Imaging Arrays for Medical Applications

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Carestream Health

RIT Quantum Limited Detector Workshop
March 2009

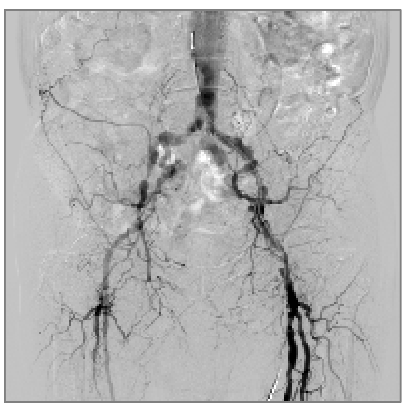
Carestream HEALTH

Outline

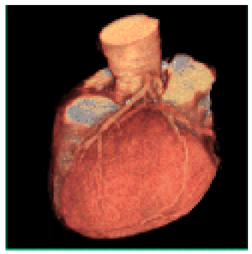
- Introduction to medical imaging modalities
  - MEV
    - PET, SPECT
  - KEV
    - CT, X-Ray
  - EV
    - Molecular Imaging, Endoscopy, NIRS
  - mEV
    - Ultrasound, MRI
- Radiography
- Molecular Imaging
- Applications for Quantum Limited Detectors

Medical Imaging Modalities

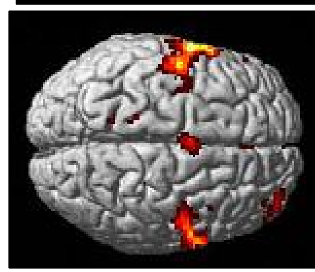
X-ray systems

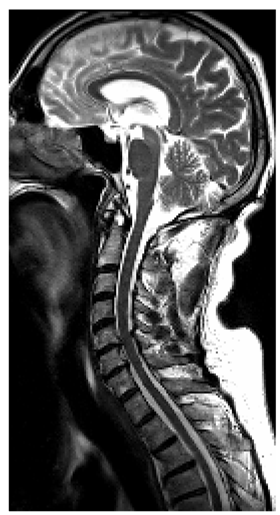


CT

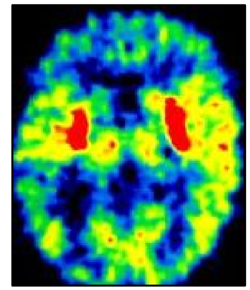


MRI





SPECT/PET

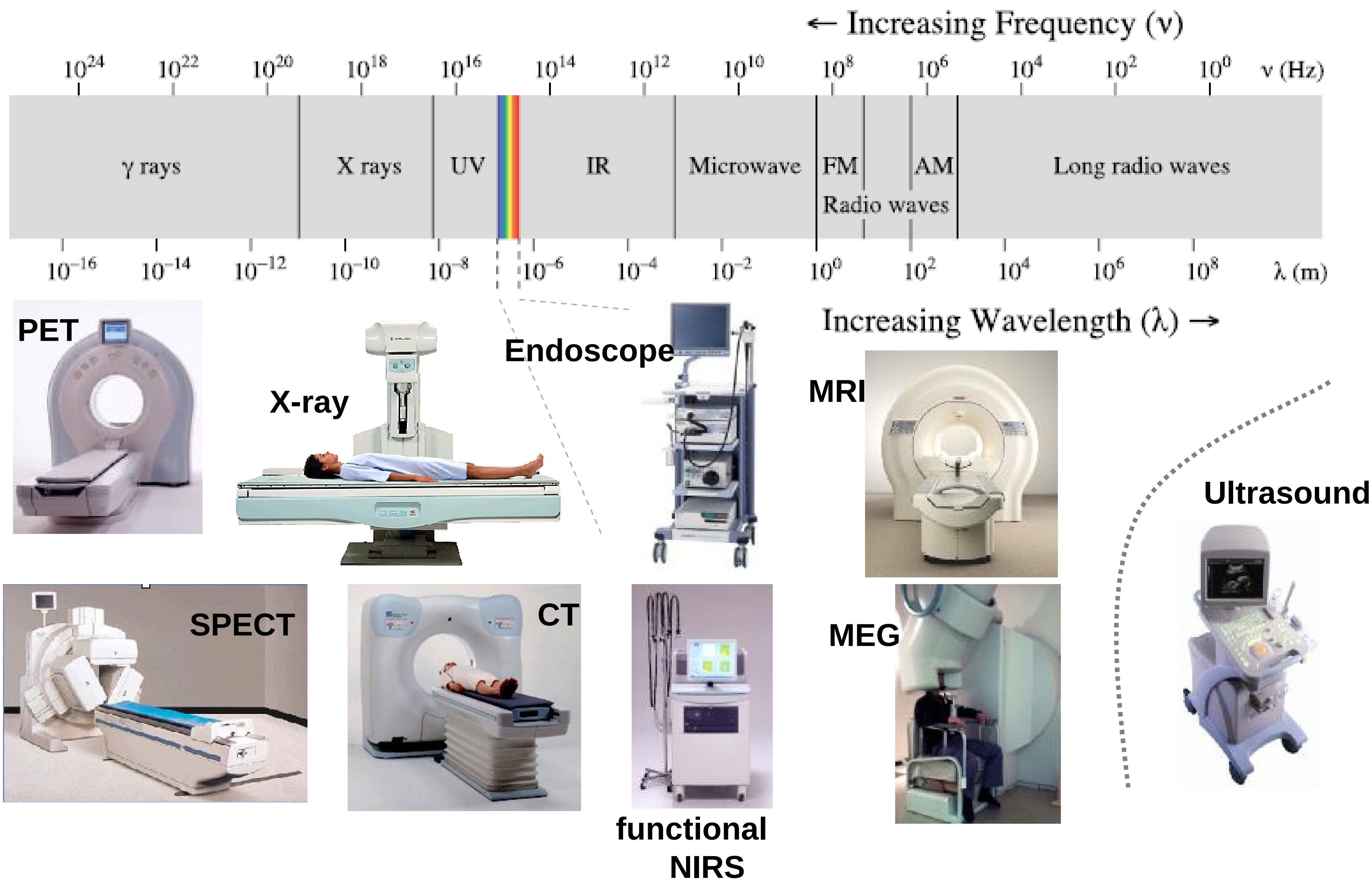


Endoscope

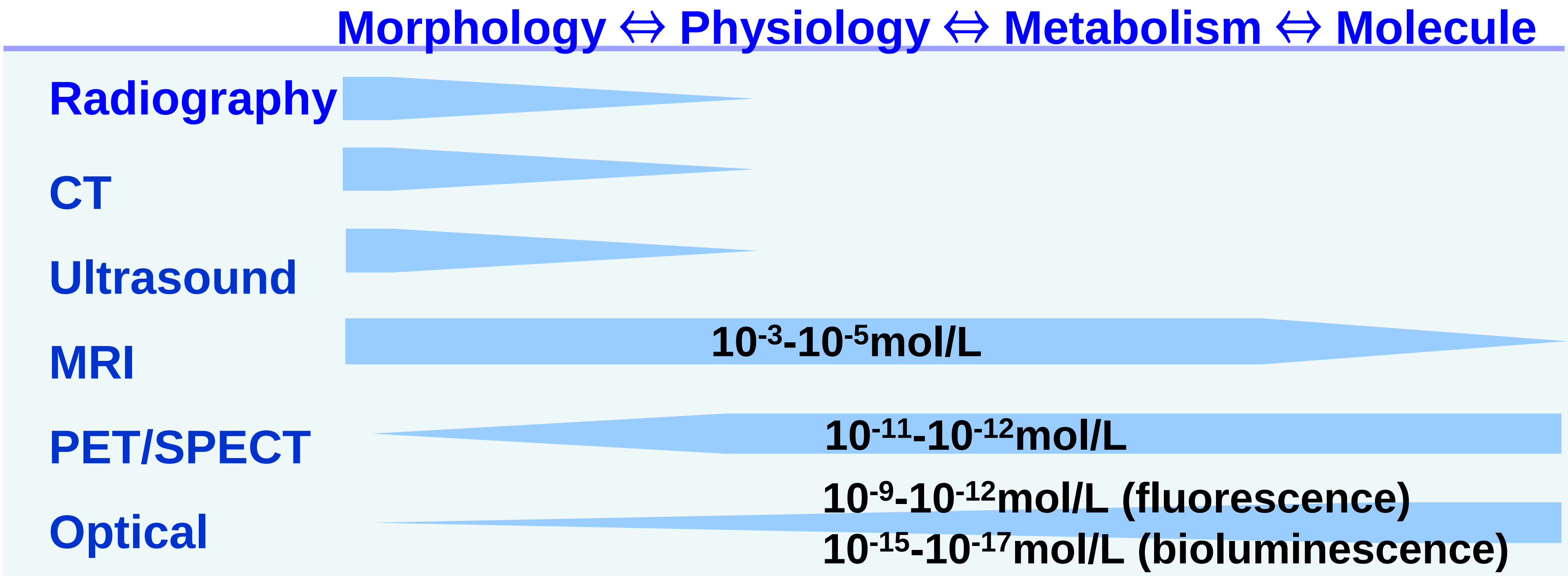
Ultrasound

Imaging Sources

(add THz imaging)

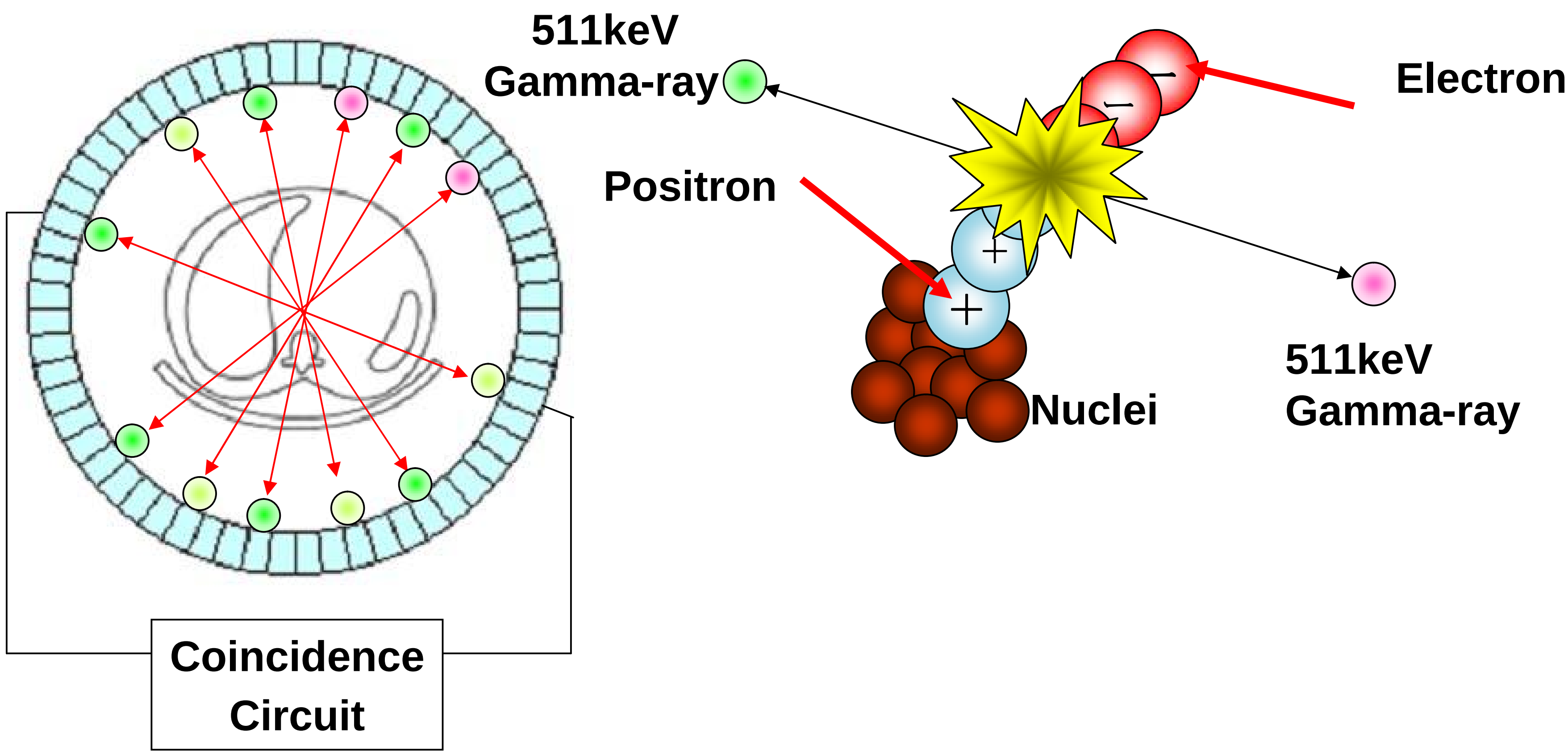


Imaging Targets

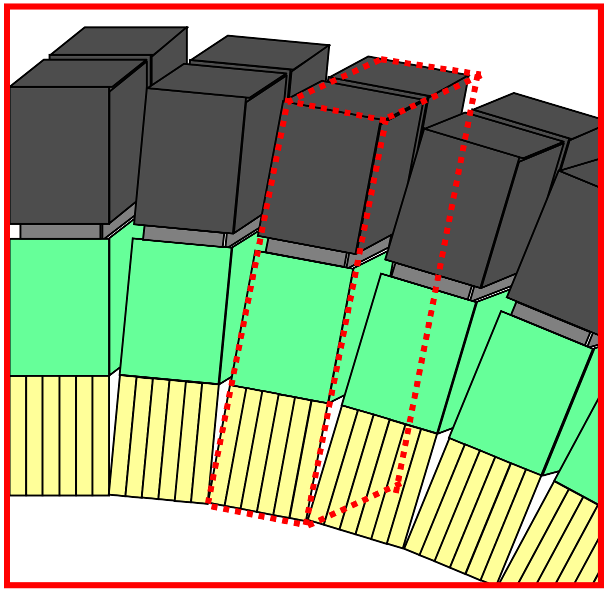


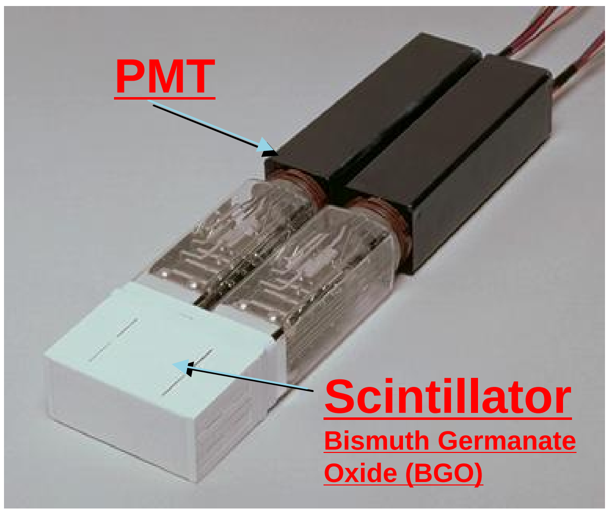
TF. Massoud et al. GENES & DEVELOPMENT 2003

