

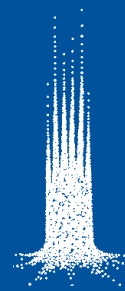
Quantitative Physiology of the Breast: Impacting Patient Care on Multiple Levels

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Duke University

BMES Annual Meeting 2008
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Current Strategies in the Breast Clinic



QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

Screening



www.madisonradiologists.com

Diagnosis

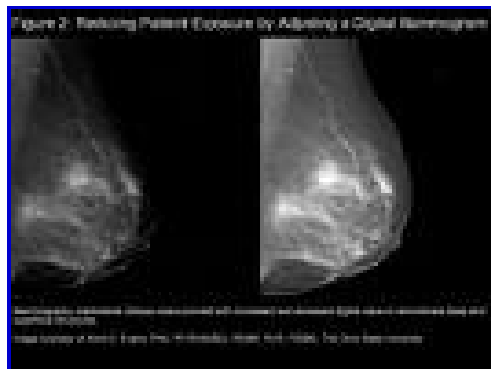


www.britannica.com

Treatment



www.cooperhealth.org



<http://images.google.com/>

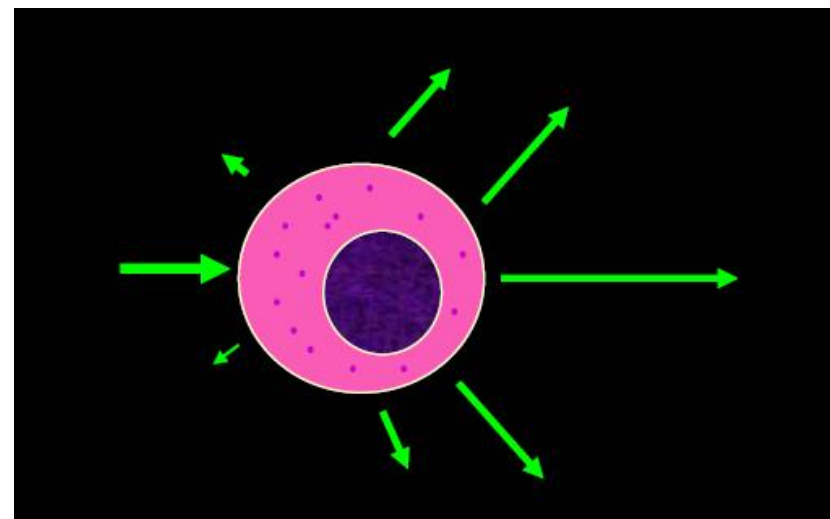
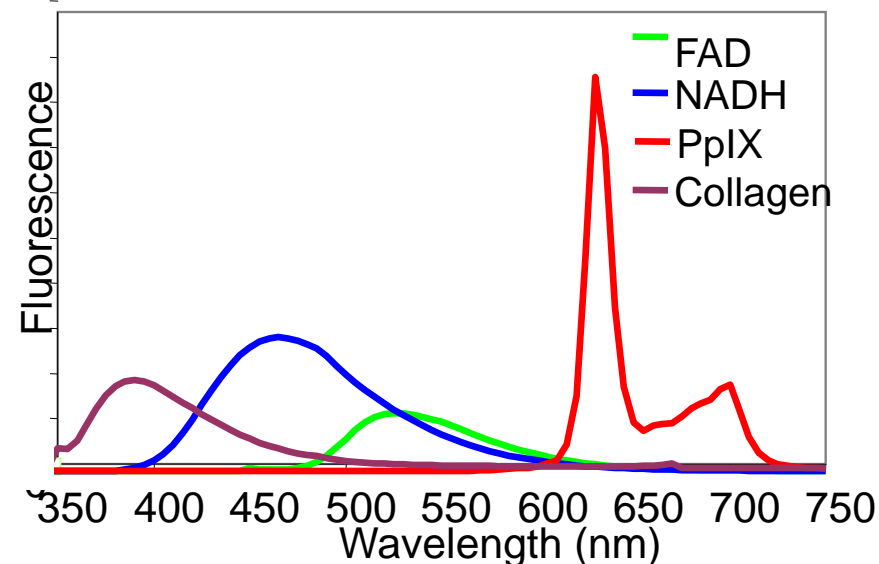
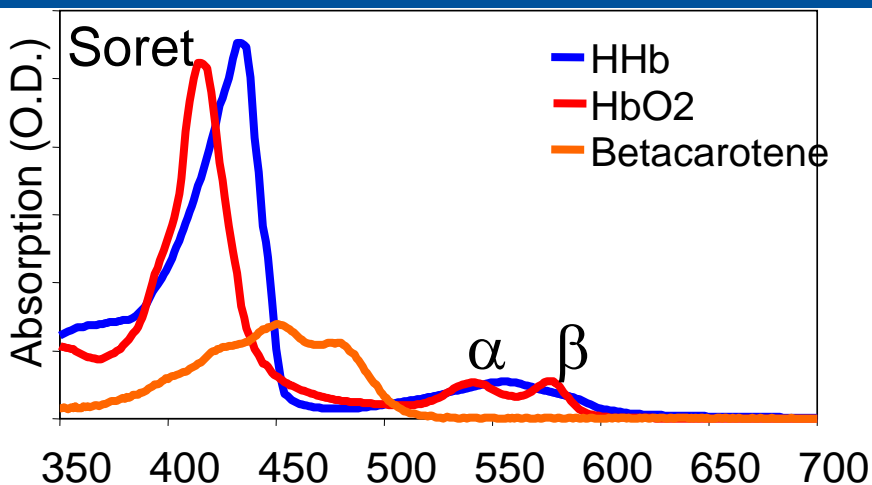
Tissue Absorbers, Scatterers and Fluorophores



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EX VIVO MARGIN ASSESSMENT



Scatterers

- Cells
- Nuclei
- Chromatin / DNA
- Mitochondria / organelles
- Melanin granules



