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Automated Gland Segmentation and Classification for Prostate Cancer Grading

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United States Mortality Data

US Mortality, 2006

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	631,636	26.0
2.	**Cancer**	**559,888**	**23.1**
3.	Cerebrovascular diseases	137,119	5.7
4.	Chronic lower respiratory diseases	124,583	5.1
5.	Accidents (unintentional injuries)	121,599	5.0
6.	Diabetes mellitus	72,449	3.0
7.	Alzheimer disease	72,432	3.0
8.	Influenza & pneumonia	56,326	2.3
9.	Nephritis*	45,344	1.9
10.	Septicemia	34,234	1.4

Source: US Mortality Data 2006, National Center for Health Statistics, Centers for Disease Control and Prevention, 2009.

Some facts and figures about cancer

2009 Estimated US Cancer Deaths*

Men (292,540)

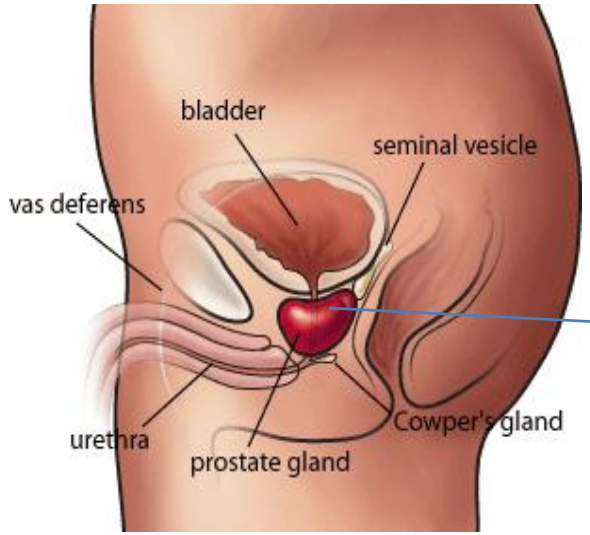
Lung & bronchus	30%
Prostate	9%
Colon & rectum	9%
Pancreas	6%
Leukemia	4%
Liver & intrahepatic bile duct	4%
Esophagus	4%
Urinary bladder	3%
Non-Hodgkin lymphoma	3%
Kidney & renal pelvis	3%
All other sites	25%

Women (269,800)

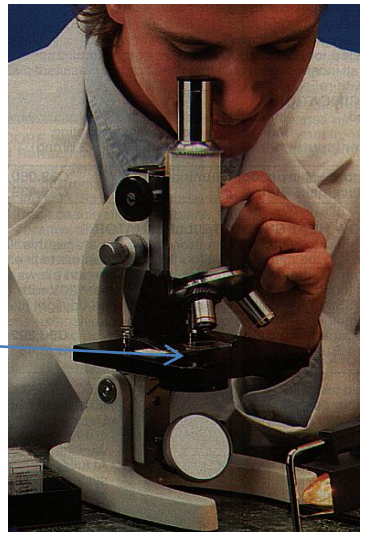
•26%	Lung & bronchus
•15%	Breast
• 9%	Colon & rectum
• 6%	Pancreas
• 5%	Ovary
• 4%	Non-Hodgkin lymphoma
• 3%	Leukemia
• 3%	Uterine corpus
• 2%	Liver & intrahepatic bile duct
• 2%	Brain/ONS
•25%	All other sites

Source: American Cancer Society, 2009.

Prostate cancer diagnosis



A tissue slide sample



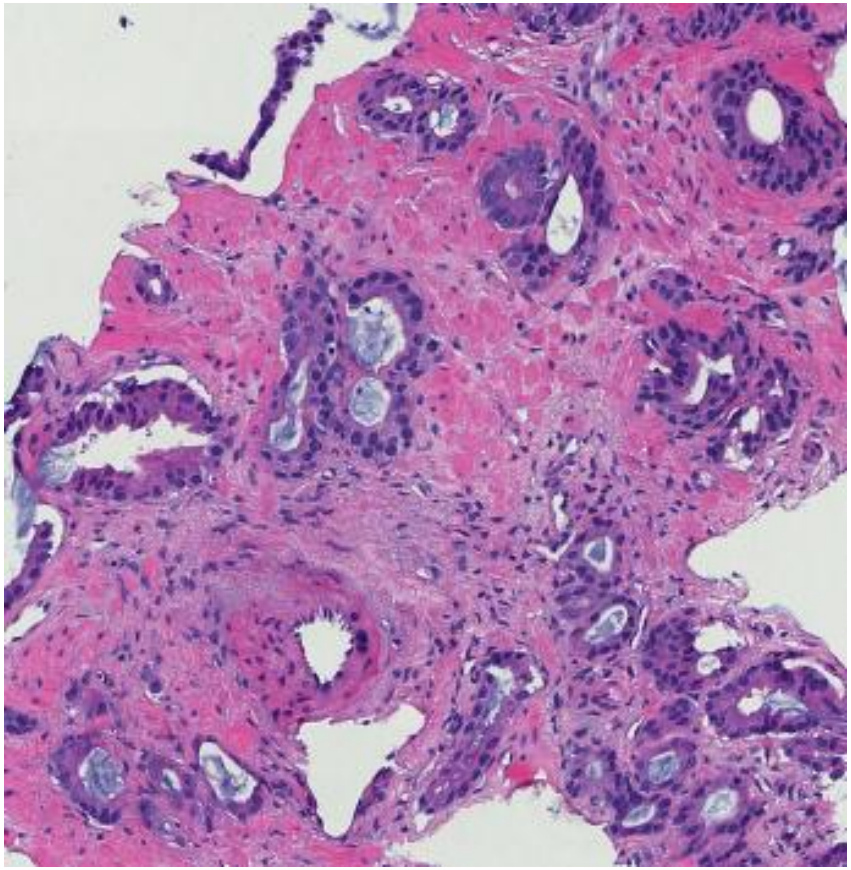
- Prostate biopsy: a procedure to obtain a sample of the prostate tissue
- Pathologists look at a tissue slide under a microscope to detect abnormal regions

- Tedious and time-consuming job
- Variation in diagnosis depending on the experience & skill of the pathologist

