Systèmes Intelligents de Perception

Digital Histopathology : a new challenge

The new big data microscope

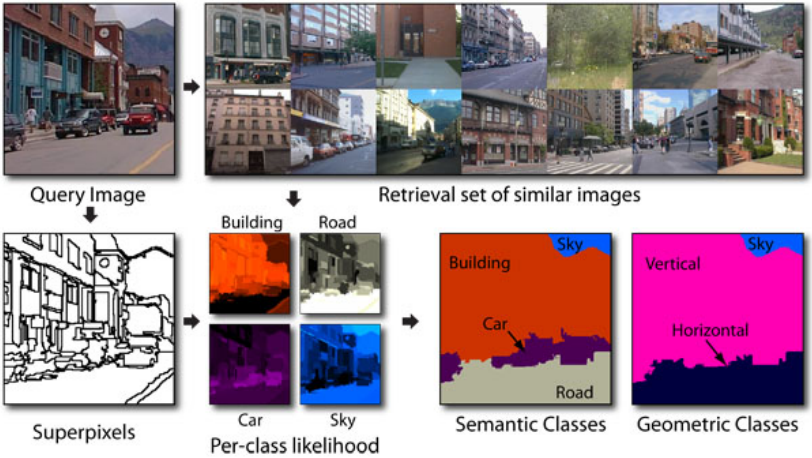
Nicolas Loménie

http://www.math-info.univ-paris5.fr/~lomn/

November 5th, 2023

The Big Picture

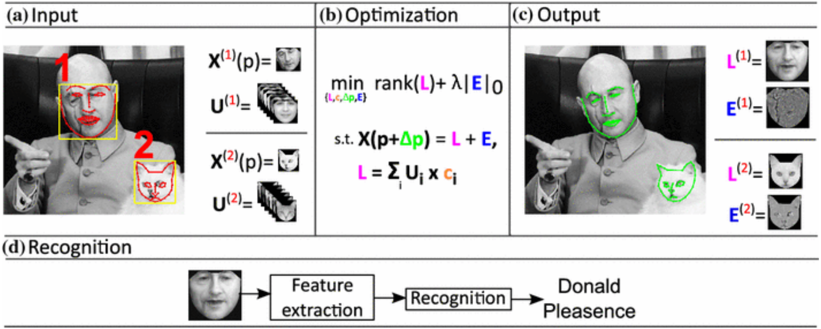
Mainstream Research Line in Computer Vision



Joseph Tighe, Svetlana Lazebnik: Superparsing - Scalable Nonparametric Image Parsing with Superpixels. International Journal of Computer Vision 101(2): 329-349 (2013) + Deep Learning (2017)

The Big Picture

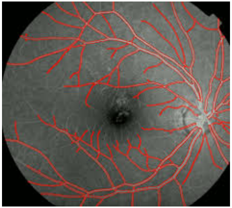
Mainstream Research Line in Computer Vision

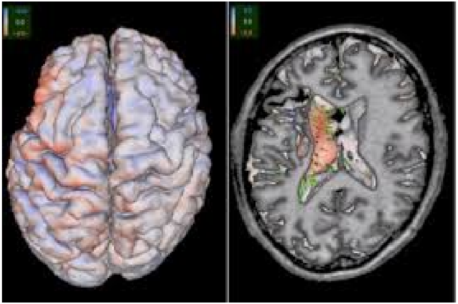


Sagonas, C., Panagakis, Y., Zafeiriou, S. et al. - Robust Statistical Frontalization of Human and Animal Faces - International Journal of Computer Vision (2017) 122(2) pp 270–291. doi:10.1007/s11263-016-0920-7

The Big Picture

Mainstream Research Line in Medical Imaging

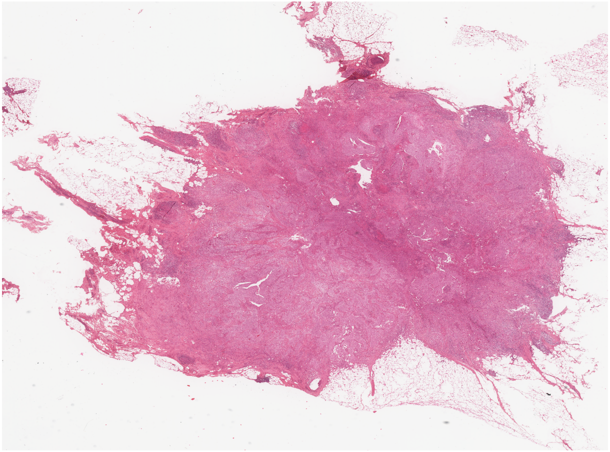




Mohammad Havaei, Axel Davy, David Warde-Farley, Antoine Biard, Aaron Courville, Yoshua Bengio, Chris Pal, Pierre-Marc Jodoin, Hugo Larochelle, Brain tumor segmentation with Deep Neural Networks, Medical Image Analysis, Volume 35, January 2017, Pages 18-31

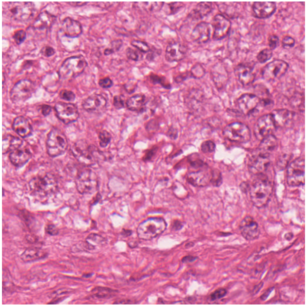
The Big Picture

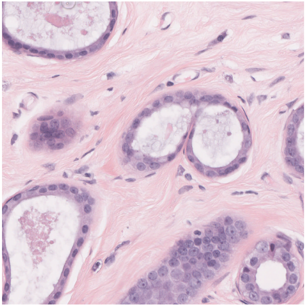
But we cannot model histopathological images the same way



The Big Picture

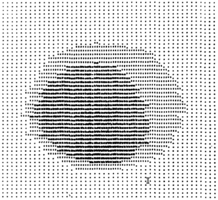
But we cannot model histopathological images the same way





A tribute to Prewitt Filtering

Lymphocyte



Lymphocyte

FIGURE 4. Boundary determinations. The same procedure has been followed as in FIGURE 3, and again the images should be compared to the photomicrographs in FIGURE 1. Note that four gray levels were used for the eosinophil in an attempt to delineate the denser regions of cytoplasmic granules in addition to the cell and nuclear-cytoplasmic boundaries.

$$\mathbf{G_x} = \begin{bmatrix} -1 & 0 & +1 \\ -1 & 0 & +1 \\ -1 & 0 & +1 \end{bmatrix} * \mathbf{A} \quad \text{and} \quad \mathbf{G_y} = \begin{bmatrix} +1 & +1 & +1 \\ 0 & 0 & 0 \\ -1 & -1 & -1 \end{bmatrix} * \mathbf{A}$$

Parametric and Nonparametric Recognition by Computer: An Application to Leukocyte Image Processing.
Judith M. S. Prewitt . Advances in Computers - 1972

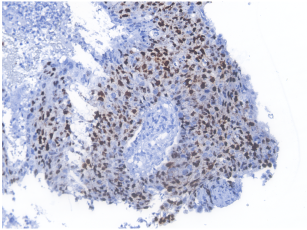
When everything started 10 years ago

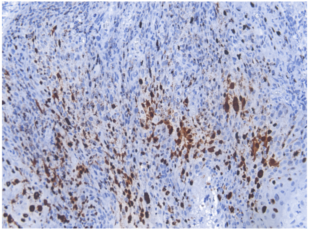
- Building up a community;
- Setting up the Digital Histopathology Challenge;
- Radiometric Filtering as usual ?
- Geometric Filtering : a new trend
- The future of histopathology

Building up a community
HEGP - INSERM / PUPH Cecile Badoual

Master Internship : Denfeng CAO - Master BME

- Objective: Automated HPV Cancer analysis + **Spatial analysis of cell microenvironement**
- Correlate immune response and micro-environment analysis of the cell to cancer pronostic





Building up a community HEGP - INSERM / PUPH Cecile Badoual

- Objective: **Automated HPV Cancer analysis** + Spatial analysis of cell microenvironement

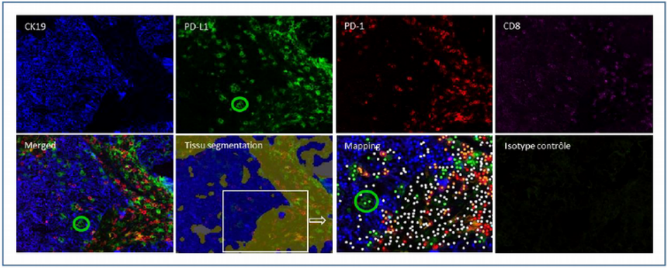
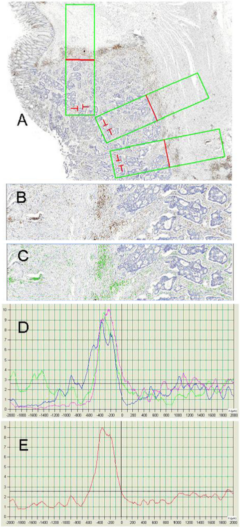
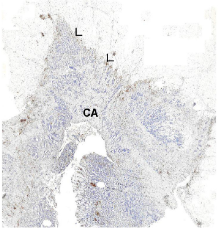


Figure 11 : Difficulties in the interpretation of the PD-L1 staining PD-L1 in epithelial nest. *Frozen tissue sections derived from patients with lung adenocarcinoma were stained by immunofluorescence with a quadruplex stainings (CK19 (blue), PD-L1 (green), PD-1(red) and CD8 (pink)) in the same slide. A tissue segmentation was done based on CK19 staining to determine epithelial and stromal area. The mapping determined the phenotype of the cells with the corresponding code : $CK19^+PD\text{-}L1^-$: blue dot; $CK19^+PD\text{-}L1^+$: yellow dot; $CK19^-PD\text{-}L1^+$: green dot, $CD8^+PD1^+$: orange dot; $CD8^+$ $PD1^-$ pink dot, $CD8^-$ $PD1^+$ red dot, others cells : white dot). The green circle identified $PD\text{-}L1^+CK19^-$ cells infiltrating the tumor nest (original magnification x200).*