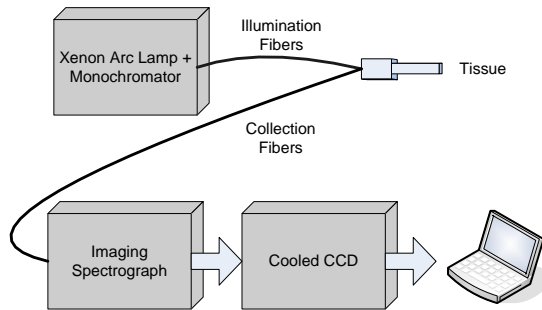
Quantitative Optical Physiology “Toolbox”

QUANT PHYSIOLOGY TOOLBOX

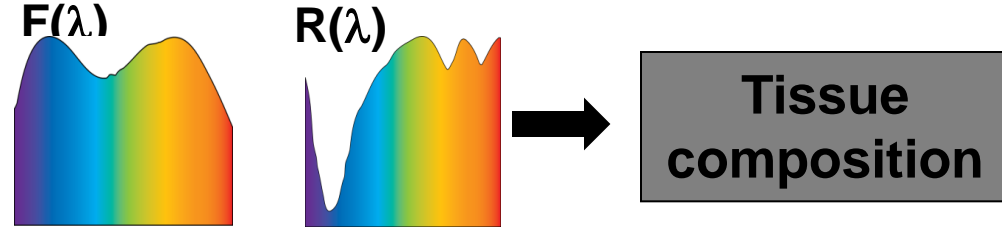
IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

Optical spectrometer

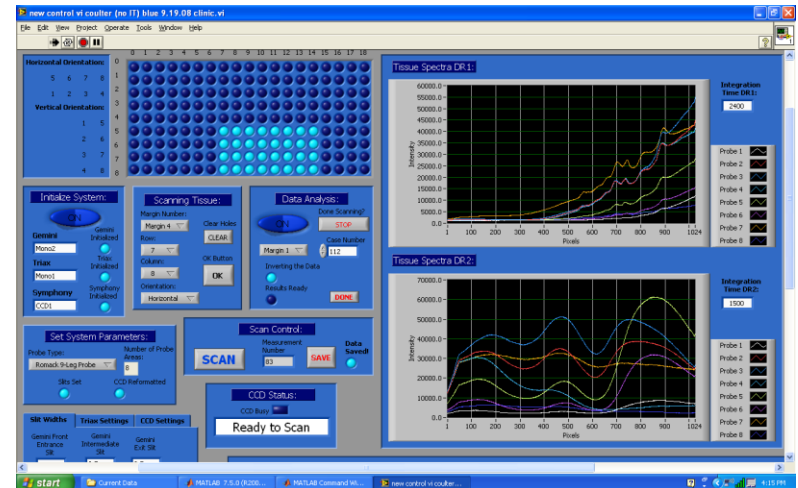
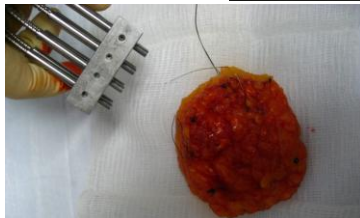
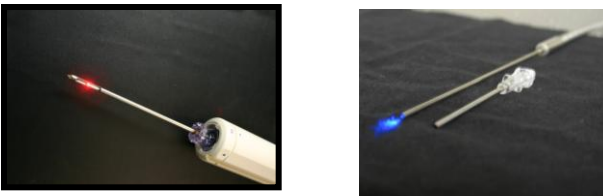


Inverse Monte Carlo Models



Real-time Control / Analysis Software

Fiber-optic probes



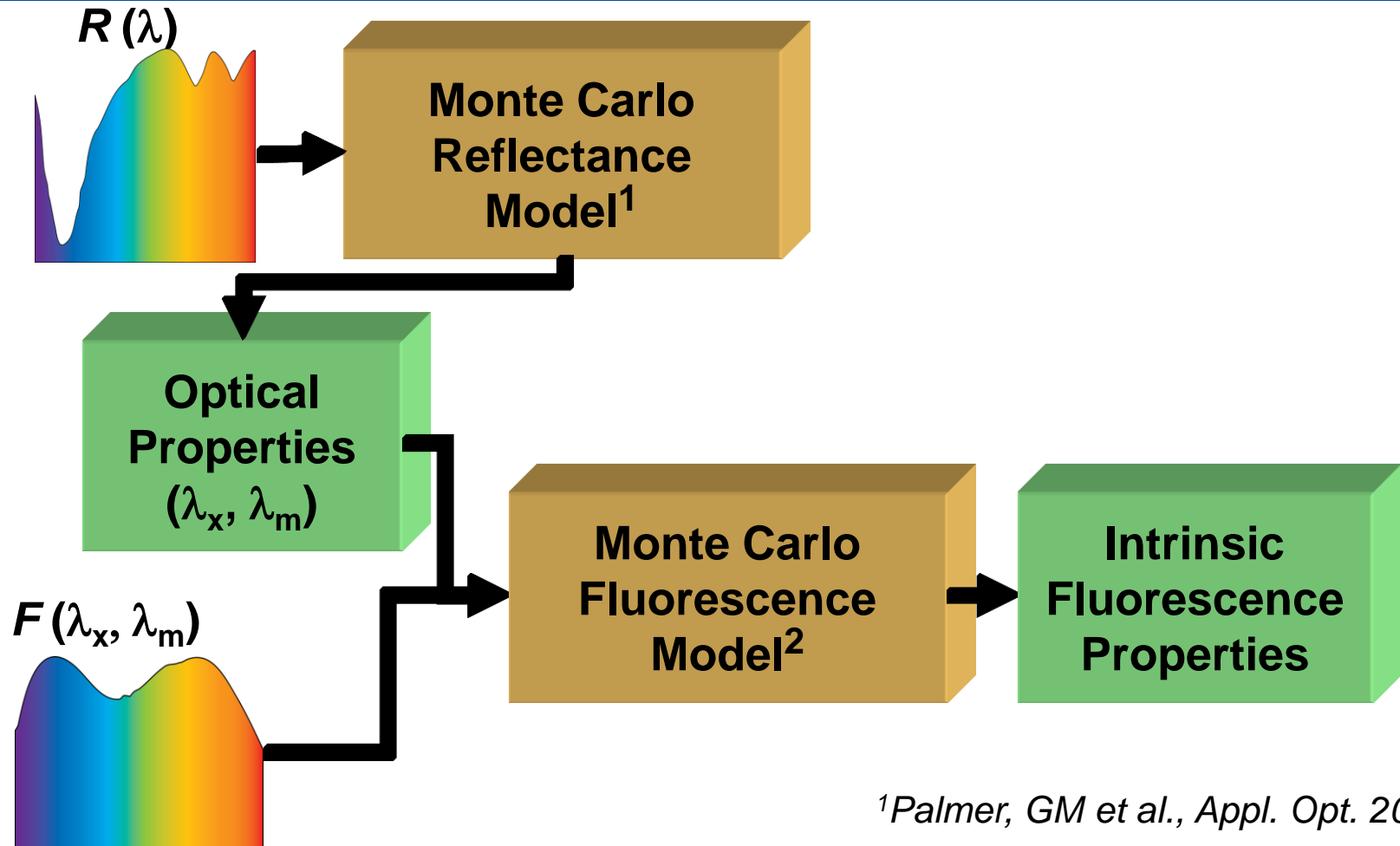
Inverse MC: An Enabling Technology for Quantitative Physiology



QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT



¹Palmer, GM et al., Appl. Opt. 2006

²Palmer, GM et al., JBO, 2008

Clinical Studies – 1) *In vivo* Optical Biopsy (40 Patients)

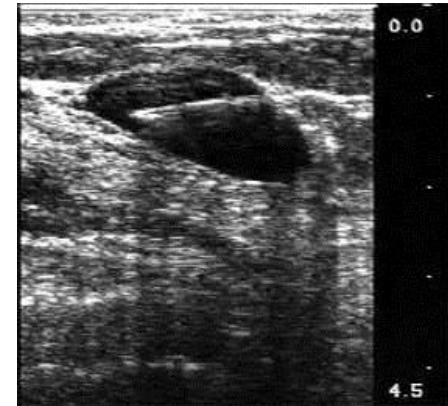


QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

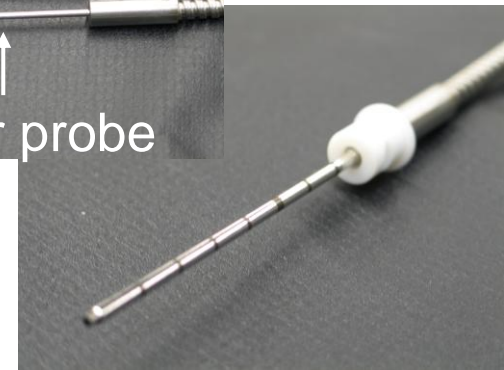
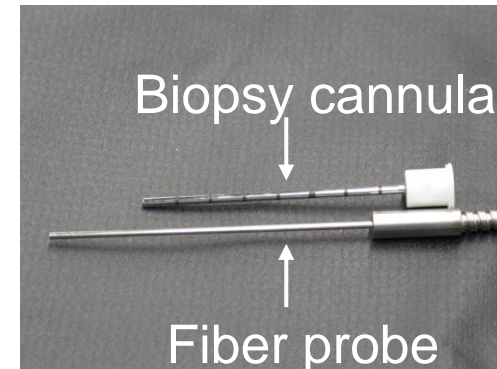
Fiber probe inserted into normal and diseased tissues under ultrasound guidance



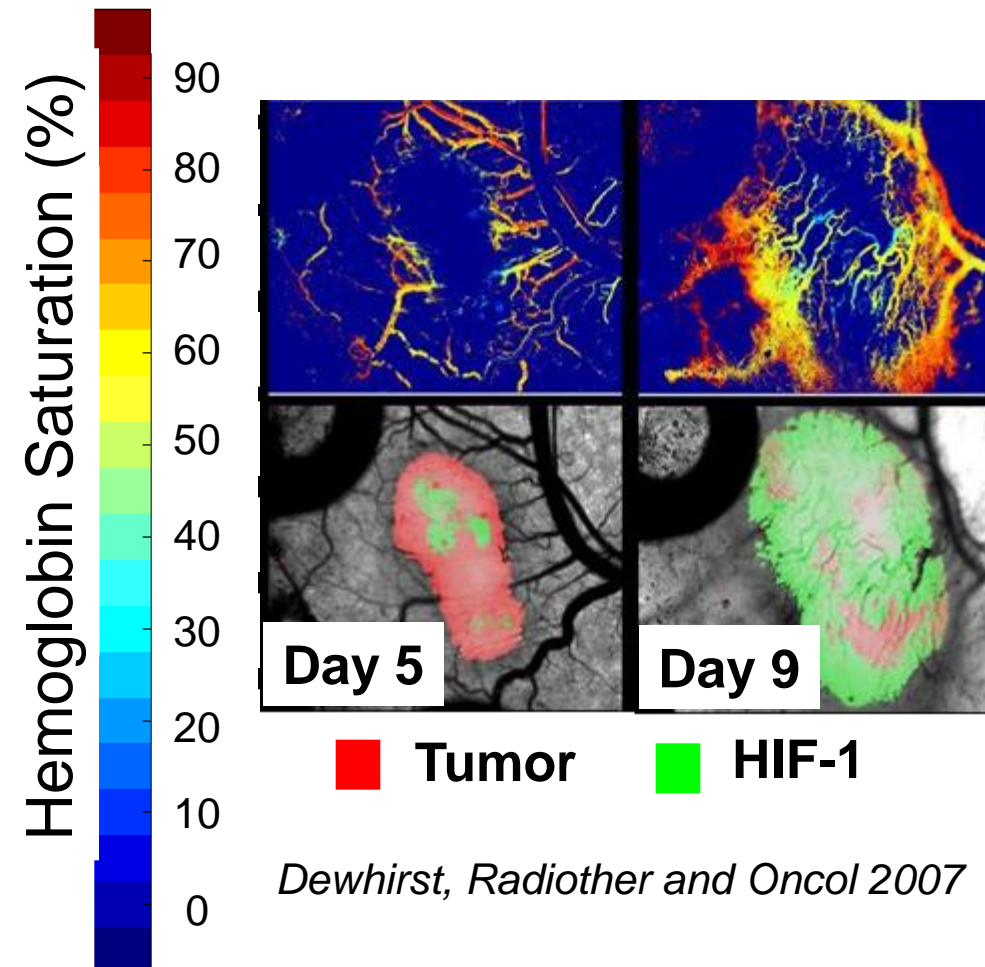
Diffuse reflectance and Fluorescence
EEM's in UV-Visible

