Automated Analysis and Classification of Melanocytic Tumor on SkinWhole Slide Images

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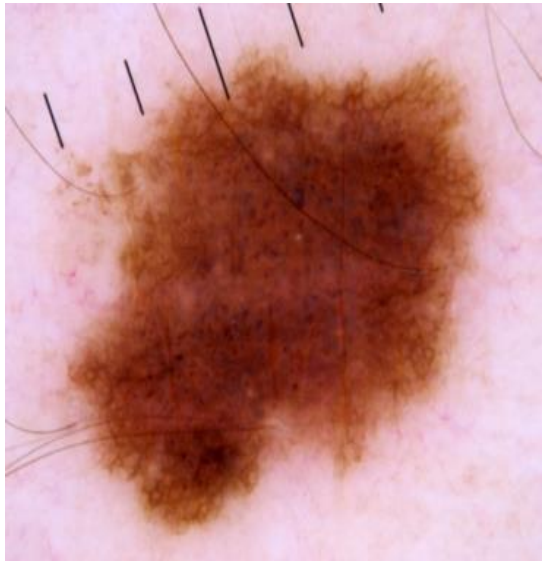
Highlights

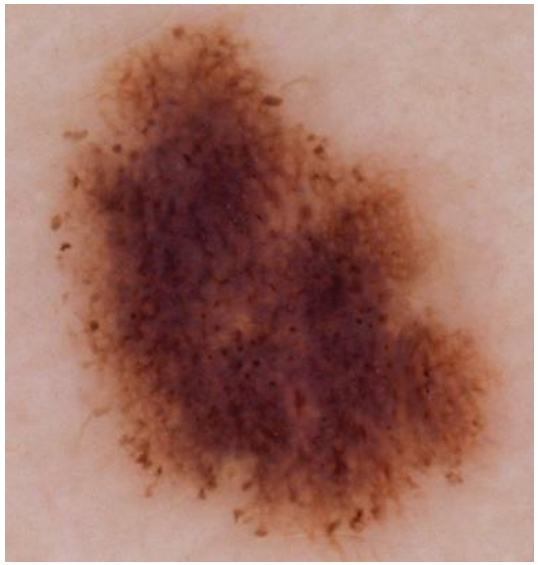
- A framework for whole slide skin image analysis
- A multiresolution framework to generate skin epidermis and dermis image tiles
- Both skin epidermis and dermis analyses are integrated for skin melanoma diagnosis
- Both cytological and textural features are used for skin image classification
- More than 95% classification accuracy is achieved

Skin Cancer & Melanoma

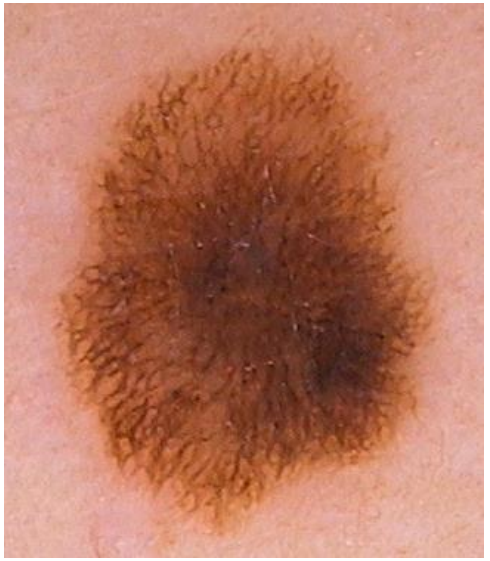
- Skin cancer: most common of all cancers
- Melanoma: most aggressive type of skin cancer
- Early detection: significantly reduce mortality
- Difficult diagnosis: similar to nevus



Compound Nevus



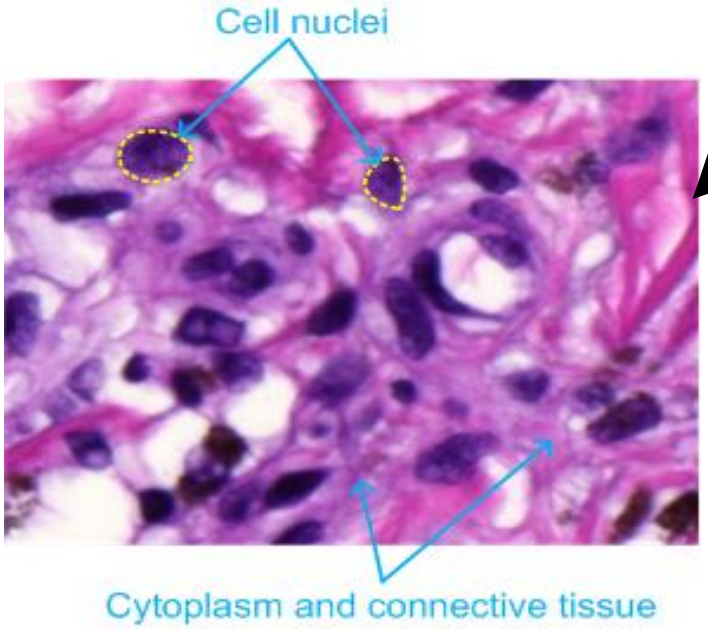
Dysplastic Nevus



Malignant Melanoma

(https://challenge.kitware.com/#challenge/n/ISIC_2017%3A_Skin_Lesion_Analysis_Towards_Melanoma_Detection)

Histological Examination



Histological slides (H&E stained) provide a cellular level view of the cell and tissue.

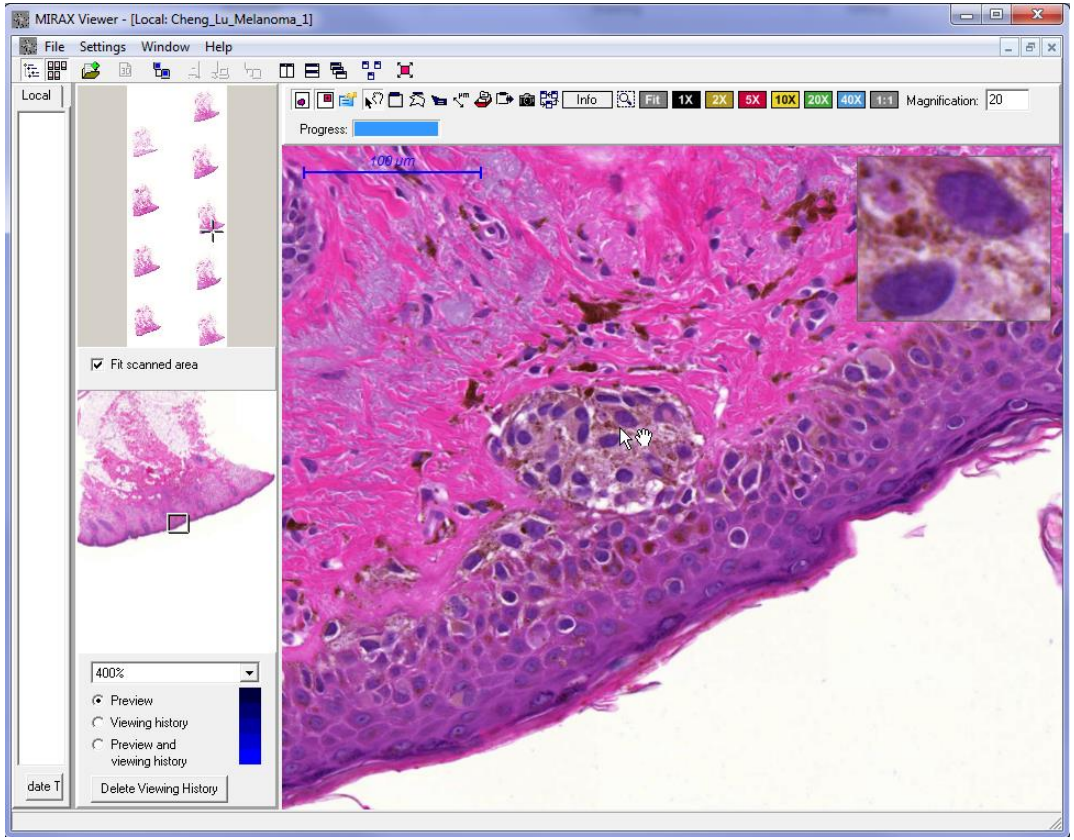
(https://en.wikipedia.org/wiki/Histology)

