

# Doctoral Defense

## Optical Reflectance Spectroscopy for Cancer Diagnosis: Analysis and Modeling

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8/16/2010

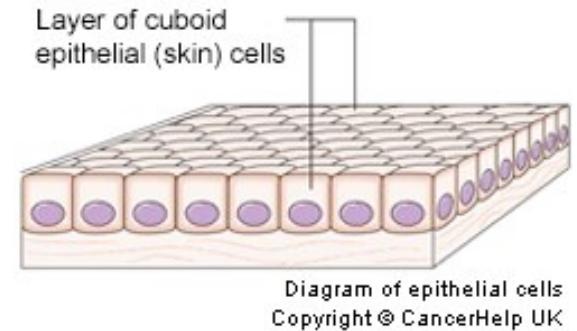
The University of Texas Department of Biomedical Engineering

# Outline

- **Background and motivation**
- **Contributions**
  - I. Oblique polarized reflectance spectroscopy for oral cancer: a pilot clinical trial
  - II. Adaptive spectral window sizes for extraction of diagnostic features from optical spectra
  - III. “Virtual probe design”: Monte Carlo simulation in the design of diagnostic instrumentation
- **Conclusion**

# Cancer facts

- Cancer is a worldwide health problem
  - Incident rate: 461.6 per 100,000 people
  - Death rate: 183.8 per 100,000
  - 40.77% of population will be diagnosed with cancer sometime during their lifetime
- 85% of cancers are of epithelial cells (cells that cover and line the body)
- Early detection is critical for cure
  - Overall survival rate: 66% (1999-2006)
  - morbidity
- This study motivated by and validated with an oral cancer dataset



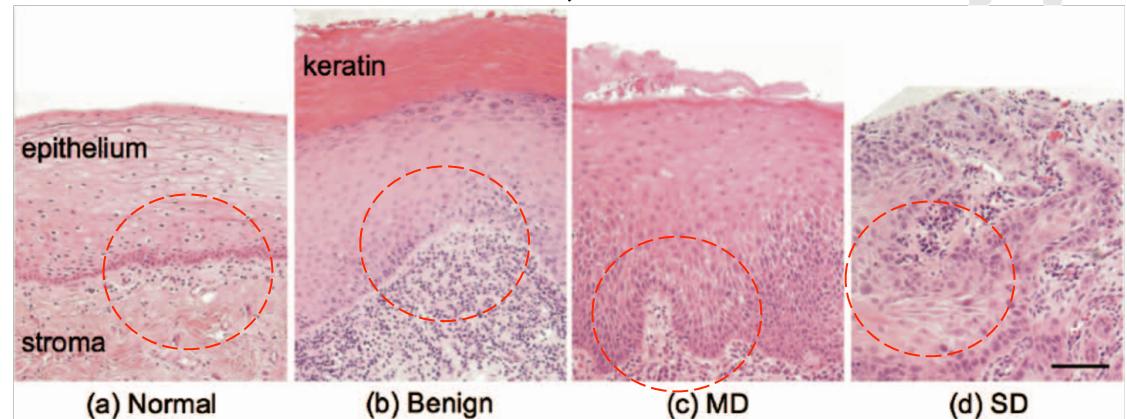
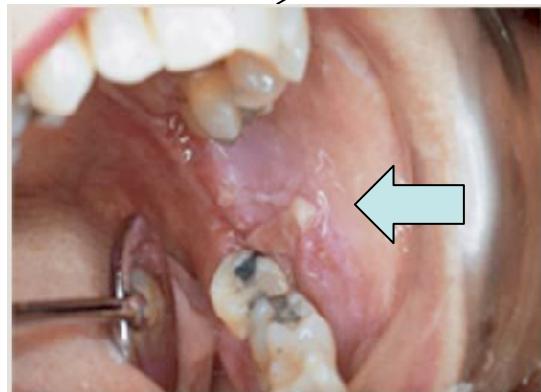
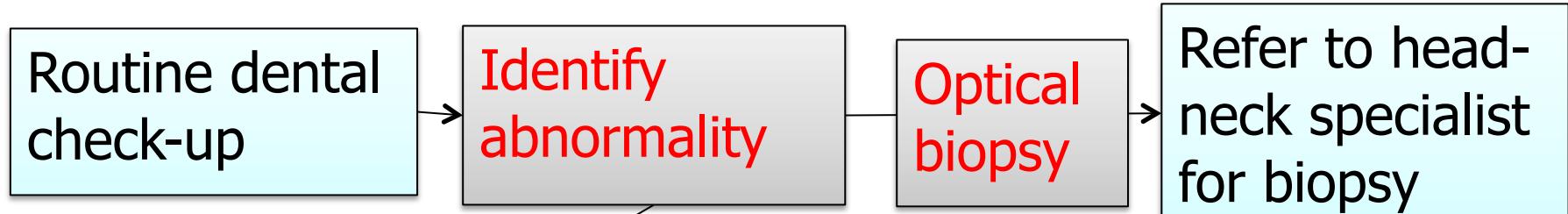
Rick Bender, former baseball player

\*\* <http://seer.cancer.gov/>

\*\* Cancer Research UK <http://www.cancerhelp.org.uk/>

\*\* Oral Cancer Foundation <http://www.oralcancerfoundation.org>

# Diagnosis of oral cancer

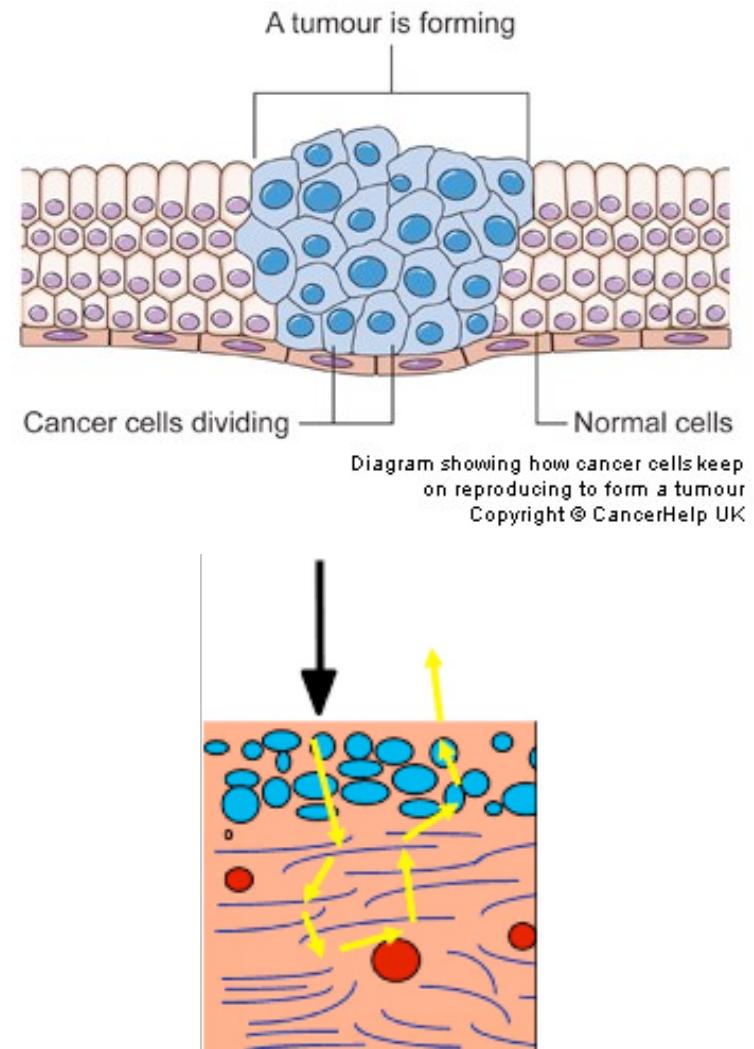


\* Sciubba, J. Oral cancer and its detection *The Journal of the American Dental Association, Am Dental Assoc, 2001*

