Local Isotropic Phase Symmetry Measure for Detection of Beta Cells and Lymphocytes

Manohar Kuse\textsuperscript{1} Yi-Fang Wang\textsuperscript{2} Vinay Kalasannavar\textsuperscript{3}
Michael Khan\textsuperscript{2} Nasir Rajpoot\textsuperscript{3}

\textsuperscript{1}The LNM Institute of Information Technology, Jaipur, INDIA
\textsuperscript{2}Life Sciences, The University of Warwick, Coventry, UK
\textsuperscript{3}Dept. of Computer Science, The University of Warwick, Coventry, UK

Histopathology Image Analysis Workshop @ 14\textsuperscript{th} International Conference on Medical Image Computing and Computer Assisted Intervention, 2011
Outline

1. Biological Introduction
2. Proposed Scheme
3. Phase Symmetry
4. Analysis of Experimental Results
5. LIPSyM applied for ICPR Lyphocytes Dataset
6. Conclusions and Future Work
1 Biological Introduction

2 Proposed Scheme

3 Phase Symmetry

4 Analysis of Experimental Results

5 LIPSyM applied for ICPR Lyphocytes Dataset

6 Conclusions and Future Work
Where are Beta Cells Found

- Islets of Langerhans are the regions of the pancreas
- Contains – $\alpha$ cells, $\beta$ cells, $\delta$ cells, $PP$ cells, $\epsilon$ cells
- Illustration courtesy of NIH (National Institute of Health)\(^1\)

\(^1\) http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/17151.jpg
Biological Background

- Diabetes associated with a reduction in functional $\beta$ cell mass.
- $\beta$ cell mass must be restored if diabetes to be cured or progress arrested.
- Post mortem analyses of $\beta$ and islet cell mass are undertaken in patients.
H-DAB Stained Pancreas Tissue Section
Motivation

- It is necessary to estimate β cell mass by immunohistochemical (IHC) staining of pancreas tissue sections.
- To assess β cell count, it is necessary to also determine the number of nuclei within the insulin stained area.
Need for Automatic Method

- Due to huge amount of data obtained, task is labour intensive.
- Single experiment may consist of 6000 images.
- Each image may have 50-300 beta cells.
- Human takes 4-5 minutes per image.
- Total time required is 2 months.
Overall Picture

1. Stain Separation
2. Compute LIPSyM
3. Find Local Maxima
4. Clustering of Peaks (Graph Based)
5. Eliminate Non-β Cells
Stain Separation

- Stain Separation
- Compute LIPSyM
- Find Local Maxima
- Clustering of Peaks (Graph Based)
- Eliminate Non-ß Cells
Stain Separation

- Ruifrok & Johnston method for color deconvolution \(^2\)
- H-DAB stained input image resolved into components of H, DAB stains.

\(^2\)A.C. Ruifrok and D.A. Johnston. Quantification of histochemical staining by color deconvolution. Anal Quant Cytol Histol, 2001.
Stain Separation

(a) Sample Image

(b) H-Stain

(c) DAB-Stain
Local Isotropic Phase Symmetry

- Stain Separation
- Compute LIPSyM
- Find Local Maxima
- Clustering of Peaks (Graph Based)
- Eliminate Non-β Cells
Computation of Symmetry Measure – LIPSyM

- **LIPSyM** - Local Isotropic Phase Symmetry Measure
- Isotropic pixel wise measure for symmetry.
- Based on Gabor Transform.
- More details later.
Overlay of LIPSyM and Sample Image
Biological Introduction
Proposed Scheme
Phase Symmetry
Analysis of Experimental Results
LIPSyM applied for ICPR Lymphocytes Dataset
Conclusions and Future Work

Finding Peaks

- Stain Separation
- Compute LIPSyM
- Find Local Maxima
- Clustering of Peaks (Graph Based)
- Eliminate Non-β Cells
Find Peaks

- Local maximums found from result of pixel-wise phase symmetry.
- Local maximums in symmetry image represent potential candidates for cells.
Find Peaks

(d) Overlay of Peaks

(e) Overlay of Peaks
Clustering Peaks

1. Stain Separation
2. Compute LIPSyM
3. Find Local Maxima
4. Clustering of Peaks (Graph Based)
5. Eliminate Non-β Cells
Clustering Peaks