Digitized Biopsy Analysis

- Digitized scanning: generate high resolution images
- Visual examination: observe digital biopsy images

Digital Scanning

Exam on Monitor

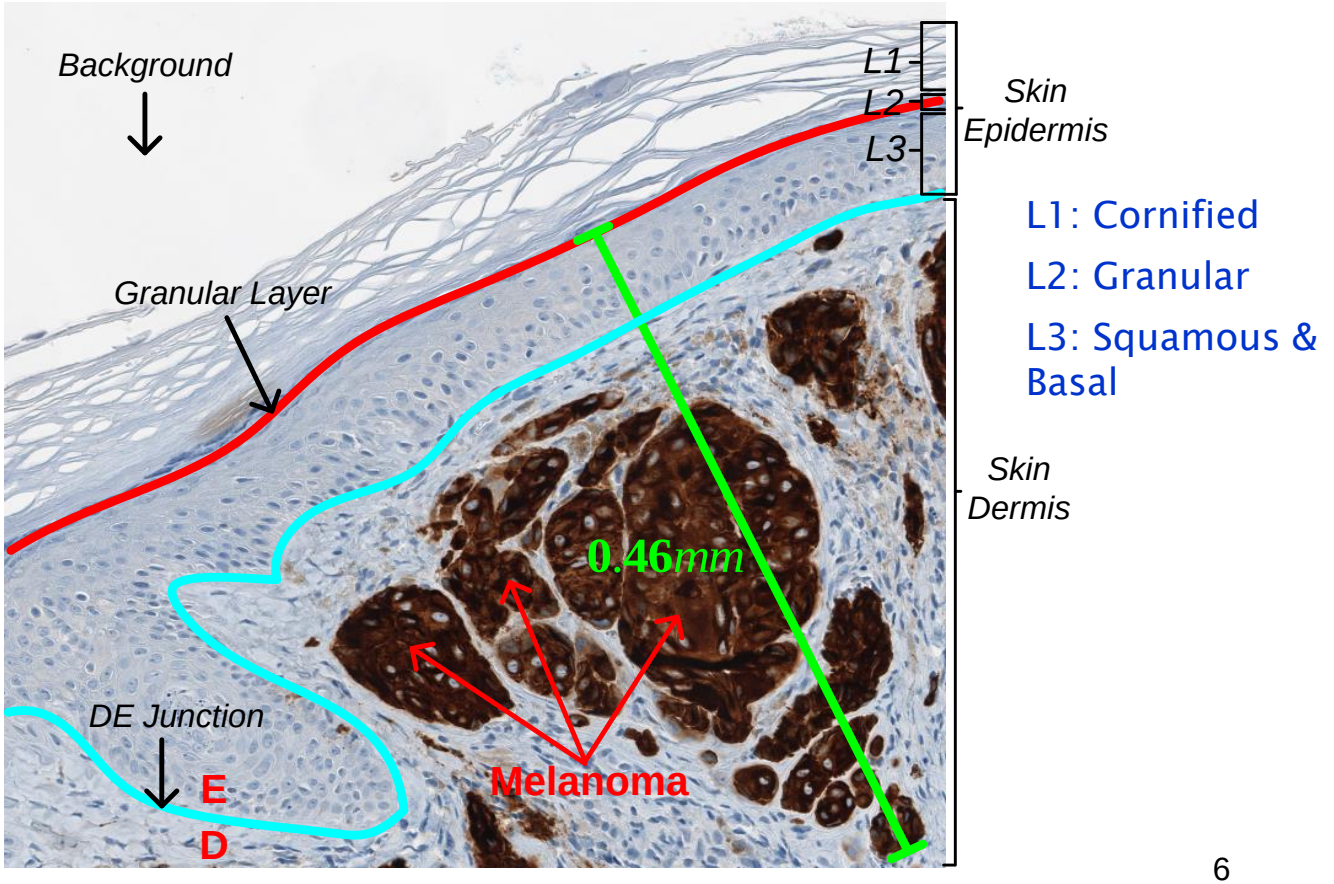


MIRAX Viewer Software

Histological Grading of Melanoma

- Breslow Thickness
  - distance from skin granular layer to the deepest tumor cell
  - the deeper the Breslow depth, the worse is the prognosis

MART-1 stained image:
Melanoma (brown color)
Other nuclei (blue color)



Motivation & Objective Statement

- Motivations
  - Manual analysis: labor-intensive, inter- and intra- observer variations
  - Computerized algorithms: objective, reliable, efficient
  - Existing works: Little works done on analyzing skin biopsy images

- Objectives:
- Automated algorithms for skin biopsy image analysis
- Automated melanoma diagnosis system
- Automated measurement of melanoma invasion depth

