Learning to Detect Cells Using Non-Overlapping Extremal Regions

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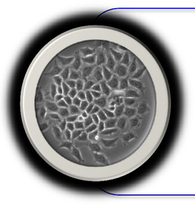
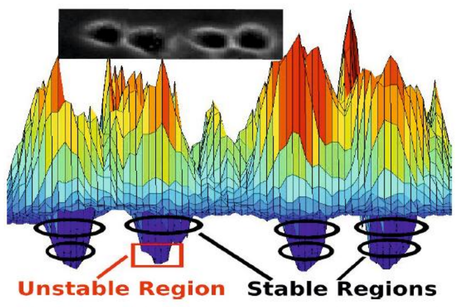


Cell detection in microscopy images is an important step in the automation of cell based-experiments. We propose a machine learning-based cell detection method applicable to different microscopy modalities. A cell model is learned from simple dot annotations; it requires few images for training and the learning can be done within a structured SVM framework.

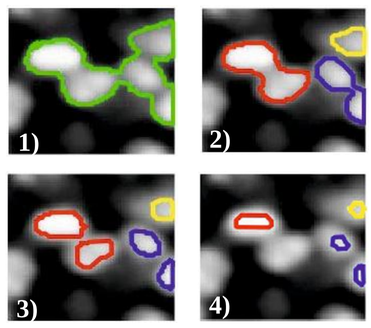
Cell Candidate Detection

Finding extremal regions

We use Maximally Stable Extremal Regions (or MSER) [6] to find a representative set of extremal regions to use as cell candidates.



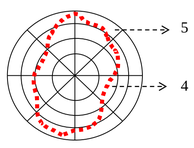
The MSER algorithm detects extremal regions that are stable in area growth while varying an intensity threshold.



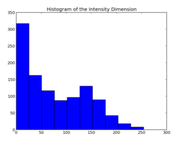
Sequence of MSER at different thresholds

Nestedness property of extremal regions: if the extremal regions overlap, then they are nested.

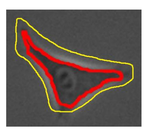
Describing extremal regions



Shape descriptor



Intensity histogram (one per colour channel)



Histogram of difference in intensities

Size bins
[0 0 0 1 0 0 0 0 0 0]

Quantized area

=

92-dimensional feature vector

Picking the best subset of non-overlapping extremal regions

The score of each region is estimated as a linear function of the features: $V_i = (\mathbf{w} \cdot \mathbf{f}_i)$, where $\mathbf{w}$ is obtained by Machine Learning (see below).

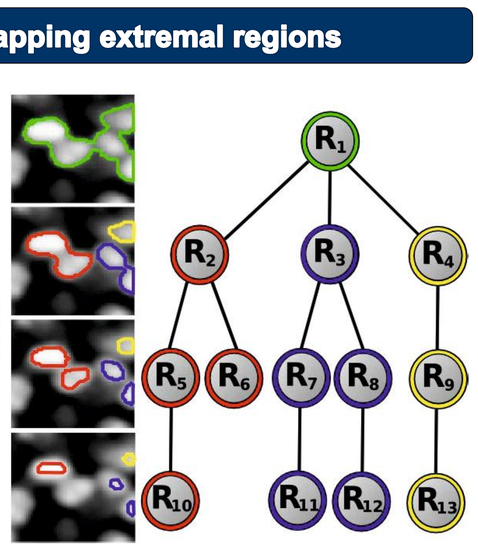
We can find the best subset of regions such that they do not overlap by solving the optimization

$$F(\mathbf{y}) = \sum_{i=1}^{N} y_i V_i \rightarrow \max_{\mathbf{y} \in \mathcal{Y}}$$

$\mathcal{Y}$ = set of all non-overlapping region sets

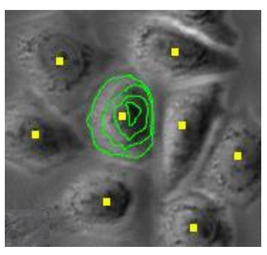
where $y_i = 1$ implies that the region R_i has been picked.

This optimization problem can be solved **exactly** via dynamic programming on trees.



Learning

Deriving the "ground truth" labels from dot annotations



Use dot annotation to obtain the class (cell or no cell) of each region in the training set:

1- Consider regions containing exactly 1 dots as positive; consider all other regions as negative.

2- Train a binary SVM classifier

3- "Ground truth" regions are obtained by picking the region with the highest score for each dot.

Learning with Structured-SVM [8]

Binary SVM does not take the non-overlap constraint into account. Instead, structured SVM learning can be used to optimize the actual performance of the inference on the training data.

This is done by minimizing the following objective (a regularized upper bound on the empirical risk):

$$\mathcal{L}(\mathbf{w}) = \frac{1}{2}||\mathbf{w}||^2 + \frac{C}{M}\sum_{j=1}^{M} \max_{\mathbf{y}^j \in \mathcal{Y}^j} \left(\sum_{i=1}^{N^j} (\mathbf{w} \cdot \mathbf{f}_i^j)\, y_i^j - \sum_{i=1}^{N^j} (\mathbf{w} \cdot \mathbf{f}_i^j)\, \bar{y}_i^j + L(\mathbf{y}^j) \right)$$

where

$$L(\mathbf{y}^j) = \sum_{i=1}^{N^j} y_i^j\, |n_i^j - 1| + U^j(\mathbf{y}^j) = \sum_{i=1}^{N^j} \left((\mathbf{w} \cdot \mathbf{f}_i^j) + |n_i^j - 1| - n_i^j \right) y_i^j$$

is a loss function that penalizes for deviation from one-to-one correspondence between regions and annotation dots. The loss decomposes over *i*, thus we can perform loss-augmented inference exactly via dynamic programming on trees

$\mathcal{Y}^j$ = Set of all non-overlapping subsets of regions in image *j*. $U^j(\mathbf{y}^j)$ = Unmatched dots in image *j*.

n_i^j = Number of dots within region *i*. $\bar{y}_i^j$ = Ground truth regions selected after binary classification.