Imaging MEV Photons
PET (Positron Emission Tomography)

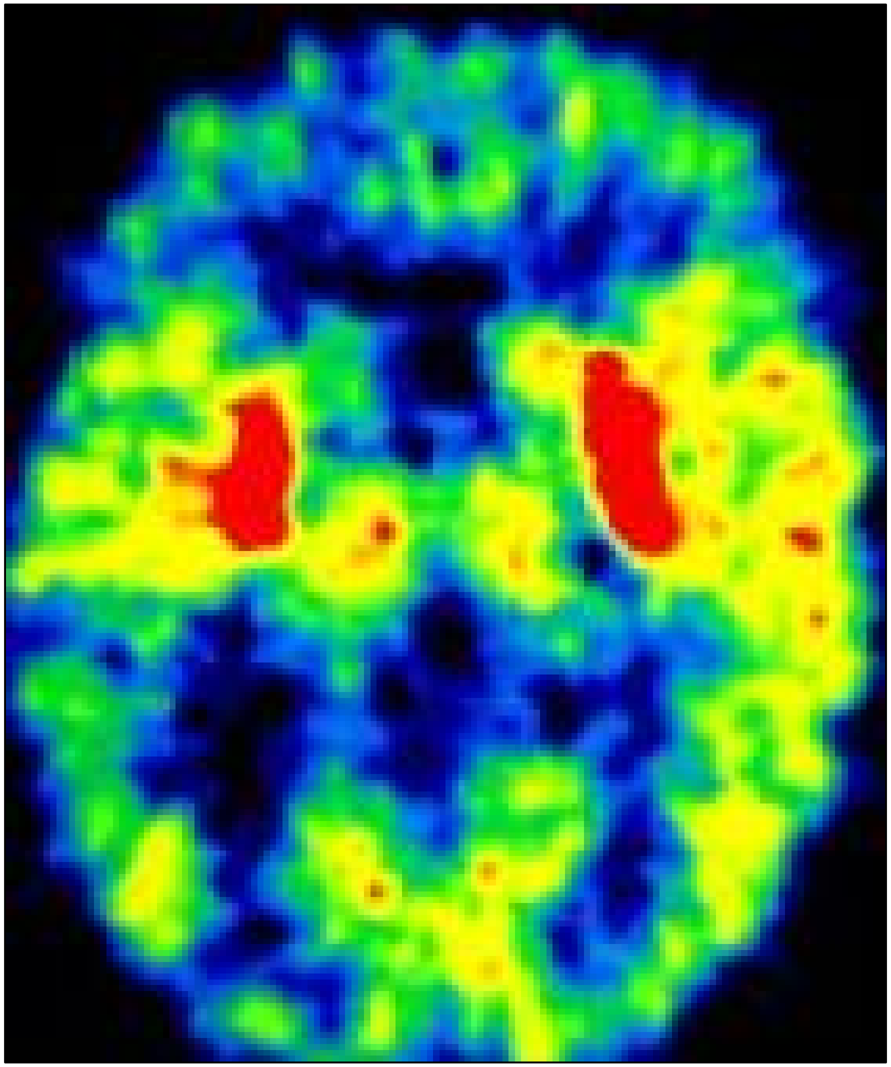


Imaging MEV Photons
PET (Positron Emission Tomography)



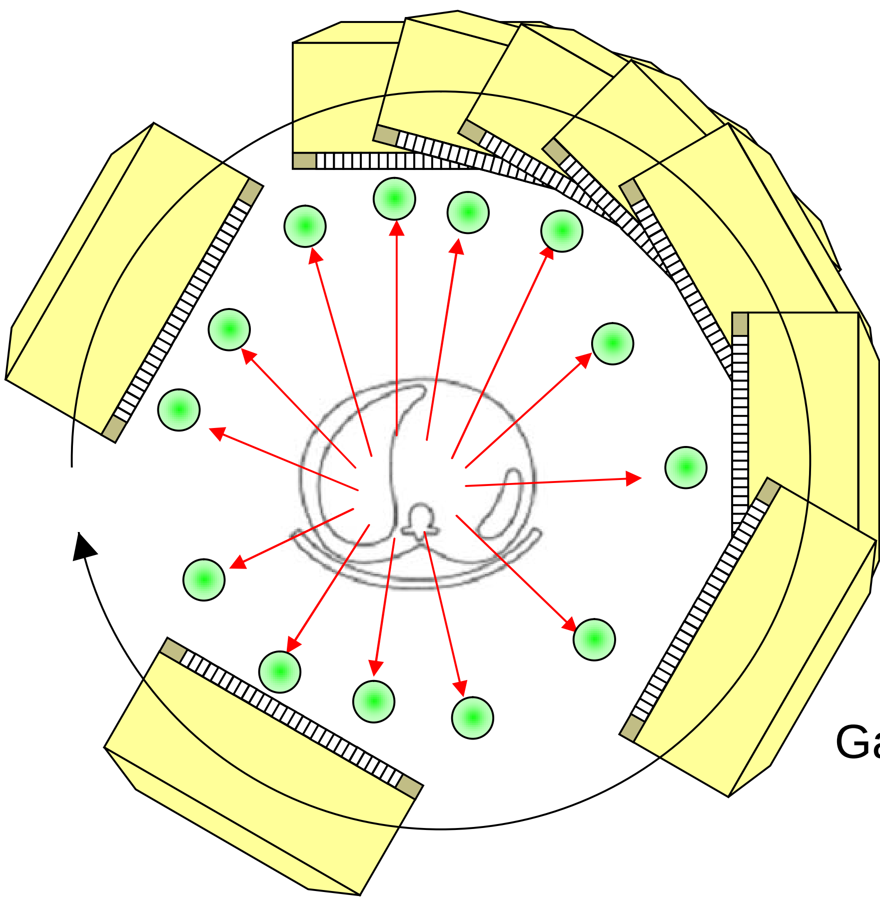


Detector Module

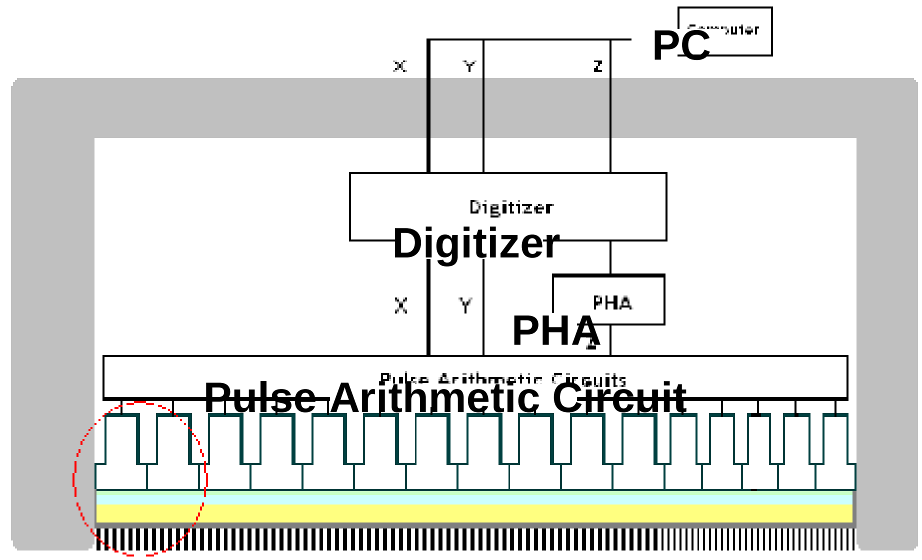


Imaging MEV Photons

SPECT (Single Photon Emission Tomography)

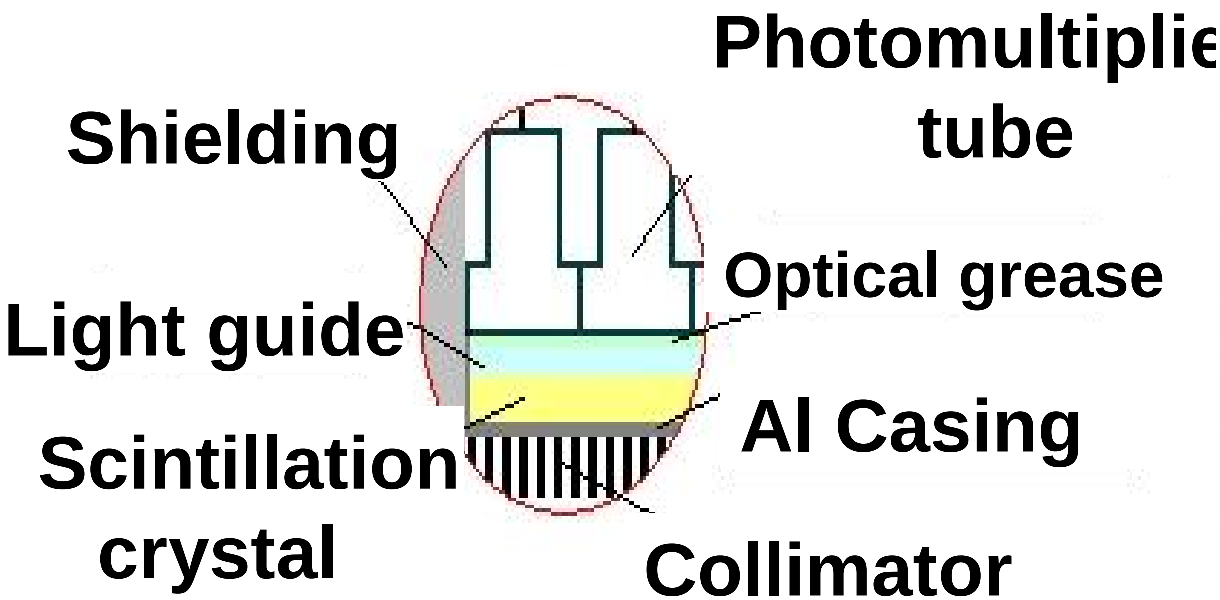


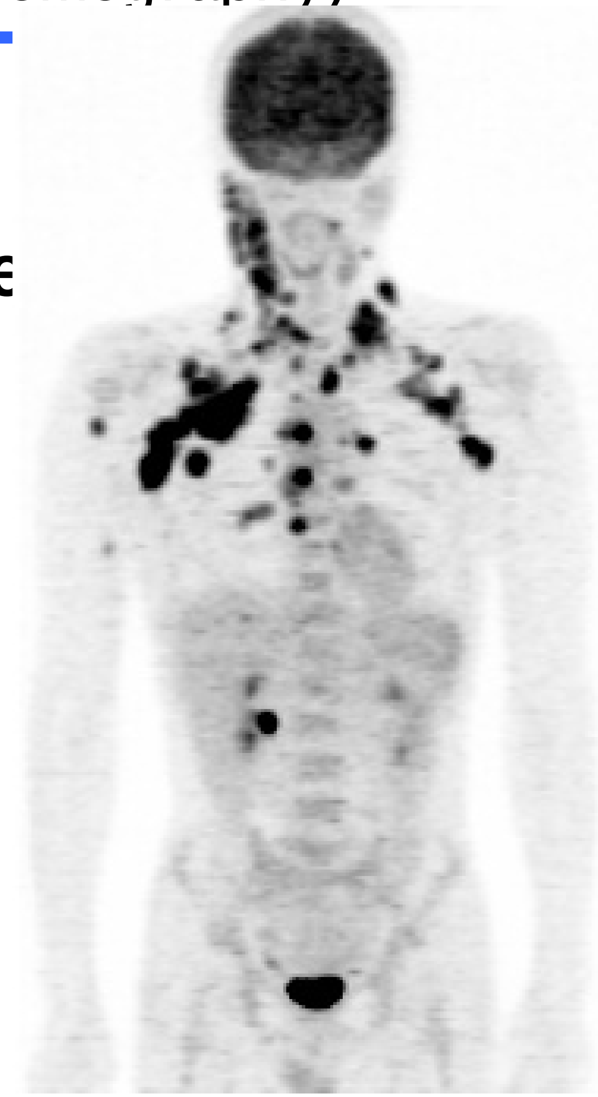
Gamma ray detector module



Imaging MEV Photons

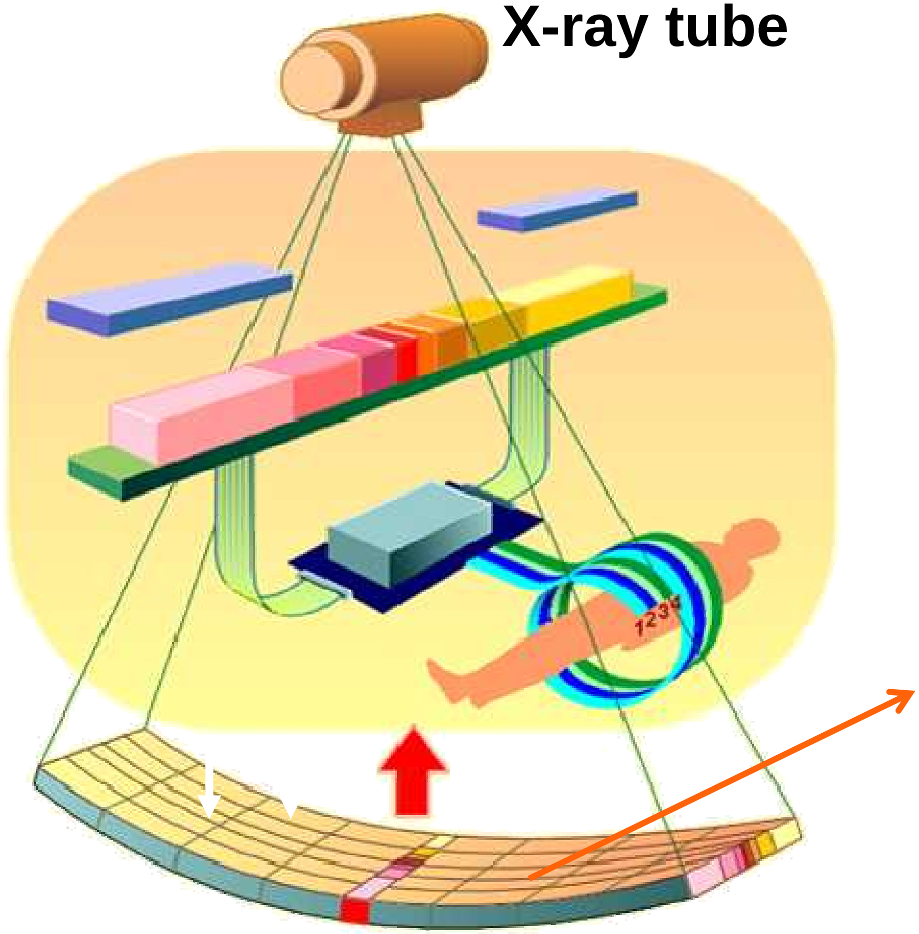
SPECT (Single Photon Emission Tomography)

