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

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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

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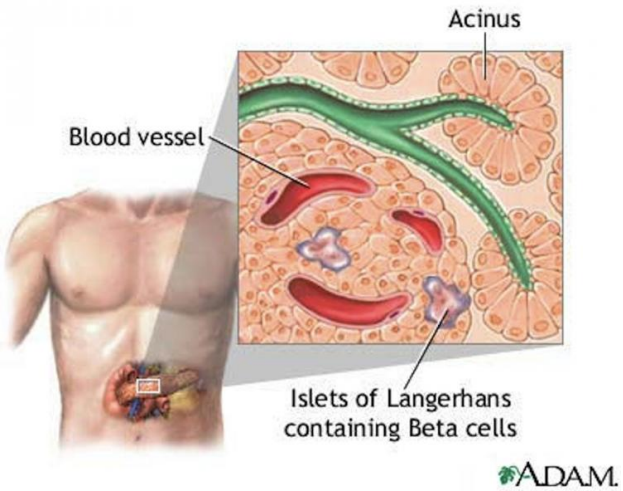
Where are Beta Cells Found

- Islets of Langerhans are the regions of the pancreas
- Contains – α cells, β cells, δ cells, *PP* cells, ϵ cells
- Illustration courtesy of NIH (National Institute of Health)[1]

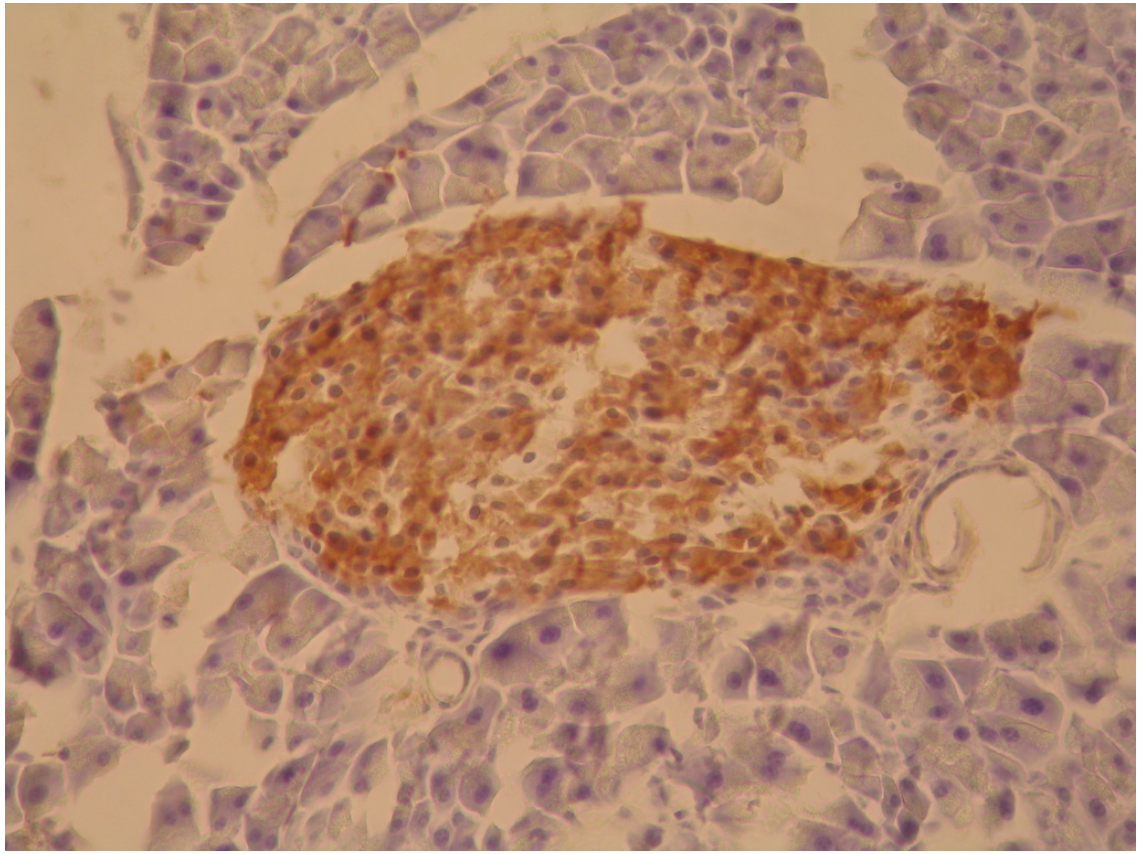


[1] http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/17151.jpg

Biological Background

- Diabetes associated with a reduction in functional β cell mass.
- β cell mass must be restored if diabetes to be cured or progress arrested.
- Post mortem analyses of β 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.

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Overall Picture

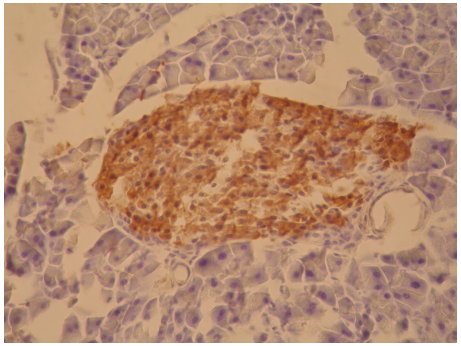
Stain Separation

Stain Separation

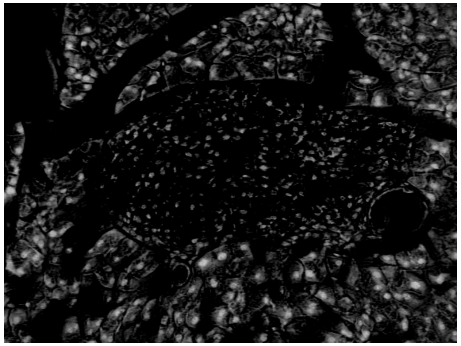
- Ruifrok & Johnston method for color deconvolution [2]
- H-DAB stained input image resolved into components of H, DAB stains.

