# Automated Mitosis Detection in Color and Multi-spectral High-Content Images in Histopathology: Application to Breast Cancer Grading in Digital Pathology

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# Outline

- Context
  - Digital Pathology
  - Breast Cancer Grading
- Research Contributions
  - Mitosis Detection Framework for Color Images
  - Mitosis Detection Framework for Multispectral Images
  - Dynamic Sampling Framework for WSI analysis
- Conclusion & Future works

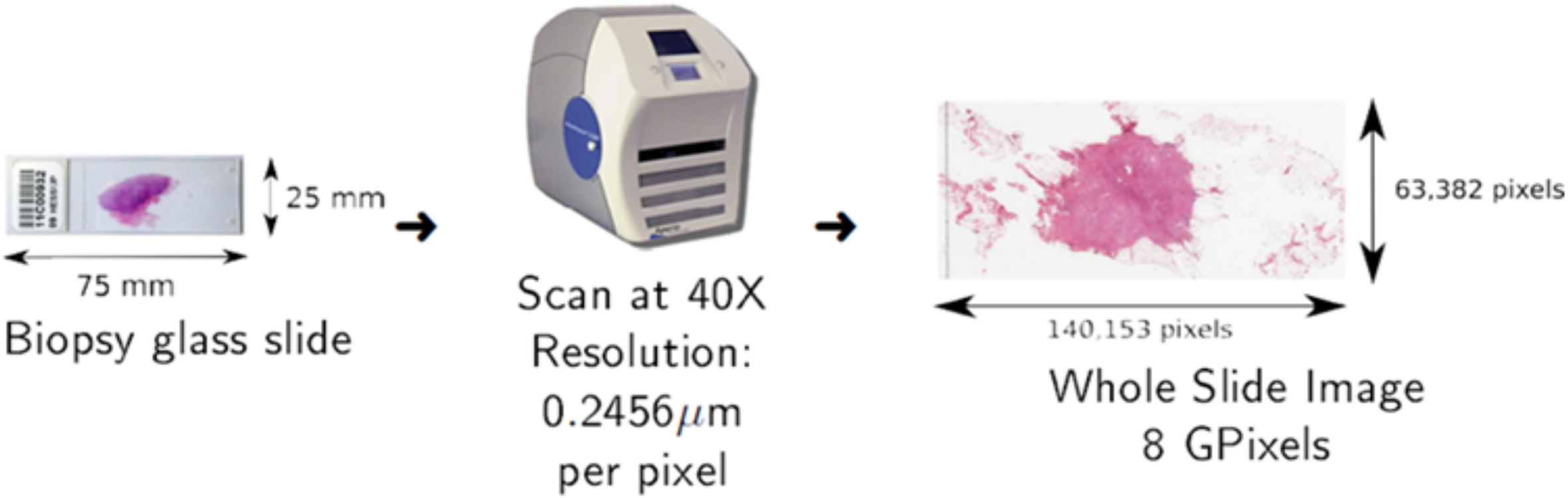
# Digital Pathology

## Slide Preparation

- Dissection / extraction
- Chemical processing
- Sectioning
- Staining - Hematoxylin & Eosin (H&E), Immunohistochemistry (IHC)

## Imaging & Visualization

- Microscope
- Slide Scanner



# Pathology vs Digital Pathology

## Pathology

- Manual analysis is labor intensive work
- Inter and intra-reader variations

## Digital Pathology

- Location independence
- Virtual slide sharing with clinicians
- Enables automated analysis techniques

# Breast Cancer Grading

## Breast Cancer

- Origin – Ductal, lobule or stromal tissues
- Proliferation – Carcinoma in Situ, Invasive
- Worldwide, Breast Cancer accounts for 22.9% of all cancer in women [1]
- 1 in 8 US women estimated to develop Invasive Breast Cancer over the course of her lifetime [2]

## ➢ Nottingham Grading System for Invasive Breast Cancer

- International grading system recommended by the World Health Organization
- 3 Criteria [3]:
  1. Gland Formation
  2. Nuclear Atypia / Pleomorphism
  3. Mitosis Count


1) Peter Boyle, et al. World cancer report 2008. IARC Press, International Agency for Research on Cancer, 2008.
2) US Breast Cancer Statistics, 2013 (http://www.breastcancer.org/symptoms/understand_bc/statistics).
3) C W Elston & I O Ellis, Pathological prognostic factors in breast cancer. Histopathology, 19(5):403-410, 1991.

# Breast Cancer Grading

## Mitosis Count

- Scan sections to find area with most mitotic activity (often at tumor edge)
- Count mitosis in 10 consecutive high power fields (HPFs) of selected area
- Skip fields with few carcinoma cells or obvious necrosis

- Score 1 ( < 10 Mitosis )
- Score 2 ( 10 ~ 19 Mitosis )
- Score 3 ( > 19 Mitosis )

- HPF is an area of microscope field diameter of 58mm (or a digitized square image 512 * 512 $\mu m^2$).

# Research Contributions

1. State-of-the-art in nuclei detection, segmentation and classification
2. Color Framework
   - Selection of color channels for different tissue component
   - Intensity (1st order statistical) and texture (2nd order statistical) features
   - Region vs patch based texture features analysis for mitosis discrimination
   - An inspection of over-sampling method for balancing the training set
3. Multispectral Framework
   - Spectral absorption responses of different tissue components
   - Multispectral-statistical features in selected Spectral Bands (SBs)
4. Whole Slide Image Analysis Framework
   - Robust strategy to explore WSI using a dynamic sampling framework
   - Extension of ITK QuadEdgeMesh data structure to handle duality of meshes
5. Proof of concept in MICO platform

# Dataset

## MITOS Benchmark (ICPR 2012)

- 5 breast cancer biopsy slides (H&E stained) provided by [4]
- In each biopsy slide, 10 HPFs at 40X magnification are selected
- 35 Training HPFs  226 mitotic nuclei (69.3%)
- 15 Evaluation HPFs 100 mitotic nuclei (30.7%)

| Scanners | Resolution per pixel | HPF dimension to cover area of $512 \times 512\ \mu m^2$ |
|---|---|---|
| Aperio Scanner | 0.2456 µm | 2084 ×2084 pixels |
| Hamamatsu Scanner | $0.2273 \times 0.22753\ \mu m$ | 2252 ×2250 pixels |
| Multispectral Microscope | 0.185 µm | 2767 × 2767 pixels |

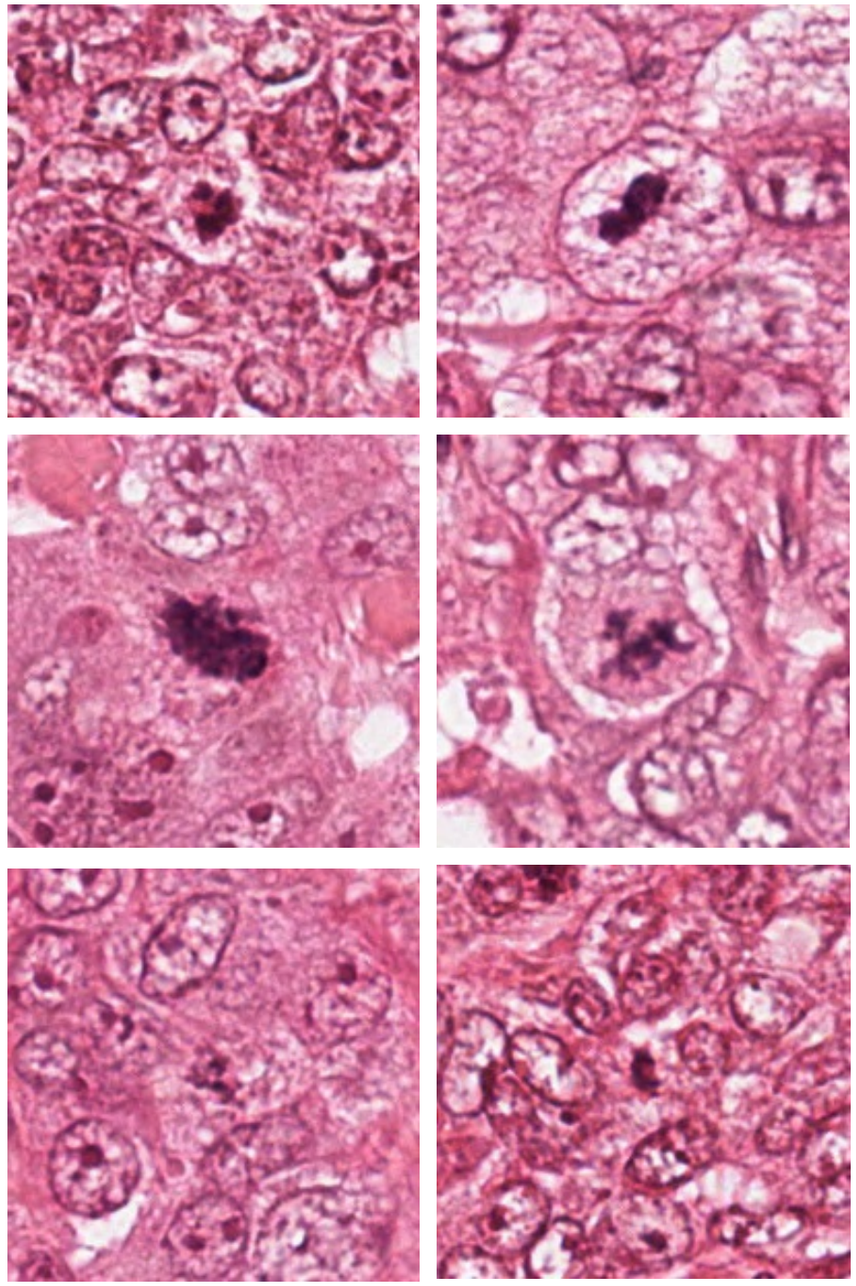
4) Team of Prof. Frederique Capron, head of Pathology department, Pitie-Salpetriere Hospital Paris.

# Mitosis Detection – A Challenging Problem

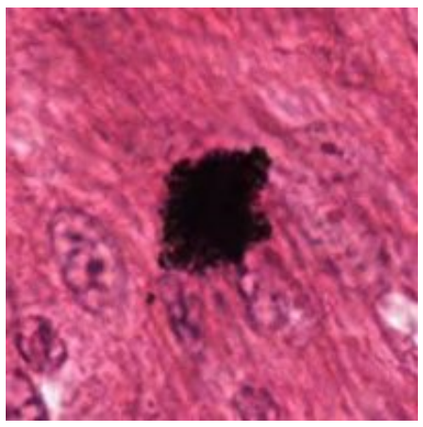
## Mitosis Detection – A Challenge

- Mitotic nuclei have
  - large variety of shape configuration
  - Texture variation
  - Low frequency of appearance in HPF
  - Similarity with other types of objects

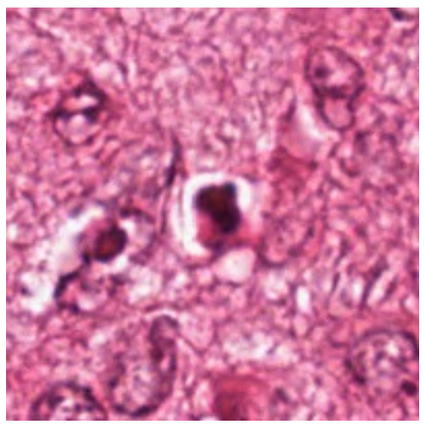
  ( e.g., apoptosis, necrosis, dust particles etc. )



Mitosis



Dust particles



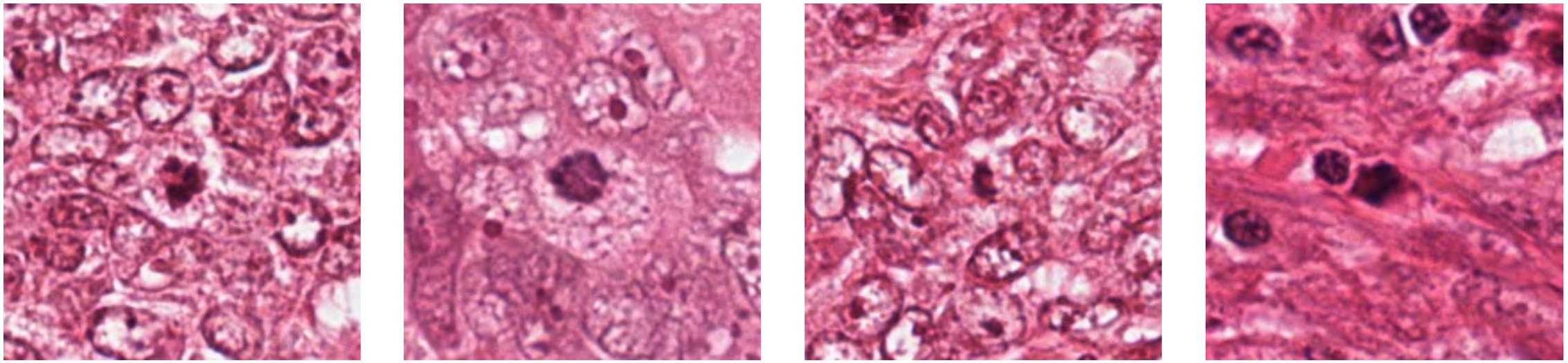
Apoptosis

# Mitosis Detection – A Challenging Problem

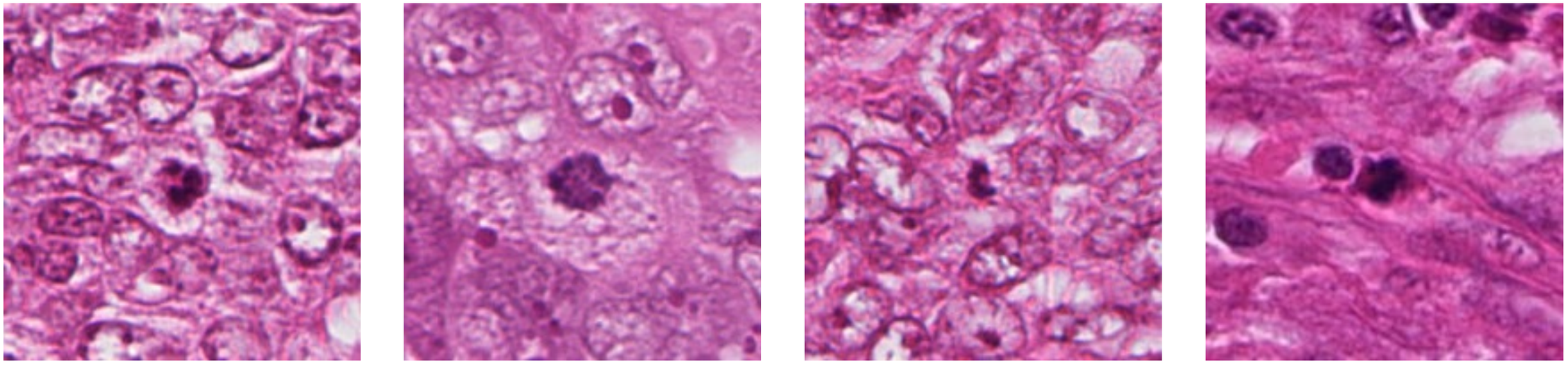
## Mitosis Detection – A Challenge

- Which one is mitotic nuclei and which is not?

Aperio



Hamamatsu

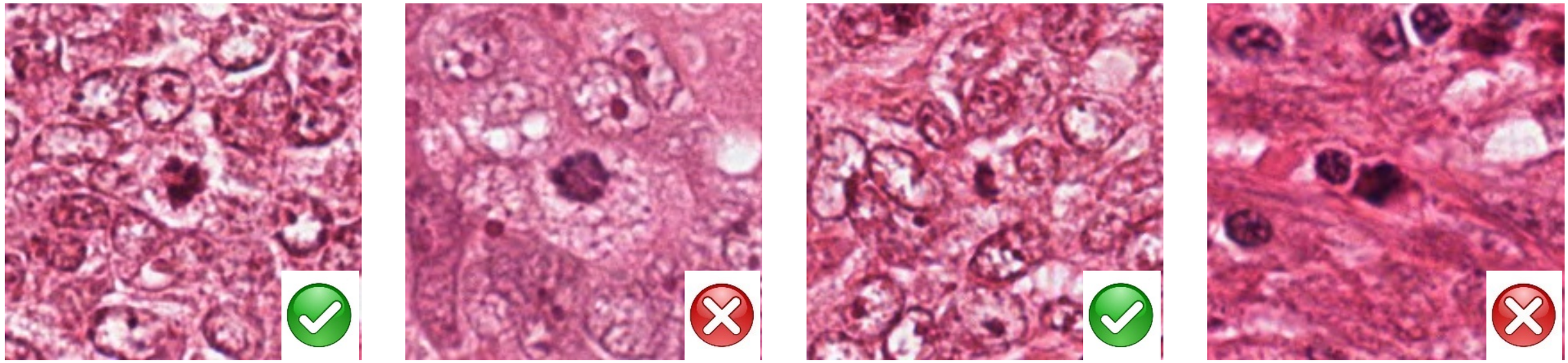


# Mitosis Detection – A Challenging Problem

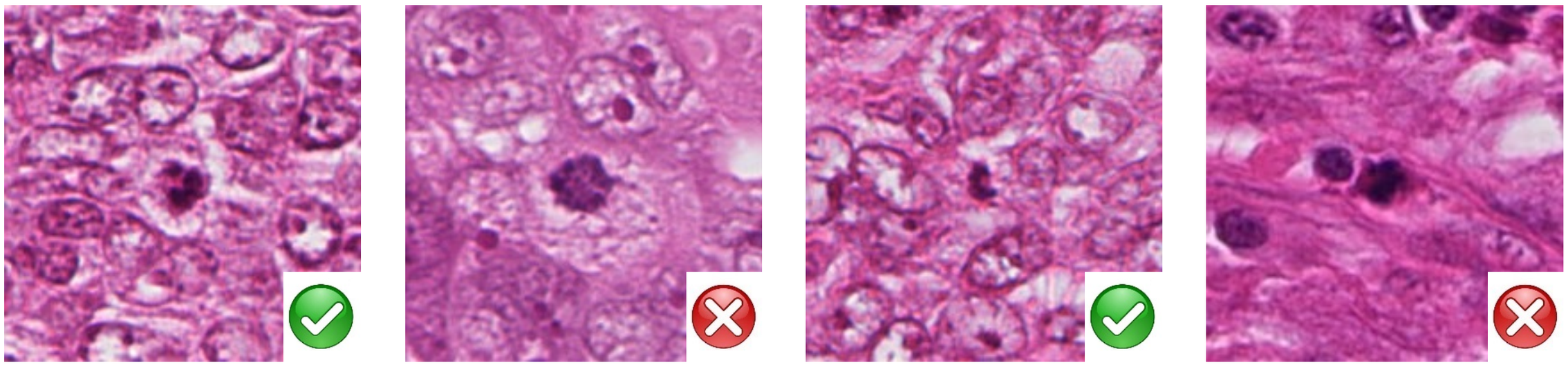
## Mitosis Detection – A Challenge

- Which one is mitotic nuclei and which is not?

Aperio

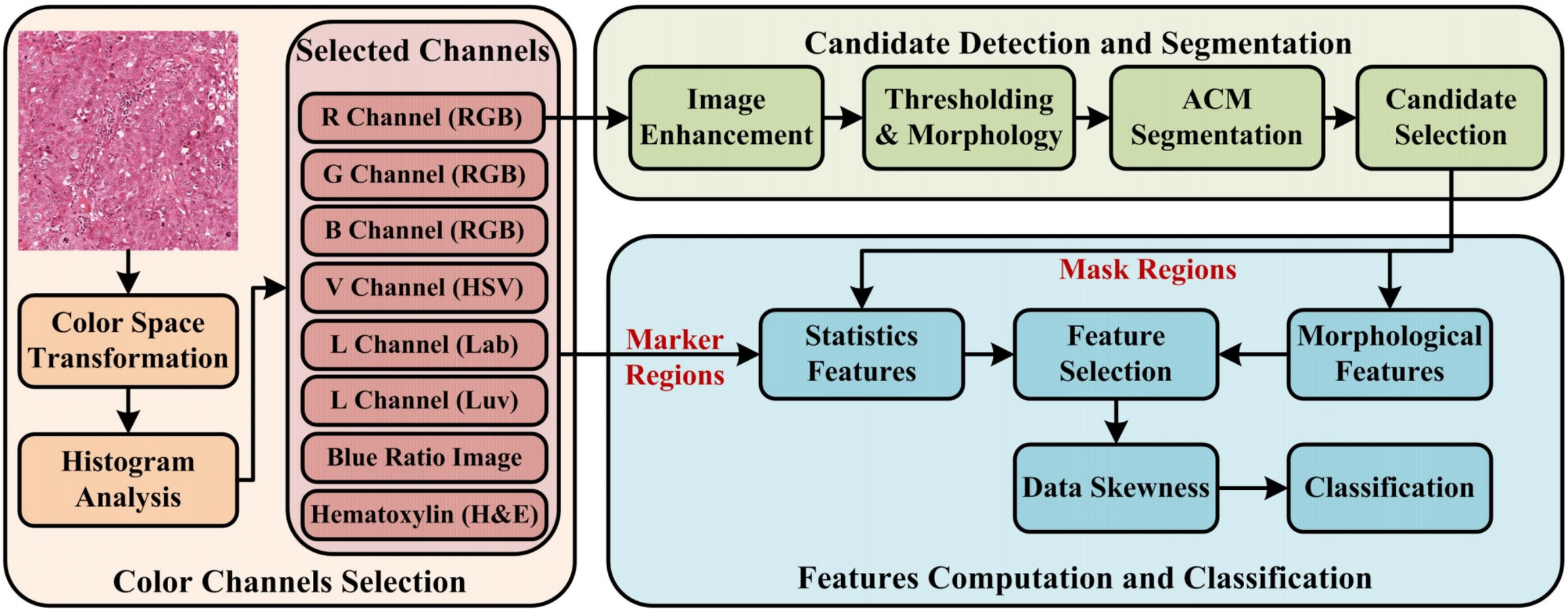


Hamamatsu



# Mitosis Detection in Color Images

## Intensity, Texture & Morphology based Mitosis detection in Color images (ITM$^2$C) Framework

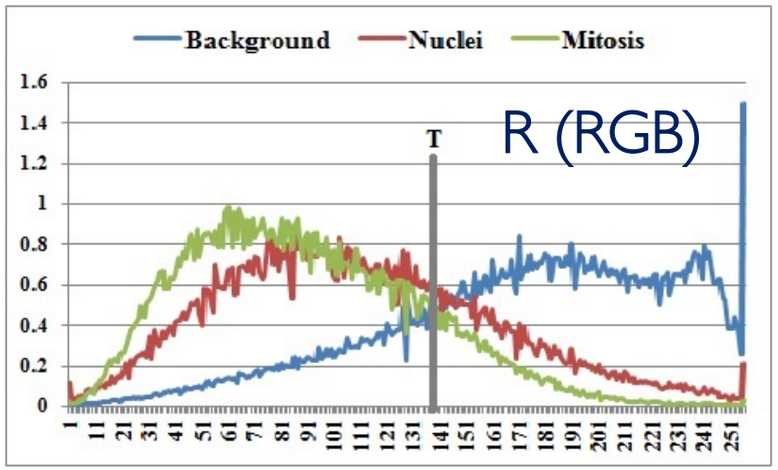


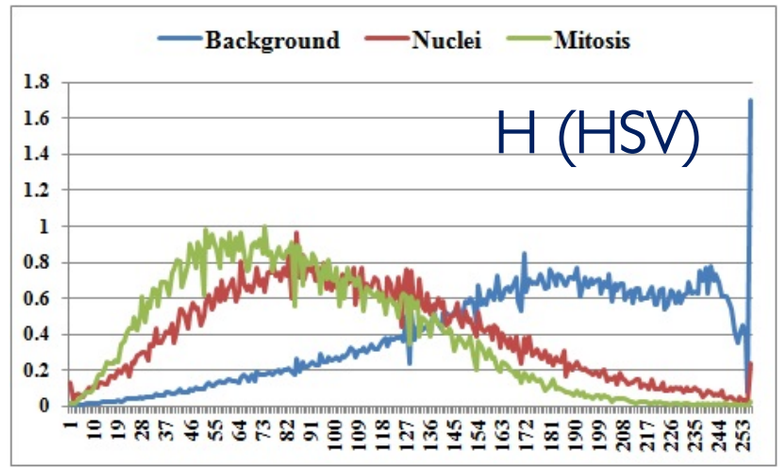

ITM$^2$C Framework

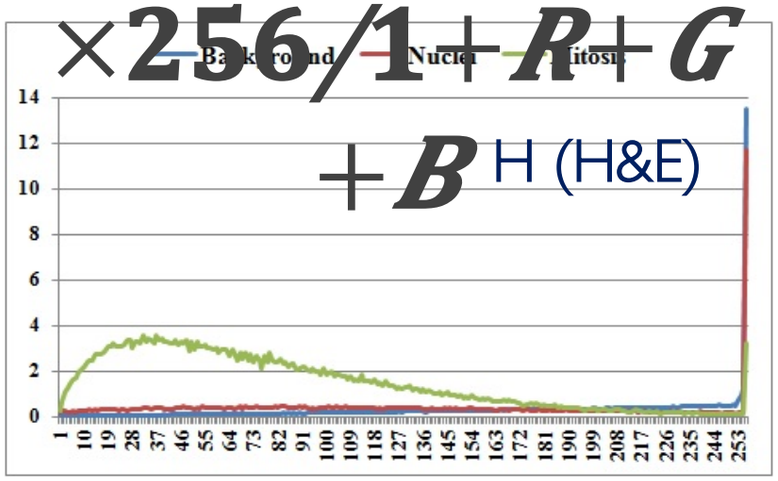
# Mitosis Detection in Color Images

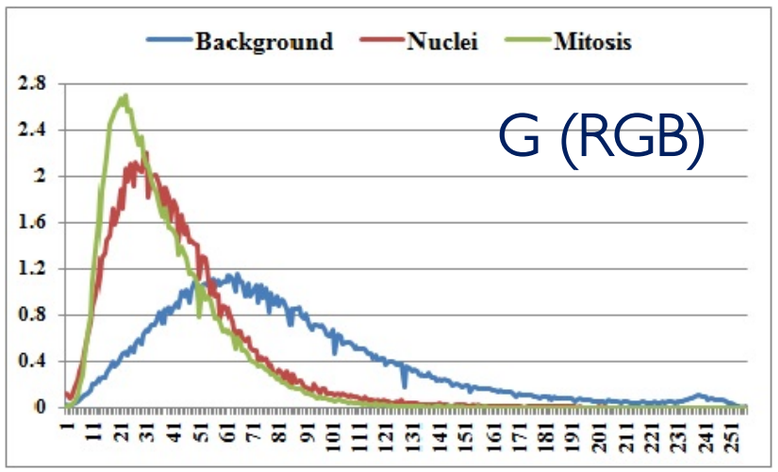
## Histogram of Selected Channels on Aperio Dataset

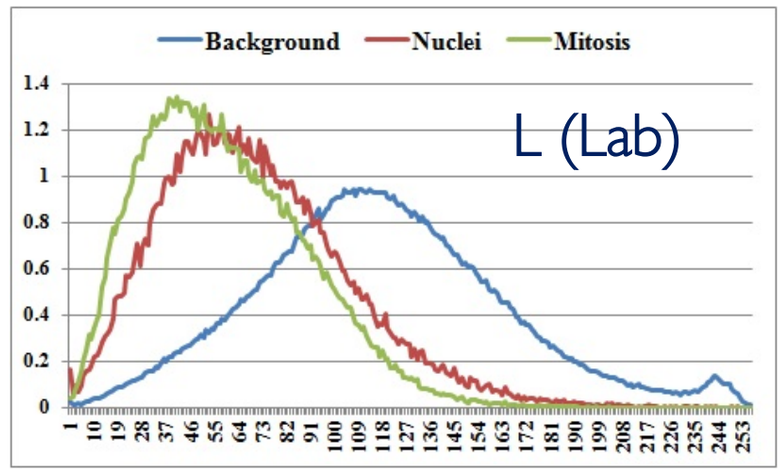
$$BlueRatio = 100 \times B/(1+R+G) \times 256/(1+R+G) + B$$

