A Set of Advanced Tools to Analyze Virtual Slides

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Company Profile

- ⇨ **Founded in 1995**
- ⇨ **French SA (corporation)**
- ⇨ **Close partnership with Amerinex Applied Imaging, Inc., New Jersey, USA**
- ⇨ **Located in Normandy, France**
- ⇨ **65% of sales made outside France**
- ⇨ **Developers of the Aphelion™ Imaging Software Suite**
- ⇨ **Custom Engineering Work***
- ⇨ **Training and consulting in the field of Imaging**
- ⇨ **Worldwide product distribution**

* ADCIS was awarded the "***Organisme au titre du Crédit d'Impôt Recherche (CIR)***" accreditation delivered by the French Minister of Higher Education and Research

Fields of Expertise

- **Expertise in the fields of Image Processing and Image Analysis**
  - Image filtering, Edge Detection, Texture Analysis, Mathematical Morphology, Measurement, Calibration, Object Processing, etc.
- **Statistical Analysis & Data Classification**
- **Hardware interface**
  - HiRes cameras
  - Optical microscopes and motorized stages
  - Scanning electron microscopes
- **Database management**
- **Secure communication (patient data)**
- **Annotation software product to share expertise**

Research Application Fields

ADCIS is involved in different research projects taking benefit of ADCIS expertise:

- ⇨ **Large Image (Virtual Slide) Processing**(1)
- ⇨ **3D Image Processing**
- ⇨ **3D Surface Model**
- ⇨ **Image Segmentation**
- ⇨ **Classification**(2) **and Statistical Analysis**(3)
- ⇨ **Image Registration**

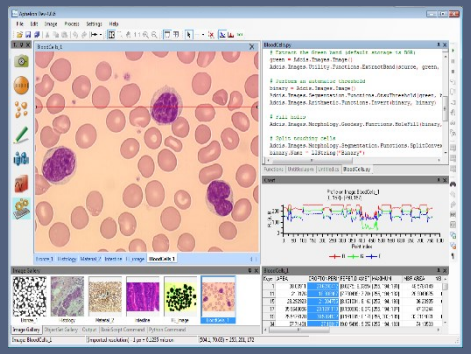
1. Partnership with the PathImage team, University of Caen and Centre François Baclesse
2. Partnership with LaTIM (Univ. Brest/Telecom Bretagne/INSERM)
3. Partnership with CBIO, Mines ParisTech

Customer References

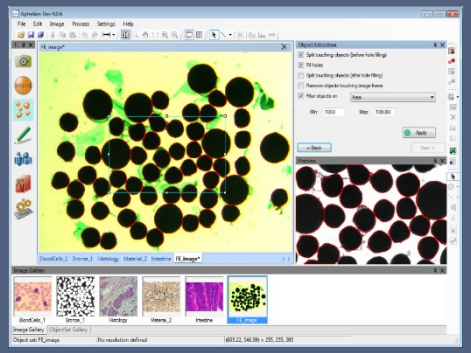
- Aerospace
- Food Industry
- Automotive
- Biology
- Chemistry
- Quality Control
- Cosmetics
- Defense
- Electronics
- Energy
- Geology
- Materials
- Pharmacology
- Research
- Remote Sensing …

The **Aphelion**™ Imaging Software Suite

- **LAB - Entry-level product, for Lab technicians**
  - To identify, calibrate, extract, and measure objects of interest



- **DEV - For application developers**
  - Work efficiently with user-configurable GUI
  - Rapidly prototype & deploy imaging projects
  - Create stand-alone, image-based applications
  - Embed Aphelion libraries as .NET components



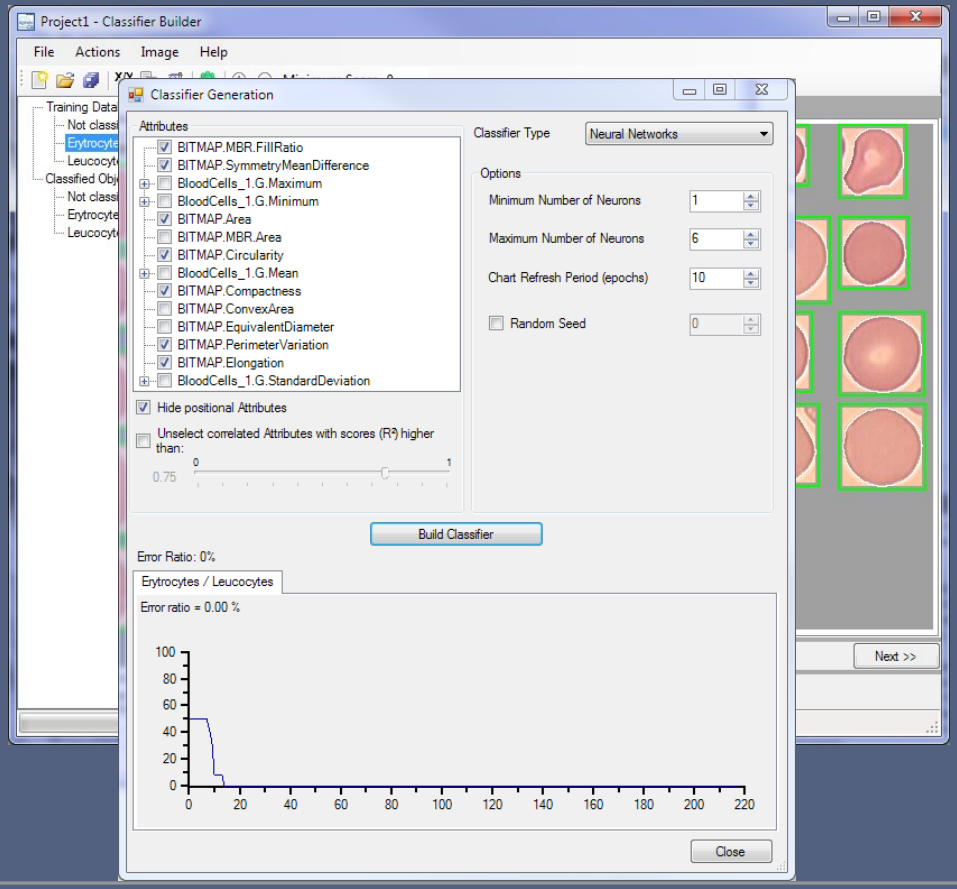
- **SDK - For programmers and OEMs**
  - To integrate Aphelion imaging capa-bilities in stand-alone systems