Unité de Technologies Chimiques et Biologiques pour la Santé - CNRS /INSERM

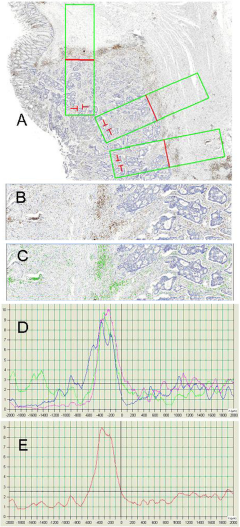


- PUPH Jean-François Emile (Ambroise Paré) - Prof. Nathalie Mignet
- Objective: **Lymphocyte Infiltration**
- Analysis of the micro-environment of the tumor



UTCBS - CNRS /INSERM

Master Internship : Tiede Armand DJIRO - Master Plurimedia



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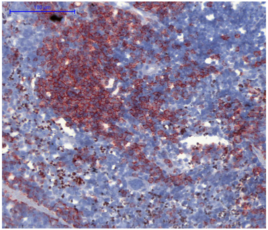
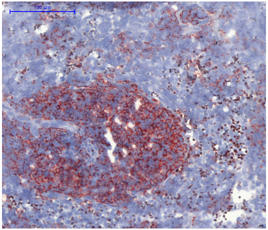
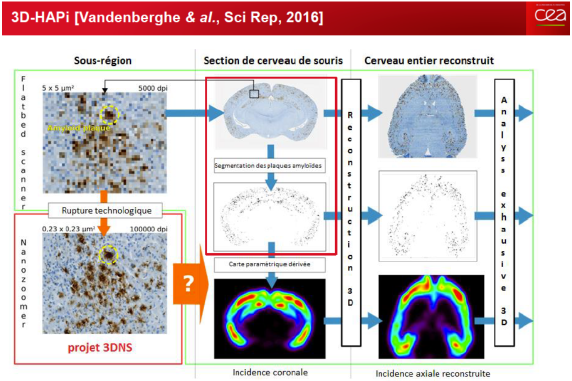




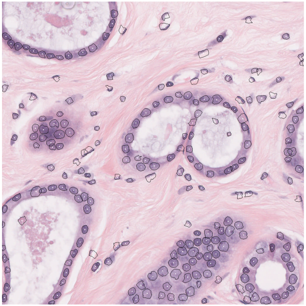
CEA - MIRCen
Thierry Delzescaux

PhD Mid-term committee - Clément Bouvier



Science. 2013 Jun 21;340(6139):1472-5. doi: 10.1126/science.1235381. BigBrain: an ultrahigh-resolution 3D human brain model. Amunts K1, Lepage C, Borgeat L, Mohlberg H, Dickscheid T, Rousseau MÉ, Bludau S, Bazin PL, Lewis LB, Oros-Peusquens AM, Shah NJ, Lippert T, Zilles K, Evans AC

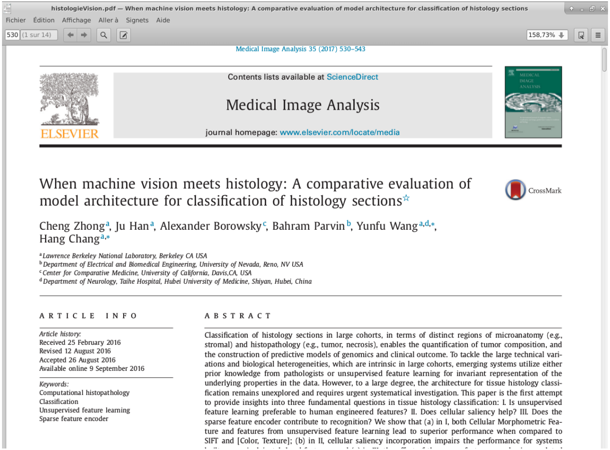
Digital Histopathology



- An ongoing big challenge: academic, industrial, societal;
- A complete ground test: closed universe, no digital model, possibility of ground truth;
- A new avenue to put together semantic filtering and image processing;
- Deep learning creeping up;

Pathology Innovation Centre of Excellence (PICOE). Digital Histopathology: A New Frontier in Canadian Healthcare. White Paper. Jan. 2012. GE Healthcare.

Digital Histopathology



histologieVision.pdf — When machine vision meets histology: A comparative evaluation of model architecture for classification of histology sections

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Medical Image Analysis 35 (2017) 530–543

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When machine vision meets histology: A comparative evaluation of model architecture for classification of histology sections☆

CrossMark

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ABSTRACT

Classification of histology sections in large cohorts, in terms of distinct regions of microanatomy (e.g., stromal) and histopathology (e.g., tumor, necrosis), enables the quantification of tumor composition, and the construction of predictive models of genomics and clinical outcome. To tackle the large technical variations and biological heterogeneities, which are intrinsic in large cohorts, emerging systems utilize either prior knowledge from pathologists or unsupervised feature learning for invariant representation of the underlying properties in the data. However, to a large degree, the architecture for tissue histology classification remains unexplored and requires urgent systematical investigation. This paper is the first attempt to provide insights into three fundamental questions in tissue histology classification: I. Is unsupervised feature learning preferable to human engineered features? II. Does cellular saliency help? III. Does the sparse feature encoder contribute to recognition? We show that (a) in I, both Cellular Morphometric Features and features from unsupervised feature learning lead to superior performance when compared to SIFT and [Color, Texture]; (b) in II, cellular saliency incorporation impairs the performance for systems