\*\* Oral Cancer Foundation <http://www.oralcancerfoundation.org>

# How optical methods capture cancer information

- Cancer causes morphological and biochemical changes in cells
- Morphological and biochemical changes perturb the interaction of light with tissue
- These interactions are monitored optically



# My Contributions: Analysis and Modeling

## Analysis

Tissue  
Experiments

Clinical Decision  
Support System  
(I), (II)

## Modeling

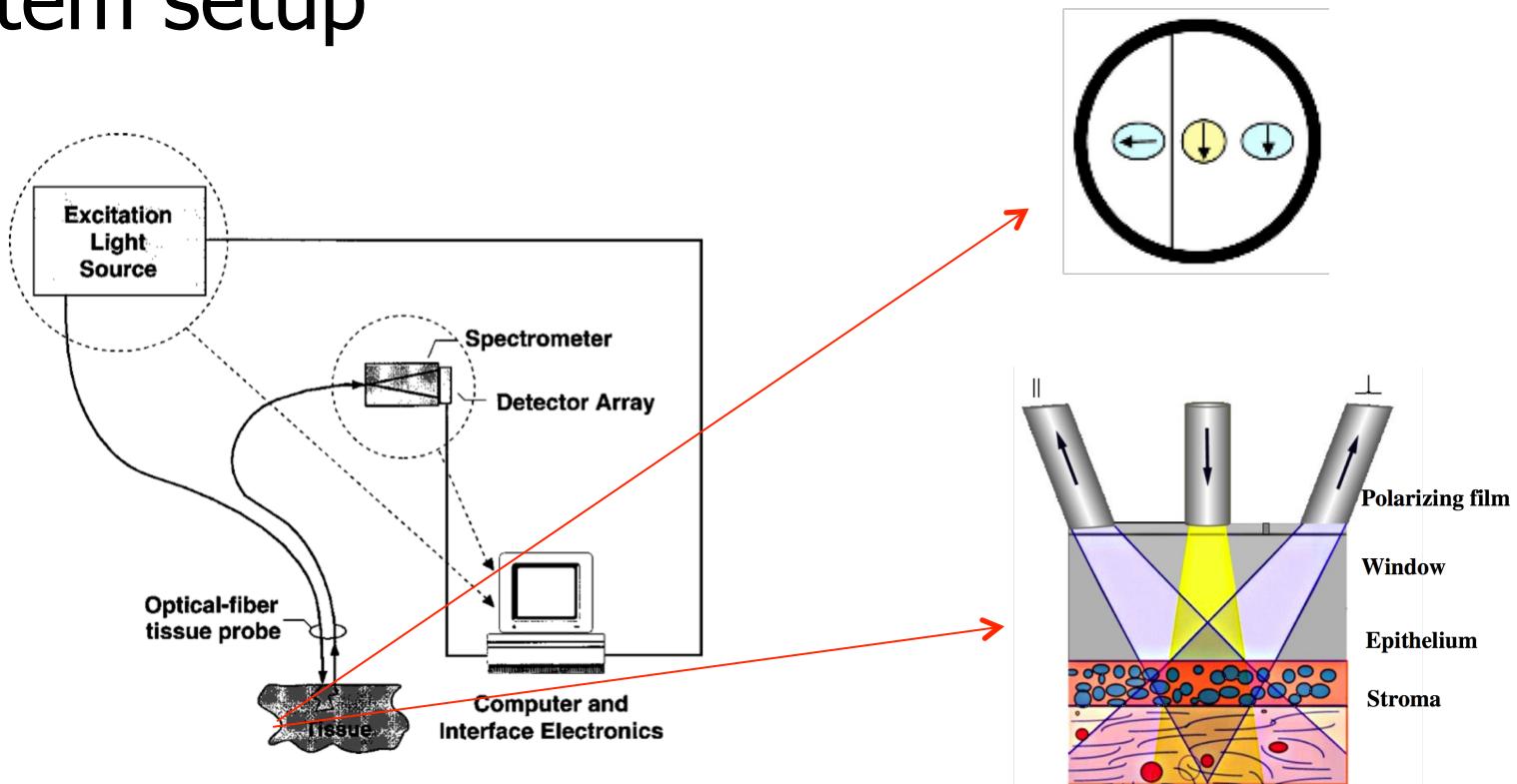
Virtual  
Experiments  
(Simulations)  
(III)

# Data analysis for pilot clinical trial

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# PRS data from pilot clinical trial

## ● System setup



Nieman, L. T., Kan, C. W., Gillenwater, A., Markey, M. K., Sokolov, K. Probing local tissue changes in the oral cavity for early detection of cancer using oblique polarized reflectance spectroscopy: a pilot clinical trial, *Journal of Biomedical Optics, SPIE*, 2008, 13, 024011

Nieman, L.; Myakov, A.; Aaron, J. & Sokolov, K., Optical Sectioning Using a Fiber Probe with an Angled Illumination-Collection Geometry: Evaluation in Engineered Tissue Phantoms, *Applied Optics, OSA*, 2004

# Data from pilot clinical trial

- Data collected at The University of Texas M. D. Anderson Cancer Center (UT MDACC)
- We measured a total of 57 sites (27 patients)
  - 22 were Normal
  - 13 were Benign
  - 12 were mild dysplasia (MD)
  - 10 were high grade dysplasia or carcinoma (SD)
- Five spectral types for each site:
  - Parallel
  - Perpendicular
  - Diffuse (Par + Per)
  - Depolarization ratio (Par-Per) / (Par+Per)
  - Parallel / Perpendicular

Nieman, L. T, Kan, C. W, Gillenwater, A., Markey, M. K. , Sokolov, K. Probing local tissue changes in the oral cavity for early detection of cancer using oblique polarized reflectance spectroscopy: a pilot clinical trial, *Journal of Biomedical Optics, SPIE*, 2008, 13, 024011

# Data analysis

- 11 Features:
  - Average nuclear size based on Mie theory model from depolarization ratio
  - 5 average intensities
  - 5 selected intensities (x nm)
- Selection of most discriminatory wavelength
  - Different wavelengths = different diagnostic power
- Exhaustive search for most discriminatory feature combinations
  - 11 features =  $2^{11}$  combinations
- Classifier: Linear Discriminant Analysis (LDA)
- Evaluation: Receiver Operating Characteristic (ROC) analysis

# Conclusion: pilot clinical trial data

- Ability to distinguish across diagnostic categories
  - AUC=0.89 for Normal vs. SD
  - AUC=0.91 for Benign vs. SD
  - AUC=0.87 for MD vs. SD
- Results correspond well with cancer progression stages
- Ability to distinguish Benign vs. MD/SD

	Normal from		MD from	
	MD	MD and SD	SD	SD
Sensitivity (%)	75	73	90	80
Specificity (%)	73	64	86	83
	Benign from		Benign from	
	MD	MD & SD	SD	Normal
Sensitivity (%)	92	86	100	85
Specificity (%)	69	61	85	73

Nieman, L. T, **Kan, C. W**, Gillenwater, A., Markey, M. K. , Sokolov, K. Probing local tissue changes in the oral cavity for early detection of cancer using oblique polarized reflectance spectroscopy: a pilot clinical trial, *Journal of Biomedical Optics, SPIE*, 2008, 13, 024011