Aphelion™ Suite: Application Fields

- **3D Image Processing, Analysis, and Visualization**
- **Classification Tools for Analysis and Understanding** (easy-to-use graphical user interface to learn, train, and generate classifiers based on Fuzzy Logic, Neural Networks, and Random Forest methods)
- **Tools for Microscopy** (driver to automate motorized stage, drivers for scanning electron microscopes, driver for energy-dispersive detectors, adaptive filter to improve signal-noise ratio preserving the quantitative information, filter for STEM-EDS images, high-throughput image support)
- **Acquisition Device Interfaces** for industrial and scientific cameras
- **Segmentation Tools for color images**
- **Image Registration Tools**
- **Image Annotation Tools**

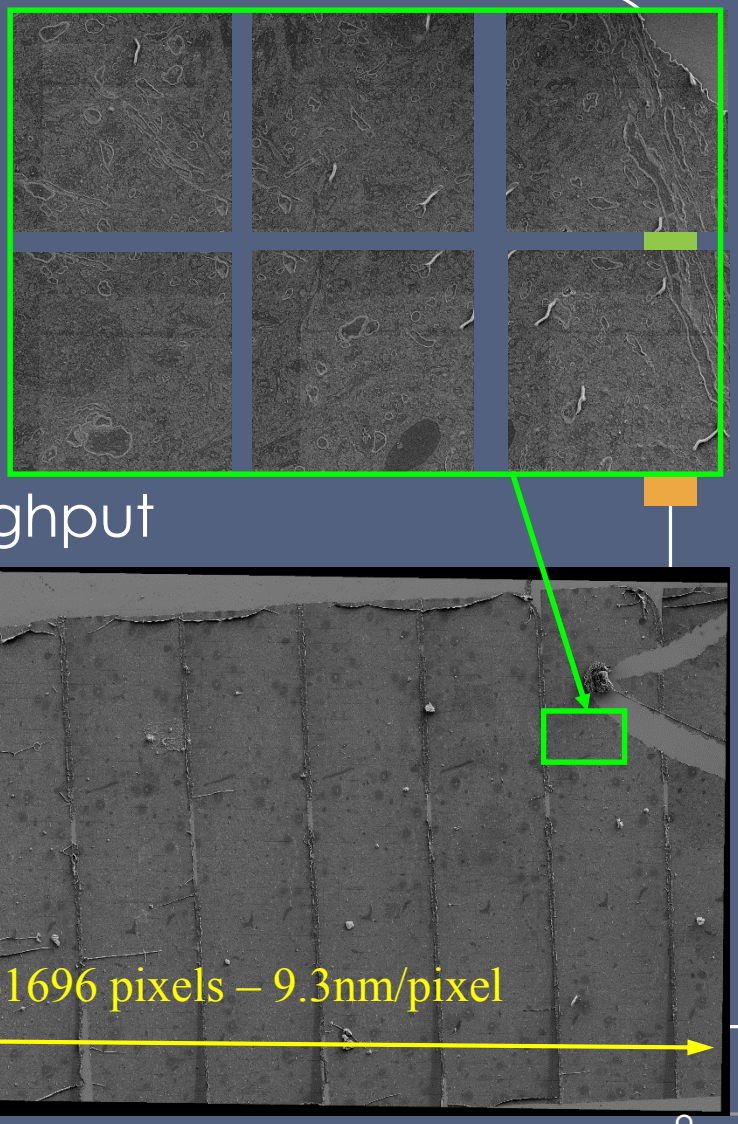
Classifier Builder

- **Learning phase** (manually classify objects)
- **Select measurements** (automatic or manual)
- **Train the classifier based on Fuzzy Logic, Neural Network, or Random Forest methods**
- **Save computed classifier** (to be later applied to a new set of images)



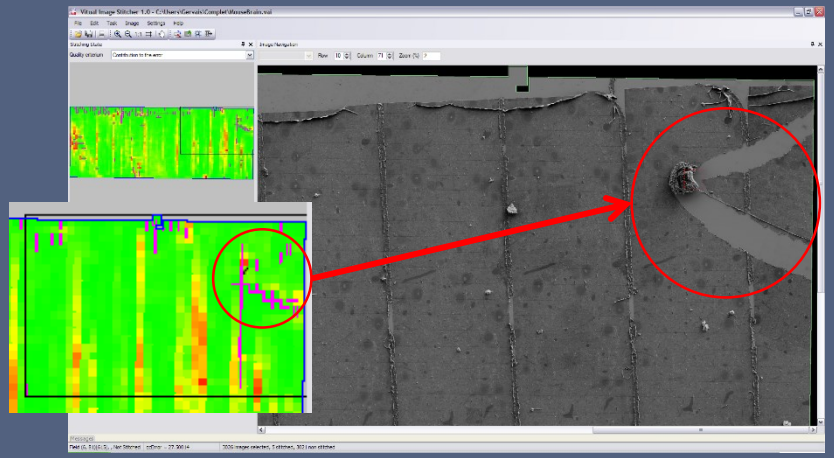
Tools for Microscopy – 1

- **Virtual Image Capture:**
  High resolution image capture in the field of microscopy
- **Virtual Image Stitcher:**
  Automatically stitch images to create a virtual slide or a large sample ready for high throughput imaging

