Acute Lymphoblastic Leukemia Detection Based on Adaptive Unsharpening and Deep Learning

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Outline

• Introduction
  o Acute Lymphoblastic Leukemia (ALL)
  o Computer Aided Diagnosis (CAD)
  o Deep Learning (DL) for ALL

• Proposed method

• Experimental results
  o Quantitative analysis
  o Qualitative analysis

• Conclusions
Acute Lymphoblastic Leukemia (ALL)

• Disease
  o Affects the blood cells, rapidly spreads
  o Fatal consequences if left untreated

• Diagnosis
  o Experienced pathologist manually inspects white cells in peripheral blood samples identifying the cells with the typical blast morphology
  o **Lymphoblasts**: white cells with an altered morphology
    ➢ Normally present in the bone marrow
    ➢ *An increased number of lymphoblasts in peripheral blood can be associated with ALL*
Computer Aided Diagnosis (CAD)

• Partially automate Lymphoblast detection process
  o Image processing
  o Machine Learning (ML)

• Three main categories
  o Handcrafted feature extraction and shallow ML classifier
  o Handcrafted feature extraction and Deep Learning (DL)
  o Pure DL
Deep Learning (DL) for ALL

• Deep Learning
  o Automatically learns data representations
  o No need for handcrafted feature extraction
  o Higher accuracy

• State of the art of DL for ALL
  o Strive towards higher classification accuracy
    ➢ More efficient learning procedures
    ➢ Original network architectures
  o However, no method deals with ALL data analysis
    ➢ No focus or quality analysis
    ➢ No preprocessing algorithm
Proposed Method (1/2)

• First DL-based method for lymphoblast detection that analyzes ALL data
  o **Focus** quality estimation
  o Adaptive **unsharpening**
  o White blood cell classification using **CNNs**
    ➢ 0: «normal»
    ➢ 1: «lymphoblast»
Proposed Method (2/2)

A) Image registration
B) Focus quality estimation and adaptive image unsharpening
C) Shallow CNNs for tuning of adaptive image unsharpening
D) Final adaptive image unsharpening
E) Deep CNN classification
Image Registration

- Color normalization and grayscale conversion

\[ M_{\text{thresh}} = \text{Otsu's binarization} \]

\[ M_{\text{fcm}} = \text{Fuzzy C-means clustering} \]
  - Discard largest class (background)

\[ M = M_{\text{thresh}} + M_{\text{fcm}} \]
  - Extraction of largest CC

- Active contour refinement

- Ellipse fitting
  - Center of ellipse: \( c_x, c_y \)
  - Axes of ellipse: \( a_{\text{max}}, a_{\text{min}} \)

- Extraction of ROI centered on \( c_x, c_y \), with size \( 1.5 \cdot a_{\text{min}} \)
Focus Quality Estimation and Adaptive Image Unsharpening (1/2)

• Estimation of focus quality
  o FQPath method
    ➢ Decomposes the input image using a visual sensitivity-like FIR filter corresponding to the out-of-focus lens
    ➢ Extracts high order statistical moment features to quantize the image sharpness level
    ➢ Vector of focus qualities \( \mathbf{f} = [f_1, f_2, \ldots, f_N] \)

• Estimation of data bias
  o Correlation coefficient between \( \mathbf{f} \) and vector of labels \( \mathbf{l} \):
    \[ b = \text{corrcoeff}(\mathbf{f}, \mathbf{l}) \]
  o Significant data bias: \( |b| > 50\% \)

Focus Quality Estimation and Adaptive Image Unsharpening (2/2)

- **Adaptive unsharpening**
  - Improving focus quality for each image until it reaches the threshold $th_{unsharp}$
    - The threshold is uniquely computed for each training subset
    - Determines which focus the images should have
  - **Unsharp masking**
    - Gaussian kernel with standard deviation $\sigma_i$
    - $\sigma_i$ is adaptively estimated for each image to reach the focus quality $th_{unsharp}$
      - $\sigma_i = \arg\min \sigma(f_i - th_{unsharp})$
  - **Threshold is computed to minimize the data bias:**
    - $th_{unsharp} = \arg\min(|b|)$
Shallow CNNs for Tuning of Adaptive Image Unsharpening (1/2)

- Tuning of \( th_{\text{unsharp}} \) using a shallow CNN
  - Train a CNN on the unsharpened samples
  - Varying \( th_{\text{unsharp}} \pm 10\%
  - Considering the value for which the CNN obtains the best classification accuracy
Shallow CNNs for Tuning of Adaptive Image Unsharpening (2/2)

- **Shallow CNN: VAR-PCANet**
  - High-accuracy baseline in several fields
  - 1 layer
  - Filters are computed as eigenvectors of input data
    - Number of filters $V$ adaptively estimated to preserve a percentage $th_{var}$ of variance of input data
      - $V = \arg \min_V \left( \sum_{v=1}^{V} \lambda_v \right) - th_{var}$
  - Feed-forward design
  - Extracts a feature vector
    - Compare samples in the feature space
    - Classification with Nearest Neighbor (1-NN) classifier
      - No training
      - Output only depends on the feature vector
Final Adaptive Image Unsharpening

• Application of tuned threshold $th_{unsharp}$
  - Both training and testing subsets
  - Set of unsharpened images $DB_{unsharp}$
Deep CNN Classification

• Pre-trained CNN
  o Limited number of samples
  o Substitute last layer
    - 1000 classes (ImageNet) → 2 classes (ALL)
    - (0: “normal”; 1: “lymphoblast”)
  o Fine tuning on the ALL database
    - Train on the training subset
    - Inference on the testing subset
Experimental Results

- **Database**
  - ALL-IDB2 dataset
  - 260 images of white cells, each with binary label
    - (0: “normal”; 1: “lymphoblast”)
  - Cropped to show only region around the cell

- **Evaluation procedure**
  - $N$-fold validation ($N = 2$) repeated 10 times, results averaged
  - Apply the proposed methodology on the training subset
    - Estimate $th_{unsharp}$, perform the final unsharpening, train the Deep CNN on $DB_{unsharp}$
    - Apply Deep CNN to perform the classification on the testing subset of $DB_{unsharp}$

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## Quantitative Analysis

<table>
<thead>
<tr>
<th>Original</th>
<th>Deep CNN</th>
<th>Accuracy (%) $(Mean_{Std})$</th>
<th>Unsharp</th>
<th>Deep CNN</th>
<th>Accuracy (%) $(Mean_{Std})$</th>
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<tbody>
<tr>
<td></td>
<td>AlexNet</td>
<td>93.76$^{2.06}$</td>
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<td>AlexNet</td>
<td>95.07$^{1.85}$</td>
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<td>ResNet50</td>
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<td>ResNet101</td>
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<td>DenseNet201</td>
<td>96.69$^{1.14}$</td>
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</table>
Qualitative Analysis

Images

Original  Unsharpened

Grad-CAM

Original  Unsharpened
Conclusions

• First ML-based for focus quality estimation, adaptive unsharpening, and classification of ALL blood samples
  o Improve sharpness of images prior to classification
  o Shallow CNN to tune the unsharpening parameters
  o Adaptively reducing bias between quality and label

• Experiments show increase in classification accuracy using state-of-the-art pretrained CNNs

• Future works
  o Databases with more samples
  o Different DL architectures
Thank you for your kind attention!

https://iebil.di.unimi.it/cnnALL/index.htm
https://homes.di.unimi.it/scotti/all/