Multimodal imaging device for intraoperative surgical guidance

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Outline

- Motivation and goals
- Overview of the system
  - Optical Component
  - Gamma Component
  - Integration and characterization
- Current status of the work
- Plans for the future

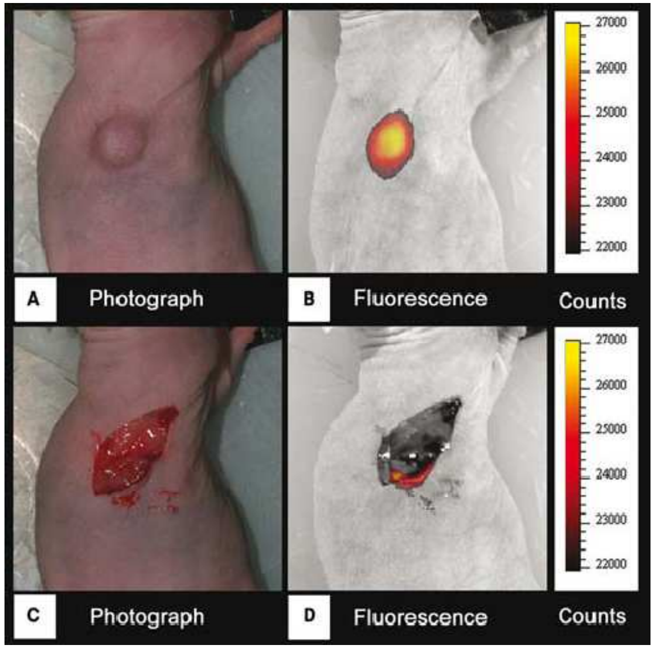
Motivation and Goals

- Develop multimodal imaging device for intraoperative surgical guidance
- Combination of NIR/visible optical and gamma modalities could aid tumor surgery and reduce the need for second surgery
- Present practice (wire localization) leads to positive margins and need for second surgery for non-palpable tumors (20-55% in breast cancer*)

*V. Velanovich et al. *Annals of Surgery*, 229(5): pp. 625-630, May1999.
A. R. Miller et al. *Journal of Surgical Oncology*, 86(3): pp. 134-140, June2004.

Strategy

- Combine complementary imaging modalities
  - Doubly labeled tracer injected into bloodstream to preferentially absorb in tumors
  - Tracer consists of nanobodies that target cells overexpressing protein HER2+, labeled with fluorescent dye and a radioisotope
  - Gamma emission imaging
    - moderate spatial resolution and high sensitivity through thick biologic tissue for localization
  - Near infrared fluorescence imaging
    - good spatial resolution for precise visualization of structures near the surface
  - Overlay the functional images on top of the structural image map (visible image)



Ann Surg Oncol (2009) 16:2717–2730

System Vision

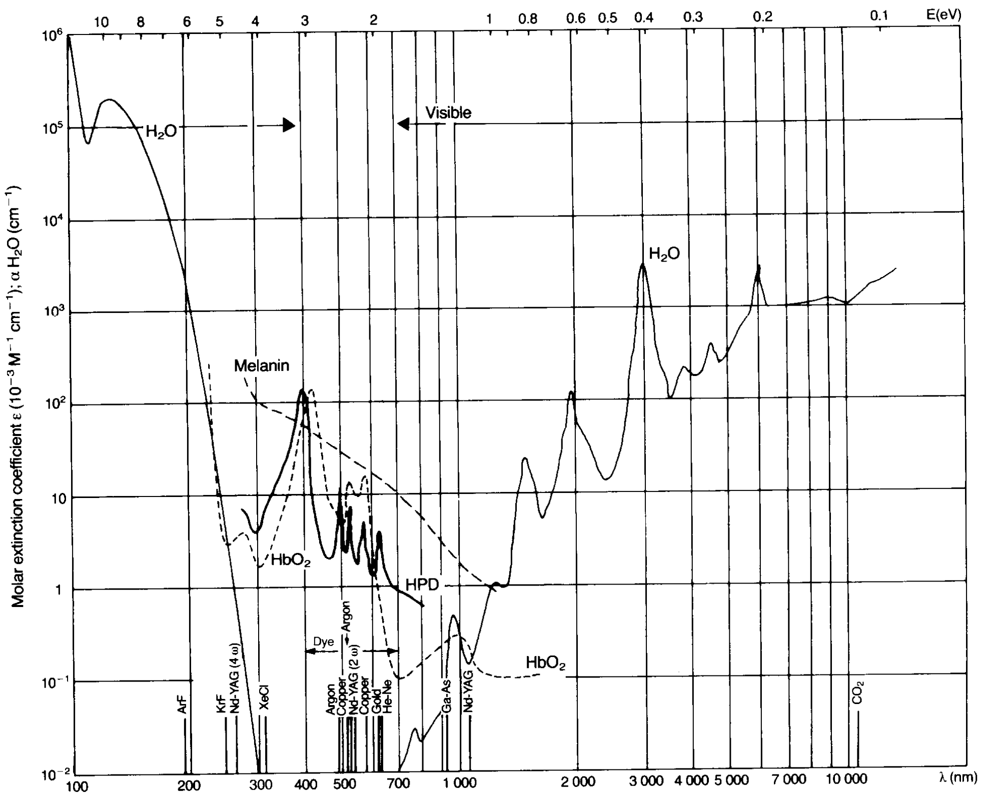
Video courtesy of Agile Engineering

Visible/NIR System

- Principle/Theory
- System design considerations
- Components Overview
  - Camera
  - Lens
  - Illumination/Filters
  - Image processing/fusion/GUI
- Phantom/Characterization Studies