[2] A.C. Ruifrok and D.A. Johnston. Quantification of histochemical staining by color deconvolution. Anal Quant Cytol Histol, 2001.

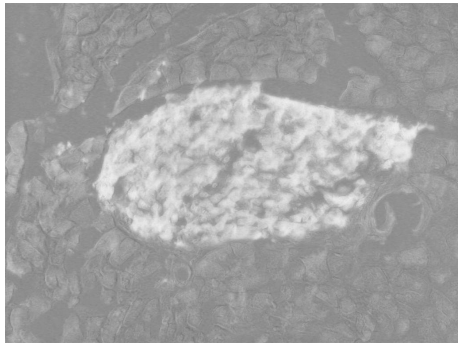
Stain Separation



(a) Sample Image



(b) H-Stain



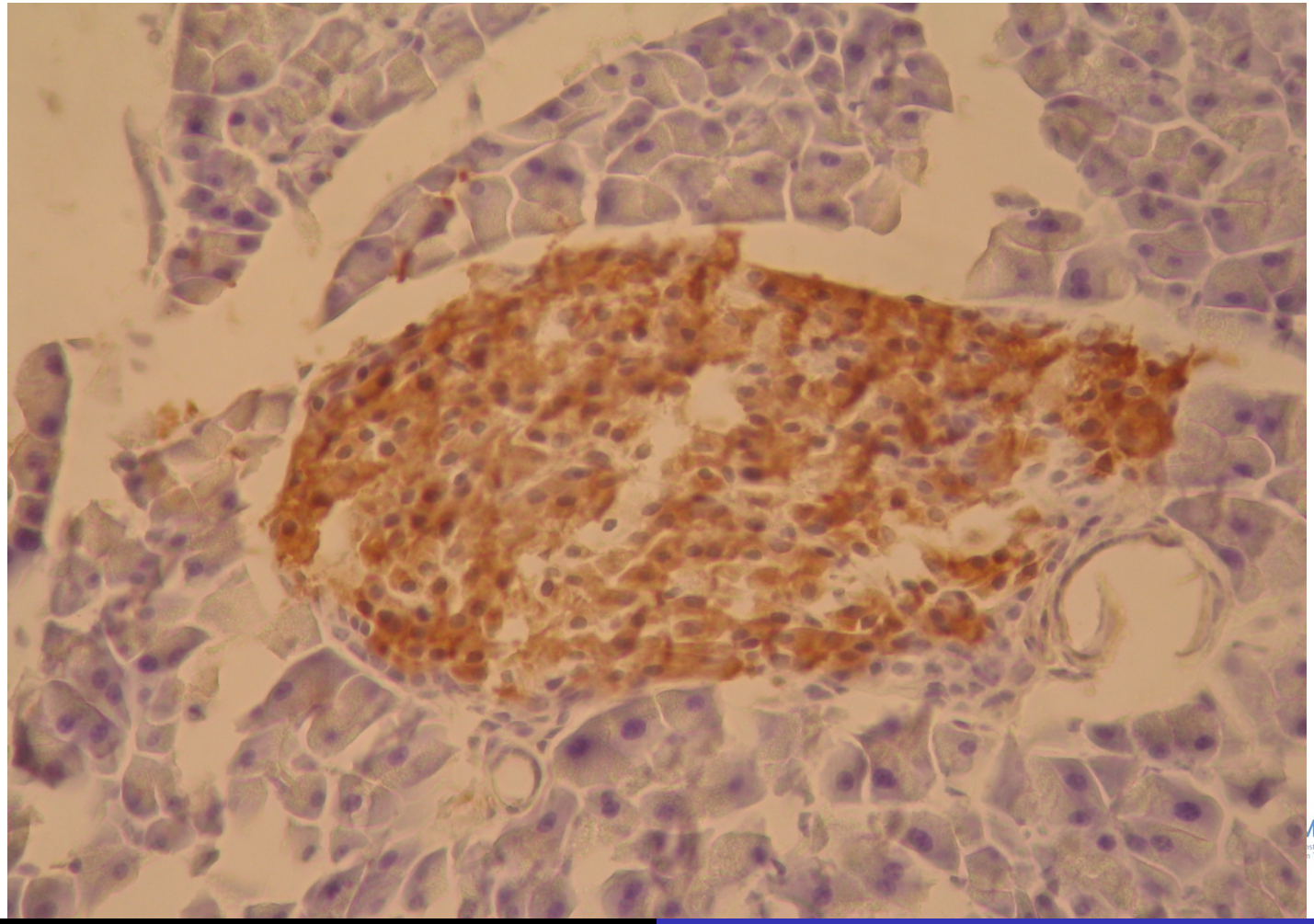