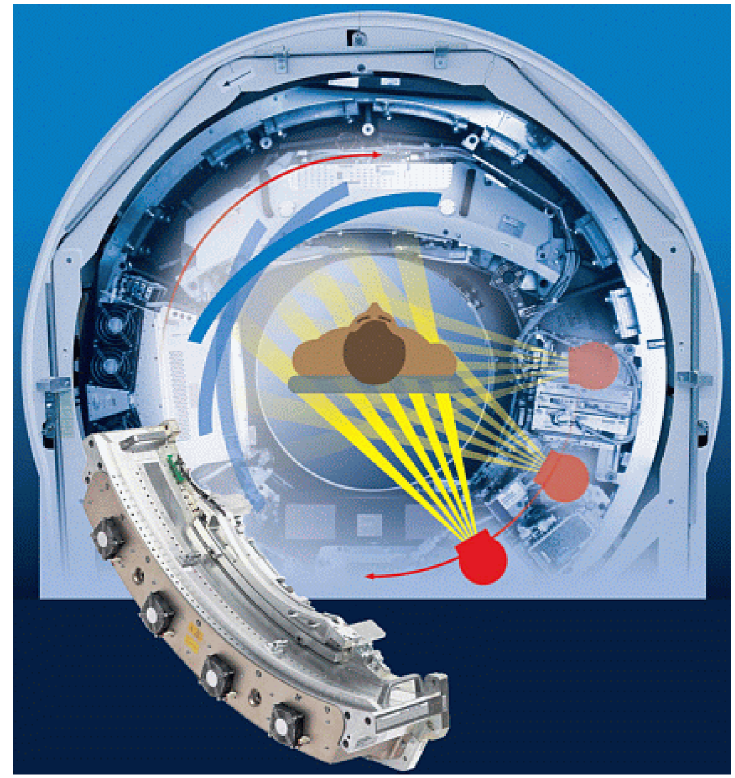




- SPECT identifies regions of abnormal uptake or deficit of a radiotracer
- Often combined with CT for attenuation correction and registration

Imaging KEV Photons
CT (Computer Tomography)



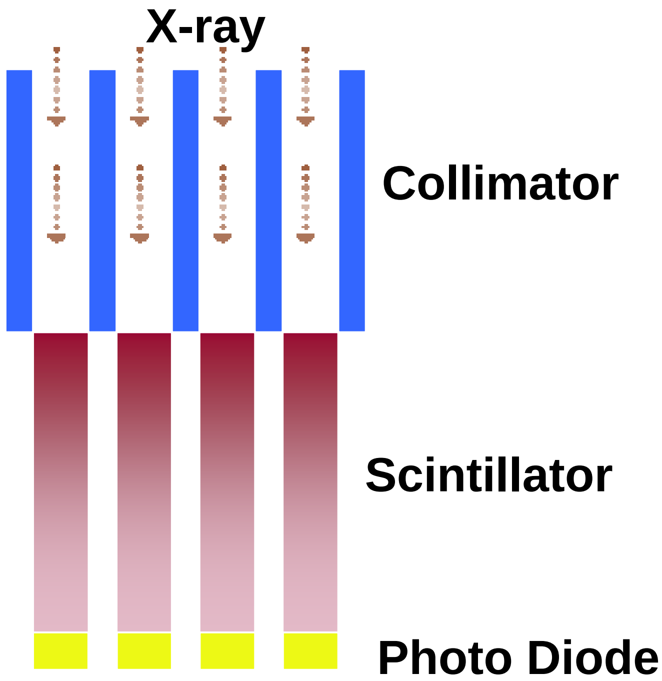


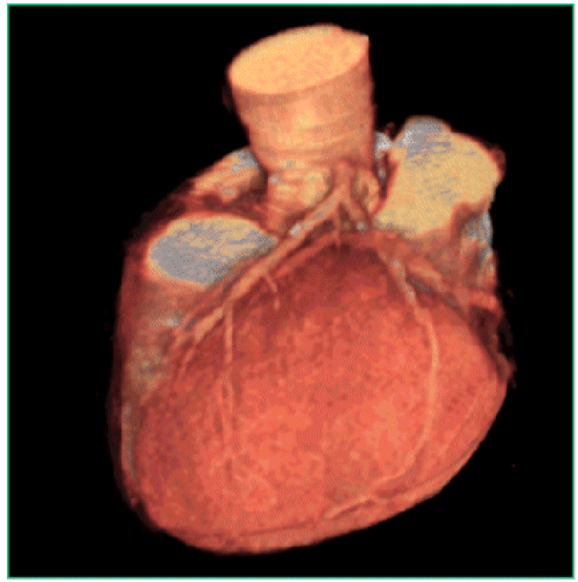
multi-slice detector

- **0.5 – 2 mm detector**
- **~ 32-256 detectors**

First dual-energy systems coming to market

Imaging KEV Photons
CT (Computer Tomography)



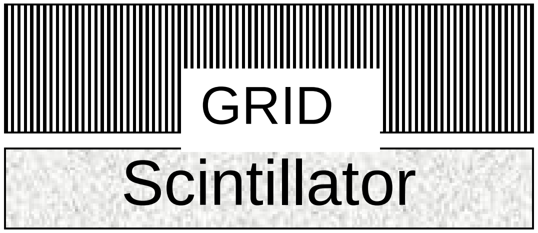


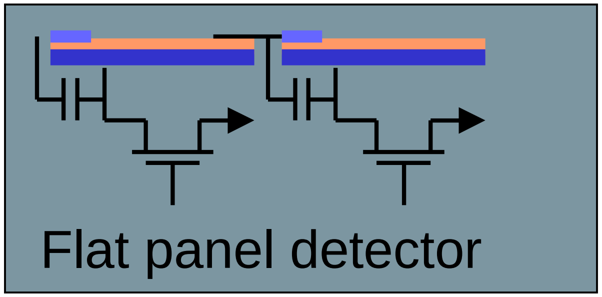
- Future CT systems may move to flat-panel detectors if the noise can be sufficiently reduced
  - Higher resolution (100 μm vs. 500 μm)
  - Larger area coverage
  - Allows area detection of entire organs without helical scan
  - Allows dynamic imaging of organs – such as dynamic angiography
- Being explored by GE and Siemens

Imaging KEV Photons
Radiography

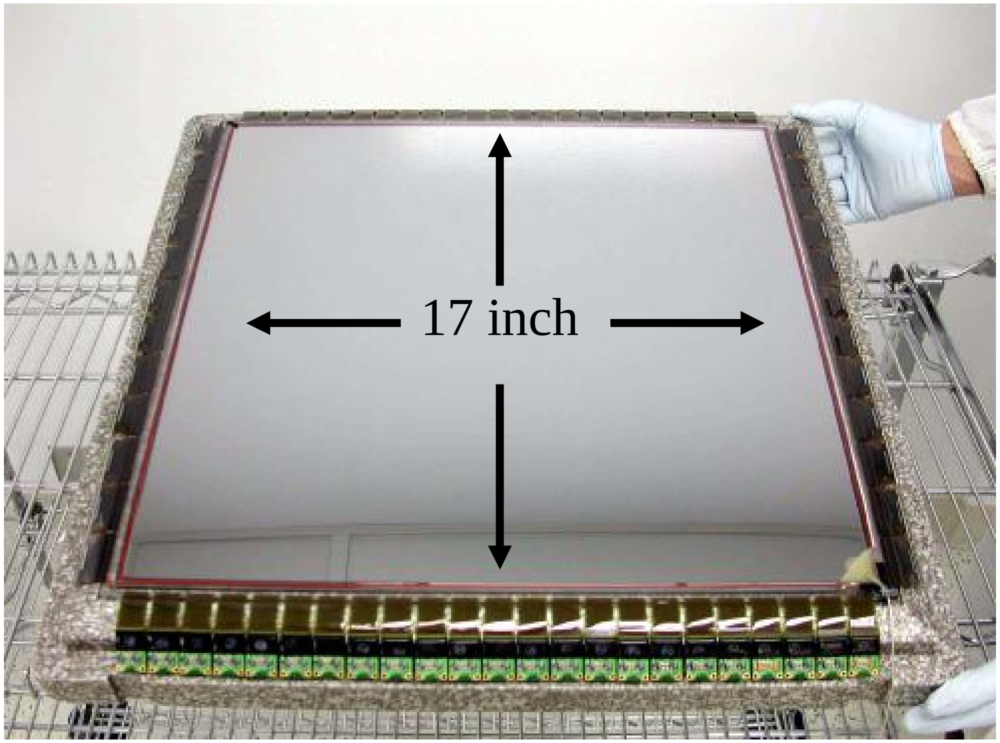
Generator
(10 – 100 KEV)

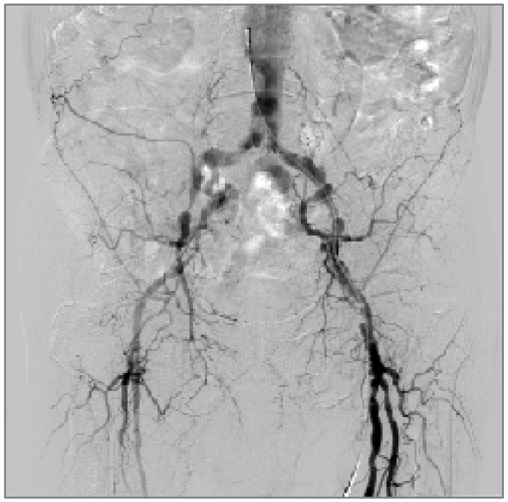
X-Ray Filter
(Al)





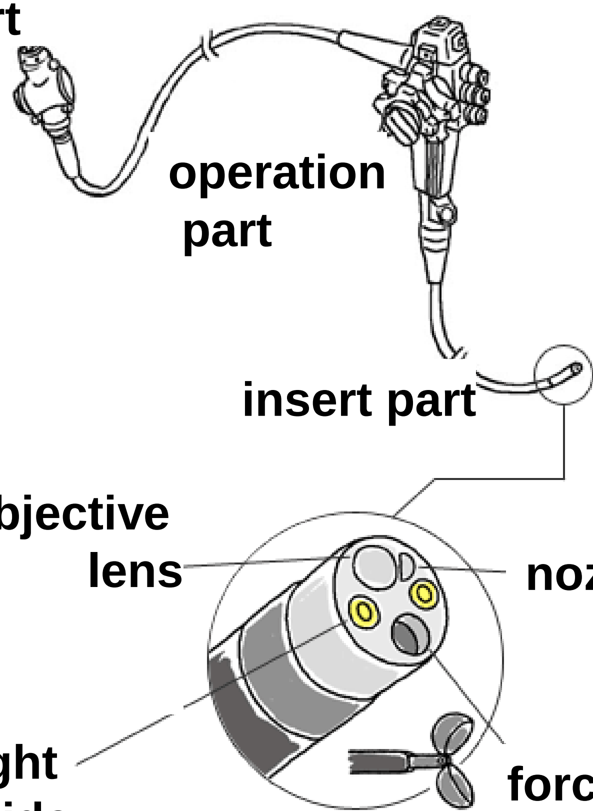
Imaging KEV Photons: Radiography
a-Si:H Flat-Panel Array: Very Large Area



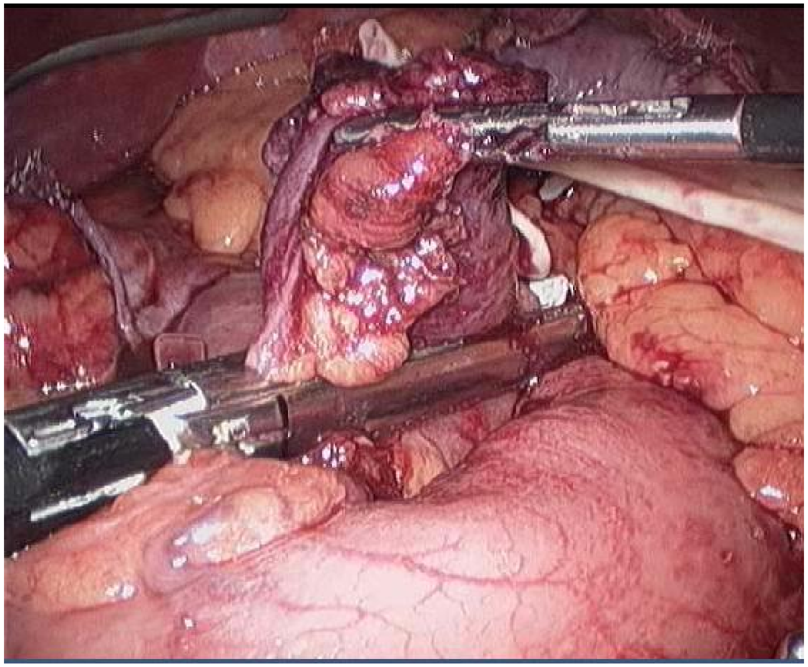


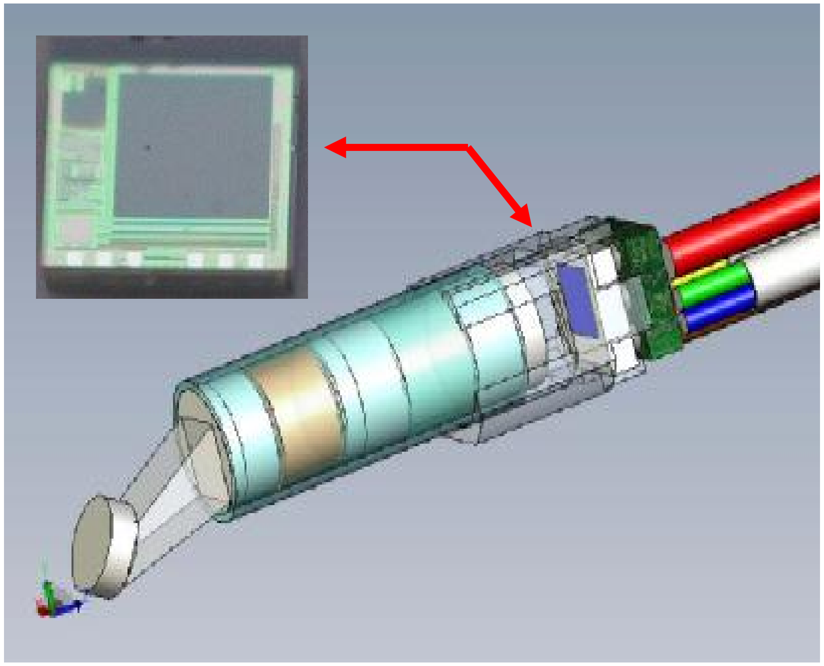
(Image courtesy Dr. B. Polischuk, Anrad Corp.)