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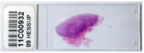

25 mm

75 mm

Biopsy glass slide

→

Scan at 40X

Resolution: 0.2456μm per pixel

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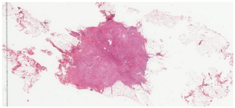


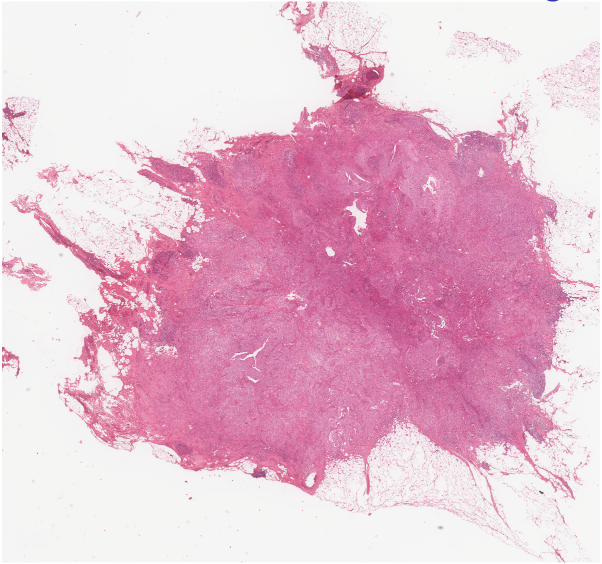
63,382 pixels

140,153 pixels

Whole Slide Image 8 GPixels

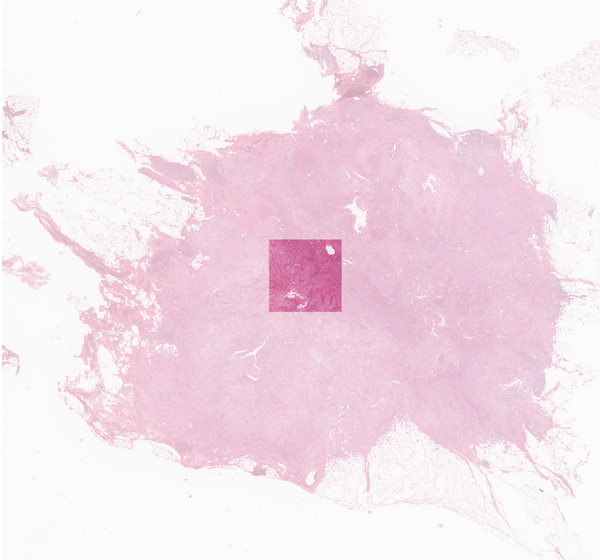
- Multi-page TIFF image
- File size (compressed): Usually 1 to 2 GB
- Image size (uncompressed): 15 to 25 GB

Whole Slide Image



1.25X
Identification of tumor area

Whole Slide Image



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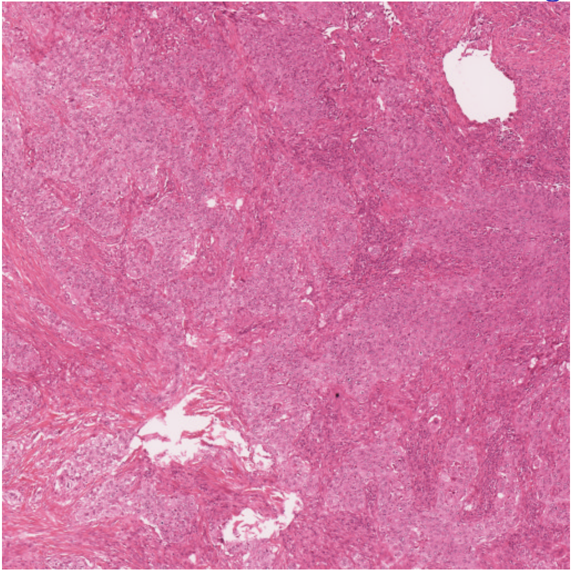

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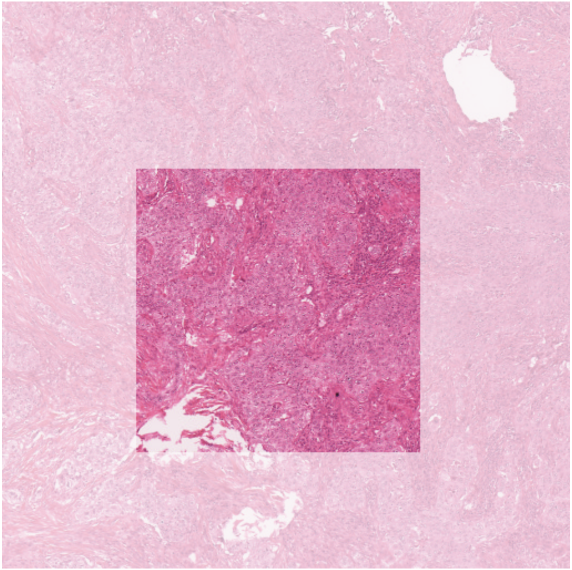