Robust tool for use at time of biopsy

- diagnostics
- prognostics / prescription
- therapeutics



Hypoxia = Aggressive tumors



□ Under hypoxic conditions, HIF-1 is upregulated

□ HIF-1 upregulates >100 genes that promote angiogenesis, anaerobic metabolism, therapy resistance, metastasis

□ **Applications**

- Drug discovery (pre-clinical)
- Prognosis
- Therapy planning
- Therapy monitoring

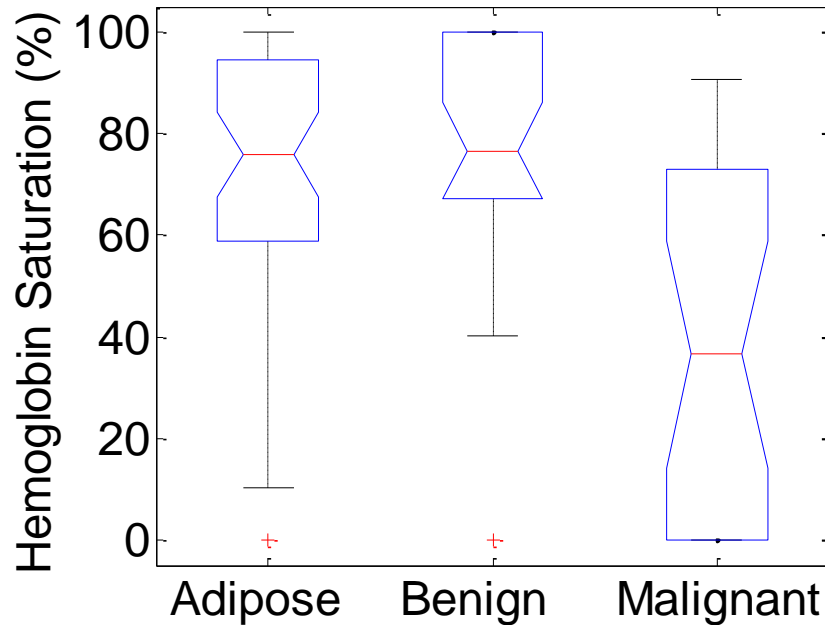
Quantitation of Tumor Oxygenation



QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT



Mean pO ₂	Malignant		Non-malignant	
	N	pO ₂	N	pO ₂
<i>Reference</i>				
Badib et al. 1969	6	21	6	41
Runkel et al. 1994	18	31.5	18	58
Hohenberger et al. 1998	32	42	6	56
Brown et al. 2008	20	24	59	39

*Hemoglobin saturation converted to pO₂ using a model of hemoglobin dissociation.
Assumptions: T = 37°C, pH = 7.4, pCO₂ = 40 mmHg, (P₅₀ = 26.6 mmHg)