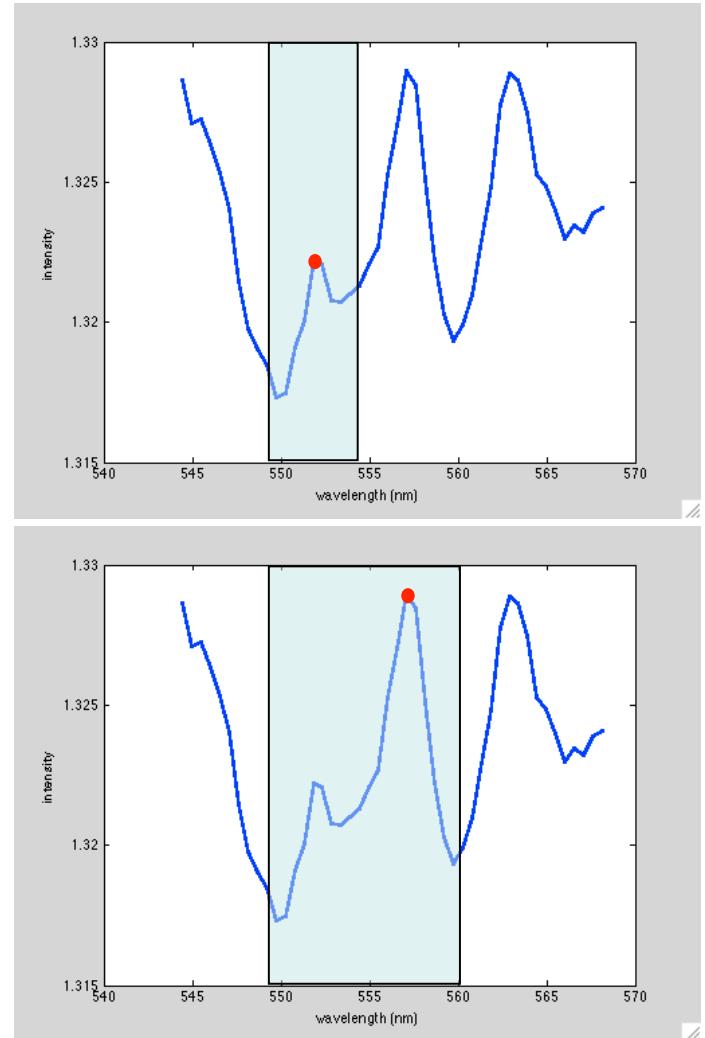
# Novel algorithm for feature extraction

- Background and motivation
- Topics
  - I. Oblique polarized reflectance spectroscopy for oral cancer: a pilot clinical trial
  - II. Adaptive spectral window sizes for extraction of diagnostic features from optical spectra
  - III. “Virtual probe design”: Monte Carlo simulation in the design of diagnostic instrumentation
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# Motivation: Windowing technique for spectral features

- Some wavelengths are more important than others
- Previous studies used windowing techniques to extract features from smaller regions of the spectrum
- Choice of spectral region for feature extraction would make difference in the performance of the extracted features

C. W. Kan, A. Y. Lee, L. T. Nieman, K. Sokolov, M. K. Markey,  
“Adaptive spectral windowing for data compression from optical spectra”, Journal of Biomedical Optics (in press)



# Feature redundancy

- Fixed-size windowing has lots of feature redundancy
- Repeated features dominate in feature space, confusing the classifier
- How do we define the windows more efficiently?

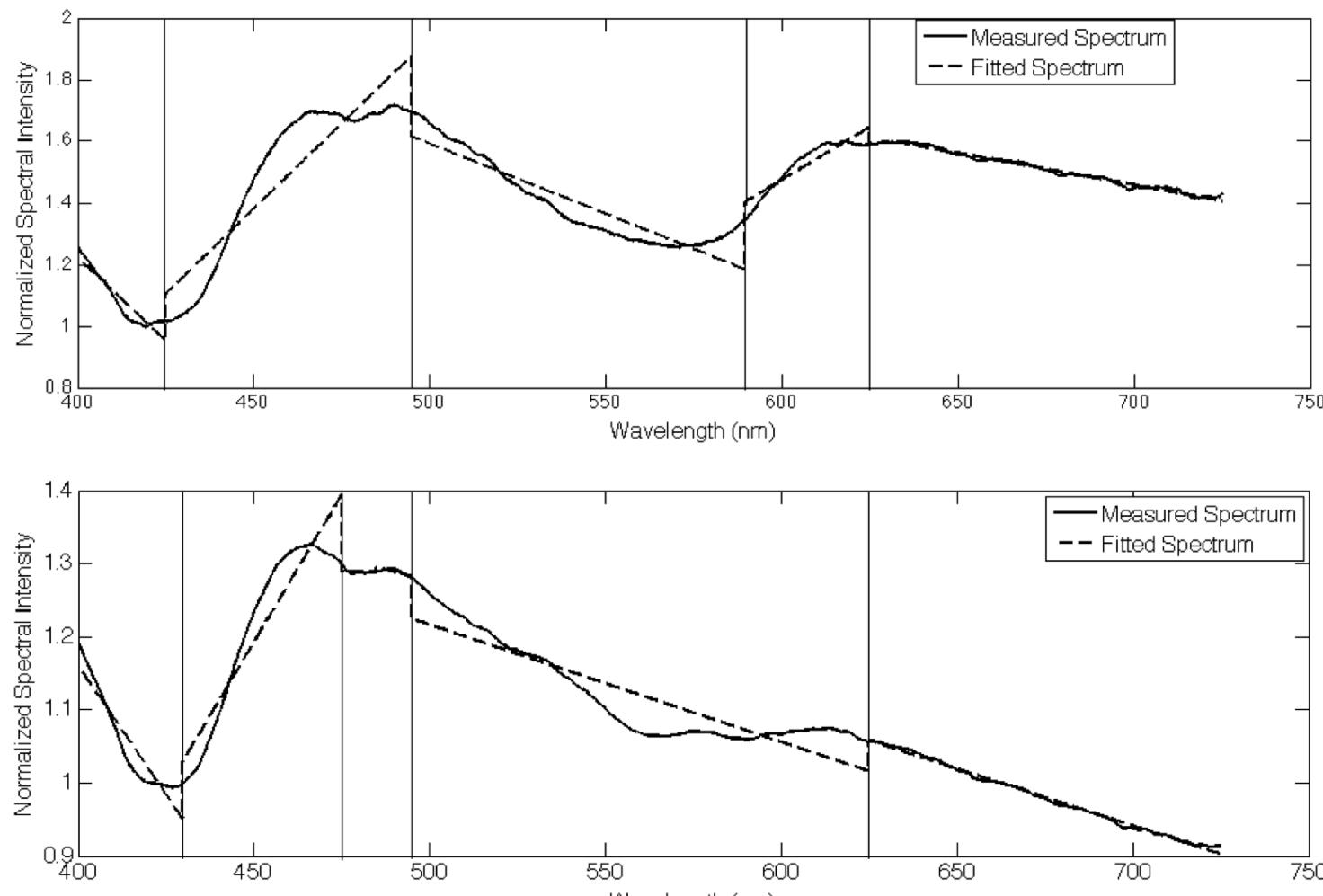
# Adaptive Windowing Algorithm

1. Set the starting point of the 1<sup>st</sup> window to be the shortest wavelength in the spectrum
2. Initial window size = 5 nm
3. Iteratively increase window size by 5 nm, perform simple linear regression, and obtain R<sup>2</sup>
4. Repeat step 3 until R<sup>2</sup><0.8
5. End the current window and the new window starts
6. Repeat steps 2-5 across the entire spectrum

**C. W. Kan**, A. Y. Lee, L. T. Nieman, K. Sokolov, M. K. Markey, “Adaptive spectral windowing for data compression from optical spectra”, Journal of Biomedical Optics (in press)

**C.W. Kan**, A. Y. Lee, N. Pham, L.T. Nieman, K. Sokolov, M.K. Markey, Adaptive spectral window sizes for feature extraction from optical spectra Proceedings of SPIE, SPIE, 2008

# Sample diffuse reflectance spectra



A normal patient (top) and a SD patient (bottom).