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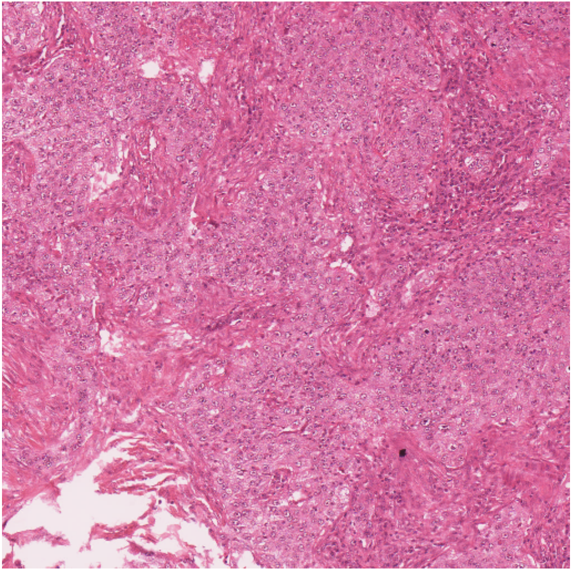

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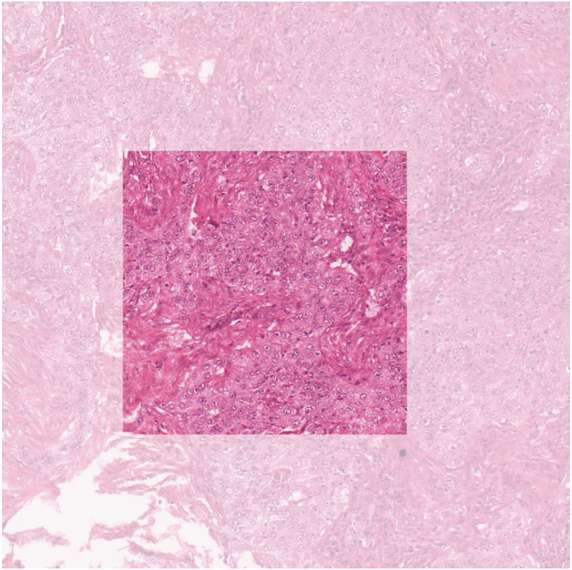

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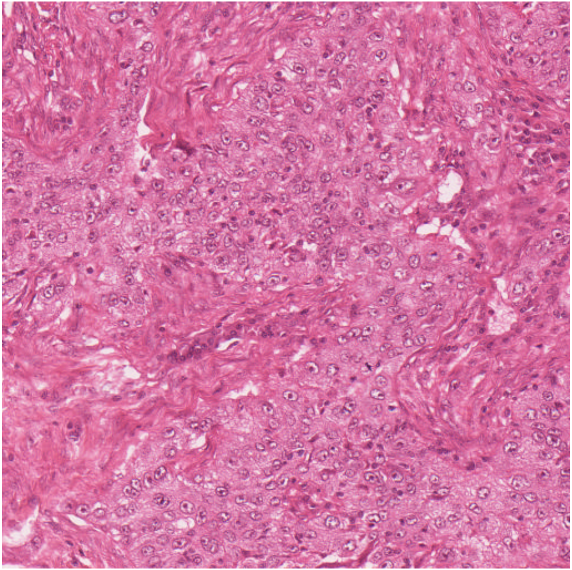
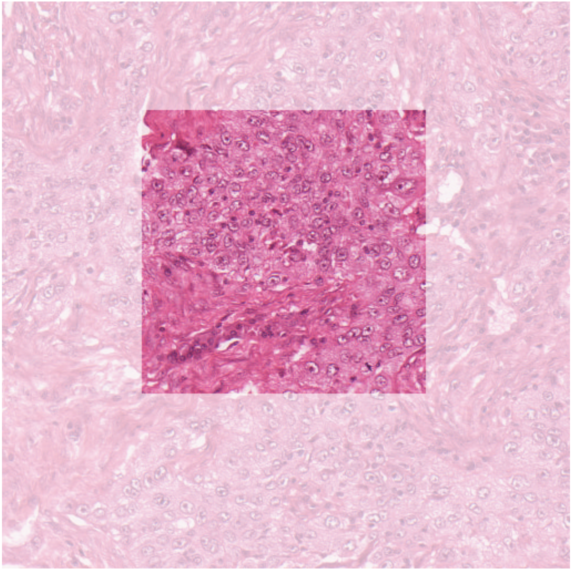