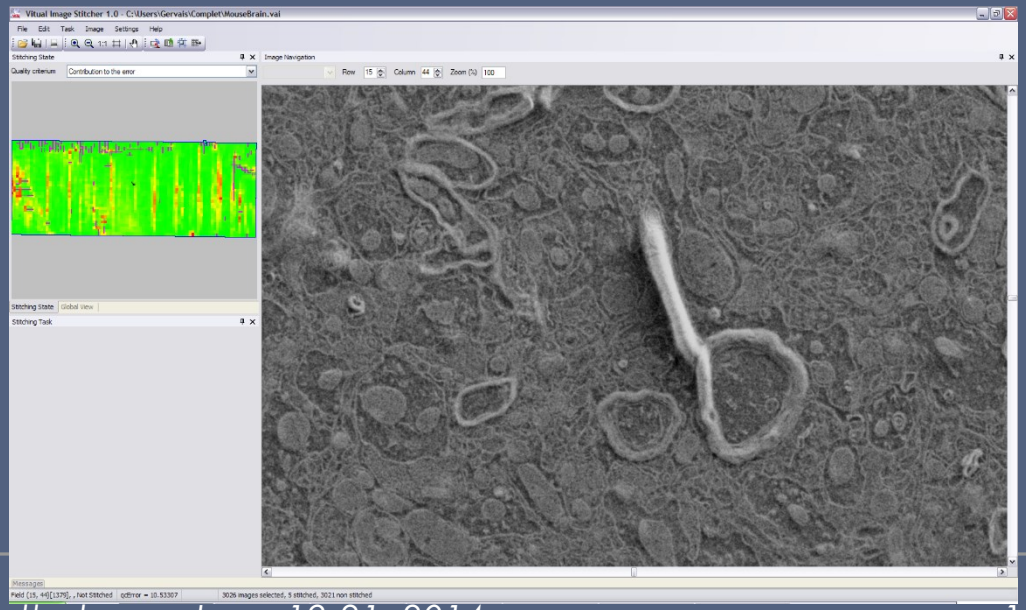


Tools for Microscopy – 2

- Global map to evaluate the automated stitching



- Accurate manual positioning based on correlation values



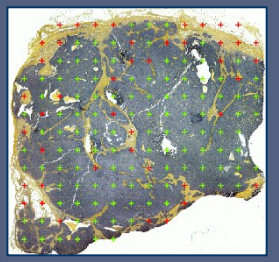
- Visualization tools to navigate inside the virtual image

Stereology Analyzer

Stereology is the scientific study of geometrical relationship between a structure which exists in the 3D space and images of the same structure defined in the 2D space (e.g., images of sections or projections)

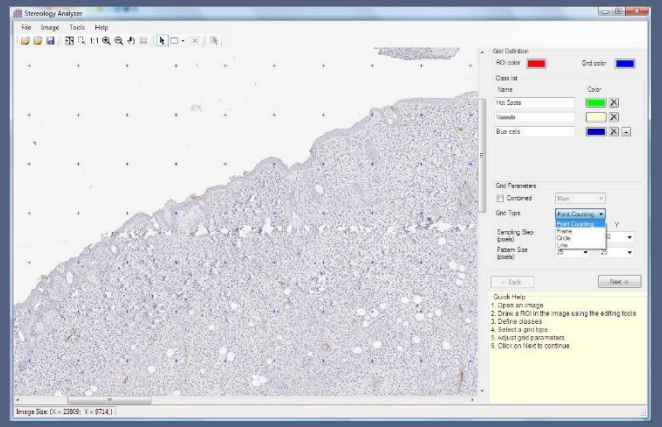
⇨ **Stereology Analyzer lets the user:**

- Define the grid type and spacing
- Manually select the object inside the structure



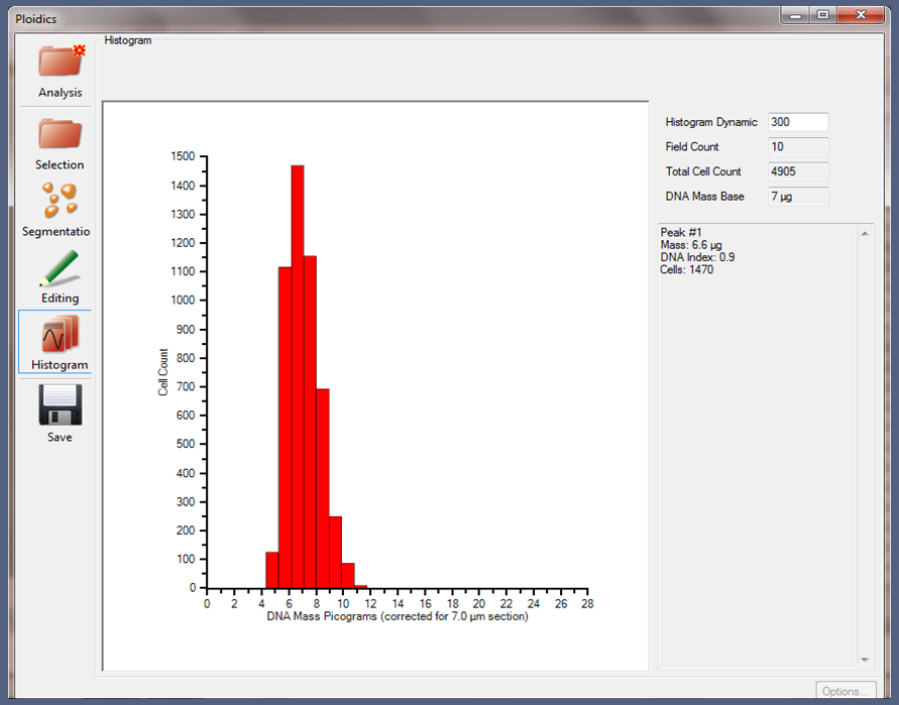
⇨ **Stereology is designed to:**

- Perform manual analysis based on statistical methods
- Quantify tumors even in complex images
- Validate automatic image processing methods



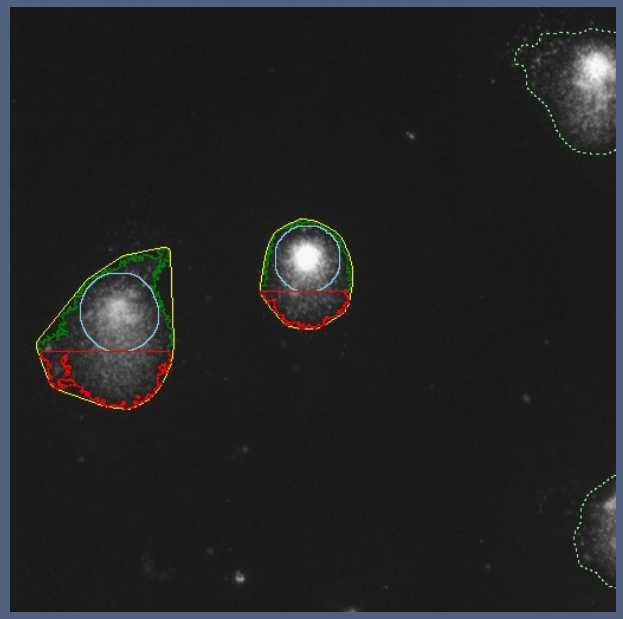
Ploidics

- **DNA Quantification in oncology Field** *(e.g., Lung, Breast, Prostate Cancers)*
  - Process control slides as reference images and then patient data
  - Compute DNA histograms
  - Export all measurements