(c) DAB-Stain

Local Isotropic Phase Symmetry

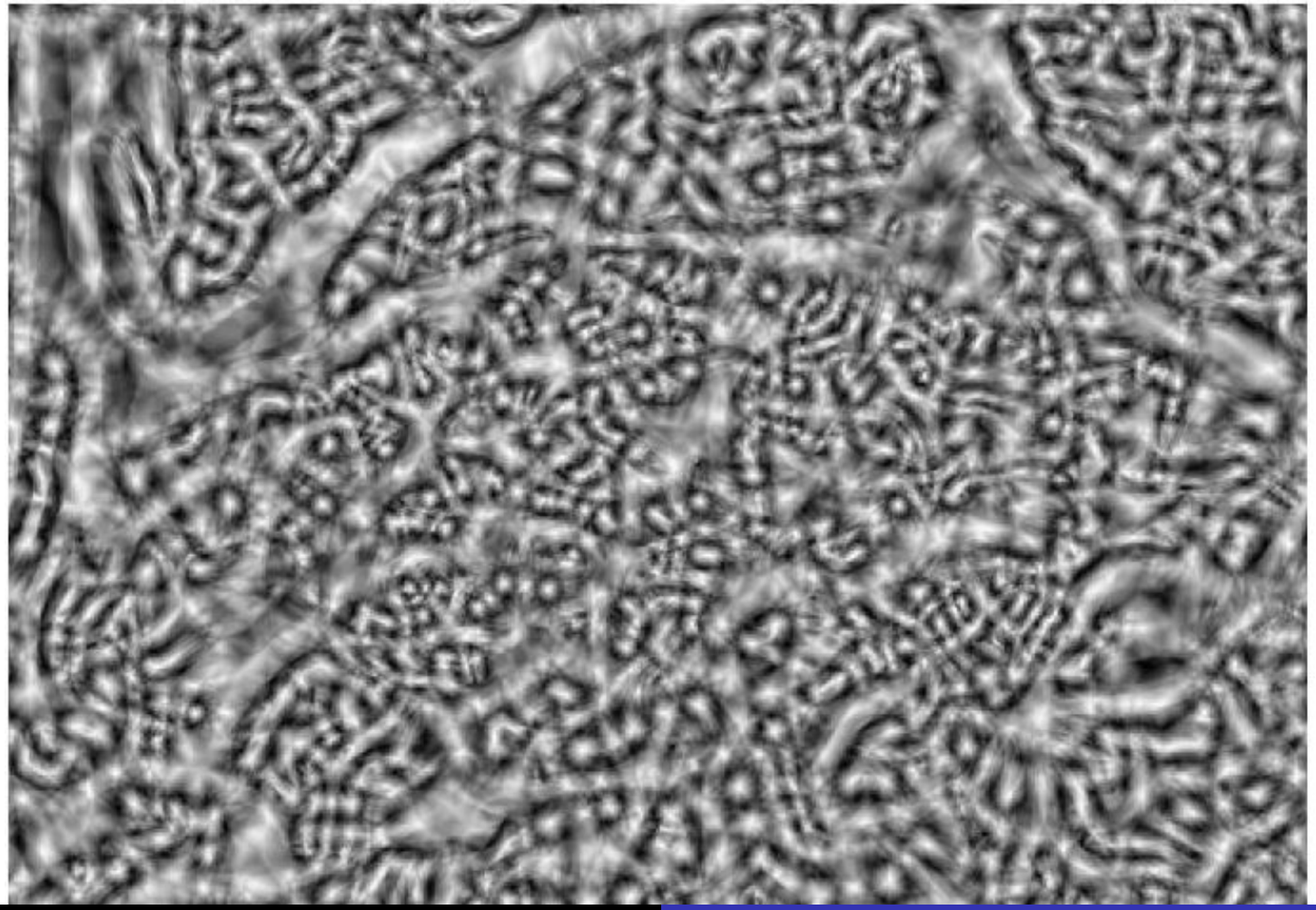
Computation of Symmetry Measure – LIPSyM

- LIPSyM - Local Isotropic Phase Symmetry Measure
- Isotropic pixel wise measure for symmetry.
- Based on Gabor Trasform.
- More details later.