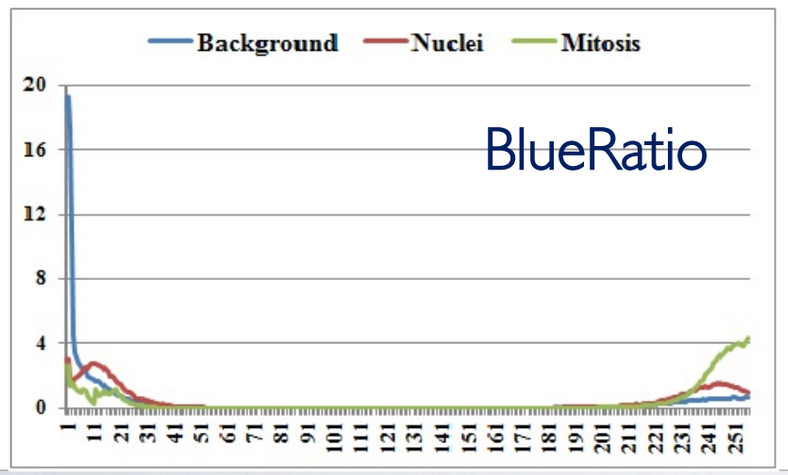


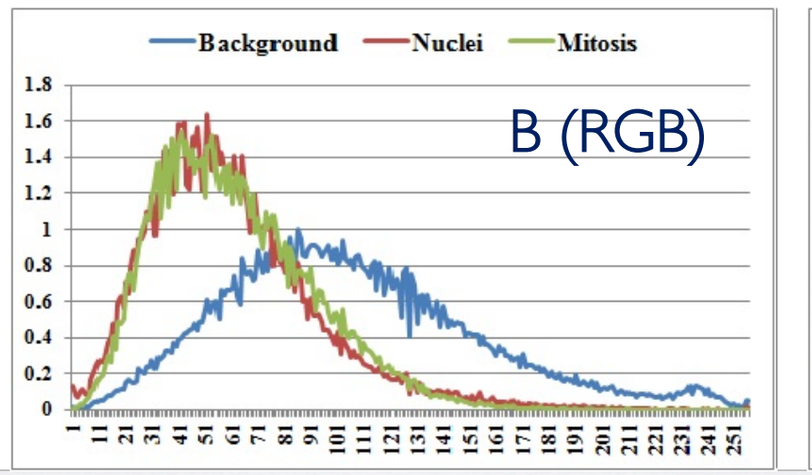



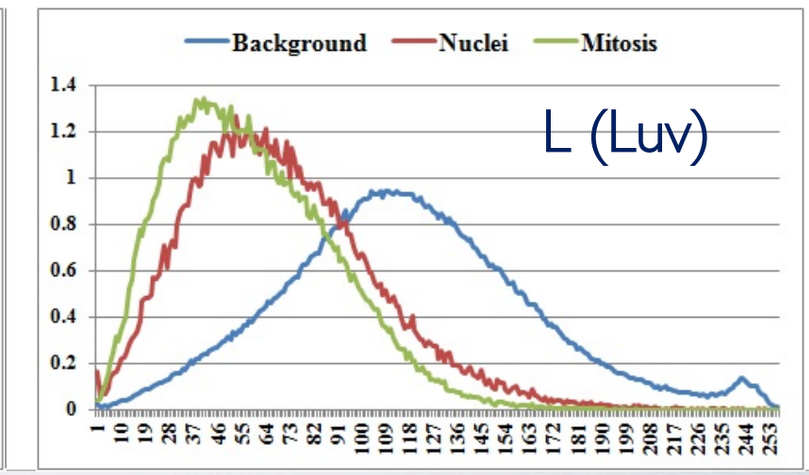



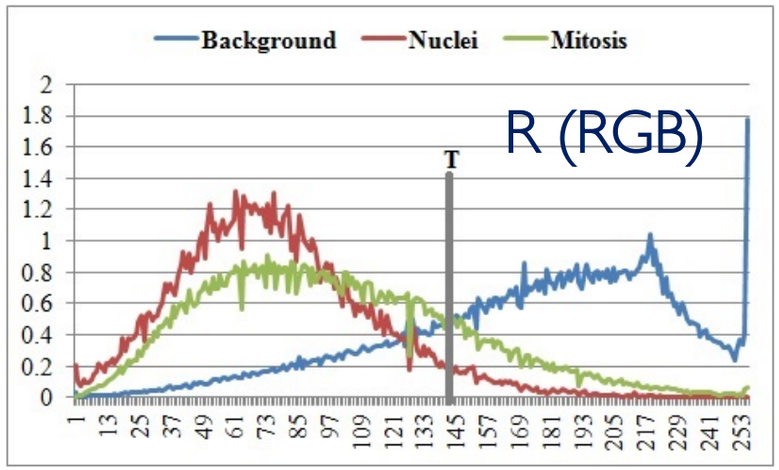



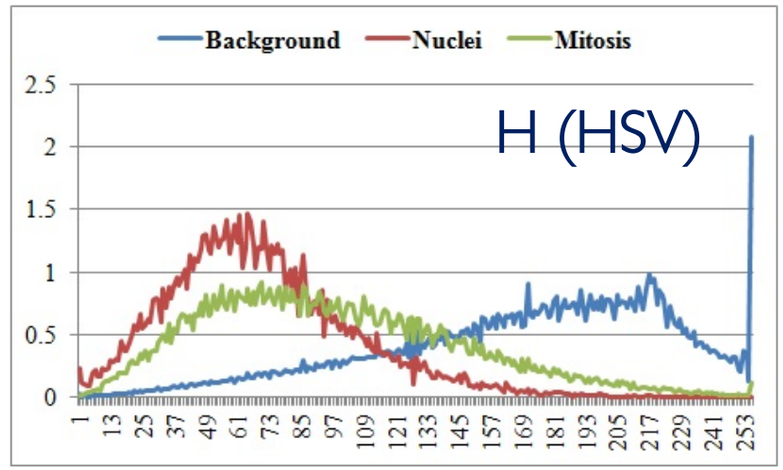



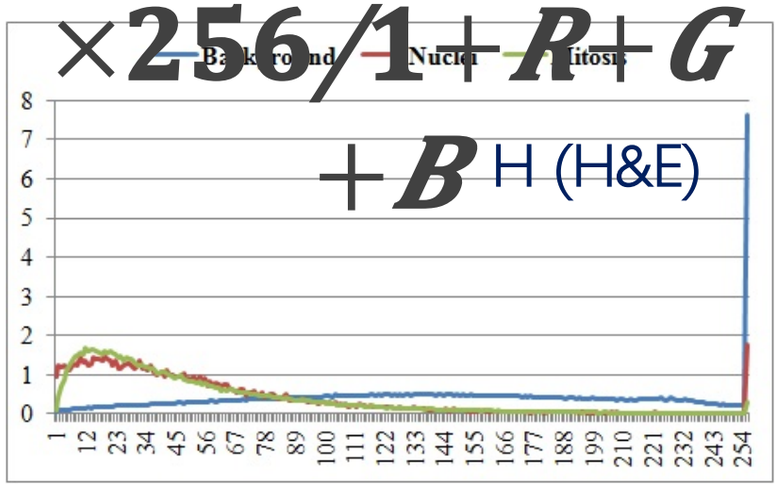
# Mitosis Detection in Color Images

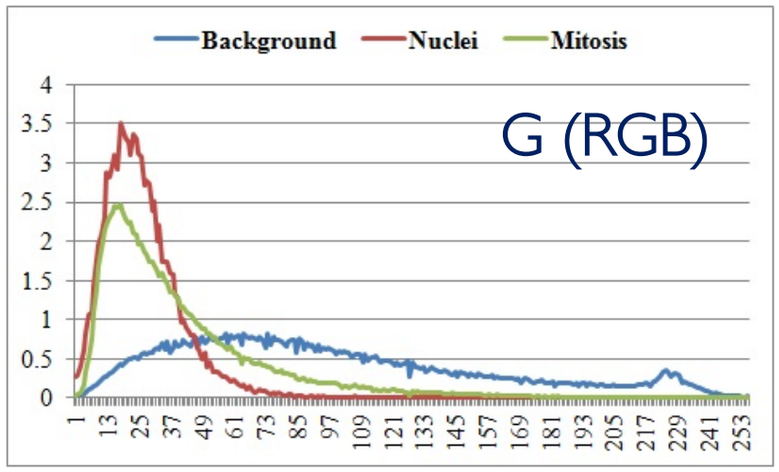
## Histogram of Selected Channels on Hamamatsu Dataset

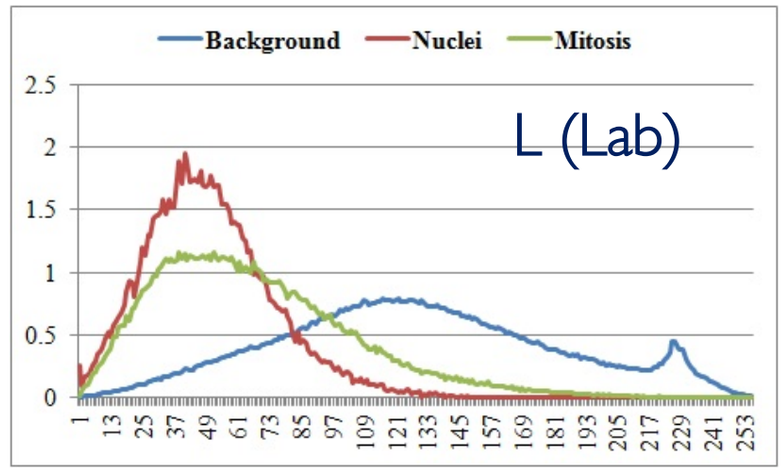
$$BlueRatio = 100 \times B/1+R+G \times 256/1+R+G + B$$

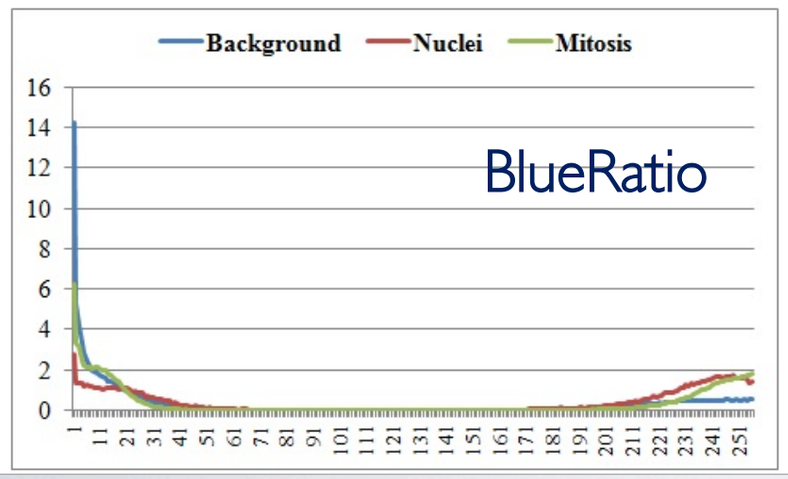


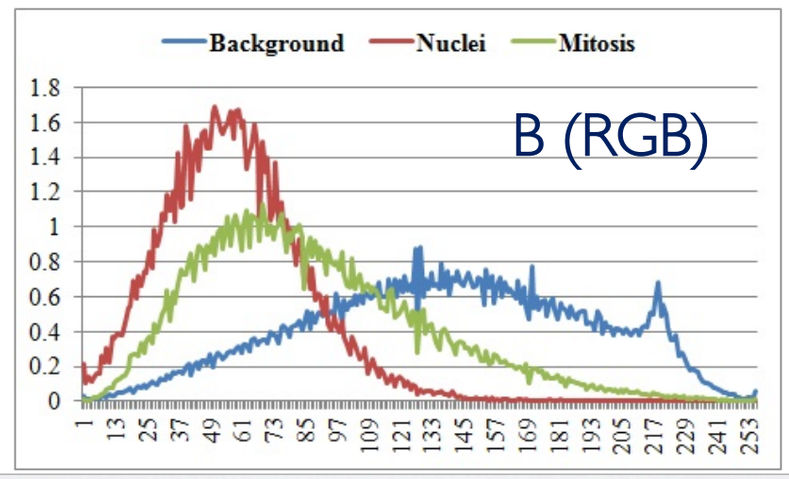



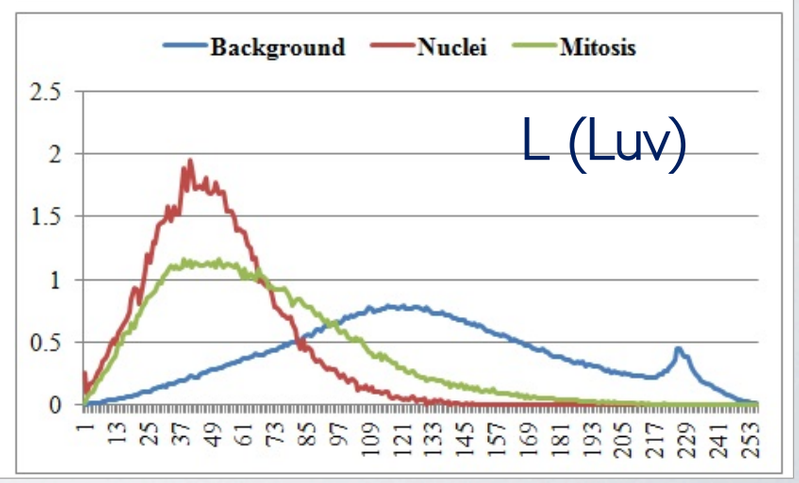



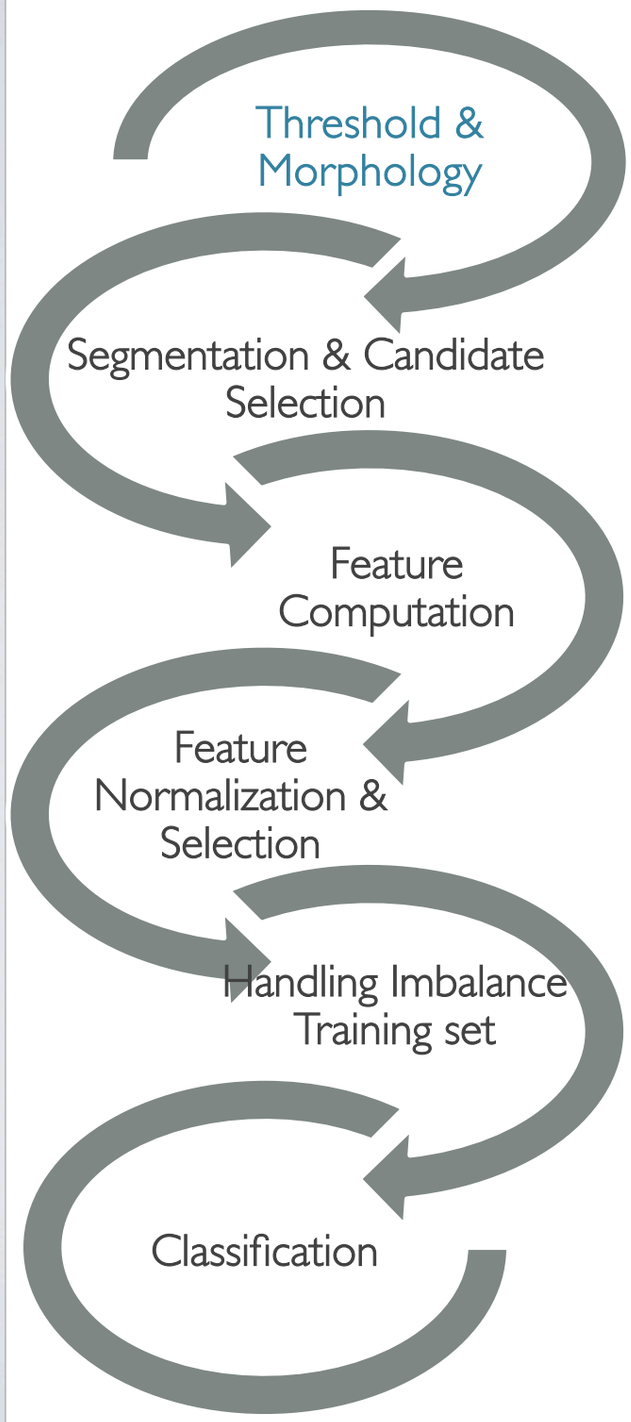



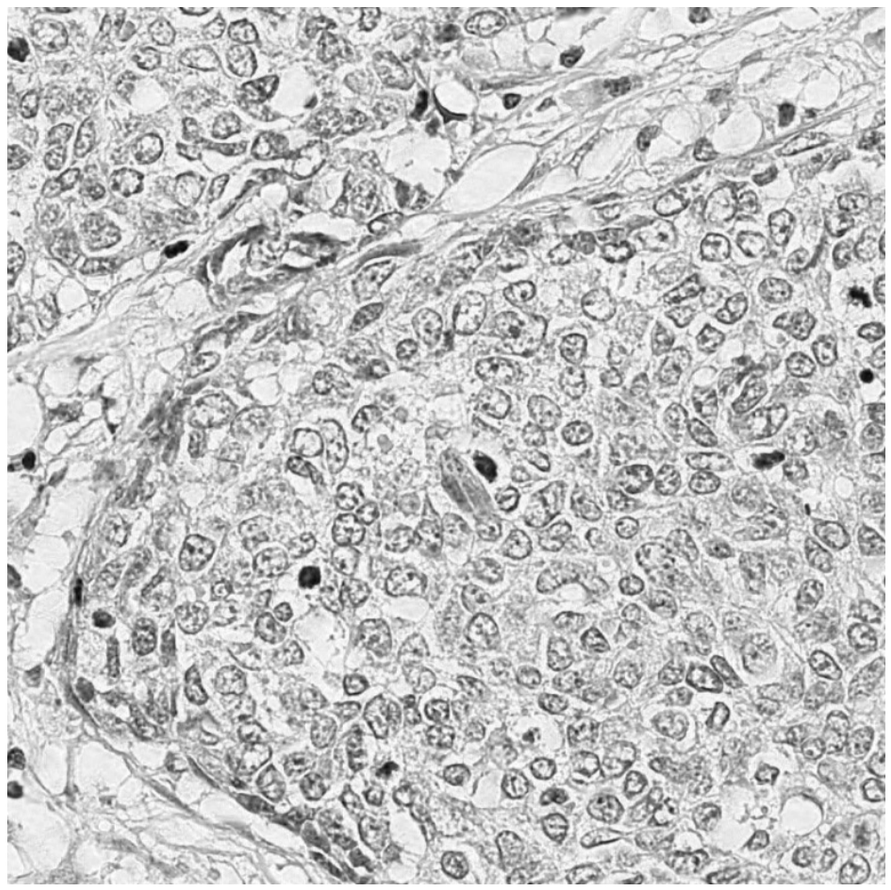



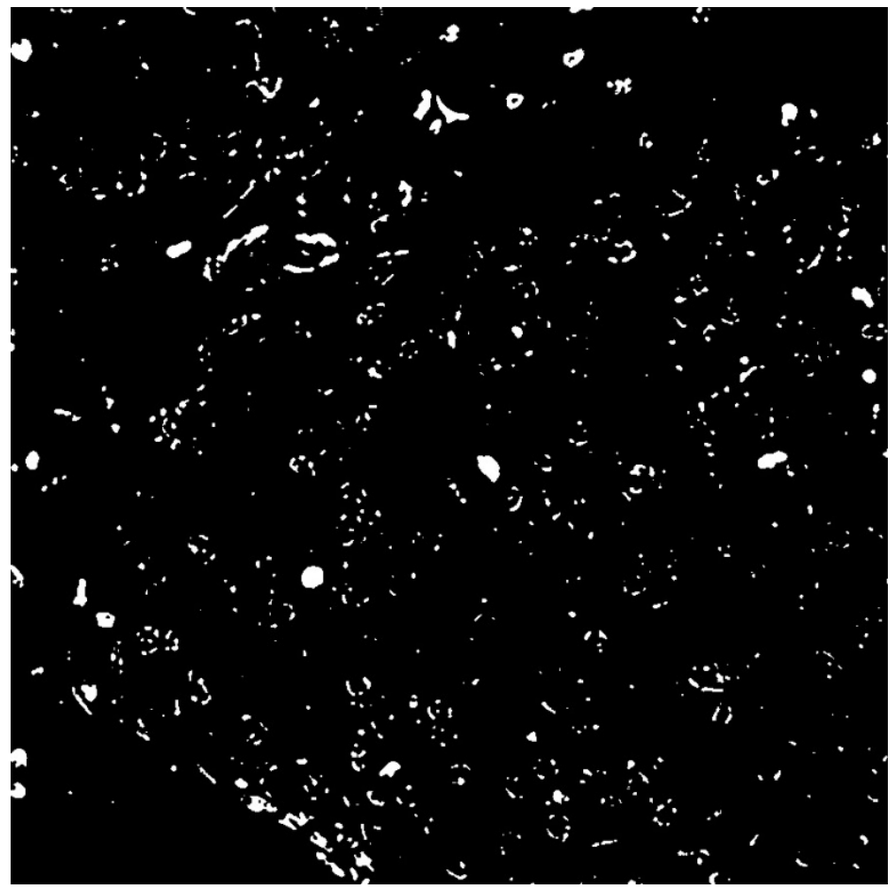
# Mitosis Detection in Color Images

## ITM²C Framework Step 1

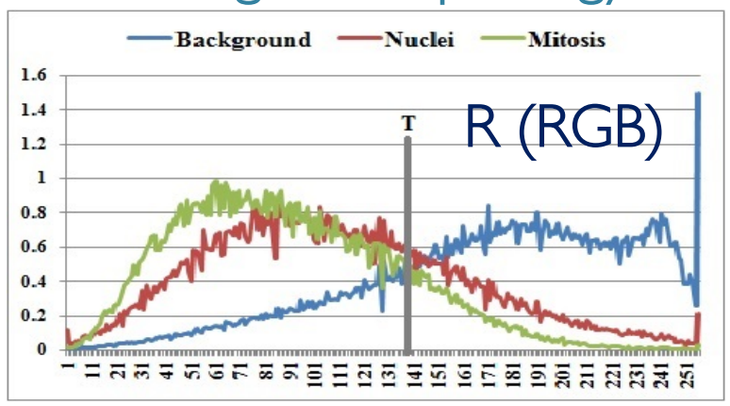


Red (RGB)

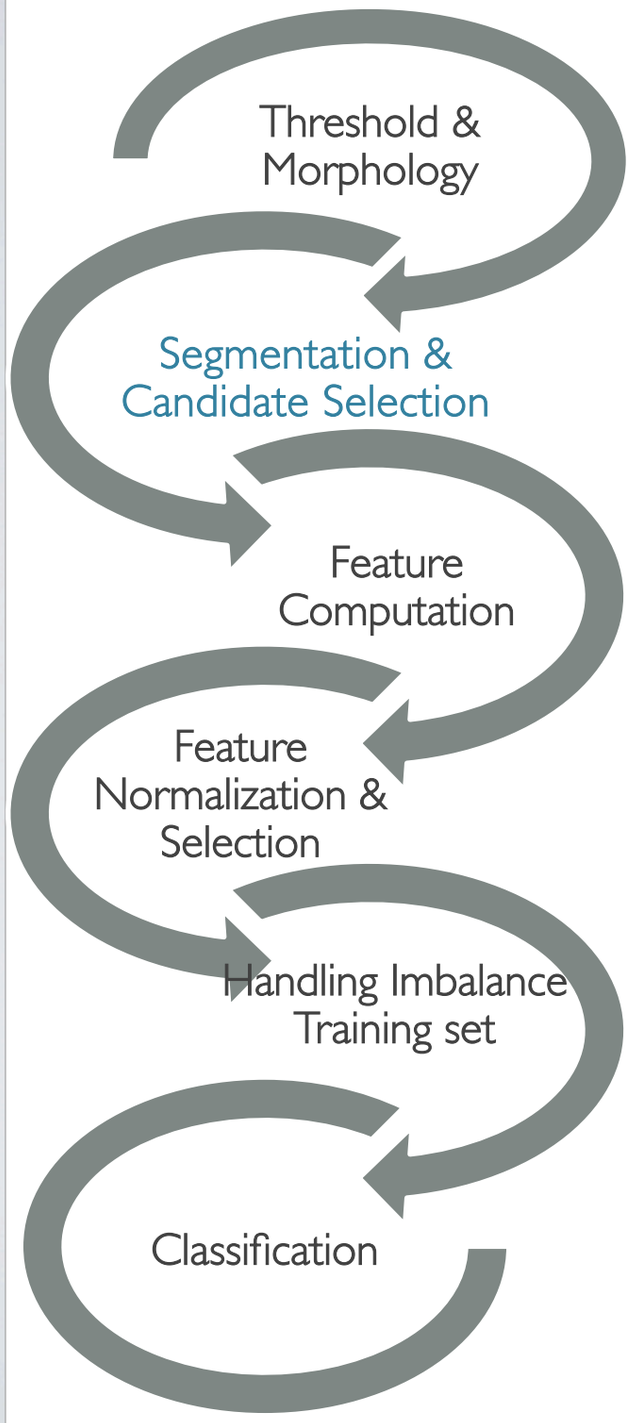


Thresholding & Morphology

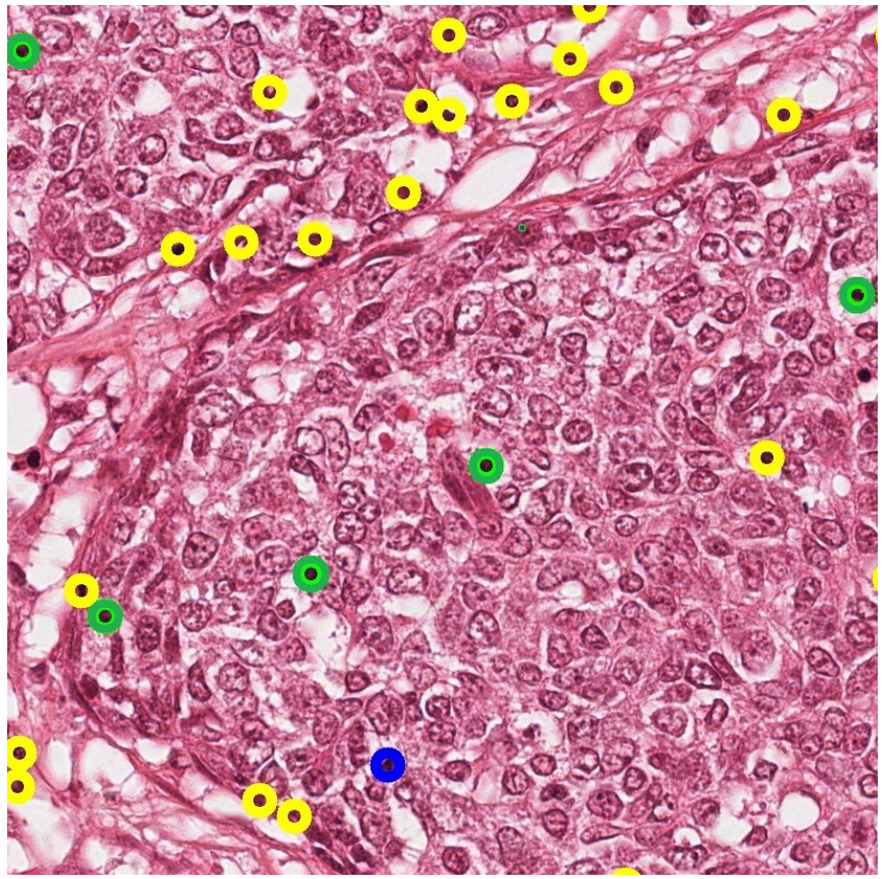


# Mitosis Detection in Color Images

## ITM$^2$C Framework Step 2

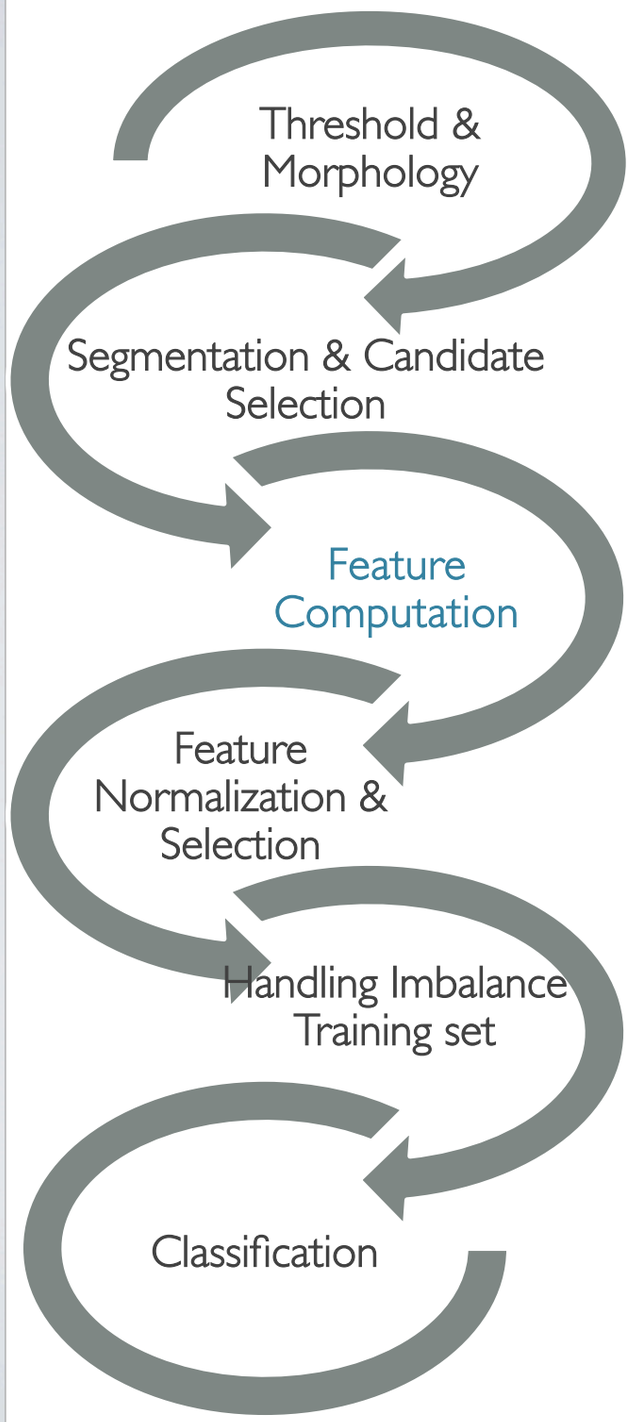



Segmentation & Candidate Selection



Selected Candidates
(TP=Green, FP=Yellow, FN-Blue)