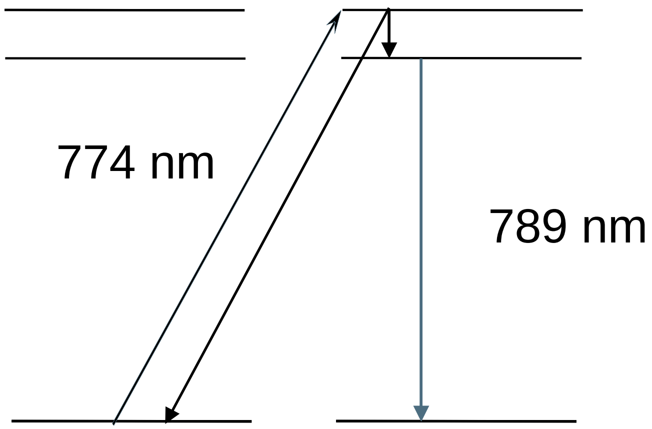
Light Propagation in Tissue

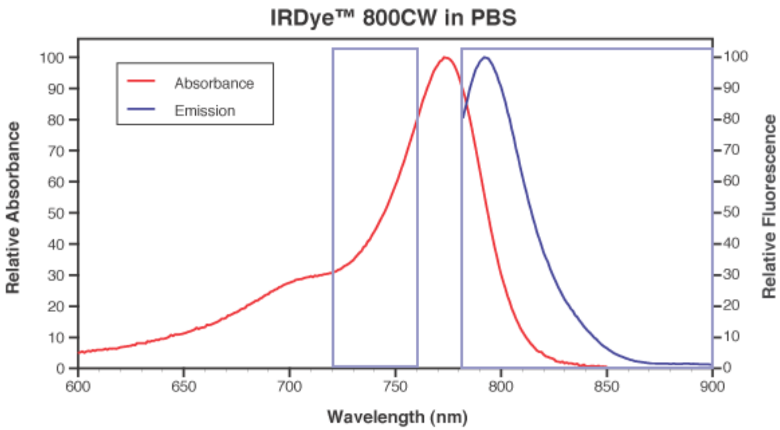
- The 600-1000 nm window is ideal for imaging due to low absorption by tissue
- Light scattering dominates absorption in this range
- Key parameters are scattering and absorption coefficients



Boulnois, JL, *Photophysical processes in recent medical laser developments: A review,* Lasers in Medical Science, Vol 1. 1986

NIR Fluorescence Imaging



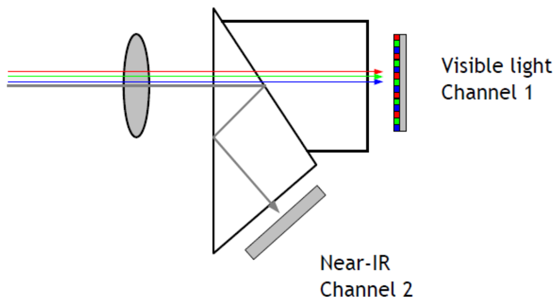


- What's being imaged is the NIR photons emitted from fluorophores under excitation
- Fluorophore excitation vs emission
  - example IRDye 800
- Use bandpass filters to minimize effects from excitation and stray light and improve signal to noise ratio
- Fluorophore considerations
  - high quantum yield
  - low photobleaching threshold
  - high absorption

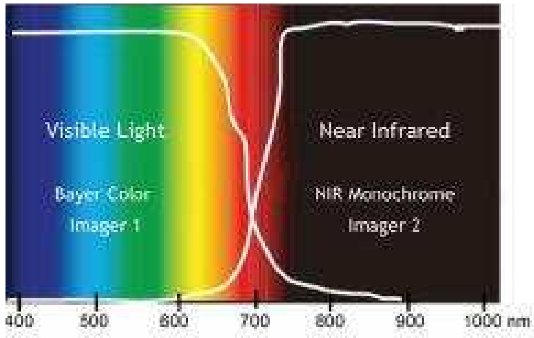
http://www.licor.com/bio/products/reagents/irdye_800cw_nhs_ester/irdye_800cw_nhs_ester.jsp

Camera

- Optical/NIR 2CCD camera uses one lens and a dichroic coating on the prism splits incoming light into two paths to two channels
- The first channel captures visible light, while the second channel images NIR light
- Real-time video capturing at 30 fps
- 1/3" CCD sensors with high sensitivity and resolution 1024x768 pixel field of view
- Image data transferred to the acquisition PC using the a Camera Link Image Acquisition board from National Instruments.