Hemoglobin Saturation Histograms

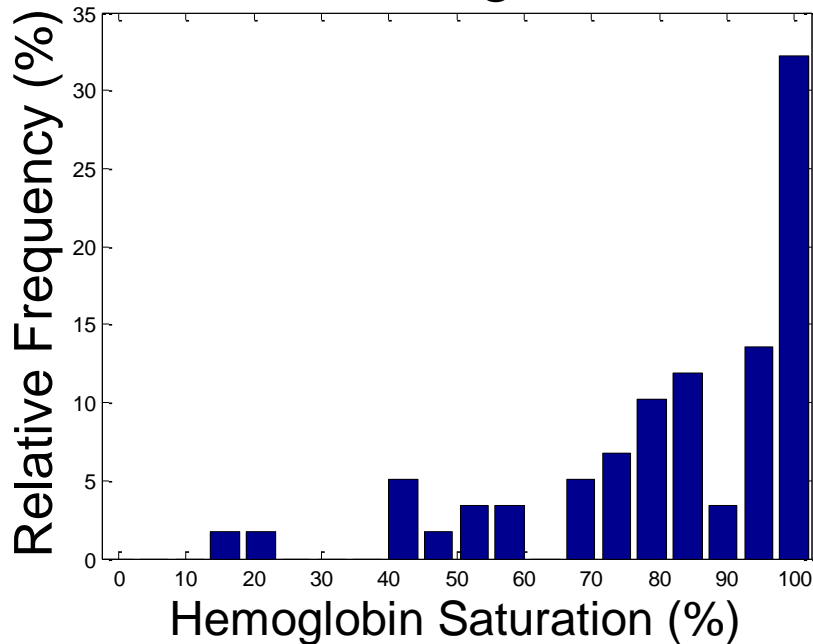


QUANT PHYSIOLOGY TOOLBOX

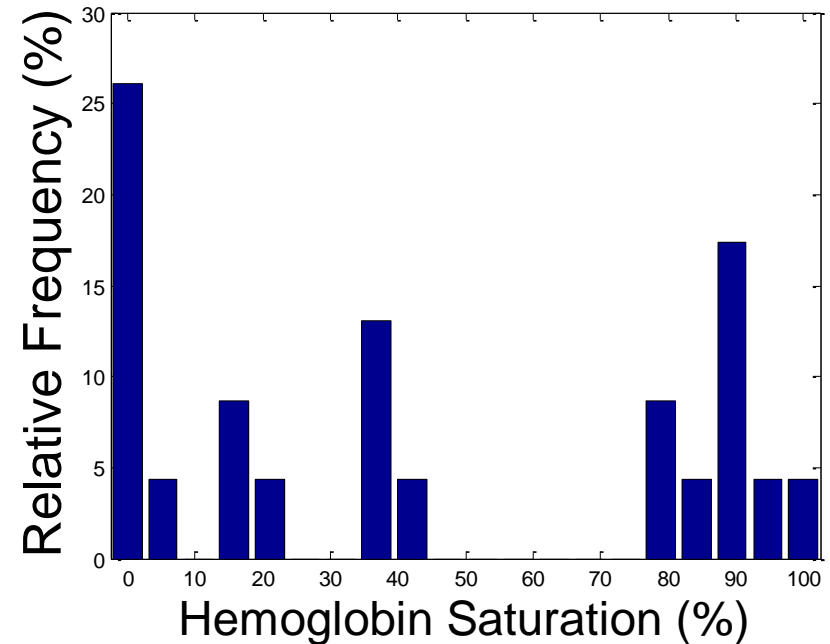
IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

Non-malignant



Malignant



Why is there such a diverse range in tumor oxygenation?

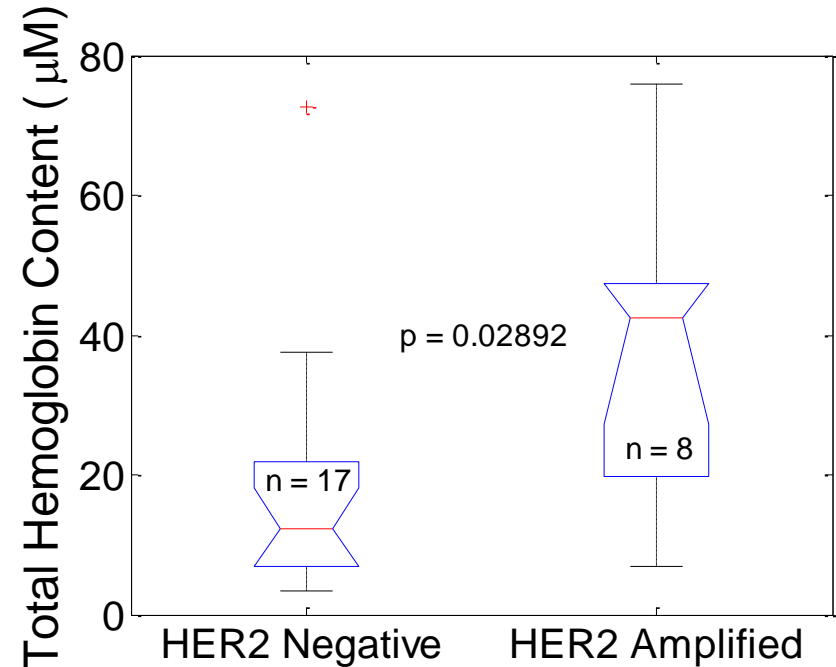
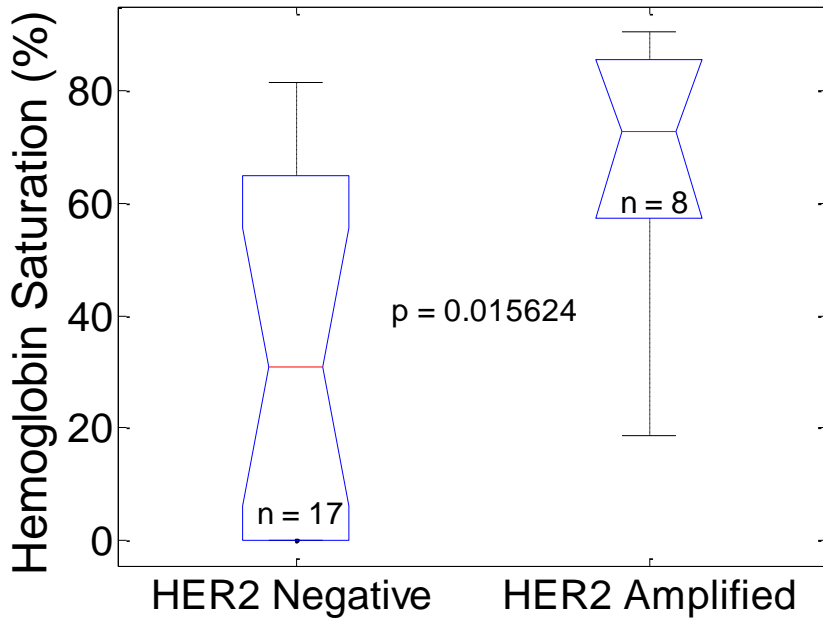


Tumor oxygenation and HER2/neu Status

QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

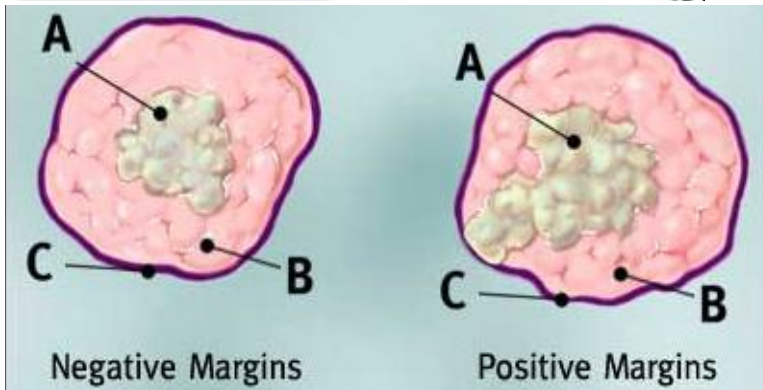


A tumor's oxygenation state at the time of diagnostic biopsy can have important prognostic and therapeutic implications!