- Peaks modeled as graph, based on threshold on distance.
- Maximal cliques used to partition the graph into subgraphs.
Clustering Peaks

(f) Overlay of Peaks

(g) Clustered Peaks
Elimination of Non-islet Cells

1. Stain Separation
2. Compute LIPSyM
3. Find Local Maxima
4. Clustering of Peaks (Graph Based)
5. Eliminate Non-fβ Cells
Elimination of Non-islet Cells

- Cells inside islet termed beta cells
- Peaks outside of islet region removed by means of creating mask of islet region
- Use of Gaussian Mixture Models (GMM)
- K-means as replacement for speed
Outline

1 Biological Introduction
2 Proposed Scheme
3 Phase Symmetry
4 Analysis of Experimental Results
5 LIPSyM applied for ICPR Lyphocytes Dataset
6 Conclusions and Future Work
Basic Motivation

- Cells form a symmetric structures
- Proposition of pixel wise symmetry measure
- Local maximums in symmetry image correspond to cells
LIPSyM – Schematic Diagram

log-Gabor Transform

Scale 1
Orient 1

Scale 1
Orient 0

Scale 2
Orient 1

Scale 2
Orient 0

Scale s
Orient 1

Scale s
Orient 0

Median

A_{1,1} E_{1,1}

A_{1,0} E_{1,0}

A_{2,1} E_{2,1}

A_{2,0} E_{2,0}

A_{s,1} E_{s,1}

A_{s,0} E_{s,0}

Median

A_{1}

A_{2}

A_{s}

Sum

/
Mathematical Abstraction

- $I$: Fourier transform of the H-stain image.
- $G_{s,o}$: Gabor filter at scale $s$, orientation $o$.

$$V_{s,o} = I \ast G_{s,o} \quad (1)$$
Mathematical Abstraction

- Responses of Gabor as Amplitude and Energy.
- \( A_{s,o}(x, y) \) : Amplitude of response at co-ordinates \((x, y)\) at scale \(s\) and orientation \(o\).
- \( E_{s,o}(x, y) \) : Energy of response at co-ordinates \((x, y)\) at scale \(s\) and orientation \(o\).

\[
A_{s,o}(x, y) = |V_{s,o}(x, y)| \tag{2}
\]

\[
E_{s,o}(x, y) = |\text{Real}\{V_{s,o}(x, y)\}| - |\text{Imag}\{V_{s,o}(x, y)\}| \tag{3}
\]
Mathematical Abstraction

- Median over orientation
- Performed to generate high values only if symmetric in all directions (Isotropic)
- Kovesi’s idea 3 of phase symmetry was anisotropic and used mean instead of median

\[
A_s(x, y) = \text{median}_{o=1,2,...,n_o} \{ A_{s,o}(x, y) \} \tag{4}
\]

\[
E_s(x, y) = \text{median}_{o=1,2,...,n_o} \{ E_{s,o}(x, y) \} \tag{5}
\]

---

3 P. Kovesi. Symmetry and asymmetry from local phase. Proc. 10th Australian Joint Conf. Artificial Intelligence, 1997.
Mathematical Abstraction

- Definition of Local Isotropic Phase Symmetry.

\[ \eta(x, y) = \frac{\sum_{s=1}^{n_s} E_s(x, y)}{\sum_{s=1}^{n_s} A_s(x, y)} \]  (6)
Why Isotropic Phase Symmetry was Important

- Use of conventional mean might result in higher values even if symmetry exist in particular directions.
- Use of median shall ensure that, we get an high value of symmetry only if, the symmetry is along all orientations.
- Green : Anisotropic
  Red : Isotropic
1. Biological Introduction
2. Proposed Scheme
3. Phase Symmetry
4. Analysis of Experimental Results
5. LIPSyM applied for ICPR Lyphocytes Dataset
6. Conclusions and Future Work
Visual Results

IMG: 40; green - correct detections; black - Wrongly Detected; Blue - Not Detected
Visual Results

IMG: 76; green - correct detections; black - Wrongly Detected; Blue - Not Detected
Visual Results

IMG: 56; green - correct detections; black - Wrongly Detected; Blue - Not Detected
Quantitative Evaluation Metrics

mention all metrics
How True is the Ground Truth?