Assist pathologists in melanoma diagnosis

Normal Benign nevus Malignant melanoma

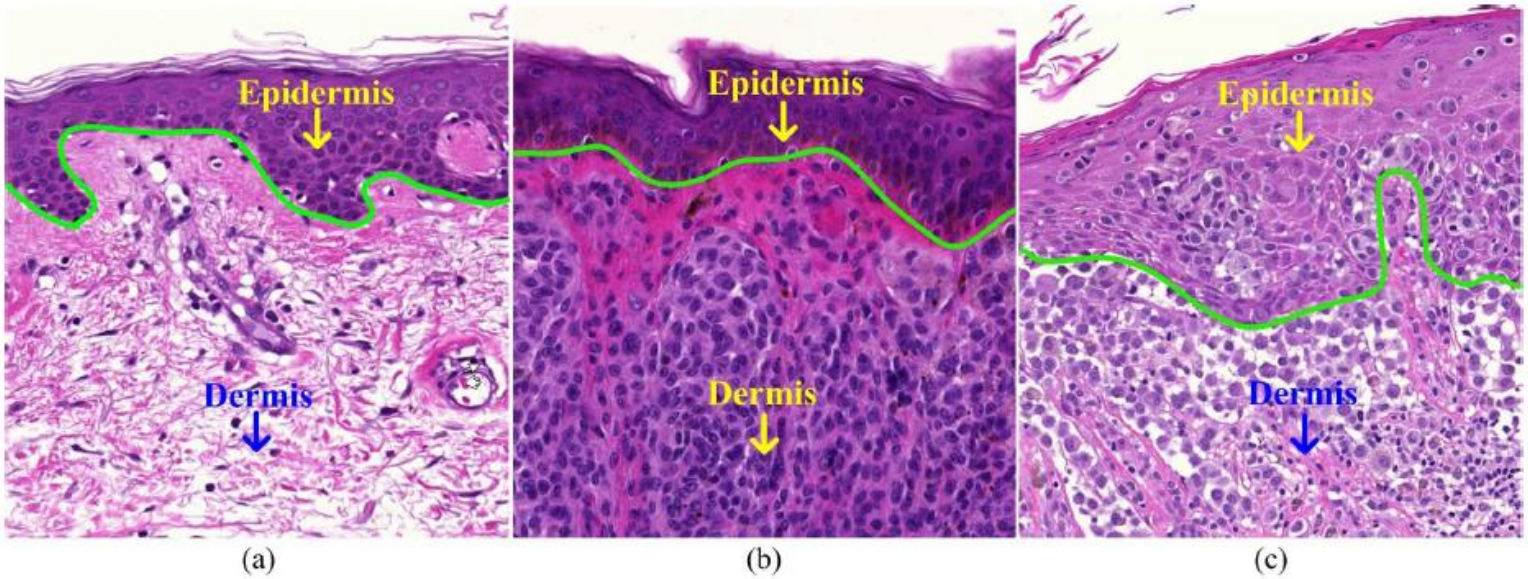
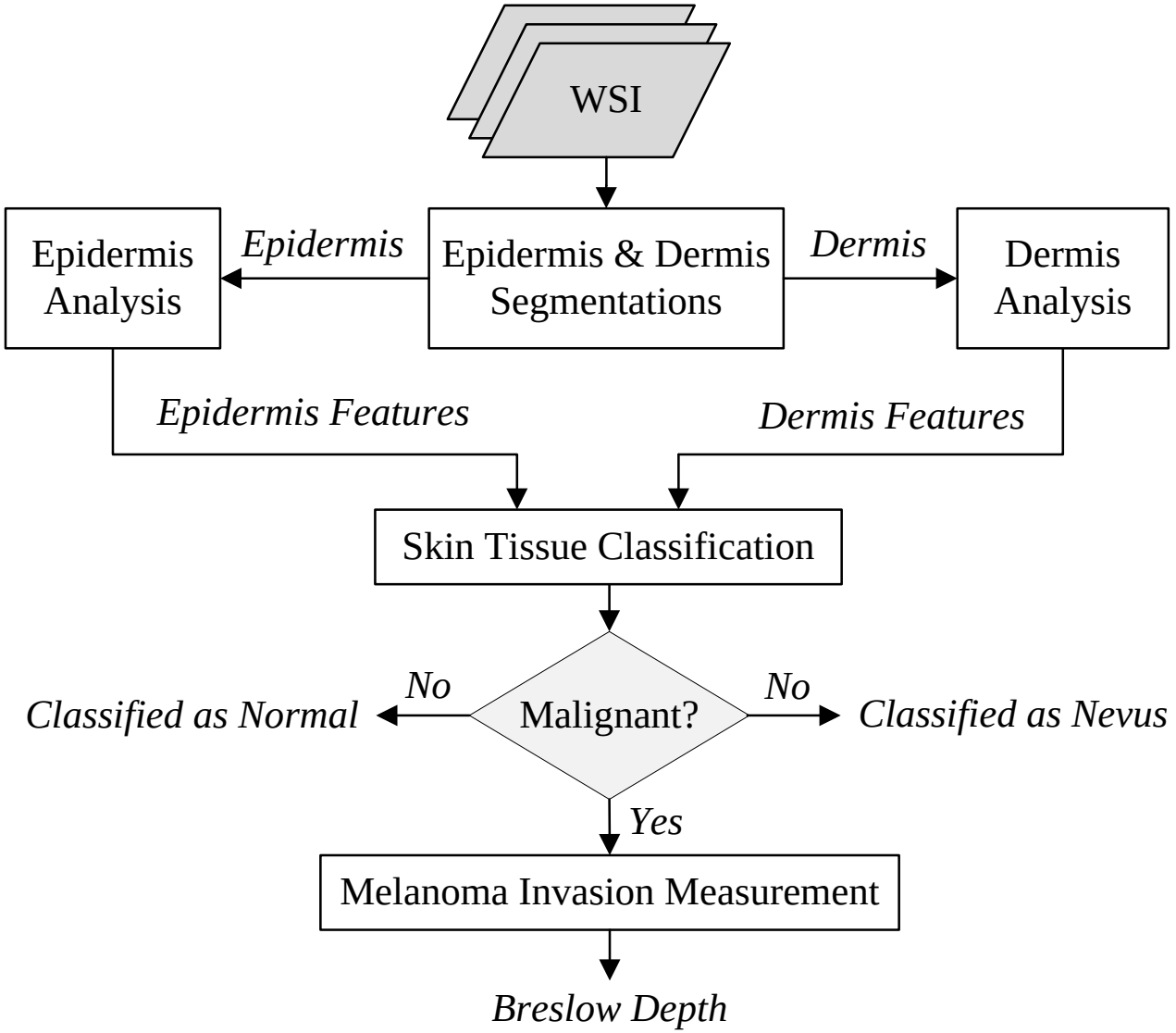


Figure 1: Examples of H&E stained skin images. (a) Normal skin. (b) Benign nevus. (c) Malignant melanoma. Note that in (a)(b)(c) green contours indicate the borders of epidermis and dermis regions. Cell nuclei in both epidermis and dermis regions are observed as blue blobs.

Proposed Framework



Epidermis Segmentation: Coarse to Fine

- This method first performs a coarse segmentation using global thresholding and shape analysis on the red channel of the image.

- A second-pass of fine segmentation using k-means algorithm is then applied to enhance the poor quality segmentation identified based on epidermis thickness measurement.

My Interpretation (from thesis)

- This method first performs a coarse segmentation based on thresholding the red channel of the H&E stained image followed by a connected components and a rule-based analysis related to area and shape.
- It then uses line segments perpendicular to the axis of the candidate region to measure its **depth**.
- If it judged too big, a fine segmentation is performed using RGB color channels to break this region into two classes, the top being epidermis.