LIPSyM



Overlay of LIPSyM and Sample Image

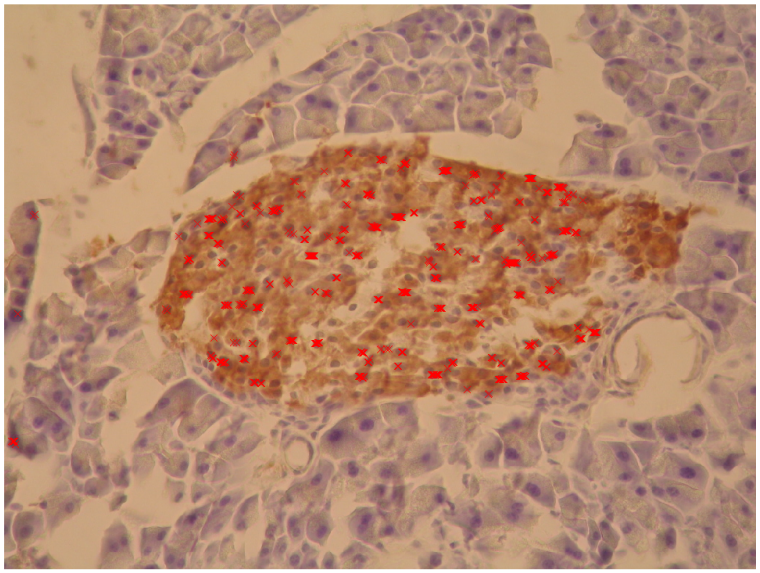


Finding Peaks

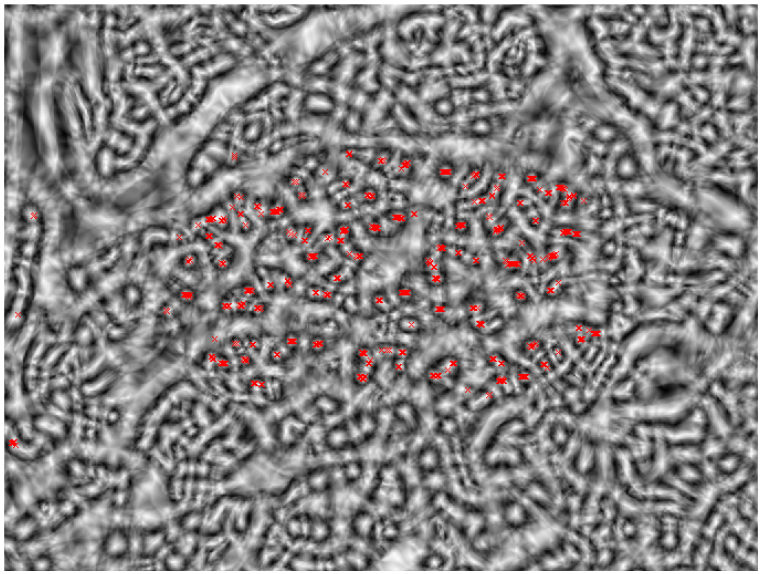
Find Peaks

- 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

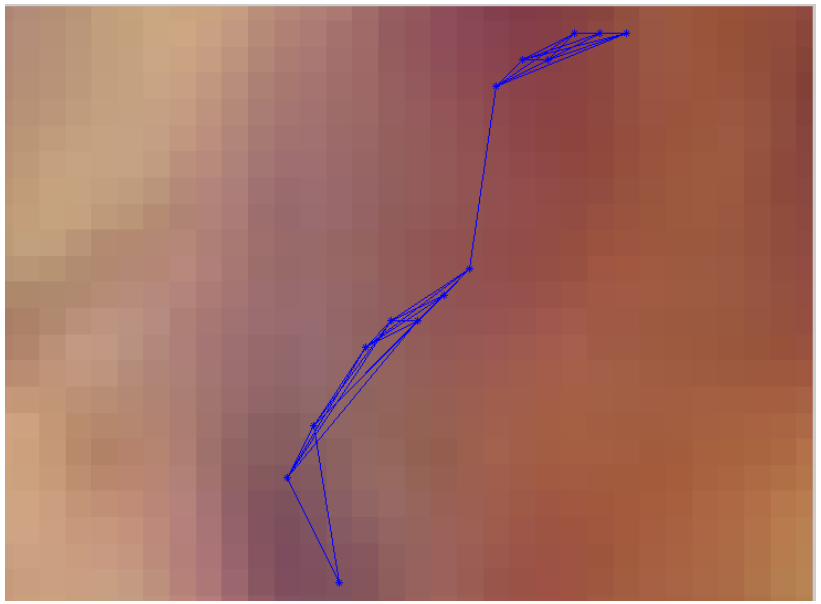


(e) Overlay of Peaks

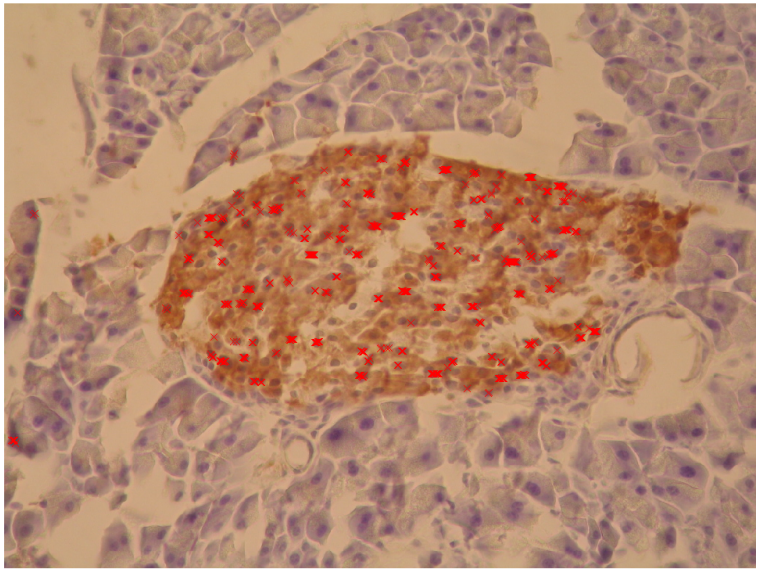
Clustering Peaks

Clustering Peaks

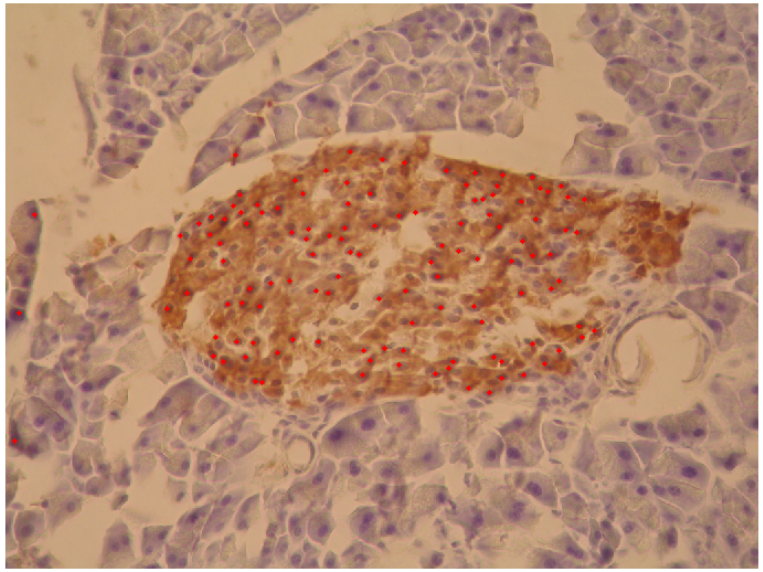
- Peaks modeled as graph, based on threshold on distance.
- Maximal cliques used to partition the graph into subgraphs.