Need for an automatic diagnostic process

Image Acquisition

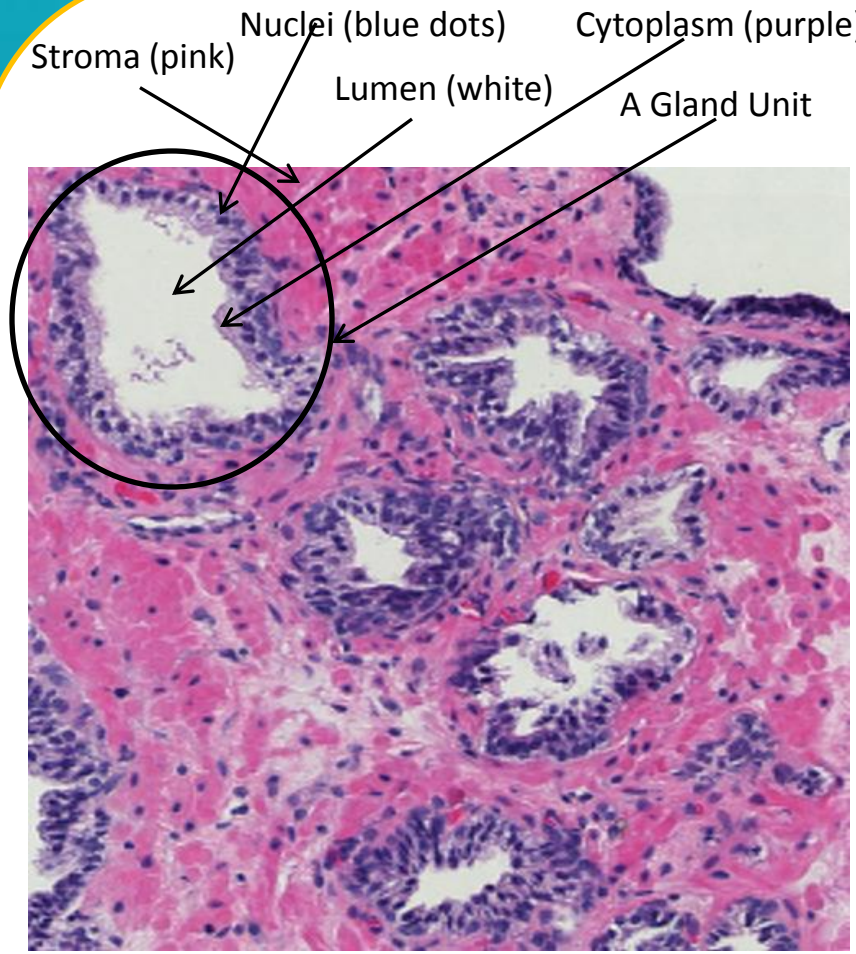
Image acquisition system



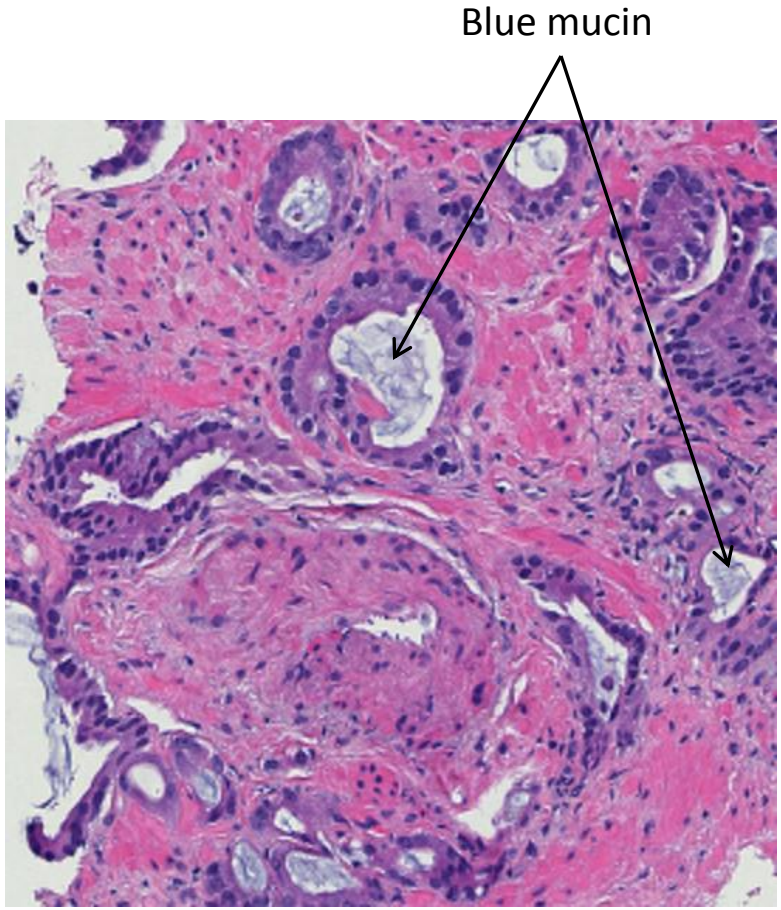
An image of a prostate tissue stained by H&E (Hematoxylin and eosin) method

(H&E is used in this work)

Prostate tissue structure



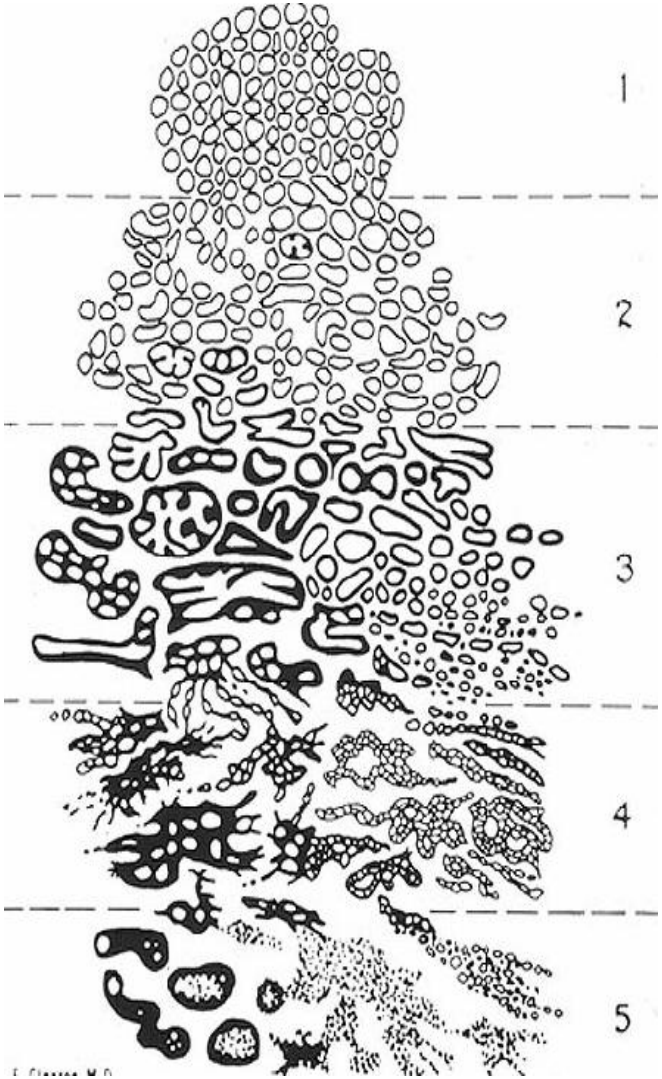
The tissue includes glands surrounded by stroma. Each gland consists of epithelial nuclei on the boundary and lumen in the center.

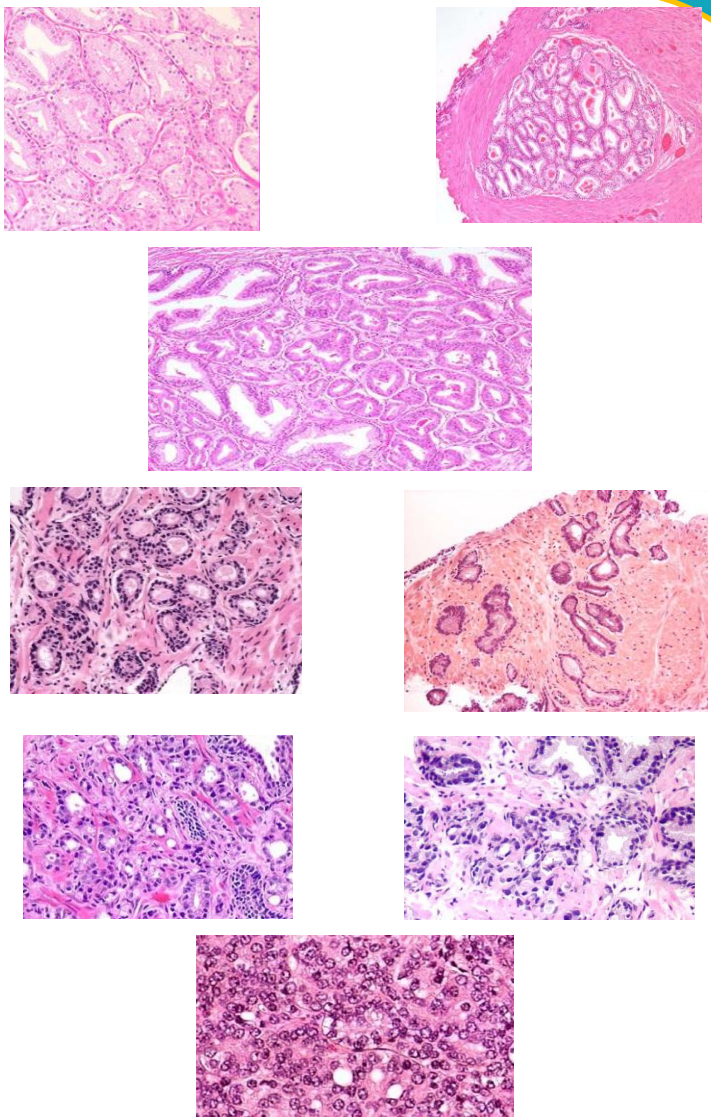


In cancer tissue, blue mucin may invade the lumen

Gleason grading system for prostate cancer

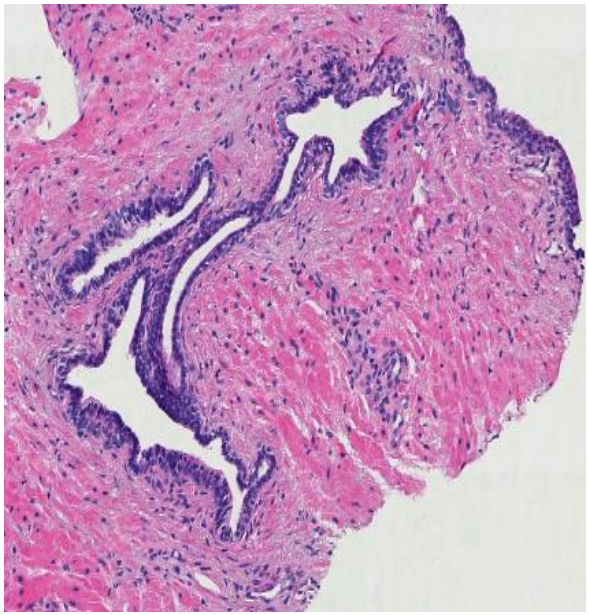
Tissue grading is based on architectural pattern of the glands



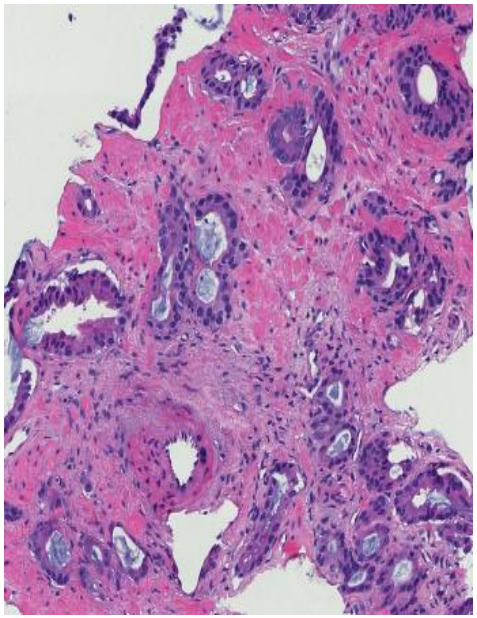


Ref: Gleason Grading of Prostatic Carcinoma , Johns Hopkins Pathology

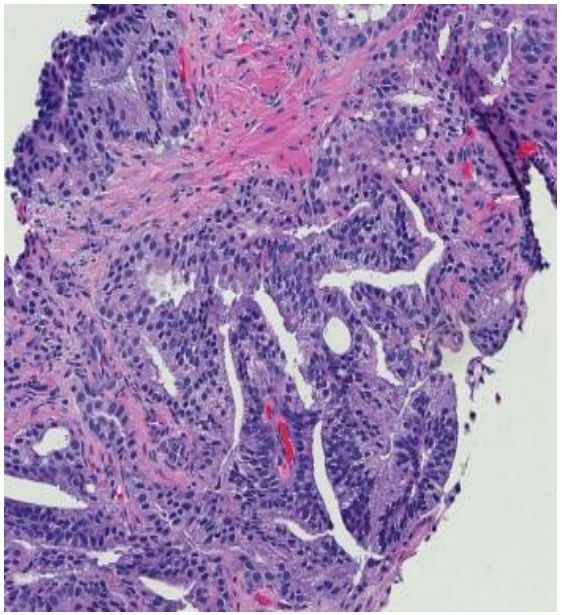
Classification problem



Benign (normal, grades 1 & 2) pattern



Grade 3 pattern



Grade 4 pattern

Not easy to find data for grade 5 cancer

Previous work

- **Non-segmentation based approach:**
  - Diamond et al. classify regions of interest into stroma, carcinoma and normal tissue based on texture features; 79.3% accuracy on 8 images
  - Doyle et al. extracted 594 features (first-order statistics, texture, wavelet) at 3 different image scales for classifying a tissue pattern as cancerous or non-cancerous; 88% accuracy on 22 test images

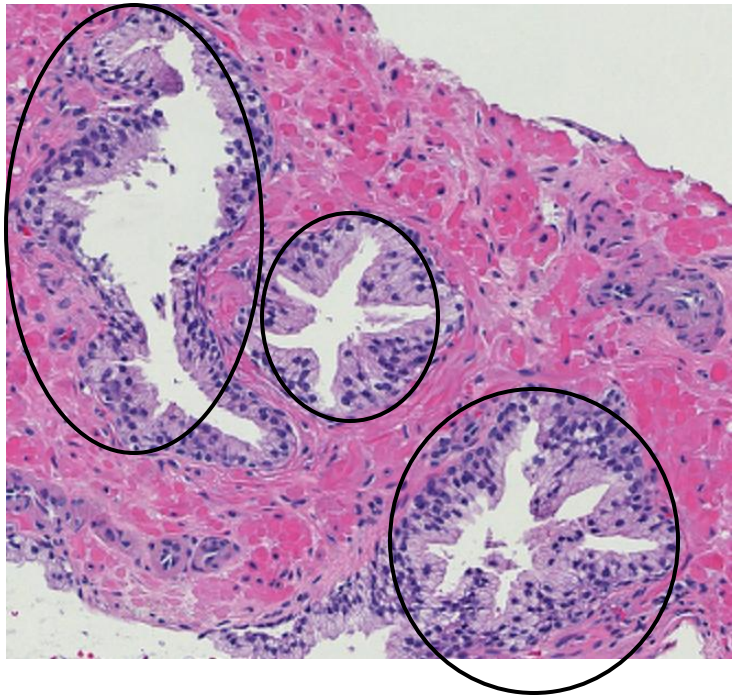
  Limitation:

  Did not analyze the tissue structure which is the grading criteria
- **Segmentation-based approach:**
  - Naik et al. segment glands from the tissue. Eight shape features for lumen and for gland inner boundary are computed; 86.35% (grade 3 vs benign), 92.9% (grade 4 vs benign), 95.19% (grade 3 vs grade 4) on a dataset of 44 images

  Limitation:

  Did not utilize the nuclei and blue mucin information in the tissue

Gland segmentation based approach



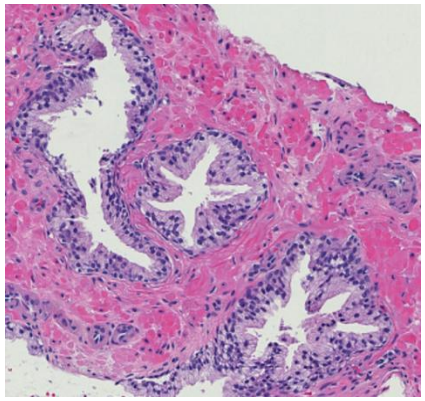
Given an input pattern:

1. Segment glands from background
2. Extract gland features (from lumen, nuclei, mucin and gland morphology)
3. Classify the pattern using multilayer perceptron, SVM, fusion of classifiers

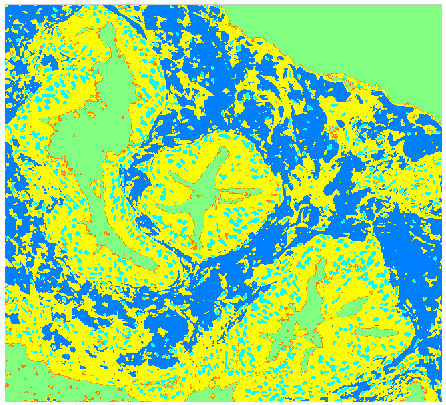
Overview of the gland segmentation

Three stages of segmentation

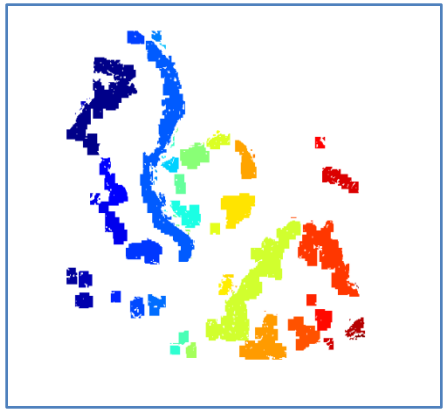
1. Pixel classification
2. Gland boundary construction
3. Complete gland segmentation



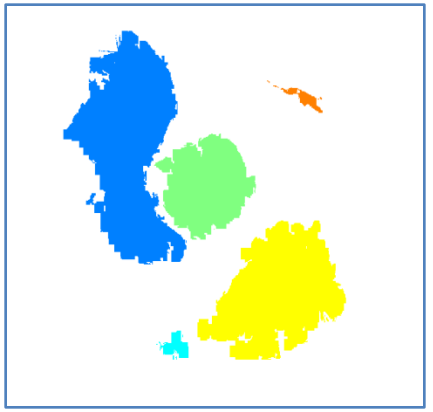
Input image



Output of step 1



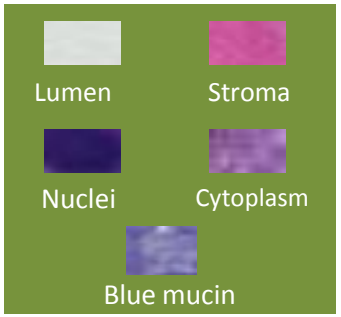
Output of step 2



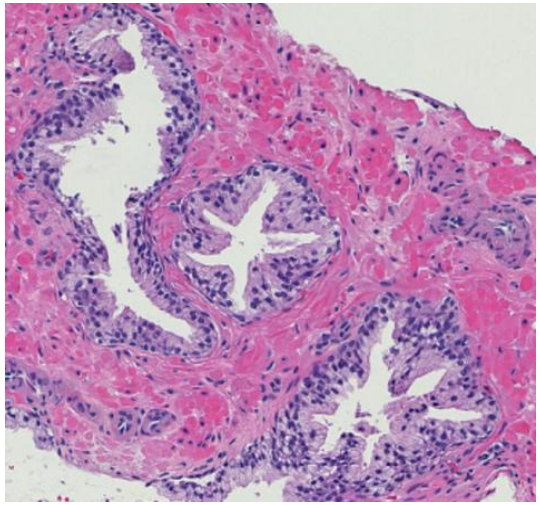
Output of step 3

1. Pixel classification

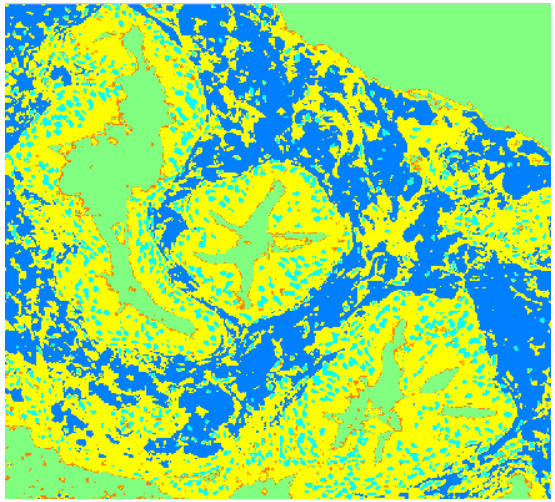
- *Make use of*: color information (La*b* color system)
- *Observation*: Each pixel belongs to one of five classes: **stroma, cytoplasm, lumen, nuclei** or **blue mucin**
- *Goal*: A labeled image in which each pixel is assigned one of five labels
- *Method*:
  - Nearest neighbor classifier
  - Training samples are typical pixels from each class
- *Result:*



Training pixels

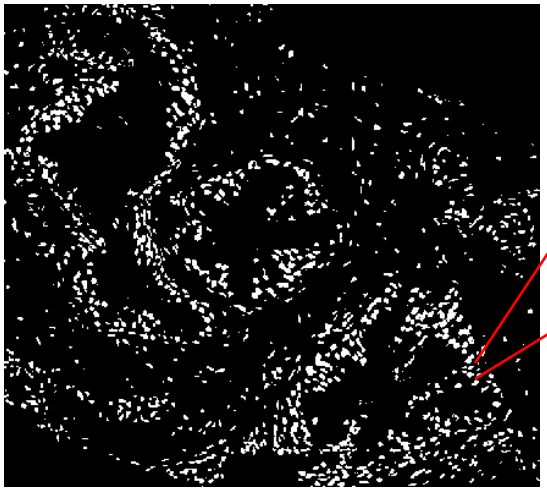


Result of step 1



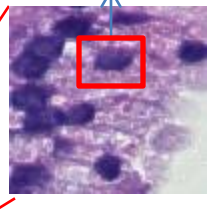
2. Gland boundary construction

- *Make use of*: nuclei and cytoplasm pixels on the gland boundary
- *Observation*: Nuclei are denser at the gland boundary than other areas; Cytoplasm can be the bridge to connect nuclei
- *Goal*: Components of Nuclei-Cytoplasm (NC)
- *Method*:

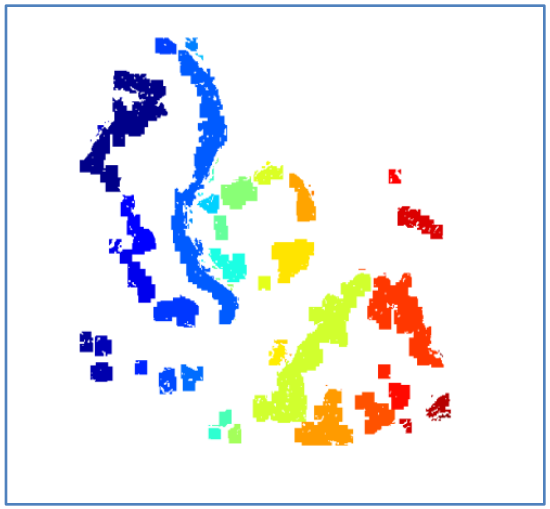


Nuclei components

Neighborhood N_i of each nuclei (size $S_1 x S_1$)



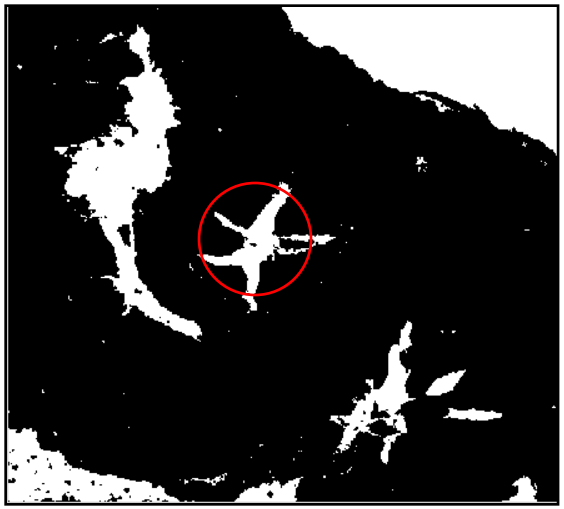
If (nuclei pixels in $N_i > T_1$) → Unify cytoplasm and nuclei pixels in N_i



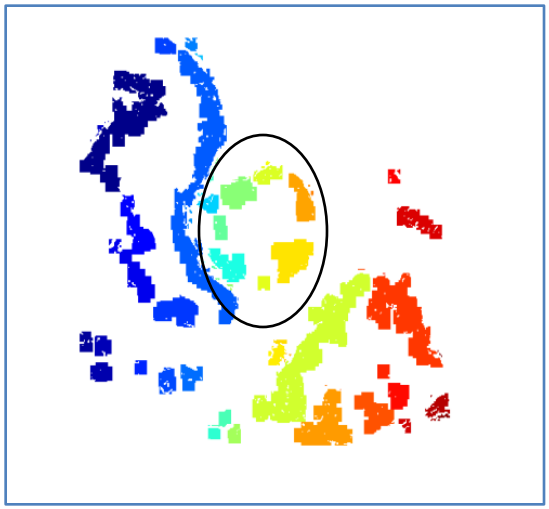
Result of step 2
(Nuclei-cytoplasm components)

3. Complete gland segmentation

- *Make use of*: lumen component
- *Observation*: lumen is surrounded by Nuclei-Cytoplasm (NC) components
- *Goal*: complete gland regions
- *Method*: lumen expanding



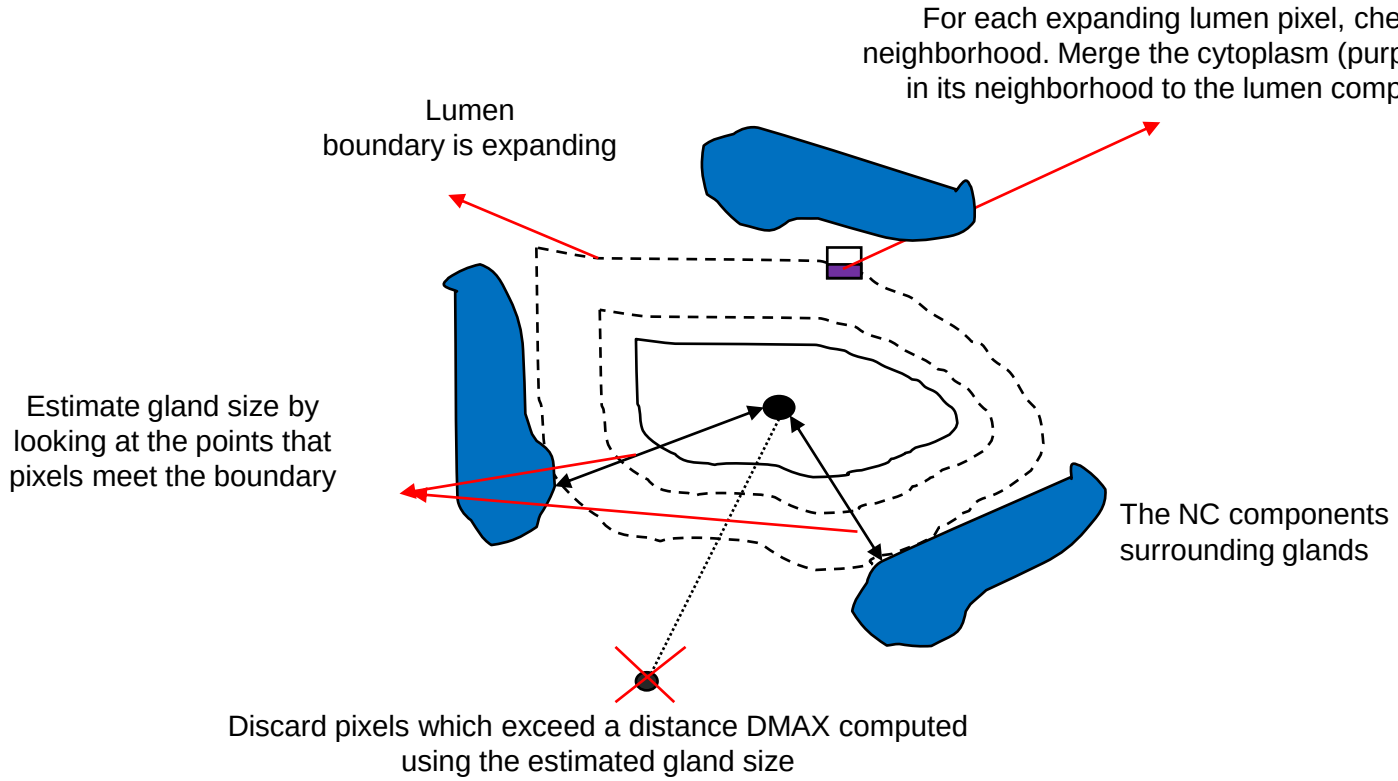
Binary image of lumen



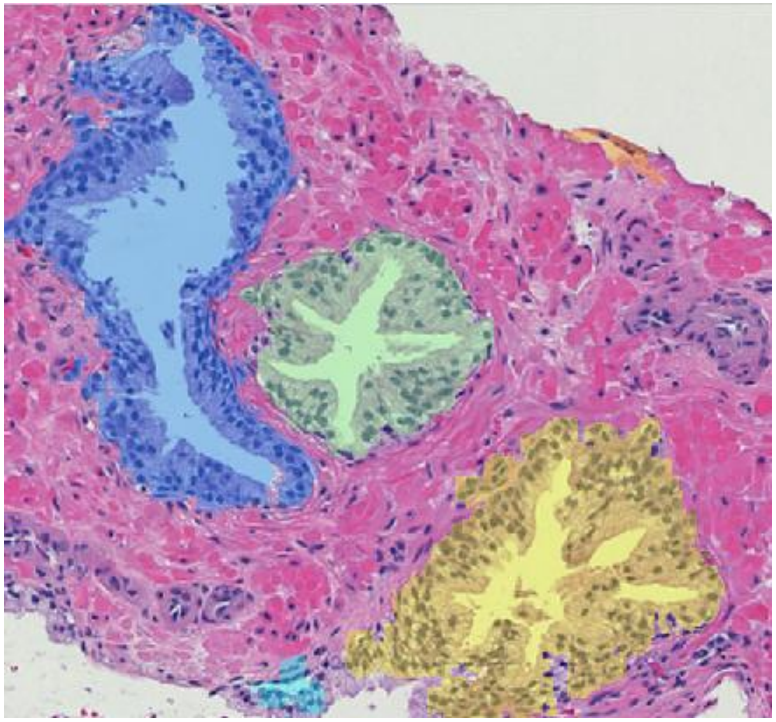
NC components (from step 2) are separated

The lumen (left) can be unified with the boundary (right) to create a complete gland

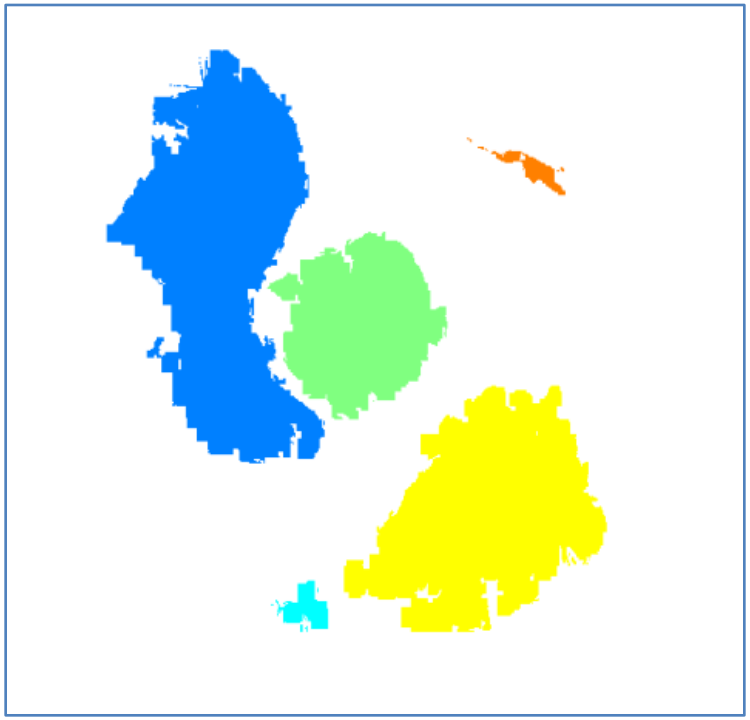
Lumen expanding algorithm



Complete Segmentation Result



Segmented glands are highlighted



Segmented gland regions only

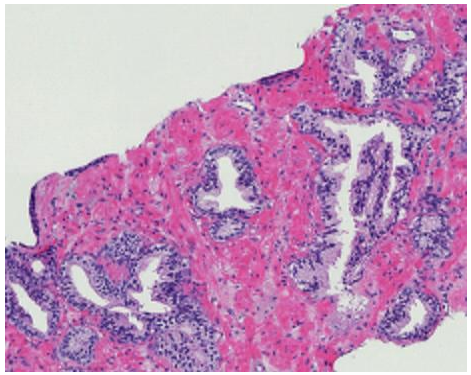
Gland feature extraction

15 features of each gland are extracted

Feature type	Feature description
Ten lumen features	Average, variance, max of lumen area; average, variance, max of lumen perimeter; average and variance of lumen roundedness; number of lumen and ratio of lumen area to total segment area.
Two nuclei features	Nuclei density and ratio of nuclei area to total segment area
Two gland size features	Average and variance of the distances from the lumen center to the nuclei boundary
Blue mucin feature	Ratio of blue mucin area to total segment area

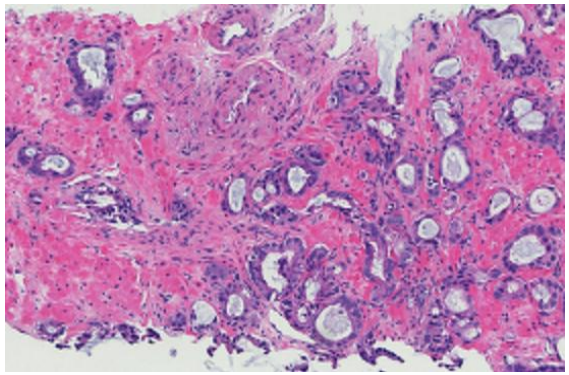
Why these features?

- Large, less uniform lumen area
- Thick gland boundary (rich of nuclei)



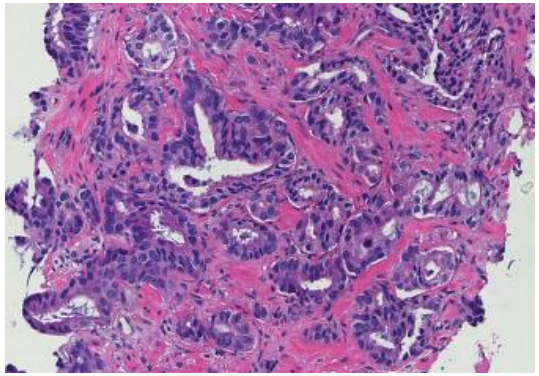
Benign

- Small, uniform lumen area
- Thin gland boundary (fewer nuclei)



Grade 3

- Small lumen area
- Nuclei are more uniformly distributed



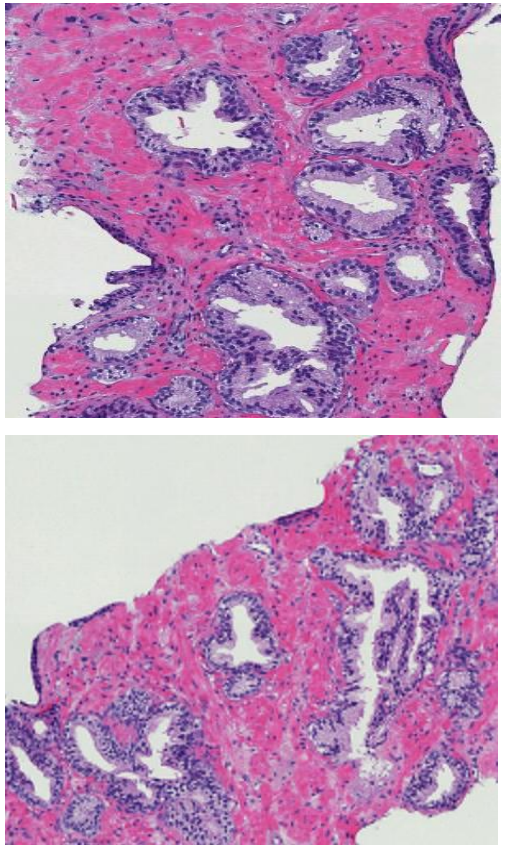
Grade 4

Features are averaged for all the glands within a pattern to create 15-dim feature vector for the pattern

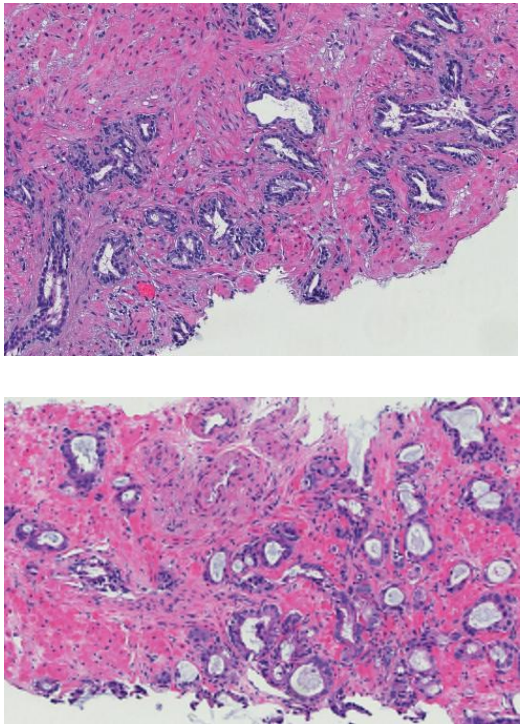
Dataset

Original data: 52 10x whole-slide images with an average size of ~90,000 x 45,000

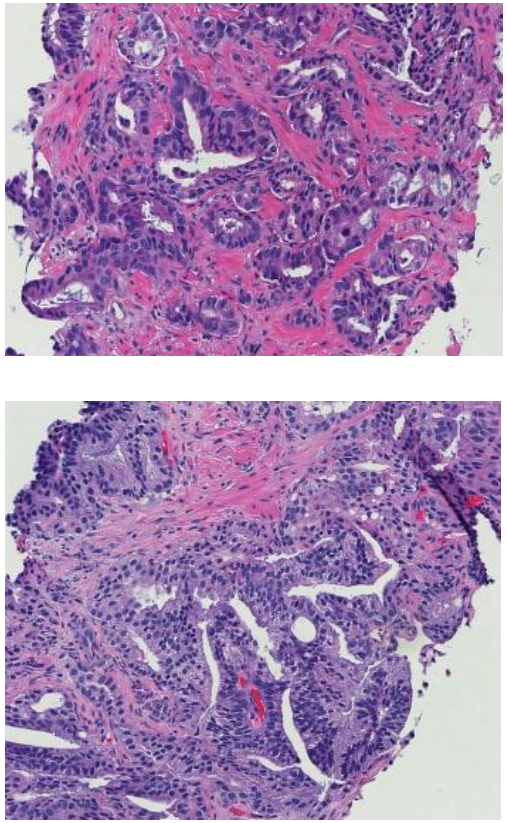
Testing data: 30 patterns of benign, 28 of grade 3, 20 of grade 4 cases. Average size: 501 x 526



Benign



Grade 3



Grade 4

Classification results

- Experimental Setup:
  - Classifiers: SVM, multilayer perceptron, classifier fusion
  - Validation: 10 runs of 10-fold cross validation
- Results:

Three-class classification

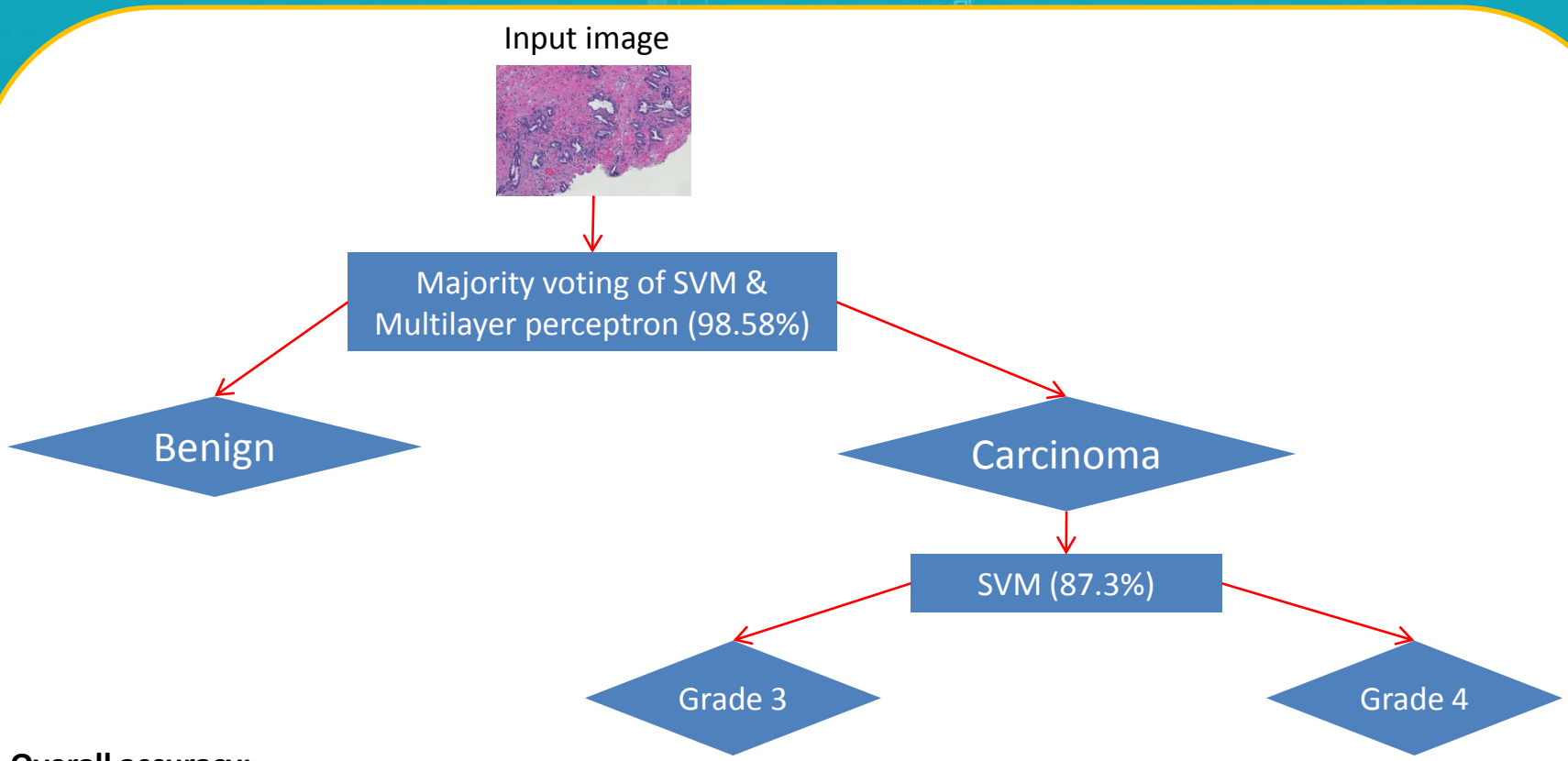
Test case	Best Classifier	Accuracy (variance)
Full feature set (15)	SVM (linear kernel, C = 10)	87.5% (1.11%)
Best subset of features (9)	Multilayer perceptron (one hidden layer, 16 hidden nodes)	88.4% (6.2%)
Classifier fusion with best subset	Max of probability of SVM & Multilayer perceptron (same parameters as above)	88.8% (1.8%)

Classifier fusion reduces the variance of cross-validation

Two-class classification

Test case	Best Classifier	Accuracy (variance)
Benign vs. grade 3	SVM (linear kernel, C = 10)	97.75% (1.35%)
Benign vs. grade 4	Multilayer perceptron (one hidden layer, 16 hidden nodes)	94% (3.55%)
Grade 3 vs. grade 4	SVM (linear kernel, C = 10)	87.3% (0.43%)
Benign vs. Carcinoma (grades 3 & 4)	Majority voting of SVM & Multilayer perceptron	98.58% (0.16%)

Hierarchical classification scheme



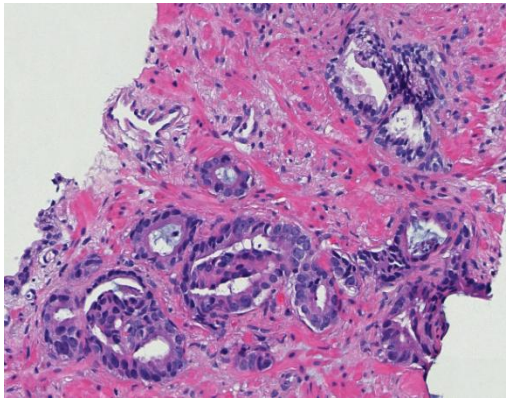
Overall accuracy:

$$p(correct) = p(\omega_B)p(I \in \omega_B|\omega_B) + p(\omega_{G3})p(I \in \omega_{G3}|\omega_{G3}) + p(\omega_{G4})p(I \in \omega_{G4}|\omega_{G4})$$
$$= \frac{30}{78} * 98.5\% + \frac{28}{78} * 98.5\% * 87.3\% + \frac{20}{78} * 98.5\% * 87.3\% = 91\%$$

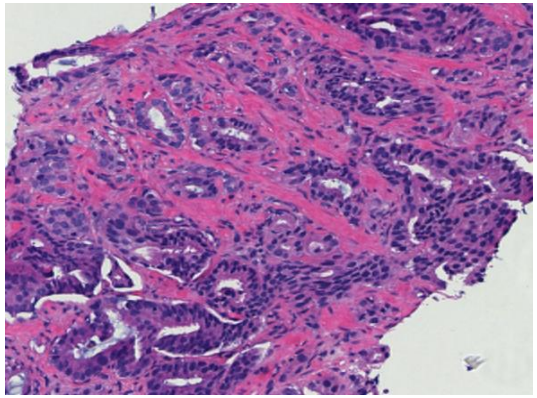
Where

$\omega_B, \omega_{G3}, \omega_{G4}$	:benign, grade 3, grade 4 class
$p(\omega_B)$	:percent of benign samples in the dataset
$p(I \in \omega_B\|\omega_B)$	:probability that the image is classified as benign while the true label is also benign (accuracy of benign case)

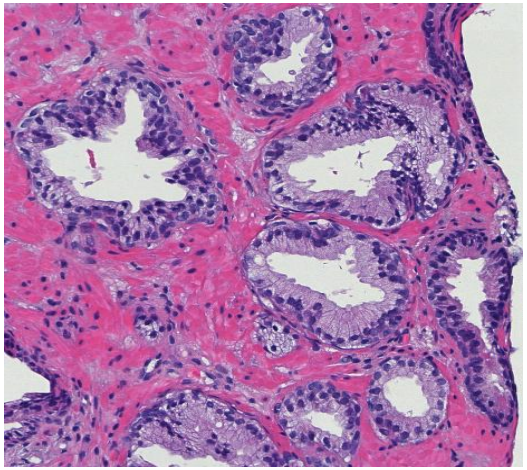
Classification examples



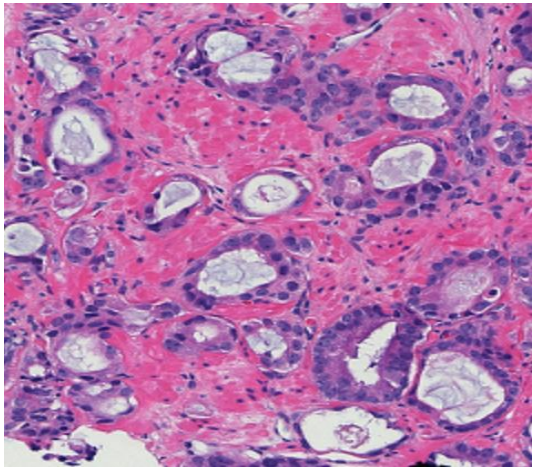
(a)



(b)



(c)



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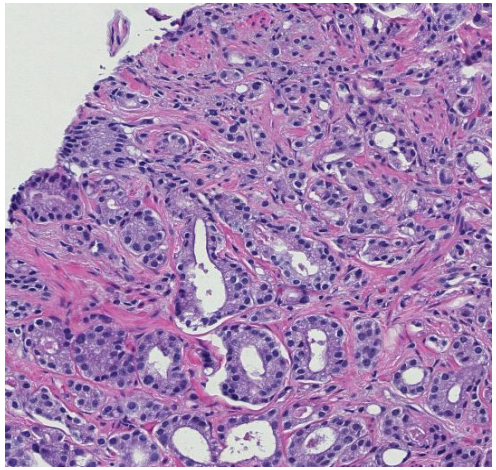

(e)

Misclassifications: (a) Grade 3 is classified as grade 4; (b) grade 4 is classified as grade 3.
Correct classifications: (c) Benign; (d) grade 3 carcinoma; (e) grade 4 carcinoma

Conclusions

- A method to automate the prostate cancer grading is presented
- Compared to non-segmentation based method, proposed method has two advantages:
  - Extracted glands not only provide grading information but also facilitate other tasks such as gland retrieval
  - Segmented glands can serve as landmarks to register different images (by different staining methods) of a tissue to improve grading results
- Future work:
  - Improve the discrimination between grade 3 and grade 4 carcinoma
  - Search for carcinoma patterns in a whole slide of tissue image (90,000 x 45,000 pixels)
  - Improve the computational efficiency (current MATLAB algorithm takes about 2.2 minutes to grade a 500 x 500 image)


Thank you