Imaging EV (vis-IR) Photons
Endoscope Imaging



Imaging EV (vis-IR) Photons
Endoscope Imaging

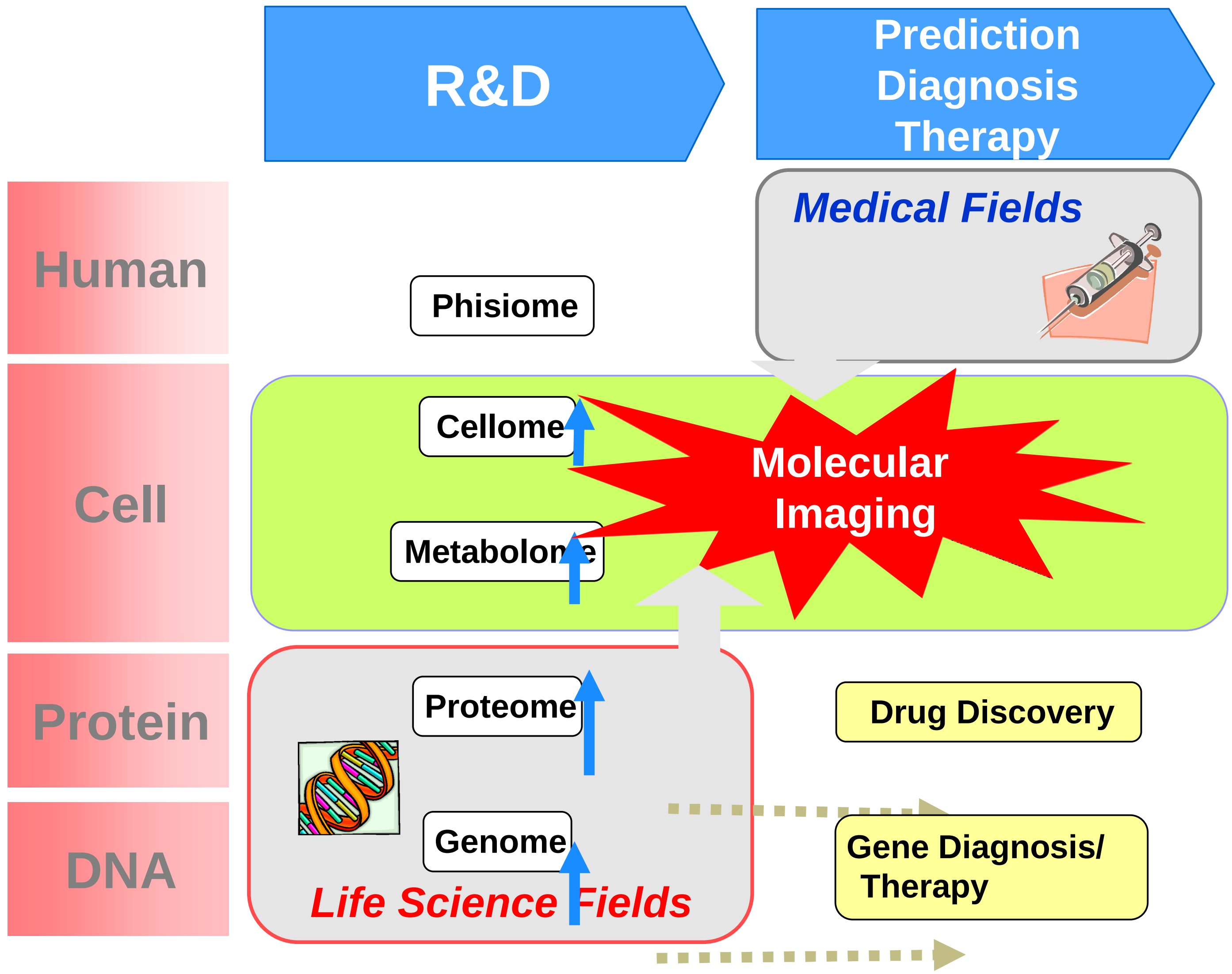




Color Image Sensors for Endoscopic Imaging

- Small area
- Low power
- Highly integrated – few leads
- High resolution
- Withstand autoclave temperatures
- Future - stereoscopic

Imaging EV (vis-IR) Photons : Molecular Imaging
Biomedical Field

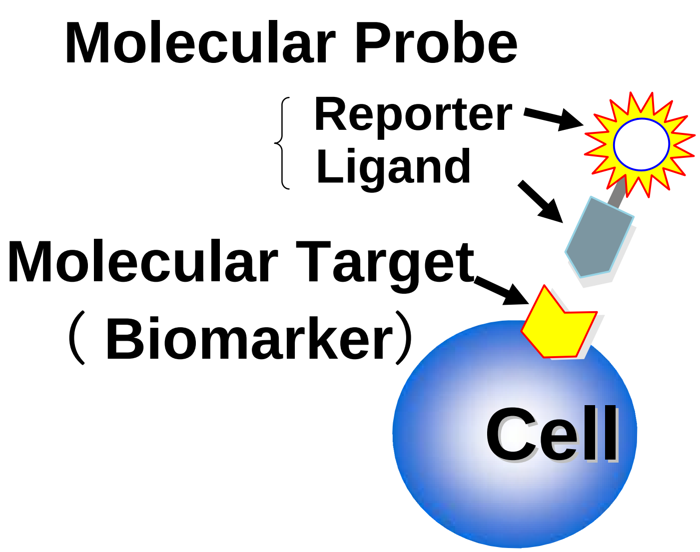


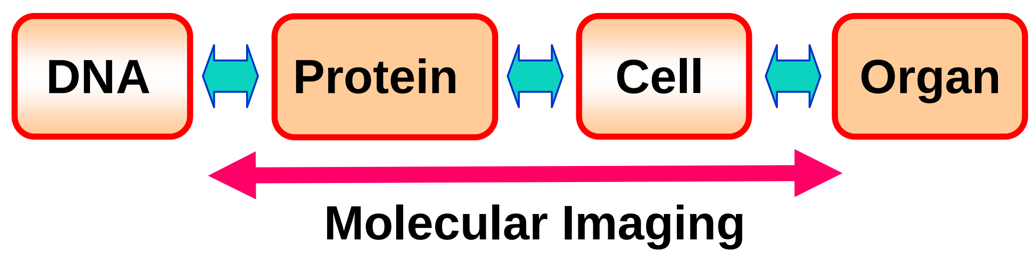
Imaging EV (vis-IR) Photons
Molecular Imaging

"MI techniques directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications."

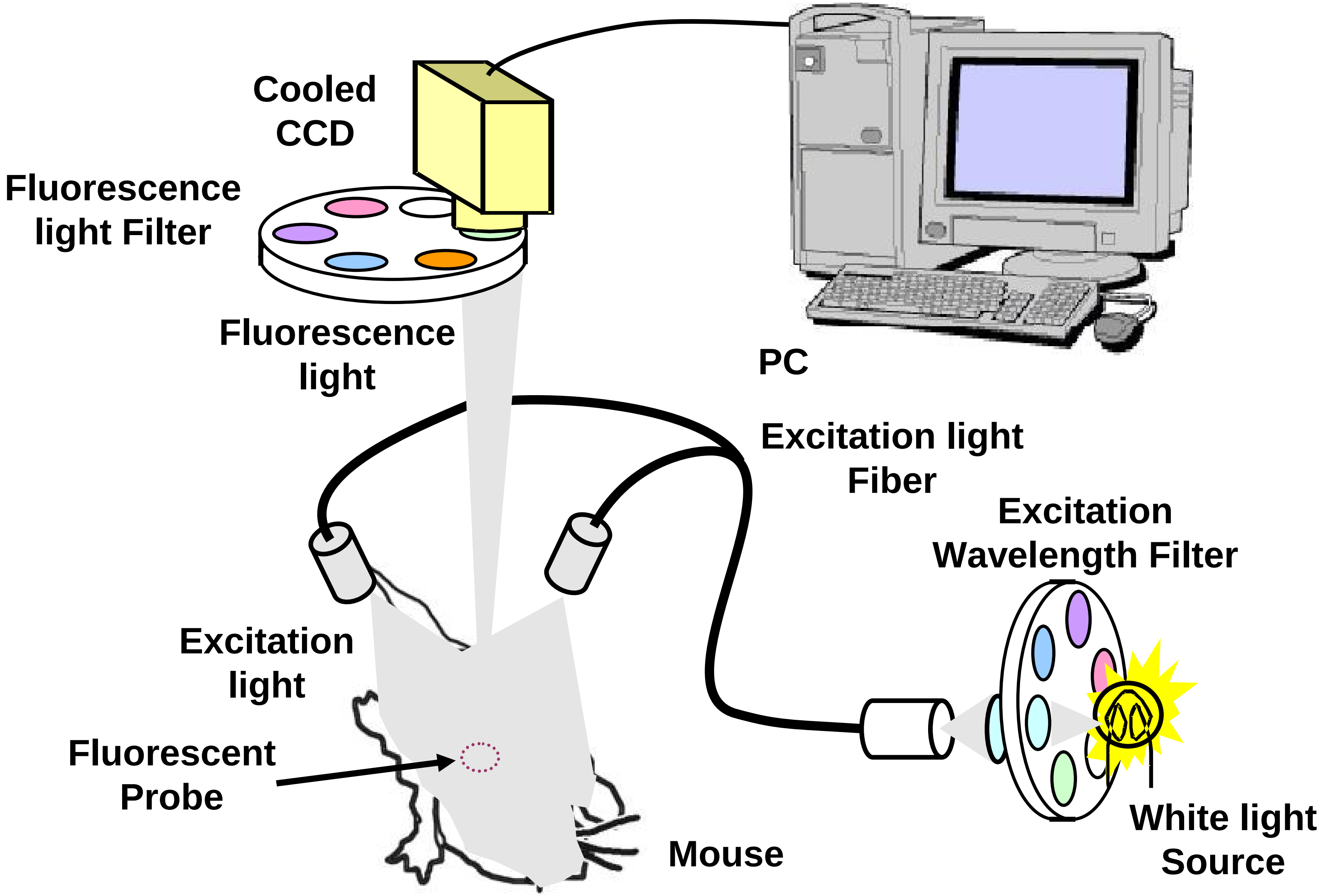
"Report of a Summit on Molecular Imaging" Radiology 2005

- ***in vivo***
- ***cellular or molecular level***
- ***imaging***

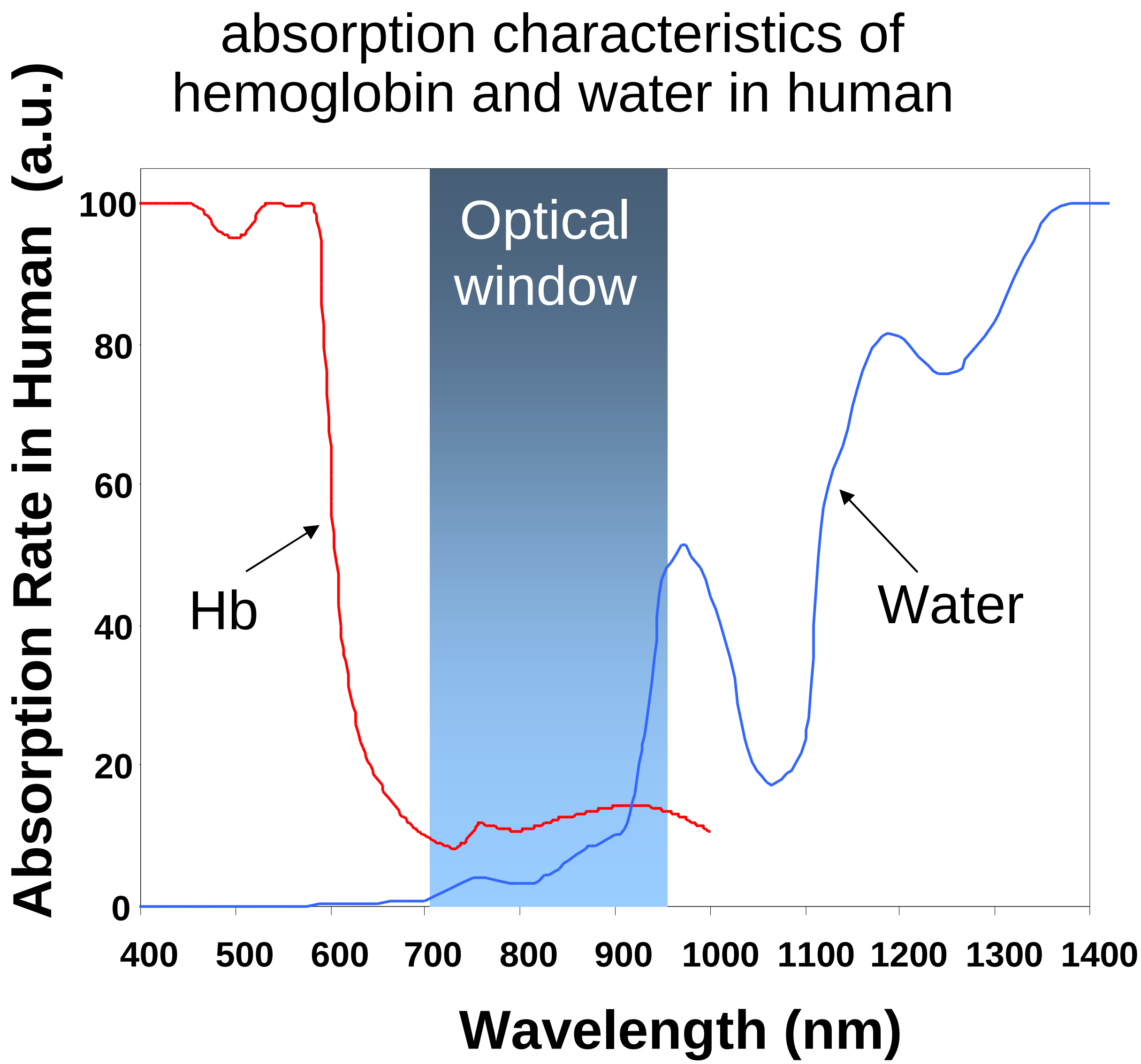




Imaging EV (vis-IR) Photons
Fluorescence Imaging



Imaging EV (vis-IR) Photons: NIRS
Optical Absorption Characteristics



Imaging EV (vis-IR) Photons: NIRS

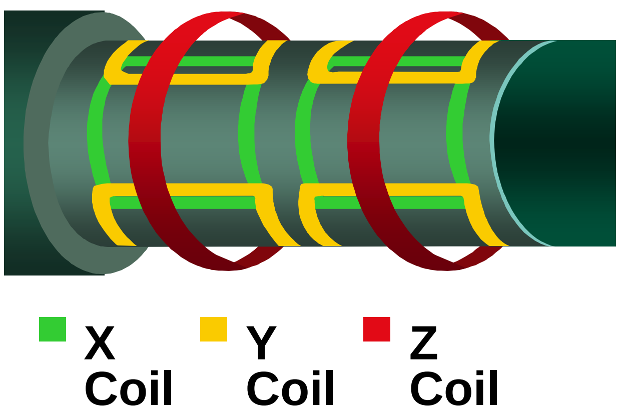
Optical Constants and Transparency of Living Subject