Clustering Peaks



(f) Overlay of Peaks



(g) Clustered Peaks

Elimination of Non-islet Cells

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

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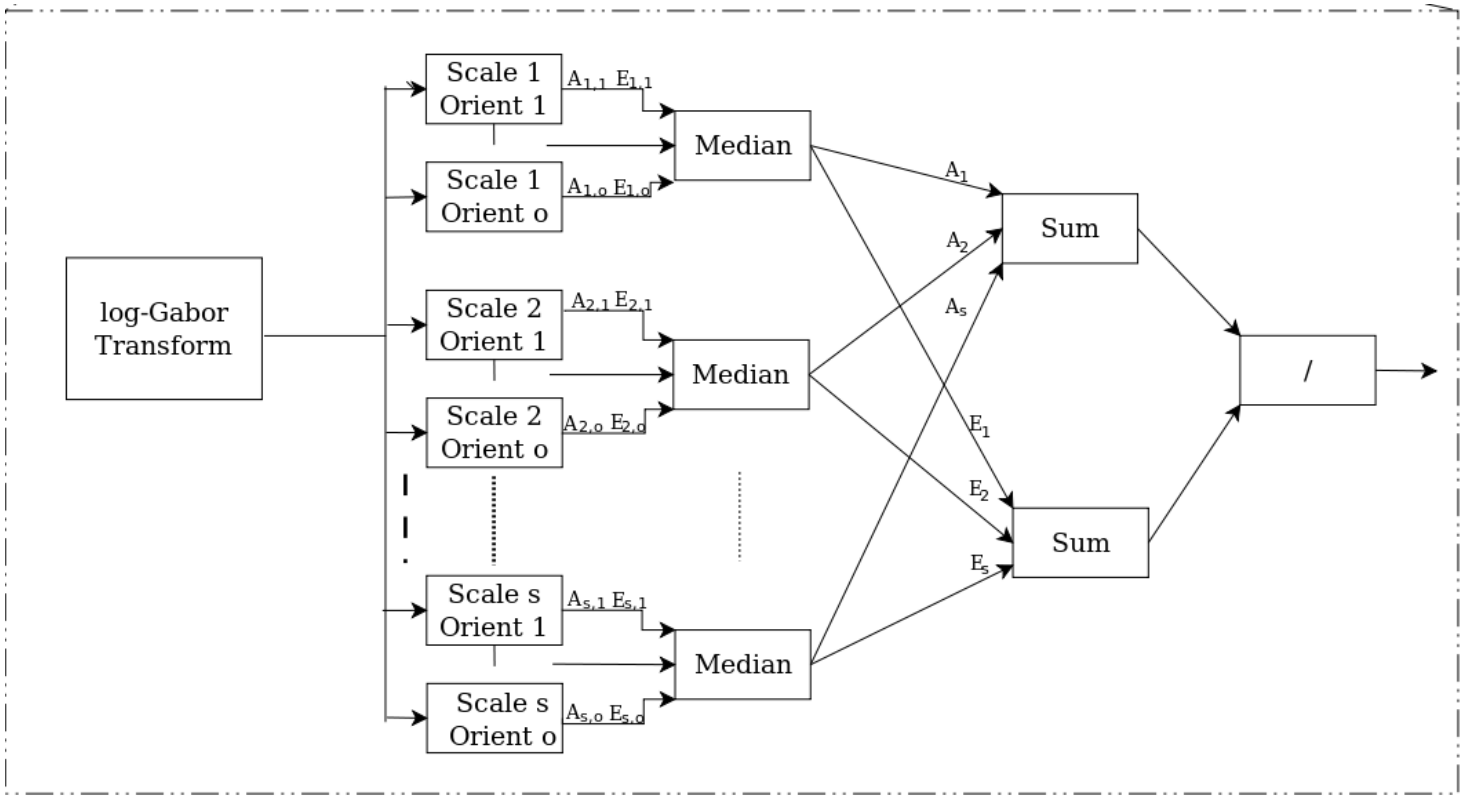
Basic Motivation

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

LIPSyM – Schematic Diagram



Mathematical Abstraction

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

$$V_{s,o} = I * G_{s,o} \tag{1}$$

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.

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

$$E_{s,o}(x, y) = |\mathrm{Real}\{V_{s,o}(x, y)\}| - |\mathrm{Imag}\{V_{s,o}(x, y)\})| \tag{3}$$

Mathematical Abstraction

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

$$A_s(x,y) = \underset{o=1,2,\ldots,n_o}{\text{median}} \{A_{s,o}(x,y)\} \tag{4}$$

$$E_s(x,y) = \underset{o=1,2,\ldots,n_o}{\text{median}} \{E_{s,o}(x,y)\} \tag{5}$$

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

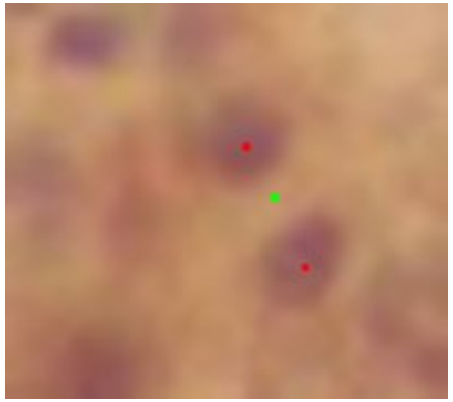
Mathematical Abstraction

- Definition of Local Isotropic Phase Symmetry.

$$\eta(x,y) = \frac{\sum_{s=1}^{n_s} E_s(x,y)}{\sum_{s=1}^{n_s} A_s(x,y)} \tag{6}$$