# Mitosis Detection in Color Images

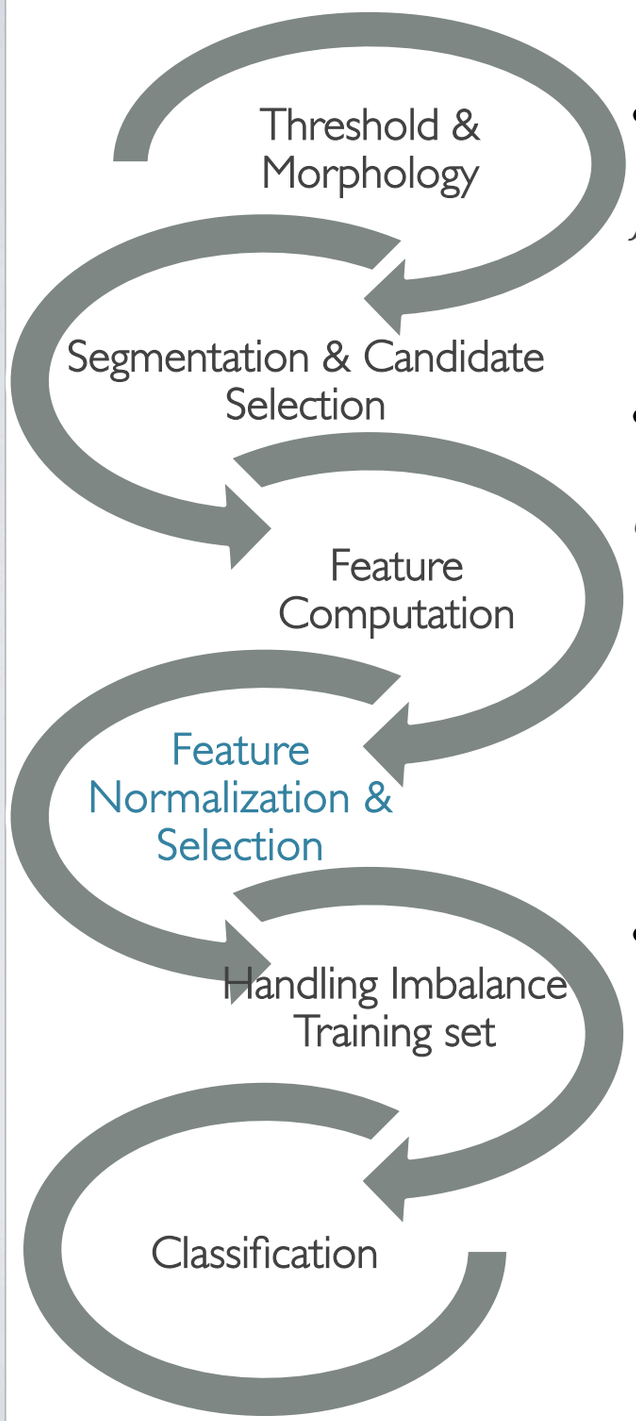



## ITM$^2$C Framework Step 3

- Morphology Features (5 Features)
  - Area, Perimeter, Roundness, Elongation, Equivalent spherical perimeter
- Intensity Features (5 Features)
  - Mean, Median, Standard Deviation, Skewness, Kurtosis
- Texture Features (18 Features)
  - Co-occurrence Features (8 Features)
    - Correction, cluster shade, cluster prominence, energy, entropy, Hara-correlation, inertia, difference moment
  - Run-Length Features (10 Features)
    - SRE, LRE, GLN, RLN, LGRE, HGRE, SRLGE, SRHGE, LRLGE, LRHGE
- Compute intensity and texture features for each color channel (total eight channels)
- Total Features = 5 + 8 ( 5 * 18 ) = 189

# Mitosis Detection in Color Images

## ITM$^2$C Framework Step 4




- Feature Normalization

$$f' = f - f_{min} / f_{max} - f_{min}$$

where $f'$ is normalized feature, $f$ is actual feature

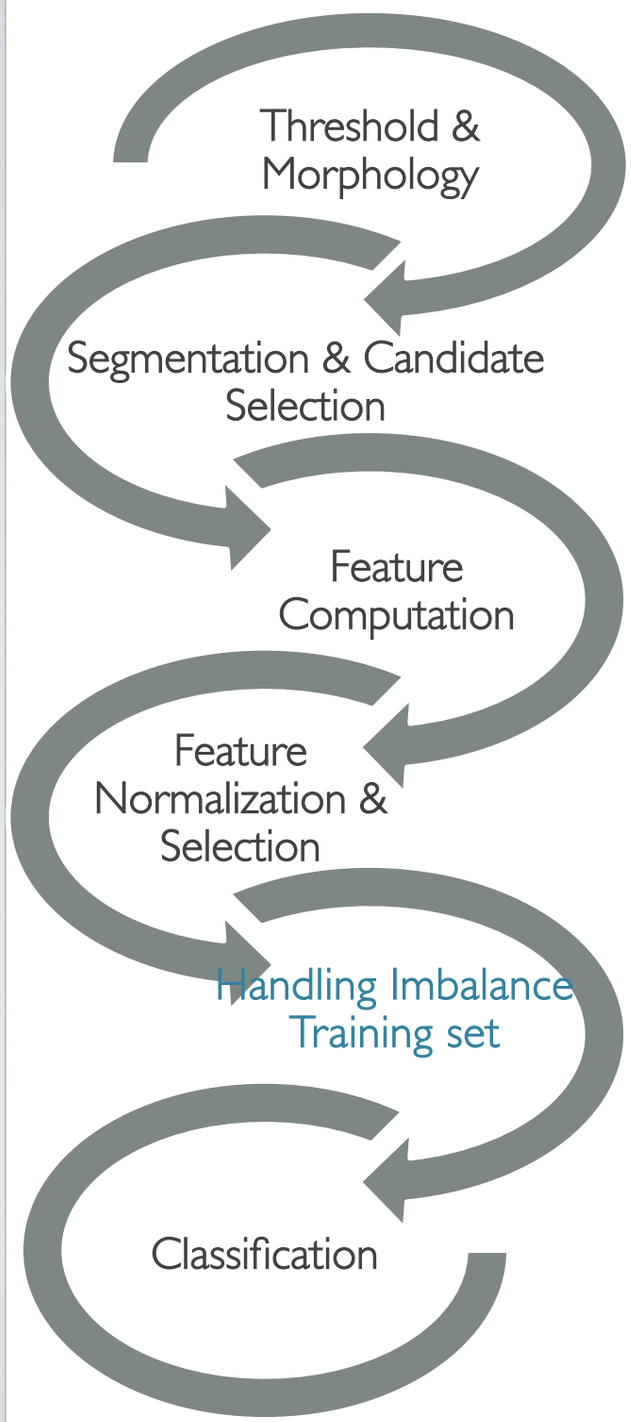
- Feature Selection using Consistency subset evaluation method

$$Consistency_S = 1 - \sum_{j=0}^{J} |D_j| - |M_j| / N$$

where $s$ is a feature subset, $J$ is the number of distinct combination of features for $s$, $|D_j|$ is the number of occurrences of the $j^{th}$ feature combination, $|M_j|$ is the cardinality of the majority class for the $j^{th}$ feature combination and $N$ is the total number of instances

- Use these subsets in conjunction with a hill climbing search method, augmented with backtracking

# Mitosis Detection in Color Images



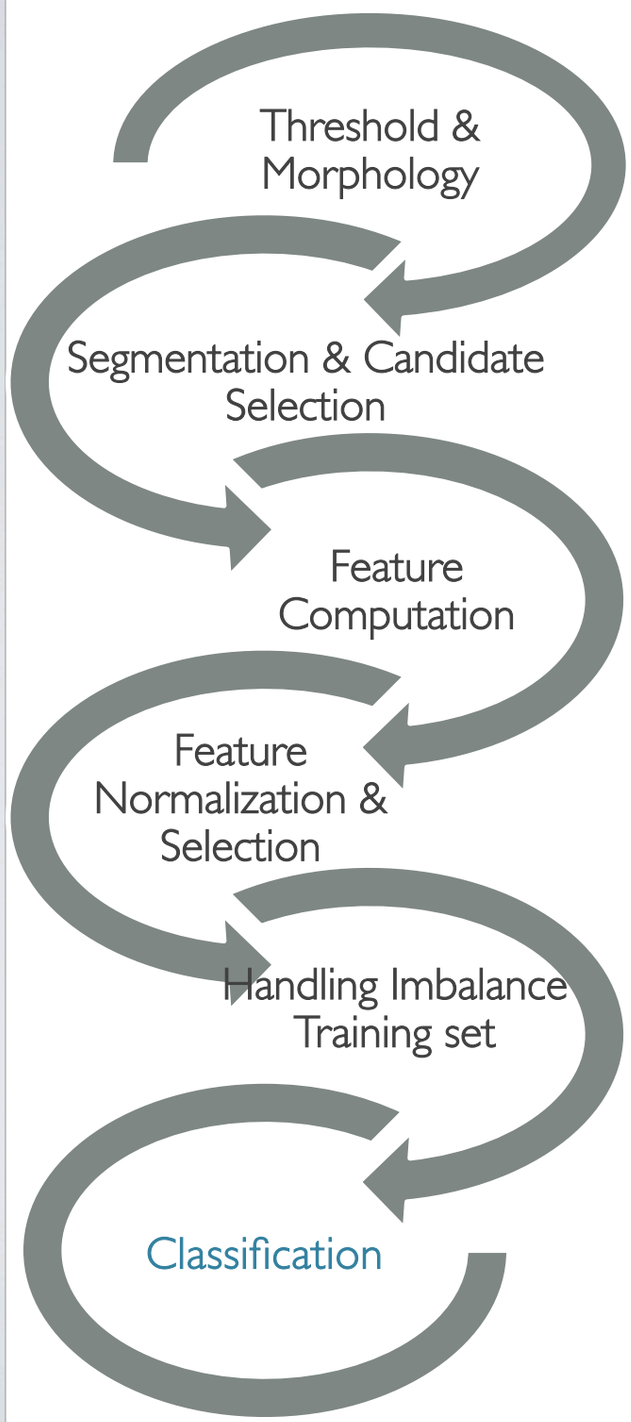

## ITM$^2$C Framework Step 5

### Handling Imbalanced Training Set

- High degree of imbalance in training set (mitosis vs non-mitosis)
- Down-sampling of non-mitosis
- Over-sampling of mitosis using Synthetic Minority Over-sampling TEchnique (SMOTE)

- 2 neighbors are selected from 5-nearest neighbors
- New instance is generated in the direction of selected 2 neighbors

# Mitosis Detection in Color Images




## ITM²C Framework Step 6

### 1. Decision Tree (DT)

$$P(C=c, X=x)=e^{F_{c}(x)} / \sum_{i=1}^{C} e^{F_{i}(x)}$$

C = a label set, X = an instance set, $F_{c}(x)$ = Functions of input variables

### 2. Multilayer Perceptron (MLP)

$$y(j) = 1/1+e^{-S(j)}$$

$$S(j)=\sum_{k=1}^{K} y(k)\, w(k,j)$$

$$w(k,j)^{t+1} = w(k,j)^{t} + \alpha\varepsilon(j)y(j) + \beta(w(k,j)^{t} - w(k,j)^{t-1}),$$

*y(j) = output of node j*

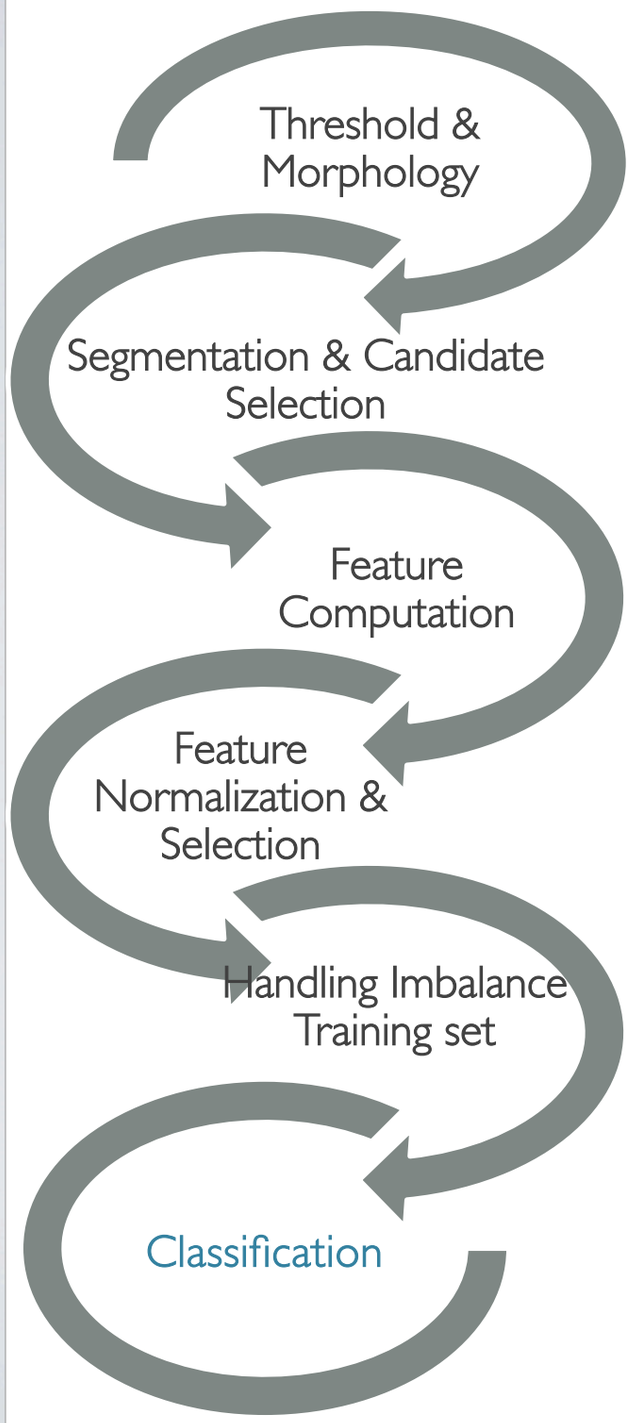
*S(j) = sum of all inputs weighted inputs of previous layer to node j*

*y(k) w(k, j) = weighted output of the previous node k to input node j,*

*K = number of inputs to node j,*

*w(k,j) = connections weights between previous node k and current node j,*

# Mitosis Detection in Color Images




## ITM²C Framework Step 6

### 3. Linear Support Vector Machine (LSVM)

$$\min_{w} 1/2 \; w^T w + \alpha \sum_{k=1}^{K} \varepsilon(w; x_k, c_k),$$

$$\varepsilon(w; x_k, c_k) = (\max(0, 1 - c_k w^T x_k))^2$$

C = a label set, X = an instance set, $\alpha$ = penalty parameter

### 4. Non-Linear Support Vector Machine (NLSVM)

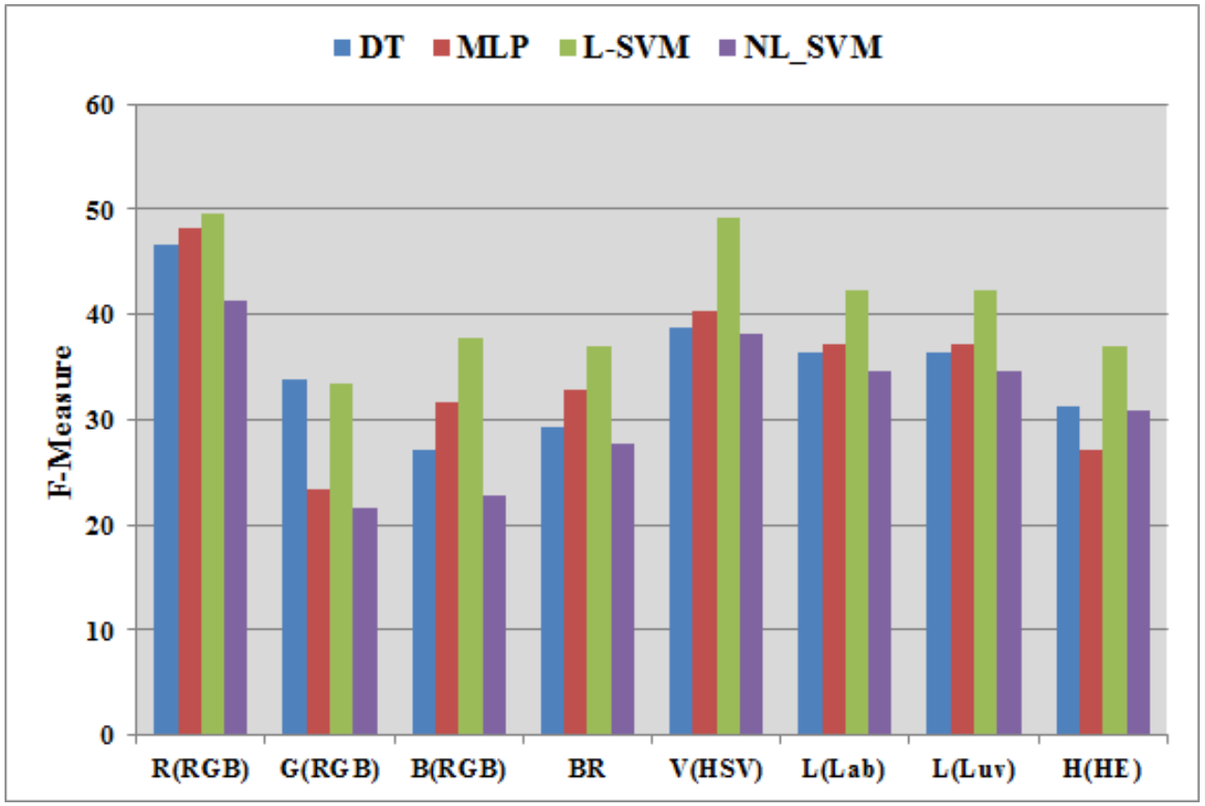
$$\min_{z,b,\xi} 1/2 \; \|z\|^2 + \alpha \sum_{k=1}^{K} \xi_k$$

$z$ = normal to the hyper planes

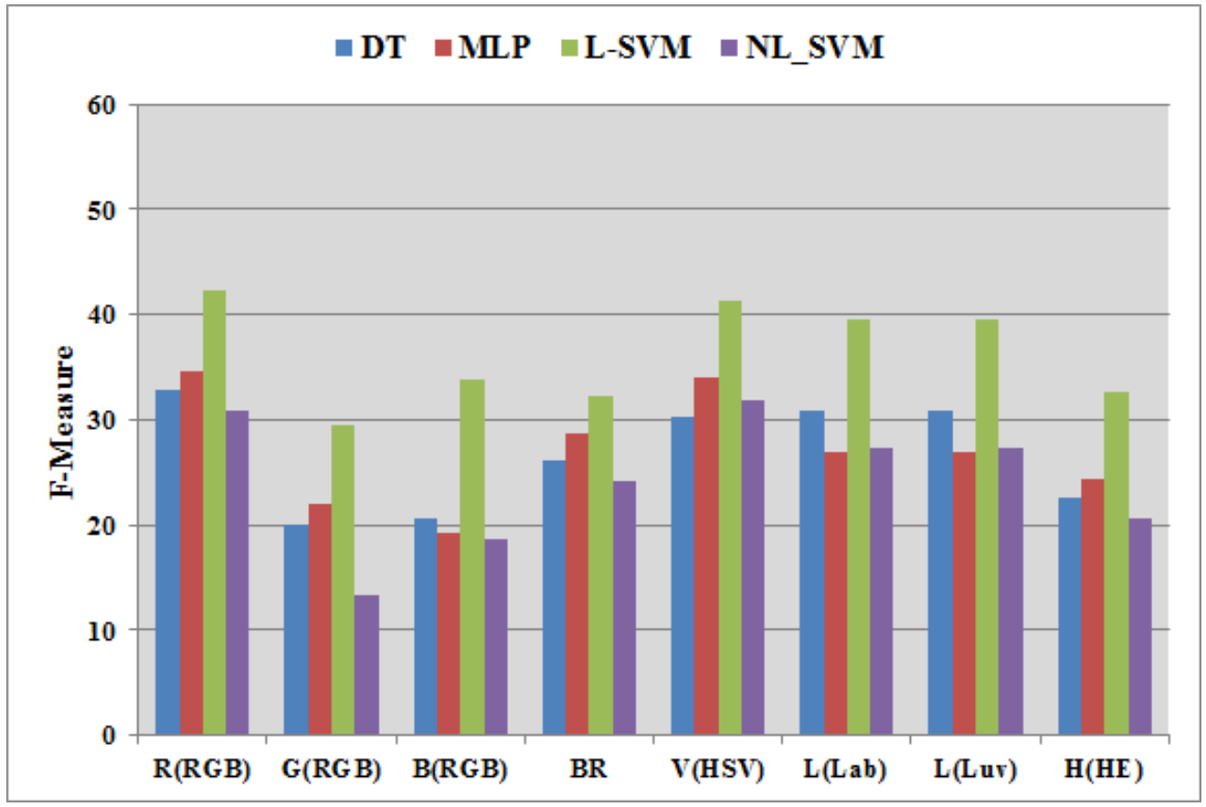
$b$ = bias which describes the distance of the decision hyper plane from origin

# Mitosis Detection in Color Images

## ITM$^2$C Classification Results using Single Channel Features




On Aperio Dataset




On Hamamatsu Dataset

# Mitosis Detection in Color Images

## ITM²C Result using All vs Selected Features on Evaluation set

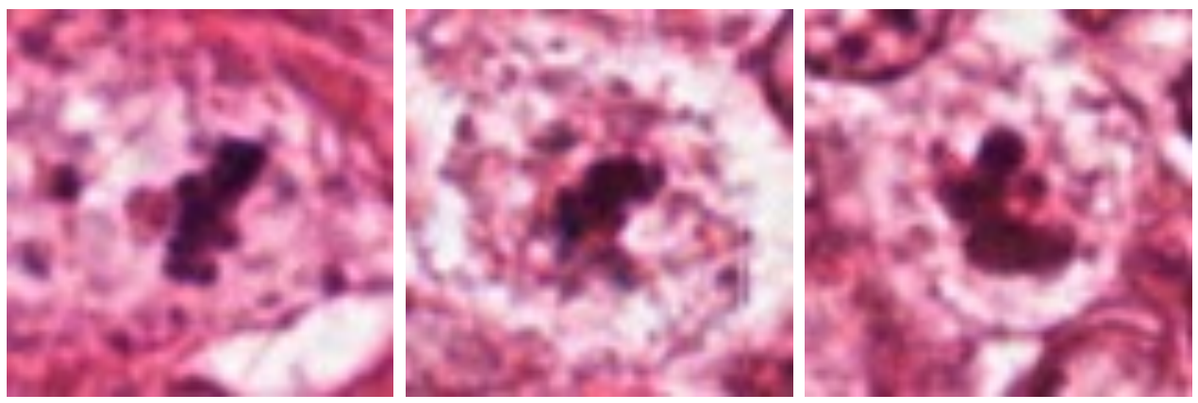
| | | Aperio Dataset | | | Hamamatsu Dataset | | |
|---|---|---|---|---|---|---|---|
| Features | Classifiers | TPR | PPV | FM | TPR | PPV | FM |
| All Features | DT | 65% | 71% | 67.71% | 60% | 62% | 60.91% |
| | MLP | 68% | 69% | 68.34% | 60% | 61% | 60.61% |
| | LSVM | 72% | 66% | 68.57% | 61% | 62% | 61.31% |
| | NLSVM | 58% | 83% | 68.24% | 53% | 73% | 61.27% |
| Selected Features | DT | 67% | 73% | 69.79% | 61% | 64% | 62.56% |
| | MLP | 66% | 74% | 69.84% | 60% | 66% | 62.83% |
| | LSVM | 74% | 71% | 72.55% | 63% | 66% | 64.62% |
| | NLSVM | 59% | 84% | 69.41% | 55% | 74% | 63.22% |

TPR = True Positive Rate
PPV = Predictive Positive Value
FM = F-Measure

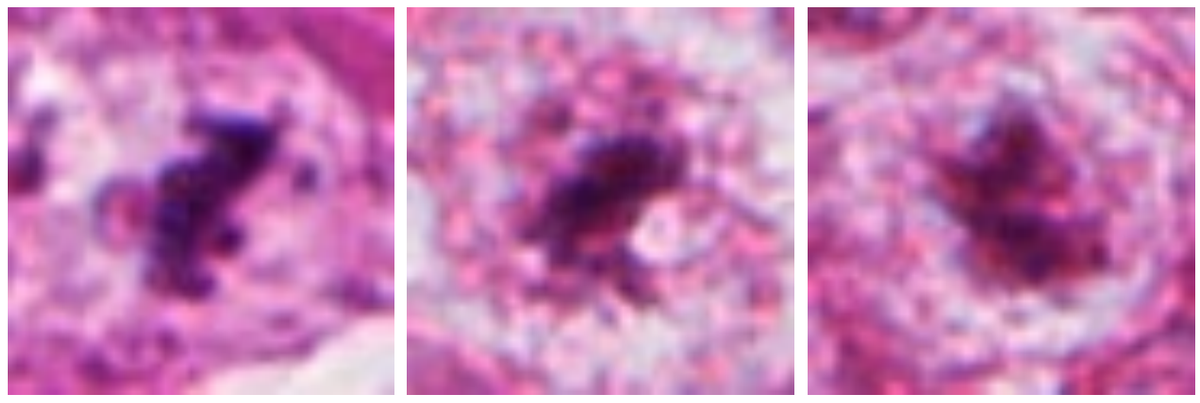
# Mitosis Detection in Color Images

## Different Patch Sizes for Feature Computation

| Patch Size in pixels | Aperio Dataset (μm) | Hamamatsu Dataset (μm) |
|---|---|---|
| Patch 80 × 80 | 19.648 × 19.648 | 18.184 × 18.202 |
| Patch 70 × 70 | 17.192 × 17.192 | 15.911 × 15.927 |
| Patch 60 × 60 | 14.736 × 14.736 | 13.638 × 13.652 |
| Patch 50 × 50 | 12.28 × 12.28 | 11.365 × 11.377 |
| Patch 40 × 40 | 9.824 × 9.824 | 9.092 × 9.101 |



