
Computational Pathology and eXplainable AI

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Sorbonne University, Paris Brain Institute

16th of April 2024



Quickly introducing myself ...



Daniel Racoceanu – daniel.racoceanu@sorbonne-universite.fr

Professor @ Sorbonne University, Faculty of Science and Eng.

PI @ Paris Brain Institute / Institut du Cerveau

CNRS - French National Center for Scientific Research

Inserm - French Nat. Institute of Health and Medical Res.

Inria team Aramis - National Institute for Research in Computer Science and Automation

AP-HP - Greater Paris University Hospitals



National University of Singapore, IPAL CNRS



- 2009-2015 – Professor @ National University of Singapore
- 2008-2014 - Director CNRS/NUS research venture IPAL Singapore
 - PI of IPAL CNRS since 2005
 - Participation to the upgrade to UMI CNRS level (previously FRE)
 - In partnership with NUS, A*STAR, CNRS, UGA (Grenoble), Sorbonne University



Pontifícia Univ. Católica del Perú (2016-2018)

4

28K Students - Law, Social Sciences, Sciences and
Engineering, Humanities, Education, Arts
11 Careers – Science & Eng





MICCAI

October 4th - 8th 2020
Latin America - Peru

MICCAI 2020

INTERNATIONAL CONFERENCE ON MEDICAL IMAGE
COMPUTING AND COMPUTER ASSISTED INTERVENTION

General
Chair





MICCAI 2020

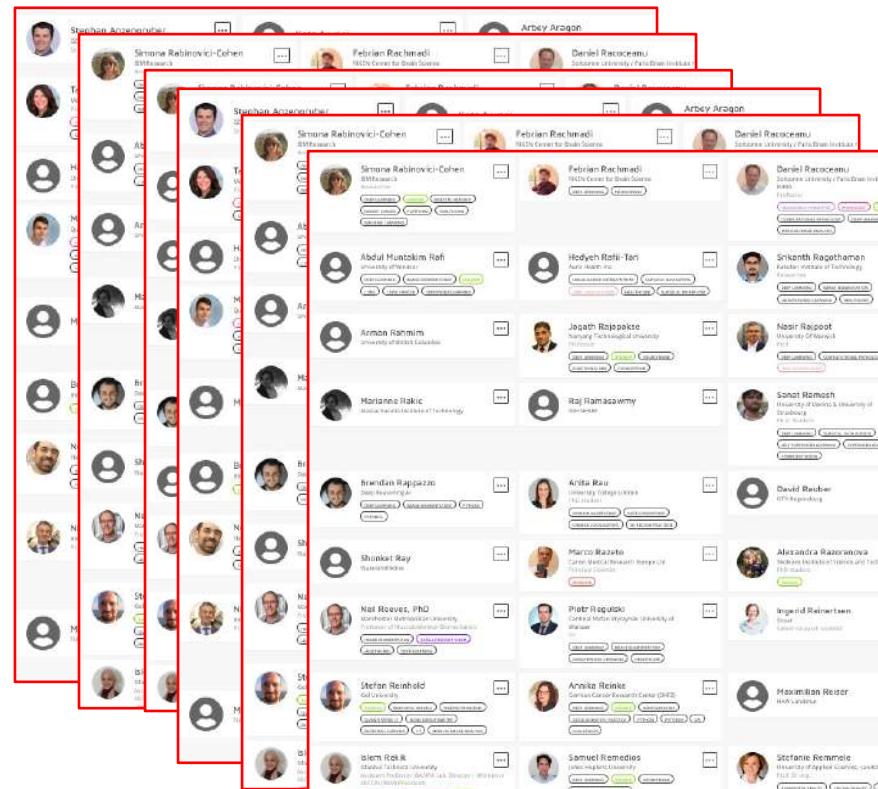
MICCAI

October 4th - 8th 2020
Latin America - Peru



INTERNATIONAL CONFERENCE ON MEDICAL IMAGE COMPUTING AND COMPUTER ASSISTED INTERVENTION

6



Total unique users: 2,781
Desktop Page Views: 779,139
Mobile Page Views: 48,735

MICCAI Board of Directors (2008-2022)

Medical Image Computing and Computer Assisted Intervention

The screenshot shows the MICCAI website's "Board Of Directors" page. At the top left is the MICCAI logo and the text "The Medical Image Computing and Computer Assisted Intervention Society". A navigation bar below includes links for ABOUT, MEMBERSHIP, EVENTS, INTEREST GROUPS, PUBLICATIONS, EDUCATION, NEWS, JOBS, and CONTACT US. The main content area has a header "Board Of Directors" and lists the names and institutions of the board members:

Name	Institution
Leo Joskowicz (President)	The Hebrew University of Jerusalem, Israel
Kevin Zhou (Treasurer)	Chinese Academy of Sciences, Beijing, China
Julia Schnabel (Secretary)	Technical University Munich & Helmholtz Center Munich, Germany
Shuo Li	Western University, London, Ontario, Canada
Guoyan Zheng	Institute for Surgical Technology & Biomechanics, Bern, Switzerland
Daniel Racoceanu	Sorbonne University, Paris, France
Lena Maier-Hein	German Cancer Research Center, Heidelberg, Germany
Marleen de Bruijne	Erasmus Medical Centre, the Netherlands and University of Copenhagen, Denmark
Caroline Essert	University of Strasbourg, France
Dong Ni	Shenzhen University, China
Linwei Wang	Rochester Institute of Technology, USA
Le Lu	Johns Hopkins University, USA
Marius Linguraru	Children's National Health System, USA
Tanveer Syeda-Mahmood	IBM Research, USA

On the left sidebar, under "About MICCAI", the "Board Of Directors" section is expanded, showing links for Officers and Staff, Student Board, Women in MICCAI, Fellows, Awards, Mission and Focus, History, Declarations and Policies, Code of Conduct Policy, Code of Conduct at MICCAI events, and Scientific Code of Ethics. At the bottom of the sidebar is a link to "MICCAI Board Working Groups".

European Society of Integrative Digital Pathology

digitalpathologysociety.org



ABOUT ▾

EVENTS ▾

RESOURCES ▾

Supporting the key role of Pathologist by Integrative Digital Pathology initiatives is the main objective of the European Society of Integrative Digital Pathology (ESDIP). This initiative – open to medical, academia and industrial participation – is fostering the emergence of compliant protocols, standards, by accelerating the dissemination and the education around these concepts and technologies in Europe and beyond.

About ESDIP



SEE MORE ➤

ECDP



SEE MORE ➤

Become a Member



SEE MORE ➤

Resources



SEE MORE ➤

Events



SEE MORE ➤

Members Area



SEE MORE ➤

Co-founder: 2016

Vice-President: 2016-2018

President : 2018-2020

Advisory Board : since 2020



ABOUT ▾

EVENTS ▾

RESOURCES

Additional Board Members

Marcia García-Rojo



Board of Advisors

Avrydas Laurinavicius



Board of Advisors

Daniel Racoceanu



Board of Advisors

Johan Lundin



Board of Advisors

Peter Hufnagl



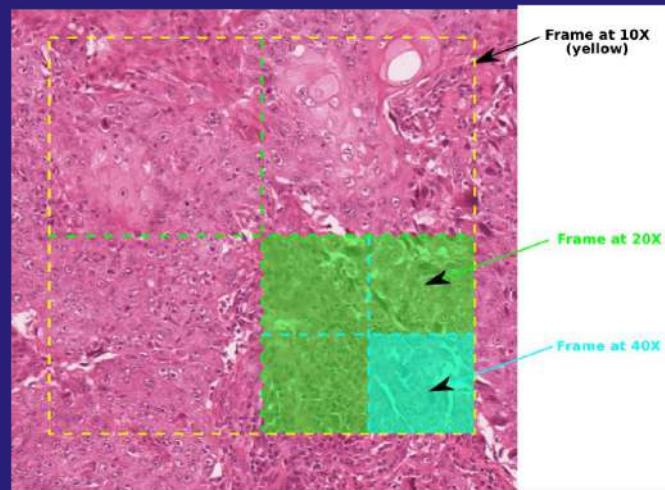
Board of Advisors

Nasir Rajpoot



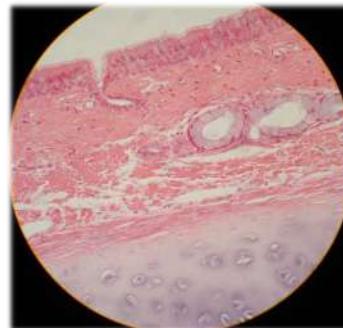
Board of Advisors

Computational Pathology



Digital Pathology

Classical Histopathology



- Diagnosis
- Disease detection
- Interpretation



Glass slide

Digital Histopathology

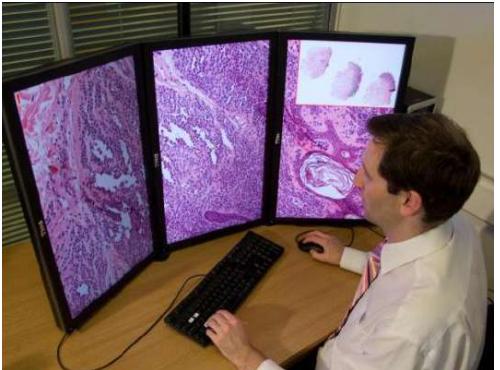


- Annotation
- Automatic analysis
- Storage
- Sharing

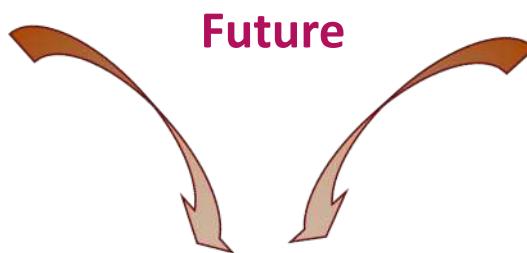


FDA allows marketing of first whole slide imaging system for digital pathology in April 2017

Collaborative decision and relevant retrieval



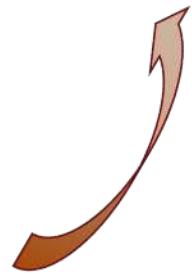
Single expert



Multidisciplinary Groups for Teaching and Decision (complex cases)