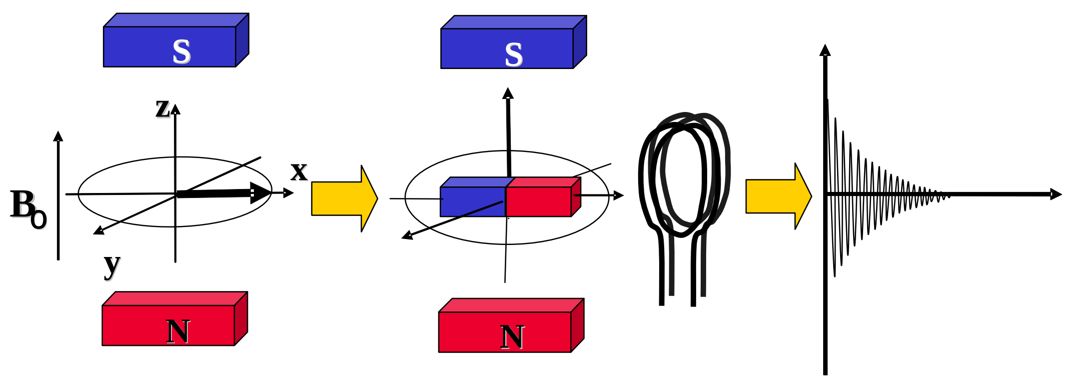
Wavelength (nm)	Absorption (cm^{-1})	Scattering (cm^{-1})	$L_{1/10}$ (mm)
400	47.00	18.00	**0.46**
450	36.00	16.00	**0.55**
500	12.00	13.00	**1.06**
550	23.00	11.00	**0.84**
600	9.60	8.90	**1.44**
650	2.70	7.60	**2.93**
700	1.50	6.80	**4.16**
750	1.30	6.50	**4.57**
810	0.72	5.60	**6.62**

1 mm ↓ 1/10

6 mm ↓ 1/10

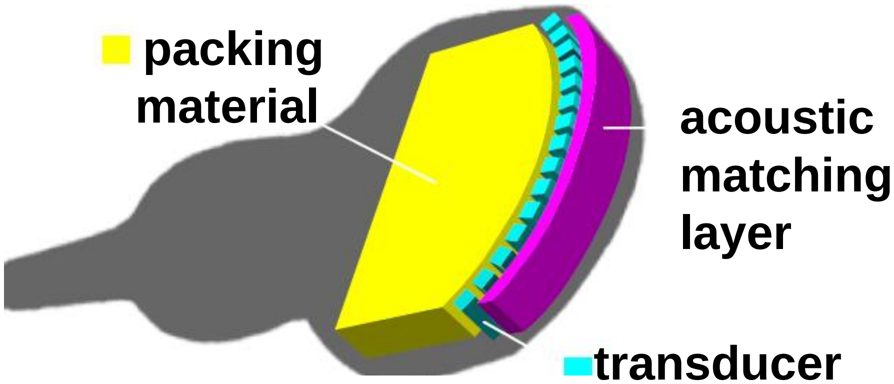
Imaging mEV Photons
Magnetic Resonance Imaging (MRI)

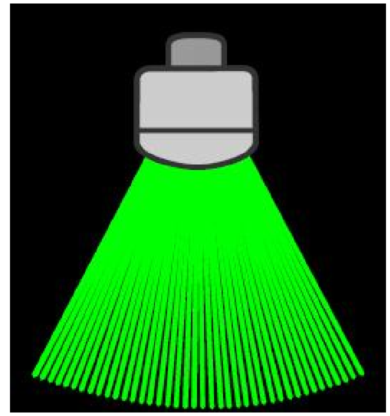




Electromagnetic induction current

Ultrasound Imaging





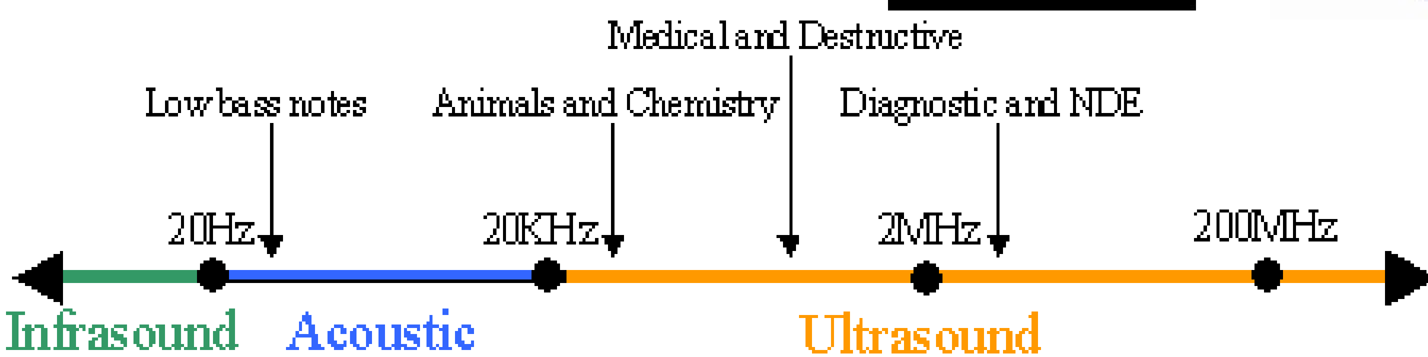


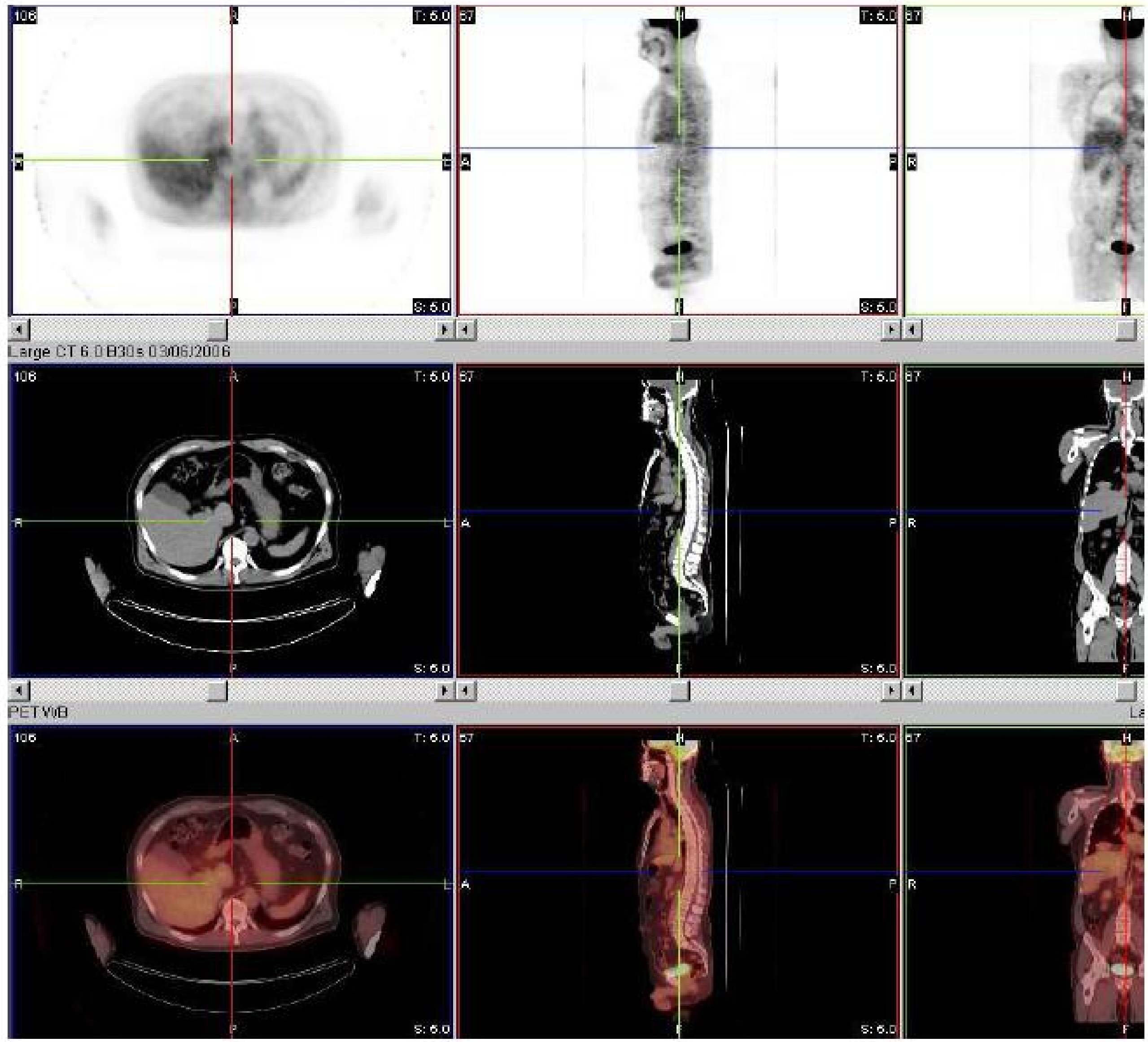
Image Fusion
PET and CT

PET Only

CT Only

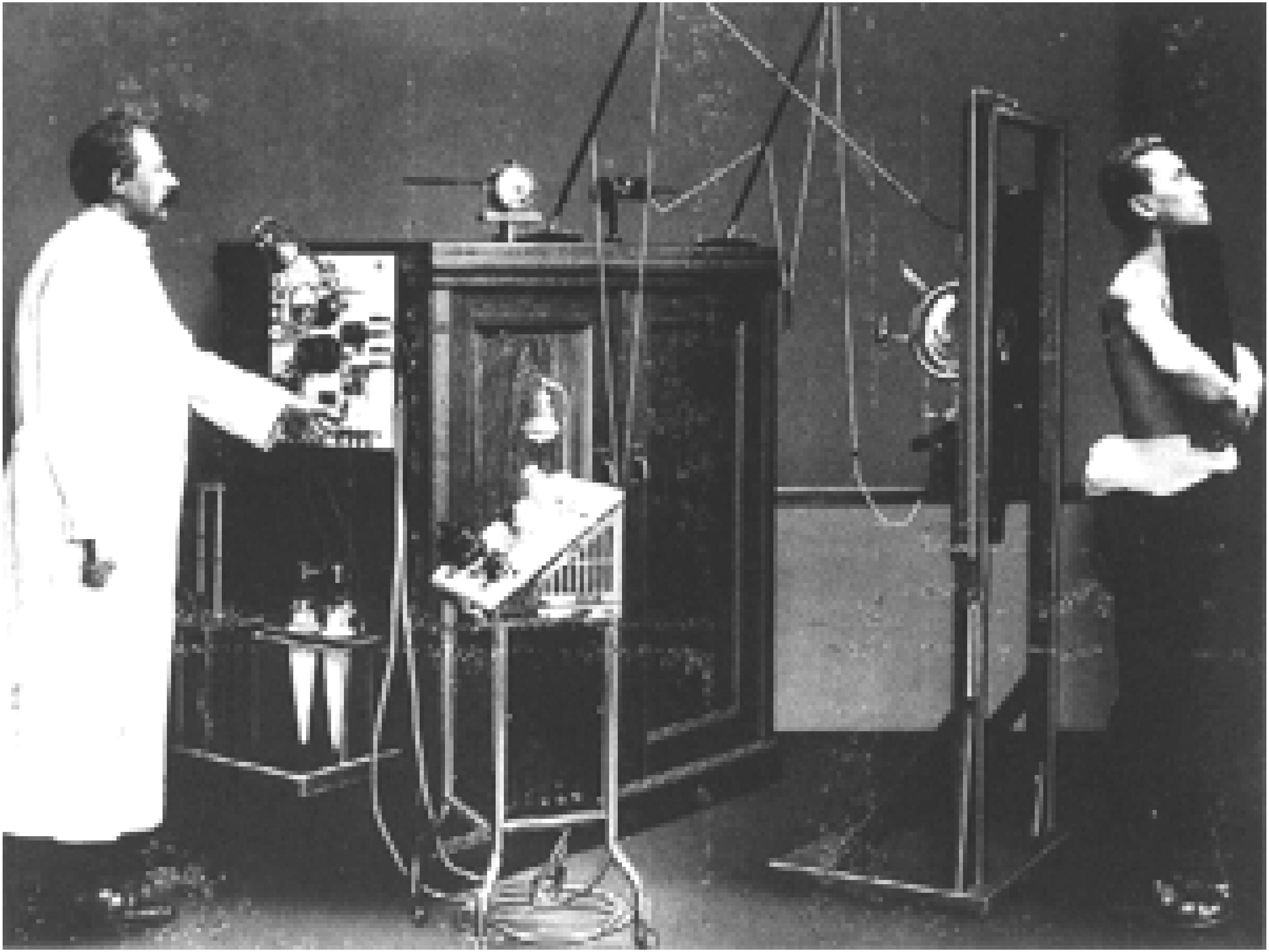
- Anatomy
- Construct density map for absorption correction

Fused Images



Outline

- Introduction to medical imaging modalities
  - X-ray, CT, MRI, SPECT, PET, Ultrasound, Endoscope, NIRS
- Radiography
  - Introduction to digital radiography
  - Clinical challenges
  - Amorphous silicon imaging arrays
  - LTPS silicon imaging arrays
  - Silicon imaging arrays
- Molecular Imaging
- Applications for Quantum Limited Detectors



DR: “Digital” Radiography

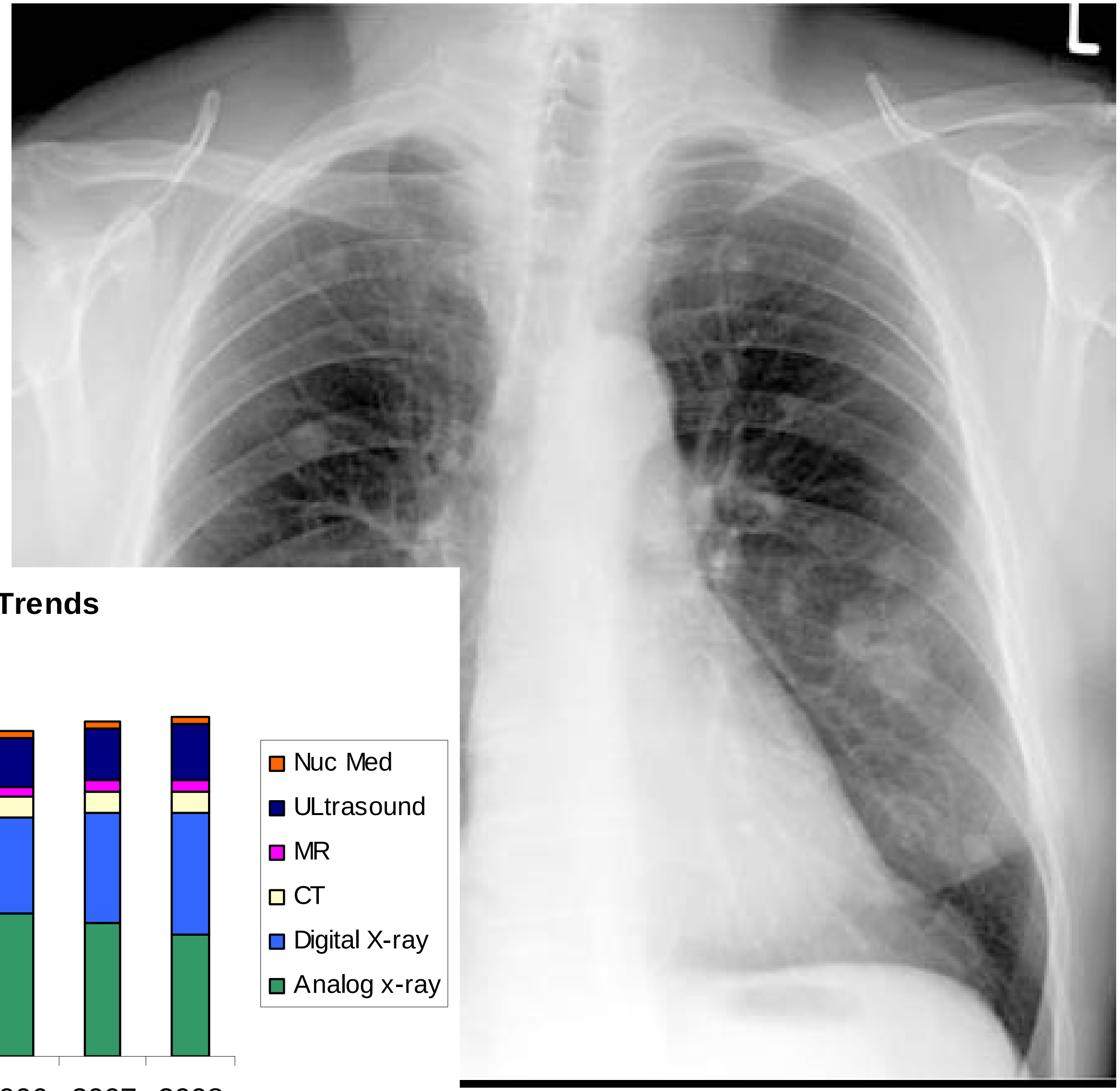
DR: 1 step acquisition with electrical “scanning”