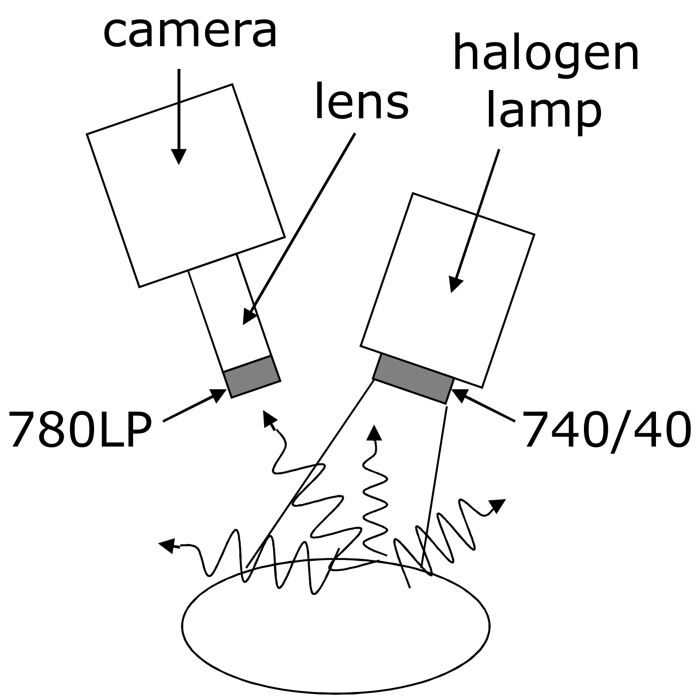
Integrated optical prism



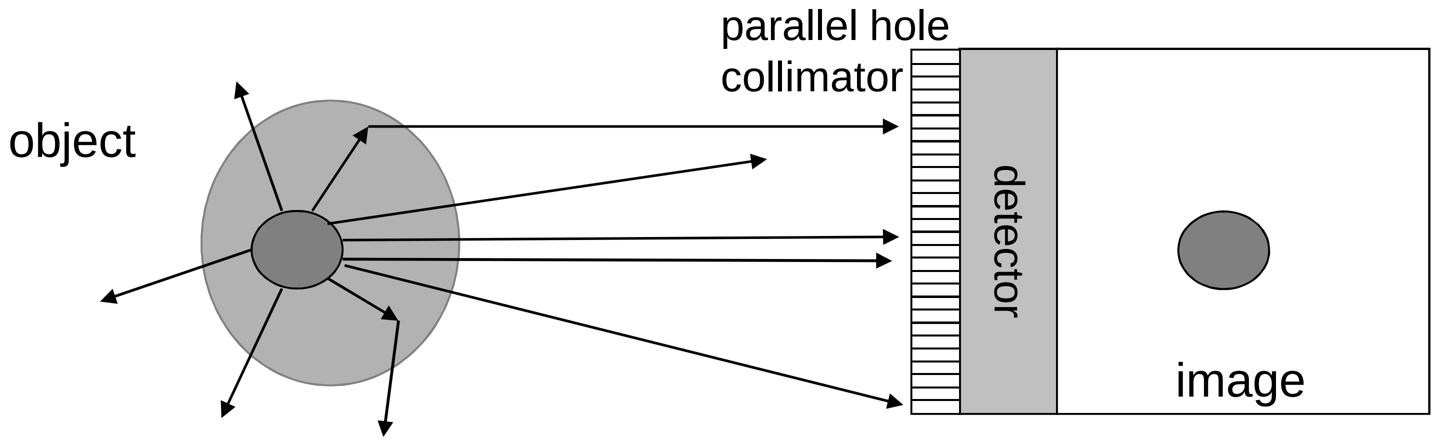
Spectral curves of Imager 1 and 2

Lens and Illumination Components

- Use a 3CCD NIR corrected lens to extend the working distance and field of view (optimal 30 cm WD and 8X10 cm FOV)
- In order to reject unwanted excitation light, filter at the lens' input transmits only NIR light longer than 780 nm.
- Fluorescence excitation light is presently provided by a 250 W tungsten halogen lamp using an excitation filter centered at 740 nm with a FWHM 40 nm.
- Excitation fluence is the main issue – need to reach 50 mW / cm^2 photobleaching limit



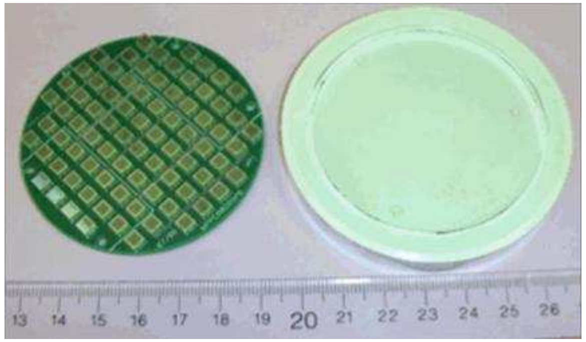
Gamma Imaging

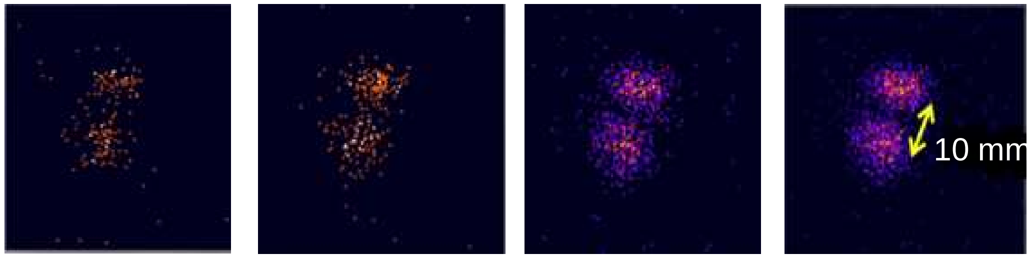


- Gamma Imaging - What's being imaged is radiation (gamma-rays) emitted by nuclear tracers (Tc99m)
- Parallel hole collimator lets through only the photons that hit the detector from an approximately perpendicular direction

