A*STAR SERC
  (May 2010 – Aug 2012)

PAWM (Pervasive Access & Wellbeing Management)

- PAWM: Pervasive Access & Wellbeing Management

- COHABIT Asia – ICT Asia
- ModCo - PEPS CNRS-UJF

- FlexMIm: Plate-forme de partage et gestion d’images médicales de grandes dimensions

- MICO: COgnitive Microscope for breast cancer grading.
  ANR TecSan (Feb. 2011 – Jan 2014)

- An integrated suite for imaging complex 3D anatomies of large cell/tissue culture systems
  A*STAR JCO (Joint Council Office)
  (Fev. 2013 - Janv 2016)

- QoL – Quality of Life
  Founded by the “Fondation TELECOM” (2012-2016)
IPAL external funding per year (since 2006)
Competitive budget granted for IPAL ONLY since 2010:
1.82 M€
out from a TOTAL of 6 M€ granted by our projects

- ICT-ASIA (Cooperation Programme France-Asia), 73K€, 4%
- A*STAR Singapore (SERC, JCO), 555K€, 30%
- ANR (French NRF), 394K€, 22%
- CNRS PEPS (France - CNRS Exploratory Programme), 139K€, 8%
- Investment for the Future (France), 639K€, 35%
- MERLION (Institut Français & SGP), 20K€, 1%
Cognitive virtual microscopy for breast cancer grading in histopathology

Whole slide image exploration using a symbolic cognitive vision approach

Daniel RACOCEANU

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daniel.racoceanu@upmc.fr

www.ipal.cnrs.fr
Scientific Challenges

BIOMEDICAL IMAGE UNDERSTANDING
BMIU Framework

**IMPACT - Therapeutic / Surgical**

- **THERAPY SIMULATION**
- **DIAGNOSIS / PROGNOSIS**
- **SURGERY & TREATMENT PLANNING**

**in cognito**

**Cognitive Vision**
- The European Research Network for Cognitive Computer Vision Systems

**in silico**

**Virtual Physiological Human**
- VPH - European Programme
- Personalized Prognosis

**in vivo/vitro**

**BioMedical Imaging**
- Signal et Information

**Modeling & Traceability**

**Validation & Knowledge discovery**
Origin of the challenge: From Hard-Coded to Semantic-Based Image Exploration

Semantic Annotation

Object classification & Advanced Computer Vision Algorithms (hard-coded knowledge)

Features Extraction (Image Analysis)
Filtering (Image Processing)

Raw Image (Pixels)

Semantic Reasoning

Primitive Computer Vision Algorithms

Bottom-Up

Top-Down

Hard-Coded Knowledge
Image Analysis

Ontology-Based Image Exploration
Interaction between ontologies and images

Coupling between knowledge and pattern recognition

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

Driving by the Ontologies and the Knowledge

- Selection of the frames, the scale, the magnification / of the regions
- Driving and parameterization of the imaging modules / toolboxes

Pattern Recognition and image exploration

- Imaging tasks / PR
  - New modality generation
  - Multi-scales approaches
    - Nuclei detection
    - Mitosis detection
  - Counting
  - Grading

Verification by the Ontologies and the Knowledge

- Gradation,
- Mitotic Count
- Validation of the results
- Cognitif safeguard

Role sharing and interaction between the AI and Pattern Recognition approaches
IPAL/BMIU

MICO (ANR TecSan 2011-2014)
COgnitive virtual MIcroscopy for digital pathology
The future of the pathology will need to be
- Ethical: traceability / reference / validation
- Dynamic: predictability / morphogenesis

The revolution of the 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
Grading Process
Breast Cancer – Canalar Carcinoma (80%)

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

- 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
Symbolic Cognitive Vision

- Cognitive vision
  - Symbolic / Semantic
  - Connexionnist

- Our approach (ANR TecSan MICO project): symbolic approach
  - Close to the medical interpretation of the pathologist
  - Ontological references (SNOMED-CT / ADICAP

(*) ADICAP: Association for the Development of Informatics in Cytology and Anatomopathology
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.
MICO Ontologies