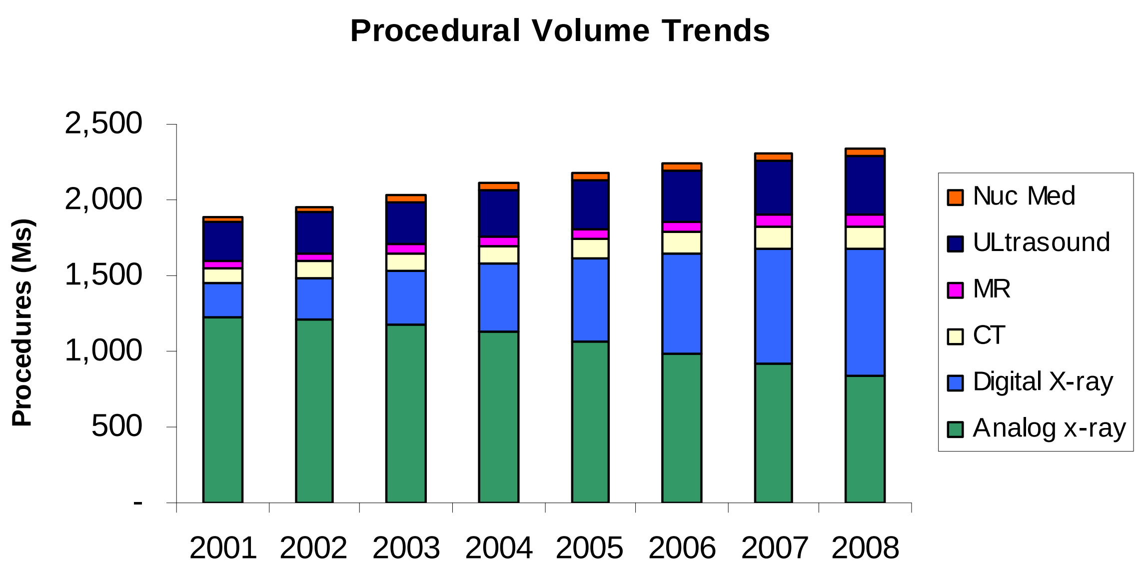
“Flat panel” and CCD based technology (introduced ~1995)

(Courtesy Imaging Dynamics Corp.)

2 Dimensional Projection Radiography

- Still most common exam
- >1.5x10^9 exams per year
- Chest imaging most common

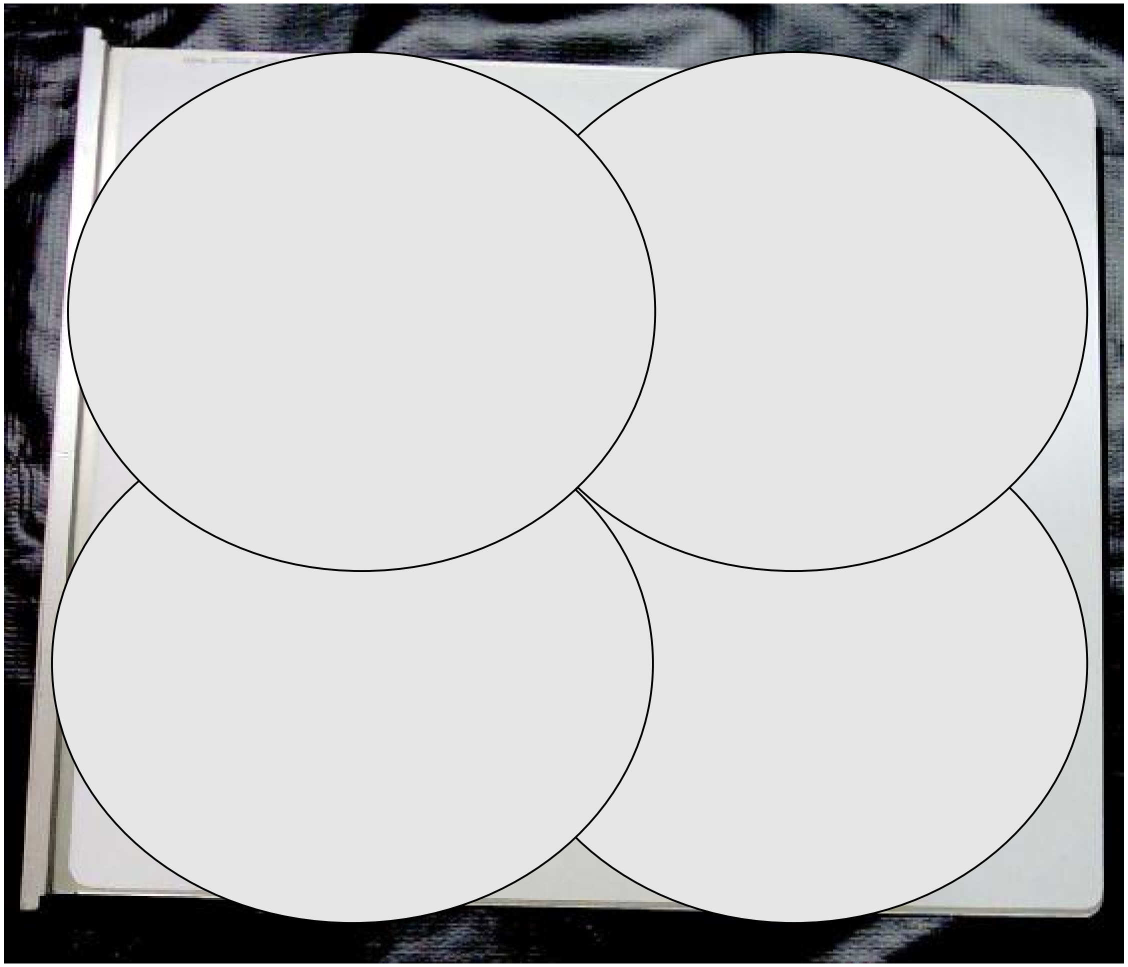




CCD Based Systems

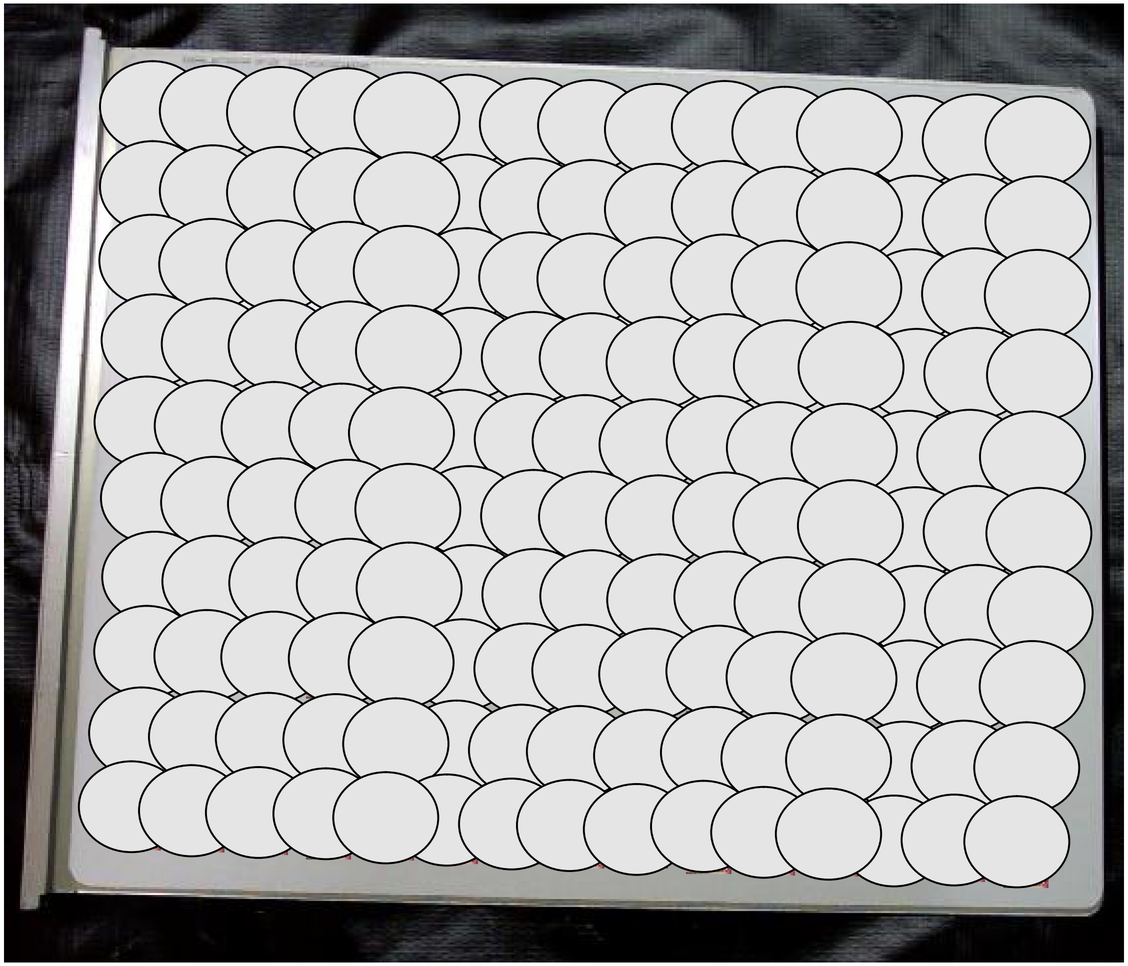
Fundamental issue with size of CCD

Multiple CCD Configuration

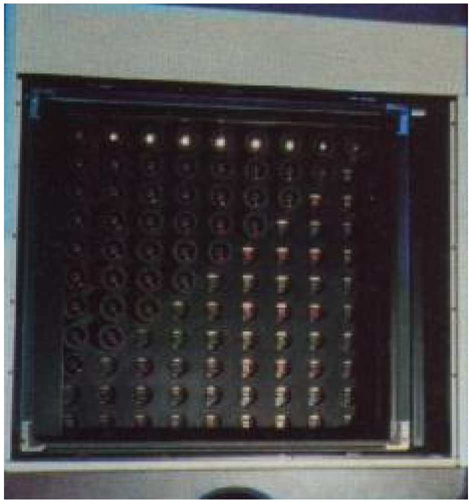


- SwissRay and Apelem
  - Reduces de-mag.

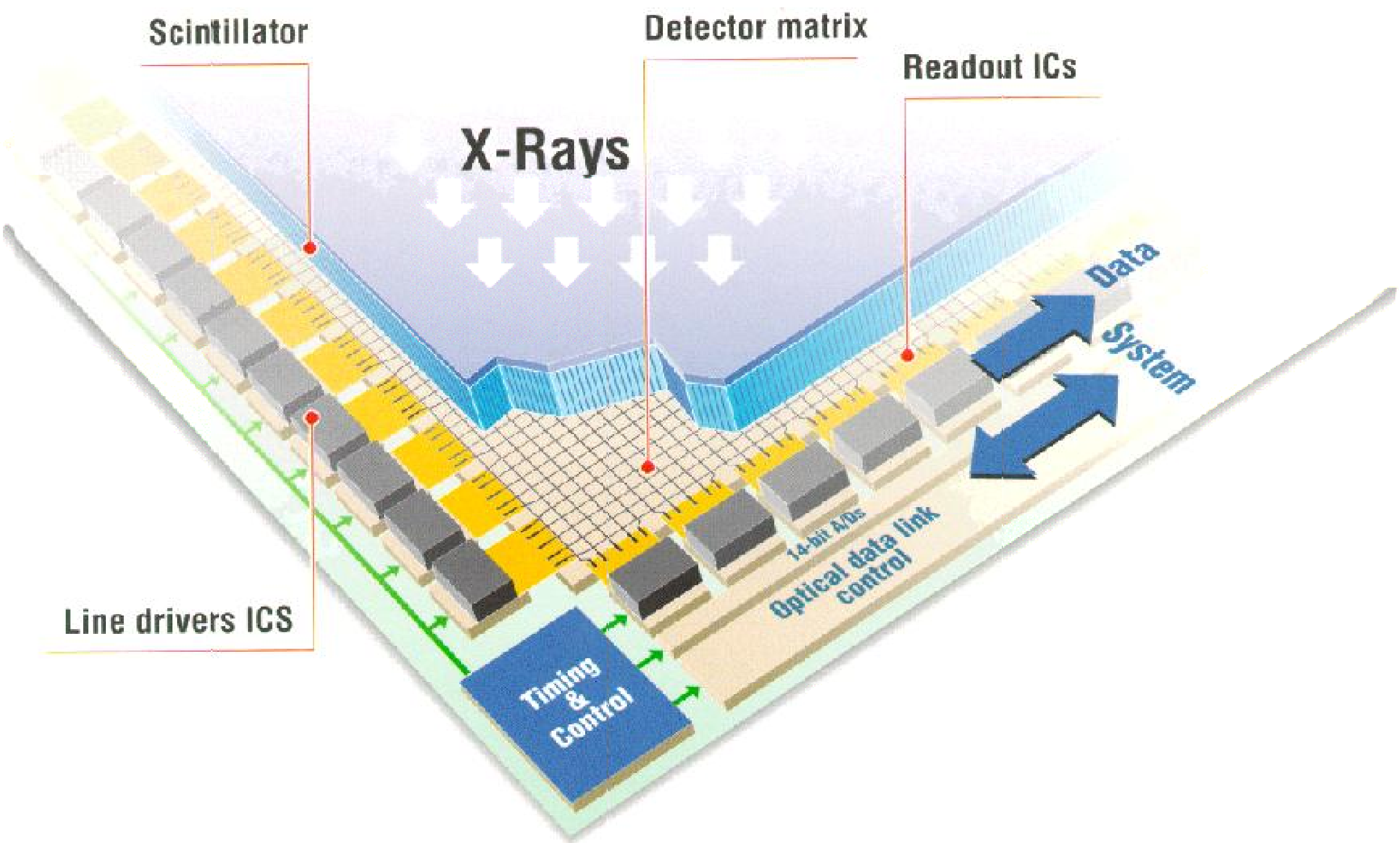
Multiple CMOS Configuration



- CaresBuilt & Star V-Ray
  - CMOS.... cheap
  - Stitching an issue !