Gamma Camera

- Single crystal (6 mm thick, 6 cm diameter) $LaBr_3$(Ce) detector read out by array of silicon photomultipliers
- Built in collaboration with JLab, WVU (based on design suggestions from UVA surgeons)
- Example: Imaging two 35 µCi Cobalt 57 sources spaced 10 mm from each other and 5 cm away from the camera

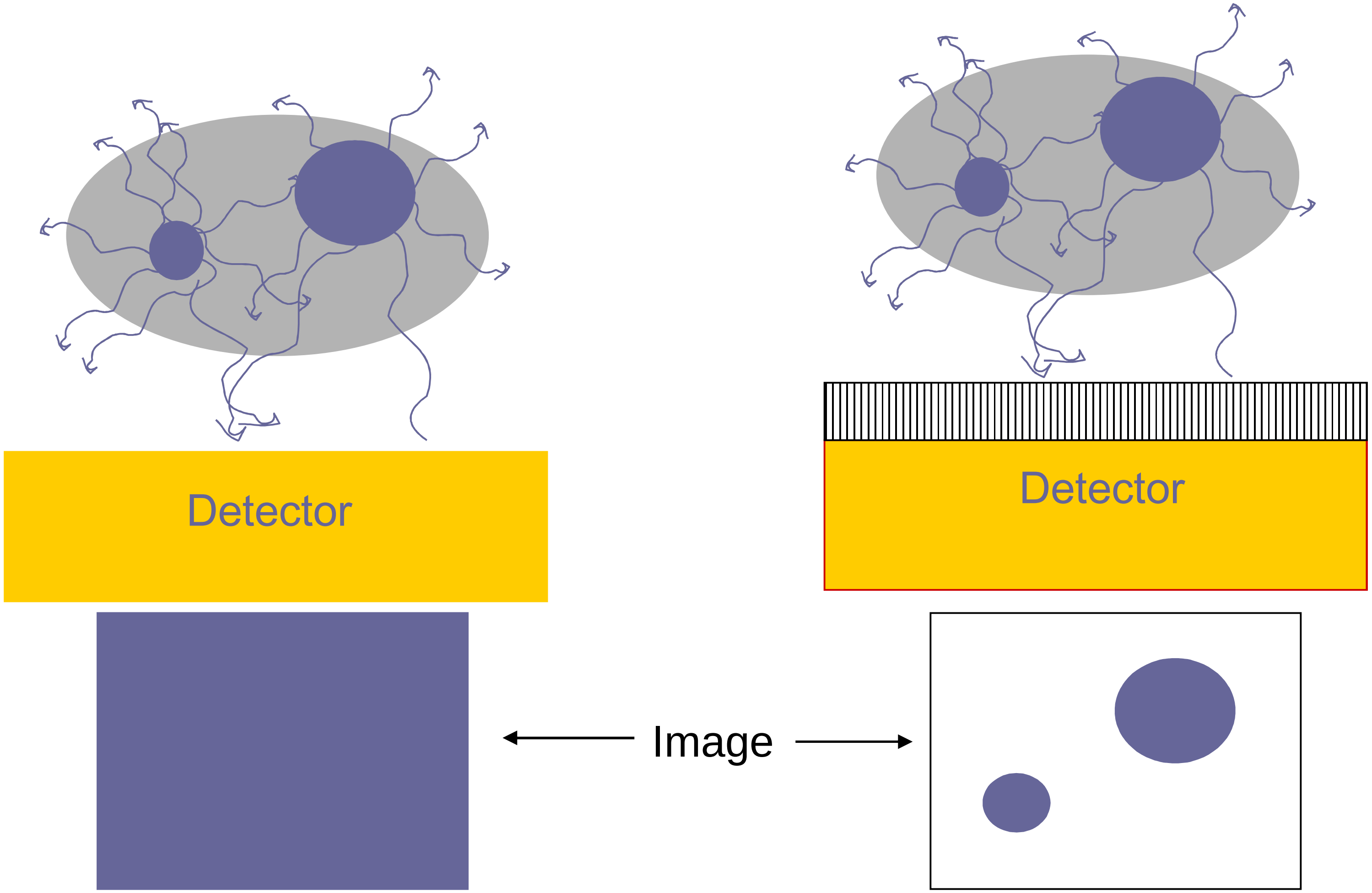




5 sec 10 sec 30 sec 60 sec

photo courtesy of S. Majewski

Parallel hole collimator



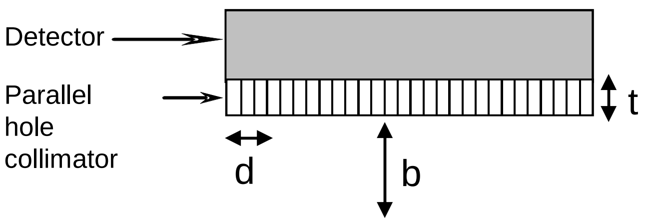
drawing courtesy of P. Judy

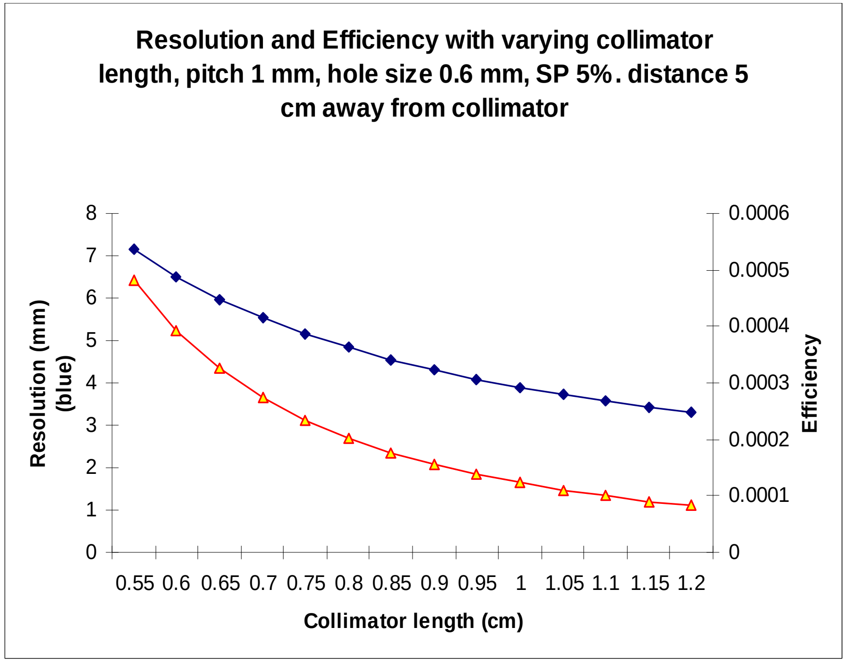
Parallel hole collimator, cont'd

- A necessary performance limiting component of any nuclear medicine imaging system
- Trade off between collimator resolution and efficiency
- Design considerations:
  - Purpose (Hi/Low res)
  - Hole/septa size/shape