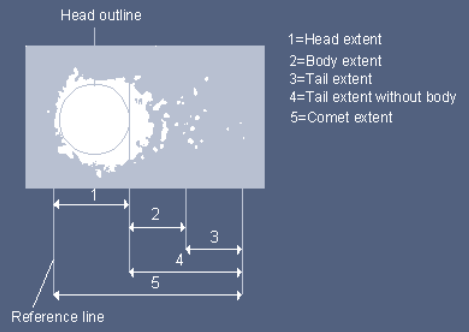


Comet Extension

Comet Assay (SCGE Assay)
Automatic quantization of damages due to genotoxic agents



- ⇨ **Configurable software**
- ⇨ **Automatic detection of comets**
- ⇨ **Automatic computation of measurements:**
  Extent, Total Intensity, Total Area, Tail extent, Tail extent moment, Tail olive moment, Tail integrated intensity, Tail intensity ratio, Tail Area, Tail Break number
- ⇨ **Batch processing mode**



Proliferation Evaluation of Breast Tumor – 1

- Slide sample from a breast biopsy
- Immunohistochemical assessment of proportion of cells stained brown with nuclear antigen Ki67, the most widely used method to compare proliferation in tumor samples

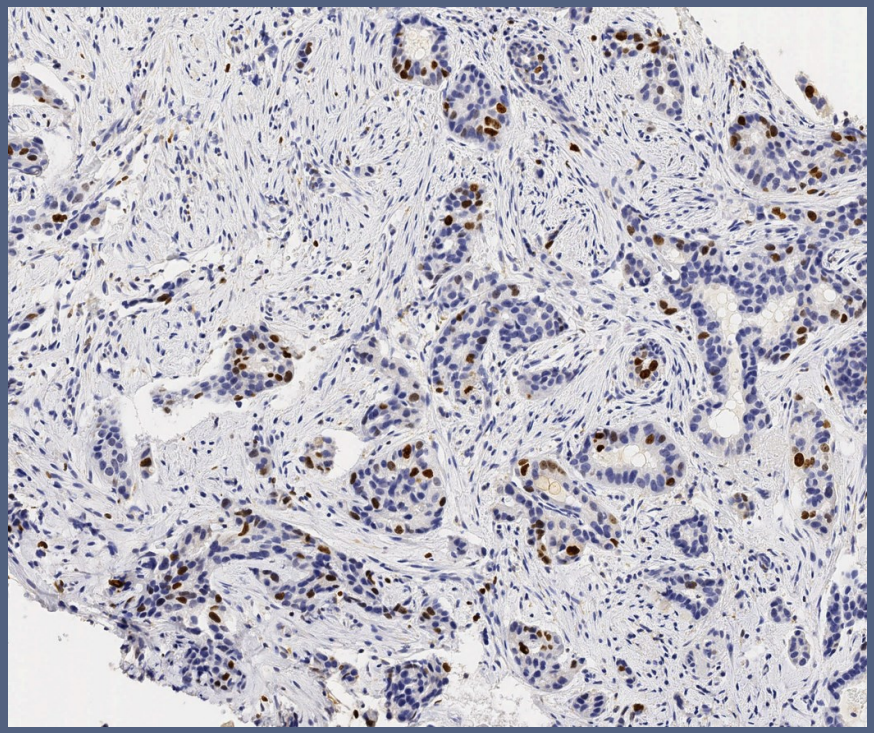


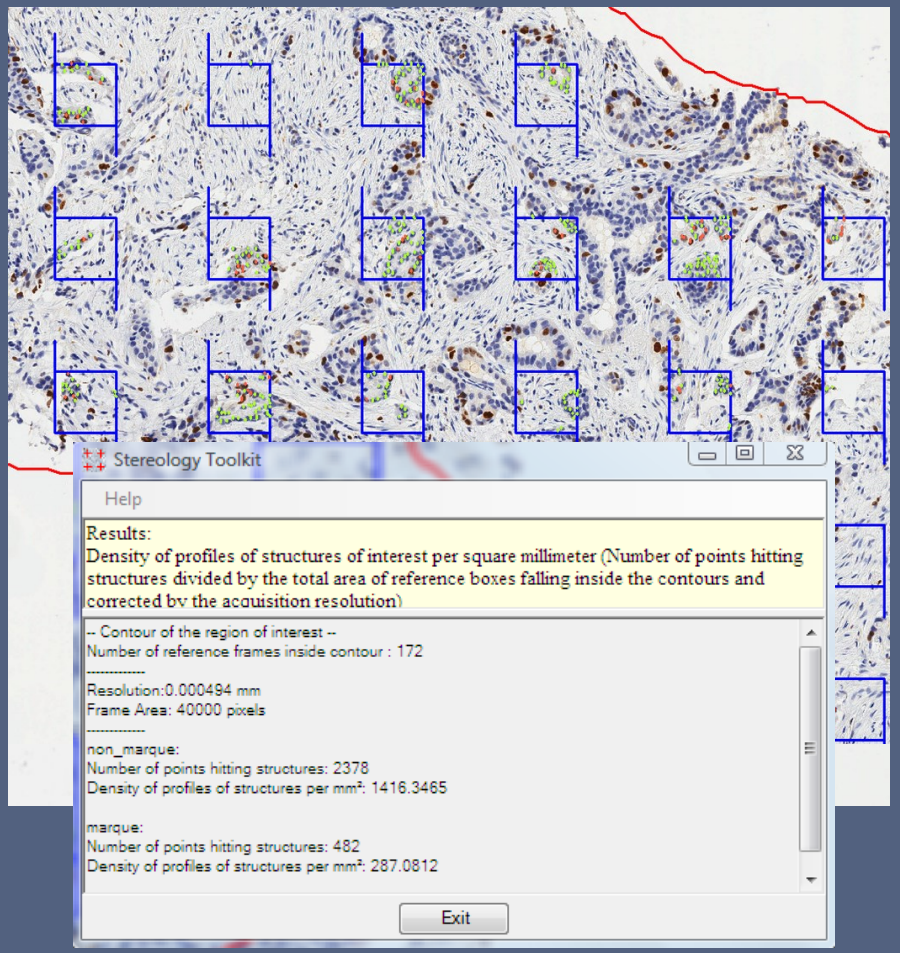
Image courtesy of PathImage team, University of Caen and Centre François Baclesse