Second expert's opinion

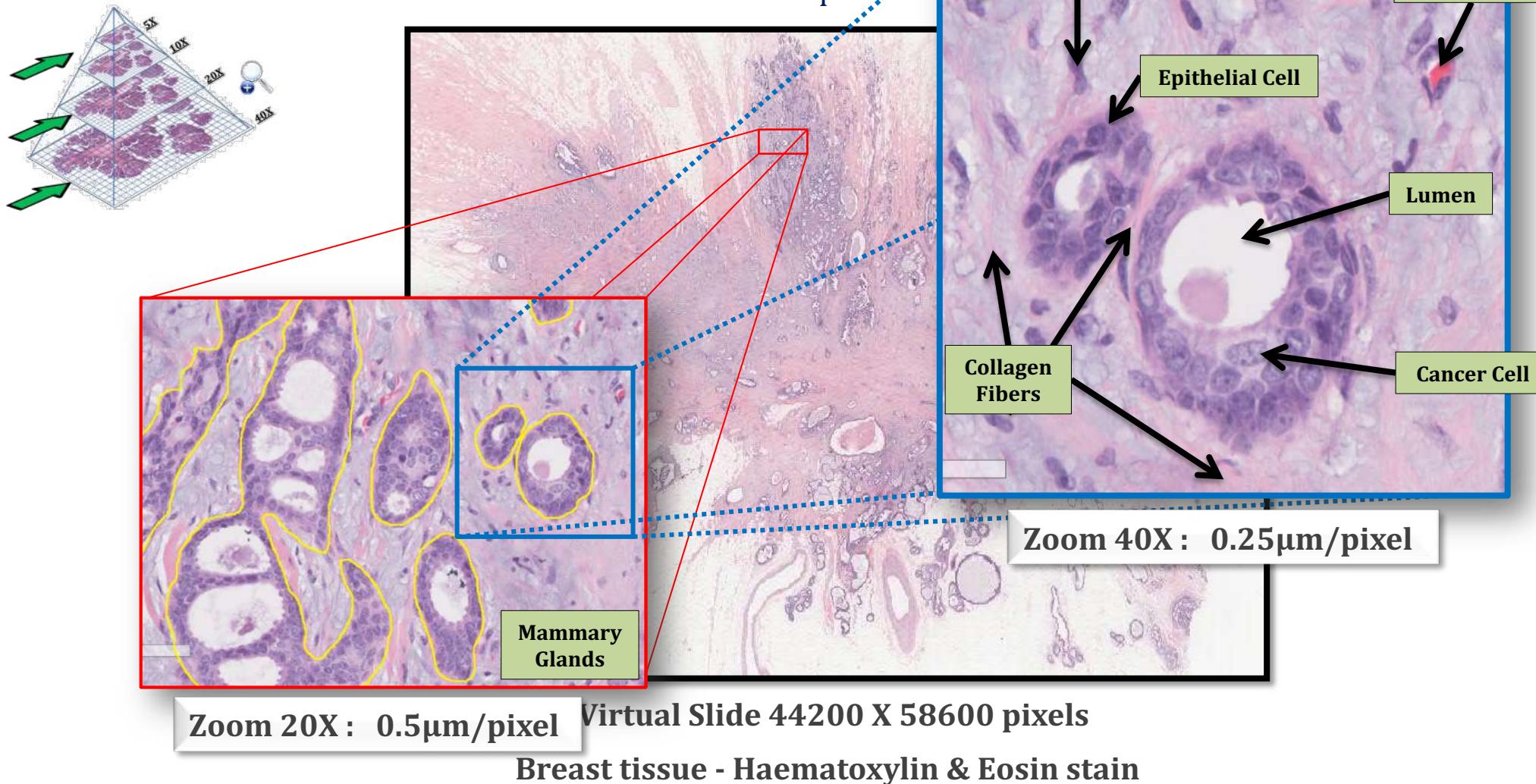


Past - 10-headed microscope

Whole Slide Images

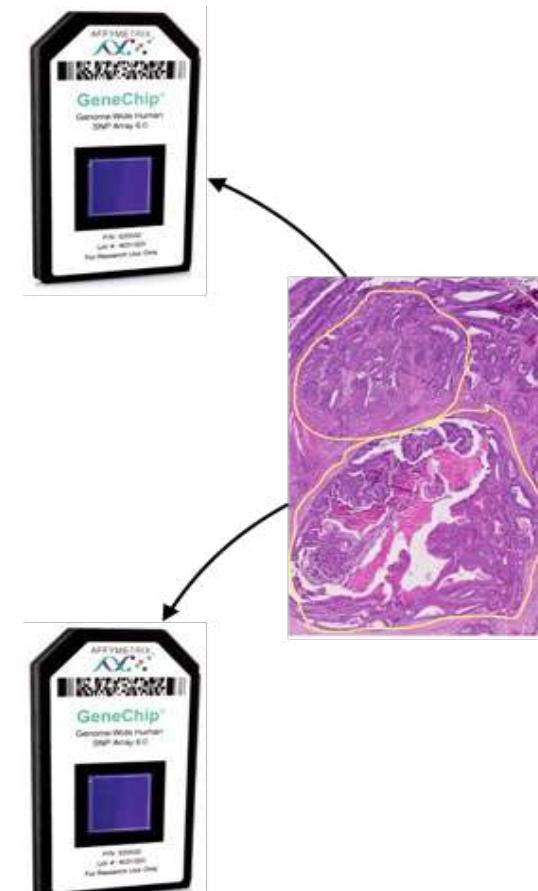
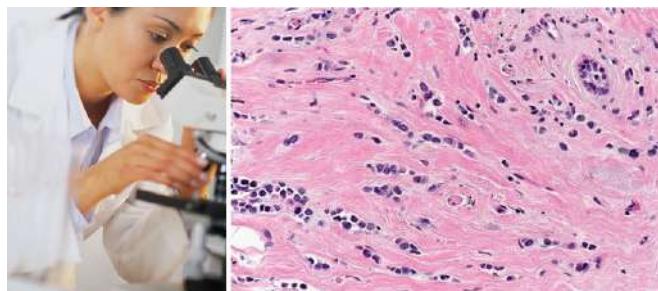
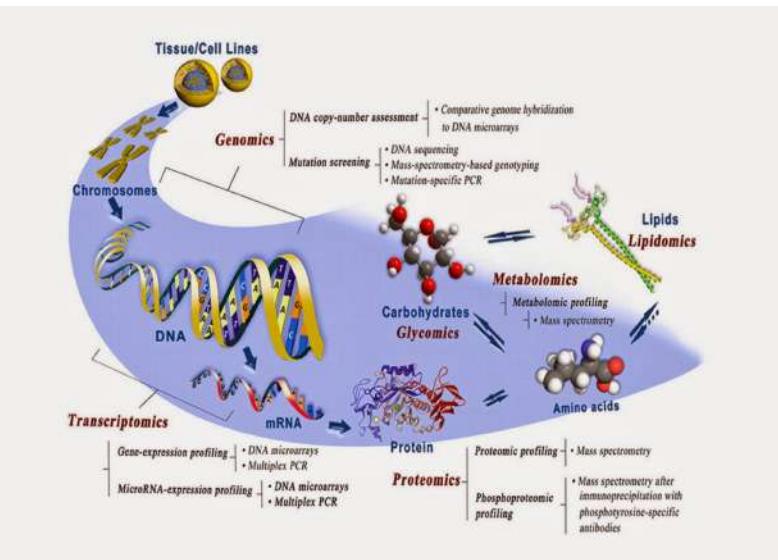
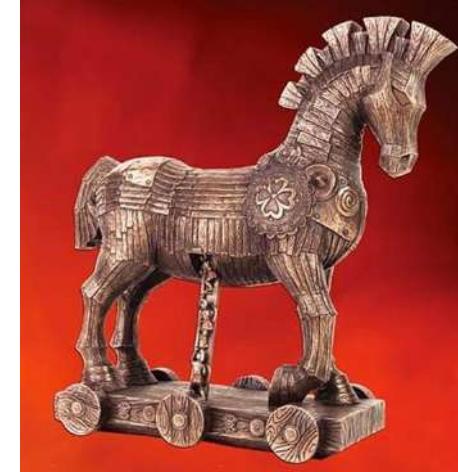
Whole Slide Imaging (Virtual Slides): Tiled pyramidal representation

→ View at specific location



Integrative Computational Pathology

- **BRIDGE** towards an operational integration of phenotypical and omics characteristics related to tumour genesis, heterogeneity, and prognosis, into the clinical routine.



Credo

Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients



Illustration by Taylor Jones for the *Healthcare Digest*



Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

- Ethics

- Traceability
- References
- Validation



Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

▫ Ethics

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- Validation

▫ Dynamics: Understand for a better Prognosis

- Multimodal data integration
- Dynamic Models
- Prognosis



Illustration by Taylor Japua for the *Hacker's Digest*.

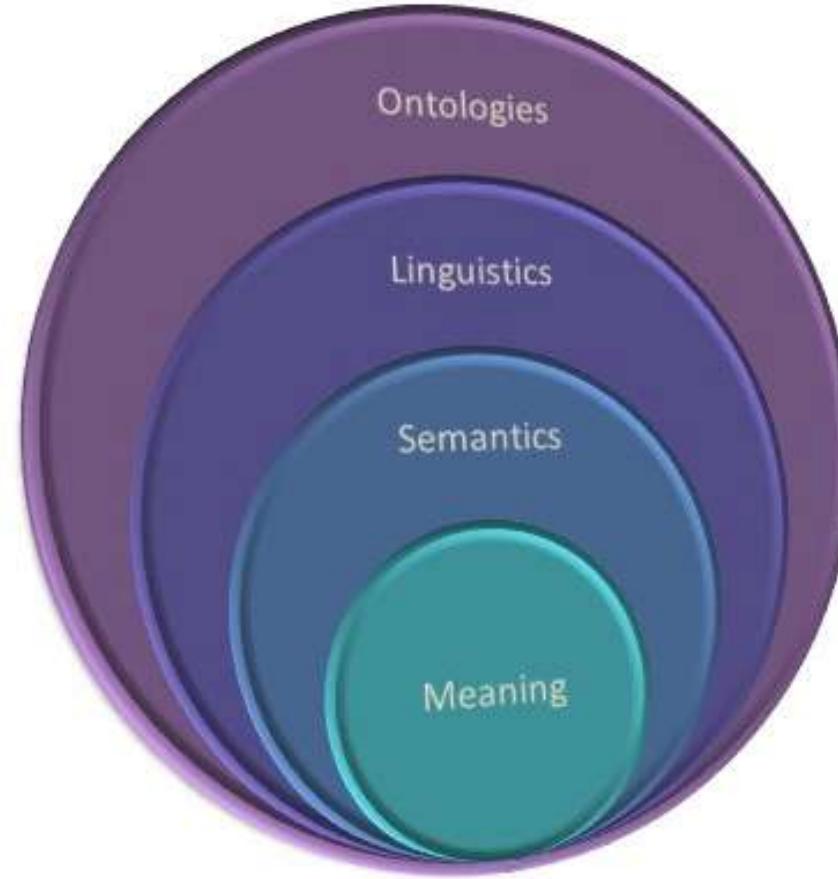


Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

– Ethics

- **Traceability – Semantics**
- References
- Validation

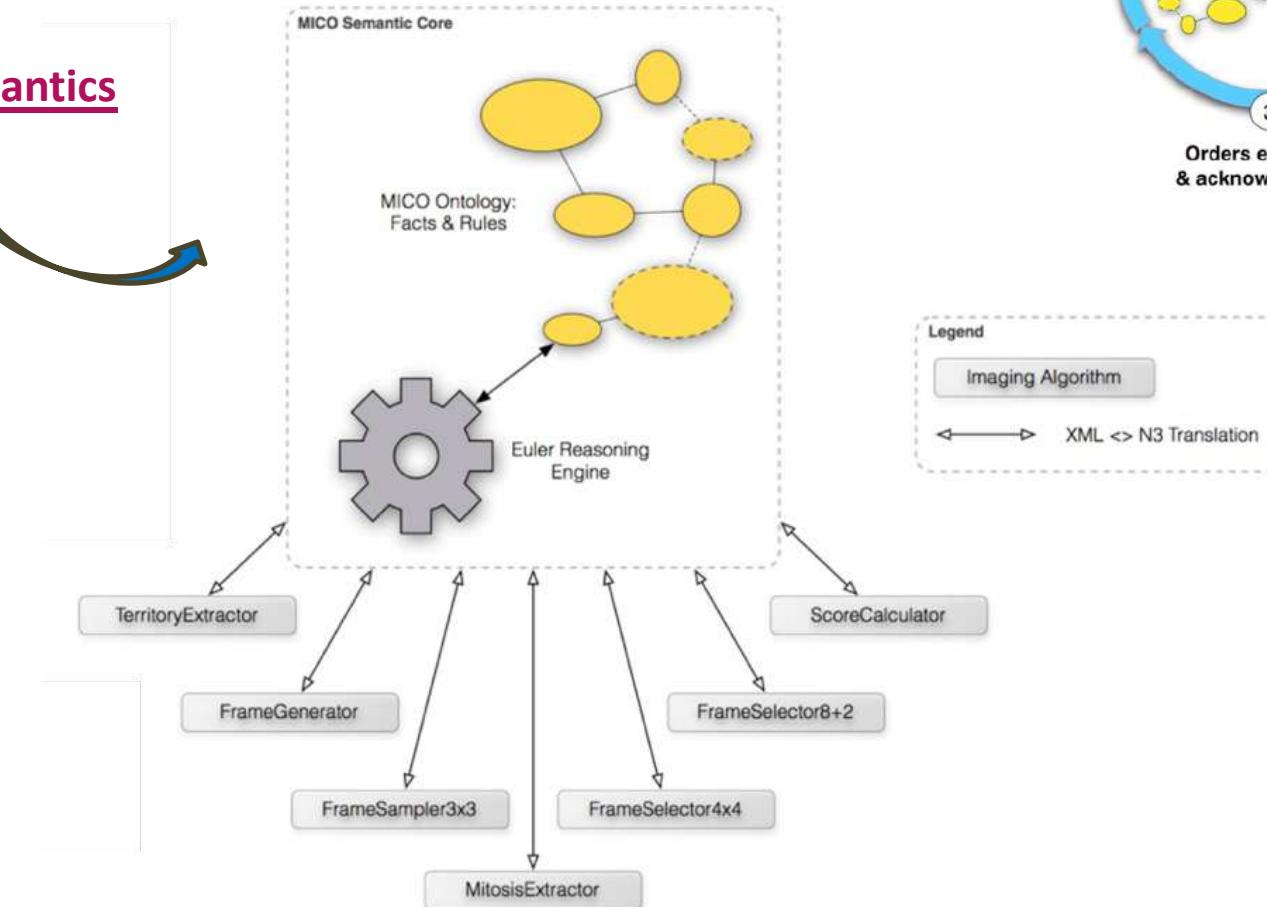


Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

– Ethics

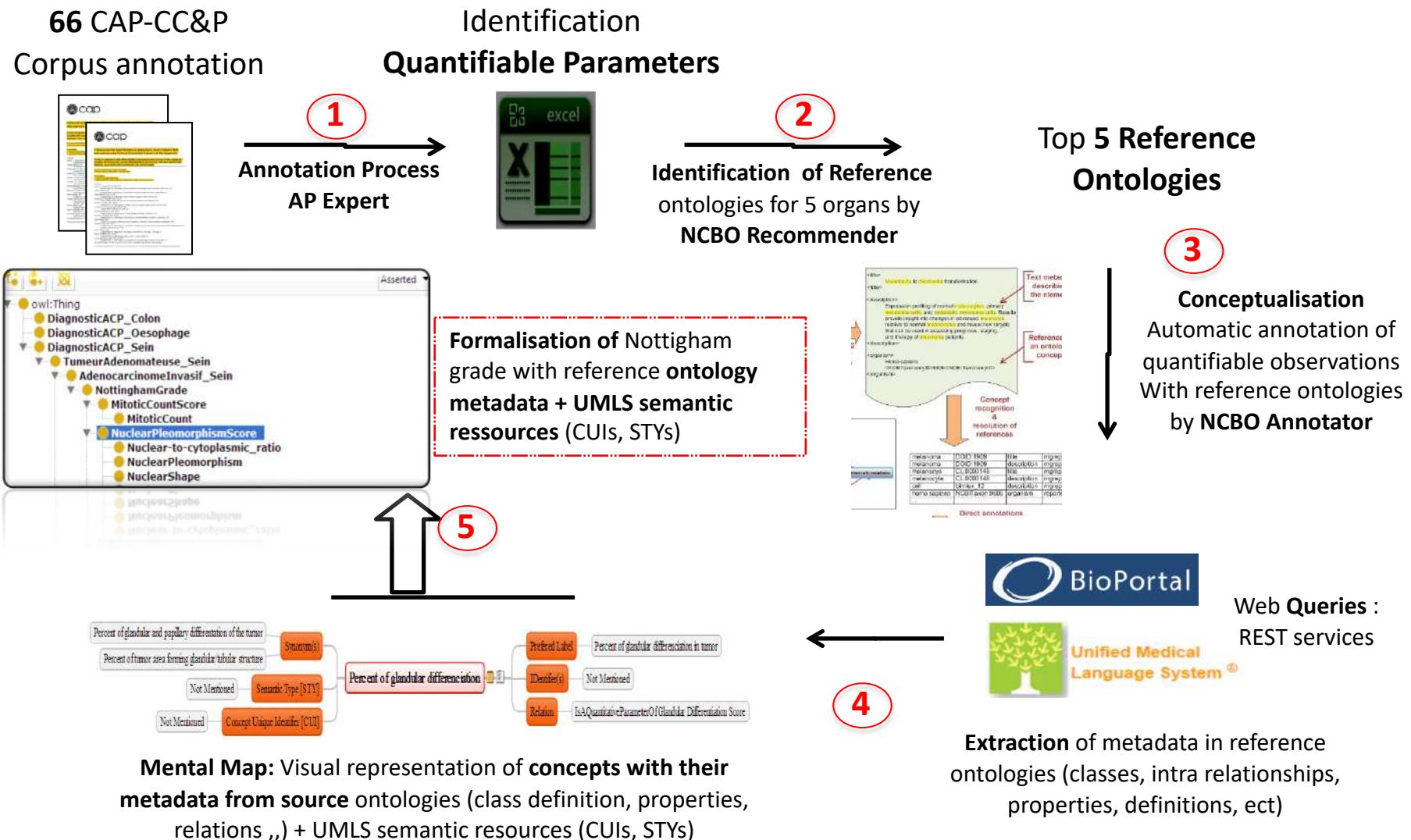
- Traceability – Semantics
- References
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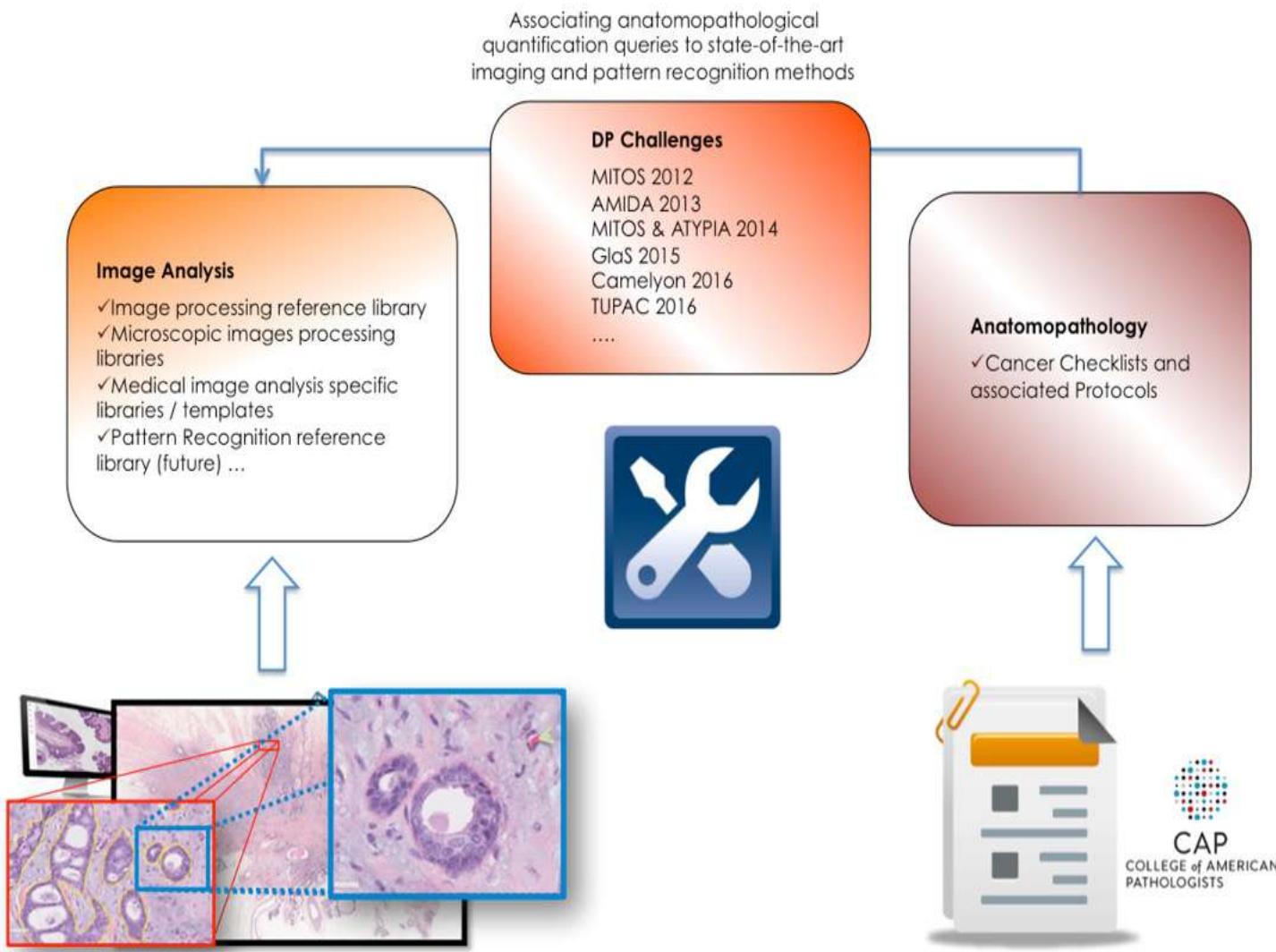
D. Racoceanu, F. Capron, (2015), CMIG - Computerized Medical Imaging and Graphics, Elsevier.