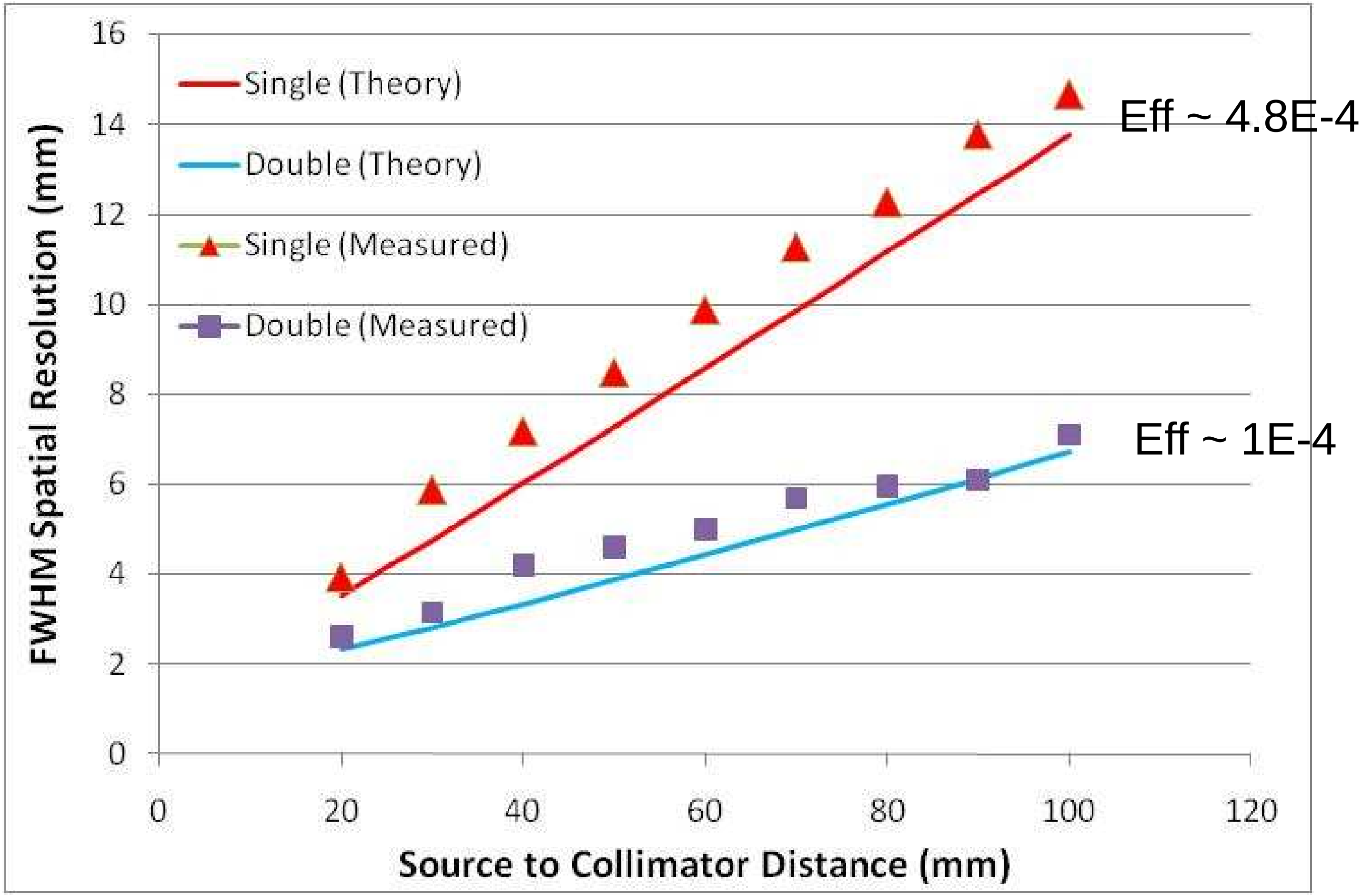
$R_{coll} \sim d(l_{eff}+b)/l_{eff}$

$g \sim K^2(d/l_{eff})^2[d^2/(d+t)^2]$





Spatial Resolution

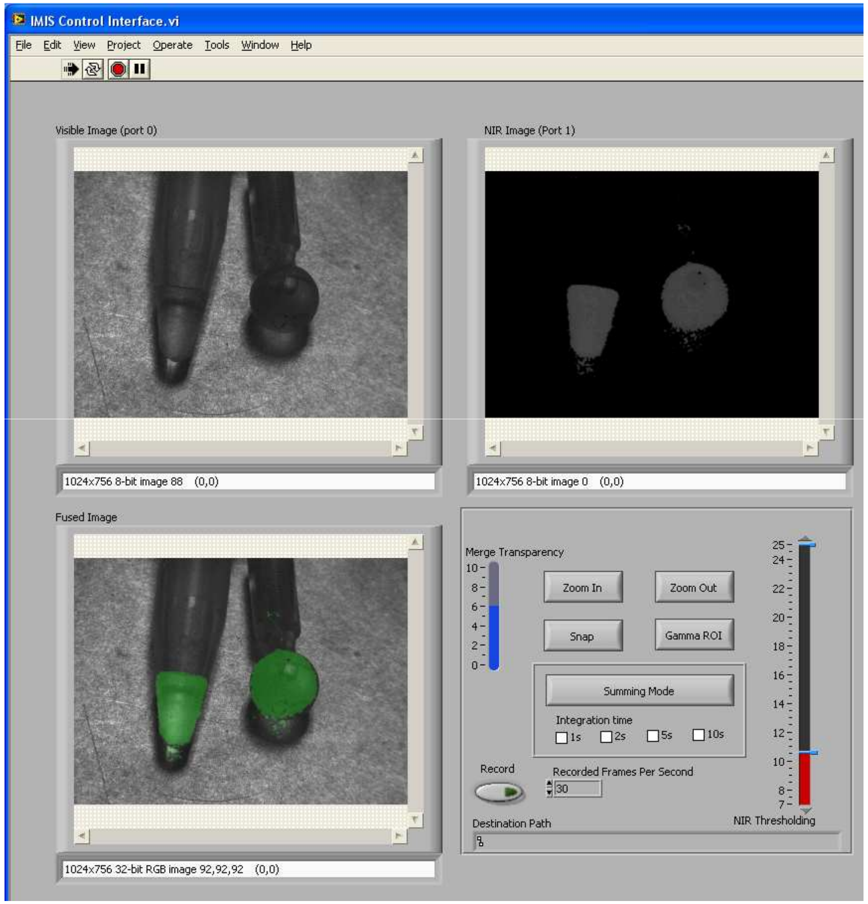


Intrinsic detector resolution of 1.5 mm assumed for calculating theoretical resolution.

graph courtesy of S. Majewski

Image display software

- Acquisition GUI designed with input from UVA surgeons
- Visible/NIR and gamma images fused in real-time
- Gamma outline obtained by a segmentation algorithm and can be turned on/off to depict tumor localization
- NIR images can be manually thresholded and fused with the visible image to allow more detailed viewing of tumor when surgeon gets close to it