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



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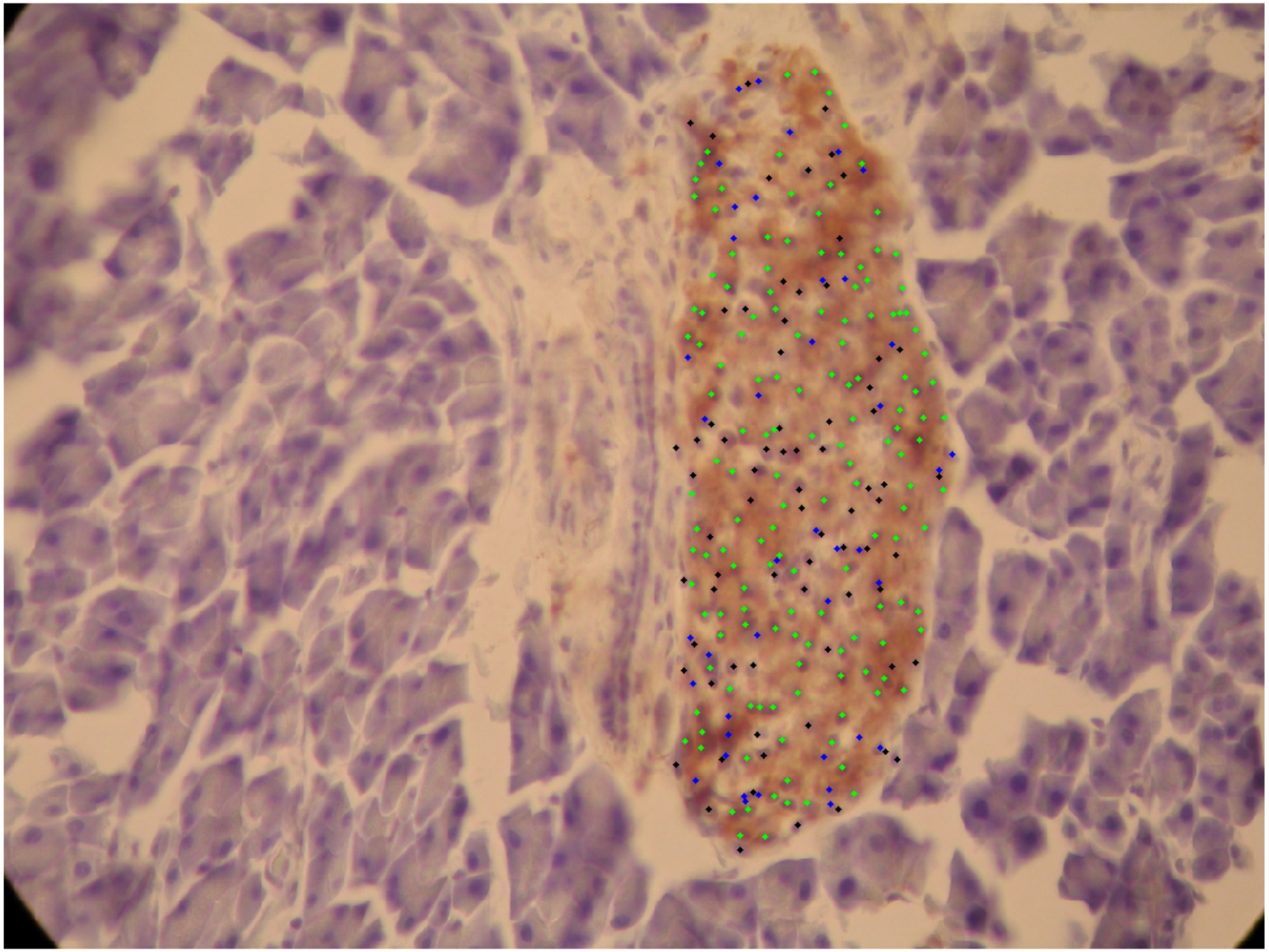
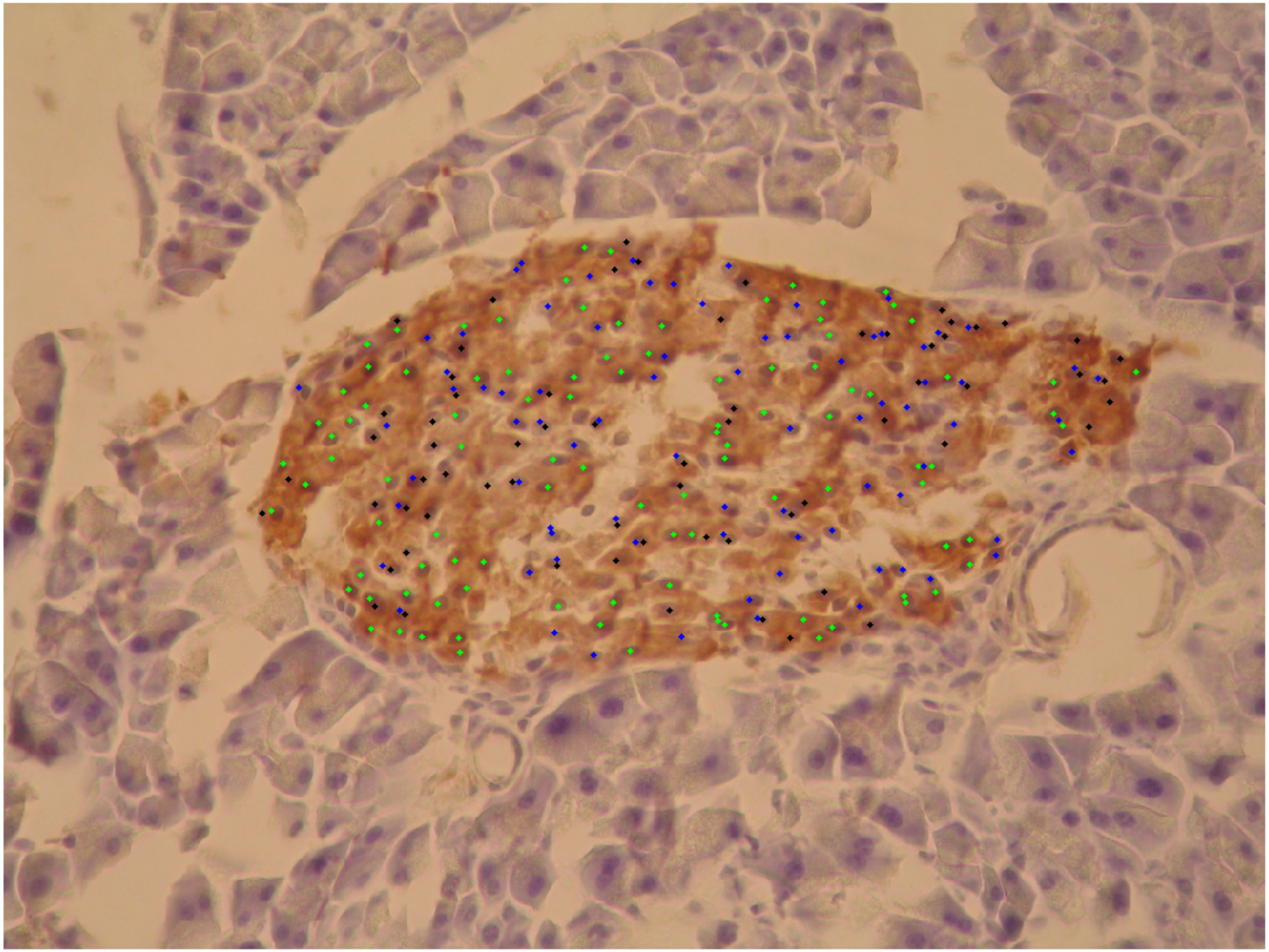
Visual Results