D. Racoceanu, F. Capron, (2016), Pathobiology : Journal of Immunopathology, Molecular and Cellular Biology.

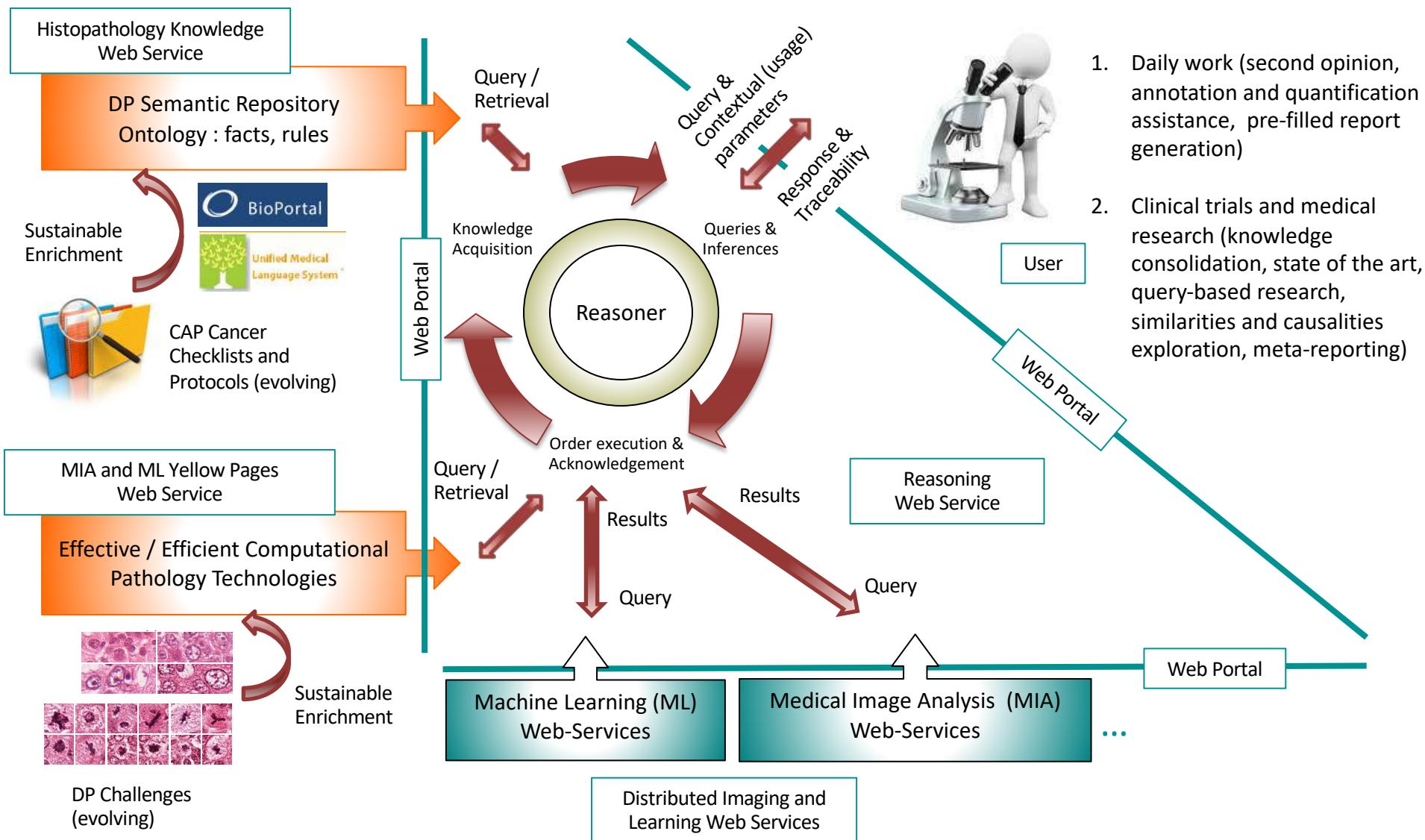
Towards a Sustainable ontology for histopathology



Bridging the semantic gap between diagnostic histopathology and image analysis



Web portal / services for Computational Pathology



Multi-IHC virtual staining production pipeline:

Cloud-based computing @ ICM

The screenshot shows the Cytomine software interface, specifically the 'Images' section for a project named 'CROHN'. The left sidebar has a dark theme with tabs for 'PROJECT: CROHN' (highlighted), 'Images' (selected), 'Annotations', 'Analysis', 'Activity', and 'Information'. The main area is titled 'Images' and displays a table with one row. The table columns are: Overview, Name, Magnification, Manual Annotations, Analysis Annotations, and Reviewed Annotations. The single entry is 'IMAGE.ndpi' with 'Unknown' magnification and zero annotations in all categories. Below the table are sections for 'Description', 'Tags', 'Properties', 'Attached files', 'Slide preview', and 'Original filename' (all showing 'No [category]'), and an 'Actions' section with buttons for 'Start review', 'Rename', 'Set calibration', 'Set magnification', 'Download', and 'Delete'. At the bottom left is a '10 per page' dropdown, and at the bottom right are navigation icons (1, <, >).

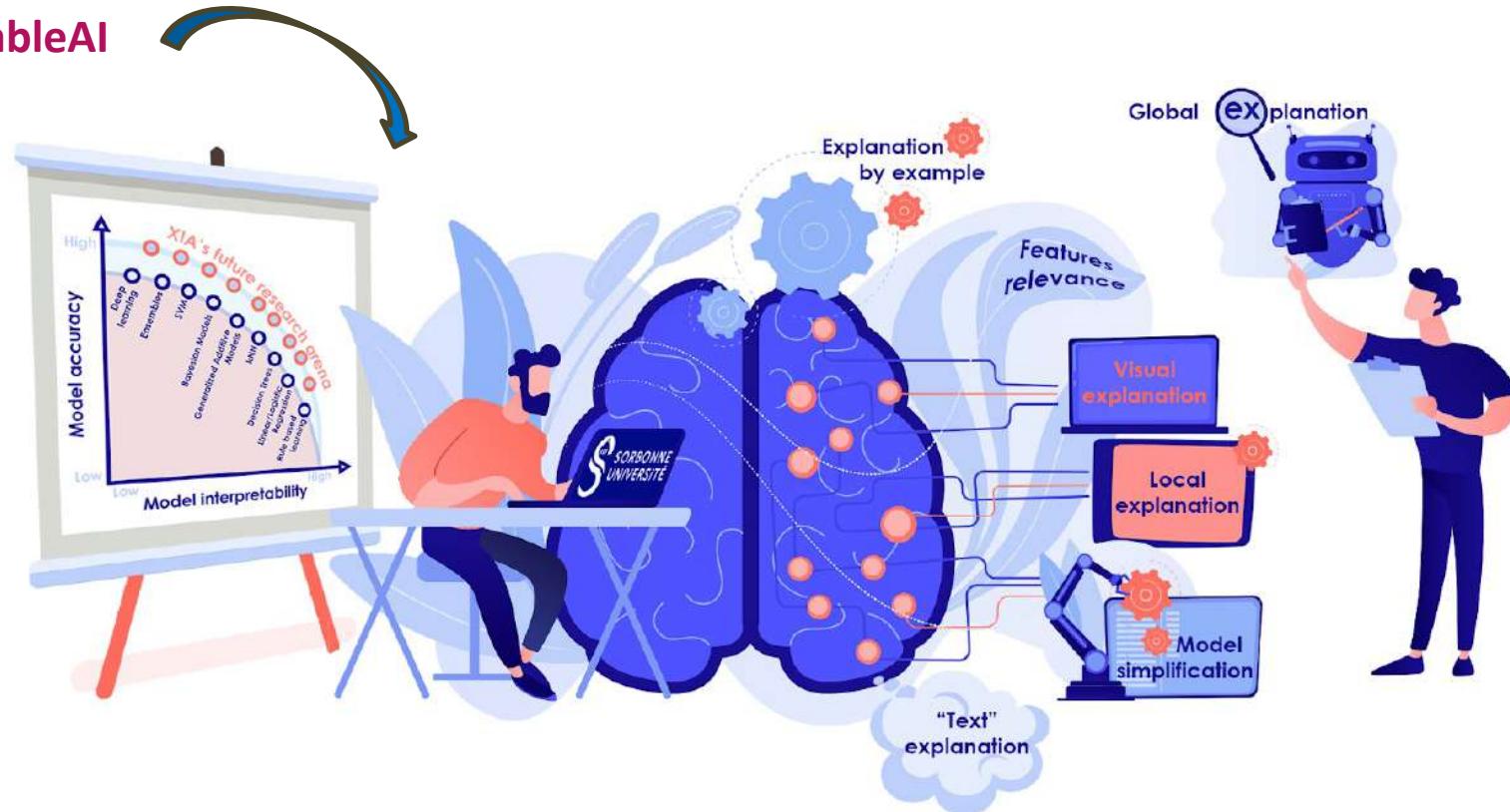
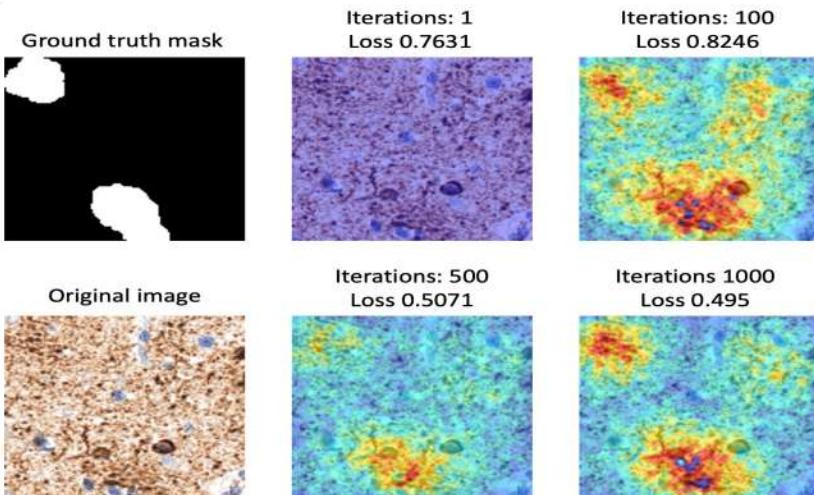
Video recorded by Ilias SARABOUT during his internship

Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

– Ethics

- Traceability – eXplainableAI
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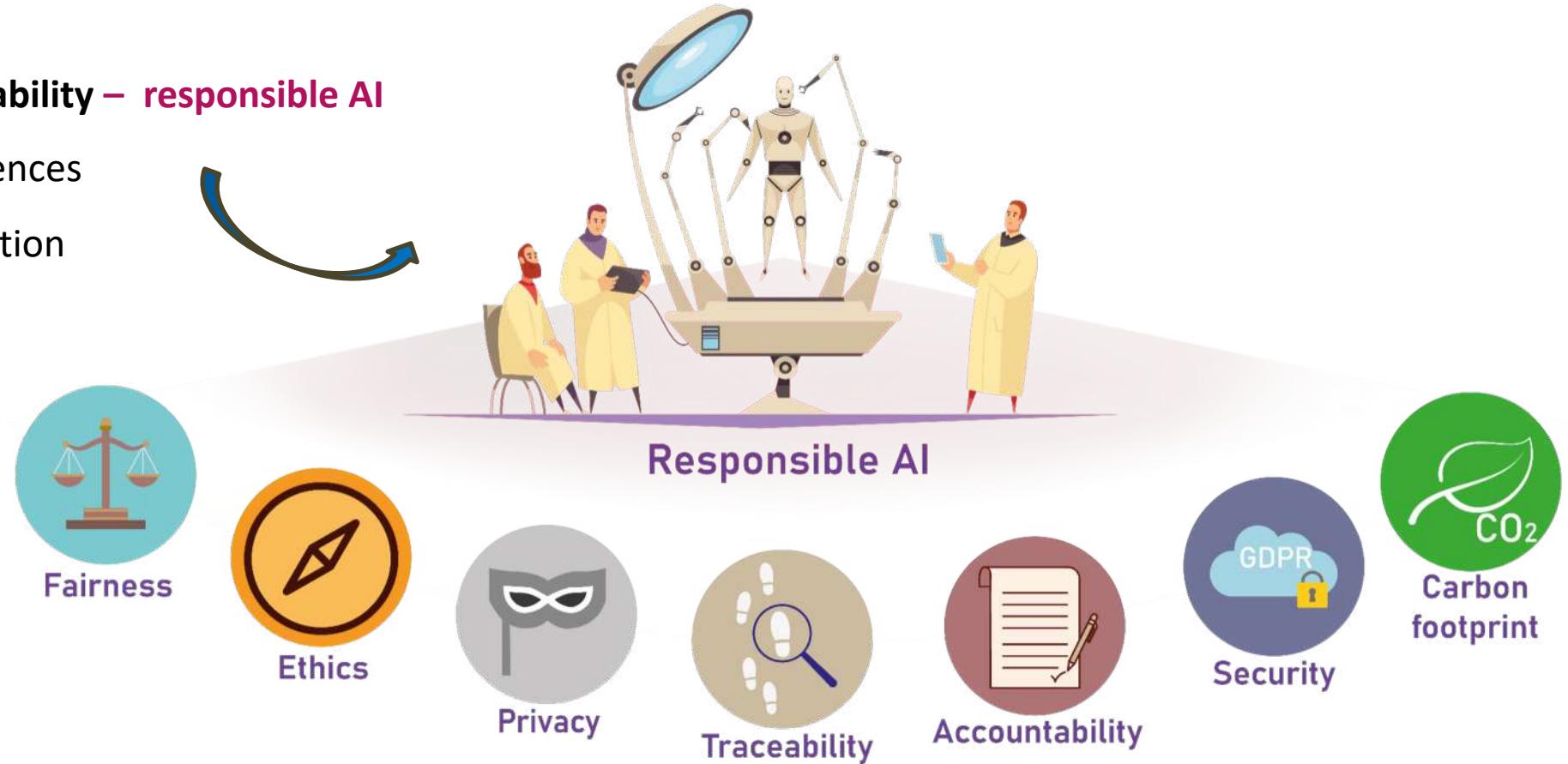


Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

– Ethics

- Traceability – responsible AI
- References
- Validation



Future of the Computational Support in Medicine

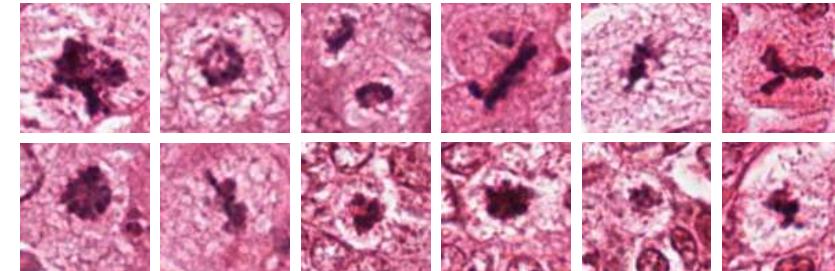
Ethics & Dynamics for the benefit of the Patients

– Ethics

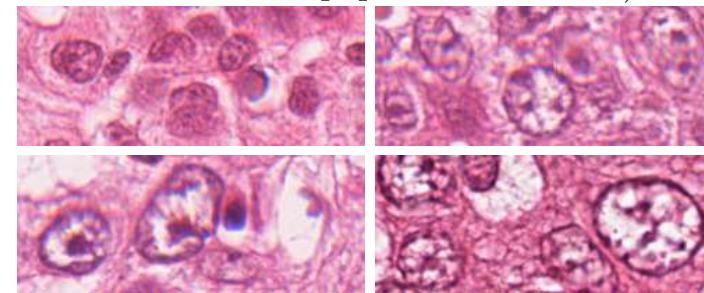
- Traceability – Semantics
- References – Challenges
- Validation



MITOS @ ICPR 2012



MITOS & ATYPIA @ ICPR 2014



And many others ...



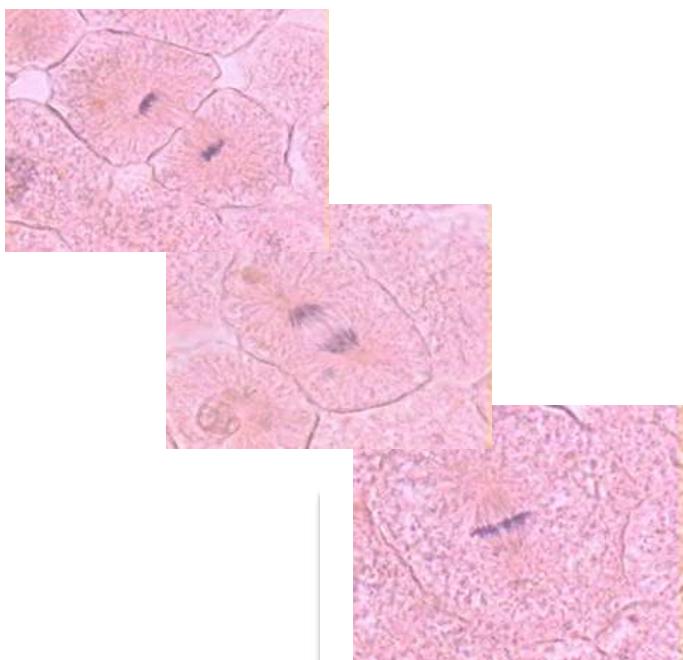
World first challenges in Digital Pathology MITOS & ATYPIA BENCHMARKING @ ICPR 2012/2014

ICPR
2012



21st Int. Conf. Pattern Recognition (ICPR 2012)
Tsukuba, Japan

130 institutions registered worldwide
Special issue in JPI - Journal
Pathology Informatics – March 2013
URL: <http://ipal.cnrs.fr/ICPR2012/>



ICPR
22nd International Conference on Pattern Recognition

24-28 August 2014 Stockholm, Sweden



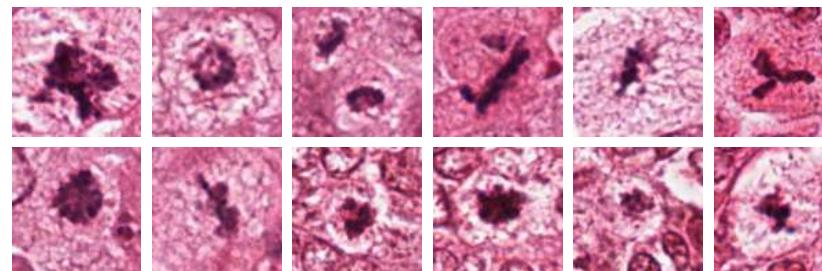
► **80 institutions / labs** registered worldwide

Detection of Mitosis

Mitotic count - **aggressivity of the tumour**.

Detection of mitosis is a challenging task :

- large variety of shape configurations
- **very low density of mitosis in one image**
- other objects are **very similar to mitotic cells**
- ...



Example of Mitotic Cells

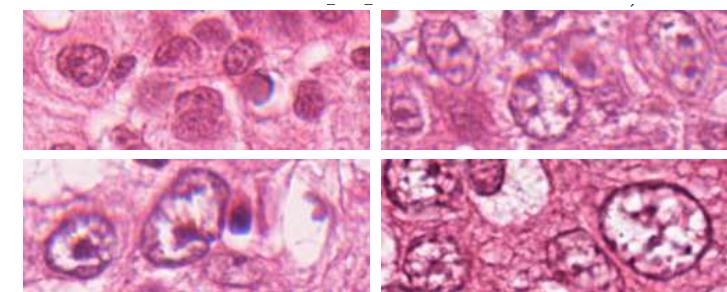
 **EURO-BIOIMAGING**

Evaluation of Nuclear Atypia

Nuclear pleomorphism - **nuclei shape variations**.

Nuclear atypia score can be estimated from criteria as

- **size of nuclei, size of nucleoli**
- **density of chromatin,**
- **thickness of nuclear membrane**
- **regularity of nuclear contour**
- **Anisonucleosis** size variation within nuclei population

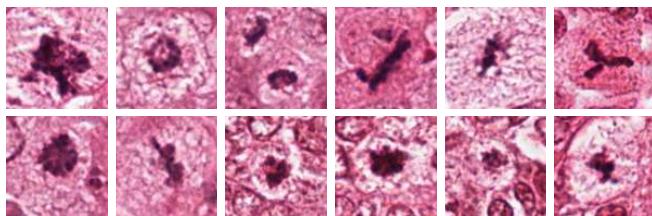


Examples of different degrees of nuclear atypia

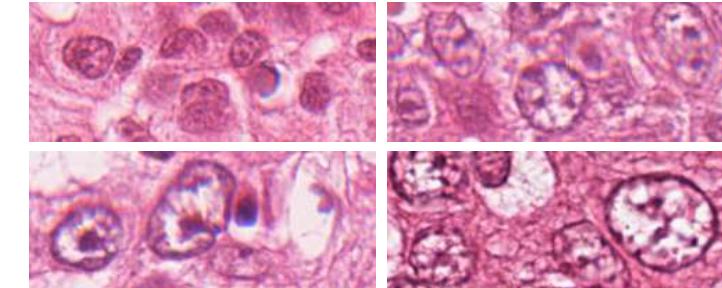
Detection of Mitosis and Evaluation of Nuclear Atypia Score in Breast Cancer Histological Images

Consolidation of an international REFERENCE DATABASE IN COMPUTATIONAL PATHOLOGY

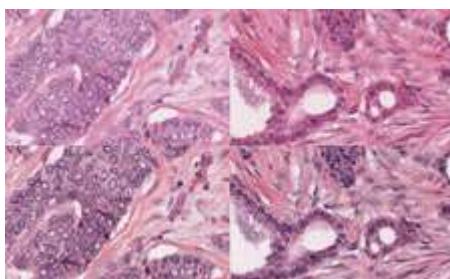
MITOS @ ICPR 2012



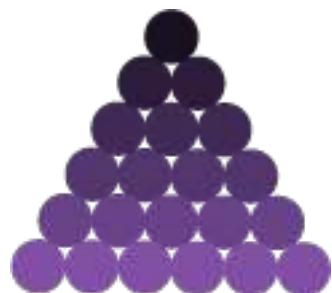
MITOS & ATYPIA @ ICPR 2014



AMIDA @ MICCAI 2013

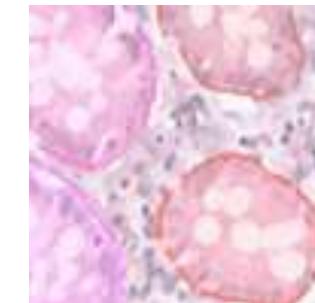


TUPAC @ MICCAI'2016



Validation
Histology
Database

GlaS @ MICCAI'2015



@ ISBI 2016 & 2017



Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

– Ethics

- Traceability – Semantics
- References – Challenges
- Validation – Clinical assessment



Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

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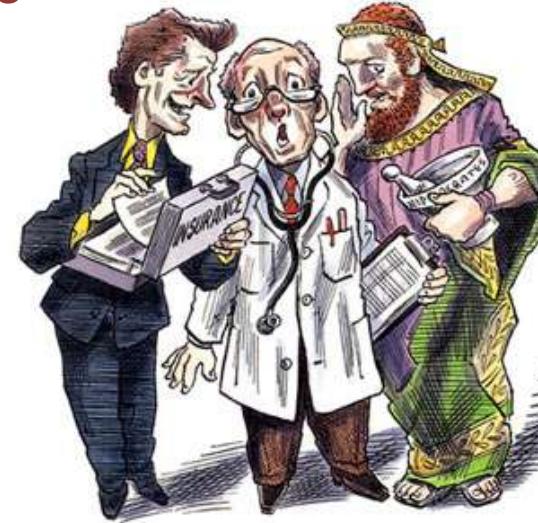


Illustration by Taylor Johnson for the Heineken Digital.

▫ Dynamics: Understand for a better Prognosis

- Multimodal data integration
- Dynamic Models
- Prognosis



Future of the Computational Support in Medicine

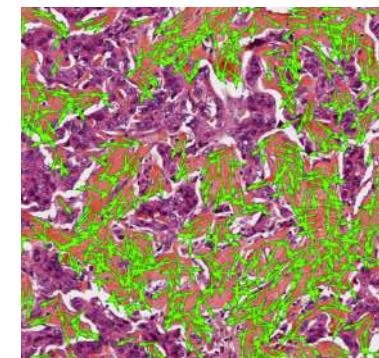
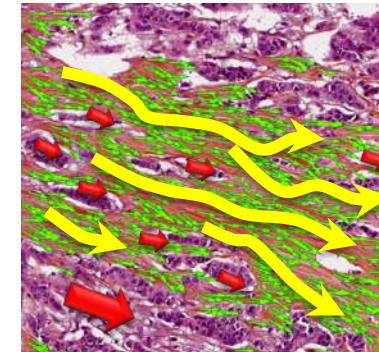
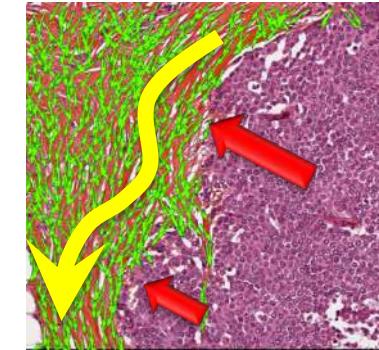
Ethics & Dynamics for the benefit of the Patients

– Ethics

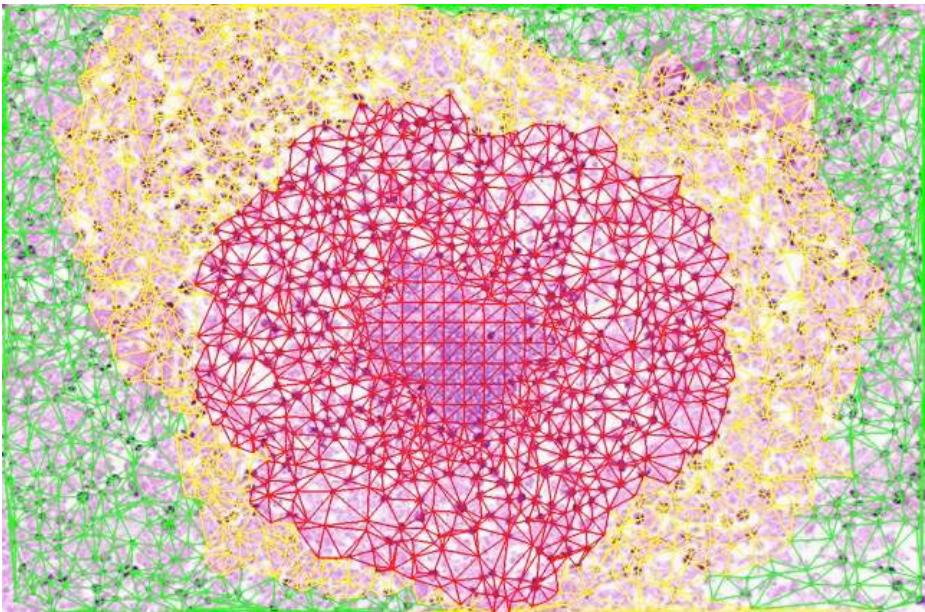
- Traceability – Semantics
- References – Challenges
- Validation – Clinical assessment

□ Dynamics: Understand and Prognose

- Multimodal data integration – Images, ...
- Dynamic Modeling
- Prognosis



Simulation in Digital Pathology ...