Mitosis Patch from Aperio Dataset

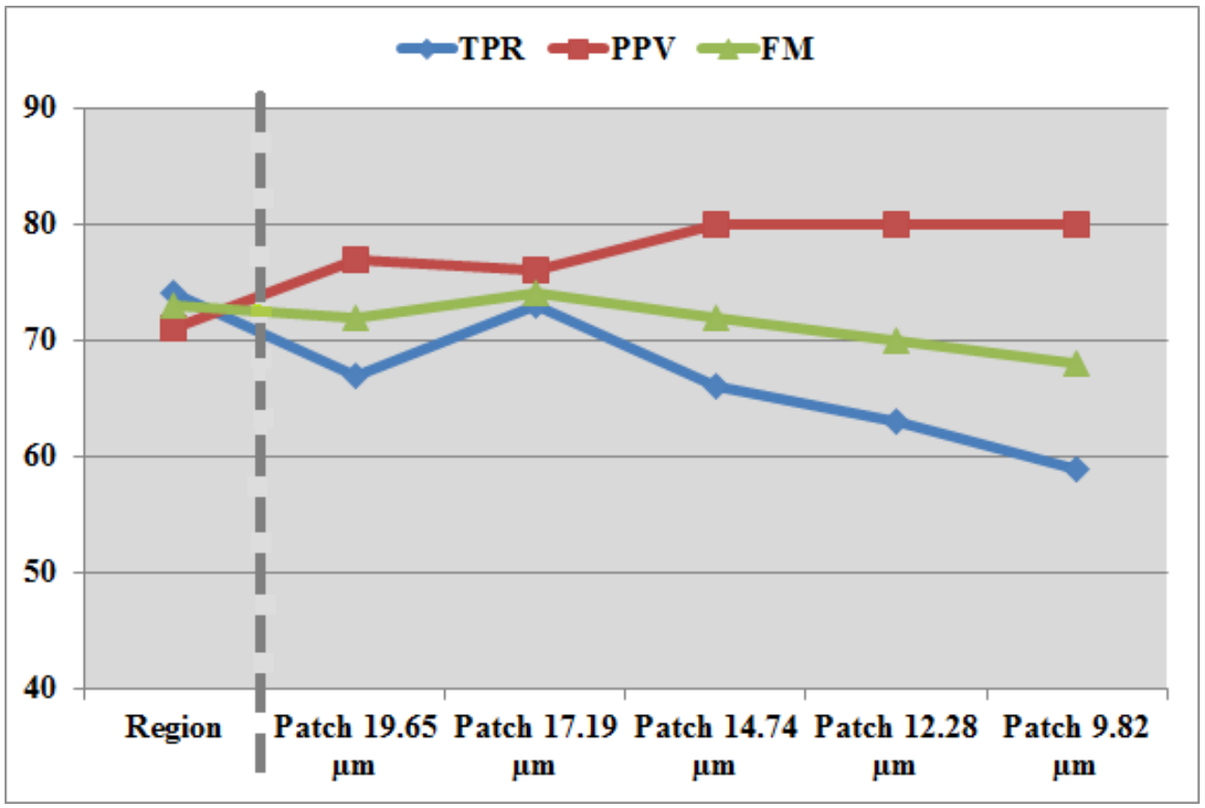


Mitosis Patch from Hamamatsu Dataset

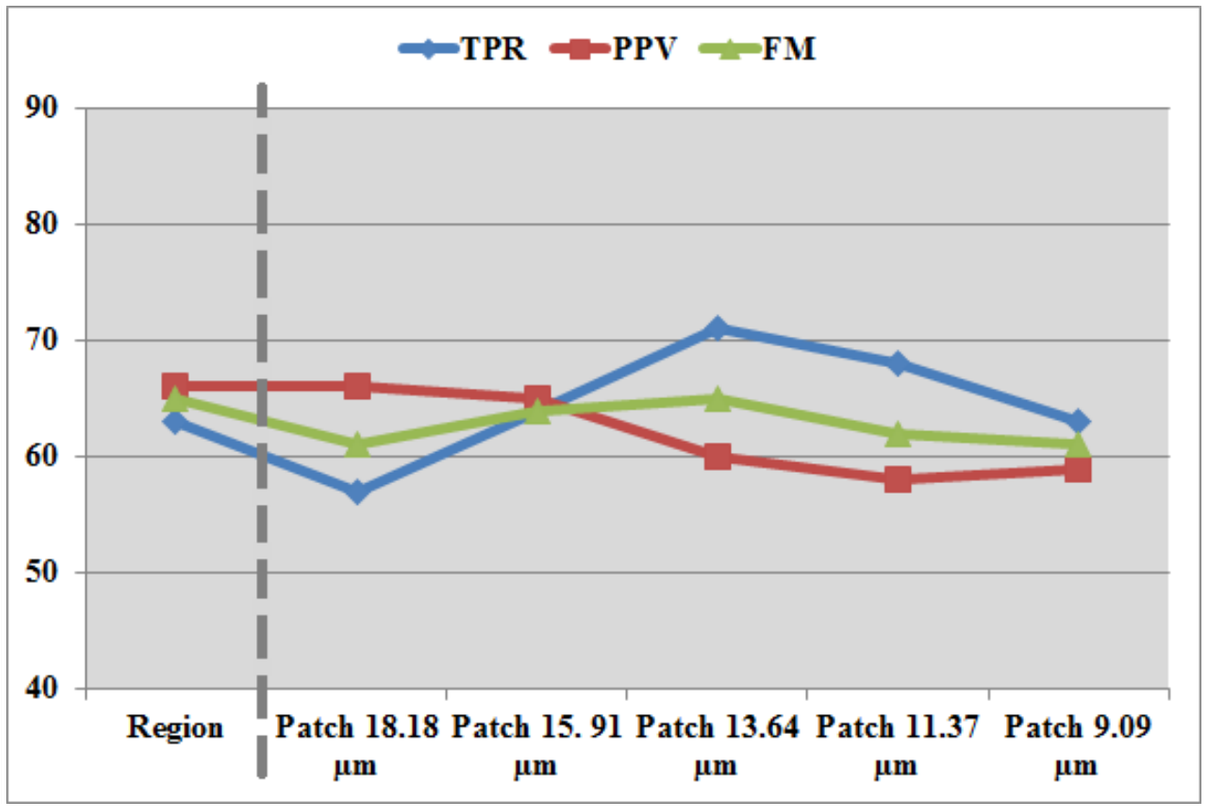
# Mitosis Detection in Color Images

## Region vs Patch Features based Classification using LSVM Classifier

- Both scanners have different information on same patch size.



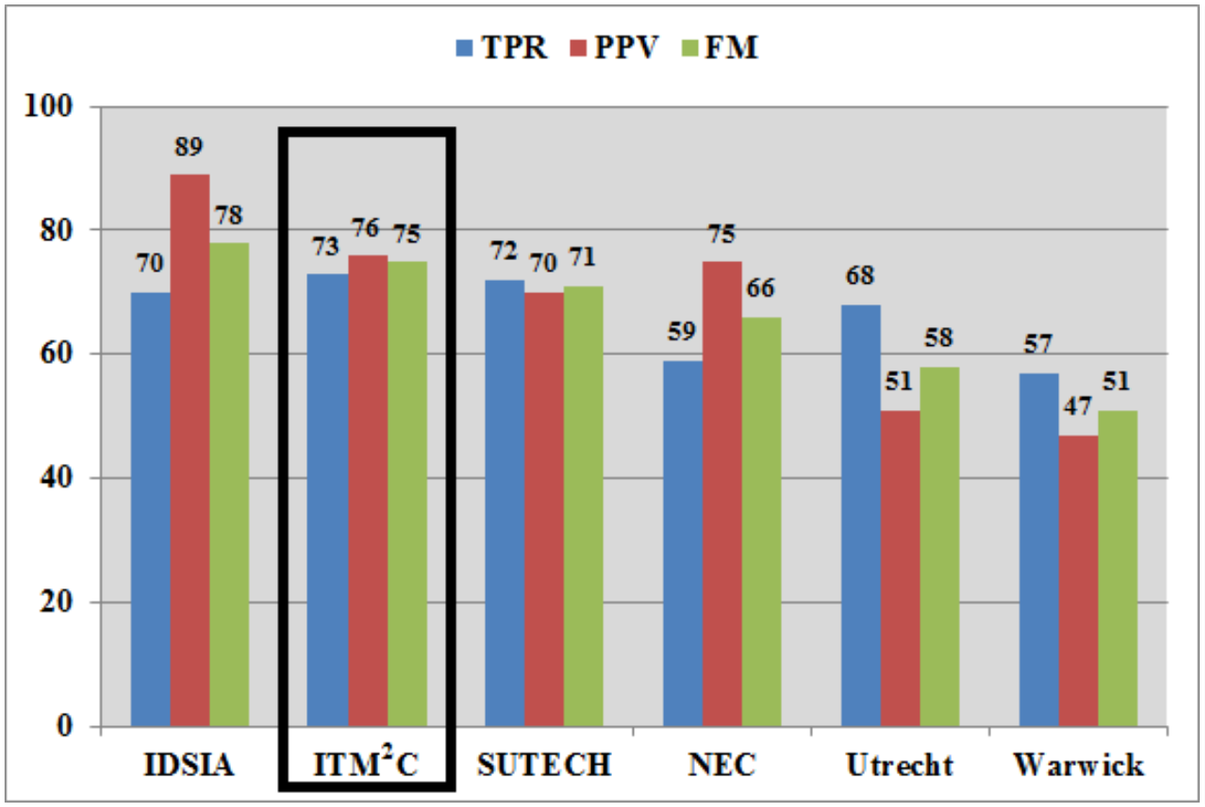

On Aperio Dataset



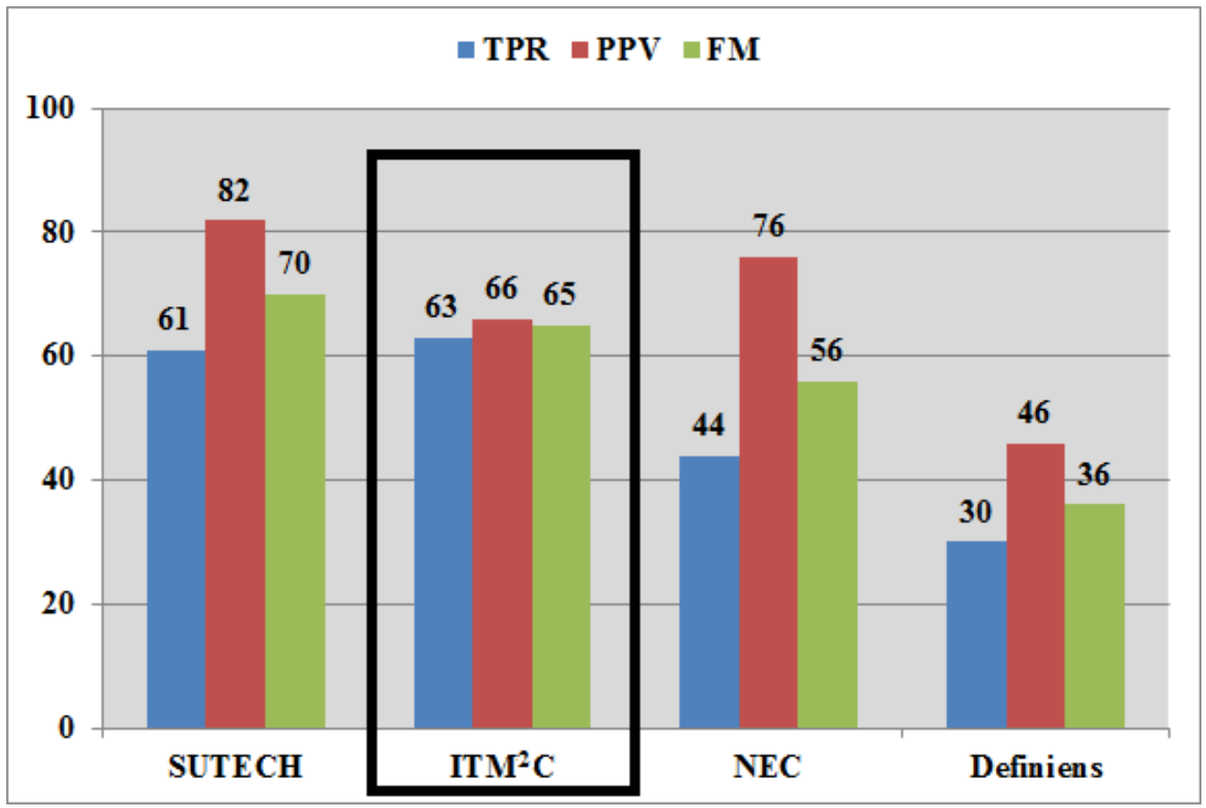

On Hamamatsu Dataset

# Mitosis Detection in Color Images

## Comparison of Results with ICPR MITOS Contest 2012




Comparison on Aperio Dataset

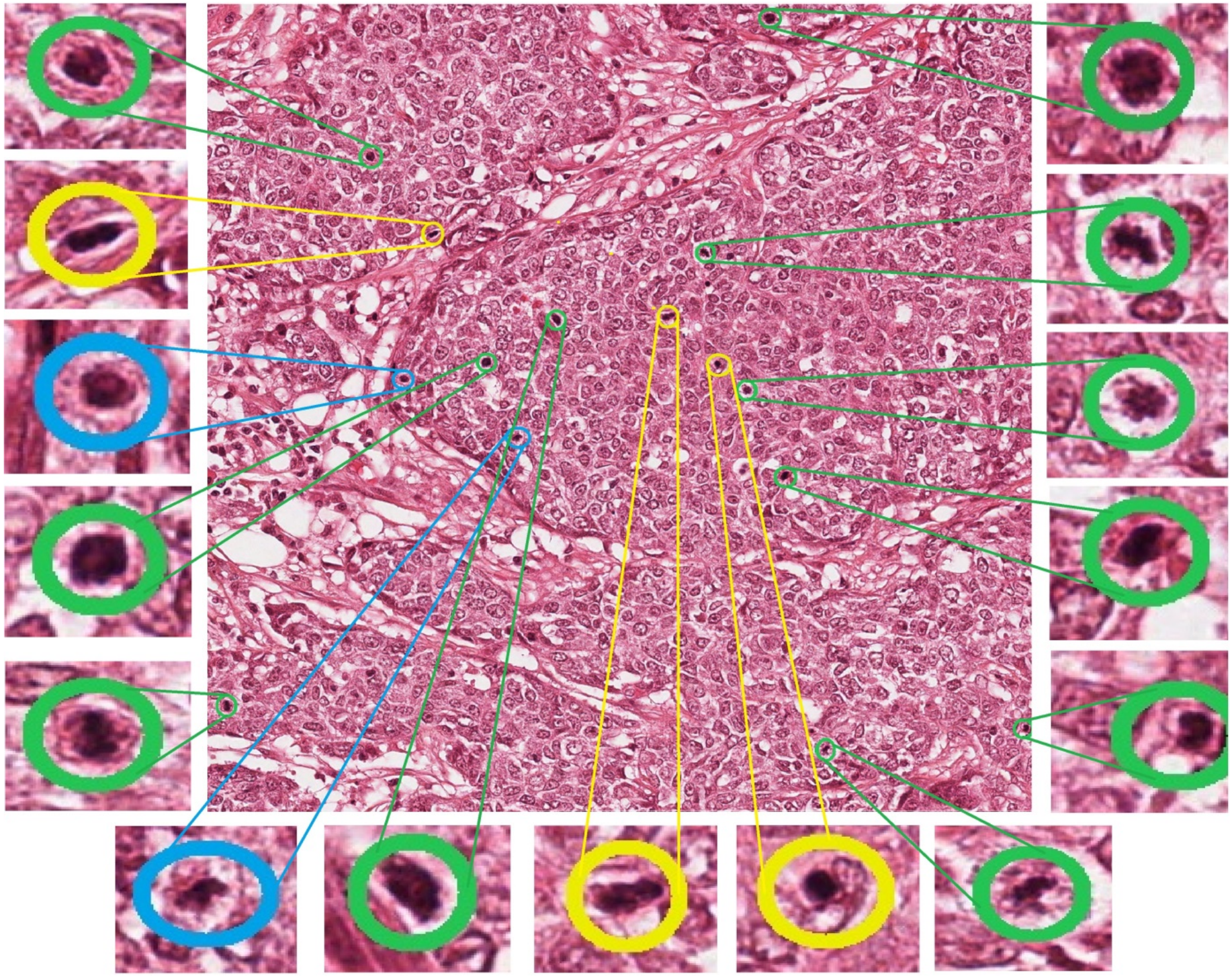



Comparison on Hamamatsu Dataset

ipal
Image & Pervasive Access Lab

# Mitosis Detection in Color Images

## Candidate Classification on Aperio Dataset (TP=Green, FP=Yellow, FN-Blue)

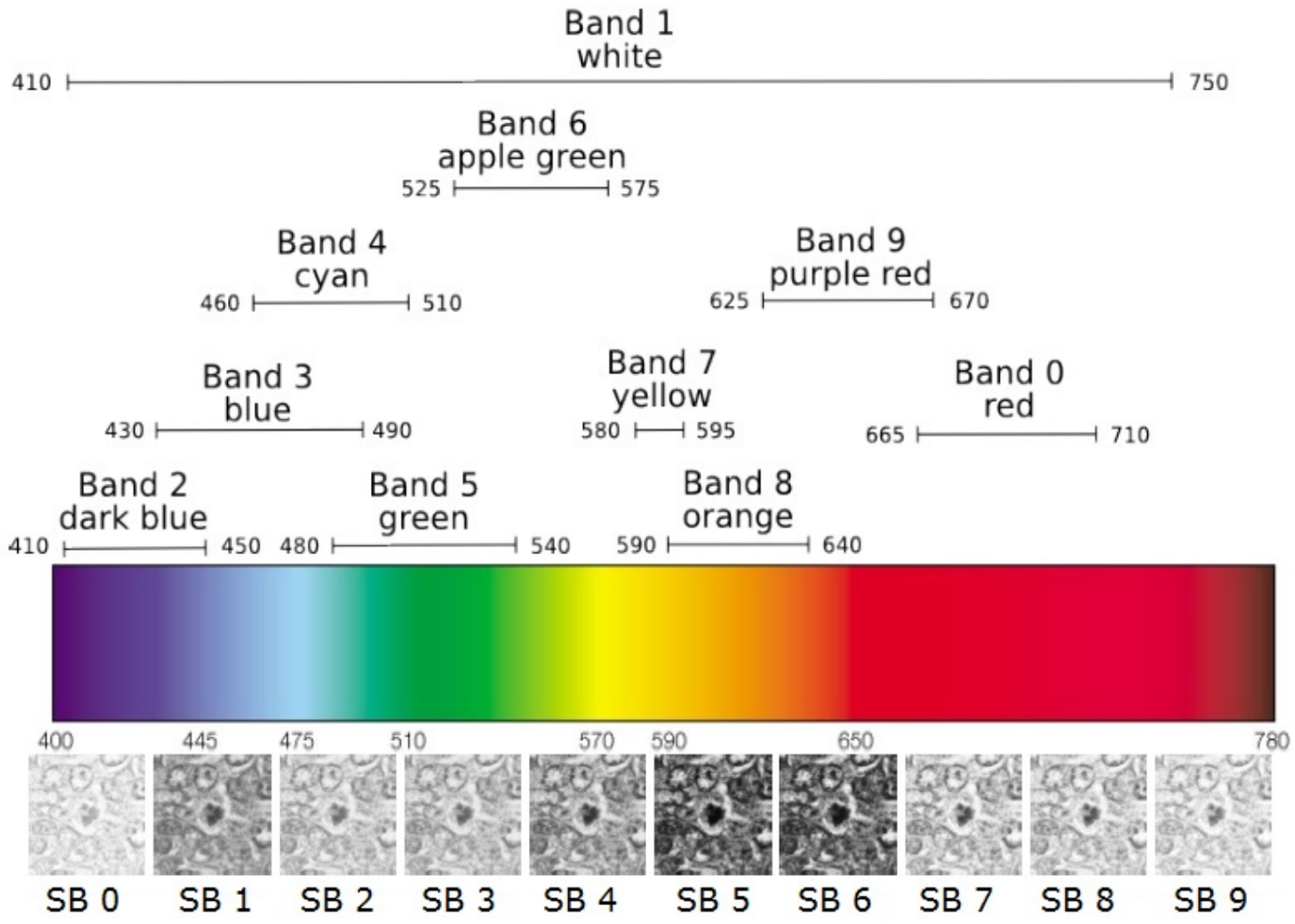


# Mitosis Detection in Multispectral Images

## Multispectral Dataset

- 10 Spectral bands
- 17 Focal Planes (layer Z-stack)
- 4 images per HPF
- 1 HPF = 4 * 17 * 10 = 680 images
- Image resolution = $251.6 \times 251.6 \mu m^2$

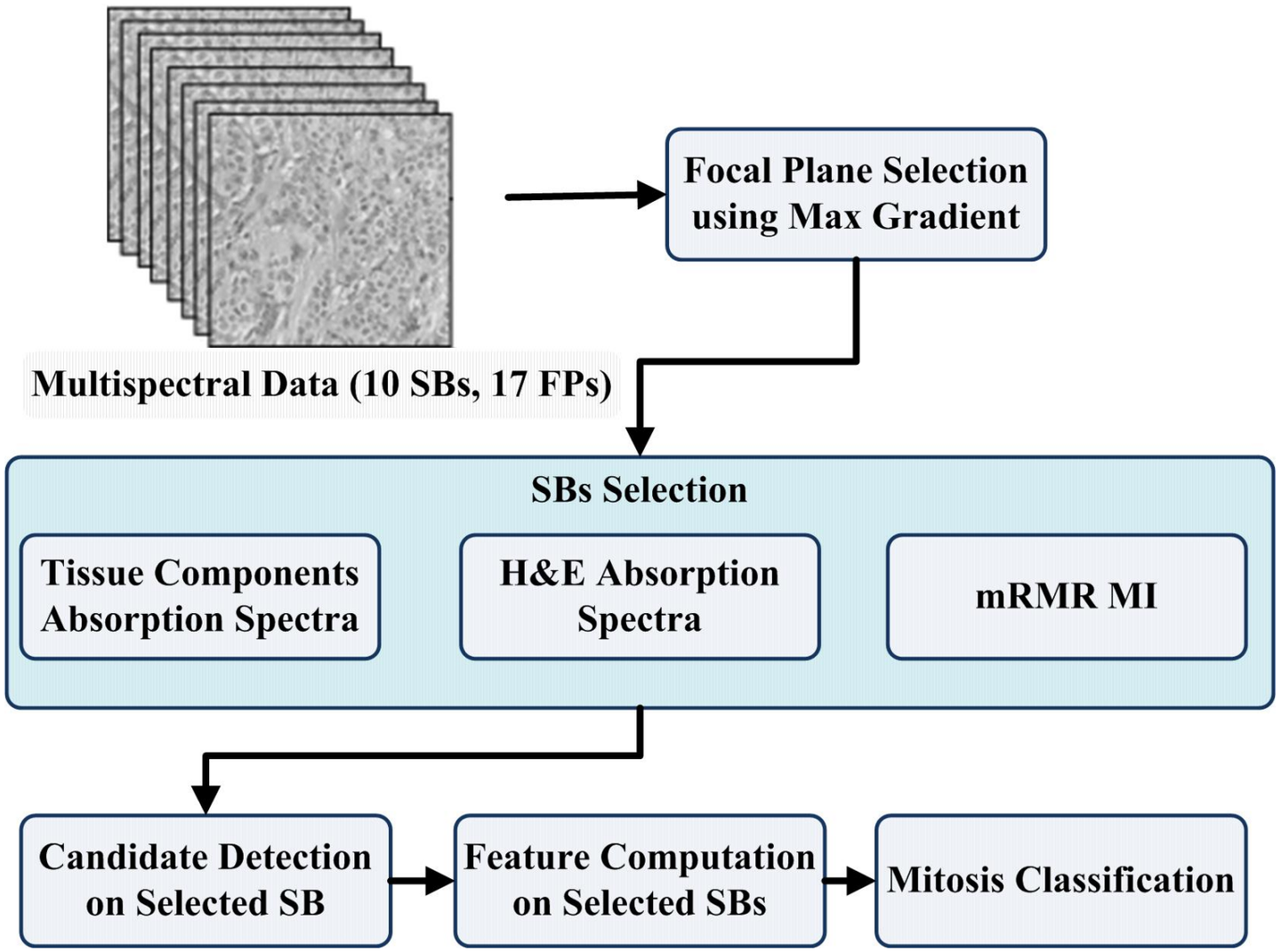
  an area of $0.063 mm^2$
- Total 50 HPF (322 mitosis)
  - 35 Training set (244 mitosis)
  - 15 Evaluation set (98 mitosis)




Spectral bands (SBs) of multispectral microscope and example of each SB

# Mitosis Detection in Multispectral Images

## Multispectral Intensity, Texture & Morphology-based Mitosis detection in Multispectral images (MITM$^3$) Framework

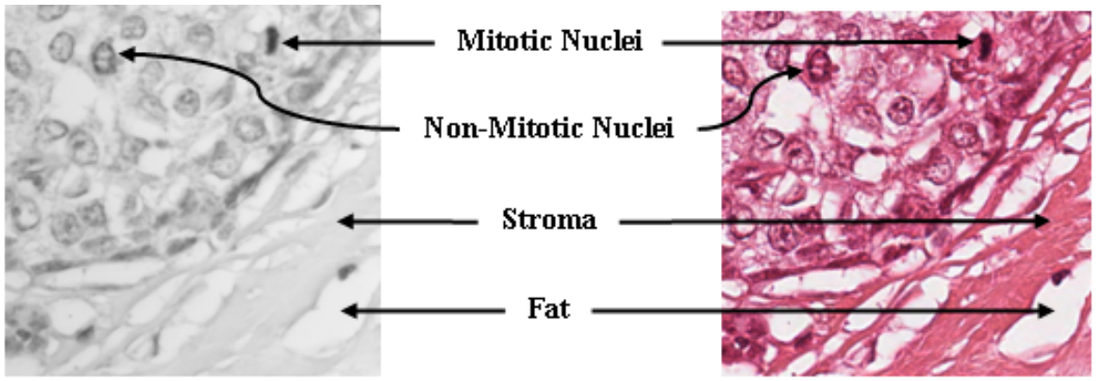



MITM$^3$ Framework

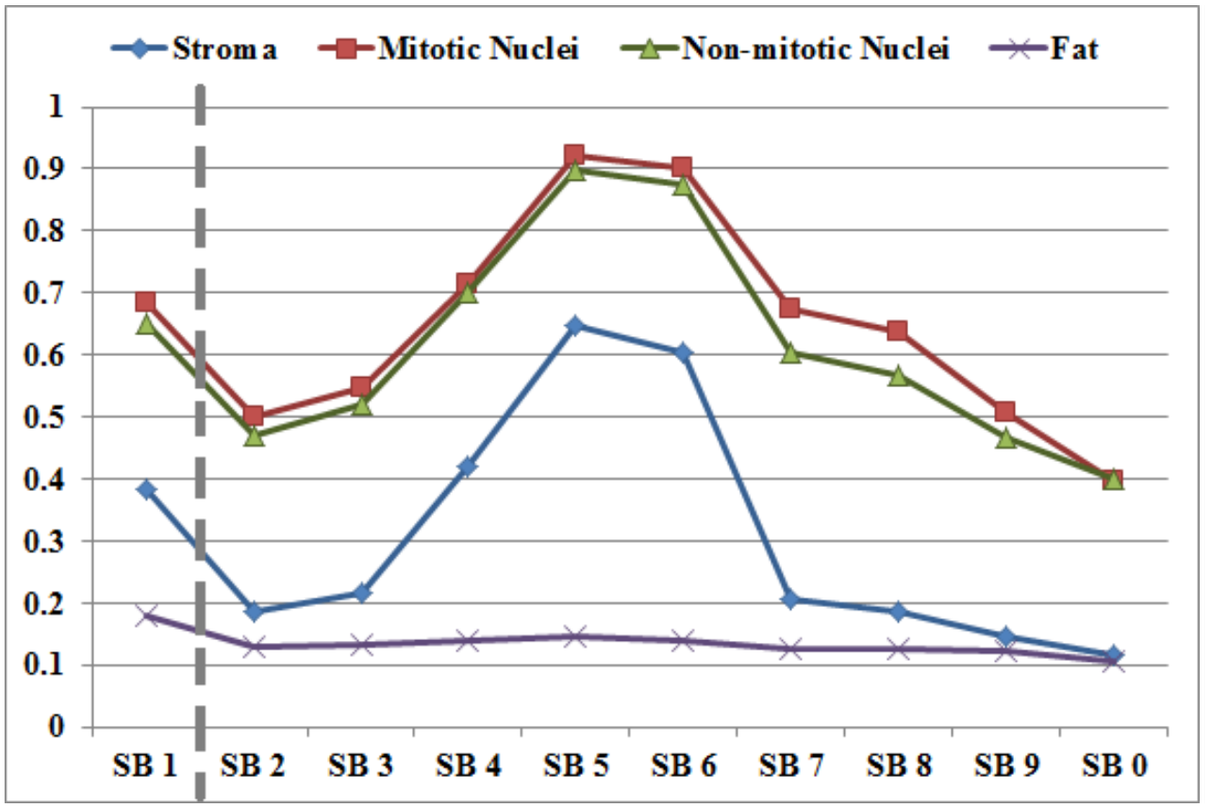
# Mitosis Detection in Multispectral Images