# Spectral Feature extraction

- Eight features extracted in each spectral window:

Feature names	Proposed by
1 Slope from linear regression	Bigio et al.
2 Intercept from linear regression	Mueller et al.
3 Minimum intensity	Kan et al.
4 Average intensity	Bigio et al.
5 Median intensity	Kan et al.
6 Maximum intensity	Kan et al.
7 Standard deviation of intensities	Kamath et al.
8 Signal energy $\sum I_i^2$ of intensities	Kamath et al.

# Performance Evaluation

- Data: from pilot clinical trial (only diffuse signals)
- Three methods are compared:
  1. No windowing
  2. Fixed window size of 20 nm (from literature)
  3. Adaptive spectral window sizes
- Two diagnostic tasks:
  - Normal vs. MD+SD
  - Benign vs. MD+SD
- Classifier: Linear Discriminant Analysis
- Cross-validation: Leave-one-out
- Receiver Operating Characteristic Analysis

# De-noising

- Thresholding on classifier outputs
  - Exclude cases when classifier fails to perform
    - classifier output all fall in range [0.4, 0.6]
    - mean negative output is greater than mean positive outputs
- Outlier removal
  - Outlier detection algorithm
  - Mahalanobis distance follows chi-square distribution

T. Raykov and G.A. Marcoulides. An introduction to applied multivariate analysis. Routledge/Psychpress, 2008.

# Results: AUCs for windowing/non-windowing

	Normal vs. MD+SD			Benign vs. MD+SD		
	Adaptive windowing	Fixed-size (20nm)	No windowing	Adaptive windowing	Fixed-size (20nm)	No windowing
Maximum AUC	0.73	0.73	0.61	0.79	0.83	0.68

- Statistical significance between AUC of windowing and no windowing
- No significant difference in AUC between adaptive and fixed-size windowing

# Results: Feature extraction statistics

	Normal vs. MD+SD			Benign vs. MD+SD		
	Adaptive windowing	Fixed-size (20nm)	No windowing	Adaptive windowing	Fixed-size (20nm)	No windowing
Number of unique features extracted	60	17	1	60	14	1
Average number of windows per spectrum	8.5	16	1	7.7	16	1
Total number of windows	374	704	44	270	560	35

- Adaptive windows use less windows than fixed-sized windows
- We decreased redundancies between fixed size windows that have similar properties

# Conclusion: adaptive windowing algorithm

- Data redundancy reduction
  - Principal Component Analysis comparison
  - Adaptive windows captures linearity
- Feature uniqueness concerns
  - Exist when initialization point varies
  - Fixed size windows have better stability, but window sizes still affects features
  - Trade-off

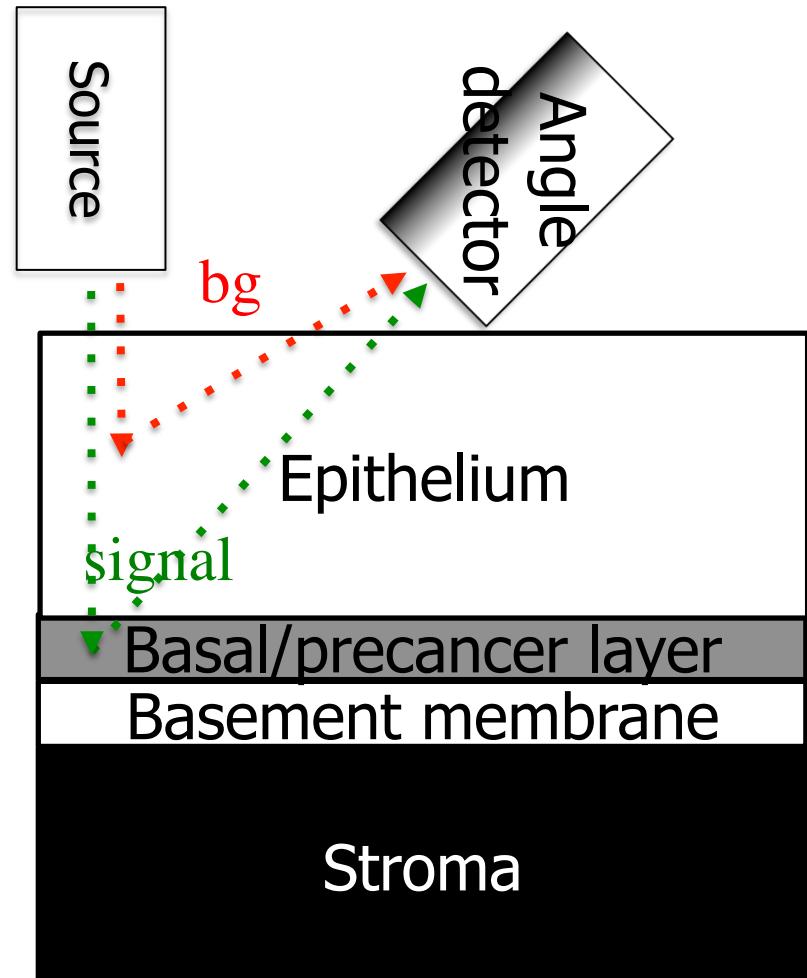
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“Adaptive spectral windowing for data compression from optical spectra”, Journal of Biomedical Optics (in press)

# Outline: Monte Carlo simulation

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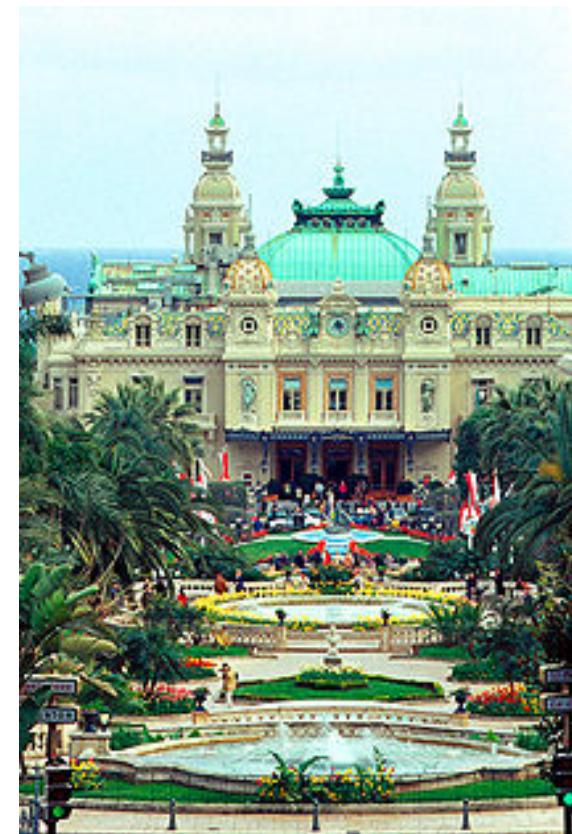
# Fundamental Questions raised from Topic (I)

- How much detected light is from the layer that we “really” care about? In other words, what is the signal-to-background ratio (s/b)?