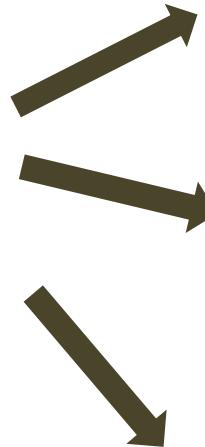


Non-hypoxic

Hypoxic

Necrotic

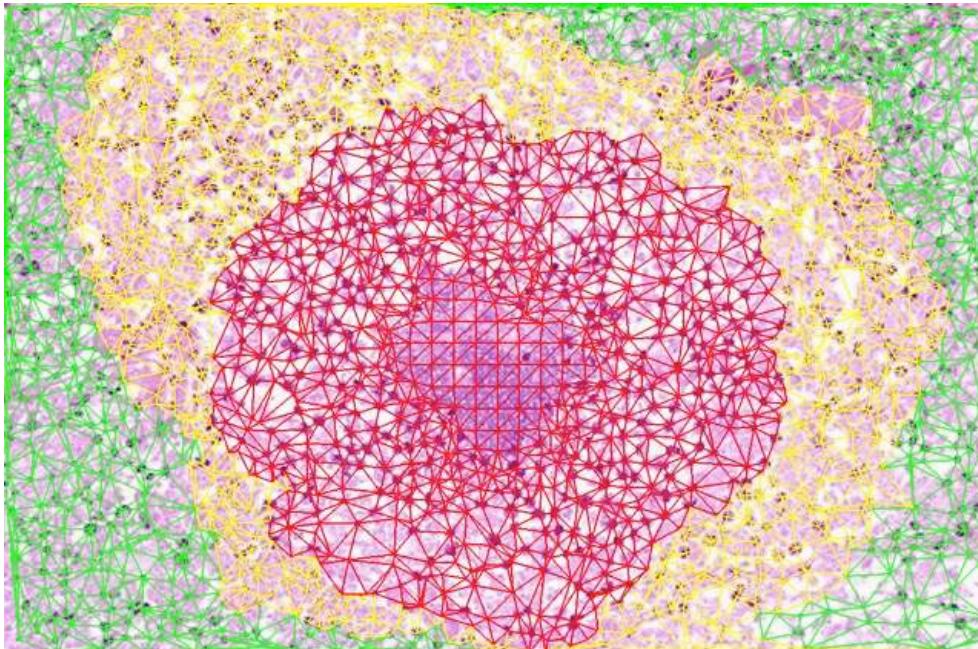
- Playing different scenarios
- Testing different profiling
- Discussing, analysing
- Educating
- Communicating
(e.g. with the patient)



- Data augmentation
- Creating synthetic data
(e.g. for DL)
- Finding correlations
- Simulating diff. therapies
- Prognosing
(one day, for sure ...)

Spatial & Temporal Tumor Heterogeneity

Topological model framework for tumor cell growth simulations :

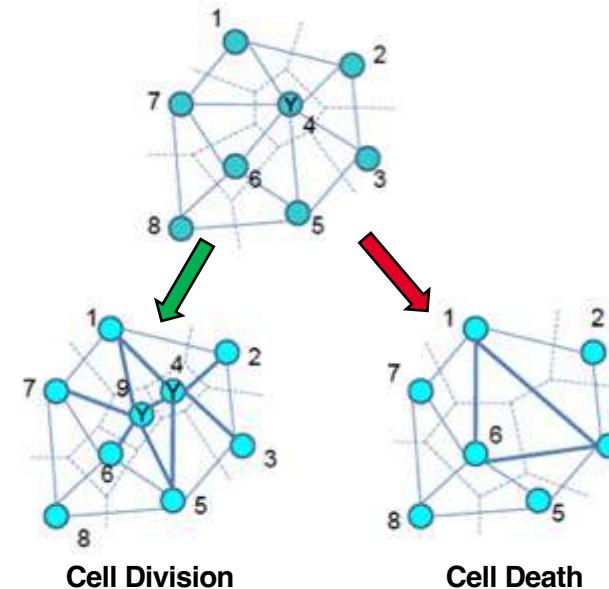


Non-hypoxic

Hypoxic

Necrotic

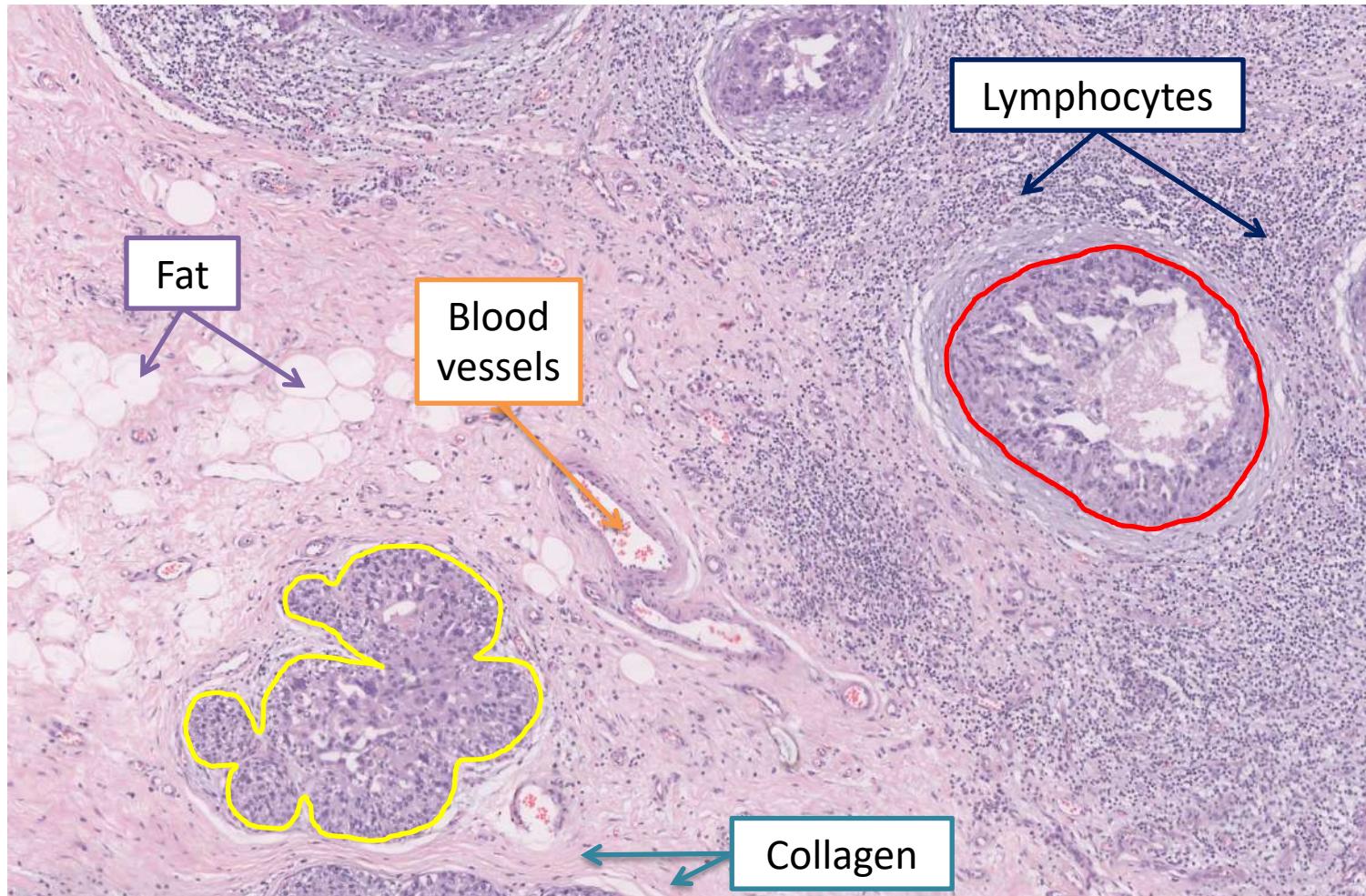
Graph Transform



Formalism that describes the dynamics of graphical structure

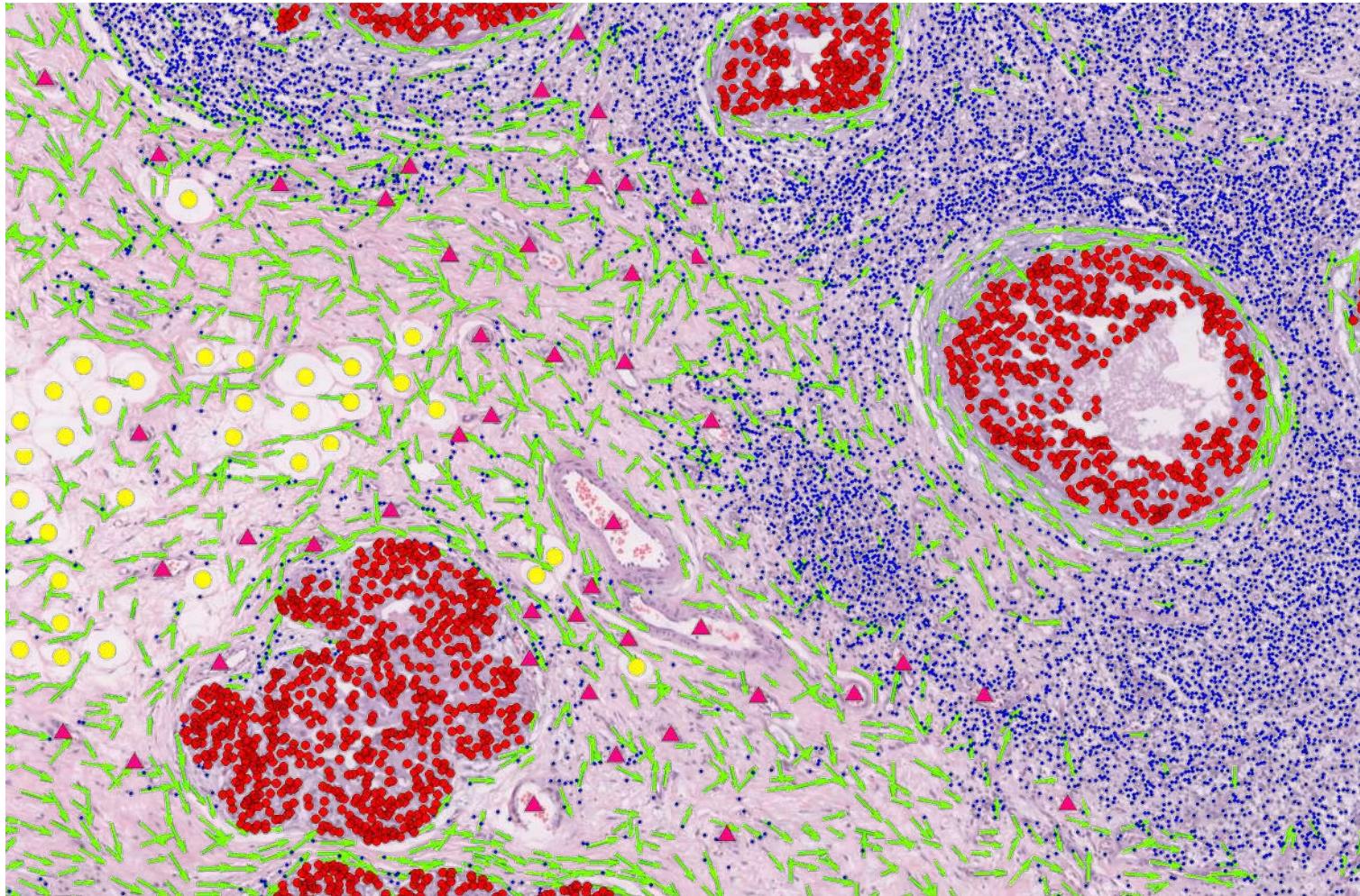
N. Loménie and D. Racoceanu, *Pattern Recognition*, 2012.