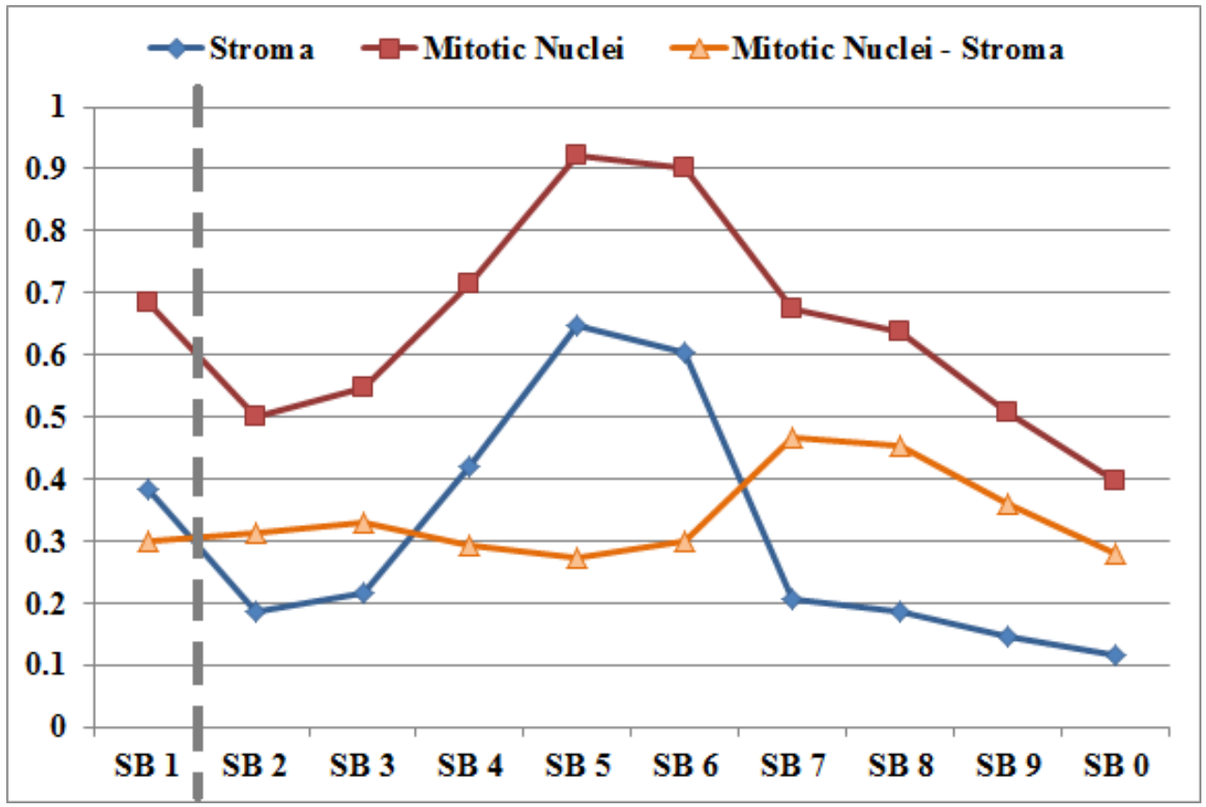
## Spectral Band Selection

### Method 1 – Tissue Spectral Absorption




Multispectral Image (SB 8) Color (RGB) Image



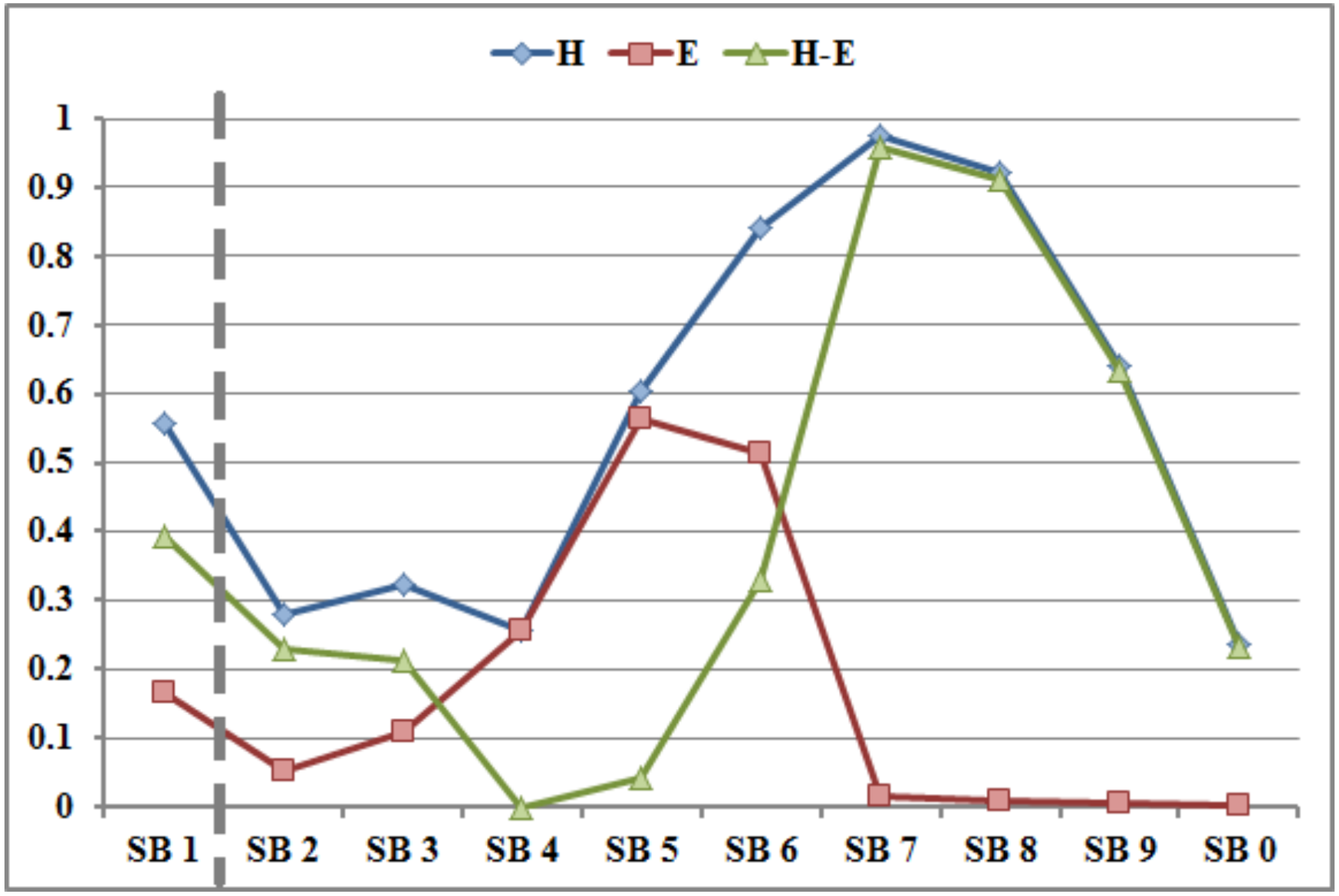




Normalized average gradient spectra of four tissue components

# Mitosis Detection in Multispectral Images

## Spectral Band Selection

### Method 2 – H & E Spectral Absorption




Normalized plot of the Hematoxylin (Blue line) and Eosin (Red line) dye absorption spectra and difference of Hematoxylin and Eosin (green line)

# Mitosis Detection in Multispectral Images

## Spectral Band Selection

### Method 3 – SBs Selection using Minimum redundancy and Maximum Relevance (mRMR)

- Relevance $D = 1/|S| \sum_{s_i \in S} MI(s_i; c_j)$
- Redundancy $R = 1/|S|^2 \sum_{s_i, s_j \in S} MI(s_i; s_j)$
- Mutual Information

$$MI(S;C) = -\sum_{s_i \in S} p(s_i) \log_2 (p(s_i)) + \sum_{s_i \in S} \sum_{c_j \in C} p(s_i, c_j) \log_2 (p s_i c_j)$$

- Incremental search method is used to find the $n$ SBs from the set $\{S_T - S_{n-1}\}$ by maximizing

$$\max_{s_i \in S_T - S_{(n-1)}} [MI(s_i; c) - 1/n-1 \sum_{s_j \in S_{(n-1)}} MI(s_i; s_j)]$$

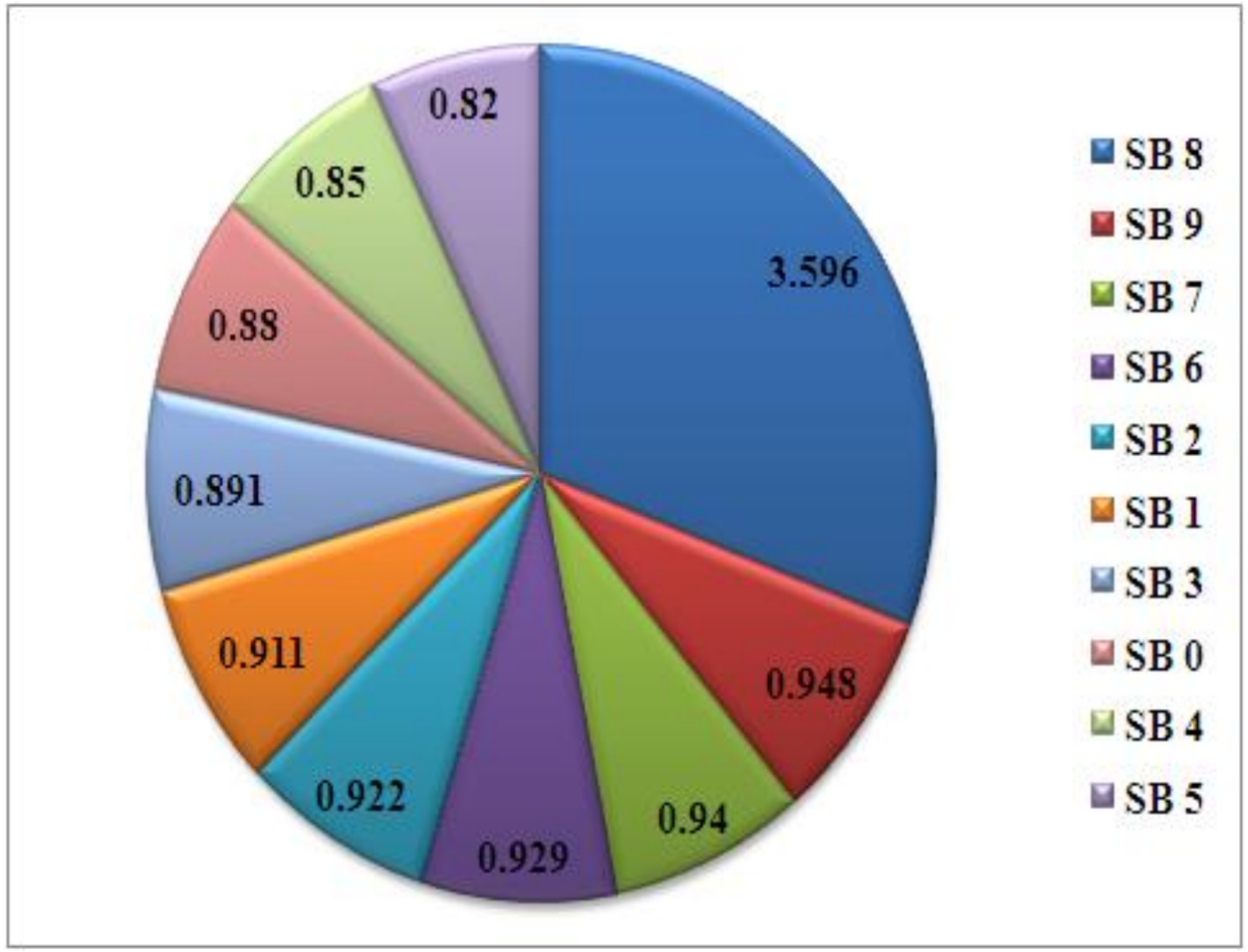
S = SBs set, C = class label, $p(s_i)$ = probability density function of SB $s_i$, $p s_i c_j$ = conditional probability density function of SB $s_i$ and class label $c_j$

# Mitosis Detection in Multispectral Images

## Spectral Band Selection

### Method 3 – SBs Selection using Minimum redundancy and Maximum Relevance (mRMR)

| SBs | MI | Accumulated MI | Accumulated MI% |
|---|---|---|---|
| SB 8 | 3.60 | 3.60 | 33% |
| SB 9 | 3.59 | 0.95 | 42% |
| SB 7 | 3.58 | 0.94 | 51% |
| SB 6 | 3.18 | 0.93 | 60% |
| SB 2 | 3.16 | 0.92 | 69% |
| SB 1 | 3.11 | 0.91 | 78% |
| SB 3 | 3.05 | 0.89 | 86% |
| SB 0 | 2.99 | 0.88 | 91% |
| SB 4 | 2.94 | 0.85 | 95% |
| SB 5 | 2.85 | 0.82 | 100% |



# Mitosis Detection in Multispectral Images

## 3 Rankings of Spectral Bands

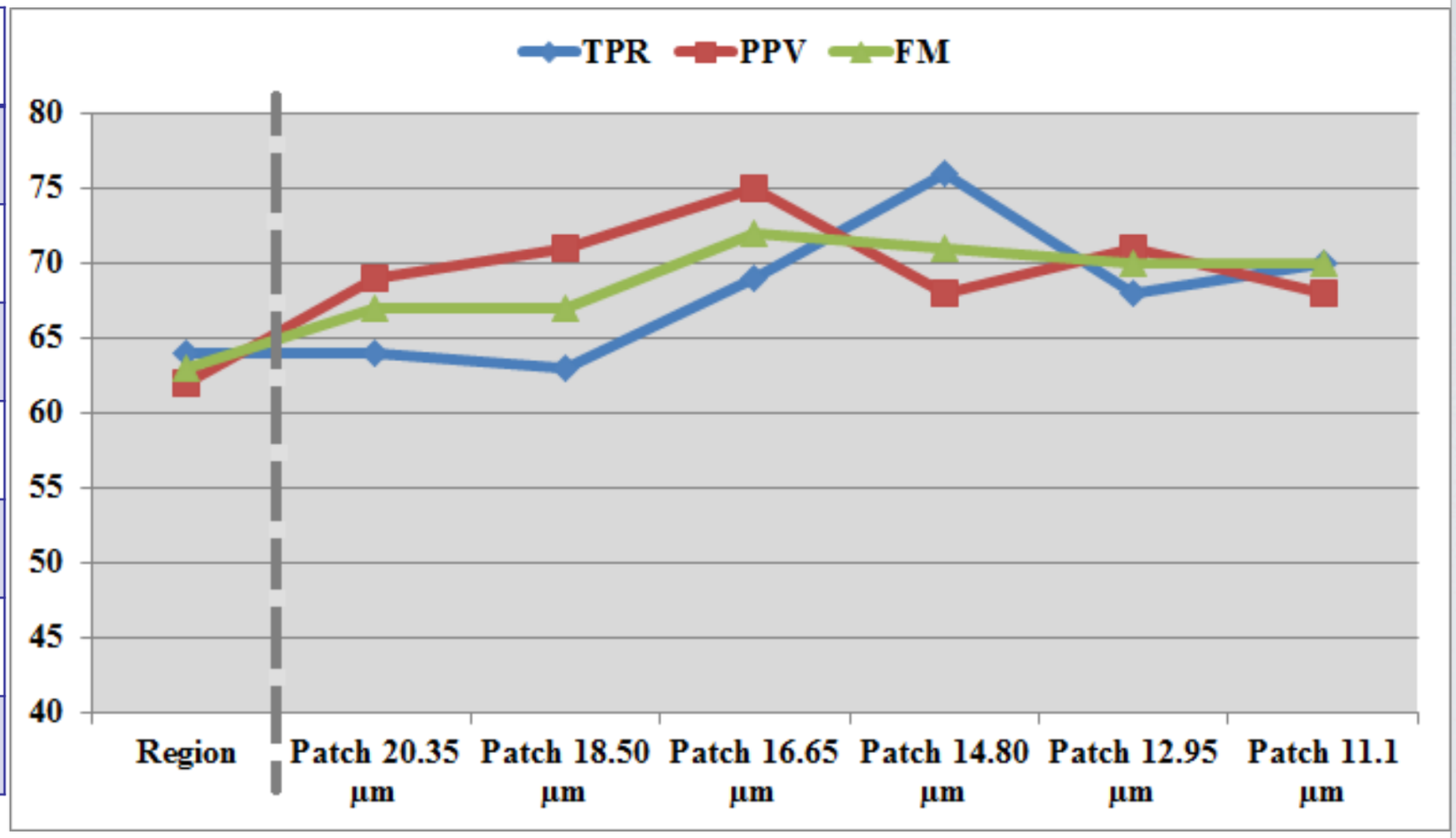
| Method 1 – Tissue Absorption Spectra | | Method 2 – H&E Absorption Spectral | | Method 3 – mRMR | |
|---|---|---|---|---|---|
| SBs | Mitosis-Cytoplasm | SBs | H-E | SBs | MI |
| SB 7 | 0.47 | SB 7 | 0.96 | SB 8 | 3.60 |
| SB 8 | 0.45 | SB 8 | 0.91 | SB 9 | 3.59 |
| SB 9 | 0.36 | SB 9 | 0.64 | SB 7 | 3.58 |
| SB 3 | 0.33 | SB 1 | 0.39 | SB 6 | 3.18 |
| SB 2 | 0.31 | SB 6 | 0.33 | SB 2 | 3.16 |
| SB 6 | 0.30 | SB 0 | 0.23 | SB 1 | 3.11 |
| SB 1 | 0.30 | SB 2 | 0.23 | SB 3 | 3.05 |
| SB 4 | 0.29 | SB 3 | 0.21 | SB 0 | 2.99 |
| SB 0 | 0.28 | SB 5 | 0.04 | SB 4 | 2.94 |
| SB 5 | 0.27 | SB 4 | 0 | SB 5 | 2.85 |

- Selected SBs are 8,9,7,6,2,1,3 and 0.

# Mitosis Detection in Multispectral Images

## Region vs Patch Features based Classification Results

| Different Patch Sizes | |
|---|---|
| Sizes in pixels | Sizes in µm |
| 110 | 20.35 20.35 |
| 100 100 | 18.50 18.50 |
| 90 90 | 16.65 16.65 |
| 80 80 | 14.82 14.80 |
| 70 70 | 12.95 12.95 |
| 60 60 | 11.1 11.1 |




Region vs Patch features based classification results using LSVM classifiers

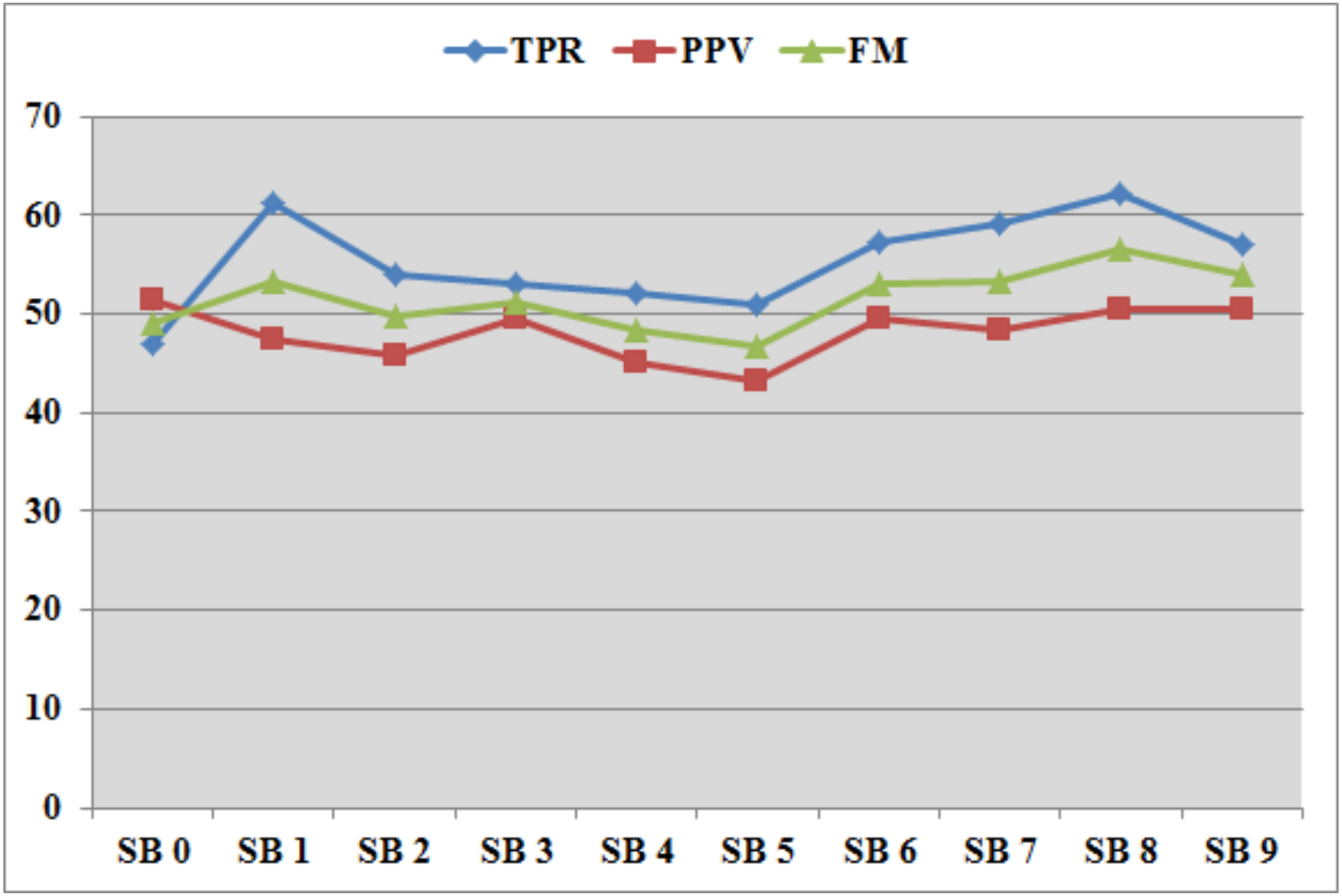
# Mitosis Detection in Multispectral Images

## MITM$^3$ Classification on Evaluation Set

| | | All SBs Features | | | Selected 8 SBs Features | | |
|---|---|---|---|---|---|---|---|
| Features | Classifiers | TPR | PPV | FM | TPR | PPV | FM |
| Region Features | DT | 67% | 53% | 59.1% | 62% | 62% | 62.24% |
| | MLP | 64% | 56% | 59.72% | 62% | 66% | 63.10% |
| | LSVM | 63% | 60% | 61.69% | 64% | 62% | 63.32% |
| | NLSVM | 54% | 68% | 60.23% | 59% | 69% | 63.74% |
| Patch size 16.65 µm Features | DT | 61% | 71% | 65.57% | 65% | 70% | 67.72% |
| | MLP | 63% | 67% | 64.92% | 66% | 70% | 68.06% |
| | LSVM | 69% | 75% | 71.96% | 74% | 73% | 73.74% |
| | NLSVM | 55% | 77% | 64.29% | 59% | 77% | 67.05 |

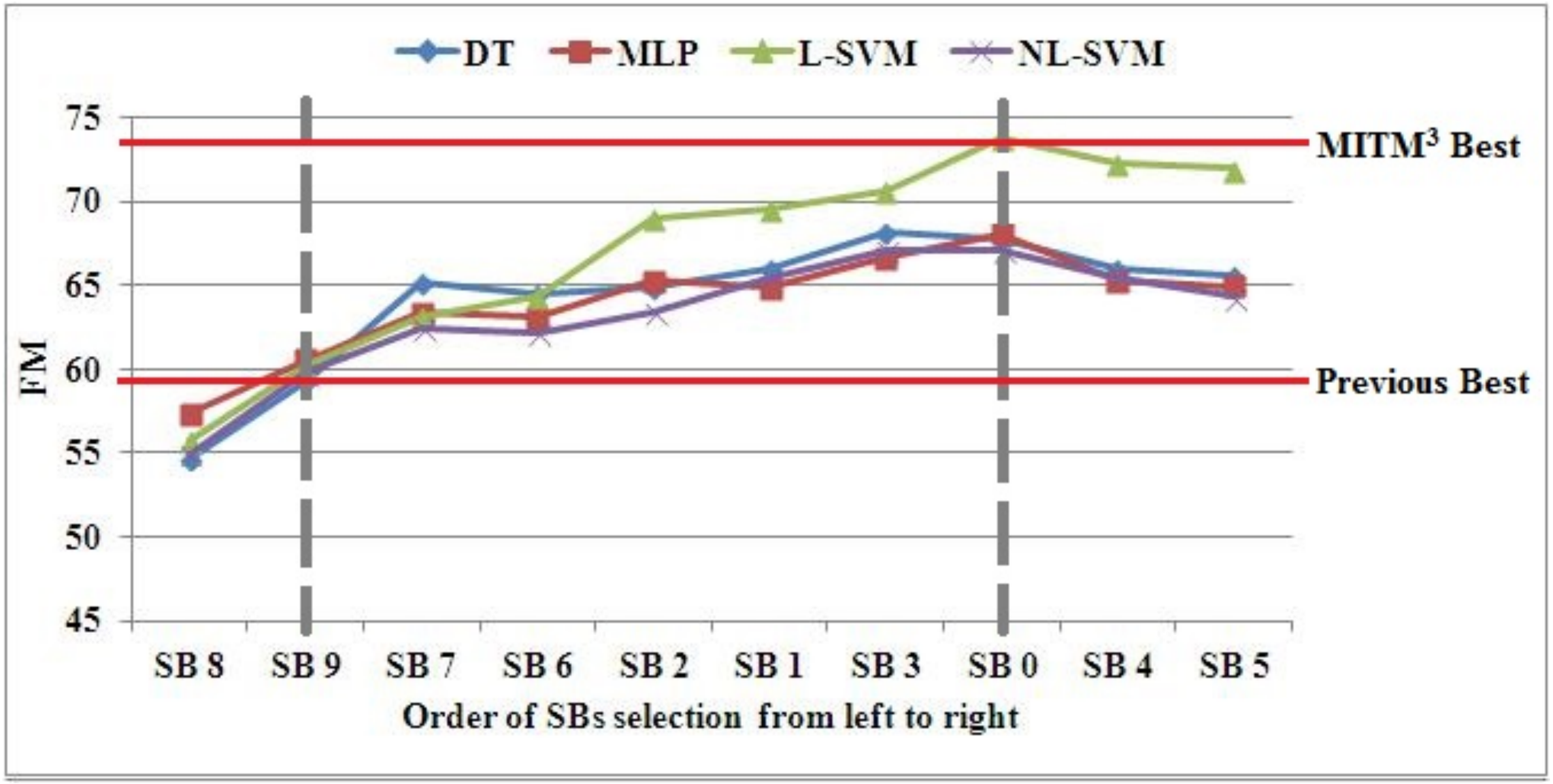
# Mitosis Detection in Multispectral Images