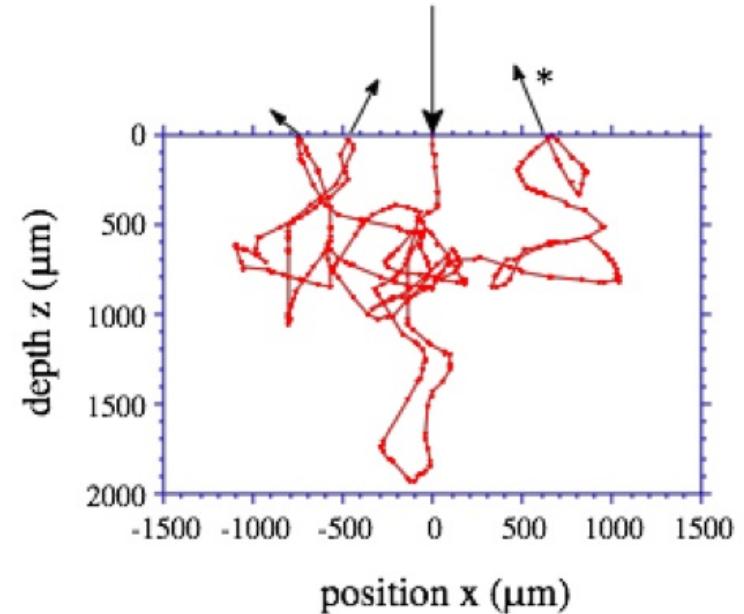
# What is Monte Carlo?

- Computational algorithms that rely on repeated **random sampling** to compute their results
- Invented by Stanislaw Ulam in 1946
- Name came from Monte Carlo Casino in Monaco
- Monte Carlo method is...
  - a statistical description of the whole system
  - flexible in tissue environment setting
- More accurate if more repetitions used



# A photon's life (in simulation)

- Photon travels in straight line until an event happens:
  - Absorption
    - weight decreases
  - Scattering
    - weight remains
    - change travel direction
- Pol-MC:
  - Stokes parameter  $S=(I, Q, U, V)$  defines polarization direction
  - Mueller matrix is the operator to modify polarization direction
  - Mueller matrix is calculated based on Mie theory (SCATMECH library)
  - Scattering angles: Jaillon sampling

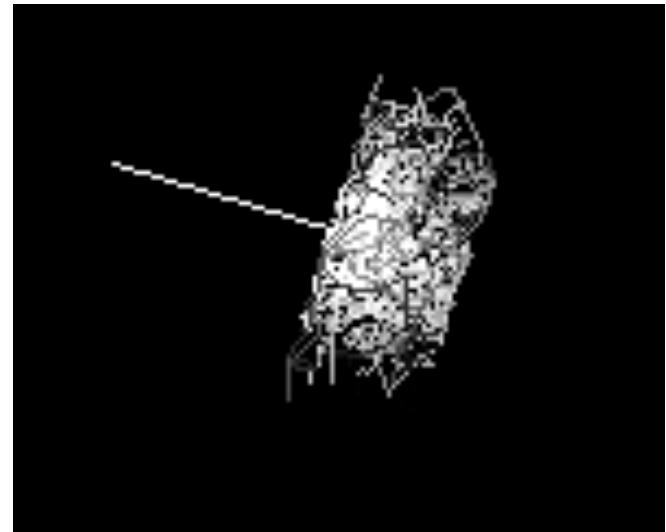


Jaillon, F. & Saint-Jalmes, H. "Description and Time Reduction of a Monte Carlo Code to Simulate Propagation of Polarized Light through Scattering Media  
*Appl. Opt., OSA, 2003, 42, 3290-3296*

Côté, D. & Vitkin, I. Robust concentration determination of optically active molecules in turbid media with validated three-dimensional polarization sensitive Monte Carlo calculations, *Optics Express, OSA, 2005*

# Algorithm

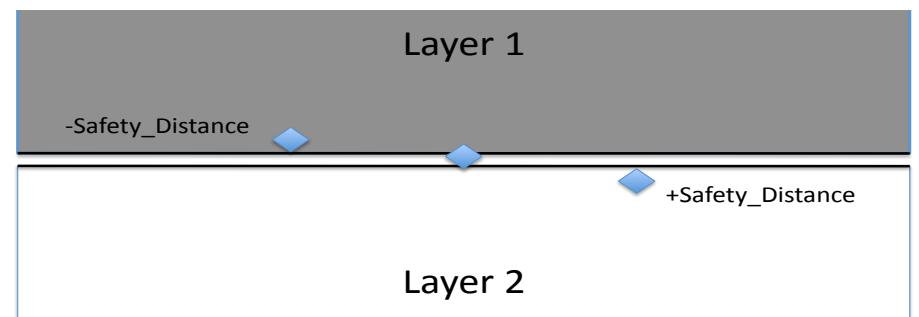
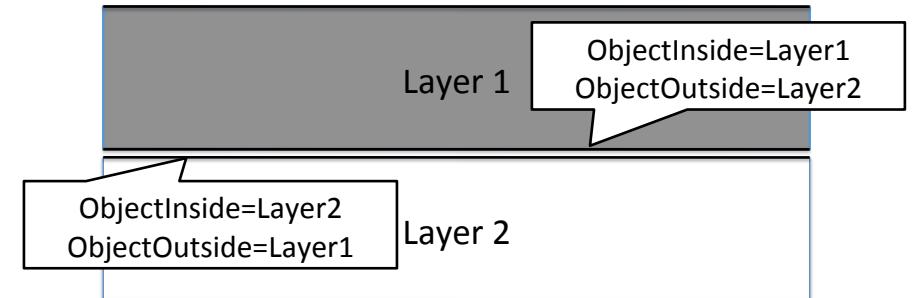
1. create photon packets with weight=1 at initial coordinates with specified Stoke's parameter (I,Q,U,V)
2. determine next event type and distance
3. update photon packet's traveling angle, and its position (scattering)
4. update the weight of the photon packet (absorption)
5. Update polarization Stoke's parameter by multiplying with Mueller matrix
6. repeat steps 2-4 until weight is too low or packet leaves tissue