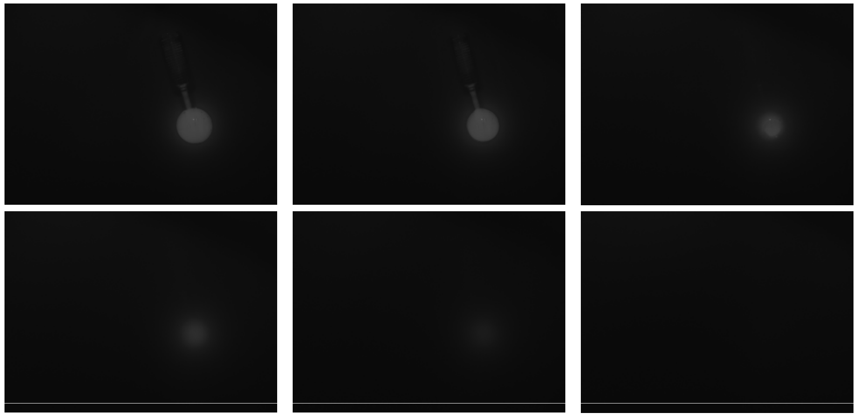
Phantom Experiments

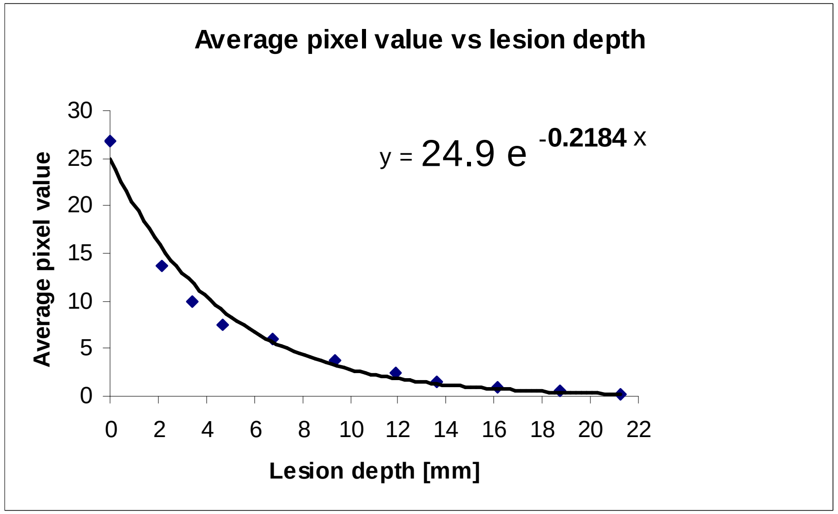
- Goal: To evaluate the performance and key characteristics of the imaging system components
  - Make phantoms with optical properties that simulate those of breast tissue
  - Literature suggests that it is important to match the absorption and scattering coefficients of the phantom mixture to the measured tissue coefficients*
  - Our approach is to use Intralipid and India Ink mixture which respectively contribute to the scattering and attenuation coefficients
  - Use gelatin to solidify the mixture