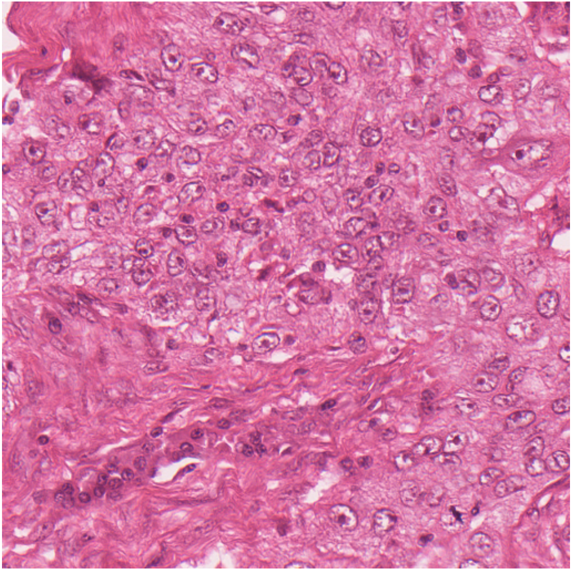
10X
Gland formation

Whole Slide Image



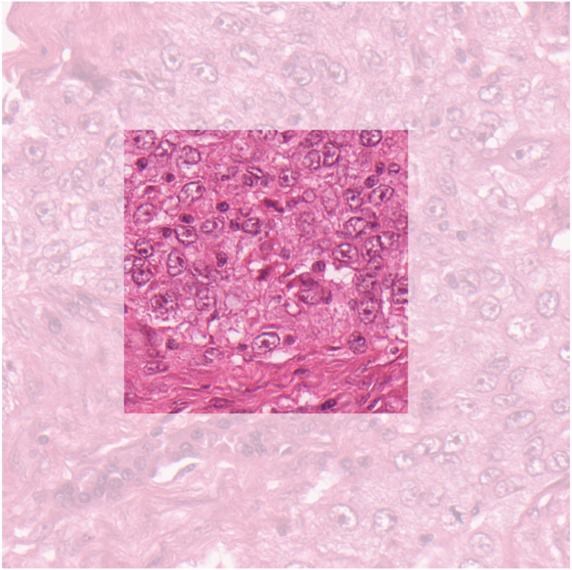
10X
Gland formation

Whole Slide Image



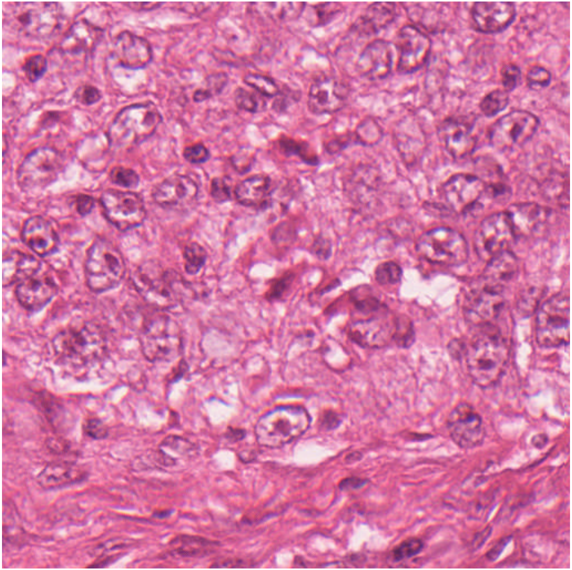
20X
Nuclei, mitosis

Whole Slide Image



20X
Nuclei, mitosis

Whole Slide Image



40X
Nuclei, mitosis

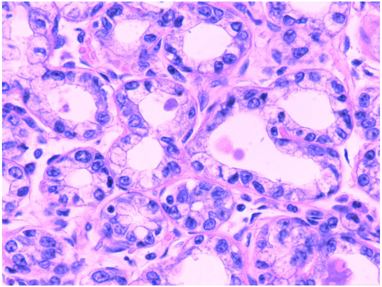
Nottingham Grading System

- International breast cancer grading system recommended by the World Health Organization
- 3 criteria:
  1. Gland (acinus) formation (score 1 - 2 - 3)
  2. Nuclear atypia / pleomorphism (score 1 - 2 - 3)
  3. Mitosis counts (score 1 - 2 - 3)
- Final grading: Add scores for acinus formation, nuclear atypia and mitosis count.
  - If total score = 3, 4 or 5 ➜ grade 1
  - If total score = 6 or 7 ➜ grade 2
  - If total score = 8 or 9 ➜ grade 3

Acinus: Any cluster of cells that resembles a many-lobed "berry", such as a raspberry. Acinus is Latin for berry.

Nottingham Grading System

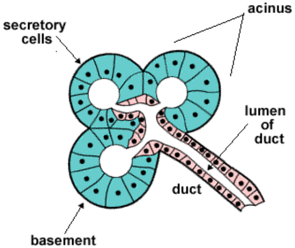
Gland Formation

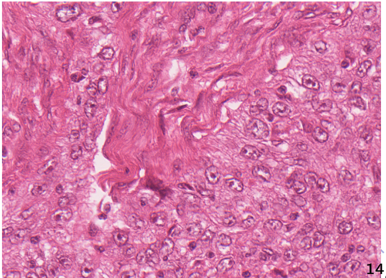


Score 1 More than 75% of the whole carcinoma forms acini

Score 2 10 $\sim$ 75% of the whole carcinoma forms acini

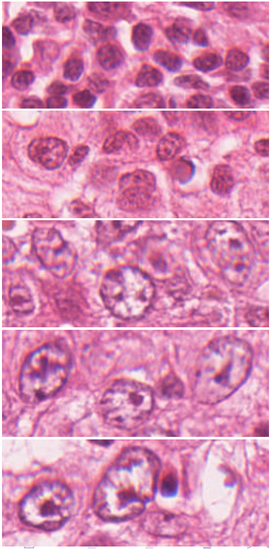
Score 3 Less than 10% of the whole carcinoma forms acini