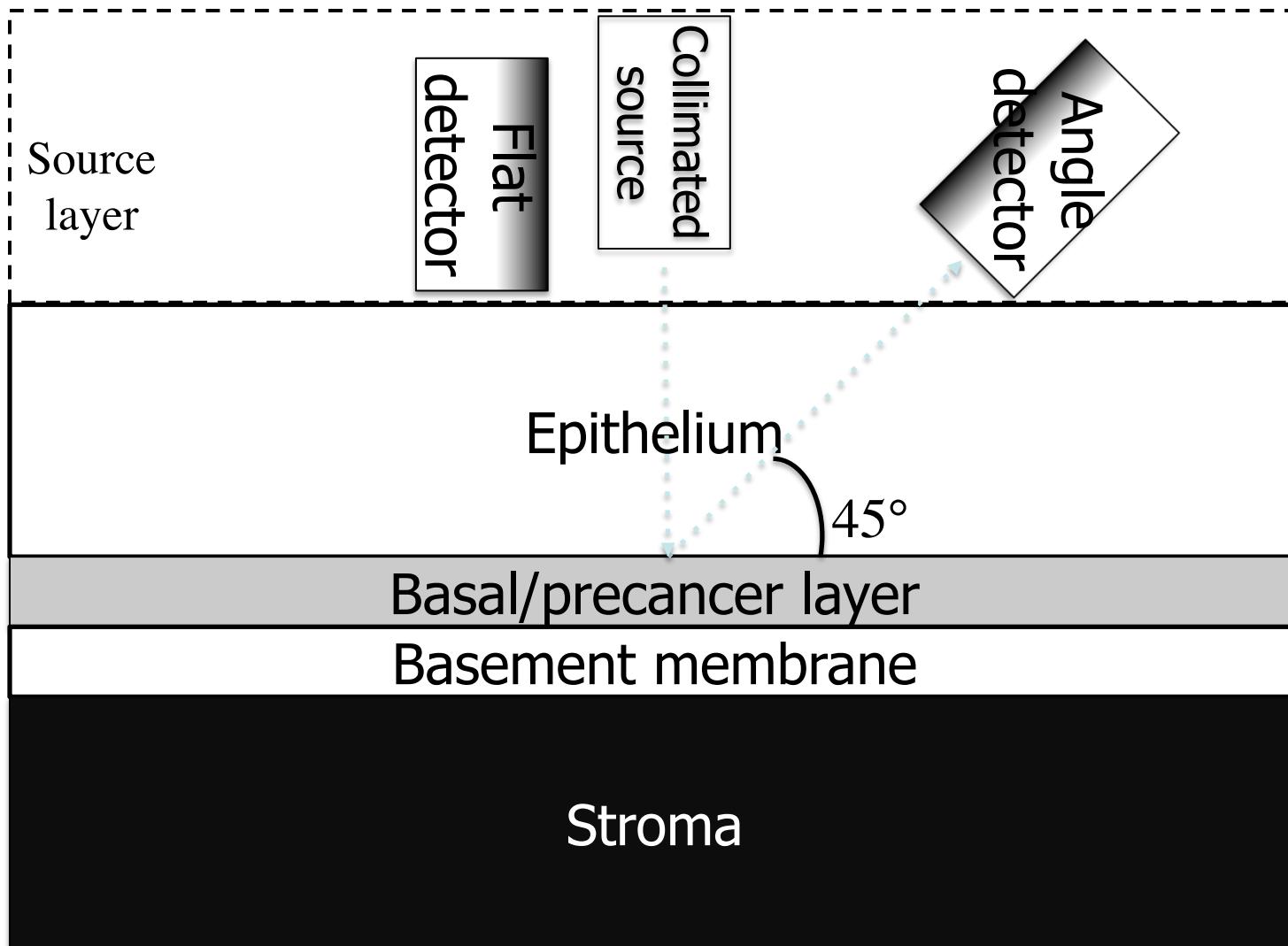
# Contributions to Pol-MC

- Multiple layers implementation
- More advanced geometry checks

- Parallel computing
- Features for “Inside-the-box” simulation



# Simulation geometry setting



# Simulation tissue parameters

	thickness ( $\mu m$ )	scattering	g	index(media)	index(scatterer)	$\mu_a$	$\mu_s$	scatterer radius( $\mu m$ )
Source layer	10000	HG**	0.5	1.335	—	0.1	1	—
Epithelium	varies	Jaillon	—	1.369	1.41	1	100	6
Basal layer	varies	Jaillon	—	1.369	1.41	1	120	varies
Stromal membrane	30	HG**	0.5	1.41	—	1	0	—
Stroma	1000	Jaillon	—	1.369	1.41	1	150	6

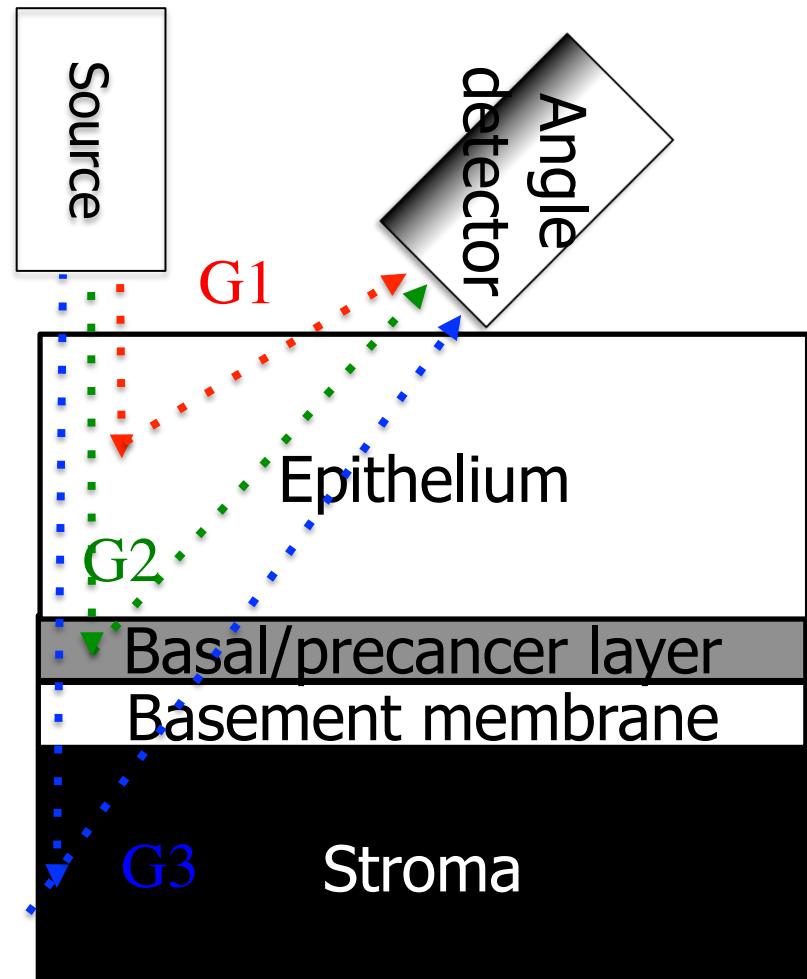
thickness and radius ( $\mu m$ )	Model 1	Model 2	Model 3	Model 4
Source layer	10000	10000	10000	10000
Epithelium	250	250	230	190
Basal layer	20	20	40	80
Stromal membrane	30	30	30	30
Stroma	1000	1000	1000	1000
Basal layer scatterer radius	6 (normal)	8 (abnormal)	8 (abnormal)	8 (abnormal)