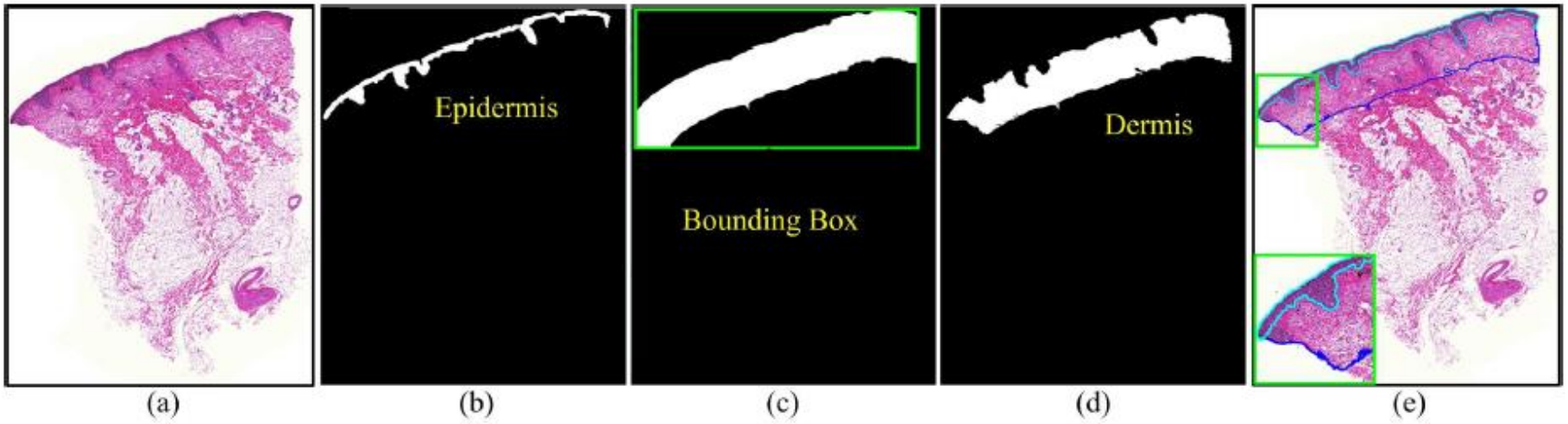


Figure 3: Epidermis and dermis segmentations. (a) Skin WSI I_l. (b) Epidermis mask b_e. (c) Epidermis and dermis mask b_{e+d}. (d) Dermis mask b_d. (e) Segmentation results. Note that in (e) segmented epidermis and dermis regions are labelled with cyan and blue contours, respectively. The bottom-left corner in (e) shows a small zoomed-in image patch.

Epidermis

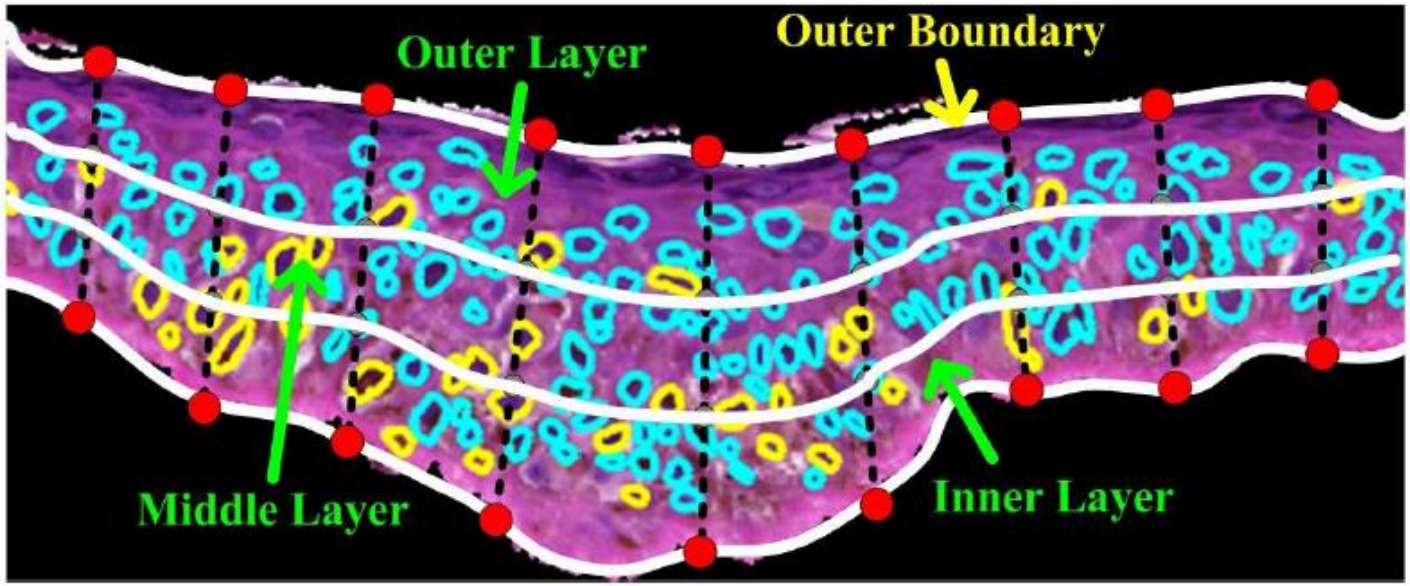


Figure 6: Division of epidermis into three sub-layers: inner layer, middle layer and outer layer. Note that yellow contours indicate detected melanocytes, and cyan contours indicate segmented keratinocytes.

Next, the epidermis is divided into three layers.

Nuclei

- All the nuclei in the epidermis are segmented, including keratinocytes and melanocytes.
- Morphological (shape) features of the nuclei are computed and the average and SD computed
- Ratio of total number of melanocytes to total number of nuclei is computed.

Epidermis Features

Table 1: Summary of epidermis features.

Feature Type	Feature Name	Label
Spatial	Ratio of melanocytes in the inner, middle and outer layer, respectively	F1-F3
Morphological	Area, Perimeter, Eccentricity, Equivalent diameter and Ellipticity (mean and SD values)	Mean: F4-F8 SD: F9-F13

Dermis Analysis

- Color Normalization
- Nuclei Segmentation (much fancier)
- Dermis Feature Computation