Clinical Studies – 2) Breast tumor margin assessment *ex vivo* (80 Patients)

Surgery (lumpectomy)



<http://www.breastcancer.org/pictures/>

- Women with stage 0,I,II undergo breast conservation surgery
- The pathologic margin status is an important predictor of local recurrence after BCS.
- 20-70% of women undergo re-excision surgery because of positive tumor margins*

The Clinical Device (alpha version)



QUANT PHYSIOLOGY TOOLB

L BIOPSY

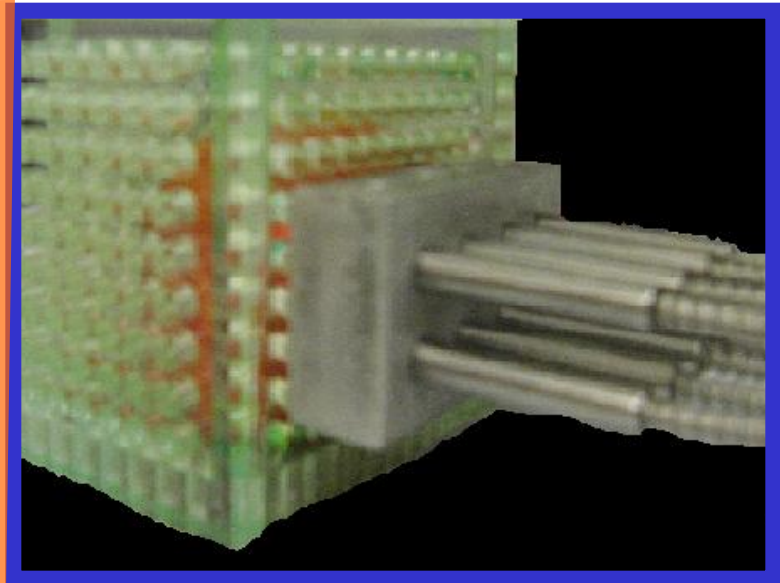
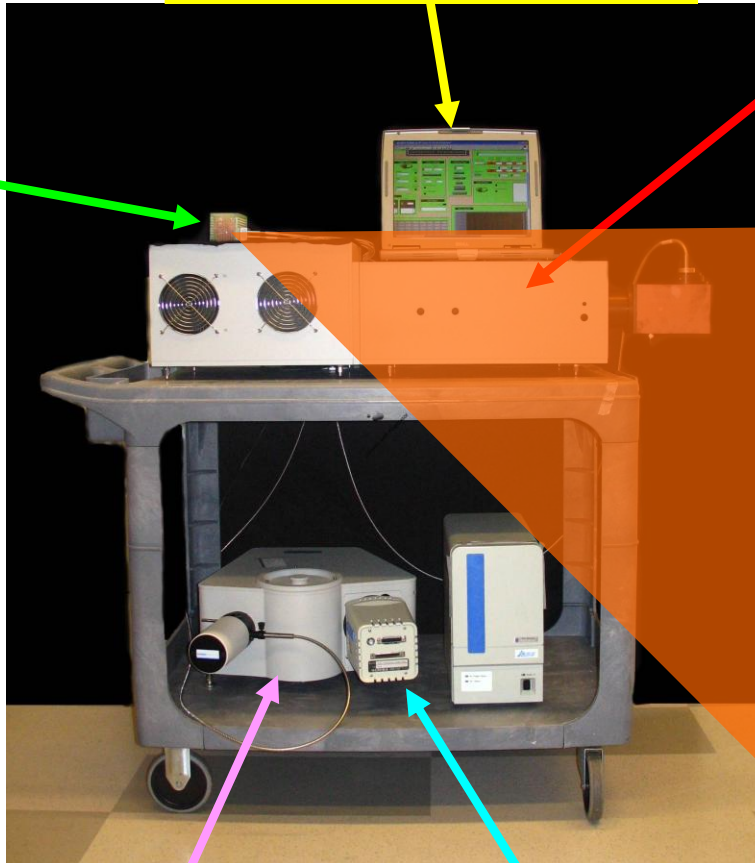
EX VIVO MARGIN ASSESSMENT