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



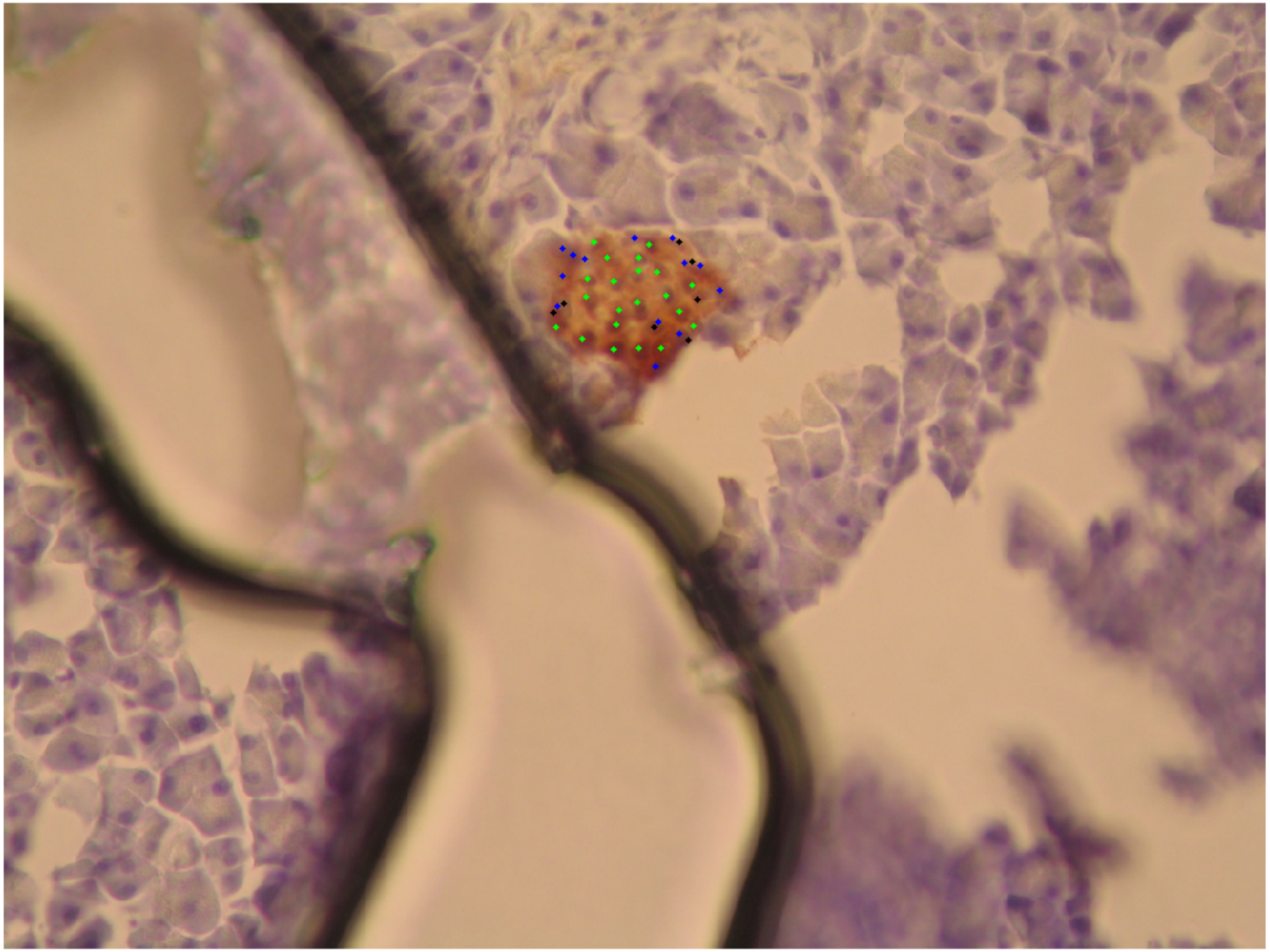
Visual Results

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

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How True is the Ground Truth?