## Plot of TPR, PPV and FM using Single SB Features with LSVM classifier



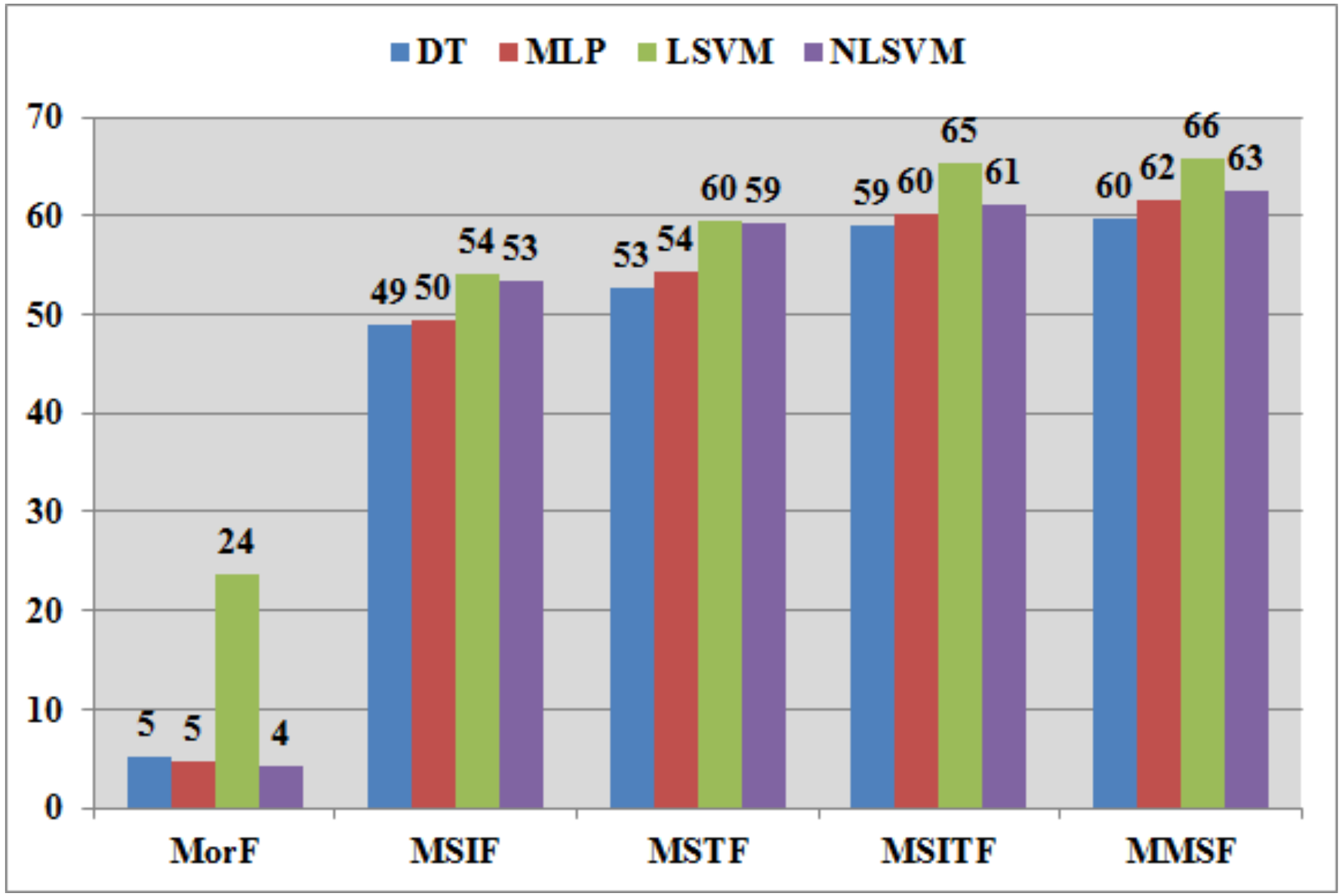
# Mitosis Detection in Multispectral Images

## Plot of FM using Accumulated Features from the order of mRMR Selection



# Mitosis Detection in Multispectral Images

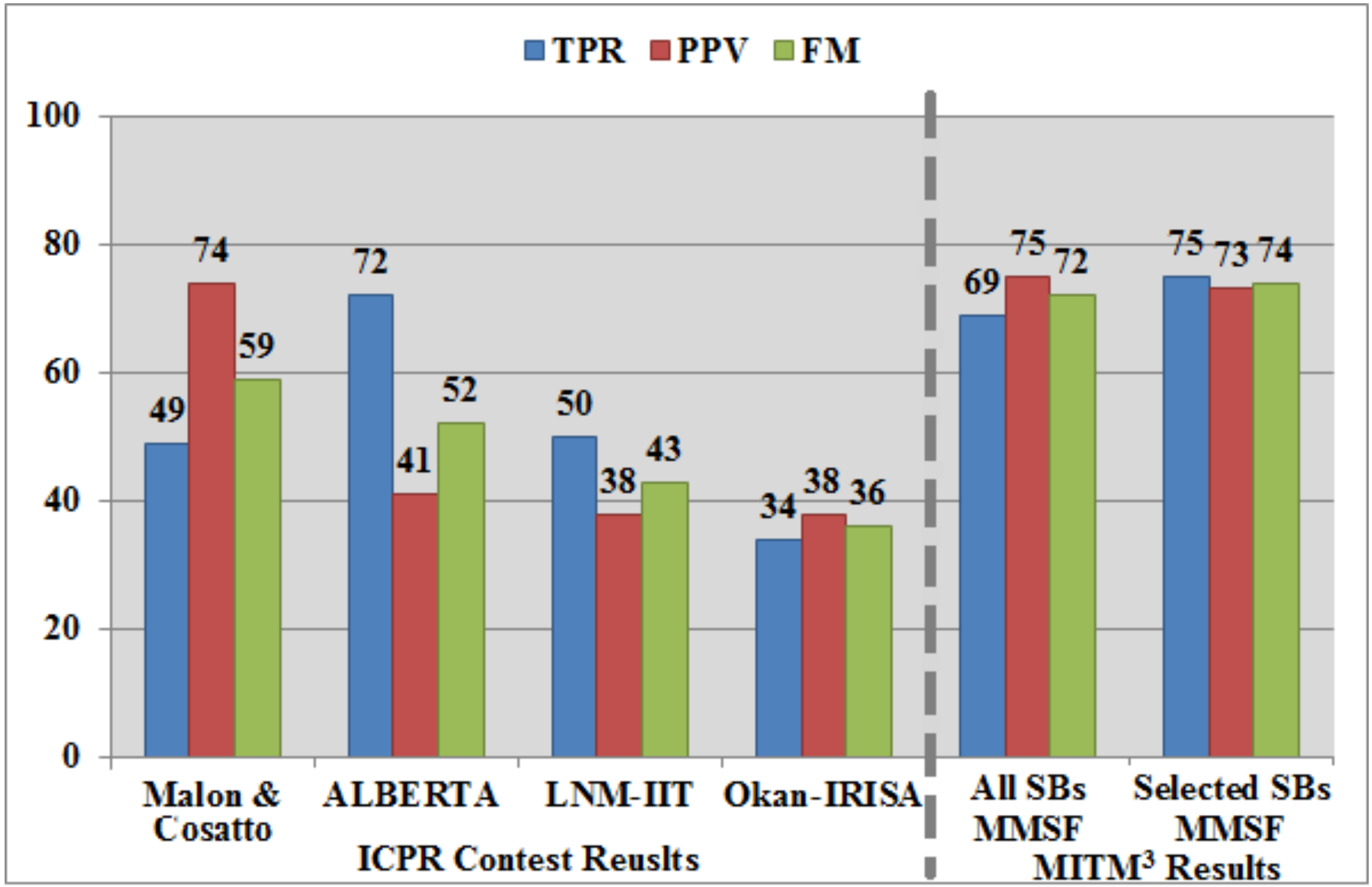
## Results on different subsets of Features using 5-Fold Cross Validation




MorF = Morphology Features
MSIF = Multi-Spectral Intensity Features
MSTF = Multi-Spectral Texture Features
MSITF = Multi-Spectral Intensity & Texture Features
MMSF = Morphological & Multispectral Statistical Features

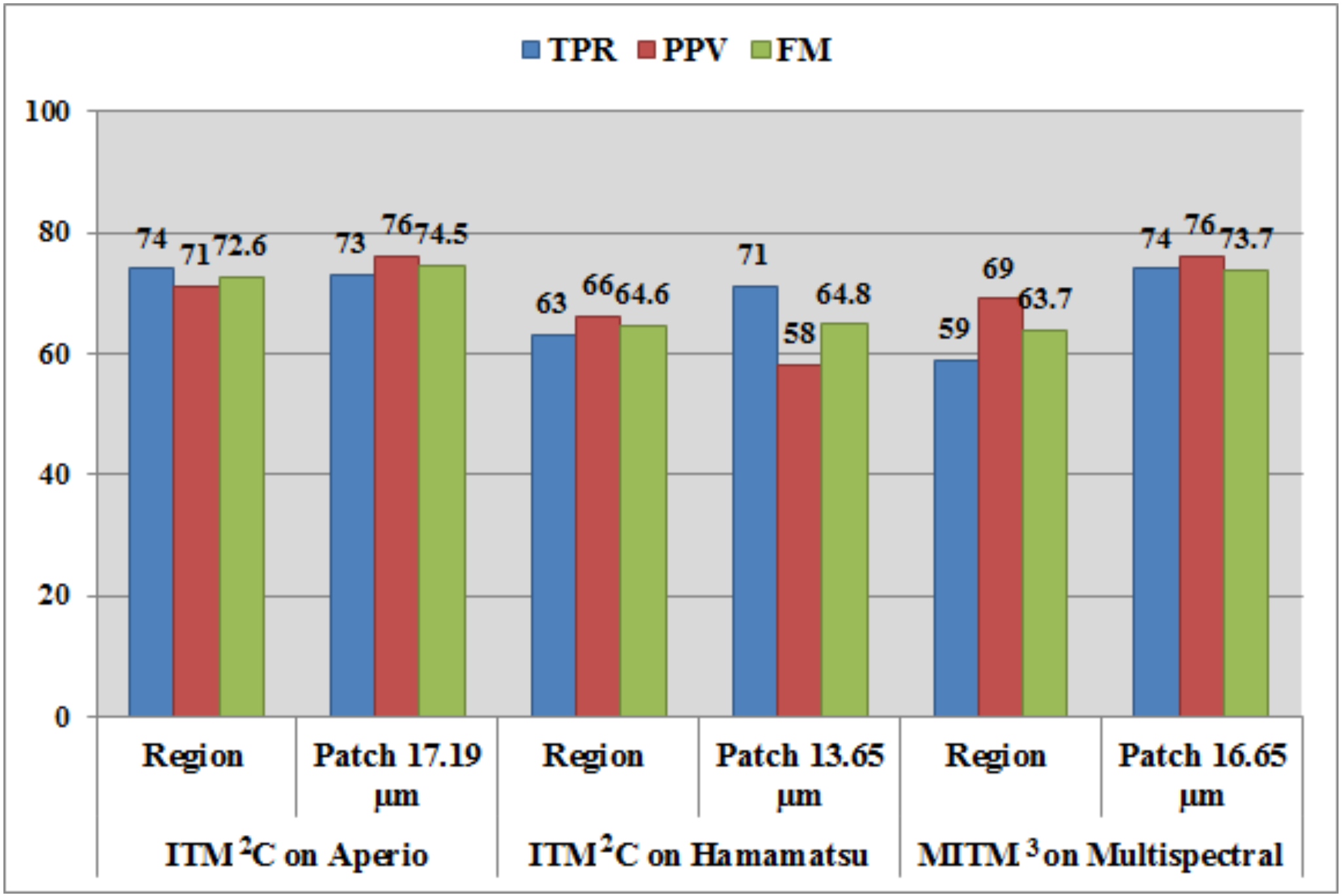
# Mitosis Detection in Multispectral Images

## Comparison of MITM$^3$ Framework with ICPR 2012 MITOS Contest



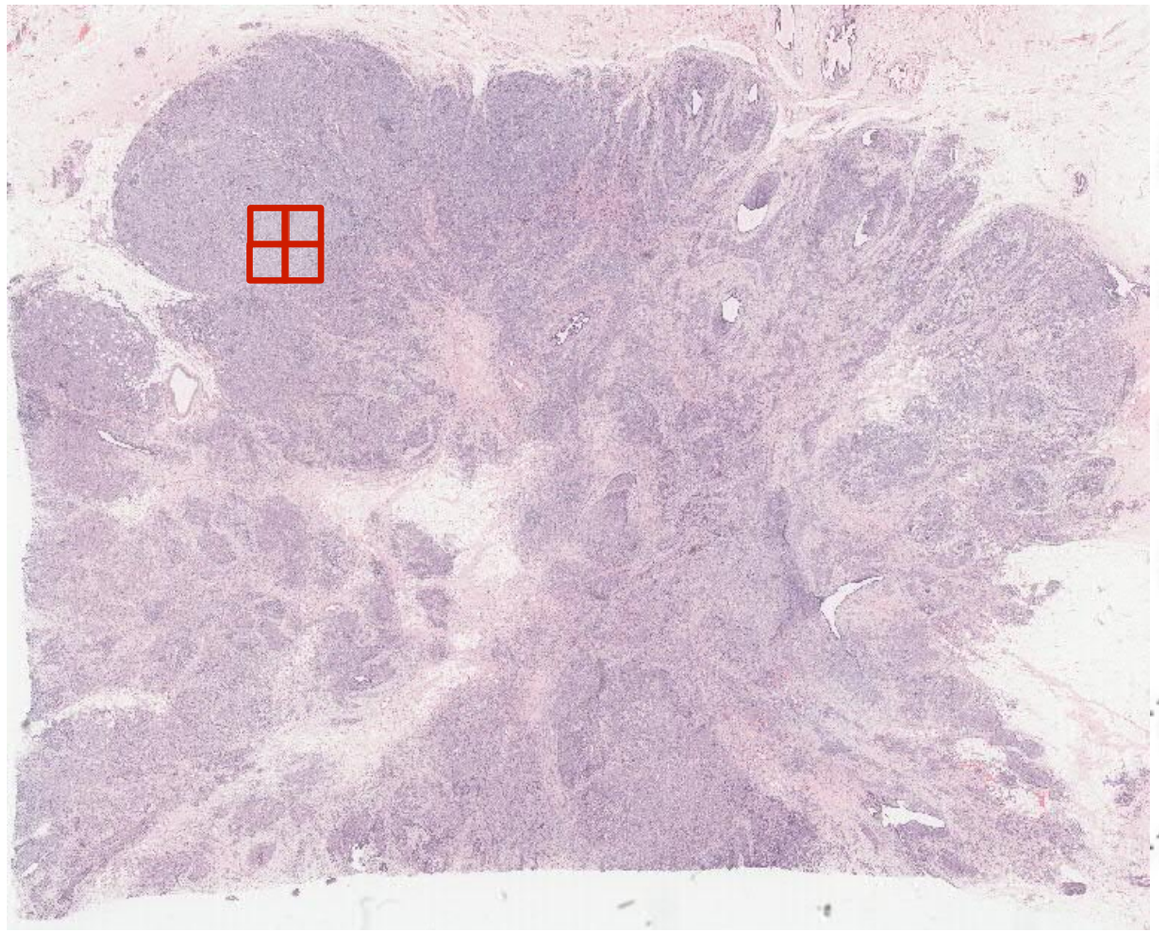
# Mitosis Detection in Multispectral Images

## Comparison of ITM$^2$C and MITM$^3$ Frameworks

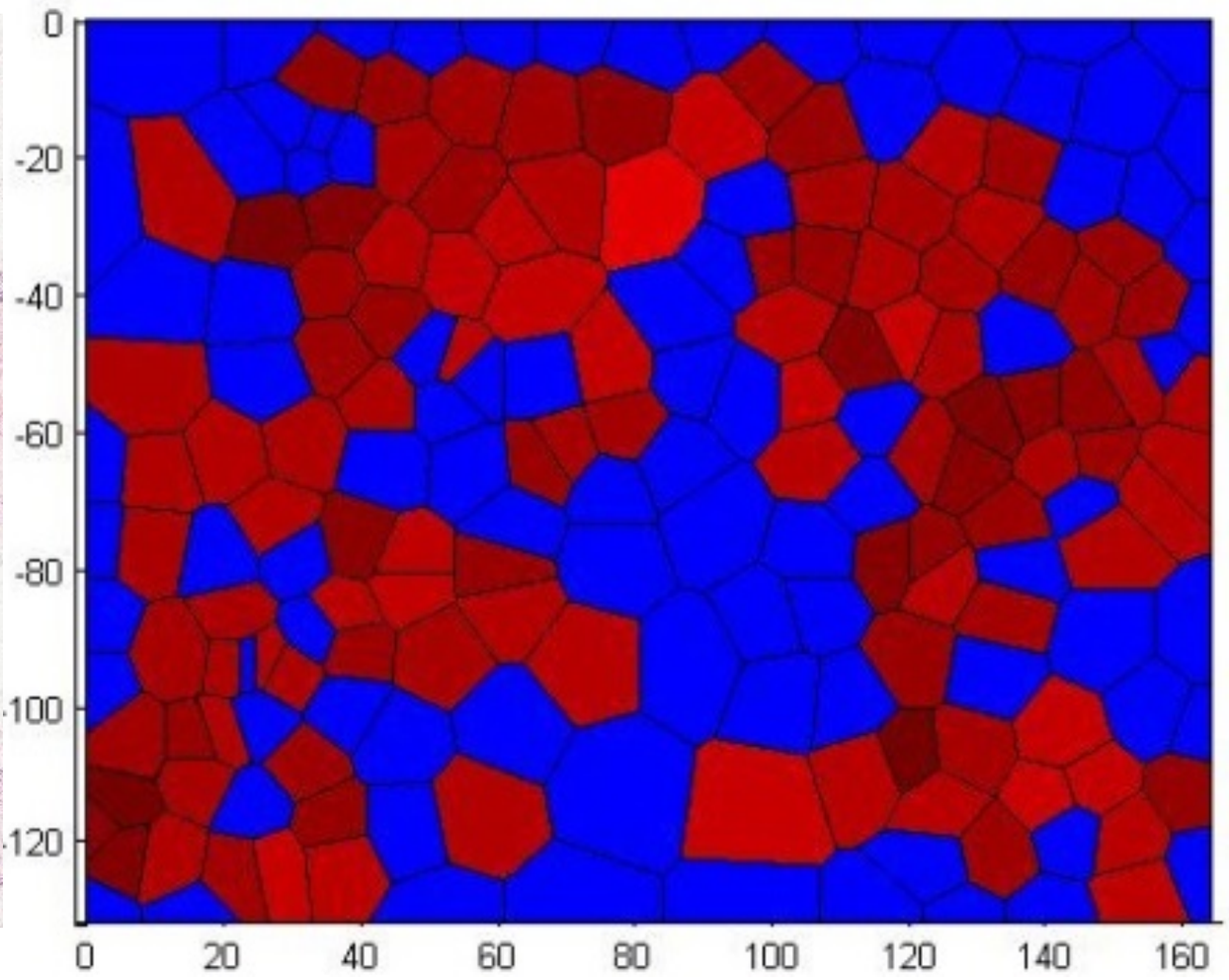


# Whole Slide Image (WSI) Analysis

## Switching from HPF to WSI Analysis



HPF analysis for mitotic count / nuclei atypia in WSI



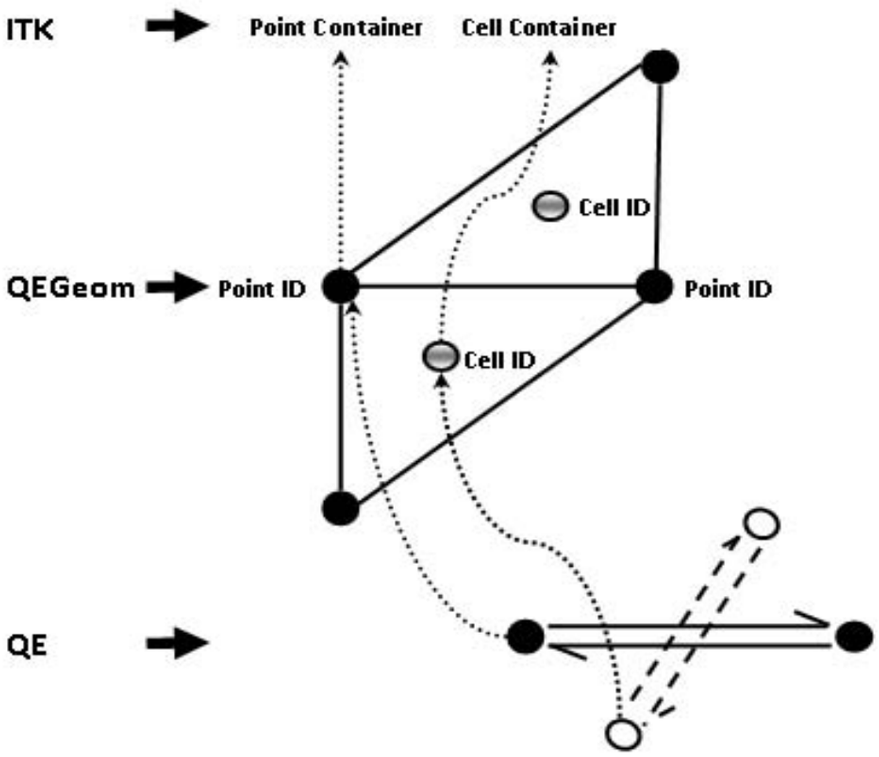

Voronoi Diagram computed using analyzed HPF of WSI

# Dynamic Sampling Framework for WSI Analysis

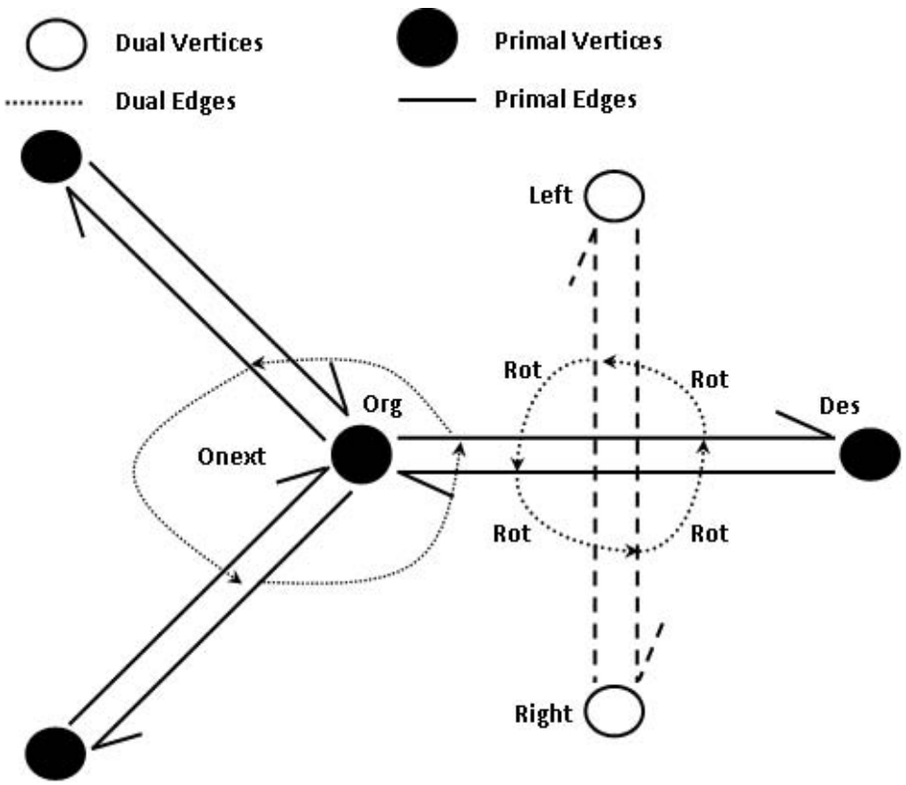
## Orientable 2-Manifold Meshes and Existing Data Structure

- *itk::QuadEdgeMesh* existing data structure in ITK can handle discrete 2-manifold surfaces
- A constant complexity local access on modifications

| | Primal | Dual |
|---|---|---|
| Geometry | Yes | No |
| Topology | Yes | Yes |