Nuclei Segmentation: They want the exact boundaries

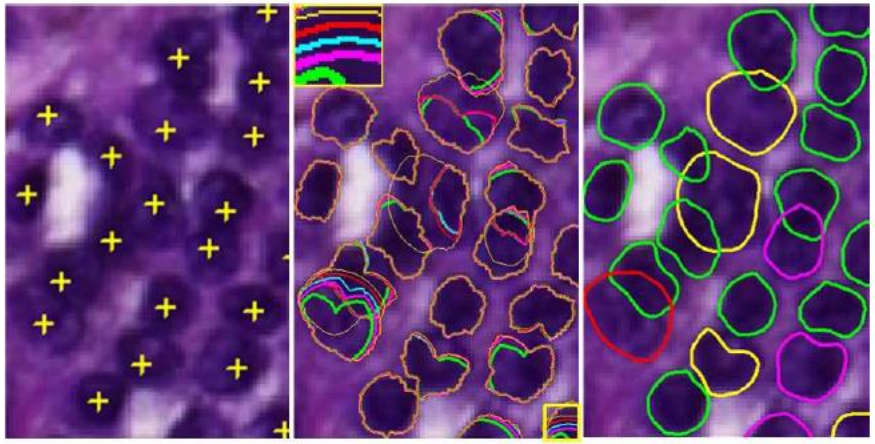
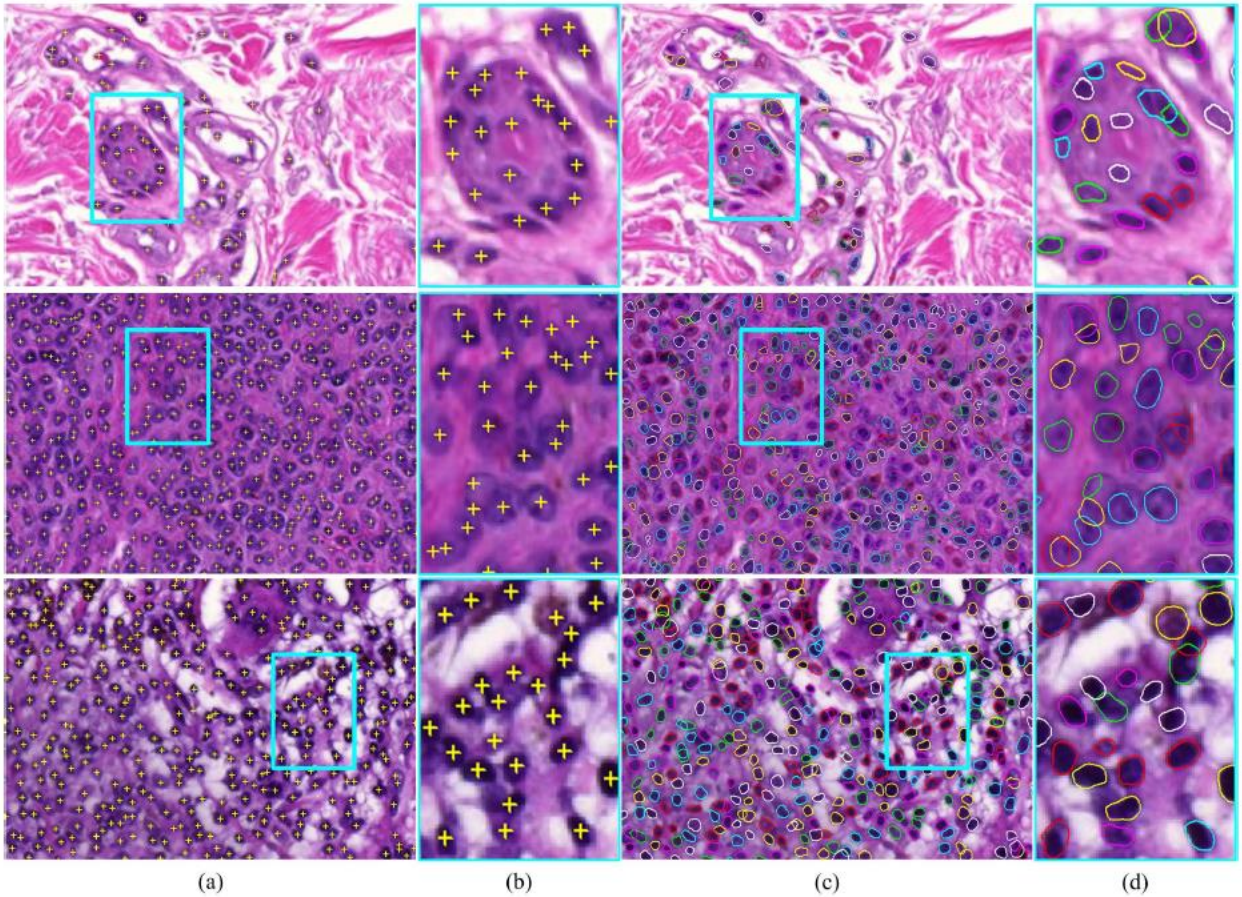


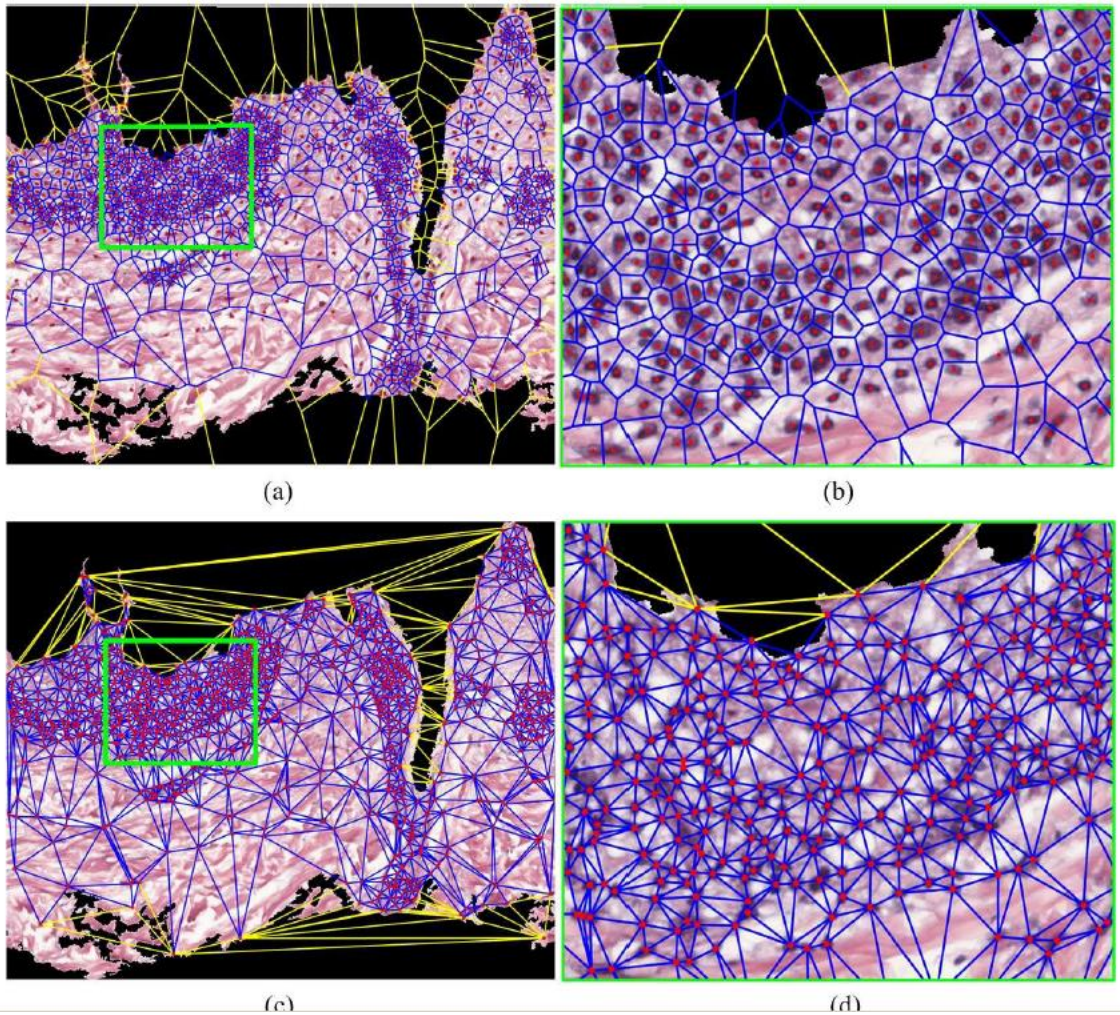
Figure 7: Illustration of nuclear segmentation. (a) Nuclear seeds + detected by gLoG kernels. (b) Nuclear candidate boundaries obtained by the mRLS method. (c) Finally obtained nuclear boundaries. Note that in (b) it contains five different color of contours each of which corresponds to different R_E values. That is green: $R_E = 7$, magenta: $R_E = 8$, cyan: $R_E = 9$, red: $R_E = 10$ and yellow: $R_E = 11$. In (b) the top-left corner shows a zoomed-in image patch in the bottom-right corner for illustrating different colors.