FORMAL WORLD

OPERATIONAL WORLD

IMAGE PROCESSING DOMAIN

HISTOPATHOLOGY DOMAIN

Domain Ontology according to the Developer

Analysis Rules

Conversion Rules

Algorithms Data Definition Ontology

XML to N3

XML Data

Domain Ontology according to the Expert

Analysis Rules

Conversion Rules

User Data Definition Ontology

XML to N3

XML Data
Figure 5.1: MICO conceptual graph

First, the whole slide image is observed by an histopathologist, for the slide territories to be annotated using Calopix user interface. Then, the relevant territories are extracted from Calopix information storage system, for them to be split into several rectangles called “frames”. Then, 50 of these frames are randomly selected, and the Cyto-Nuclear Atypia (CNA) of the cells within the selected frames is analysed. The result of a frame CNA analysis is a CNA score. The computed CNA scores are used for the initialisation step of a Voronoi diagram based CNA analysis. Figure 5.3 shows the evolution (50 samples, 150 samples, 400 samples) of a Voronoi driven CNA analysis on a very large histopathological slide image. The final overall CNA grade is the grade of the most atypical frame.
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)
Mitotic Detection Results

Candidate Detection: Yellow spots highlight candidate for Mitosis

Candidate Classification: The yellow colour for true positives, green for false positive and the blue for false negatives
Grading strategy

- Mitosis analysis algorithm

Stereology frame selection from the ROA (1 frame selected for each 3x3 frames square) → Mitosis count on each selected frames → Selection of the 4x4 frames area having the highest mitotic count sum → Mitosis count on all the frames within the selected 4x4 area → Selection of the 10 consecutive frames having the highest mitosis count → The SUM of mitosis counts among the 10 frames is computed

25
Cognitive-visual whole slide image exploration

“Ontology at the helm”

Glass box

Black boxes

Reasoner & Ontology

Imaging tools
Assistant numériques

- Reconnaissance de formes
Assistant numériques

- «Match» de cohérence des informations produites
initiative leaded by IPAL

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

- Key information:
  - Multimodal data:
    - Fast scanners (Aperio & Hamamatsu)
    - Multispectral Multifocal Microscopy
  - March 31st, 2012: submit a paper about the proposed method to ICPR 2012
  - April 27th, 2012: submit an abstract (1 page) of their method.
  - August 1st, 2012: evaluation data set available.
  - September 10th, 2012: deadline for participants to send their results.
  - November 11th, 2012: mitosis detection contest meeting will take place during ICPR 2012 in Tsukuba, Japan. Contestants will make a short presentation of their method and results.
  - Special issue in JPI - Journal Pathology Informatics – March 2013
Participants to the international benchmark

About 120 institutions registered to the contest
Grading strategy

- Nuclear polymorphism analysis algorithm

Frames selection for CNA analysis using Voronoi diagram, and CNA analysis on the selected frames. Return the CNA scores of the analyzed frames.

1. Random selection of 50 frames from the ROA
2. CNA analysis on each selected frame
3. Select the frame with the higher CNA score
4. Draw Voronoi diagram
5. Select the Voronoi neighbor of the selected frame, having the highest CNA score
6. Analyze the closest frame on the limit between the two selected frames
7. Continuing Voronoi based selection and CNA analysis until at least 10% of ROA frames are analyzed
H&E stained surgical breast images
40x magnification

1024×1024 frames where the nuclei have been manually delineated by pathologists
Nuclei extraction challenges

Problems:
• Nuclei non-homogeneity
• Nuclei vary a lot in terms of size, shape and cytoplasm 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
- 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.
The training set used for the LDA consists of 6 1024 images where the nuclei have been manually delineated.

This problem is largely improved by using the shape prior information as the AC model allows to extract the overlapping nuclei.

Tochemical staining by color deconvolution, a marked point process model with strong prior shape information for extraction of multiple, selective cell nuclei detection, is proposed.

REFERENCES


RESULTS

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

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

Figure 3: Comparing results on a single H&E image of high grade
Sequential algorithm: computation time

- Processing time ratio

![Pie chart showing processing times for different events: Initialisation (360.53 s), Naissance (105.67 s), Attache (225.96 s), Mort (895.77 s)].

- Initialisation: 360.53 s
- Naissance: 105.67 s
- Attache: 225.96 s
- Mort: 895.77 s
We have presented two Marked Point Process (MPP) based models for cell nuclei segmentation.

The first one, using arbitrarily-shaped objects, is adapted for small radius range due to the presence of nuclei with quite different appearances and uniformly dark nuclei at the same time. Moreover, results may vary but which do not vary much in size and in term of appearance. This kind of models. The second column shows the name of the method: ESO for Elliptically-shaped objects and ASO for Arbitrarily-shaped objects, using a small radius range.

On each result, we show the matched nuclei (which are both in the manually segmented nuclei) in blue, the missing ones in green and the incorrect detections in red. The clustering of nuclei segmented together, thus the radius range can be greater using the MPP model with elliptically-shaped objects. Forcing an ellipticity of a shape reduces the number of false positives.

In order to deal with these problems, we considered an MPP model with strong prior shape information for extraction of multiple, arbitrarily-shaped objects.