Nottingham Grading System

Nuclear Atypia

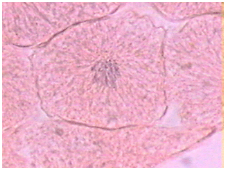


Score 1 Nuclei only slightly larger than benign breast epithelium ($< 1.5\times$ normal area); minor variation in size, shape and chromatin pattern

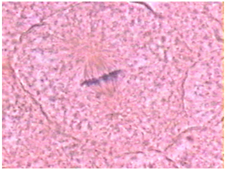
Score 2 Nuclei distinctly enlarged ($1.5 \sim 2\times$ normal area), often vesicular, nucleoli visible;
may be distinctly variable in size and shape but not always

Score 3 Markedly enlarged vesicular nuclei ($> 2\times$ normal area), nucleoli often prominent; generally marked variation in size and shape but atypia not necessarily extreme

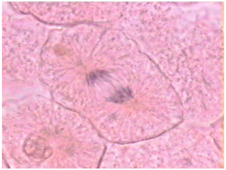
Mitosis



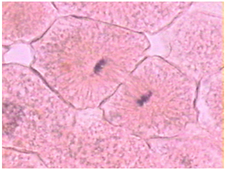
❶ **Prophase**: The chromatin condenses into a highly ordered structure called a chromosome.



❷ **Metaphase**: Chromosomes align in the middle of the cell.



❸ **Anaphase**: Each chromatid moves to opposite poles of the cell, the opposite ends of the mitotic spindle, near the microtubule organizing centers.

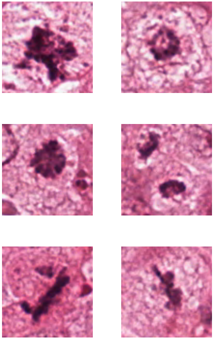


❹ **Telophase**: Two daughter nuclei form in the cell.

Nottingham Grading System

Mitosis Counts

- Scan sections to find area with most mitotic activity (often at tumor edge).
- In this area count definite mitoses in 10 consecutive fields.
- Skip fields with few carcinoma cells or obvious necrosis.

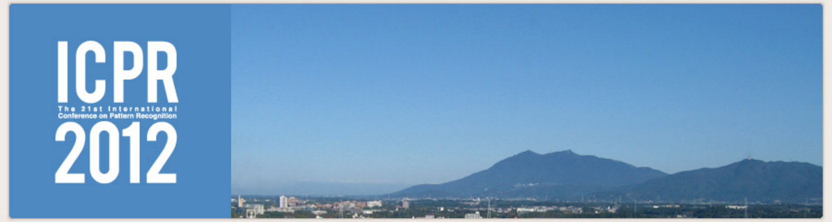


For a microscope field diameter of 58 mm (or a digitized square image $512 \times 512 \mu m^2$):

Score 1	Score 2	Score 3
≤ 9 mitosis	$10 \sim 19$ mitosis	≥ 20 mitosis

Mitosis Detection Contest

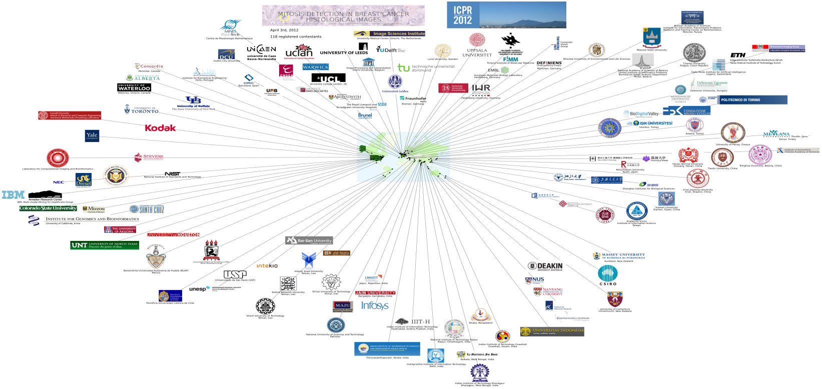
An ICPR 2012 Contest



Roux Ludovic, Racoceanu Daniel, Loménie Nicolas, Kulikova Maria, Irshad Humayun, Klossa Jacques, Capron Frédérique, Genestie Catherine, Le Naour Gilles, N Gurcan Metin Mitosis detection in breast cancer histological images: An ICPR 2012 contest J Pathol Inform 2013, 4:8 (30 May 2013)

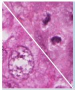
Challenges (An ICPR 2012 Contest)

125 registered contestants in 39 countries - IPAL lab - Singapore



Cited in IEEE Journal of Biomedical and Health Informatics, vol. 18, no. 2, March 2014 : Toward Automatic Mitotic Cell Detection and Segmentation in Multispectral Histopathological Images.

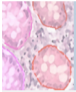
Mitosis Detection + Nuclear Atypia Grand Challenge etc.



Open for submissions
Data download
Associated with: ICPR 2014
Hosted on: grand-challenge.org

MITOS-ATYPIA-14

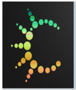
MITOS & ATYPIA 14 Contest, hosted by conference ICPR 2014 Detection of mitosis and evaluation of nuclear atypia on breast cancer H&E stained images



Data download
Workshop: Oct 05, 2015
Associated with: MICCAI 2015

Gland Segmentation Challenge

Gland morphology is used to assess the degree of malignancy of several adenocarcinomas, including prostate, breast, lung, and colon. This challenge evaluates gland segmentation algorithms on images of H&E stained slides, consisting of a variety of histologic grades.