QuadEdgeMesh Structure



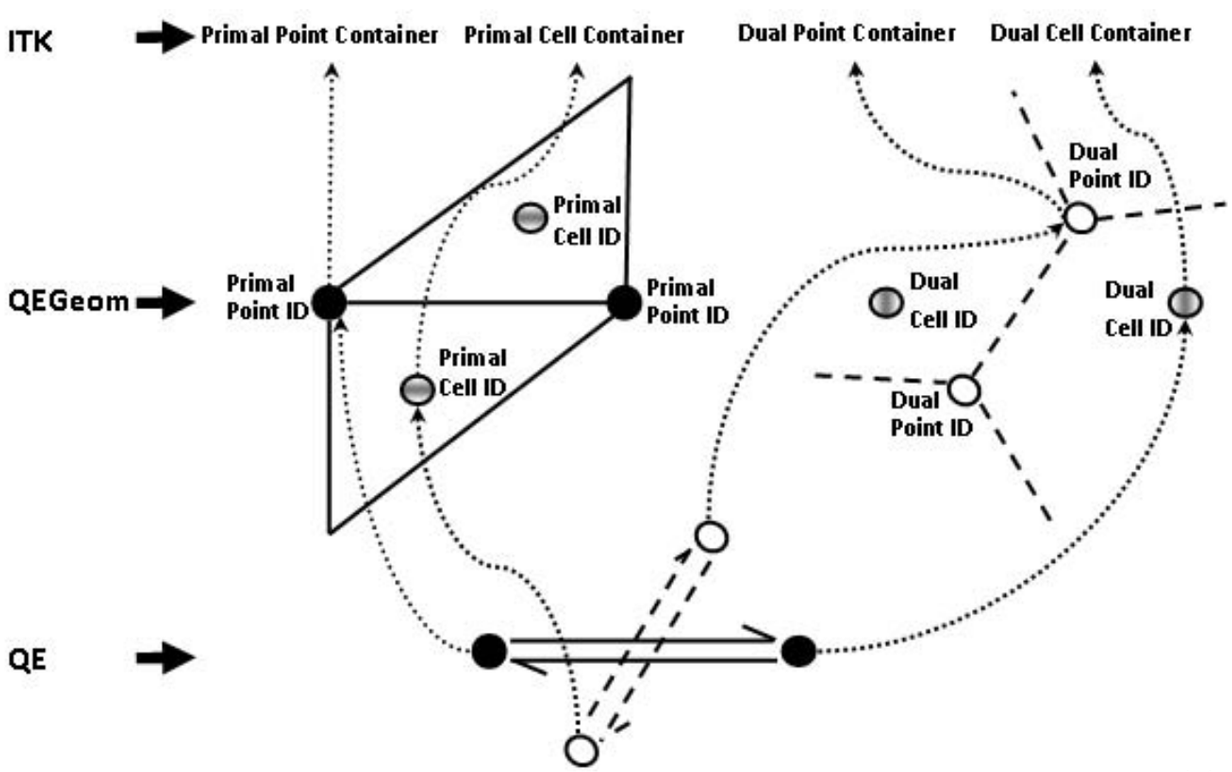

QuadEdge Structure

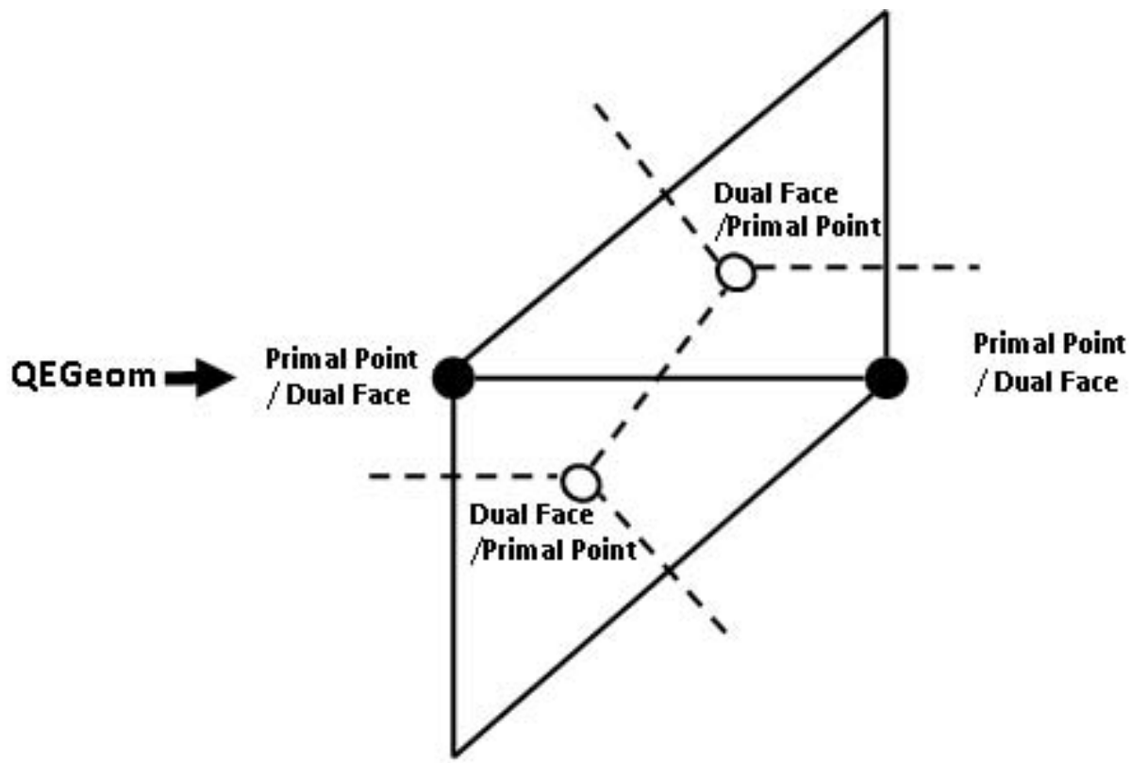
# Dynamic Sampling Framework for WSI Analysis

## Orientable 2-Manifold Meshes and NewData Structure

- Proposed an extension of existing ITK data structure for Orientable 2-manifold meshes to handle duality
- *itk::QuadEdgeMeshWithDual* new data structure and a filter that transform primal mesh to primal/ dual mesh

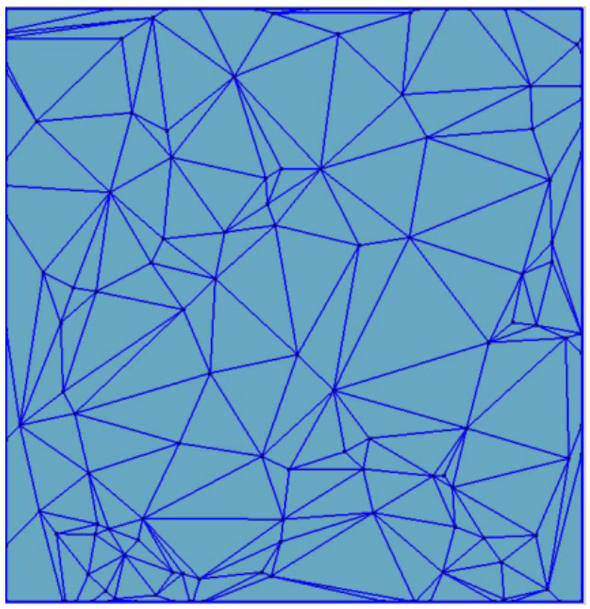
| | | Old Structure | New Structure |
|---|---|---|---|
| Changes | OriginRefType | Point ID, Cell ID | Pair< Point, Cell >, Pair< Cell, Point > |
| Additions | Dual Containers | - | Dual Pointers, Cells and EdgeCells Containers |

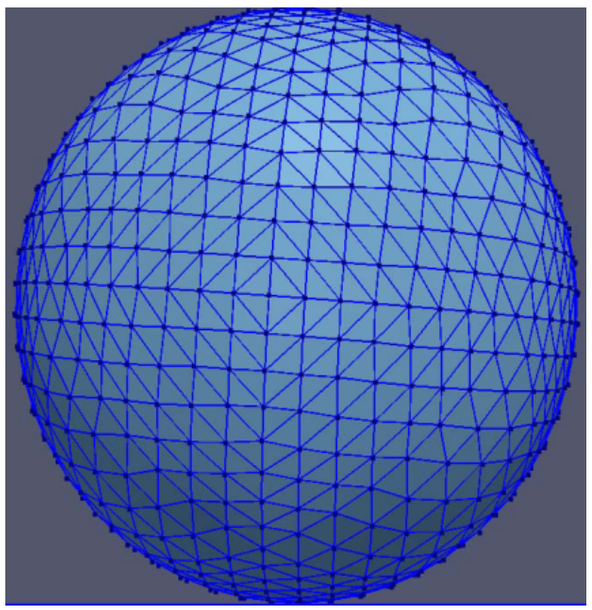


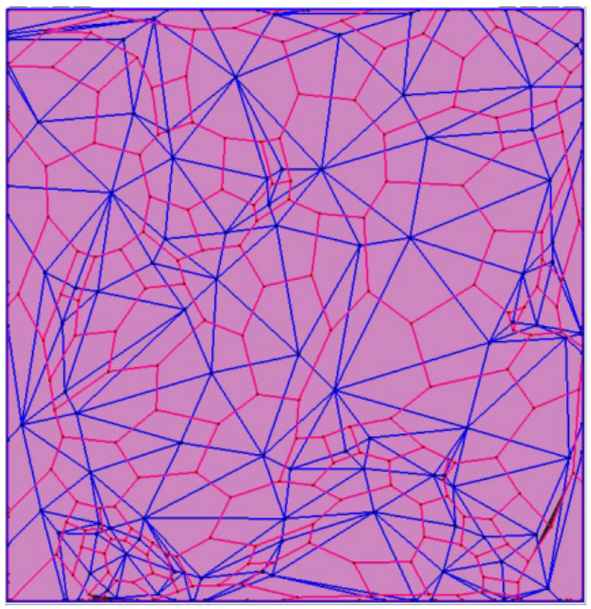
# Dynamic Sampling Framework for WSI Analysis

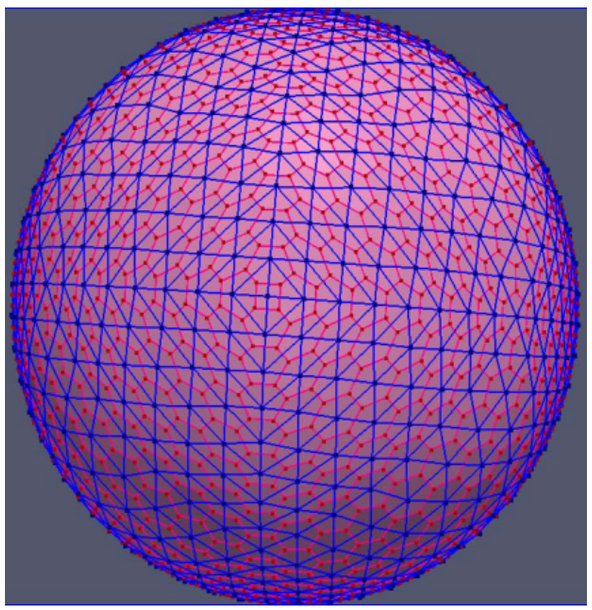
## Planer Delaunay/Voronoi Mesh and Non-Planer Triangulation/Simplex Mesh



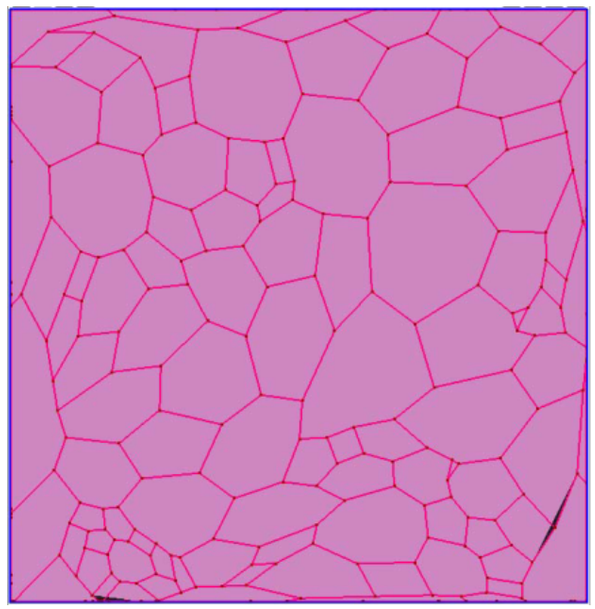


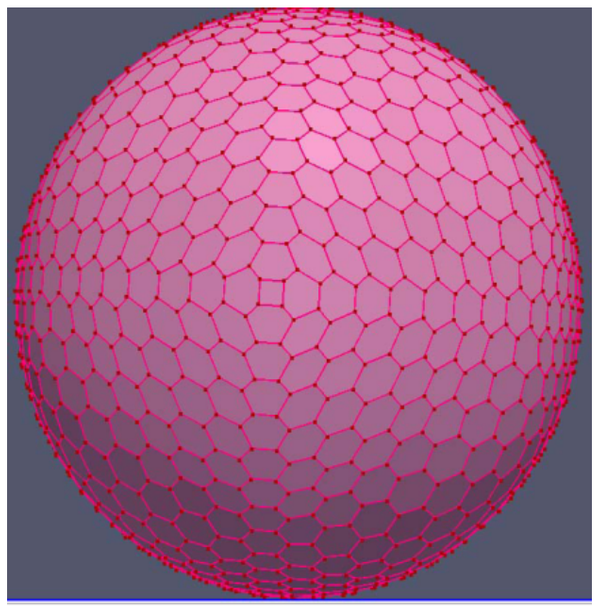
Primal Mesh





Primal with dual Mesh





Dual Mesh

# MICO Project

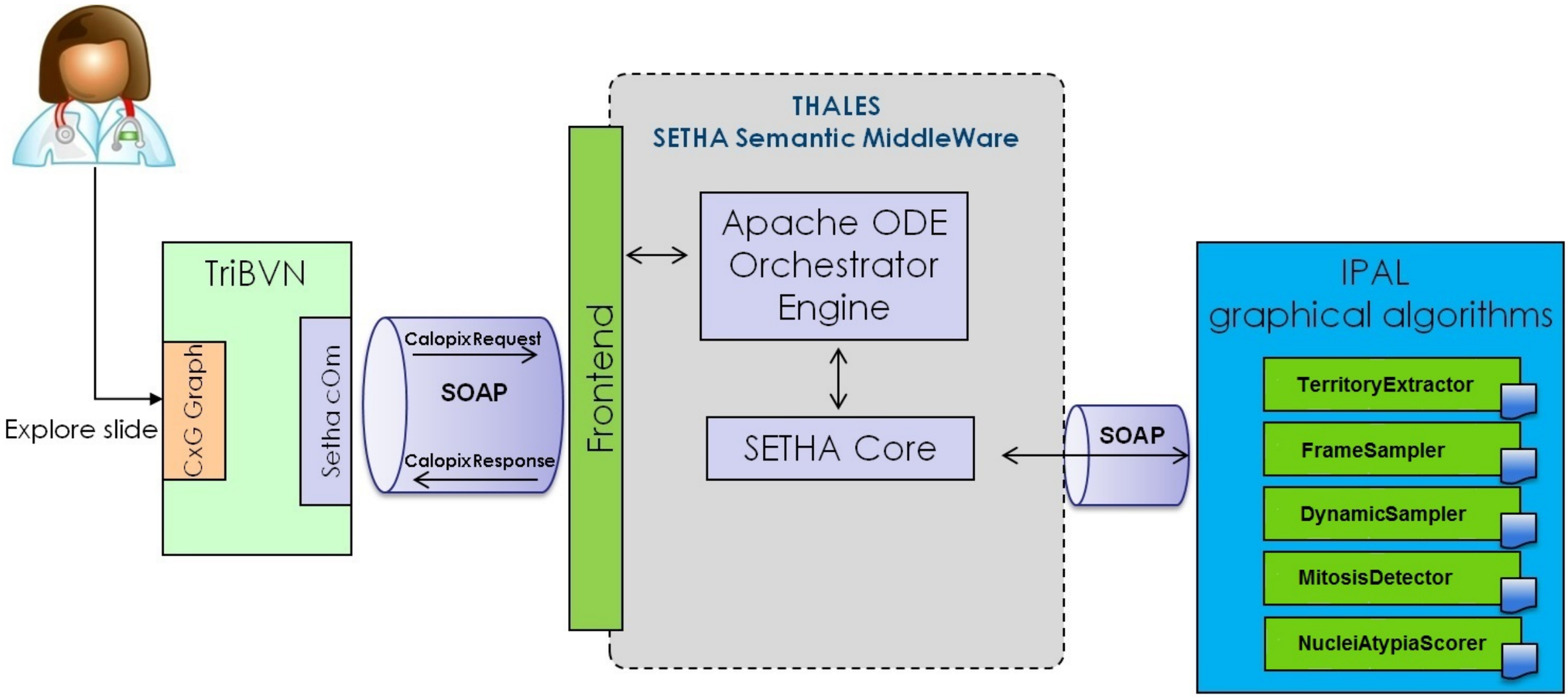
## MICO Project (ANR TecSan)

- COgnitive virtual MIcroscope for Breast Cancer Grading (MICO) Project
  - Funded by French National Research Agency (ANR)
  - Launched in Feb, 2011 – Jul, 2014 (3.5 Years)

| | |
|---|---|
| | **IPAL — University Joseph Fourier**<br>Image Processing, Ontologies, Reasoning |
| | **Pitié-Salpêtrière Hospital**<br>Pathologists, Expertise on breast cancer |
| | **University Pierre and Marie Curie**<br>Contextual graphs, GPU |
| | **TRIBVN**<br>User interface |
| | **Agfa HealthCare**<br>Ontologies, Reasoning |
| | **Thales**<br>Semantic middleware |

MICO ANR TecSan Project Partners

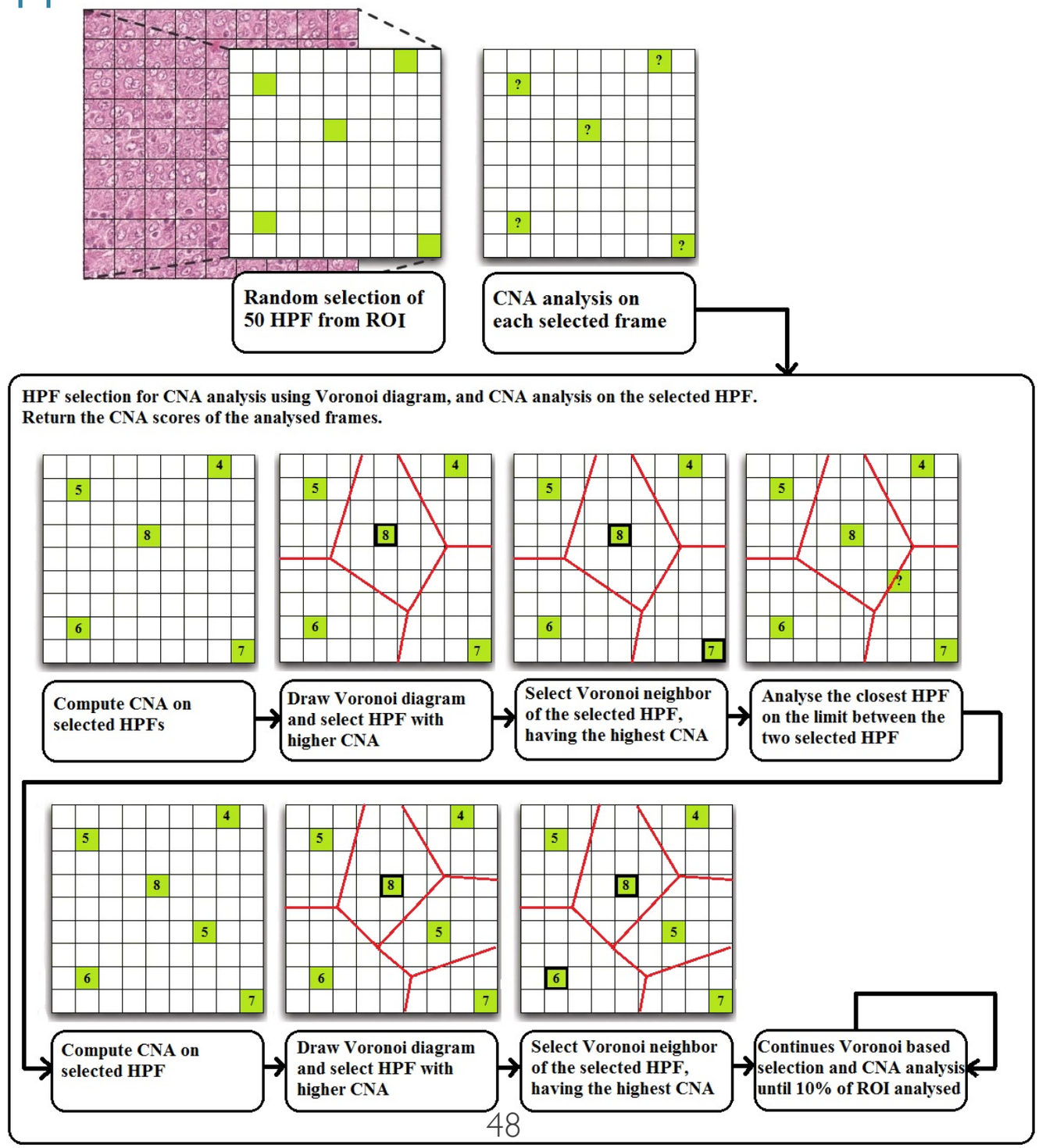
## MICO Architecture




MICO 2.0 Architecture

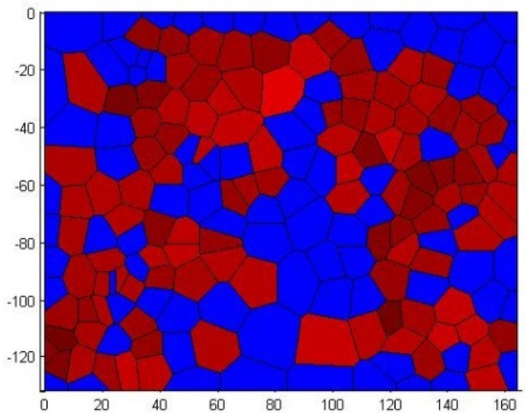
# MICO Project

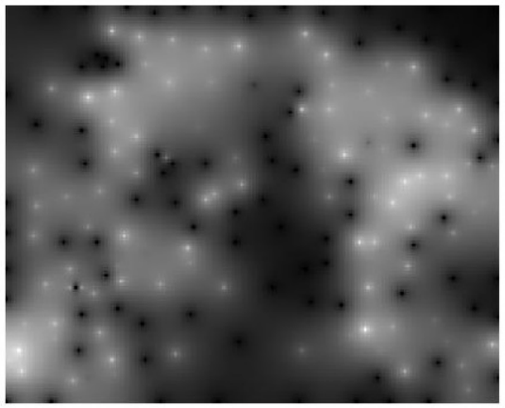
## Dynamic Sampling applied over ROI for CNA Evaluation



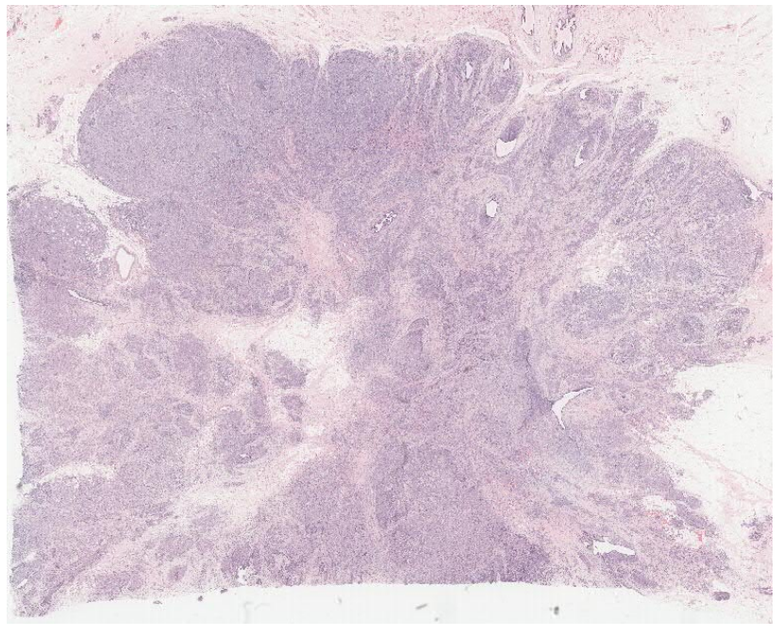
# MICO Project

## Dynamic Sampling applied over WSI: Incrementally Voronoi Diagram

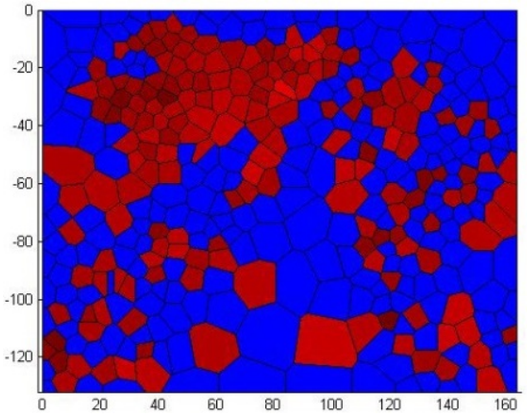


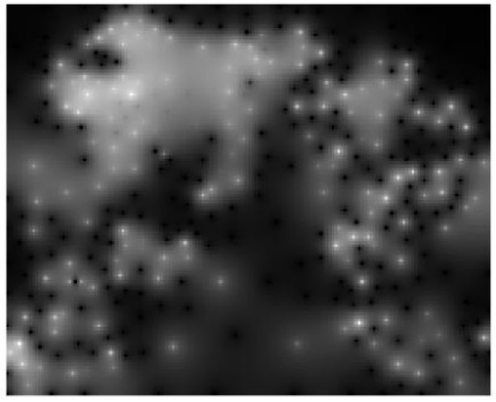



After 200 Iteration

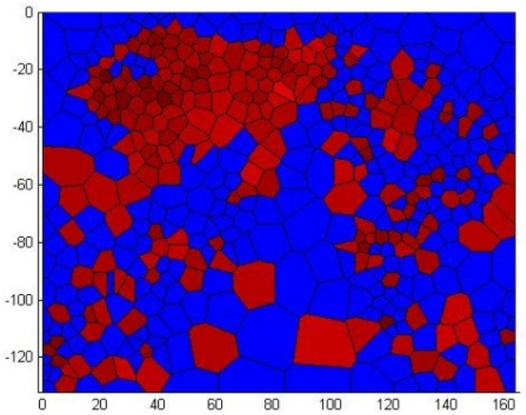


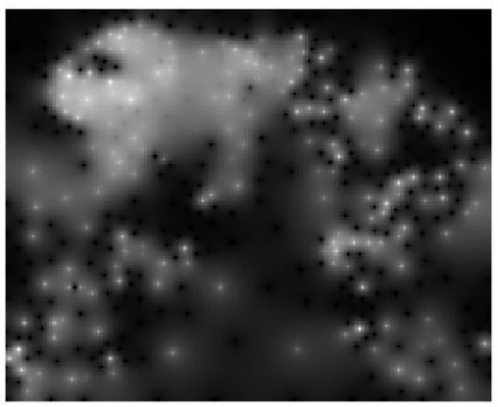
Actual WSI



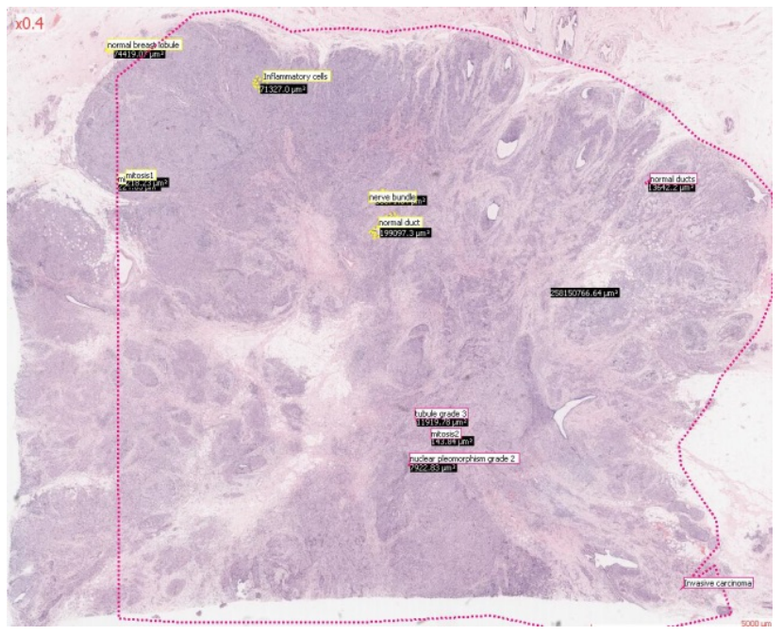



After 300 Iteration



After 500 Iteration

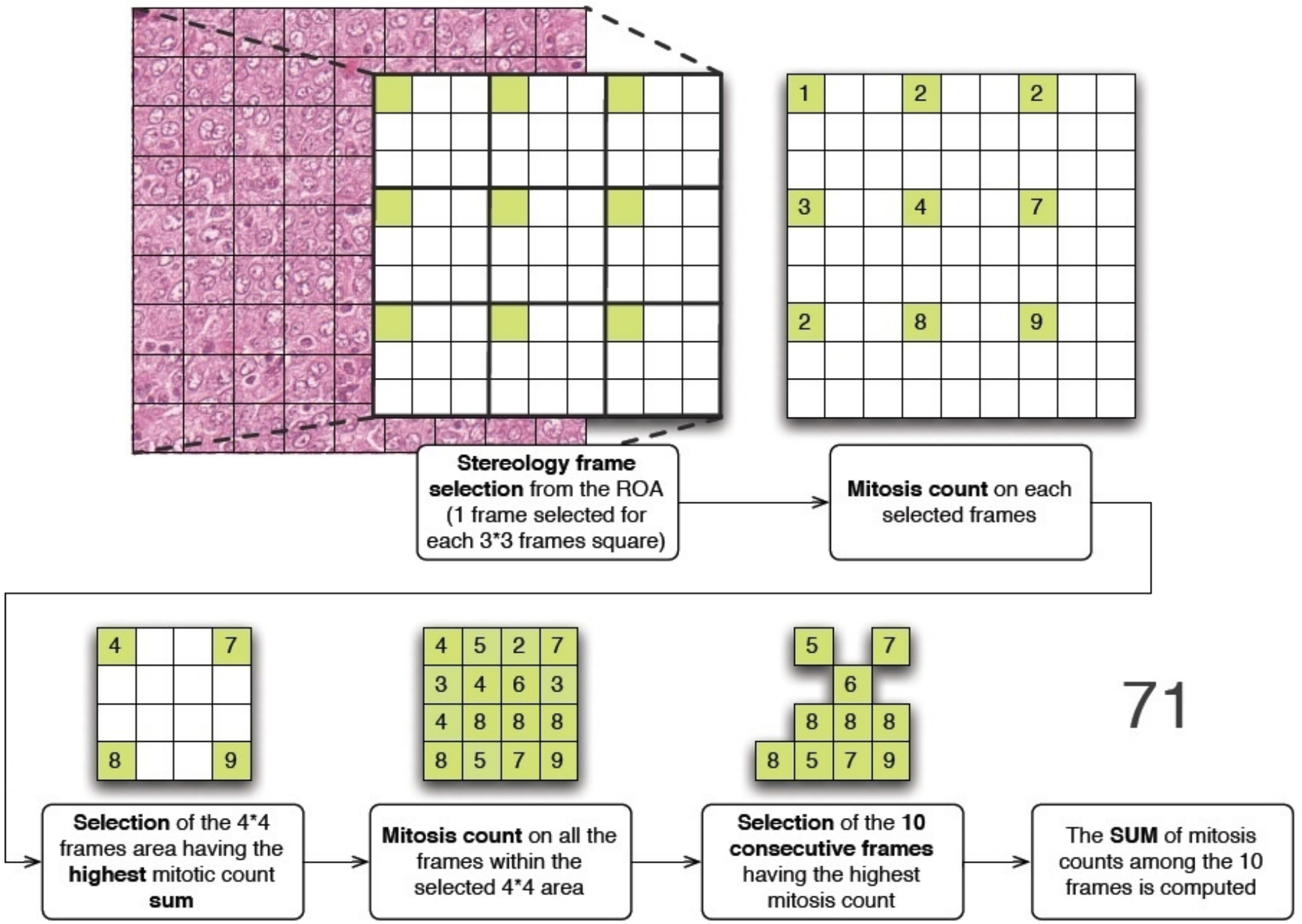



Annotated WSI

# MICO Project

## Stereology Framework for evaluation of ITM$^2$C framework in MICO

- TerritoryExtractor
- FrameGenerator
- FrameSampler 3×3
- FrameSampler 4×4
- ITM2C Framework
- MitosisScorer