Flat-Panel Detector Construction



Flat-panel Detector Construction

Image courtesy Mr. K. Schwarz, Direct Radiography Corp.

System Configuration

X-ray Generator

Synchronization Control
(enables “Advanced Applications”)

Detector housing
Grid and AEC

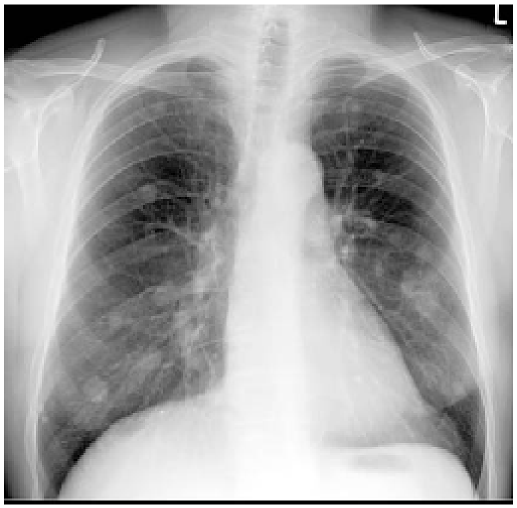
Control PC and PACS

Flat-Panel Detector Advantages

- Highest image quality due to high collection effic.
- Inherently digital information
  - Allows quantitative analysis of image information
  - Allows easy distribution to remote destinations
- One step acquisition of images
  - Fast delivery of image
  - Improves efficiency of workflow
- Significantly reduced profile & weight
- No geometric/magnetic distortion
- Computer controlled & integrated with x-ray delivery
  - Enables advanced applications

Current Clinical Situation

General Rad.



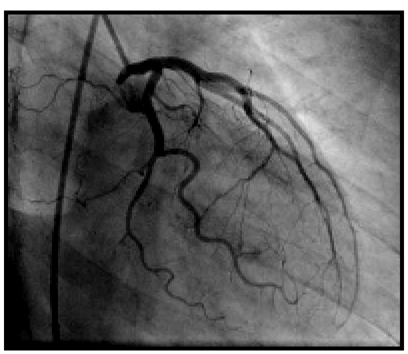
Mammography

Flat-Panel Detectors

Megavoltage

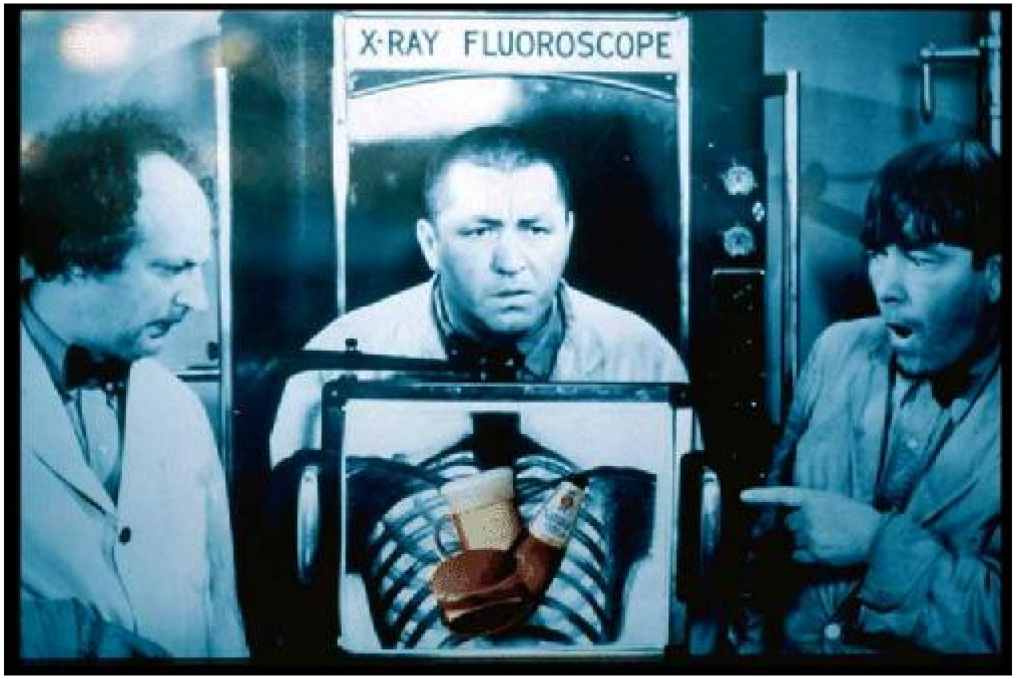
Real Time Imaging

Cardiac

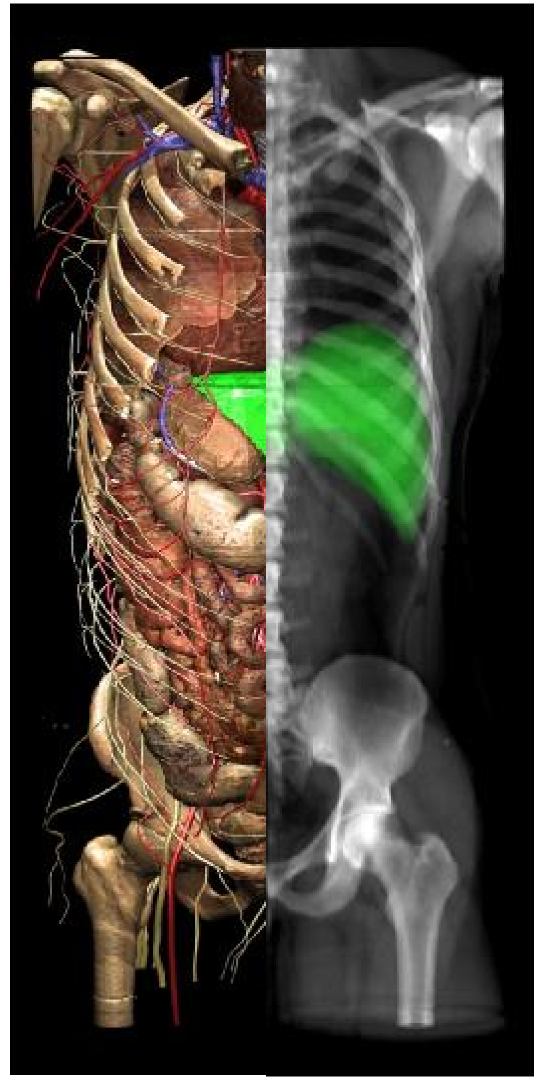


DSA/Fluoro.

Anatomical Noise



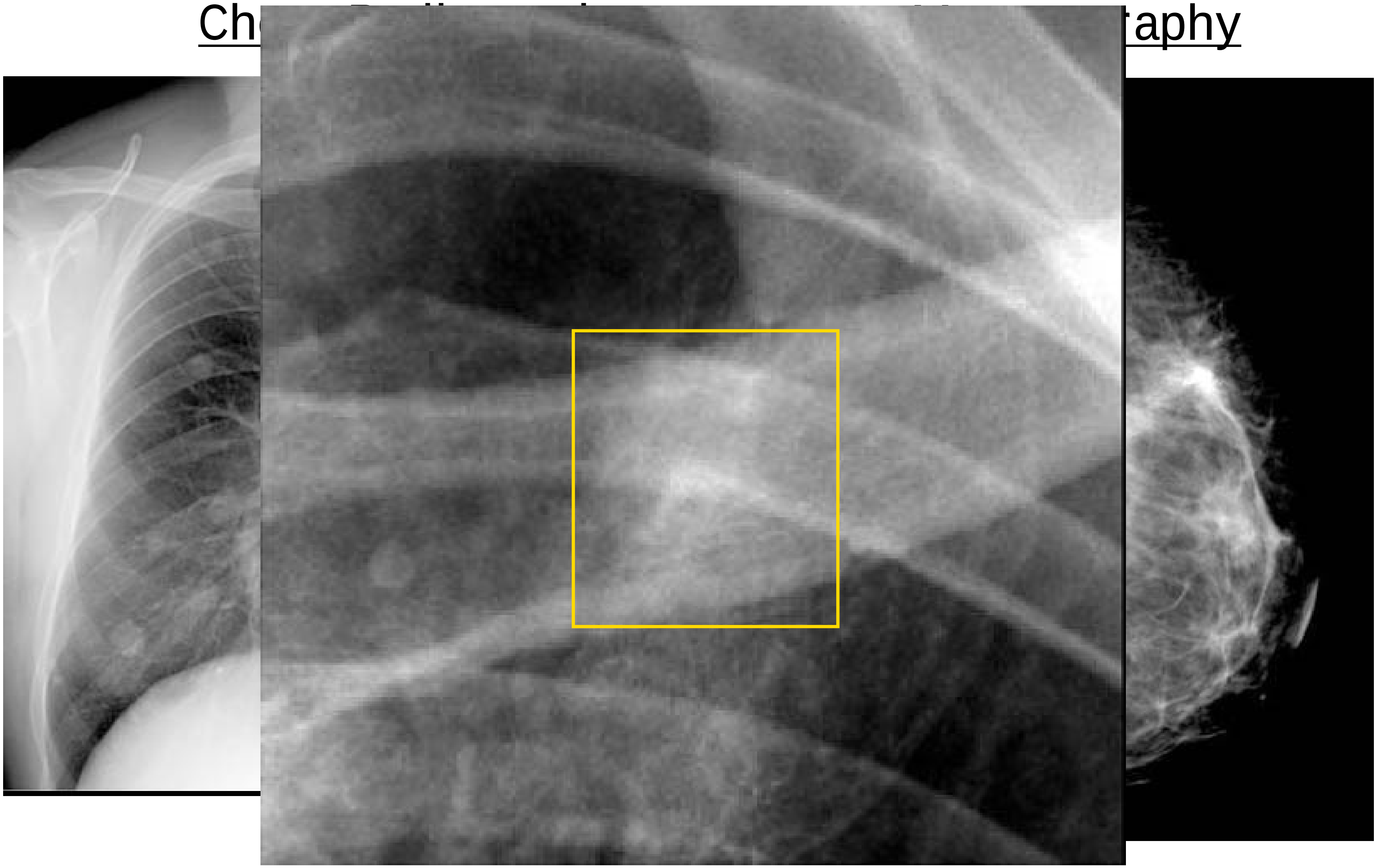
3-Dim 2-Dim



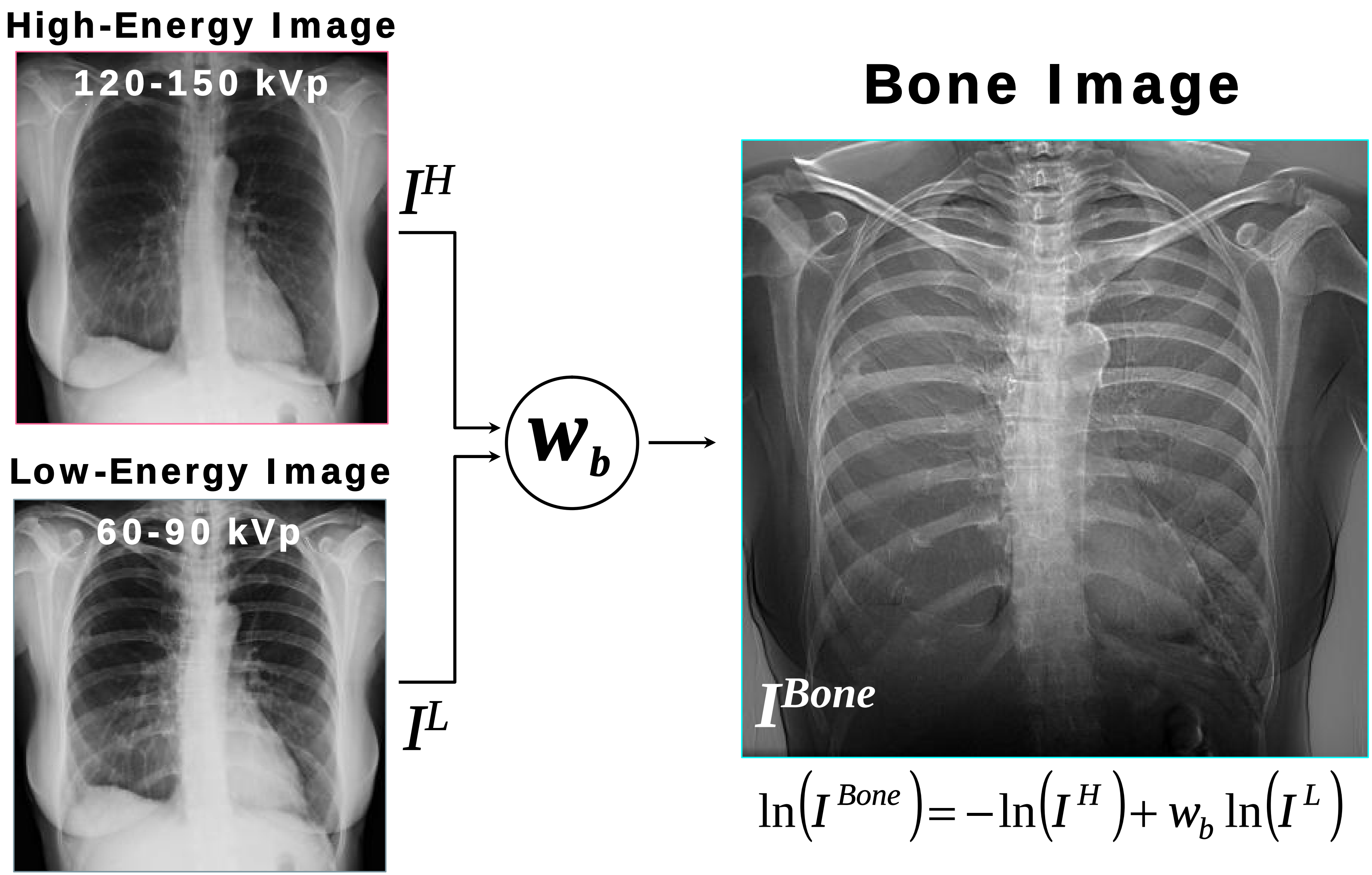
- 3 dim. structure projected into 2 dim.
  - Overlapping structures obscure clinical details
  - Anatomical structure noise > x10 detector noise