Results are detailed in Table 1:

<table>
<thead>
<tr>
<th>Image</th>
<th>Method</th>
<th>Manually</th>
<th>Detected</th>
<th>Matched</th>
<th>F. P.</th>
<th>F. N.</th>
<th>Jaccard</th>
<th>F-measure</th>
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<td>67</td>
<td>0.33</td>
<td>0.49</td>
</tr>
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</table>

Table 1: Quantitative results on a H&E image 01 of grade 1 and 02 of grade 3

\[
F\text{-}\text{measure} = \frac{2 \cdot TP}{2 \cdot TP + FN + FP}
\]

\[
Jaccard \text{ index} = \frac{TP}{TP + FN + FP}
\]
Performances of the Parallel Algorithm

Computation time in seconds on 3326x2971 pixel image:

<table>
<thead>
<tr>
<th></th>
<th>Initialization</th>
<th>Birth</th>
<th>Energy</th>
<th>Death</th>
<th>Total</th>
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</thead>
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<tr>
<td>Sequential</td>
<td>360.53</td>
<td>105.67</td>
<td>895.77</td>
<td>225.96</td>
<td>1583.02</td>
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<td>Multi-core</td>
<td>37.34</td>
<td>19.96</td>
<td>156.73</td>
<td>31.23</td>
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<tr>
<td>GPU</td>
<td>2.52</td>
<td>2.41</td>
<td>94.98</td>
<td>36.36</td>
<td>136.37</td>
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</table>

Acceleration ratio:

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<th>Birth</th>
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<th>Death</th>
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IPAL/BMIU

**FlexMIm (Grand Emprunt, FUI project 2013-2016)**
Collaborative Telepathology based on semantic imaging
Next step: FlexMIm translational project

- 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.
Etablissements impliqués et lien avec l’ARS

27 établissements impliqués dans FlexMIm

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<th>CHU APHP</th>
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17 établissements impliqués dans ARSIF

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Plate-Forme de Télépathologie

Avis diagnostique par télépathologie conventionnelle

Pathologiste requérant

Demande d’avis

Dysplasie sur MiCI
Biopsies de prostate
Cancer du sein

Utilisation des outils FlexMIm

Pathologiste requis

Pathologiste requis
Valeur technologique et innovation

1. Un workflow exploitant le Cloud pour gérer, analyser et partager des données médicales de taille grandissante : simplification de l’exploitation, services additionnels, contrôle de la qualité

2. Des algorithmes permettant de pré-analyser la qualité d’une lame virtuelle pour permettre l’interprétation des lames

3. Des algorithmes de compression validés par les pathologistes pour assurer une visualisation fluide et fiable sur stations de travail et mobiles

4. Pour une plate-forme d’échanges multi-thématiques entre pathologistes (unique en France)

Vers une plate-forme d’échanges mais aussi d’aide automatique au diagnostic ou à l’établissement de scores pronostiques dans les cancers
IPAL/BMIU

A*STAR JCO IAMS (2013-2016)
Integrated Autonomous Microscopy Systems: “Imaging anatomies of complex 3D cell culture systems”
Specific aims:
- Suite of automated microscopy systems that can perform experiments automatically for a contiguous period of several days or weeks. **Complex 3D cell cultures.**

Hypotheses:
- Enable biological experiments (otherwise currently impossible to perform) to be carried out **systematically.** We will provide enabling technologies to progress biological studies on 3D cell cultures and to **advance new pharmaceutical development.**

Methodology:
- Human neural stem cells, neurospheres, reconstructed skin and intestinal spheroids/crypts. **Assortment of microscopy techniques, which includes light sheet, confocal, super-resolution**
Combine microscopic exploration with symbolic and quantitative models and modalities.

- **Biomedical Data**
  - Clinical
  - Biological
  - Microscopic
  - Multimodal Imagery

- **Systemic Biomedical Model**
  - Molecular, Cellular
  - Cytology, Histology
  - Physiology
  - Model

- **Modalities Guided by Models**
  - Instrumentation
  - Technologies
  - Exploration strategy

- **Informatics, Computer Science**
  - Multi granular images analysis
  - Ontologies, Semantic Annotation, Reasoning
  - Content-Based Indexing
  - Interactive Query Strategies (Relevance Feedback)
  - Learning, Classification, Regression, Prognosis

**Personalized Data**

**Ontologies and Reasoning at the Helm**
Acknowledgement

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- M. Olivier MORERE, IPAL/CNRS-A*STAR
- Prof. Frédérique CAPRON, Hospital Pitié -Salpêtrière,
- Dr Jacques KLOSSA, TRIBVN