# Signal-to-background ratio calculation and photon categories

Categories of photons: G1,G2,G3

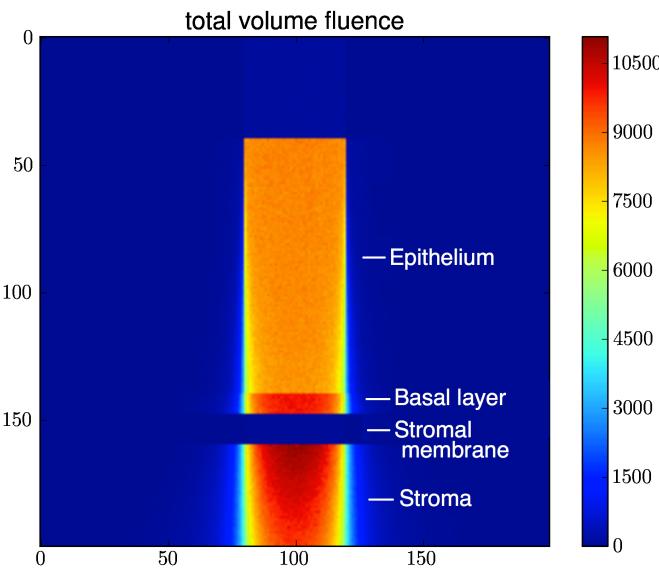
Definition of s/b:

$$s/b = \frac{\sum w_{G2}}{\sum w_{G1} + \sum w_{G3}}$$

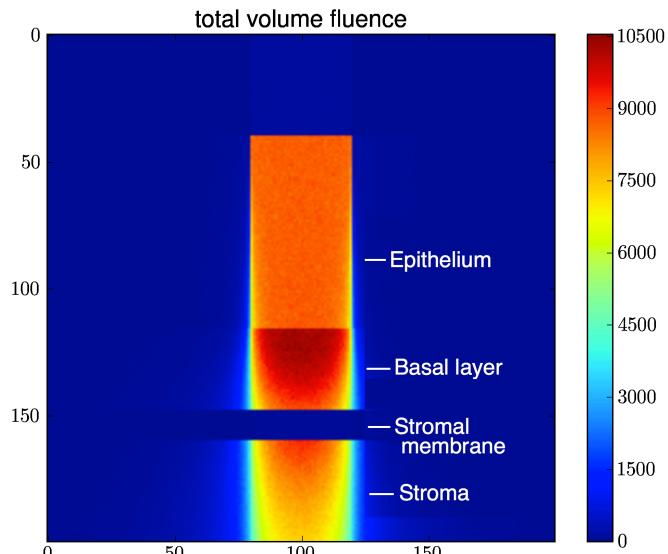


# Results: Fluence plots

Model 2  
Basal thickness=20



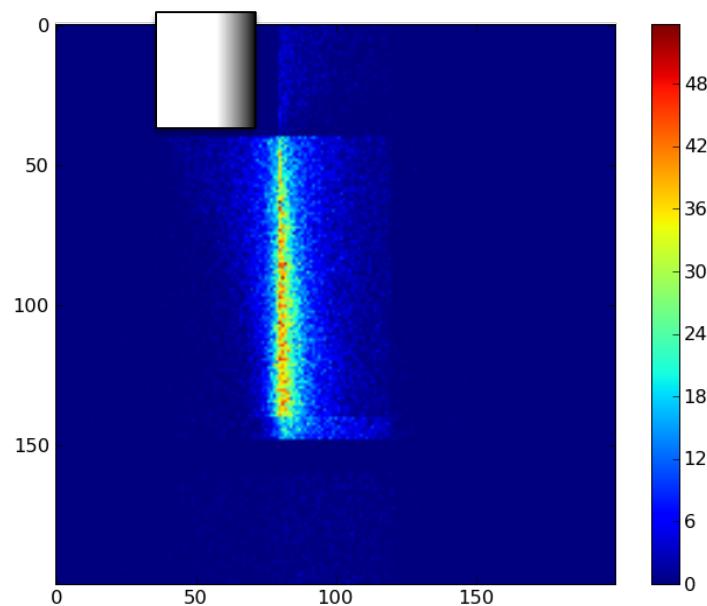
Model 4  
Basal thickness=80



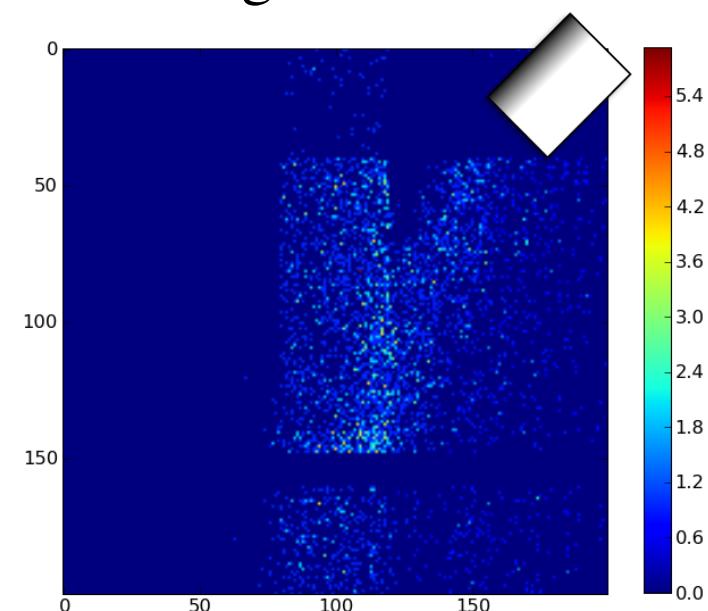
$10^9$  photon run takes 300 core-hours

# Flat vs. angled detectors

Flat detector



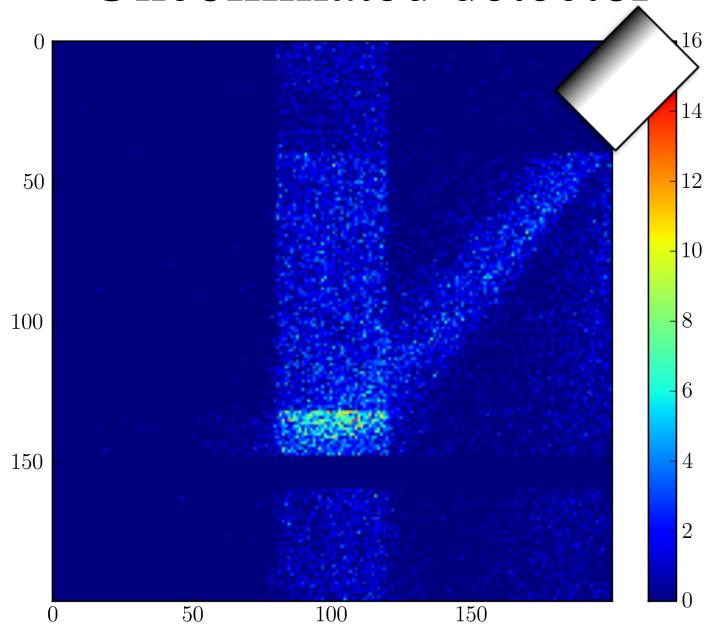
Angled detector



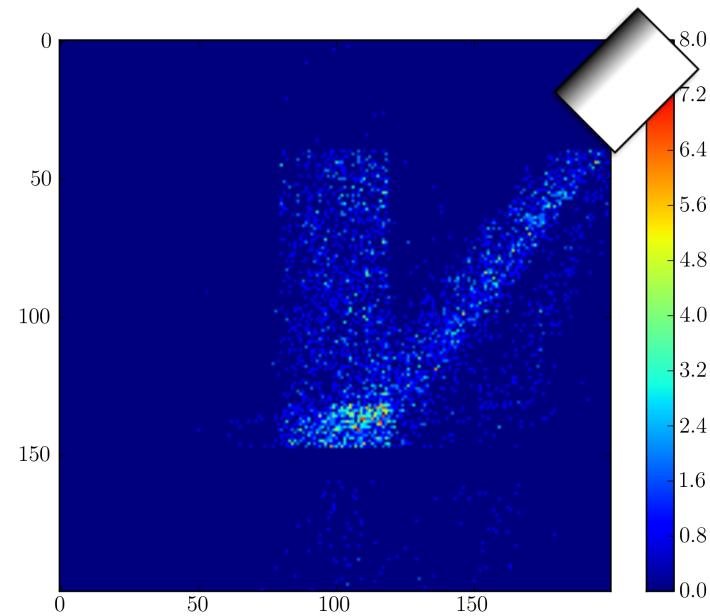
The ability to separate signals for different detectors