Proliferation Evaluation of Breast Tumor – 2

- ⇨ Breast biopsy slide acquired using a high throughput system at x20 magnification
- ⇨ Sample size is 15.12 x 12.63 mm²
- ⇨ Pixel size is 0.494 µm
- ⇨ Tiled image size is 30,600 x 25,557 pixels
- ⇨ This virtual slide (tiled image) can either be manually analyzed using Stereology Analyzer or automatically analyzed using Aphelion™ Dev

Proliferation Evaluation of Breast Tumor – Manual Analysis

- **Analysis using Stereology Analyzer**
- **User defines:**
  - Regions of Interest
  - Method of counting (e.g., Frame, Point)
  - Grid spacing. In this case, the Frame counting method is selected
- **User manually highlights biomarkers in each frame**
- **Number of marked cells is automatically computed**



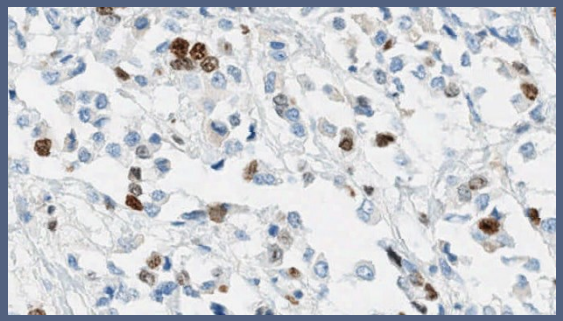
Analysis report courtesy of Myriam Oger (PathImage team)

Proliferation Evaluation of Breast Tumor – Automated Analysis – 1

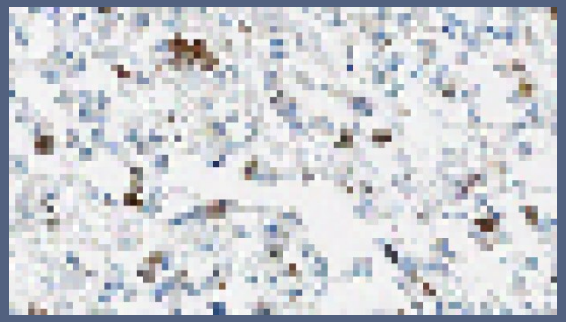
- **Automated analysis based on a sequence of image processing operations developed using Aphelion™ Dev**
- **Strategy to process a very large image**
  - Decimate the large image into a set of "power of 2" images to reduce the size of the image and speed up the processing speed, but keep structures of interest
  - Extract the structure of interest in an automatic manner (Tissue and proliferating marked cells in the example)
  - Once all structures of interest are detected and converted into "*Regions of Interest*", process each ROI individually, and convert the ROI back to its full resolution