Tumor Micro-Environment Heterogeneity



Tumor Micro-Environment Heterogeneity

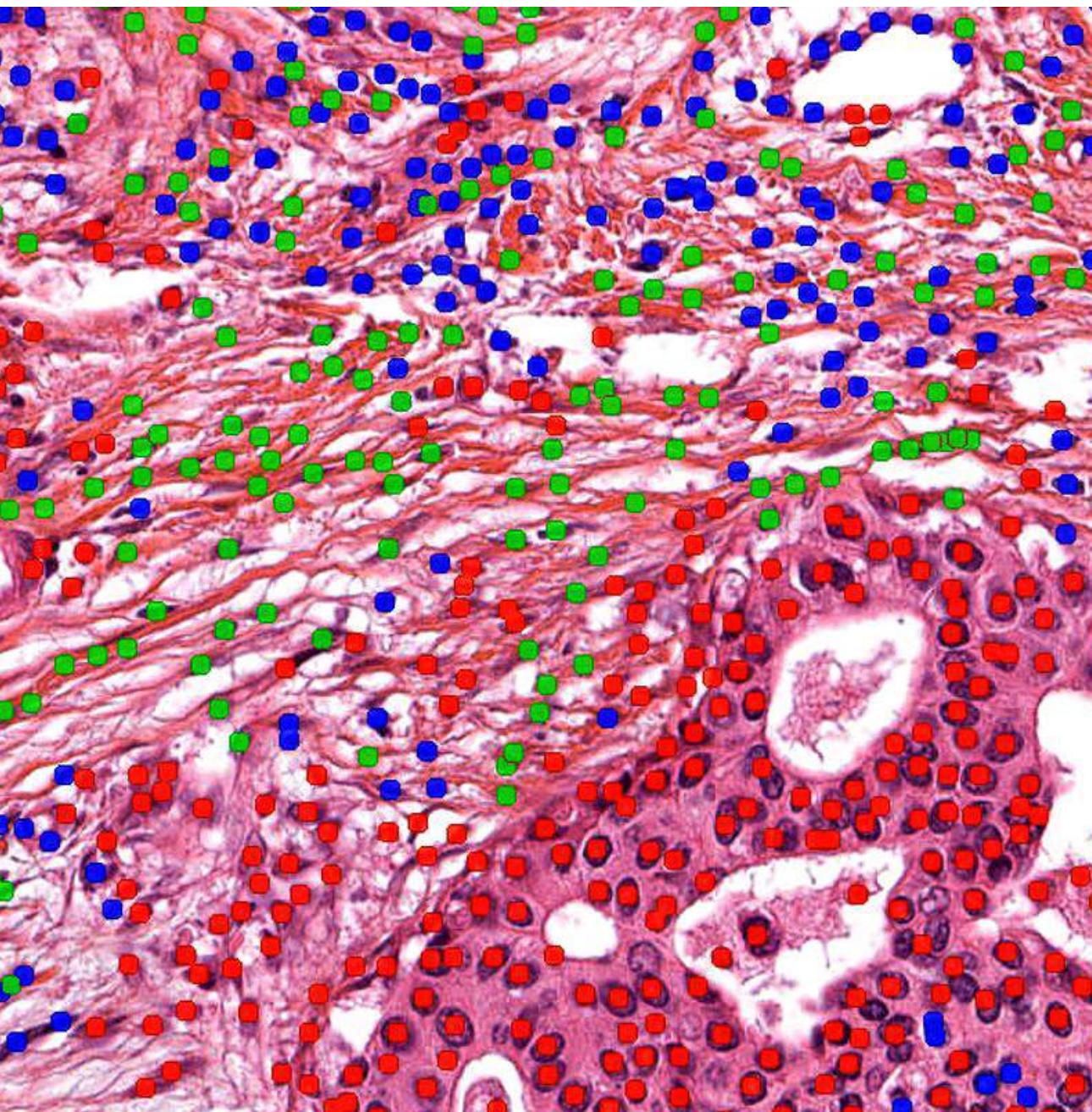
- Cancer cells
- Immune cells
- ✓ Collagen
- Adipocytes
- ▲ Blood vessels



**Spatial heterogeneity
in cancer ecosystem**

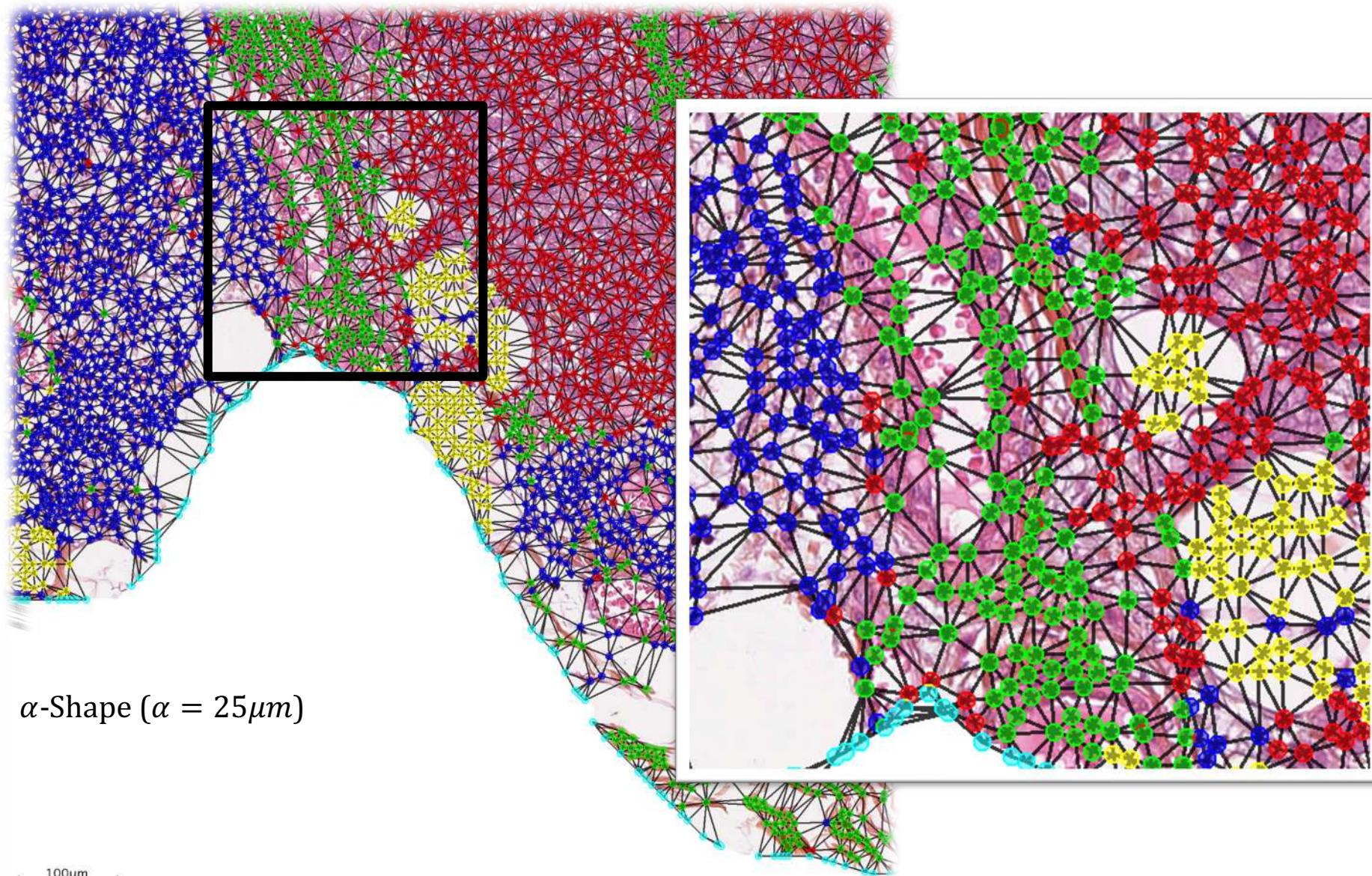


Quantitative analysis of spatial heterotypic interactions in TME: Proximity/Adjacency, Surroundedness/Enclosedness, Betweenness



- Cancer cells
- Immune cells
- Collagen + Fibroblasts
- Adipocytes

Spatial organization of histological structures



Spatial organization of histological structures

Sparsity:

Immune cell aggregates

Envelope immune cell aggregates

Cancer cells

- highly enclosed by immune cells

- surrounded by immune cells

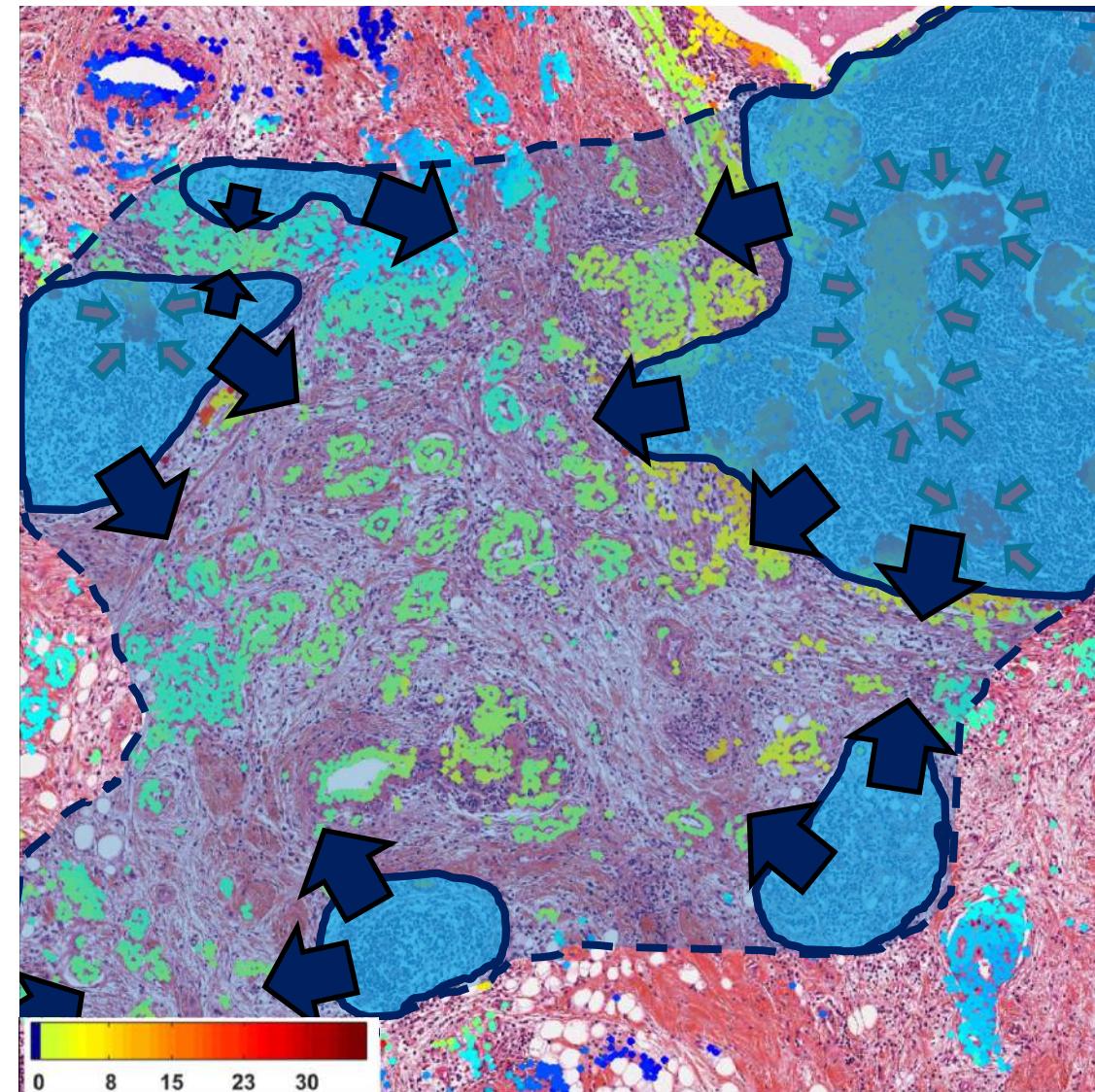
- between distant immune cell aggregates

- free from immune cells

Sparsity function:

$$\Gamma(G_X) = \frac{1}{N+1} \sum_{n=0}^N \zeta \circ \gamma_n(G_X)$$

$N = 5$



$$\zeta(G_X)(G_Y)$$

$$n = 5$$

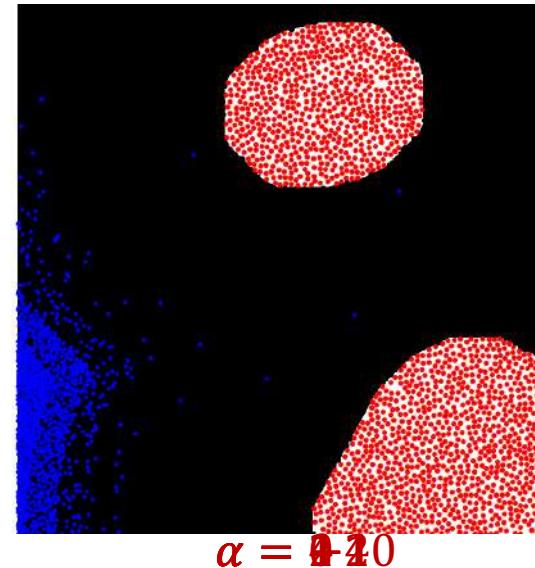
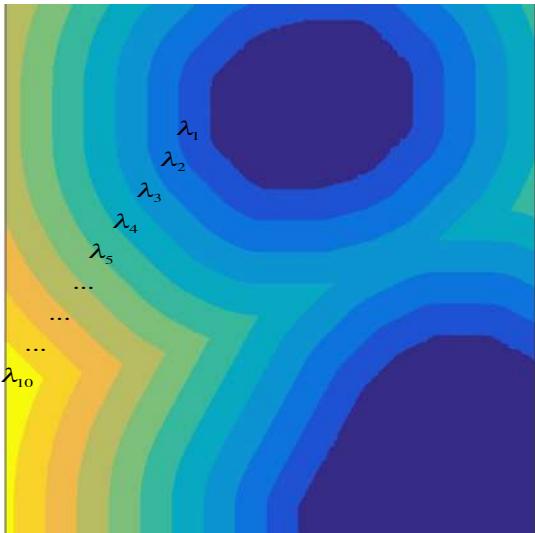
• $X = \text{immune cells}$

$$\zeta(G) = \sum_{n=0}^k \varphi_n(G) \quad \text{with} \quad \varphi_k(G) = \varphi_{k'}(G), \forall k' \geq k$$

• $Y = \text{cancer cells}$

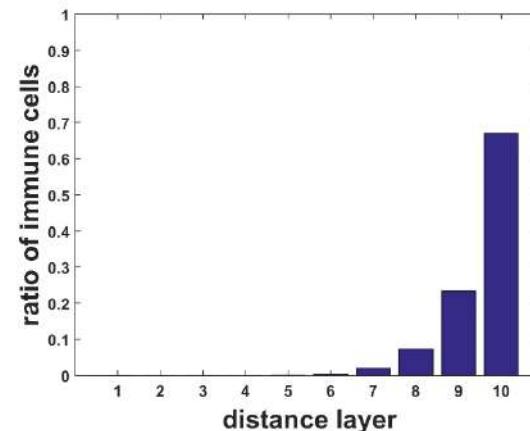
Tumor Microenvironment

□ A model of immune cells spatial distribution:



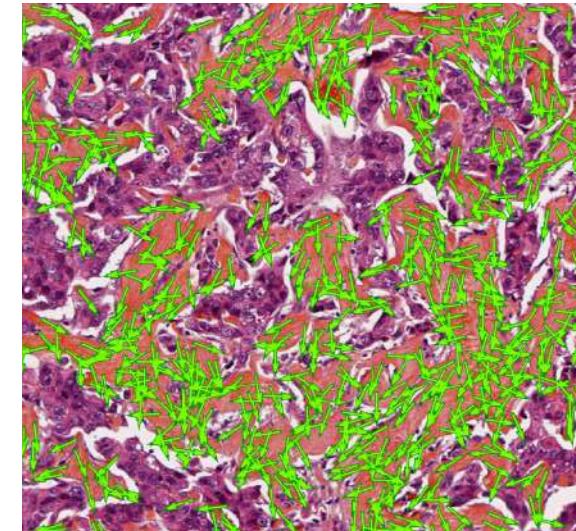
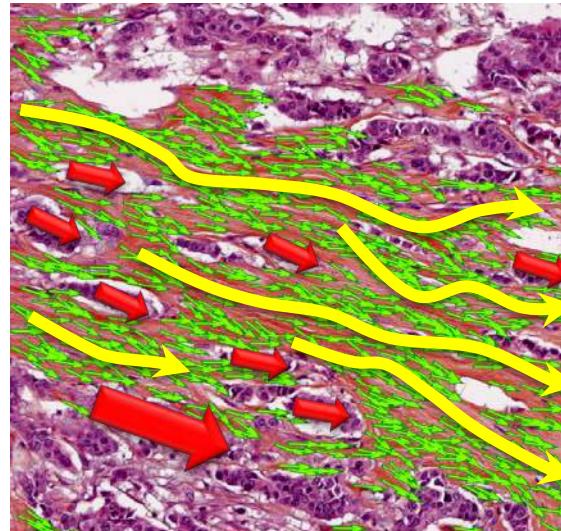
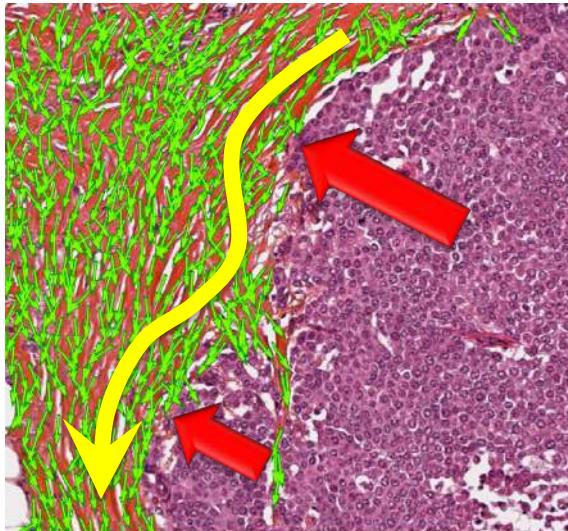
- Distance map
- Quantization (parameter k)
- Weight coefficients: $\lambda_i = \frac{i^{-\alpha}}{\sum_{i=1}^k i^{-\alpha}}$ (parameter)

- $\alpha > 0$: immune cells close to tumor
- $\alpha < 0$: immune cells distant from tumor
- $\alpha = 0$: uniformly distributed



Tumor Microenvironment

□ Heterogeneity of the spatial organization of collagen fibers:



- Orientation
- Density
- Spatial proximity
- Surroundedness
- Stretchiness

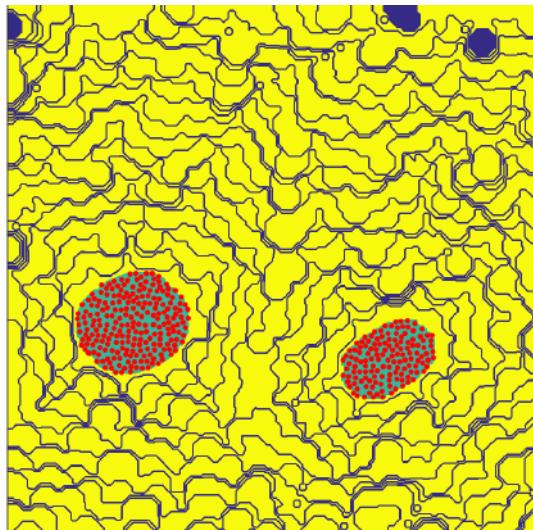
Tumor Microenvironment

□ A model of collagen spatial arrangement:

- Reshaping (parameter γ)
- Distance map
- Quantization (parameter k)
- Dilation (parameter R)

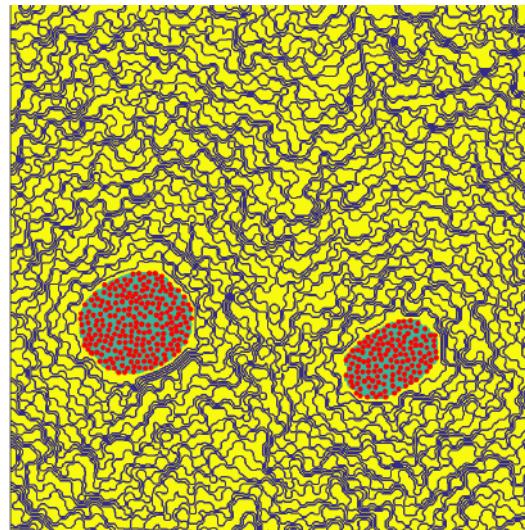
➤ Morphological deformations of tumor patterns define various distance maps, which are quantized.

stretchiness



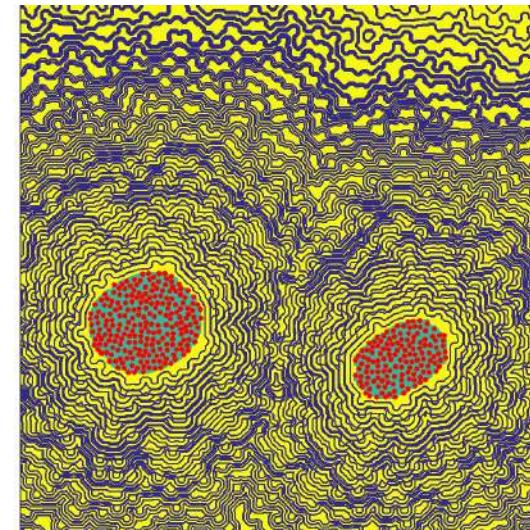
$$\{k, R, \gamma\} = \{11, 40, 60\}$$

thickness



$$\{1, 50, 30\}$$

density and spatial proximity



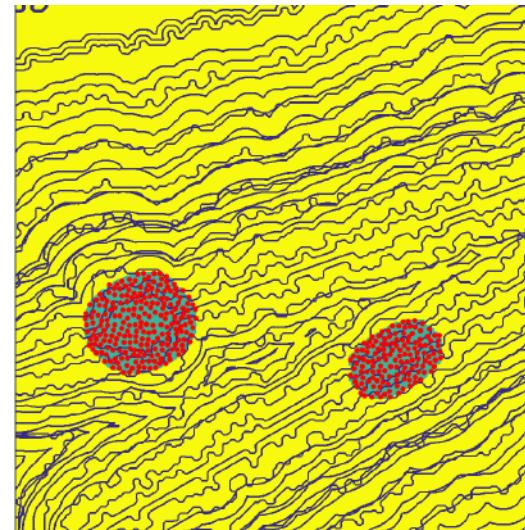
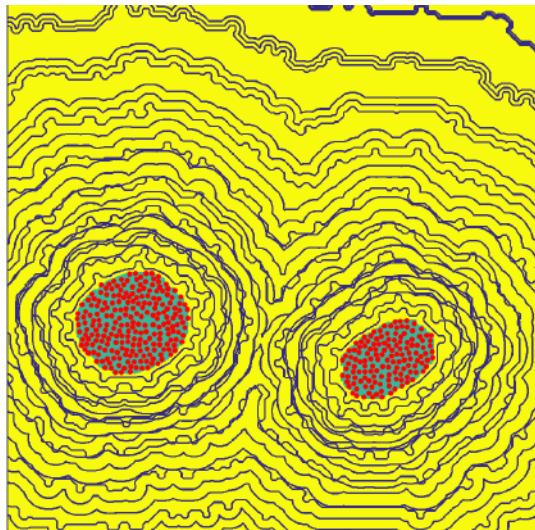
$$\{1, 2, 4, 3, 5\}$$

Tumor Microenvironment

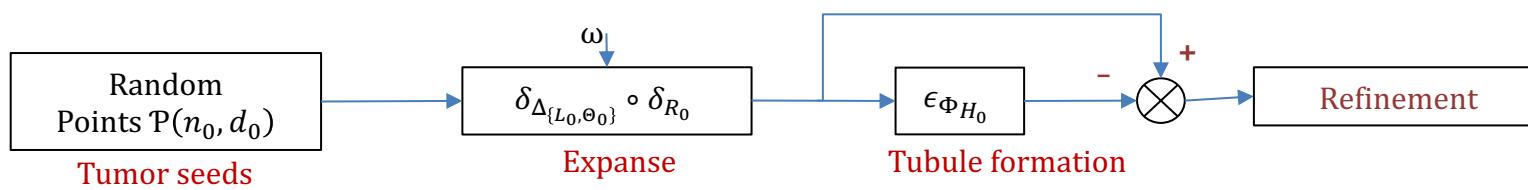
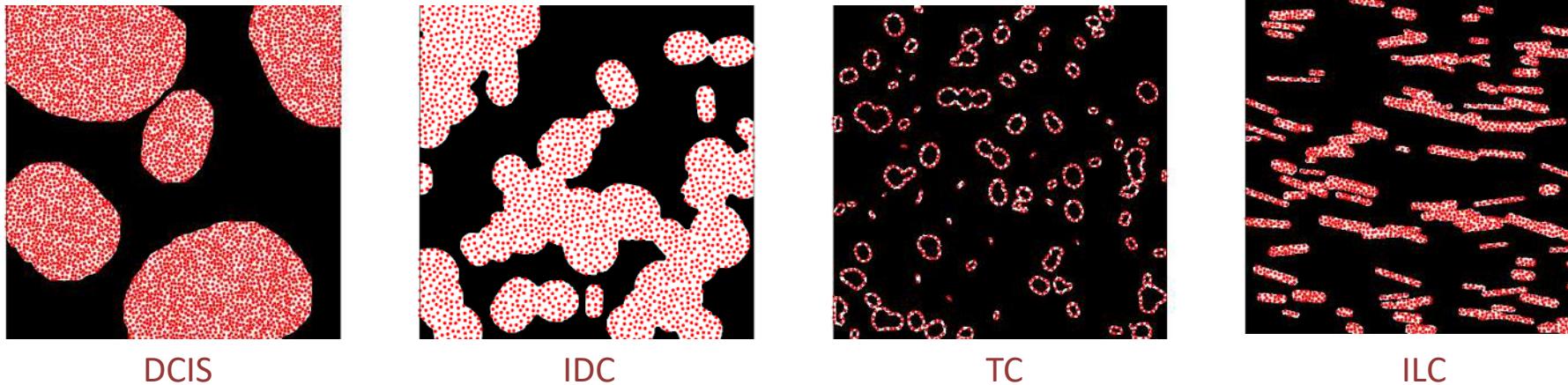
□ A model of collagen spatial arrangement:

- Reshaping (parameter γ)
 - Distance map
 - Quantization (parameter k)
 - Dilation (parameter R)
- Morphological deformations of tumor patterns define various distance maps, which are quantized.

Orientation relative to tumor



Tumor Patterns Modeling

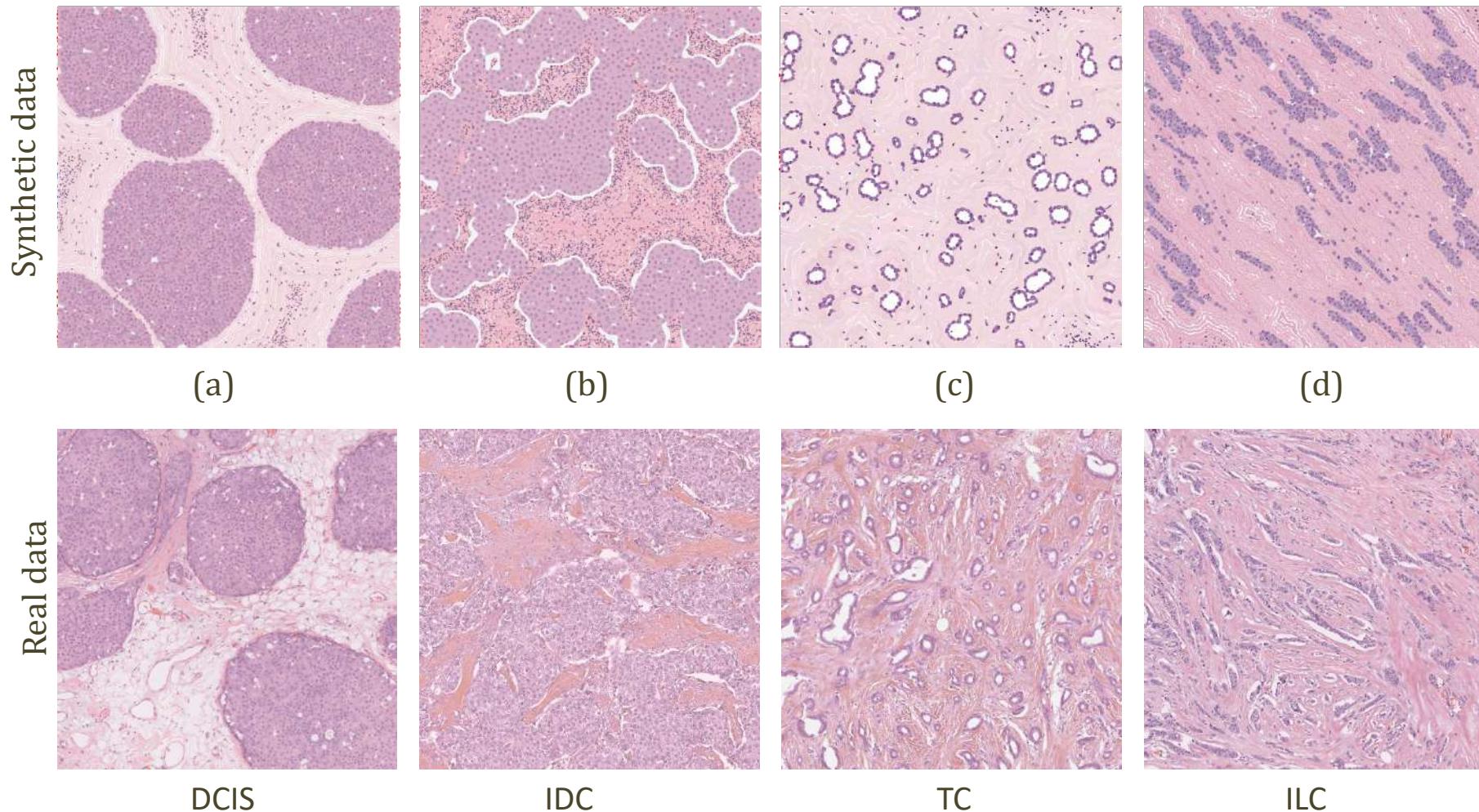


	n_0	d_0
(a)	$\mathcal{N}_1(7, 2)$	800
(b)	$\mathcal{N}_1(40, 8)$	100
(c)	$\mathcal{N}_1(85, 5)$	40
(d)	$\mathcal{N}_1(100, 5)$	40

$\mathcal{N}_n(\mu, \sigma)$: n random values generated from a normal distribution

$\mathcal{U}_n(a, b)$: n random values generated from a discrete uniform distribution

Qualitative Results



Ben Cheikh, B., Bor-Angelier, C., Racoceanu, D. (2017). A Model of Tumor Architecture and Spatial Interactions with the Microenvironment in Breast Carcinoma, SPIE Medical Imaging, Orlando, Florida, United States.