*Optical Phantoms for Multimodality Imaging, S Jiang and BW Pogue
ST Flock et al, **Optical Properties of Intralipid:** A Phantom Medium for Light Propagation Studies, *Lasers in Surgery and Medicine* **12516519 (1992)**

Optical system sensitivity

- Acrylic sphere filled with IRDye800 placed in a box phantom that is slowly filled with optically tissue equivalent liquid
- Verify the total attenuation coefficient of liquid mixture matches theory
- Expected exponential drop off in pixel intensity versus lesion depth as well as the light penetration depth

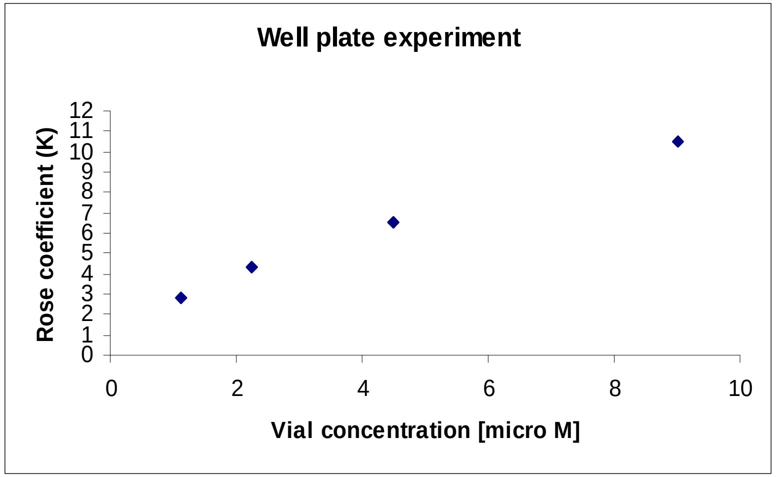




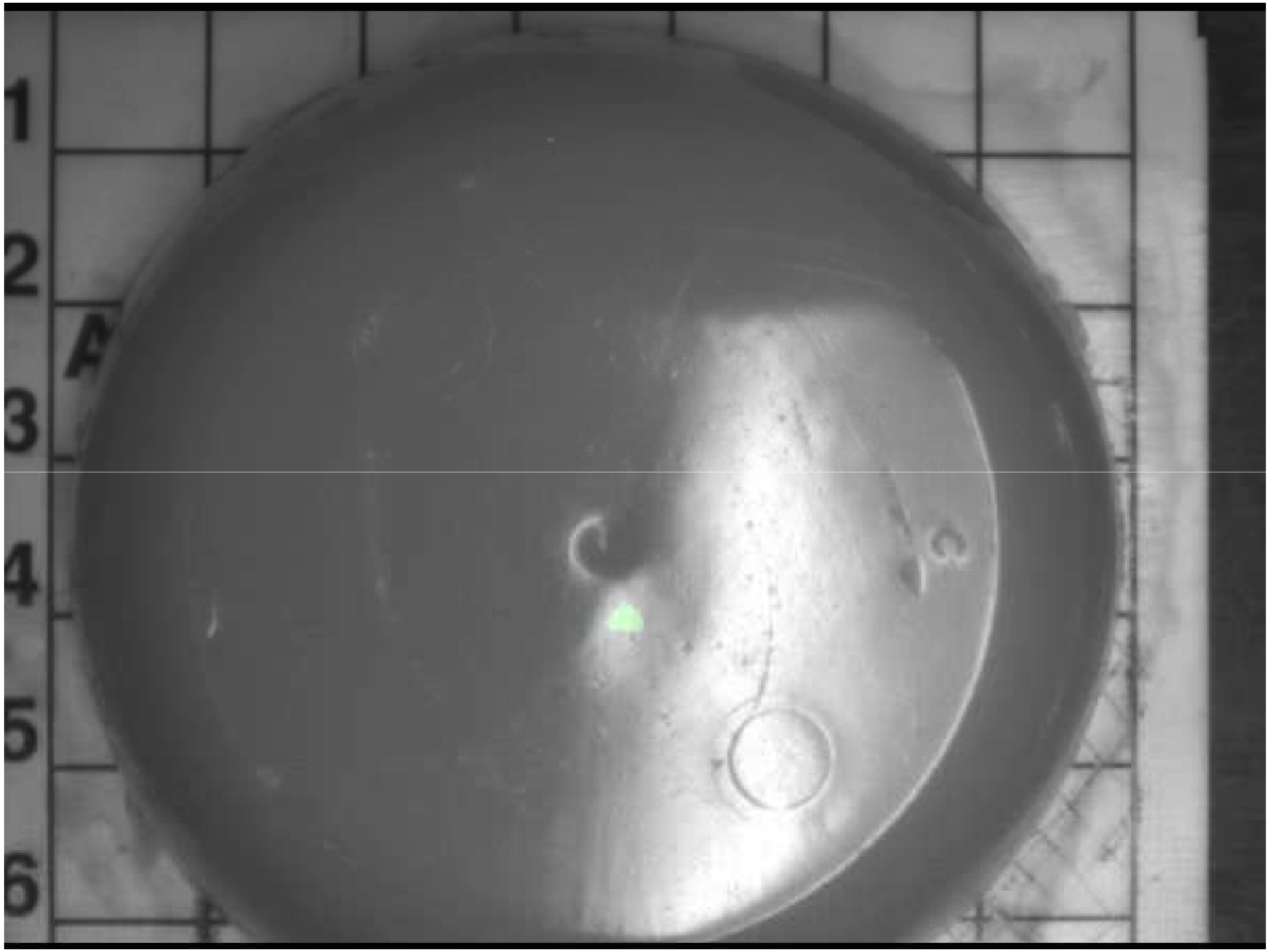
Optical system sensitivity, cont'd

- Well plate filled with IRDye800 in decreasing concentration
- Use Rose criterion to deduct limit of detectable fluorophore concentration

$$K = \frac{|N_{fluorophore} - N_{background}|}{\sqrt{N_{background}}}$$



Example surgery movie



Current Status

- Basic optical/gamma characterization
  - Optimize excitation flux, characterize output of several candidate NIR fluorophores (e.g. depth-dependent resolution and SNR in tumor-simulating phantoms)
  - Fine tune control software for NIR/visible camera

- Carry out a mouse study to confirm the tracer binding affinity to cancer cells

Mouse Study

- Goal: Test the tracer binding affinity to HER2+ tumors
- MDA-MB-435 (control) cells are subcutaneously injected into the right hind of female nude nu/nu athymic mice (6 weeks old). Other six mice are injected with HER2+ cells (LS174T) in a similar fashion
- Tumors are allowed to grow for 2 weeks to reach a diameter of approximately 0.5-1 cc.
- Once the tumor is grown, we would inject the mice with the fluorophore/Tc99m labeled nanobody tracer to evaluate the binding affinity by imaging