Image Decimation – 1

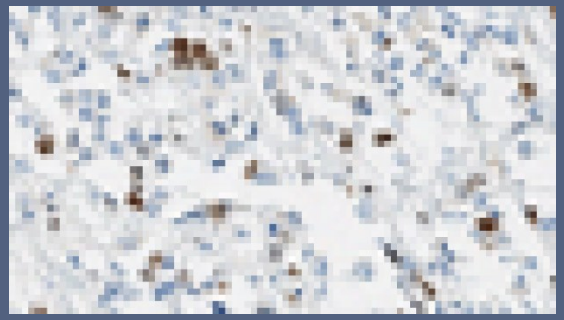
Full resolution image



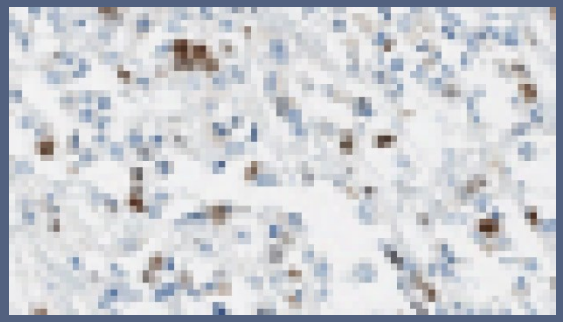
Nearest neighbor



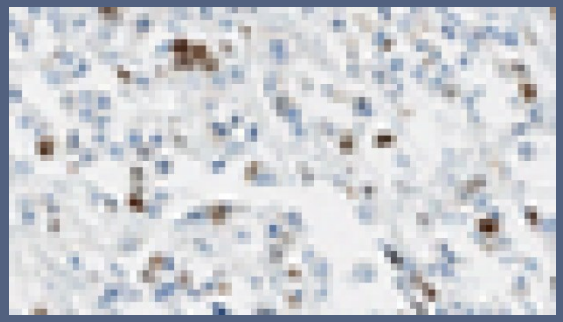
Wavelet



1/8 down-scaling



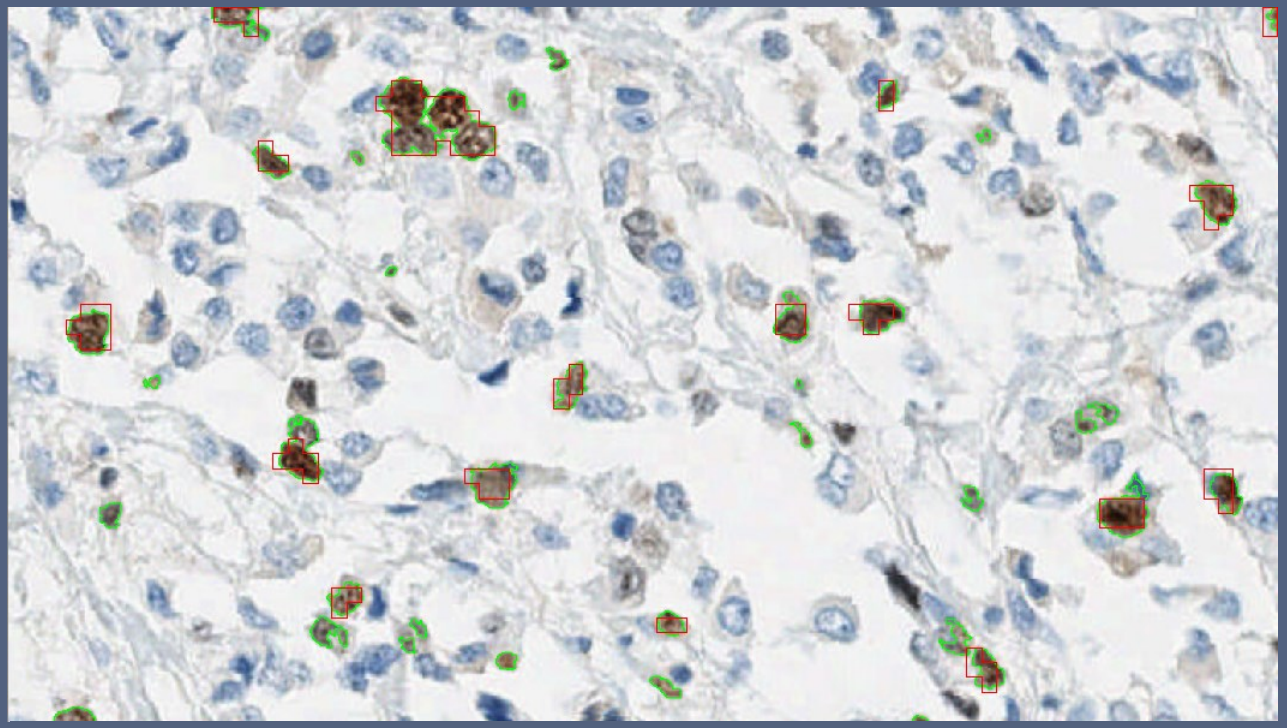
Bilinear



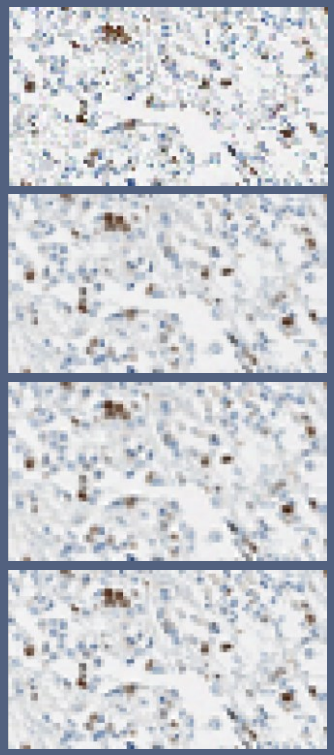
Bicubic

Image Decimation - 2

Marked cell detection on images down-scaled using different decimation techniques