Normal

Skin Nevus

Melanoma



Voronoi Diagram

Delaunay Triangles

Feature type		Feature name	Label
Textural	Histogram	Mean, Variance, Skewness, Kurtosis, Energy and Entropy	F14-F19
	Haralick	Contrast, Correlation, Energy, Entropy, Homogeneity and Dissimilarity (in 4 directions: 0°, 45°, 90° and 135°)	0°: F20-F25 45°: F26-F31 90°: F32-F37 135°: F38-F43
Cytological	Morphological	Area, Perimeter, Eccentricity, Equivalent diameter and Ellipticity (mean and SD values)	Mean: F44-F48 SD: F49-F53
	Statistical	Average intensity, Average contrast, Smoothness, Third moment, Uniformity and Entropy (mean and SD values)	Mean: F54-F59 SD: F60-F65
	Architectural	Area and Perimeter of Voronoi diagrams, Area and Perimeter of Delaunay triangles (mean and SD values)	Mean: F66-F69 SD: F70-F73

Texture features

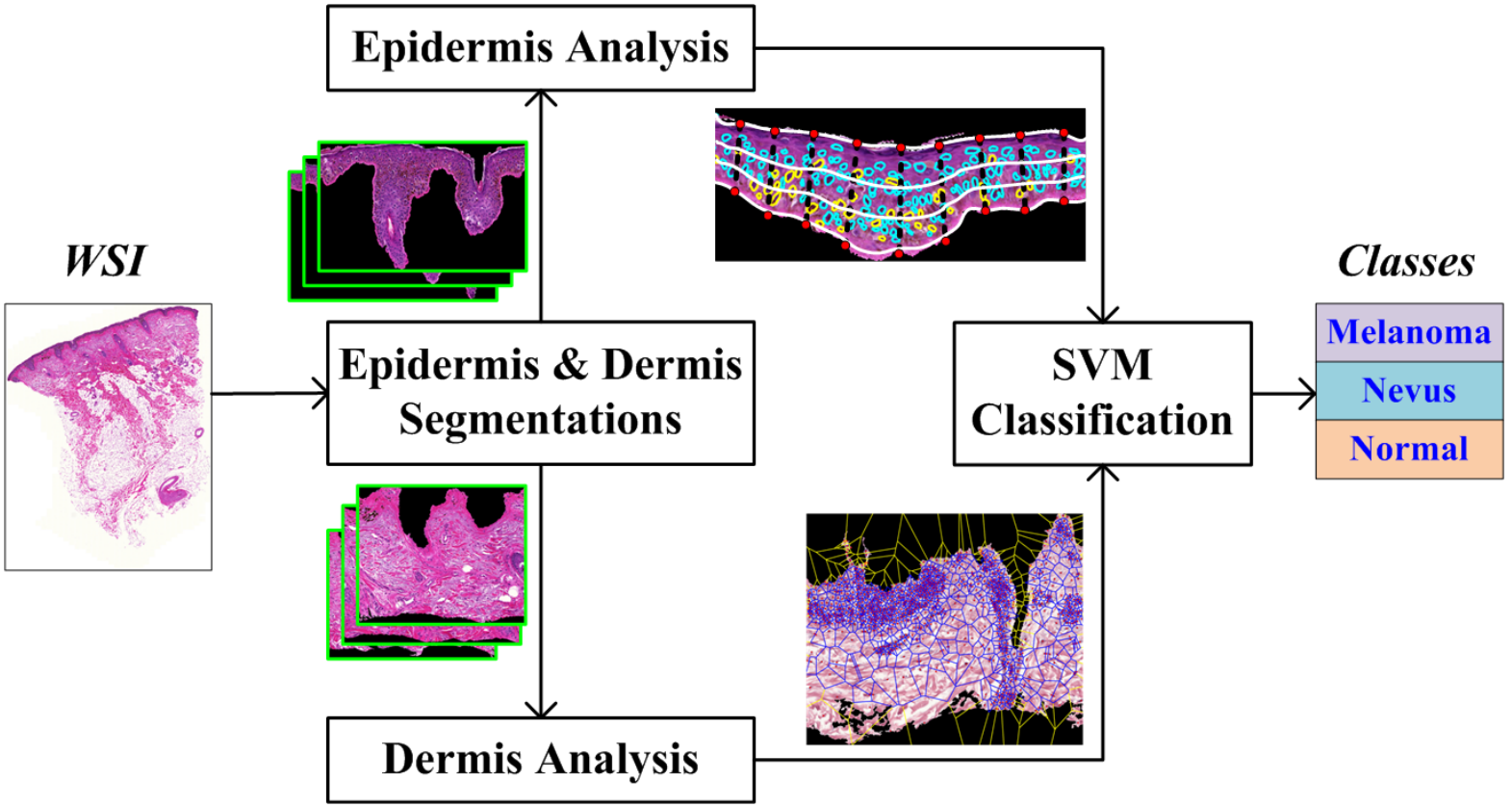
Shape features

Color features

Architectural features

Skin WSI Analysis and Classification

- Epidermis Analysis: 13 features (3 spatial distribution features & 10 nuclear morphological features)
- Dermis Analysis: 60 features (30 textural features & 30 cytological features)



Experiments on Classification

- **Test strategies**
  - I: melanoma **VS** non-melanoma
  - II: normal **VS** nevus **VS** melanoma
  - III: lentiginous **VS** superficial spreading **VS** nodular
  - IV: normal **VS** nevus **VS** lentiginous **VS** superficial spreading **VS** nodular

Tissue Classes		NO.
Normal		17
Nevus (compound)		17
Melanoma	lentiginous	9
	superficial spreading	18
	nodular	5
Total		66

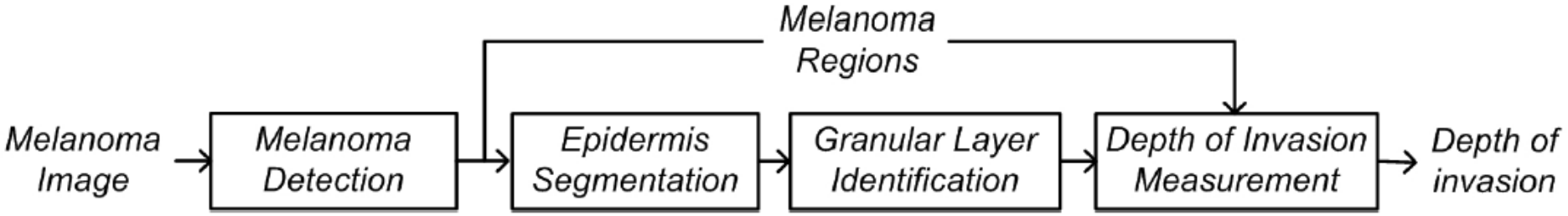
- **Ten-fold cross evaluation**

Techniques	Average classification accuracies (%)			
	I	II	III	IV
LM technique [2015]	88.86	89.07	90.17	90.24
Proposed with all features	97.90	95.78	91.32	91.98
Proposed with feature selection	97.80	98.08	95.81	95.73