Associated with: ISBI 2016
Hosted on: grand-challenge.org

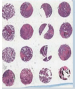
CAMELYON16

The goal of this challenge is to evaluate new and existing algorithms for automated detection of cancer metastasis in digitized lymph node tissue sections. Two large datasets from both the Radboud University Medical Center and the University Medical Center Utrecht are provided.

Open for submissions
Data download
Associated with: MICCAI 2016

Tumor Proliferation Assessment Challenge (TUPAC)

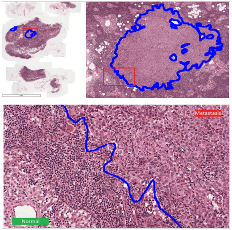
Evaluate methods that predict the tumor proliferation score directly from whole-slide images.



Open for submissions
Associated with: ISBI 2017

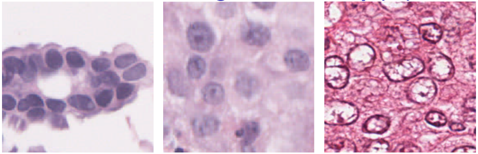
Tissue Microarray Analysis for Thyroid Cancer

Tissue microarrays (TMAs) can provide new biomarkers that could be of value in diagnosis, predicting outcome and response to therapy. Goal of this challenge is to build predictions models for thyroid cancer from TMAs.



Nuclei detection

Let's read through some survey papers

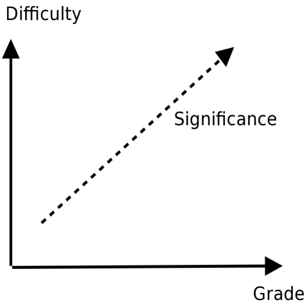


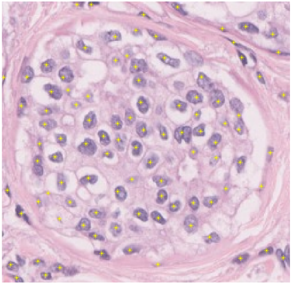
- Gurcan MN, Madabhushi A, Rajpoot N. (2010) Pattern Recognition in Histopathological Images: An ICPR 2010 Contest. *Proceedings of the 20th International conference on Recognizing patterns in signals, speech, images, and videos. ICPR'2010* , Istanbul, Turkey. Springer-Verlag, Berlin, Heidelberg; 226-234.

- Gurcan MN, Boucheron LE, Can A, Madabhushi A, Rajpoot NM, Yener B. (2009) Histopathological image analysis : a review. *IEEE Reviews in Biomedical Engineering*, **2**: 147-171.

Nuclei detection

No generic low-level procedure

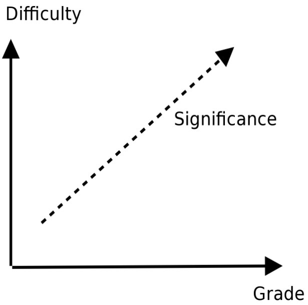


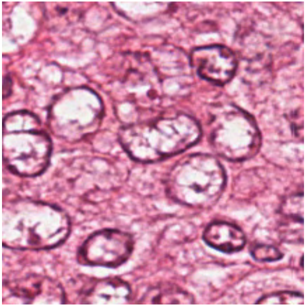


Nuclei detection

Nuclei detection

No generic low-level procedure



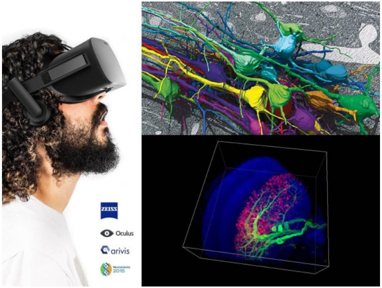


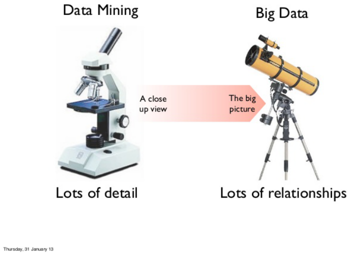
Wrap up

- Emerging field;
- More and more graph-based analysis;

Andrew Janowczyk, Scott Doyle, Hannah Gilmore, Anant Madabhushi - **A resolution adaptive deep hierarchical (radhical)** *learning scheme applied to nuclear segmentation of digital pathology images - 2016/4/1 - Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization*
Basavanhally, Ganesan, Agner, Monaco, Feldman, Tomaszewski. (2010) Computerized image-based detection and **grading of lymphocytic infiltration** *in HER2+ breast cancer histopathology,* IEEE Trans Biomed Eng., **57***:642-653.*
When machine vision meets histology *: A comparative evaluation of model*

Horizon





Coming into Focus : Computational Pathology as **the New Big Data Microscope** - *The American Journal of Pathology - Cellular and Molecular Biology of disease - Kevin A. Roth, - March 2015, Volume 185, Issue 3, Pages 600–601*

Et maintenant ......

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