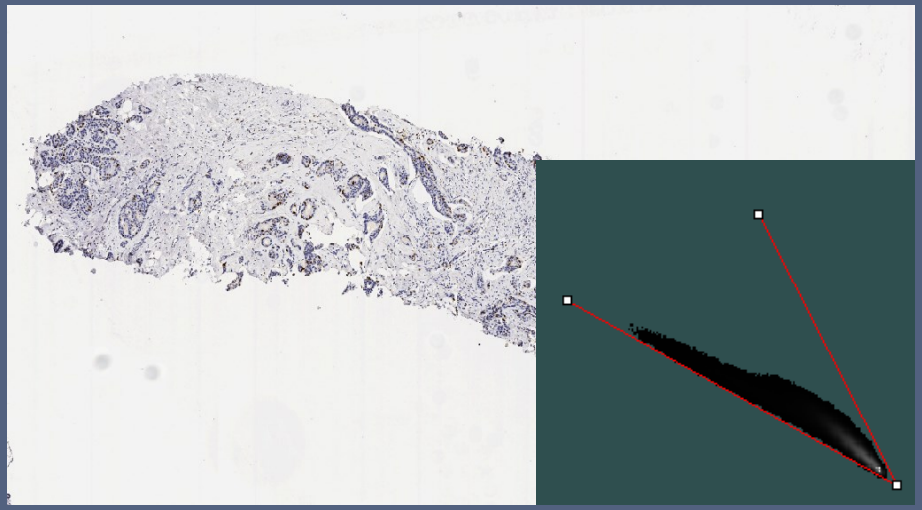


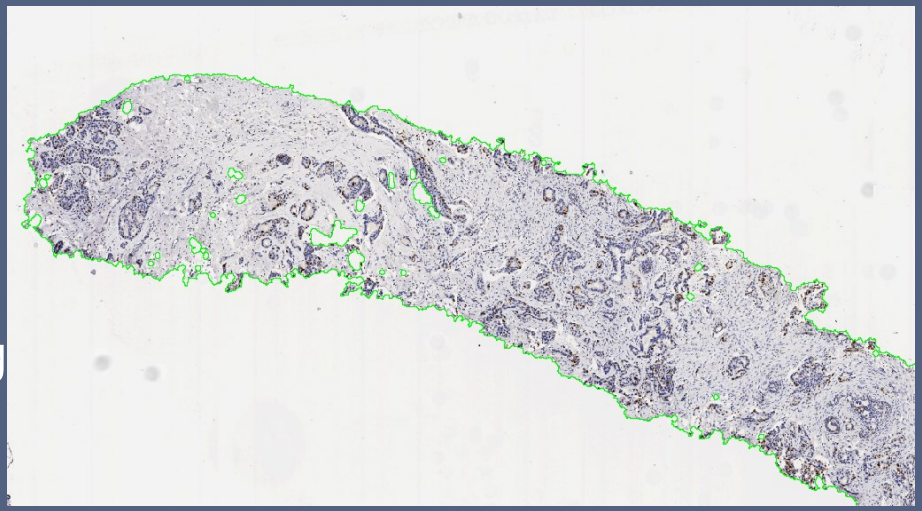
Cell detection in wavelet image



Proliferation Evaluation of Breast Tumor – Automated Analysis – 2

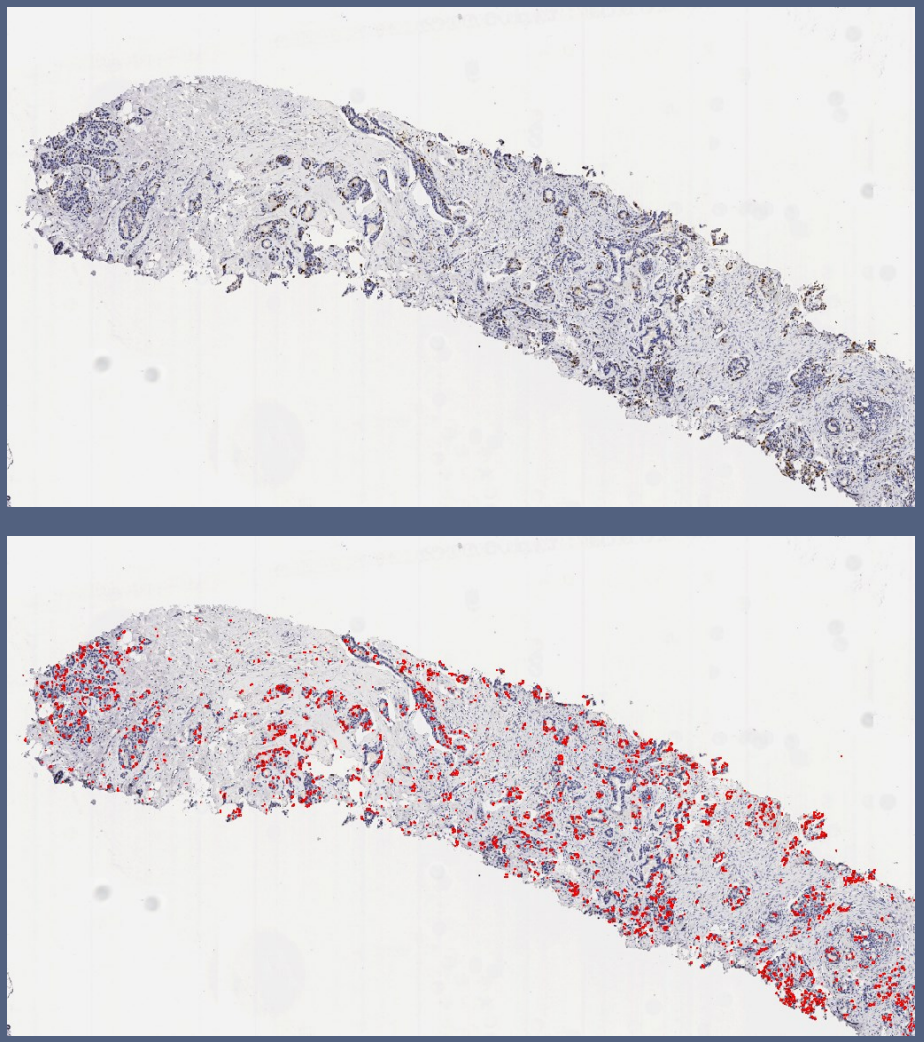
- **Extraction of the tissue area from the decimated image** (1/8-scaled image)
  - Color transform to get normalized stained image
  - Extract the green channel
  - Perform a threshold
  - Perform a morphological closing
  - Perform a hole filling





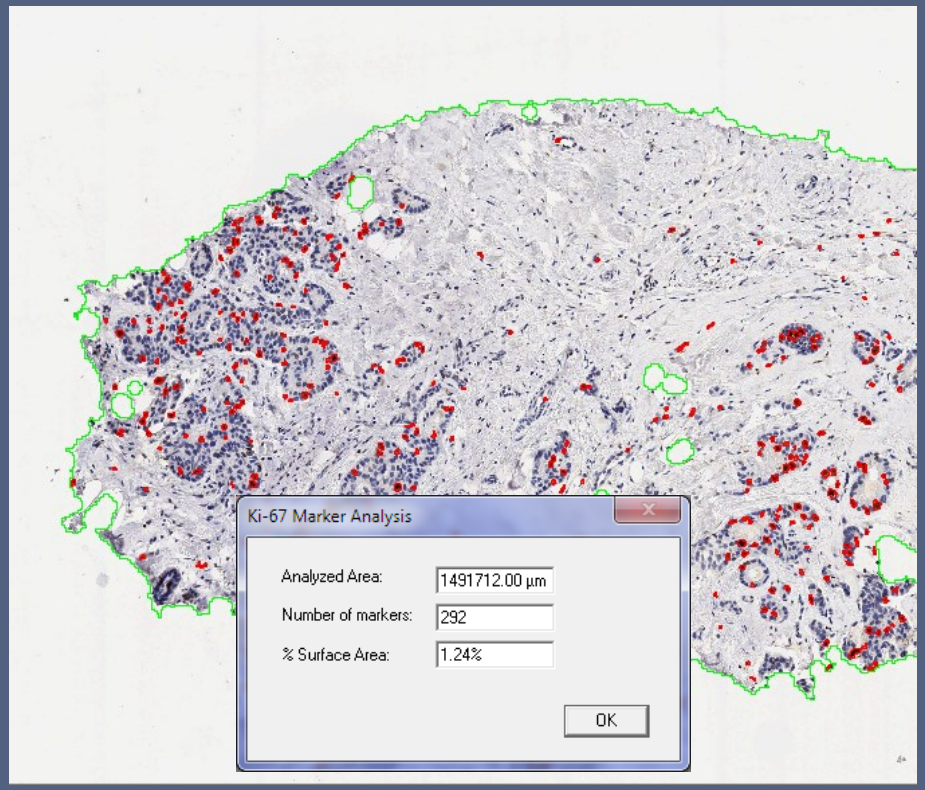
Proliferation Evaluation of Breast Tumor – Automated Analysis – 3