Feature selection: Sequential Feature Selection method

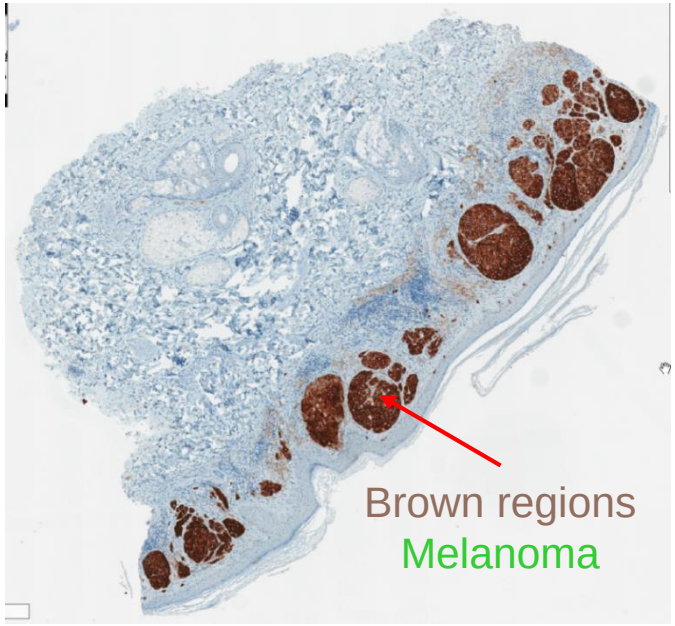
Melanoma Invasion Measurement

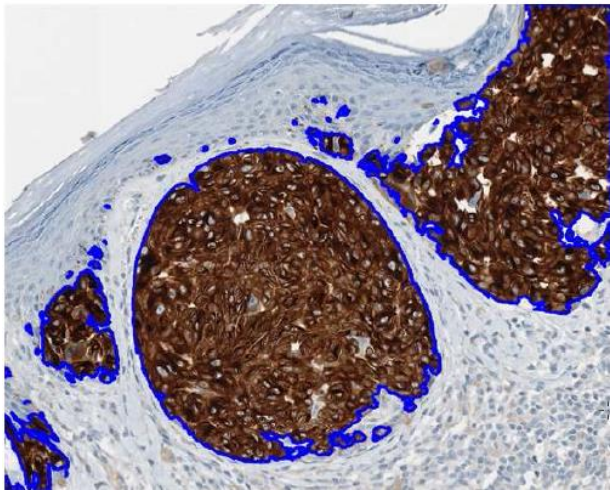
- Using MART-1 stained skin biopsy images

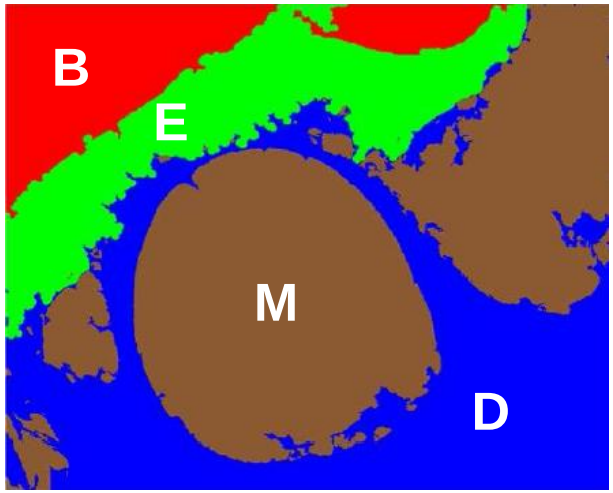


RGB color features are used

Multi-thresholding is used







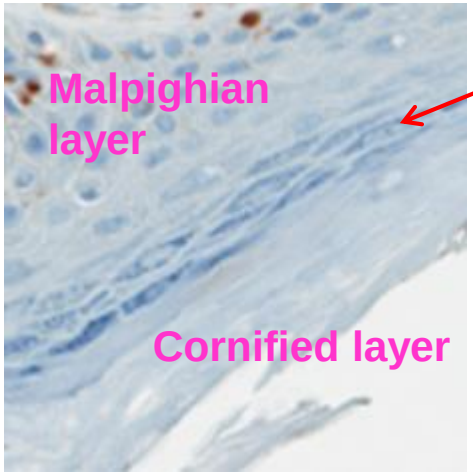
MART-1 stained skin biopsy

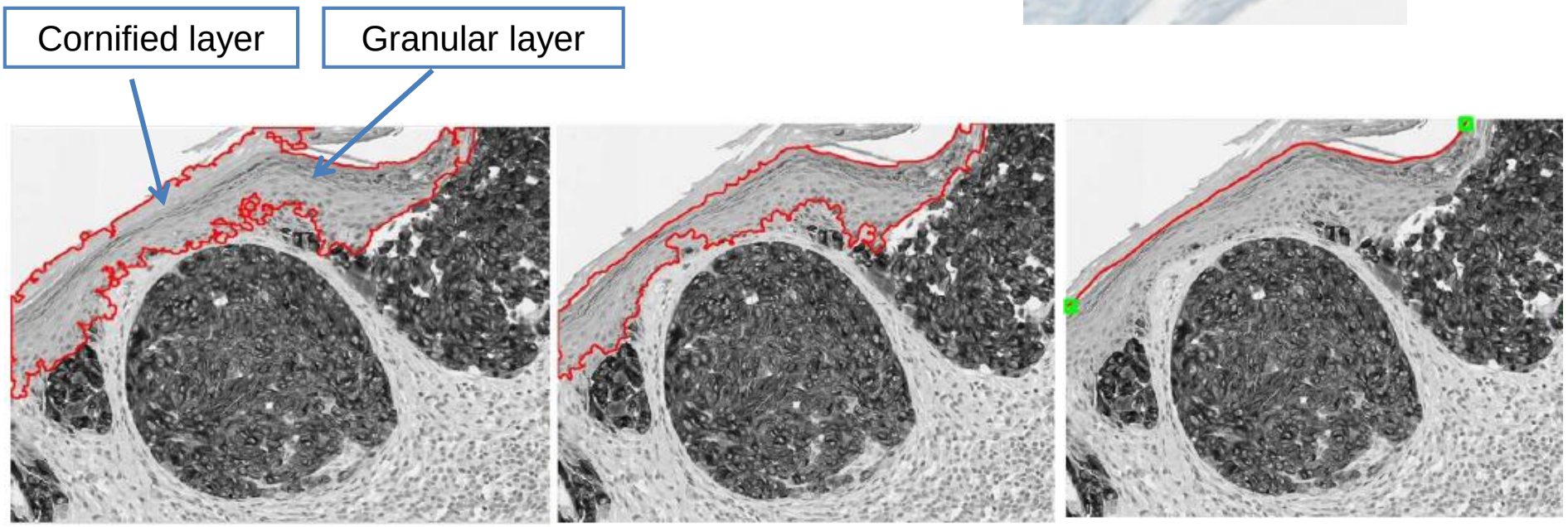
Melanoma segmentation

Image segmentation

Granular Layer Identification

- Granular layer-middle layer within epidermis
- Cornified layer-lighter intensities than other layers
- A Bayesian classification-to remove cornified layer pixels