# Uncollimated vs. Collimated

Uncollimated detector



Collimated detector



Collimation equals to  
NA of 0.35

# Results: signal-to-background ratio

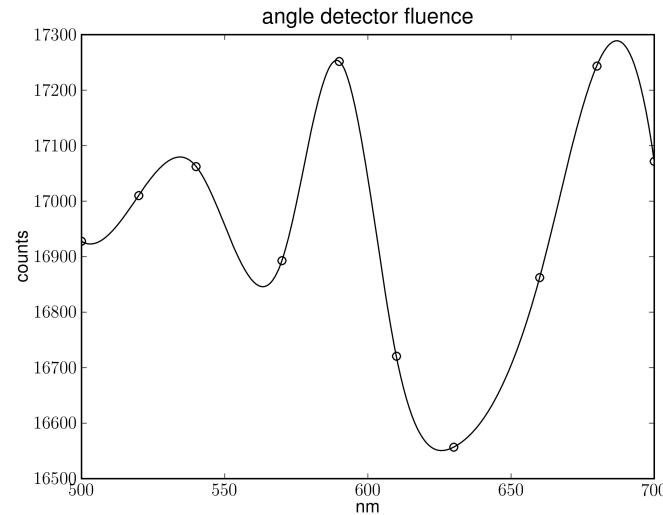
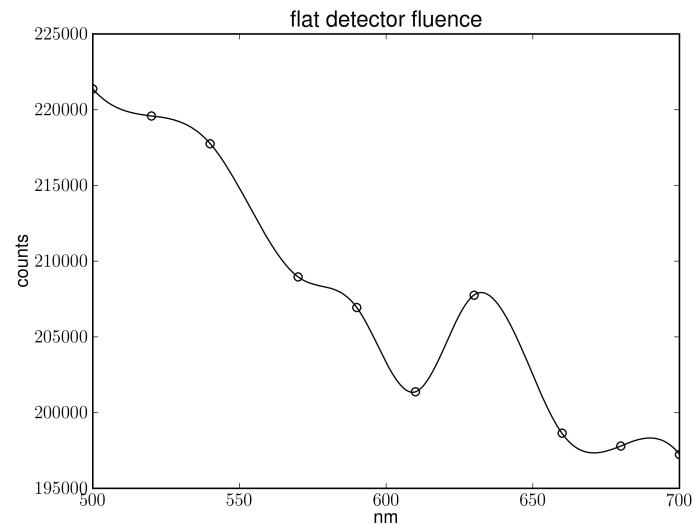
s/b for an angle detector: collimated

	<b>Epithelium</b>	<b>Basal/ precancer</b>	<b>Stroma</b>	<b>s/b</b>
Model 1	8986	33157	1746	3.09
Model 2	636	7006	1191	3.83
Model 3	558	13458	1156	7.85
Model 4	385	23491	1003	16.92

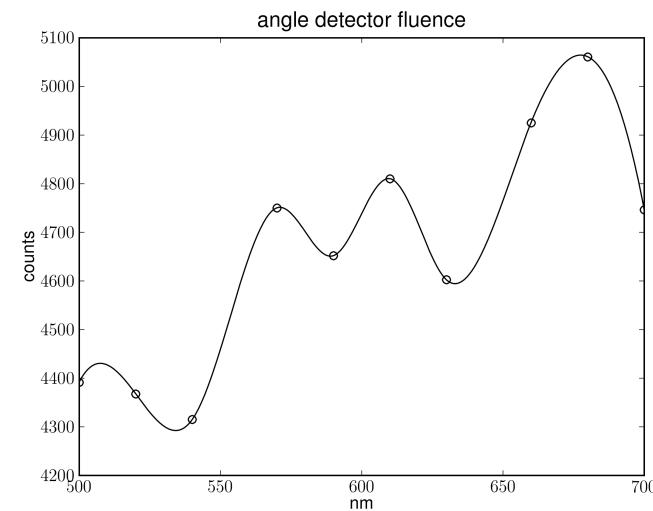
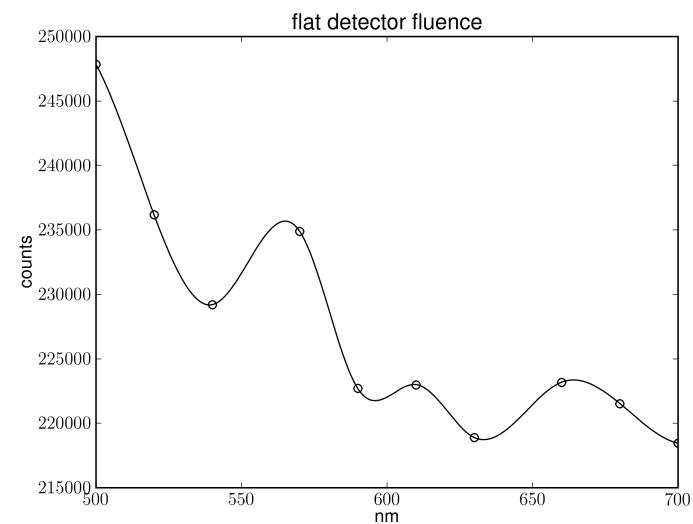
s/b for an angle detector: uncollimated

	<b>Epithelium</b>	<b>Basal/ precancer</b>	<b>Stroma</b>	<b>s/b</b>
Model 1	163053	51621	43415	0.25
Model 2	111216	21342	25489	0.16
Model 3	110726	42718	23006	0.32
Model 4	108527	87430	19167	0.68

# Simulated spectra for flat and angled detectors



Model 1



Model 3

# Conclusions for “Virtual probe design”

## ● Contributions:

- Multi-layer Monte Carlo that uses Mie theory
- Definition of theoretical signal-to-background ratio
- Proof-of-concept: “Virtual probe design”

## ● Challenges:

- Extremely computationally intensive
- Polarized Monte Carlo is difficult to implement

**C. W. Kan, K. Travis, D. C. Cote, K. Sokolov, M. K. Markey,**  
“Virtual probe design”: Monte Carlo simulation in the design of  
diagnostic instrumentation (in preparation)

# Conclusions and future work

## ● Major contributions

- Analysis
  - Analysis shows ability to distinguish between benign and MD+SD
  - A novel spectral processing technique to reduce feature redundancy
- Modeling
  - Monte Carlo simulation enables looking “inside the box”
  - Allows evaluation of feasibility and / or accuracy of instrumentation

## ● Future work

- Spectral features vs. Monte Carlo parameters
- More flexible geometry definitions in Pol-MC
- Faster, more highly optimized Monte Carlo algorithms

# Thank you!

- UT Biomedical Informatics Lab (BMIL)
  - Dr. Mia K. Markey
  - Dr. Mehul Sampat
  - Dr. Hyunjin Shin
  - Dr. Shalini Gupta
  - Gautam Muralidhar
  - Shuang Liu
  - Juhun Lee
  - Andy Y. Lee
  - Harrison Hocker
  - Alfredo Miranda
  - James Salazar
- Dr. Alan Bovik
- Dr. Andrew Dunn
- UT Biomedical Optics and Nanoparticle Diagnosis (BOND)
  - Dr. Konstantin V. Sokolov
  - Dr. Linda Nieman
  - Dr. Jesse Aaron
  - Kort Travis
  - Pratixa Joshi
  - Tim Larson
  - Justina Tam
  - Ryna Karnik
  - Avi Murthy
  - Doug Yeager
- Centre de Recherche Université Laval
  - Dr. Daniel Côté