Future of the Computational Support in Medicine

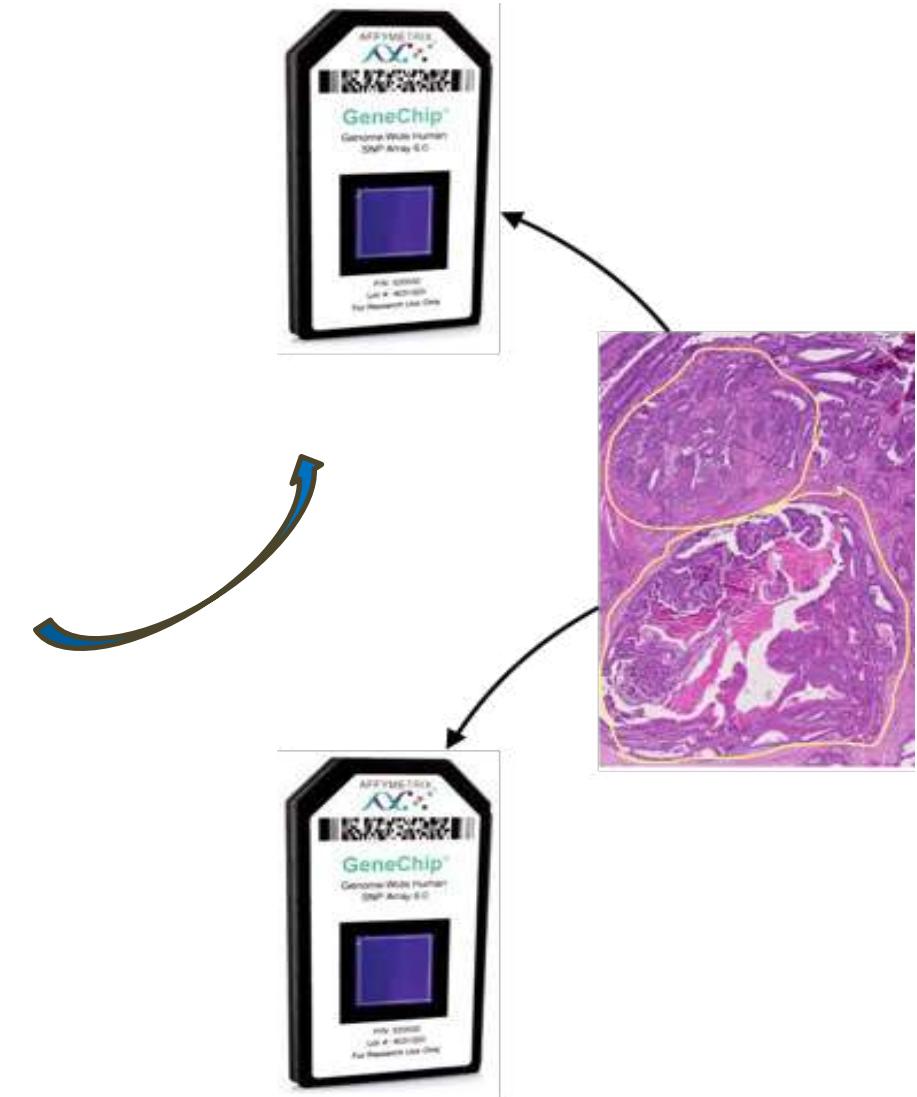
Ethics & Dynamics for the benefit of the Patients

– Ethics

- Traceability – Semantics
- References – Challenges
- Validation – Clinical assessment

□ Dynamics: Understand and Prognose

- Multimodal data integration - Images, Omics, ...
- Dynamic Modeling
- Prognosis



Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

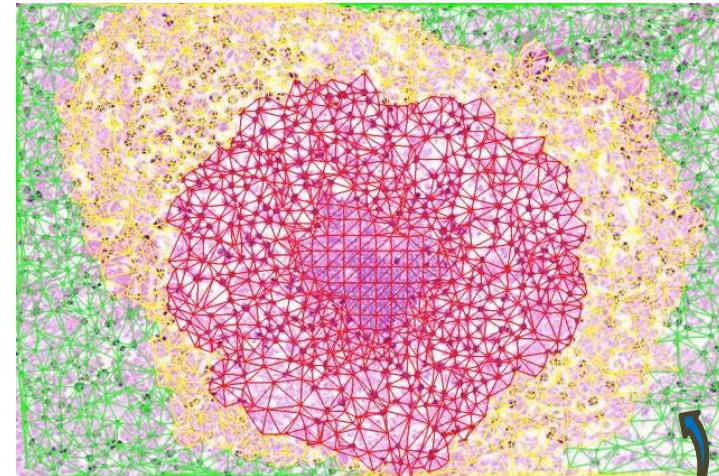
– Ethics

- Traceability – [Semantics](#)
- References – [Challenges](#)
- Validation – [Clinical assessment](#)

□ Dynamics: Understand and Prognose

- Multimodal data integration – [Images, Omics, ...](#)
- **Dynamic Modeling** – [Morphogenesis / Pathogenesis \(i.e. tumour growing\)](#)
- Prognosis

Tumour growing assessment / estimation / simulation

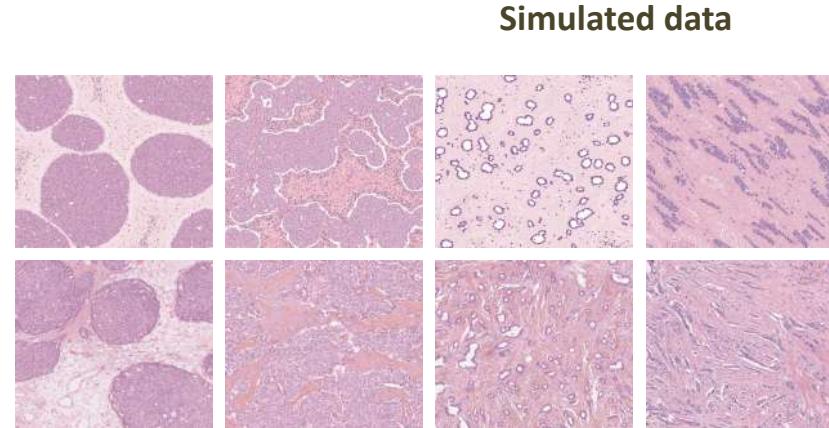


Future of the Computational Support in Medicine

Ethics & Dynamics for the benefit of the Patients

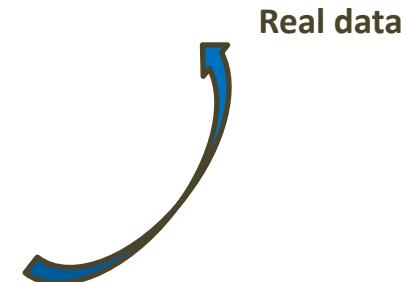
– Ethics

- Traceability – Semantics
- References – Challenges
- Validation – Clinical assessment



□ Dynamics: Understand and Prognose

- Multimodal data integration – Imaging & Omics
- **Dynamic models** – Morphogenesis / Pathogenesis
 - Assessment / estimation / simulation
- Prognosis



Future of the Computational Support in Medicine

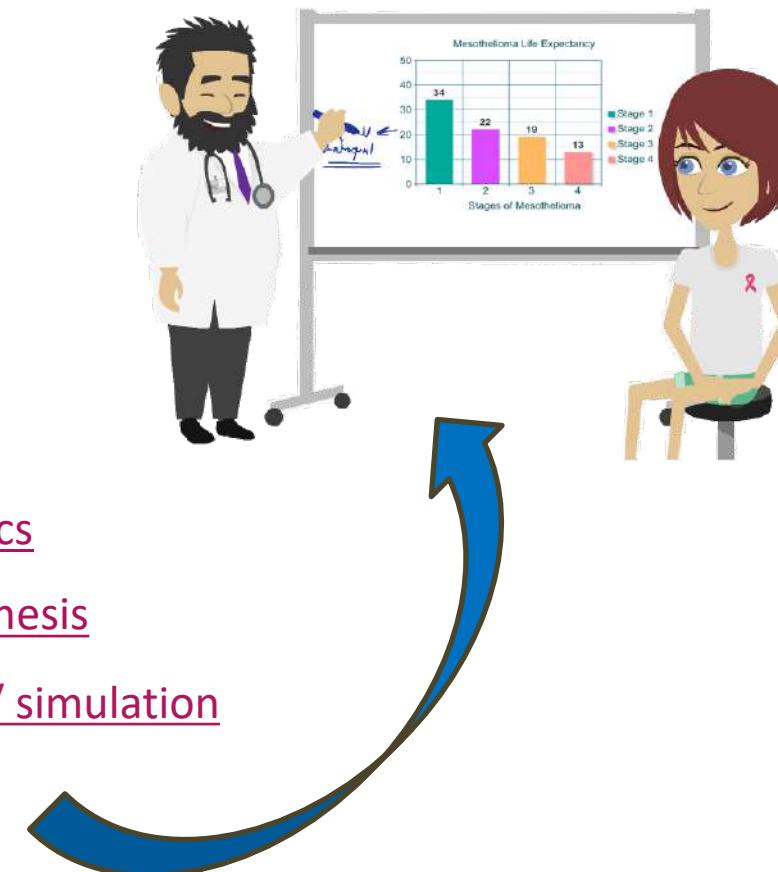
Ethics & Dynamics for the benefit of the Patients

– Ethics

- Traceability – [Semantics](#)
- References – [Challenges](#)
- Validation – [Clinical assessment](#)

□ Dynamics: Understand and Prognose

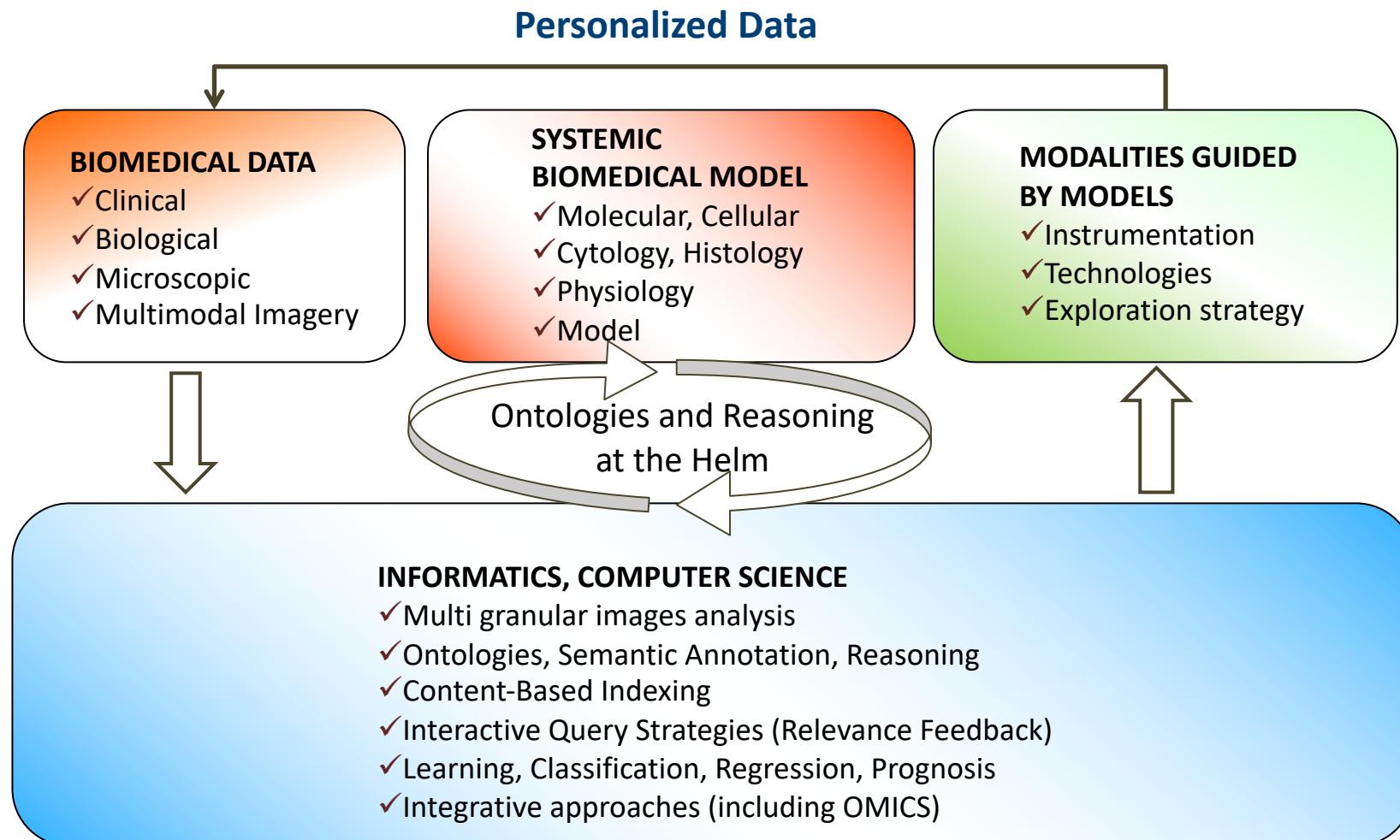
- Multimodal data integration – [Imaging & Omics](#)
- Dynamic models – [Morphogenesis / Pathogenesis](#)
 - [Assessment / estimation / simulation](#)
- Prognosis - [Life expectancy estimation](#)



The big picture

Integrative microscopy driven by the models

The key role of the image – validation, visualisation



THANK YOU

