Automated Analysis and Classification of Melanocytic Tumor on Skin Whole 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
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
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
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

WSI

Epidermis Analysis

Epidermis & Dermis Segmentations

Dermis Analysis

Epidermis Features

Dermis Features

Skin Tissue Classification

Malignant?

Classified as Normal

No

Yes

Melanoma Invasion Measurement

Breslow Depth

Classified as Nevus
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.
Next, the epidermis is divided into three layers.

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.
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>
<thead>
<tr>
<th>Feature Type</th>
<th>Feature Name</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial</td>
<td>Ratio of melanocytes in the inner, middle and outer layer, respectively</td>
<td>F1-F3</td>
</tr>
<tr>
<td>Morphological</td>
<td>Area, Perimeter, Eccentricity, Equivalent diameter and Ellipticity (mean and SD values)</td>
<td>Mean: F4-F8 SD: F9-F13</td>
</tr>
</tbody>
</table>
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.
Voronoi Diagram

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

- **Ten-fold cross evaluation**

<table>
<thead>
<tr>
<th>Tissue Classes</th>
<th>NO.</th>
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<tr>
<td>Normal</td>
<td>17</td>
</tr>
<tr>
<td>Nevus (compound)</td>
<td>17</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
</tr>
<tr>
<td>lentiginous</td>
<td>9</td>
</tr>
<tr>
<td>superficial spreading</td>
<td>18</td>
</tr>
<tr>
<td>nodular</td>
<td>5</td>
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<tr>
<td>Total</td>
<td>66</td>
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<table>
<thead>
<tr>
<th>Techniques</th>
<th>Average classification accuracies (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>LM technique [2015]</td>
<td>88.86</td>
</tr>
<tr>
<td>Proposed with all features</td>
<td>97.90</td>
</tr>
<tr>
<td>Proposed with feature selection</td>
<td>97.80</td>
</tr>
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Feature selection: Sequential Feature Selection method
Melanoma Invasion Measurement

- Using MART-1 stained skin biopsy images

![Diagram showing the process of melanoma invasion measurement](image)

- RGB color features are used
- Multi-thresholding is used
Granular Layer Identification

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

<table>
<thead>
<tr>
<th>Techniques</th>
<th>AE (microns)</th>
<th>SD (microns)</th>
<th>APE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mokhtari et al. [2014]</td>
<td>28.03</td>
<td>29.70</td>
<td>10.66</td>
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<tr>
<td>Noroozi et al. [2015]</td>
<td>20.54</td>
<td>17.21</td>
<td>6.81</td>
</tr>
<tr>
<td>Proposed</td>
<td>10.95</td>
<td>17.49</td>
<td>3.53</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Automatic &amp; Efficient &amp; Robust</td>
<td>▪ Some of techniques need off-line training;</td>
</tr>
<tr>
<td>▪ Second-opinion for pathologist in cancer diagnosis</td>
<td>▪ Some of techniques need appropriate parameter settings</td>
</tr>
<tr>
<td>▪ Outperform existing techniques.</td>
<td></td>
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</table>
• Refereed Journals:


