Detection of Cervical Cancer from Evoked Tissue Fluorescence Images Using 2- and 3-way Methods

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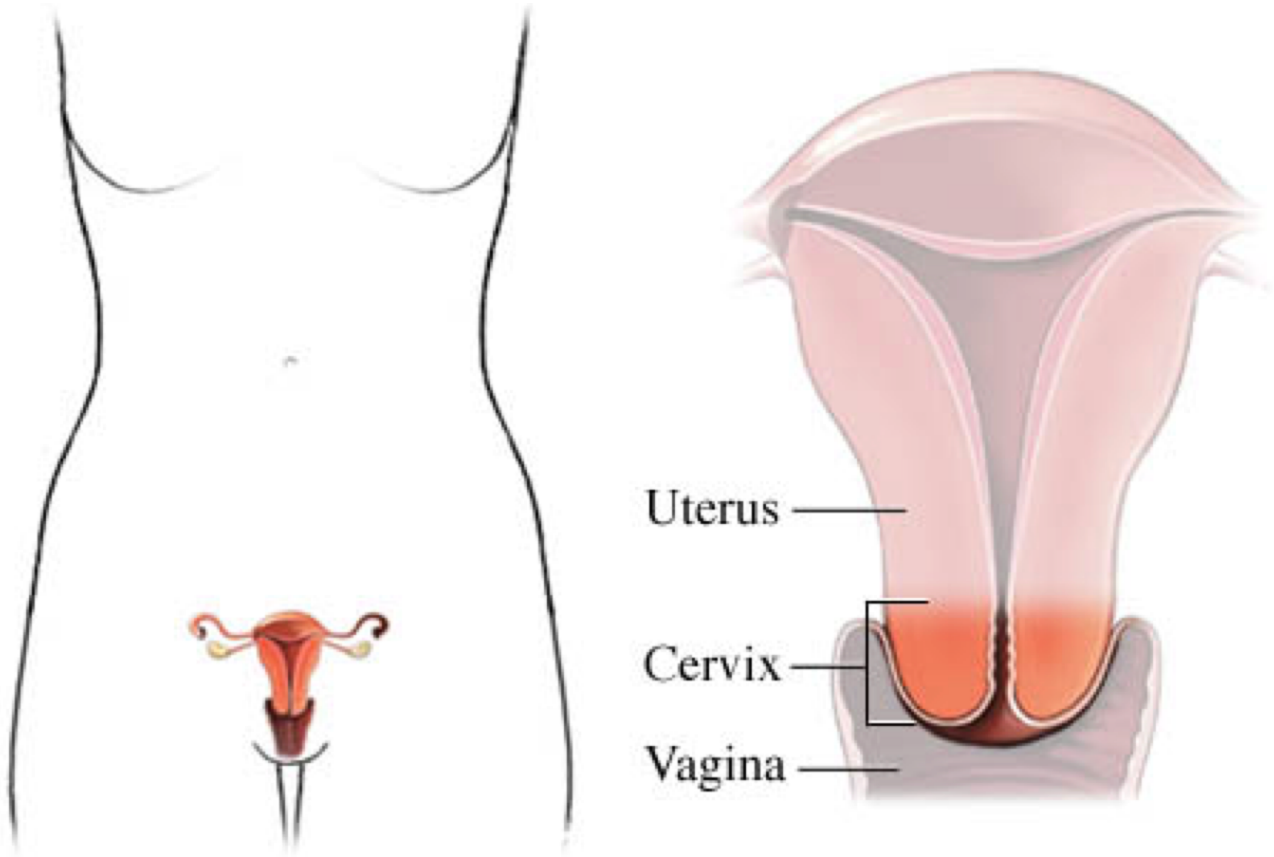
Cervical Cancer

- Pap smears credited with reducing cervical cancer mortality by detecting pre-cancerous cells, but…
- Sensitivity of Pap smears reported as 29-56%
- Abnormal Pap smear-> colposcopic examaination, but….
- Colposcopy success depends on interpretation and therefore experience of examiner
- Colposcopic impressions correlate with biopsies as little as 35% of the time

Goal of this work

- Develop a method to classify cervical tissue
  - More sensitive and specific than current methods
  - Doesn't require high level of experience to use
  - Can be easily administered

The Cervix



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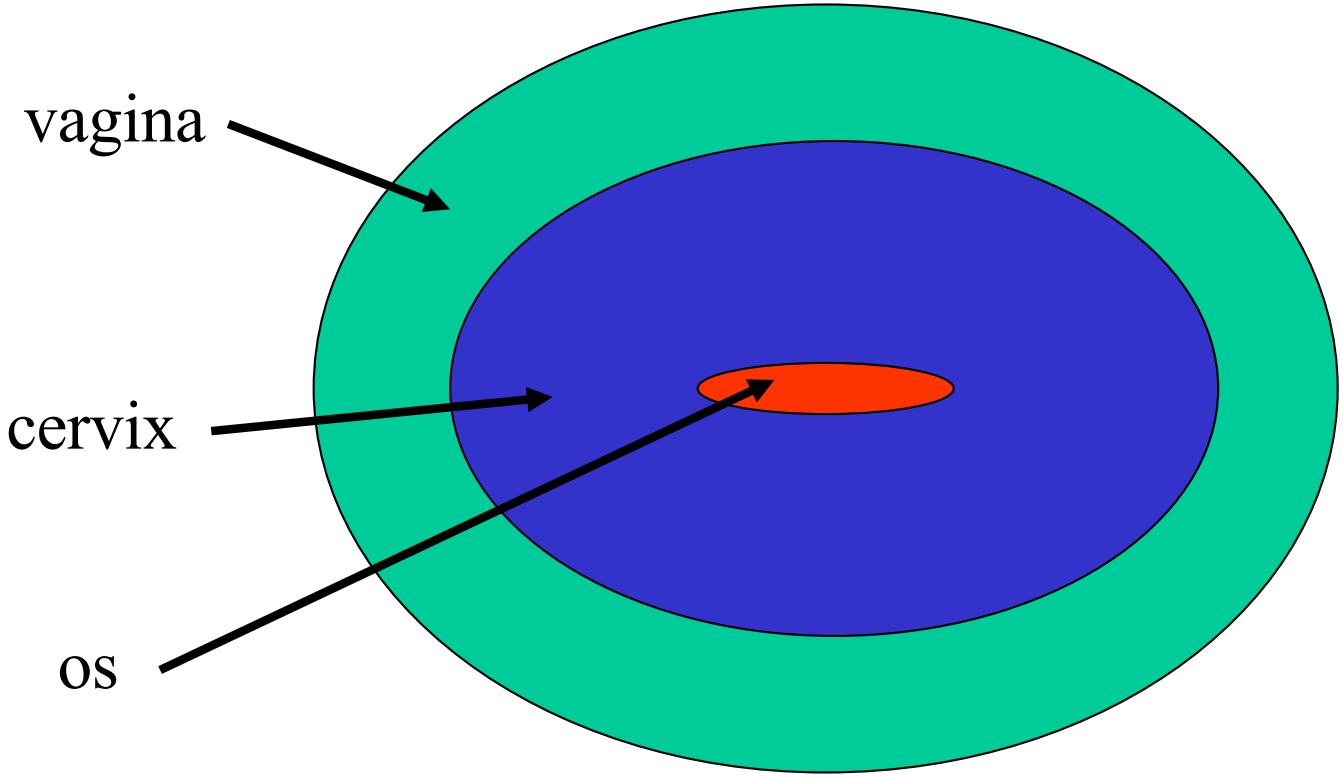
Images of the Cervix



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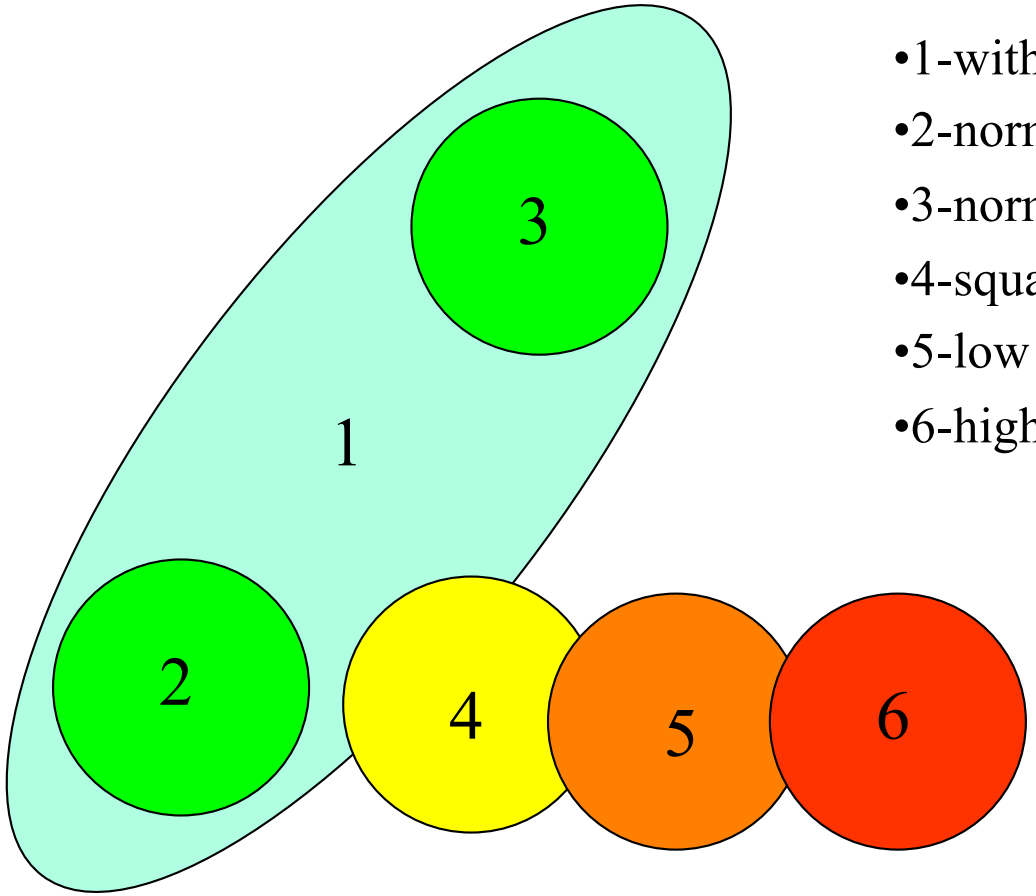
The Data

- Colposcopic Images
  - Interpreted by experts
  - Areas of tissue type identified
- Biopsies
  - Tissue type confirmed using staining and microscopy
  - Areas identified on images
  - “Gold Standard”
- Evoked Tissue Fluorescence Images
  - Excitation Emission Fluorescence Images

Classes of Tissue

- 1-within normal limits
- 2-normal squamous
- 3-normal columnar
- 4-squamous metaplasia
- 5-low SIL (Squamous Intraepithelial Lesion)
- 6-high SIL

Similarity of Tissue Types



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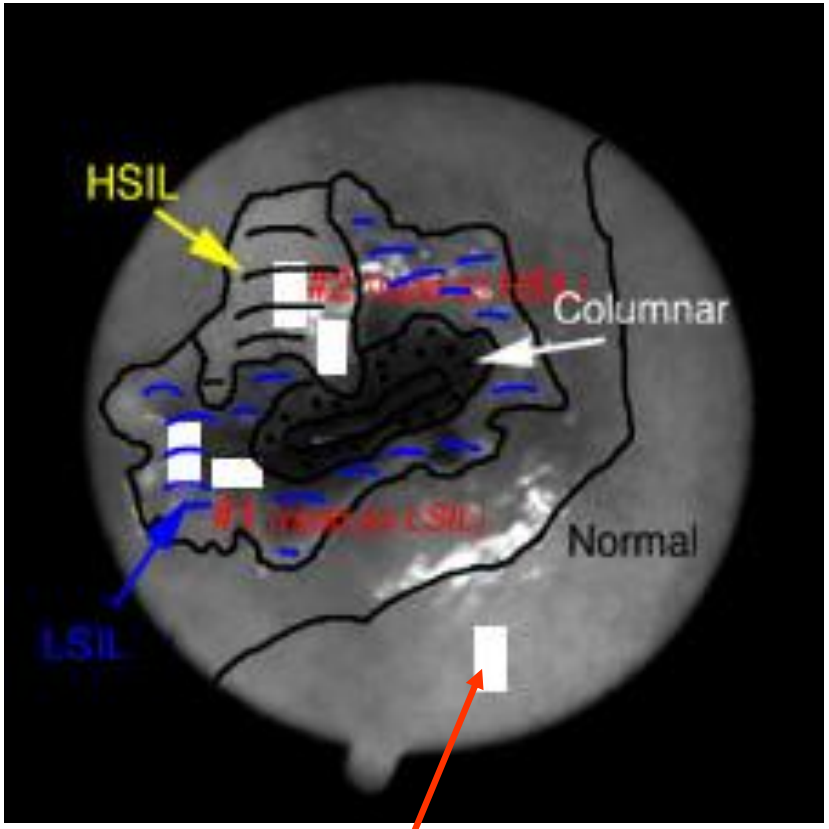
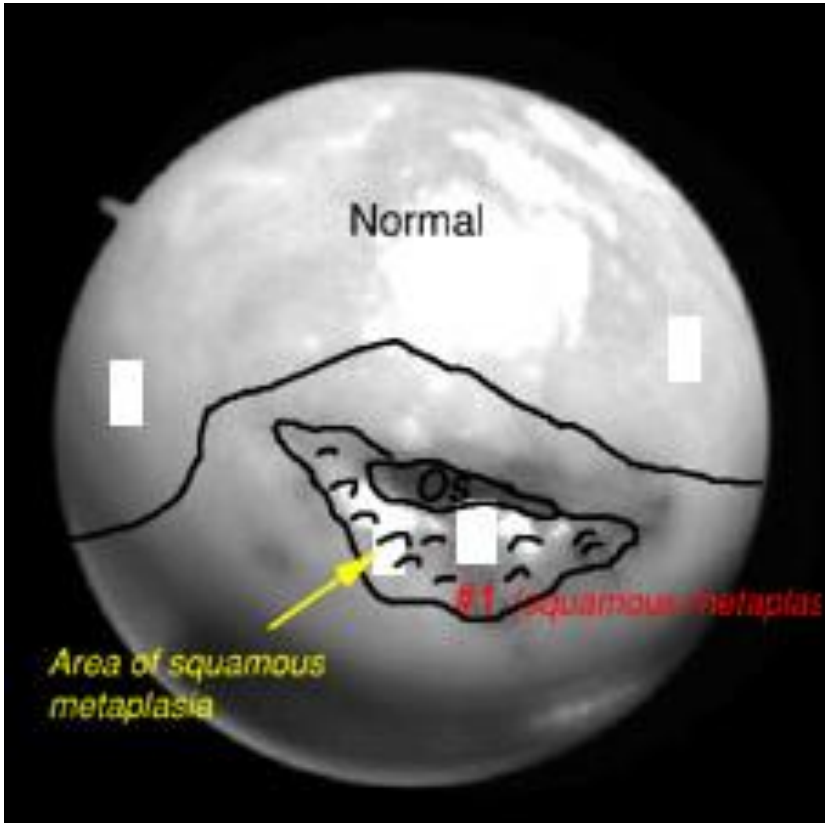
Colposcopic Images and Biopsies





Biopsy locations

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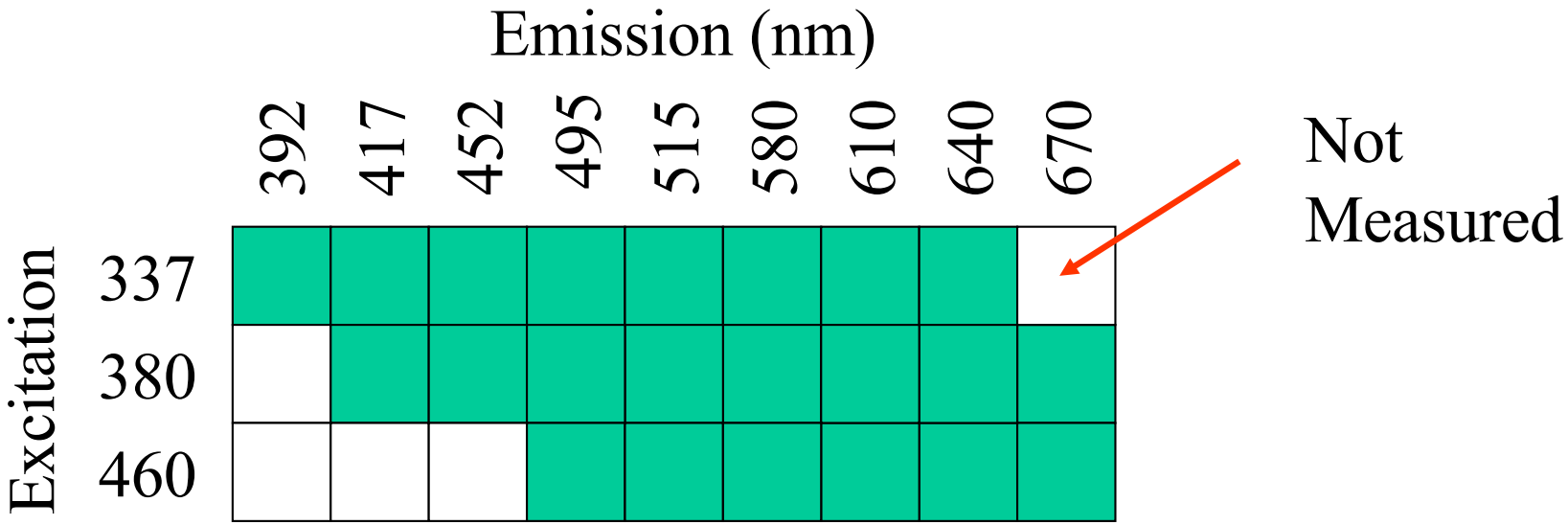
The ETF Images

- Combinations of
  - 3 excitation wavelengths
  - 9 emission wavelengths
  - 22 combinations measured



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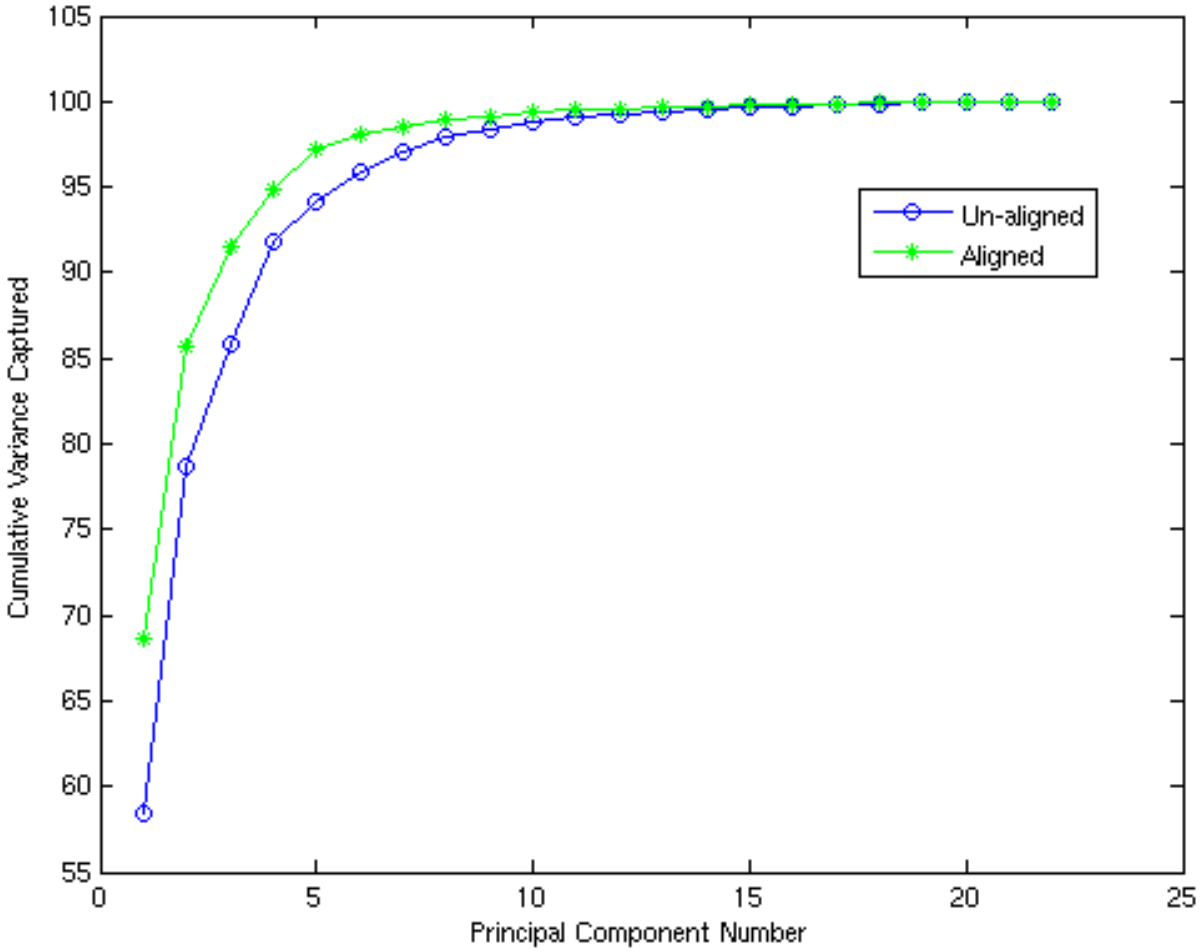
Preprocessing Issues

- Image alignment
  - Measurements take about 60s
  - Patient movement an issue
- Patient to patient variability

Image Alignment

- Images at different wavelengths look different
- …but sub-images should be correlated
  - Should be most correlated when properly aligned
  - Want big PCs to get bigger and small ones to get smaller
  - Used Varimax criteria on singular values: $$\frac{\sum_{i=1}^{n} s_i^4}{\left(\sum_{i=1}^{n} s_i\right)^4}$$

Variance Captured Before and After Alignment



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Model Development

- Align images
- Center to normal squamous tissue on each patient / OR center to mean of all tissues
- Pool all patients - center & scale
- OPTIONALLY: GLS deweighting based on a single class

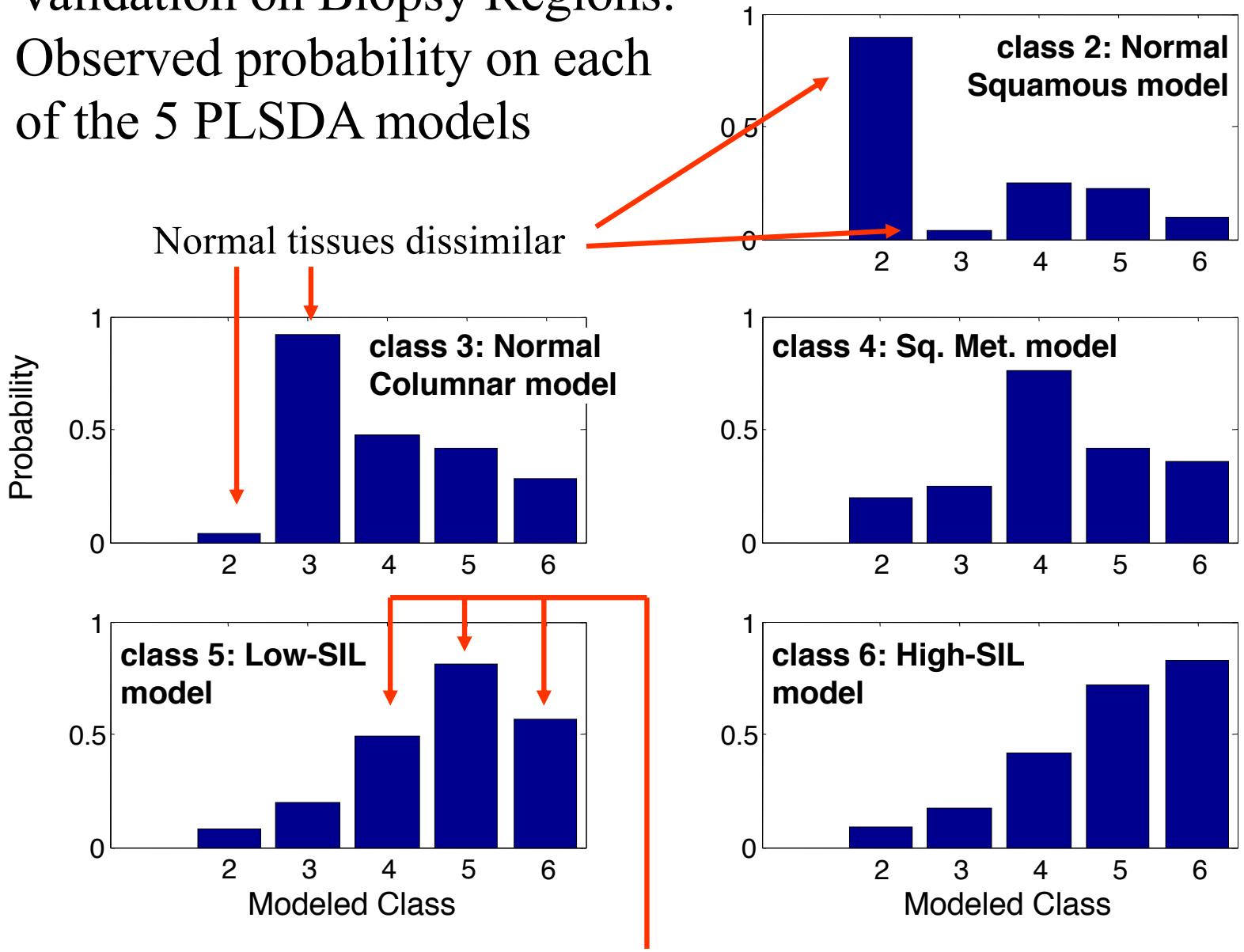
Calibration

- PLS-DA on EACH CLASS
- take predicted y for each class and
  - threshold
  - convert levels of disease to SIL scale

Application

- Align
- Center each patient image to its own mean (NOTE: high levels of SIL will bias)
- Apply model
- Identify absolute “normal”, repeat (1)-(2) using centering to NORMAL

Validation on Biopsy Regions: Observed probability on each of the 5 PLSDA models



Three disease states very similar!

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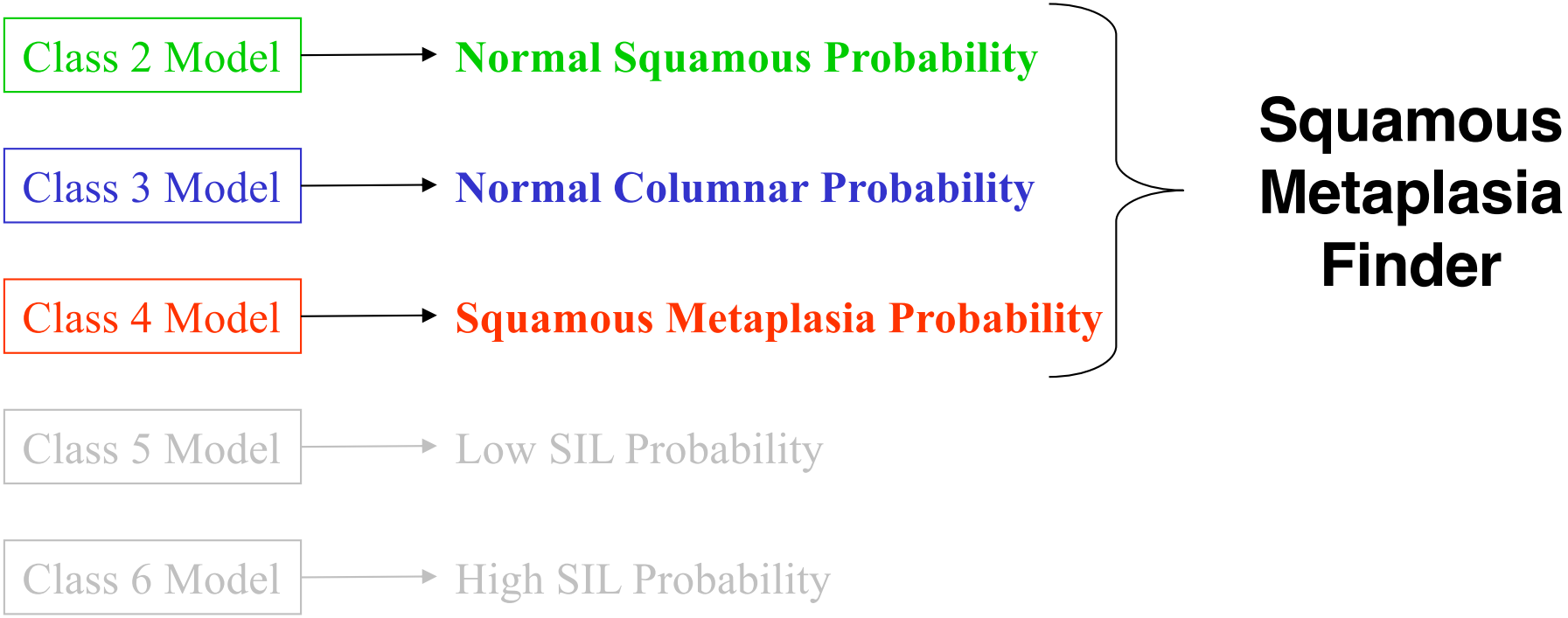
Diagnostic False-Color Images



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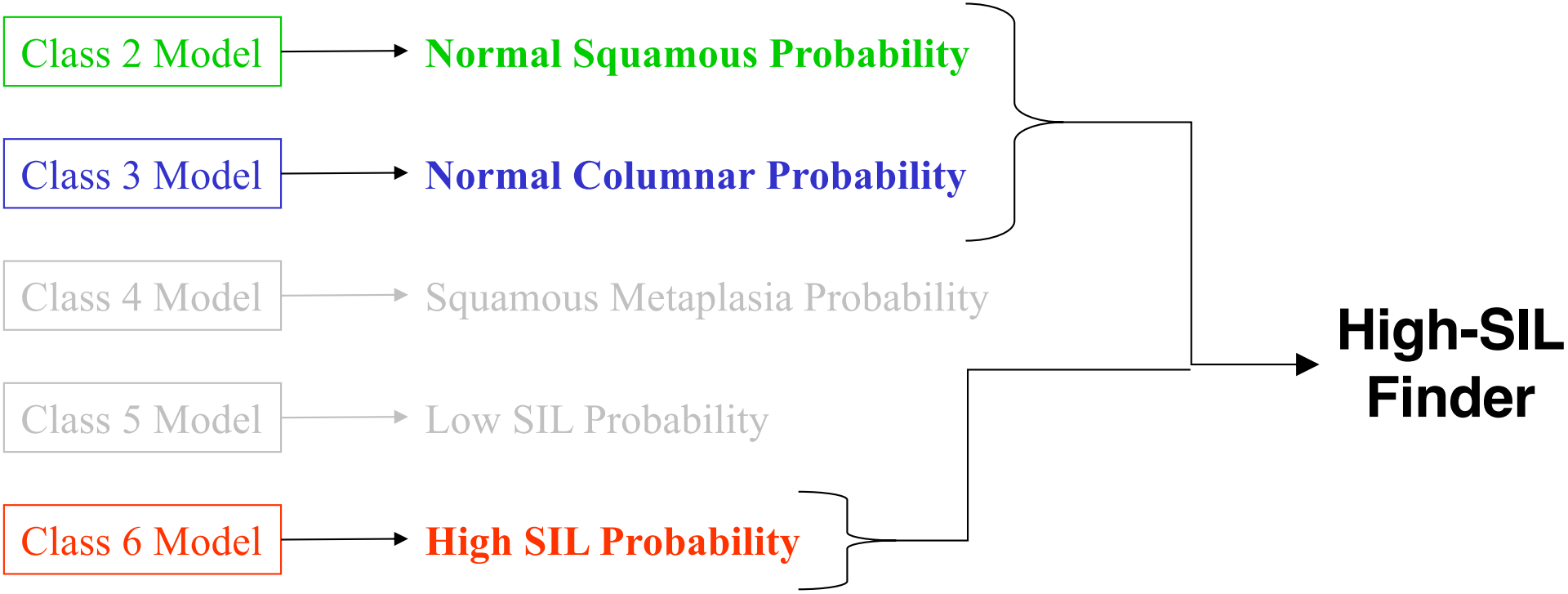
Diagnostic False-Color Images



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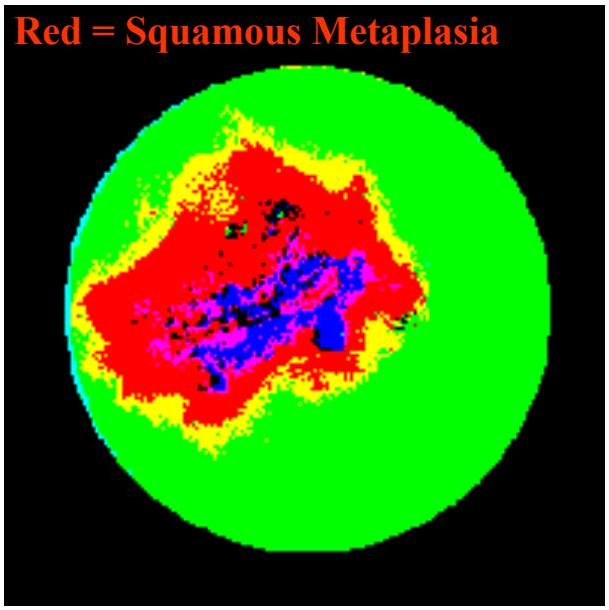
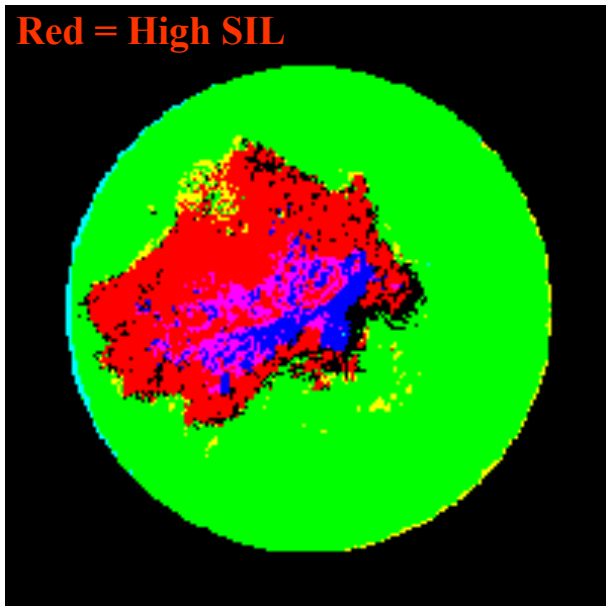
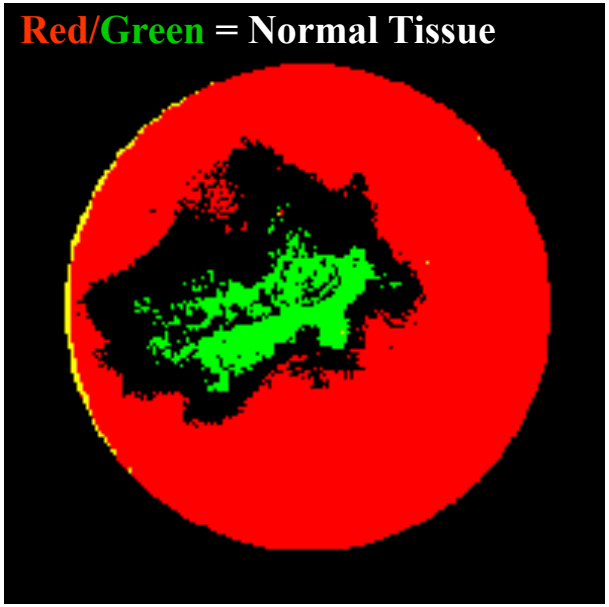
Squamous Met. Finder - Classes: 4,2,3

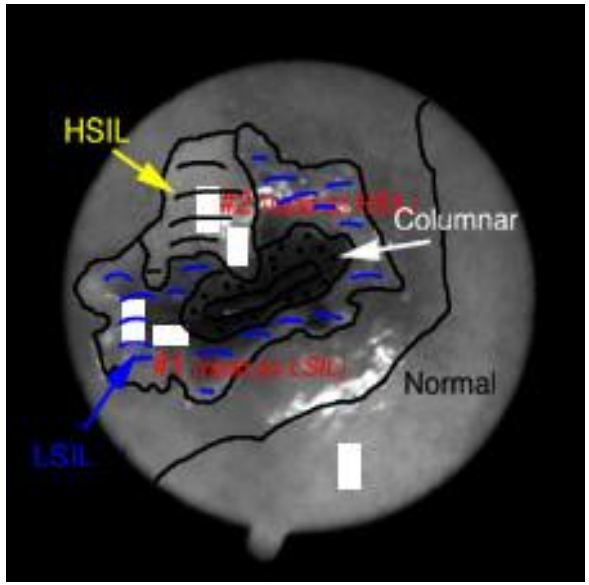


Hi-SIL Finder - Classes: 6,2,3



Normal Tissue Finder - Classes: 2,3

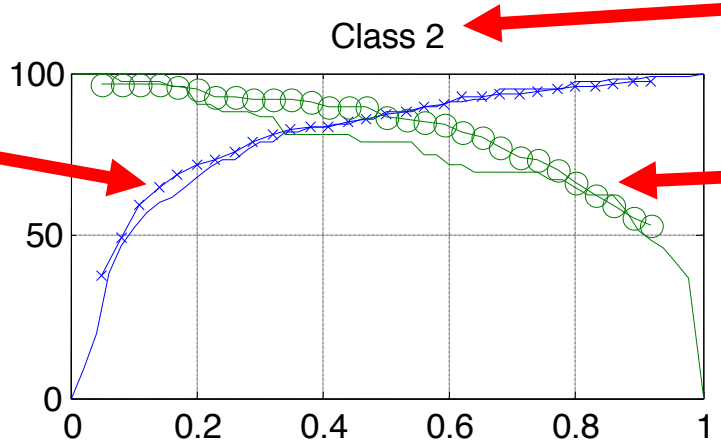




aD047

red, green, blue

Key to ROC Plots



modeled class
(i.e. 2 vs 3-6)

Specificity

Sensitivity

PLS-DA threshold

sensitivity / specificity (at crossing)
n: = results for class "n" model
cv = cross-validation results
val = validation results

	cv	val
2:	87/87	79/87
3:	86/86	78/84
4:	55/55	58/52
5:	64/64	68/55
6:	69/69	82/68

(sens/spec)

Sensitivity (crossval)
Sensitivity (validation)
Specificity (crossval)
Specificity (validation)

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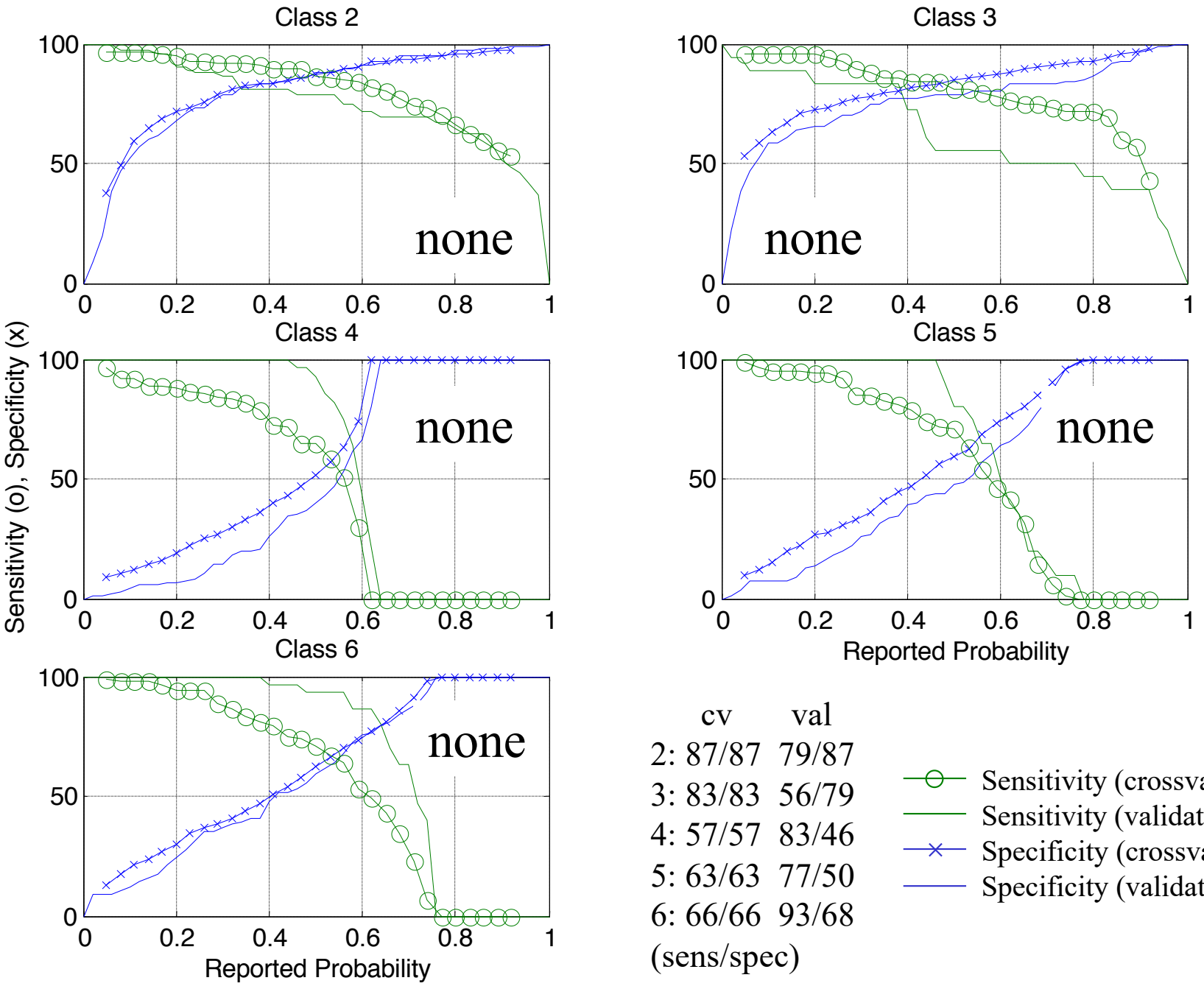

	cv	val
2:	87/87	79/87
3:	83/83	56/79
4:	57/57	83/46
5:	63/63	77/50
6:	66/66	93/68

(sens/spec)

Sensitivity (crossval)
Sensitivity (validation)
Specificity (crossval)
Specificity (validation)

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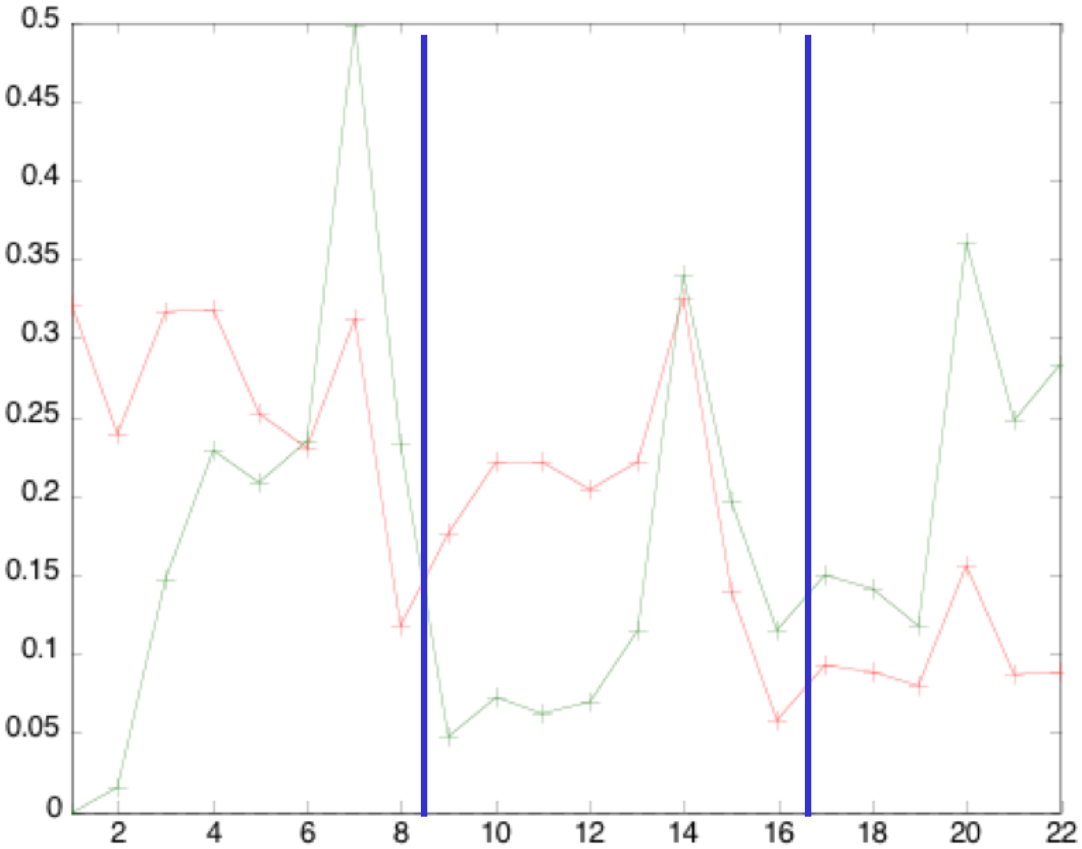
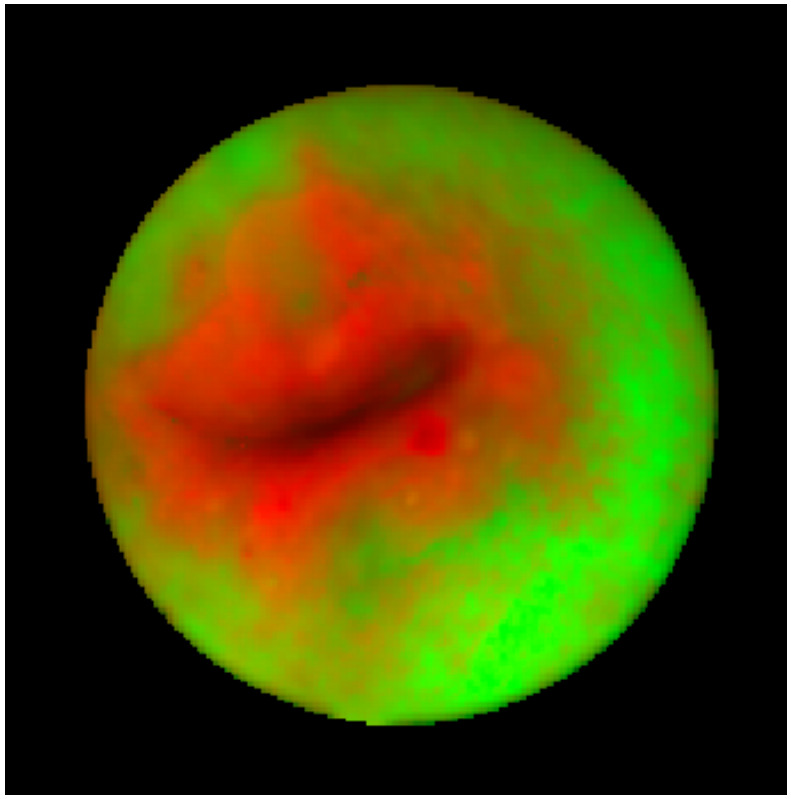
Multivariate Curve Resolution
(On pseudo first-order data)





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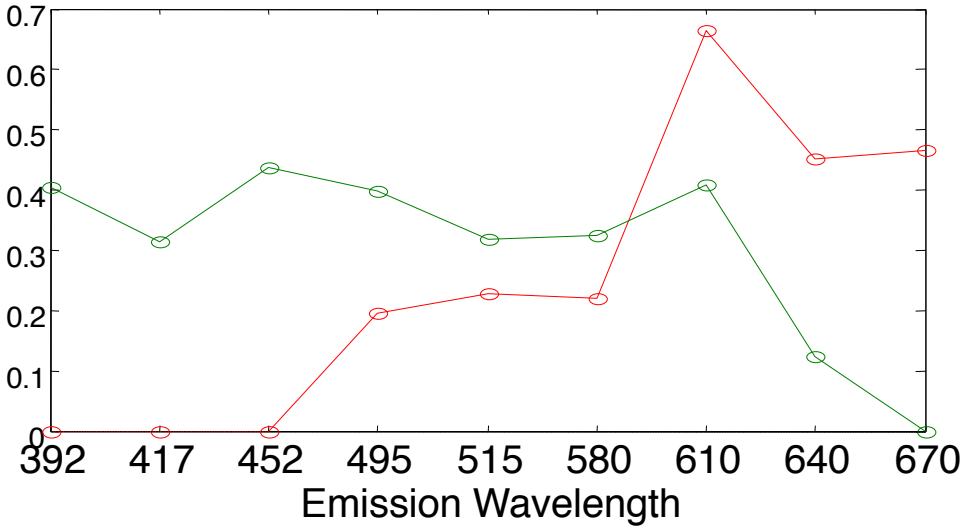
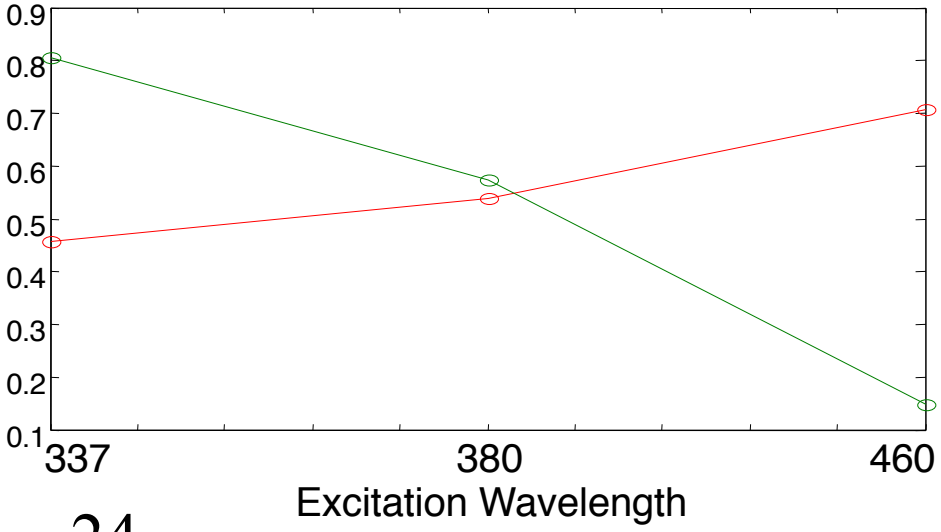
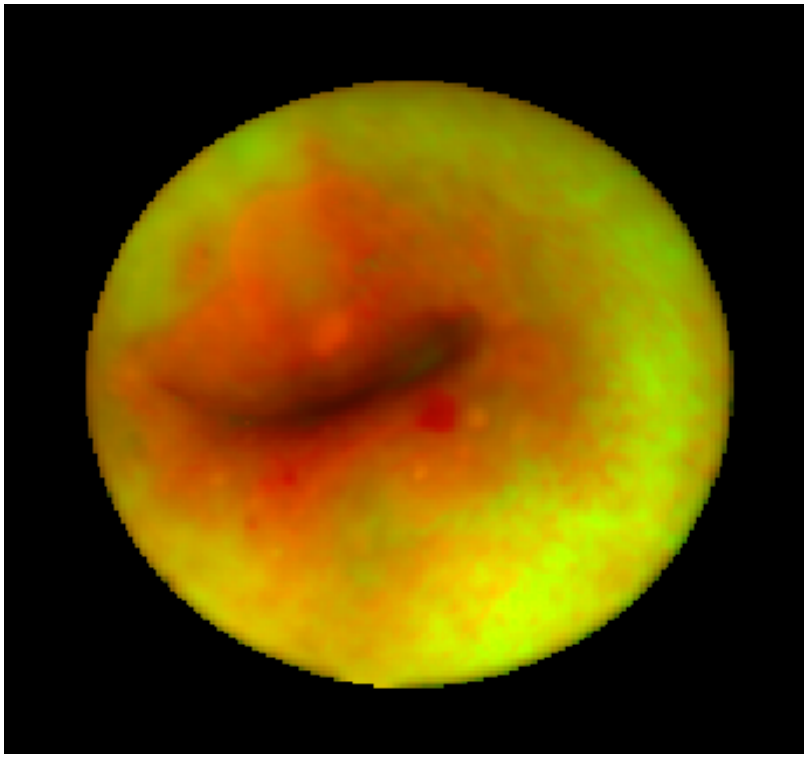
Parallel Factor Analysis
(On second-order data)







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Summary

- ETF based device very close to clinical usefulness
- Mis-classifications tend to be on progression of disease
- Pre-processing critical
- PLS-DA effective
- Issues
  - Only translational motion considered in alignment
  - Other preprocessing and DA methods to consider