Computer + software

Xenon lamp +
monochromator

Tissue
interface

Probe interfaced with tissue



Spectrograph

CCD

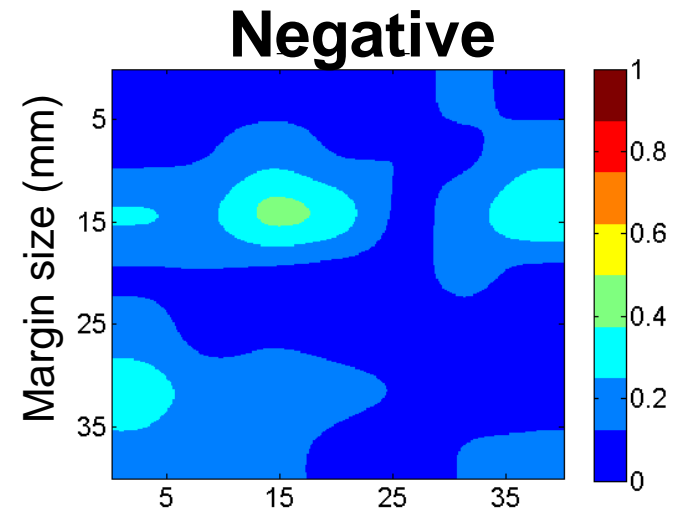
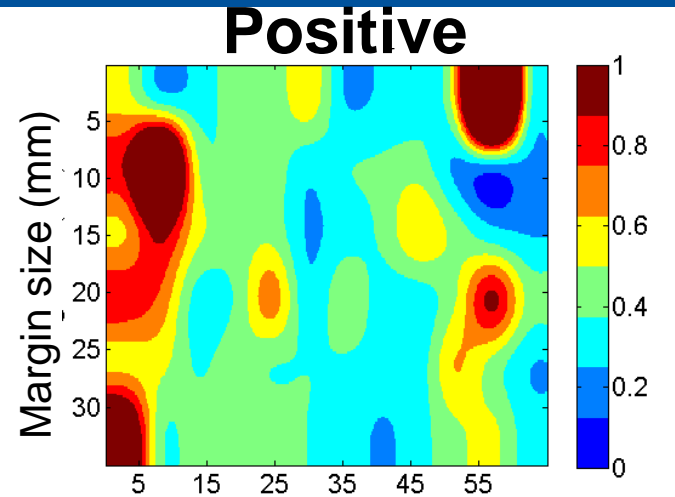
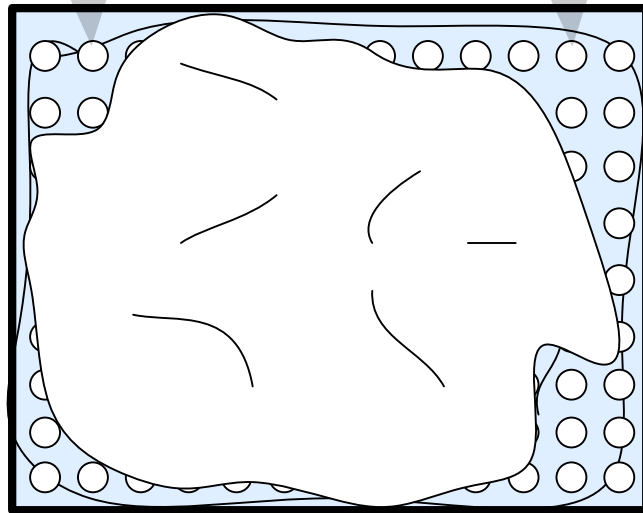
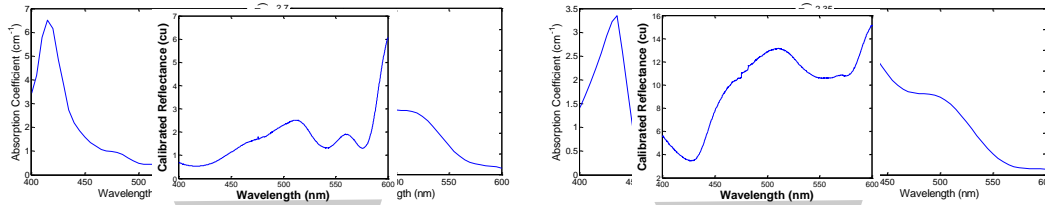
Informative Parameter Maps From Diffuse Reflectance



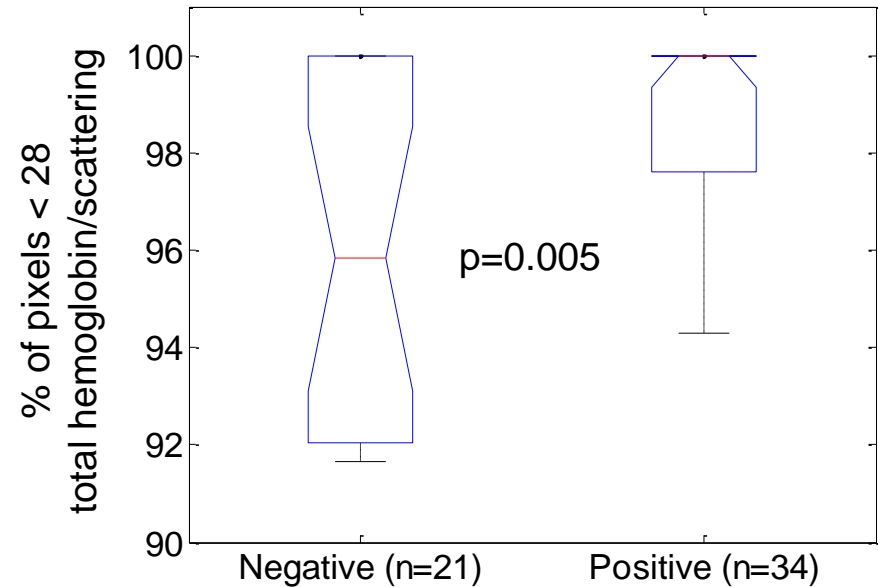
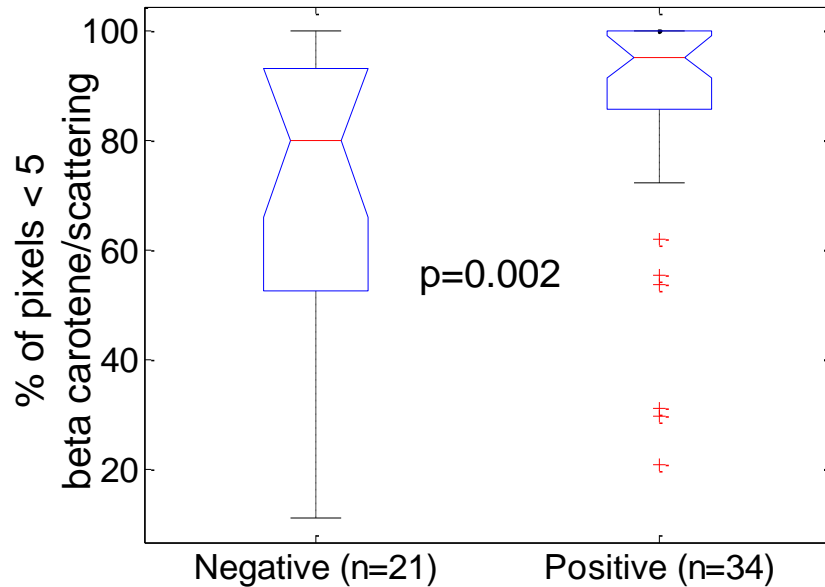
QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