- **Extraction of the proliferating marked cells from the decimated image** (1/8-scaled image)
  - Extract the blue channel
  - Perform a threshold
  - Convert to an objectset
  - Filter objects based on the mean intensity in the red band



Proliferation Evaluation of Breast Tumor – Automated Analysis – 4

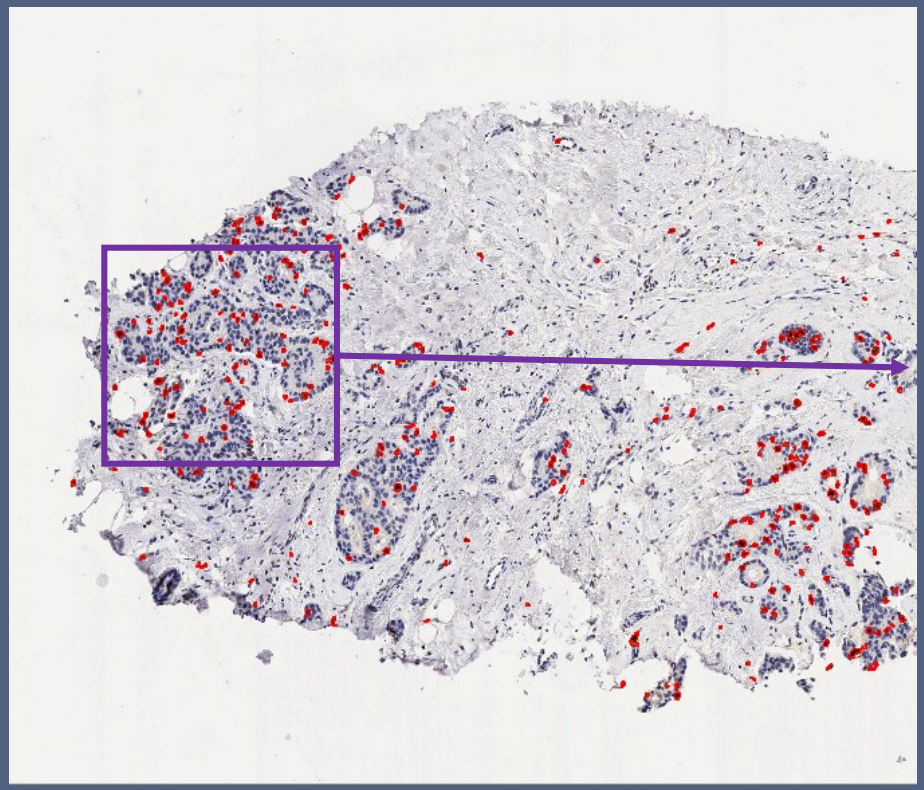
- **Extraction of the proliferating marked cells from the high-resolution image**
  - Upscale the proliferating marked cells detected from the decimated image
  - Color transform to get normalized stained image
  - Color transform to enhance the color difference
  - Perform a threshold on the red channel
  - Perform morphological transforms
  - Convert to an objectset
  - Filter objects based on the surface area
  - Compute measurements

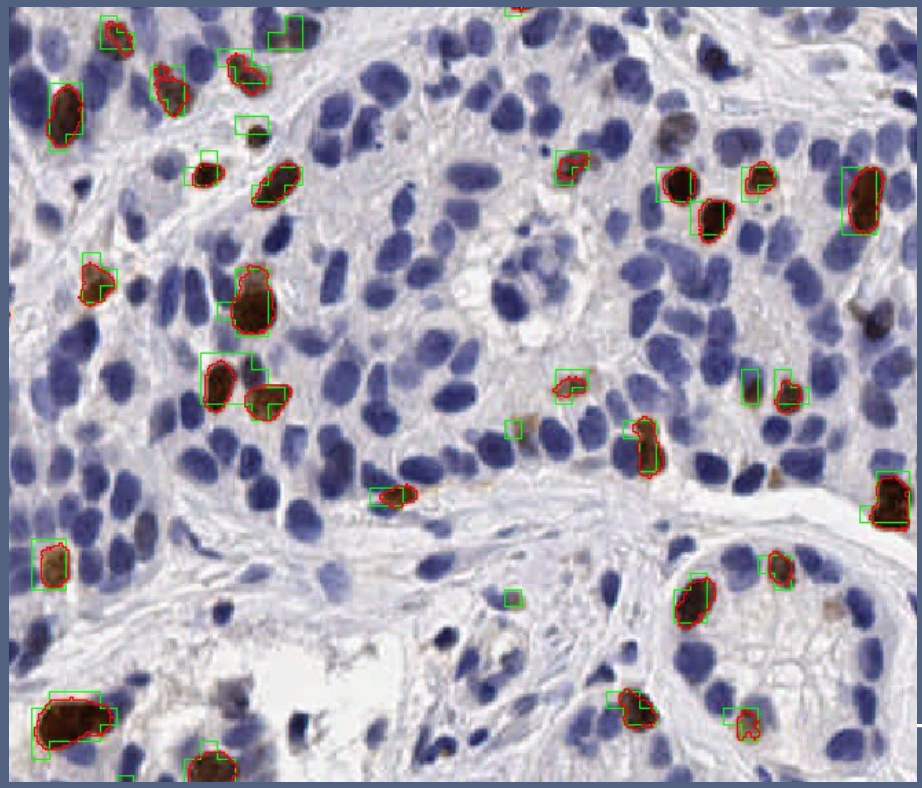


Proliferation Evaluation of Breast Tumor – Automated Analysis – 5

⇨ **Zoom in a local detection**

Captured image with detected proliferating marked cells at high and low resolution





Conclusion

- Processing large images means facing new challenges in terms of number of pixels to be captured, processed and then analyzed generating billions of measurements that need to be interpreted
- Powerful software products should support the processing of very large images on regular PCs
- High Throughput imaging combined with image processing and analysis can dramatically help pathologists to share their expertise with imaging developers and provide very sophisticated tools
- Future development will support Cloud based architecture