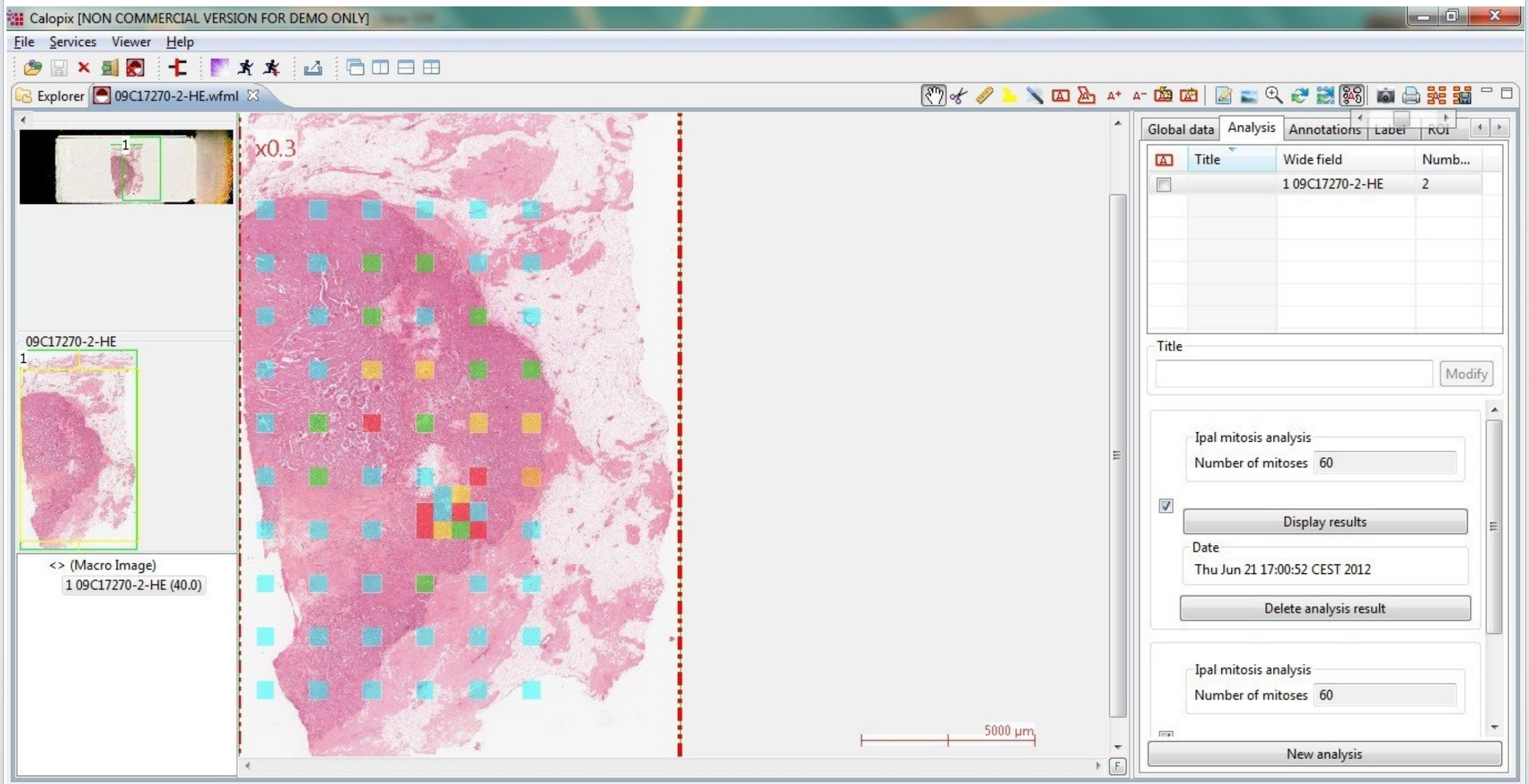



Stereology Flow used for Mitosis Score over a ROI

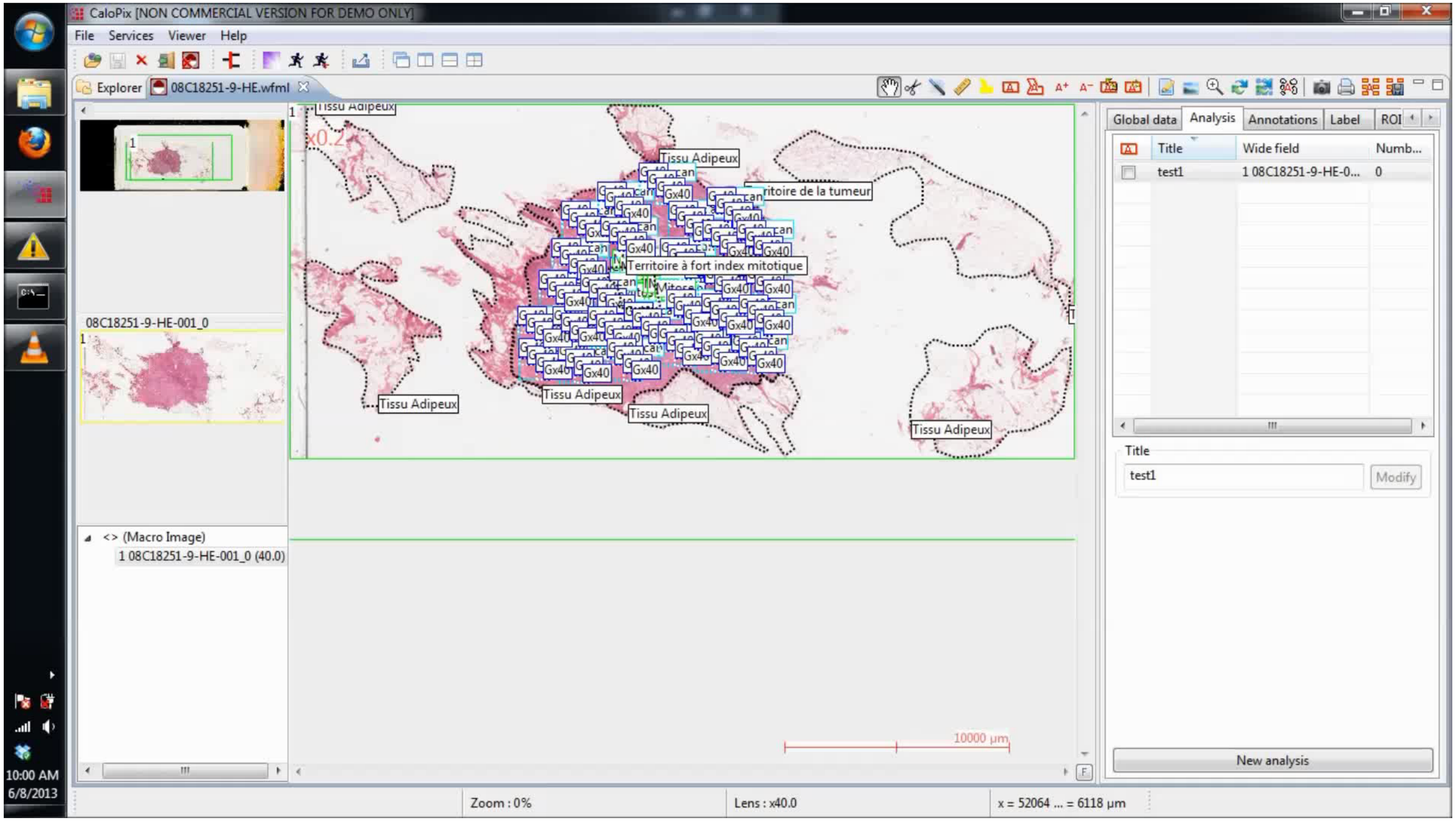
# MICO Project

## WSI analyzed by ITM²C Framework are displayed on Calopix platform

The color code is based on the number of mitosis detected in the frame (from blue for zero mitosis to red for 10 or more mitosis.



# Mitosis Detector Integration in Calopix



# Conclusion & Future works

## Summary

- Proposed automated mitosis detection framework for different scanners and multispectral microscope
- Efficient and generic strategies (Stereology & Dynamic Sampling) to explore WSI
- Evaluation of these frameworks in MICO platform

## Future work

- Expand proposed frameworks from two-class problem to multi-class problem and classify other microscopic objects like lymphocytes, apoptosis, normal nuclei, cancer nuclei
- Main area of Interests:
  - Machine Learning
  - Computer Vision
  - Pattern Recognition
  - Medical Image Analysis

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# Reference


*Intellectual Property*

- *"**MitosisDetector** – Mitosis Detector for Histopathology"*, **H. Irshad**, L. Roux, D. Racoceanu, *Copyright CNRS (CNRS Statement Software) No. DL 05963-01 for 2955 IPAL UMI, 2013*.

*Journals*

1. **H. Irshad**, A. Gouaillard, L. Roux, D. Racoceanu, "Multispectral Band Selection and Spatial Characterization: Application to Mitosis Detection in Breast Cancer Histopathology", in *Computerized Medical Imaging and Graphics (CMIG)*, (Submitted).
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10. **H. Irshad**, L. Roux, O. Morère, D. Racoceanu, G. L. Naour, and F. Capron, "Détection automatique et calcul du compte de mitoses sur lames H&E", in *Recherche en Imagerie et Technologies pour la Santé (RITS)*, Bordeaux, France, Apr., 2013.
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# Questions ?


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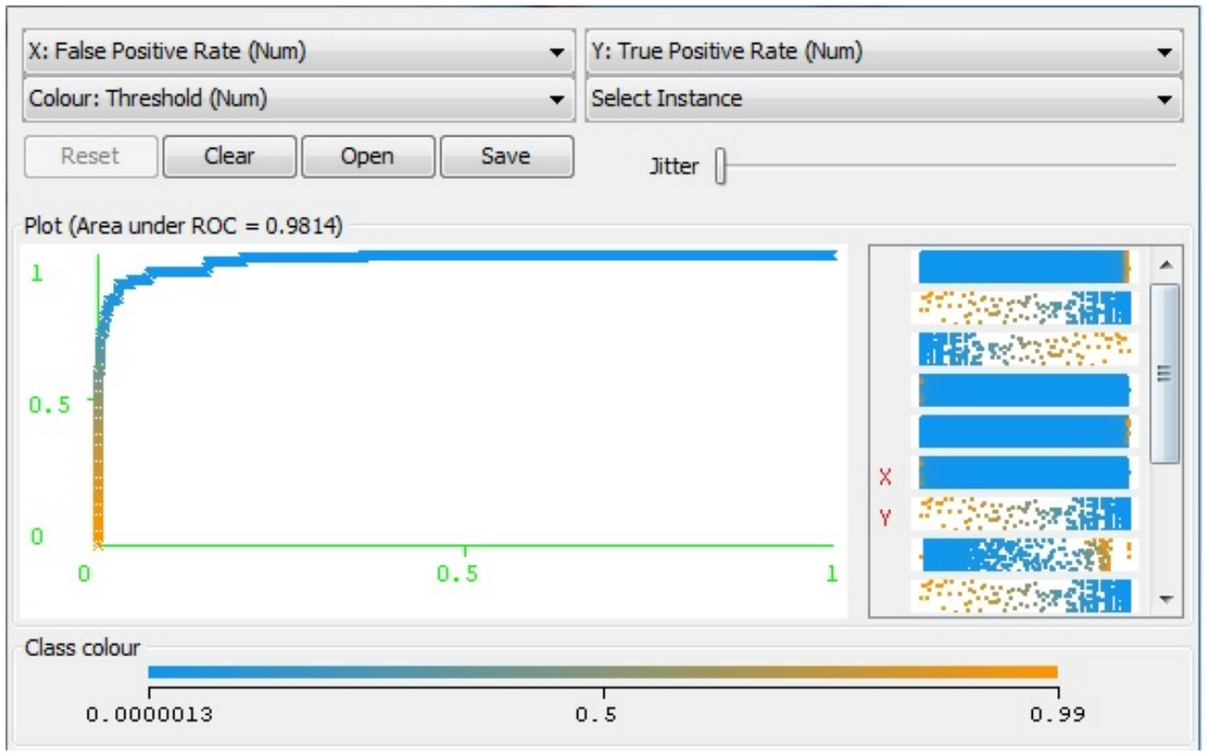
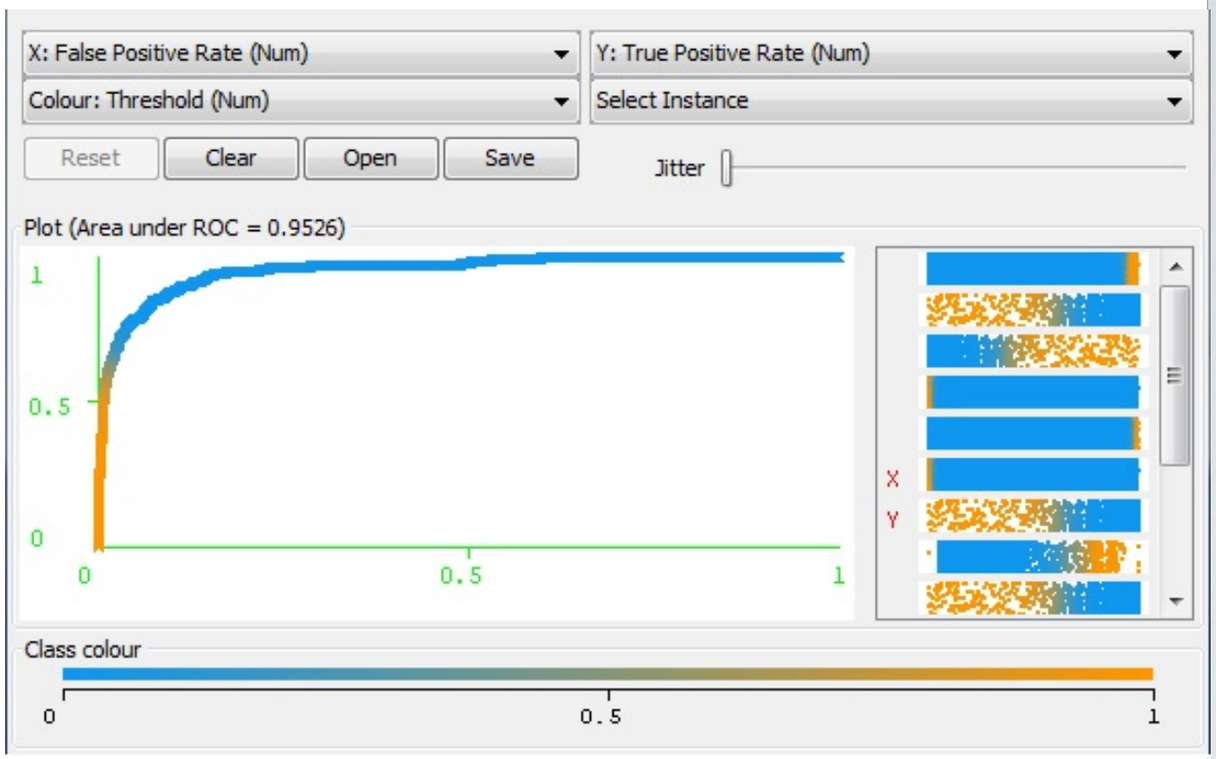
# Mitosis Detection in Color Images

## Receiver Operating Characteristic (ROC) curve of patch based features with LSVM Classifier



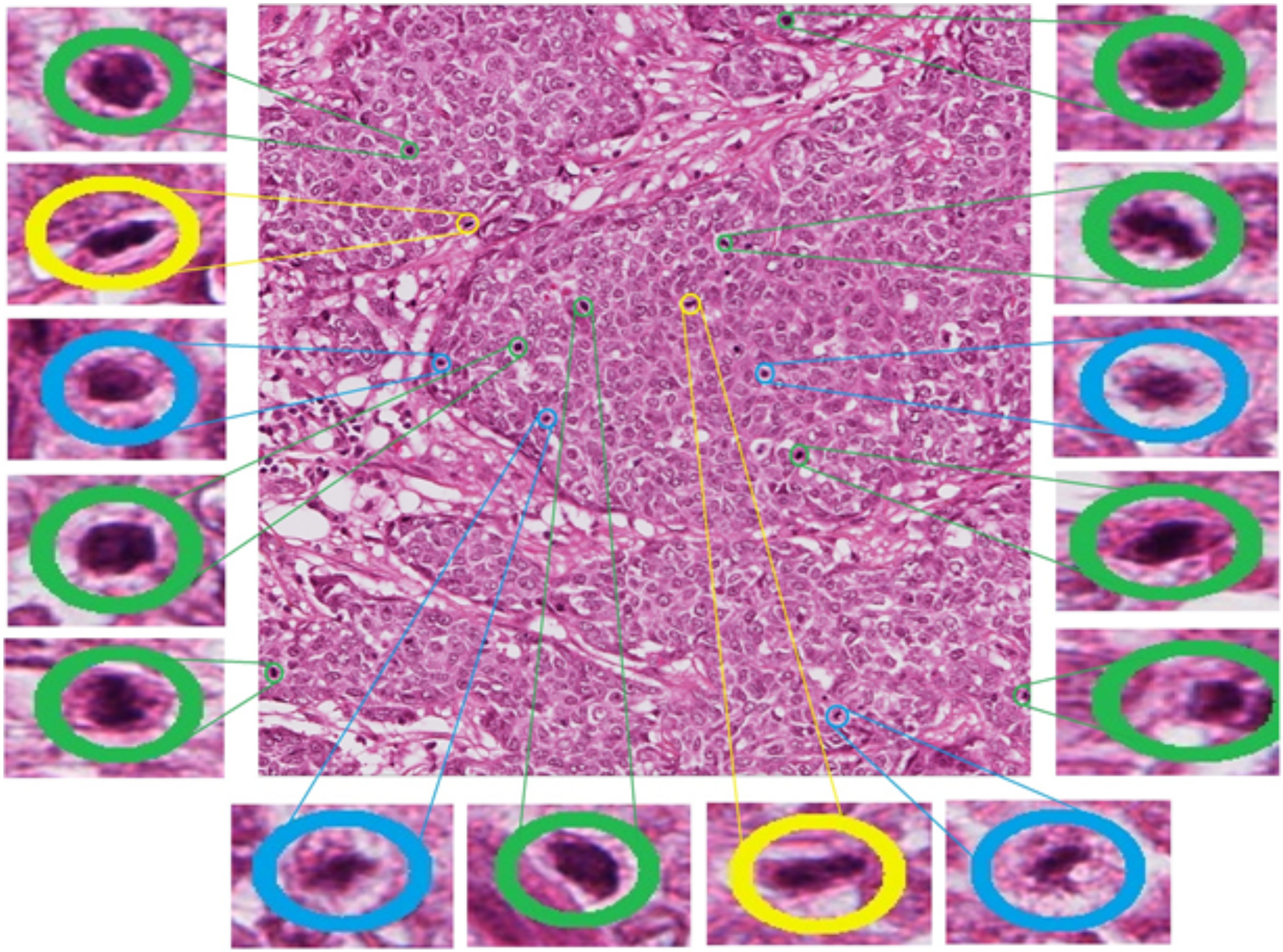

On Aperio Dataset




On Hamamatsu Dataset

# Mitosis Detection in Color Images

## Candidate Classification on Hamamatsu Dataset TP=Green, FP=Yellow, FN-Blue)



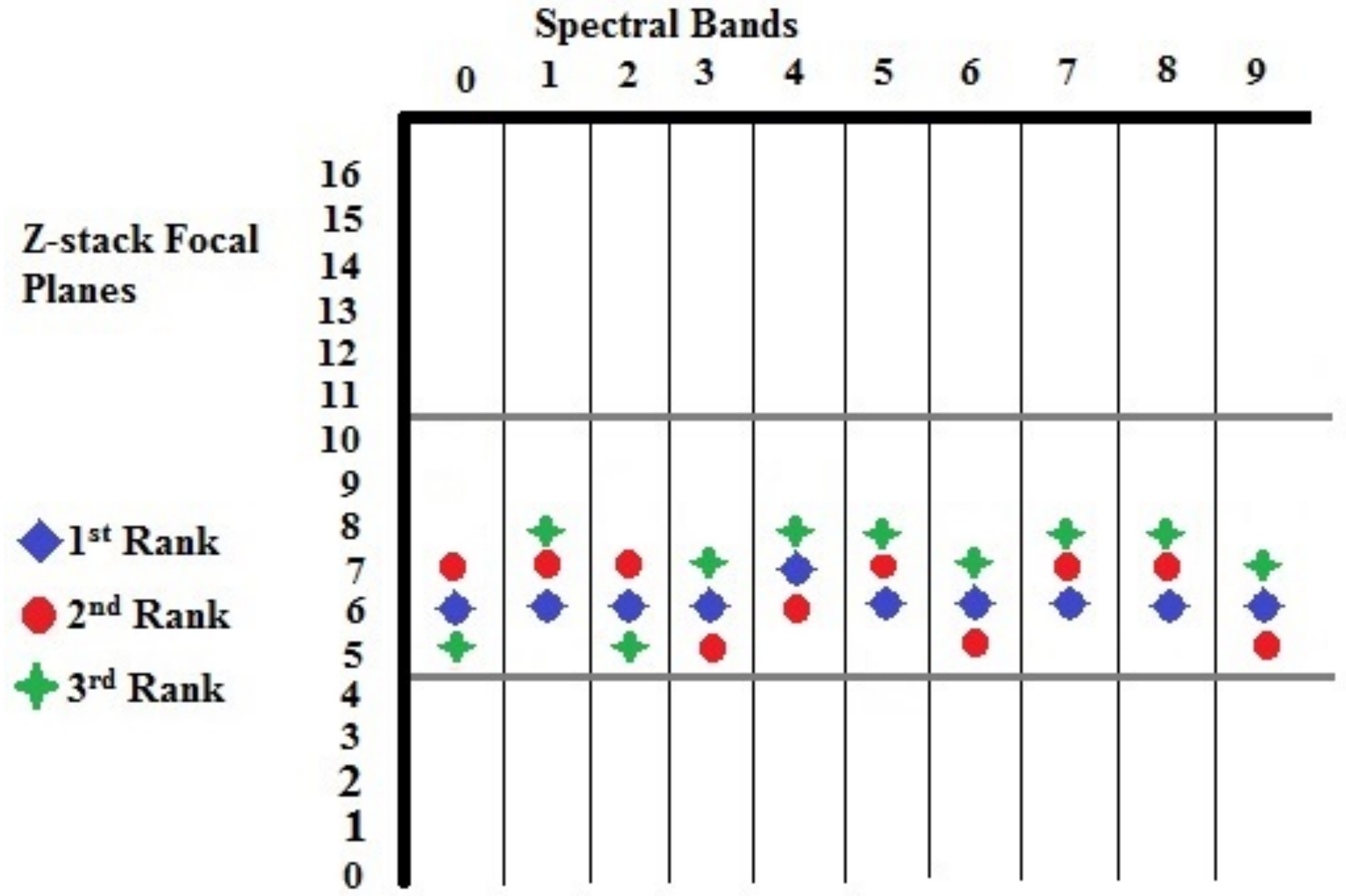
# Mitosis Detection in Multispectral Images

## Classification Results with White, Red, Green and Blue SBs using 5-Fold Cross Validation

| Features | Classifiers | TPR | PPV | FM |
|---|---|---|---|---|
| Red SBs (SB 0,8,9) | DT | 51% | 63% | 56.11% |
| | MLP | 48% | 71% | 57.46% |
| | LSVM | 67% | 56% | 61.19% |
| | NLSVM | 49% | 75% | 59.19% |
| Green SBs (SB 5,6,7) | DT | 50% | 68% | 57.55% |
| | MLP | 50% | 65% | 56.84% |
| | LSVM | 65% | 58% | 61.14% |
| | NLSVM | 48% | 78% | 59.39% |
| Blue SBs (SB 2,3,4) | DT | 43% | 59% | 49.82% |
| | MLP | 46% | 69% | 55.49% |
| | LSVM | 54% | 60% | 56.81% |
| | NLSVM | 46% | 75% | 56.65% |
| White SB (SB 1) | DT | 42% | 65% | 51.32% |
| | MLP | 44% | 74% | 55.15% |
| | LSVM | 56% | 52% | 54.11% |
| | NLSVM | 44% | 77% | 55.84% |

# Mitosis Detection in Multispectral Images

## Top 3 Ranked Focal Planes



# Dynamic Sampling Framework for WSI Analysis

## Dynamic Sampling for Cyto-Nuclear Atypia Score

- A dynamic sampling framework was developed based on computational geometry for Cyto-Nuclear Atypia (CAN) evaluation to avoid exhaustive analysis on WSI
- Main steps of method are:
    1. Pathologest annotated territories by observing WSI using Calopix user interface
    2. Territories are extracted from WSI and split into several HPF frames
    3. 50 HPF are randomly selected for computation CNA scores using Christophe and Maria method [5]
    4. These scores are used for initialization of Voronoi diagram
    5. Next HPF is selected based on two criteria
        1. At least one of its neighboring Voronoi cells has a high score that control the convergence of method towards areas with high score
        2. The distance between the new sample and its neighbors is not too short that prevents oversampling
    6. The final overall CNA score is the grade of the most atypia frame

5) Christophe & Maria, Marked point processes with simple and complex shape objects for cell nuclei extraction from breast cancer H&E images, SPIE Medical Imaging, 2013.

# Dynamic Sampling Framework for WSI Analysis

## Dynamic Sampling Algorithm

**Input:** Current frames E, Voronoi Diagram $VD_E$, p, d, $max_E$

**Output:** updated frames E, Voronoi Diagram $VD_E$, $max_E$

Compute $V_E$

Sort $V_E$ according to decreasing distance to E

**for** every $x \in VE$ **do**

    **if** Distance(x, E) > d **then**

        **if** MaxScore(x) > p × $max_E$ **then**

            E = E ∪{x}

            Update $VD_E$

            $max_E$ = max(S(x), $max_E$ )

            break loop

        **end if**

    **Else**

        Break loop

    **End if**

**End for**