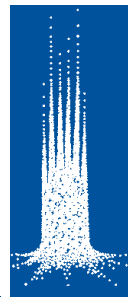
EX VIVO MARGIN ASSESSMENT



Diagnostic Parameters



The parameter ratios shown above indicate there are significant differences between normal and cancerous margins



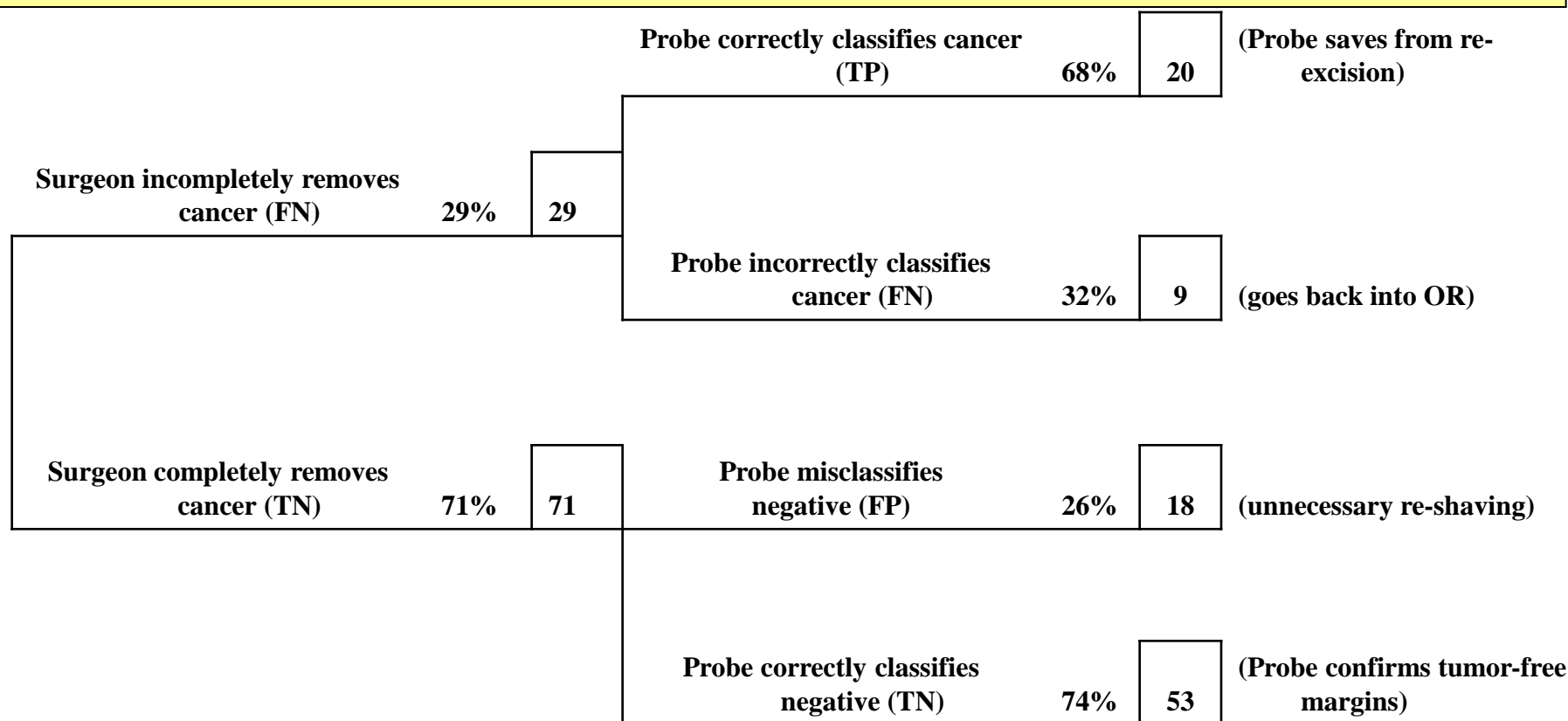
What is the Potential Clinical Impact?

QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

Without probe: 29% re-excision rate, 65% unnecessary tissue removal rate

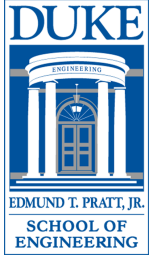


With probe: 9% re-excision rate, 18% unnecessary tissue removal rate

Summary and Future Directions



- Quantitative optical spectroscopy of the breast may be a useful tool for clinical breast cancer management
 - Results from over 150 patients in 2 parallel clinical studies are promising
 - Applications: Diagnostic biopsy, prognosis and prediction, therapeutic monitoring, surgical margin assessment
- Future directions:
 - *Optical biopsy*: Investigate optical biomarkers which predict response, or are modulated by response to neo-adjuvant chemotherapy (pilot study underway)
 - *Margin assessment*: Complete 150-patient clinical study; Complete development of faster beta device



Acknowledgements



QUANT PHYSIOLOGY TOOLBOX

IN VIVO OPTICAL BIOPSY

EX VIVO MARGIN ASSESSMENT

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Special thanks to all the patients who participated in our clinical studies