Epidermis including cornified layer pixels

Epidermis excluding cornified layer pixels

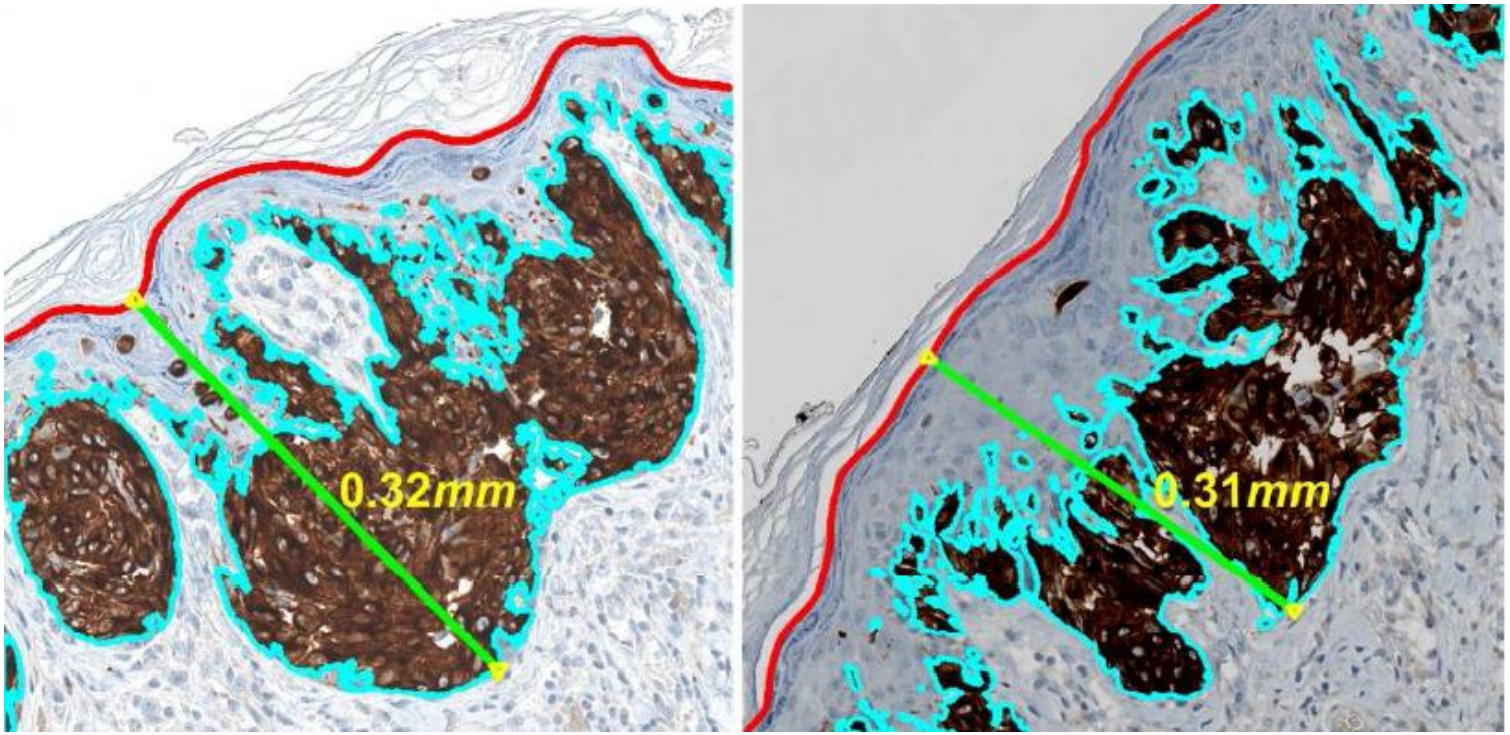
Identified granular layer

Invasion Depth Measurement

- Invasion measurement – using multi-resolution Hausdorff distance measure

$$DoI = \max_i \left[\min_j \| m_i - g_j \| \right]$$

m_i: Melanoma boundary points g_j: Granular layer points



Evaluations & Comparisons

- AE: average error; SD: standard deviation; APE: average percentage of error

Techniques	AE (microns)	SD (microns)	APE (%)
Mokhtari *et al. [2014]*	28.03	29.70	10.66
Noroozi *et al. [2015]*	20.54	17.21	6.81
Proposed	10.95	17.49	3.53

Normalized errors with respect to Ground Truth

Conclusion

- Several automated techniques for ROIs detection & segmentation in biopsy images
- Automated skin whole slide biopsy image analysis
  - Automated melanoma invasion depth measurement

Pros	Cons
▪ Automatic & Efficient & Robust ▪ Second-opinion for pathologist in cancer diagnosis ▪ Outperform existing techniques.	▪ Some of techniques need off-line training; ▪ Some of techniques need appropriate parameter settings

Publications

- **Refereed Journals:**
- **Hongming Xu,** Richard Berendt, Naresh Jha and Mrinal Mandal, “Automatic measurement of melanoma depth of invasion in skin histopathological images”, ***Micron***, *vol.97, pp.56-67,* 2017.
- **Hongming Xu,** Cheng Lu, Richard Berendt, Naresh Jha and Mrinal Mandal, “Automatic nuclear segmentation using multi-scale radial line scanning with dynamic programming”, *accepted by* ***IEEE Transactions on Biomedical Engineering (TBME)***, January, 2017.
- Cheng Lu, **Hongming Xu**, Jun Xu, Hannah Gilmore, Mrinal Mandal and Anant Madabhushi, “Multiple-pass voting technique for nuclei detection in histopathological Images”, *accepted by* ***Scientific Report***, August, 2016.
- **Hongming Xu**, Cheng Lu, Richard Berendt, Naresh Jha and Mrinal Mandal, “Automatic nuclei detection based on generalized Laplacian of Gaussian filters”, ***IEEE Journal of Biomedical and Health Informatics (JBHI)***, vol.21, no.3, pp.826-837, 2017.
- **Hongming Xu** and Mrinal Mandal, “Epidermis segmentation in skin histopathological images based on thickness measurement and k-means algorithm”, ***EURASIP Journal on Image and Video Processing,*** *vol.2015, no.1, pp.1-14, 2015.*
- **Hongming Xu**, Cheng Lu, and Mrinal Mandal, “An efficient technique for nuclei segmentation based on ellipse descriptor analysis and improved seed detection algorithm,” ***IEEE Journal of Biomedical and Health Informatics (JBHI)****, vol.18, no.5, pp.1729-1741, 2014.*