- Subjectivity in markings by humans
- Other human factors – Fatigue, Boredom.

| Testing | Ground Truth | Sensitivity (%) | PPV (%) | F1-score (%) | $\mu_d$ | $\sigma_d$ | $\mu_n$ | $\sigma_n$ |
|---------|--------------|----------------|---------|--------------|---------|-----------|---------|-----------|
| A       | B            | 40.42          | 54.42   | 45.82        | 10.49   | 3.78      | 22.95   | 29.13     |
| B       | C            | 51.03          | 44.58   | 47.35        | 6.39    | 2.01      | 13.95   | 16.31     |
| A       | C            | 54.96          | 63.48   | 45.77        | 5.69    | 1.56      | 18.95   | 24.25     |
| A       | FGT (B+C)    | 52.75          | 59.99   | 54.64        | 9.52    | 4.32      | 13.05   | 12.36     |
| B       | FGT (A+C)    | 55.84          | 45.80   | 49.65        | 5.69    | 2.30      | 23.70   | 35.27     |
| C       | FGT (A+B)    | 56.73          | 54.86   | 54.82        | 6.18    | 1.86      | 19.10   | 22.49     |
| LIPSyM  | FGT (A+B+C)  | 63.22          | 60.63   | 60.82        | 7.82    | 2.82      | 10.35   | 9.39      |

**Table:** Comparison of three experts’ (A, B, and C) markings against each other and against the fused ground truth (FGT).
LIPSyM as a tool for Biologists & Pathologists

Available for Download:
http://www2.warwick.ac.uk/fac/sci/dcs/research/combi/projects/bic/lipsym
Available for Download:
http://www2.warwick.ac.uk/fac/sci/dcs/research/combi/projects/bic/lipsym
The data-set contains following:

- 20 H-DAB stained images
- Corresponding ground truth markings by 3 experts
- Fused ground truth
- Result of LIPSyM
1 Biological Introduction
2 Proposed Scheme
3 Phase Symmetry
4 Analysis of Experimental Results
5 LIPSyM applied for ICPR Lyphocytes Dataset
6 Conclusions and Future Work
“PR in HIMA” contest @ ICPR-2010
Contains images of breast tissue with lymphocytic infiltration stained with Hematoxylin & Eosin (H&E)
Task: detection of lymphocytes
LIPSyM applied for detection of lymphocytes
Results of LIPSyM compared with contestants

---

4 M. Gurcan, A. Madabhushi, and N. Rajpoot. Pattern recognition in histopathological images: an ICPR 2010 contest. Recognizing Patterns in Signals, Speech, Images and Videos, 2010
LIPSyM based method works better than methods proposed in the contest.

| Method                | PPV(%) | Sensitivity (%) | F1-score (%) | $\mu_d$ | $\sigma_d$ | $\mu_n$ | $\sigma_n$ |
|-----------------------|--------|----------------|--------------|---------|-----------|---------|-----------|
| LIPSyM                | 70.08  | 70.21          | 69.84        | 3.14    | 0.93      | 4.3     | 3.09      |
| Kuse et al.           | 65.23  | 69.99          | 67.29        | 3.04    | 3.40      | 14.01   | 4.4       |
| Cheng et al.          | –      | –              | –            | 8.10    | 6.98      | 26.67   | 12.5      |
| Graf et al.           | –      | –              | –            | 7.60    | 6.30      | 24.50   | 16.2      |
| Panagiotakis et al.   | –      | –              | –            | 2.87    | 3.80      | 14.23   | 6.3       |

**Table:** Experimental results for the detection of lymphocytes; best results are shown in **bold**.
1. Biological Introduction
2. Proposed Scheme
3. Phase Symmetry
4. Analysis of Experimental Results
5. LIPSyM applied for ICPR Lyphocytes Dataset
6. Conclusions and Future Work
Conclusions and Future Work

Conclusions

- Proposed an Isotropic Symmetry Measure – LIPSyM
- Application of LIPSyM for beta cells detections and lymphocytes detection.
- Automatic methods give higher sensitivity than manual markings.

Future Work

- Stain normalization, to adjust for variations of illumination and concentration of staining.
- Procedure to adaptively select the parameters used.
- Demarcation of boundaries
Thanks :)

Kuse M., Wang YF, Kalasannavar V., Khan M., Rajpoot N.