- Harvest the tumors post imaging to observe where the probe is located at the cellular level by looking at the histological tumor slices through a NIR microscope

Breast Tumor Margins Study

- Goal: Aid surgery of HER2+ breast tumors and reduce positive margins
- Human-compatible nanobodies that target cells overexpressing HER2+ developed by collaborators at the Vrije Universiteit Brussel (VUB) in Belgium
- Ultimate test for the system and the tracer
- Compare post surgery images looking for positive margins to present practice data

Plans for the future

- Integration of NIR/gamma components
- Design and carry out a human study to characterize the system
- Evaluate the ease of use of the system for the surgeon and follow up to address their possible issues
- Determine the improvement in surgery outcome by imaging post surgery

Questions and Comments

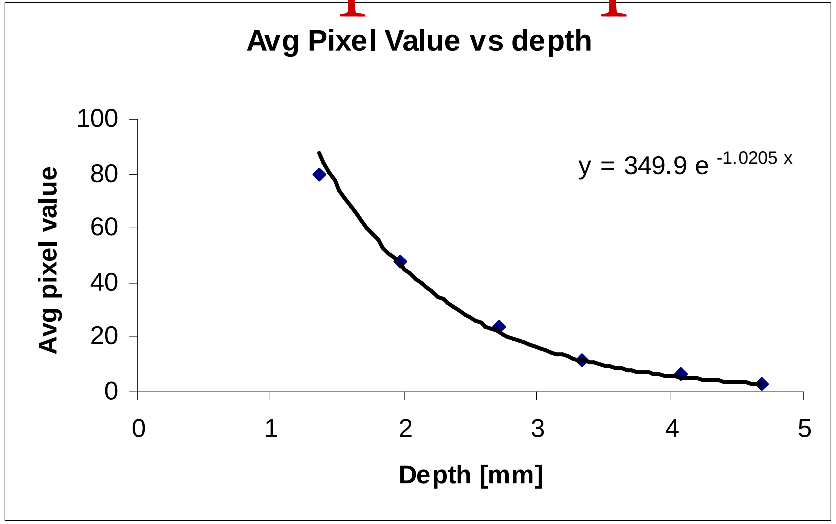
Sentinel Lymph Node Biopsy (SLN)

- Goal: Evaluate ease of use of the system to the surgeon and determine its performance independently of the labeled tracer
- Non-targeted fluorescent contrast agent and gamma tracer injected intradermally and circumferentially around the primary lesion or the scar from biopsy of the primary lesion for sentinel lymph node biopsy
- The tracers are secreted to the lymph nodes (eliminates possible issues stemming from tracer binding to the tumors) and guided by IMIS to allow testing solely the imaging system
- Lymph nodes size compared pre and post resection

Advantages over present practice

- More streamlined pre-operative and intraoperative procedures
- Specifically, in tumor margin delineation
  - Lower re-excision rates / Smaller excised tissue volumes
  - Does not require dedicated pathology team on standby
  - Can be used in palpable and non-palpable excisions
  - Decreased anesthesia time / cost

Verification of optical phantom mu



Limit of detectable fluorophore concentration