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

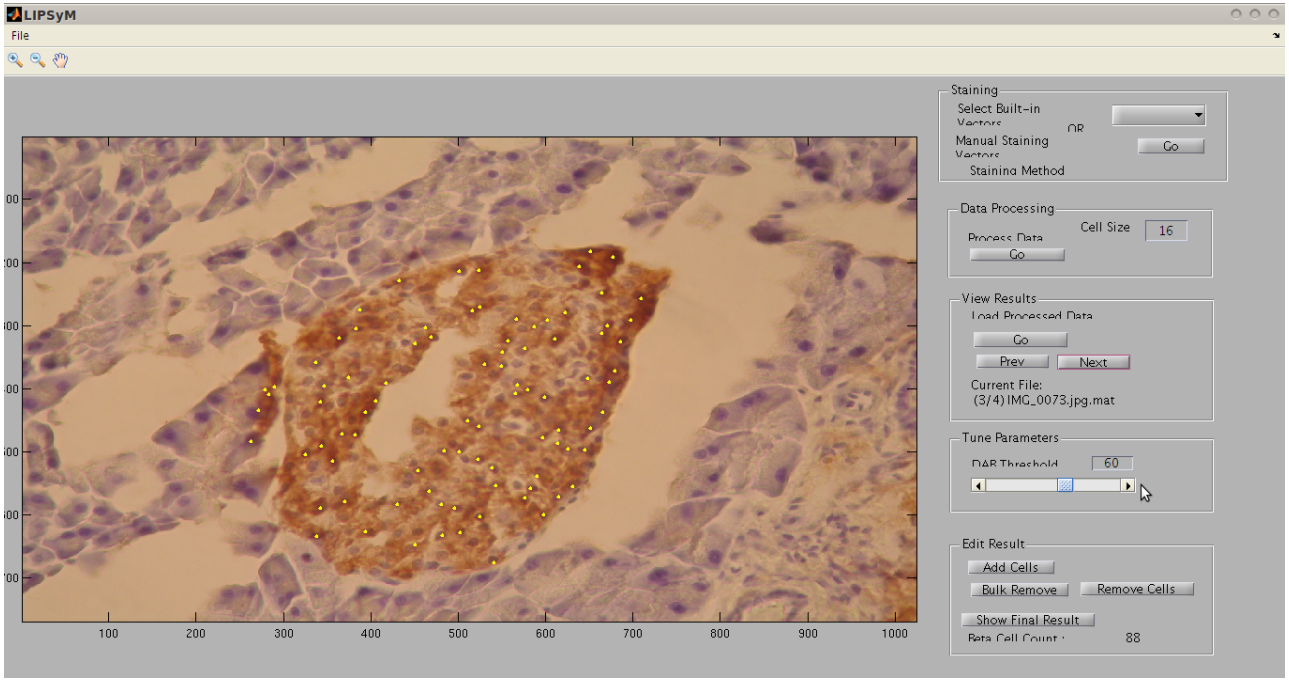
Testing	Ground Truth	Sensitivity (%)	PPV (%)	F1-score (%)	μ_d	σ_d	μ_n	σ_n
A	B	40.42	54.42	45.82	10.49	3.78	22.95	29.13
B	C	51.03	44.58	47.35	6.39	2.01	13.95	16.31
A	C	54.96	63.48	45.77	5.69	1.56	18.95	24.25
A	FGT (B+C)	52.75	59.99	54.64	9.52	4.32	13.05	12.36
B	FGT (A+C)	55.84	45.80	49.65	5.69	2.30	23.70	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 & Patholoists

Available for Download :

http://www2.warwick.ac.uk/fac/sci/dcs/research/combi/projects/bic/lipsym



Warwick Beta Cell Dataset

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

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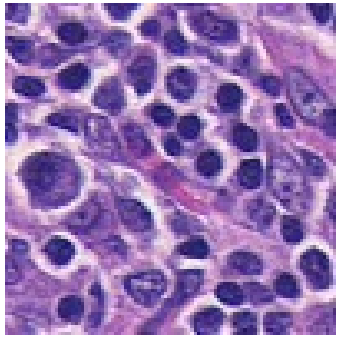
LIPSyM applied for ICPR Lymphocytes Dataset

- "PR in HIMA" contest @ ICPR-2010 [4]
- 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

Result of LIPSyM – ICPR Lymphocytes Dataset

LIPSyM based method works better than methods proposed in the contest.

Method	PPV(%)	Sensitivity (%)	F1-score (%)	μ_d	σ_d	μ_n	σ_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**.

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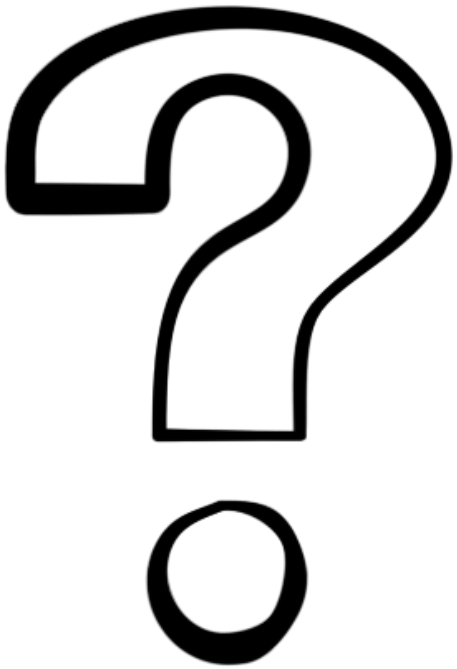
Conclusions and Future Work

- 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 :)