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Results

Legend

S+I = Structured SVM + inference. Uses inference with the weight vector learned by the structured SVM.

B+I = Binary SVM + inference. Uses the output of a binary SVM and does the full inference.

DC = Direct comparison. Uses the output of a binary SVM and select the regions with the maximum positive score to resolve overlapping regions.

B+Y = Method by Bernardis and Yu [1].

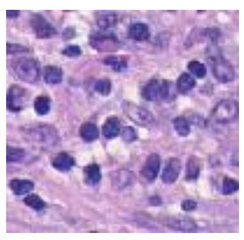
Yellow dots = Human annotations.

Dashed green/red contour = Cell detected automatically.

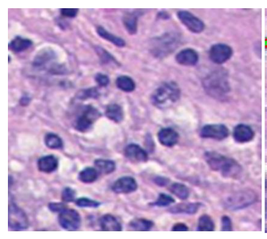
Precision=TP/(TP + FP)

Recall=TP/(TP + FN)

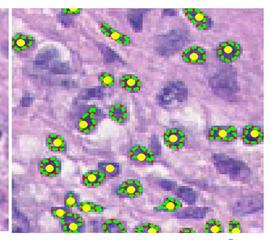
Histopathology Breast Cancer



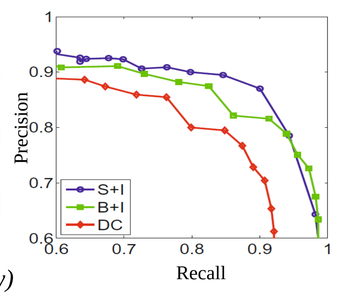
-Discrimination between similar structures



Input



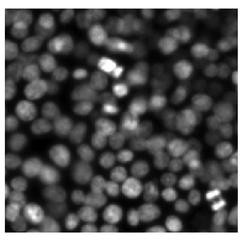
Output (green/red)
User Annotations (yellow)



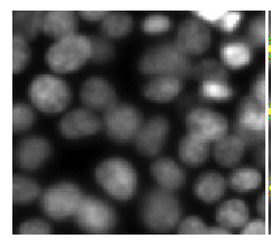
Lymphocyte detection in histopathology images, ICPR 2010

Methods	Prec.	Rec.	F_1-Score	$\mu_d \pm \sigma_d$	$\mu_n \pm \sigma_n$
Our method	**86.99**	**90.03**	**88.48**	**1.68** ± 2.55	**2.90** ± 2.13
Kuse *et al.* [4]	70.21	70.08	69.84	3.14 ± 0.93	4.30 ± 3.09
Bernardis *et al.* [1]	-	-	-	3.13 ± 3.08	12.7 ± 8.70
Kuse *et al.* [5]	65.23	69.99	67.29	3.04 ± 3.40	14.01 ± 4.4
Cheng *et al.* [2]	-	-	-	8.10 ± 6.98	6.98 ± 12.5
Graf *et al.* [3]	-	-	-	7.60 ± 6.30	24.5 ± 16.2
Panagiotakis *et al.* [7]	-	-	-	2.87 ± 3.80	14.23 ± 6.3

Human Embryonic Kidney cells on fluorescence microscopy



-Low-contrast
-Fading boundaries
-Cells out of focus
-Cell overlap



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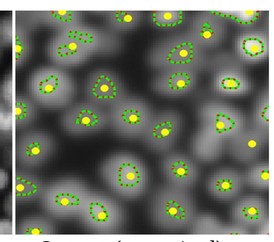
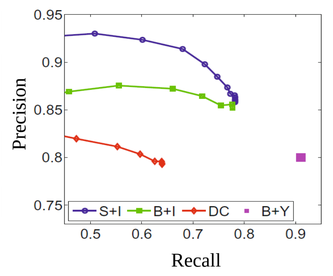
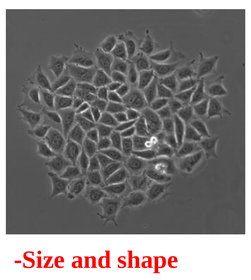


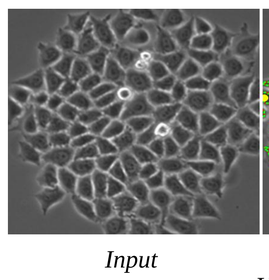
Output (green/red)
User Annotations (yellow)



HeLa cells on phase contrast microscopy



-Size and shape variability



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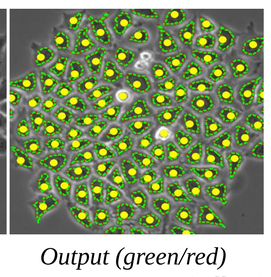

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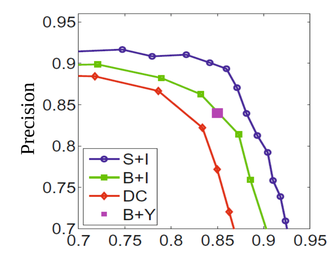

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Acknowledgement

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