Anatomical Noise in Projection Radiography

Ch aphy

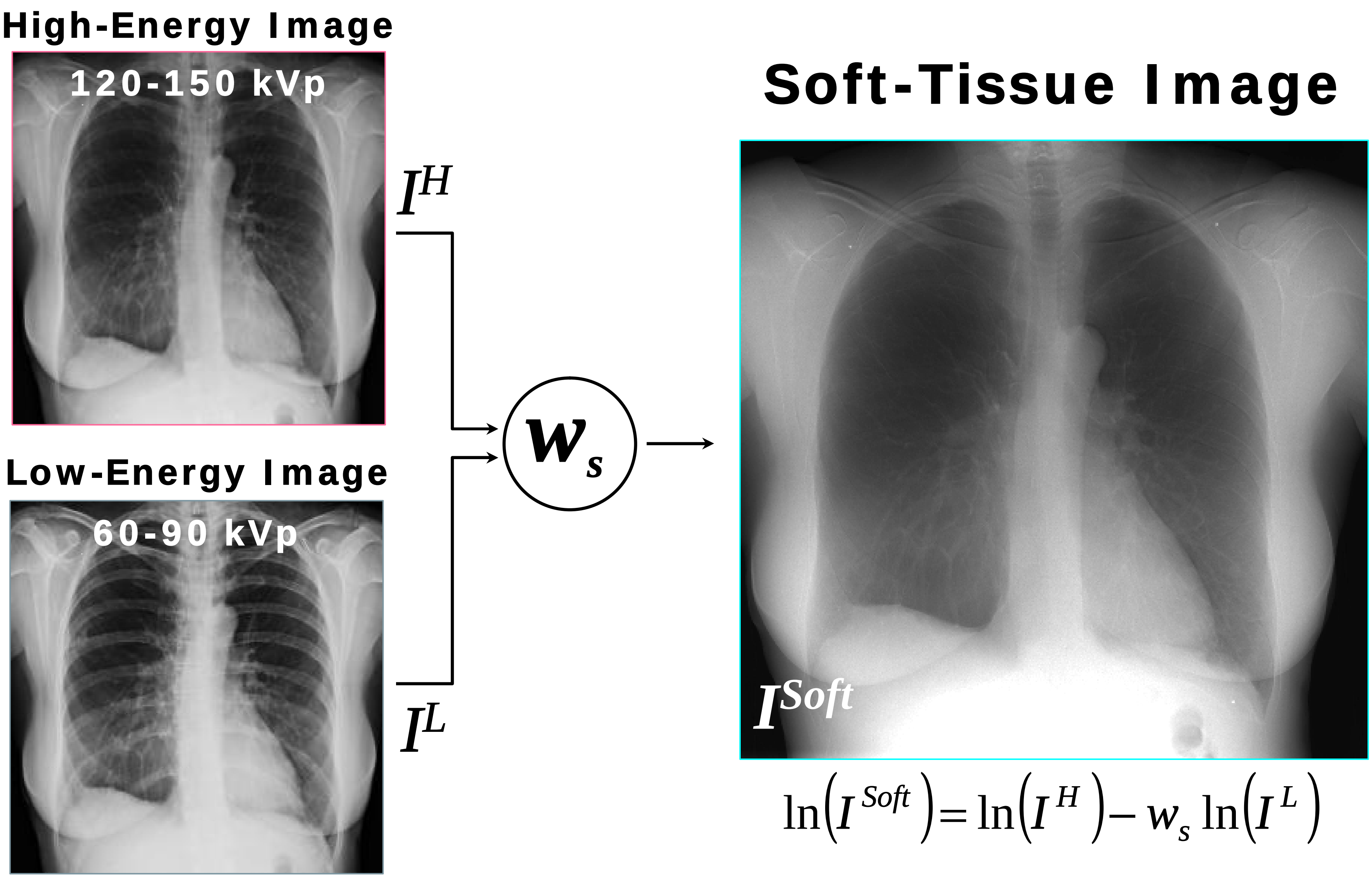


Tissue Discrimination: Dual-Energy Imaging



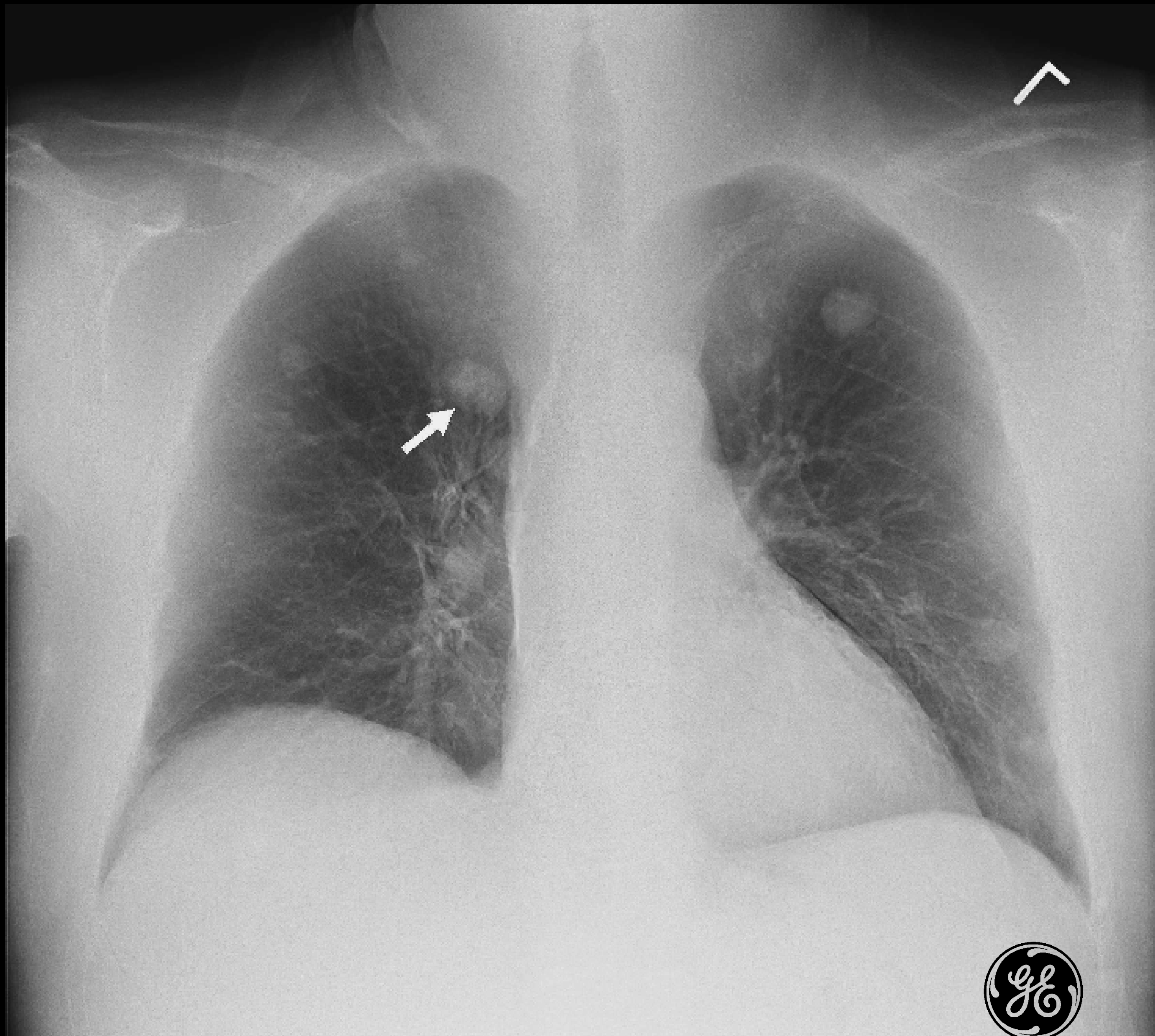
$$\ln\left(I^{Bone}\right) = -\ln\left(I^{H}\right) + w_b \ln\left(I^{L}\right)$$

Tissue Discrimination: Dual-Energy Imaging



$$\ln\left(I^{Soft}\right) = \ln\left(I^{H}\right) - w_s \ln\left(I^{L}\right)$$

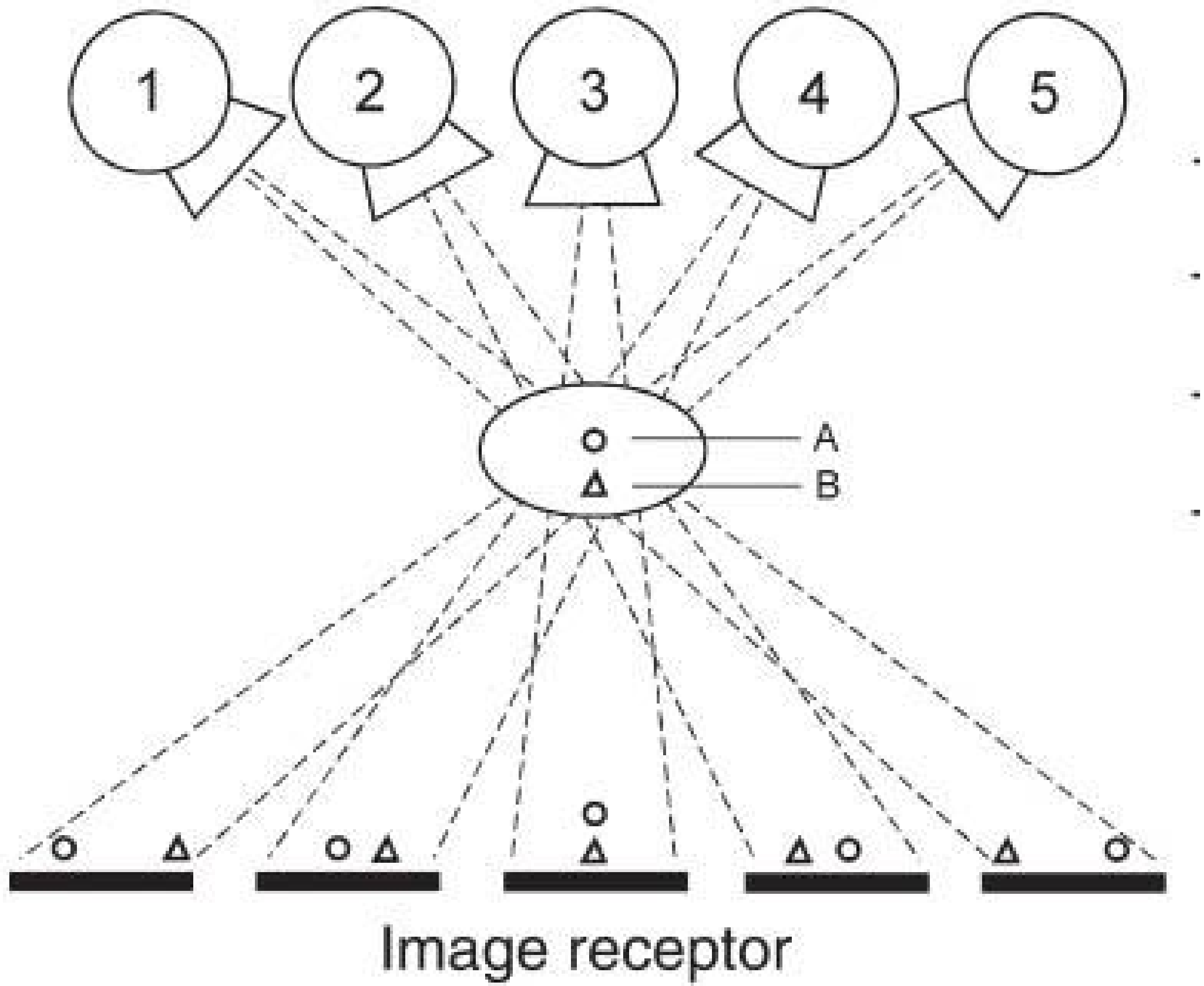
Dual-Energy Increases Conspicuity of Subtle lesions



(Courtesy: JM Sabol, GE Healthcare and RC Gilkeson, Dept. Radiology Case Western Univ.)

Spatial Discrimination: Tomosynthesis

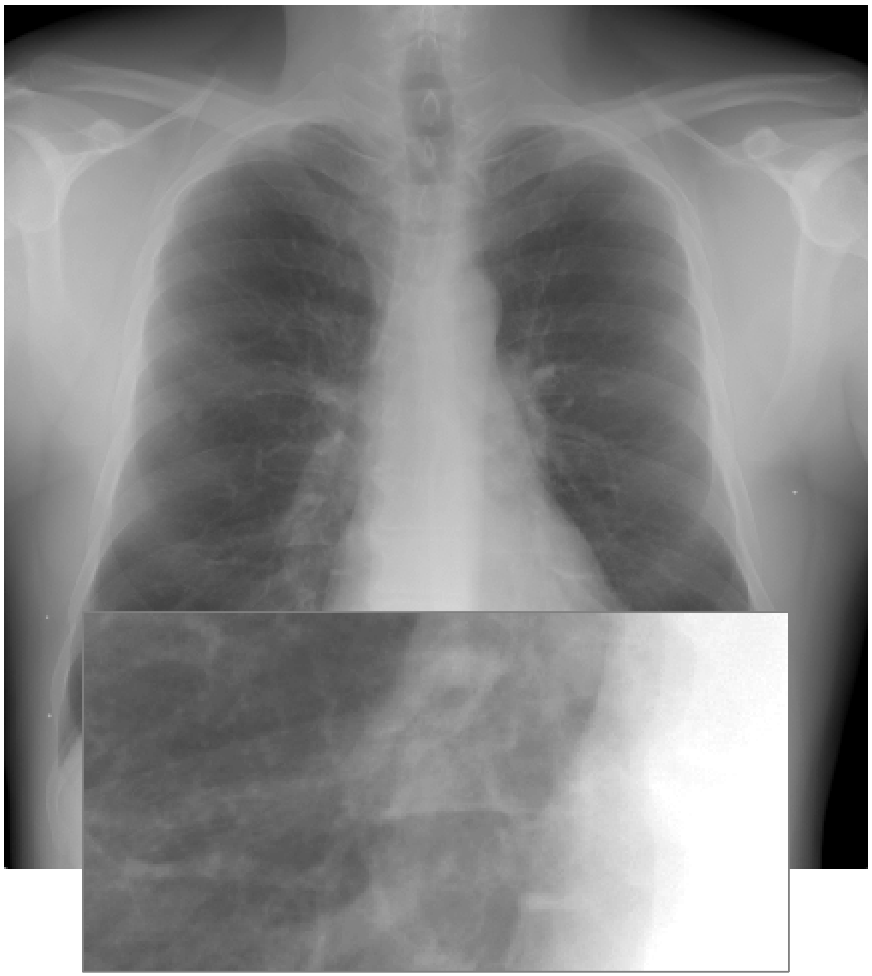
Utilizes parallax relative motions between shots

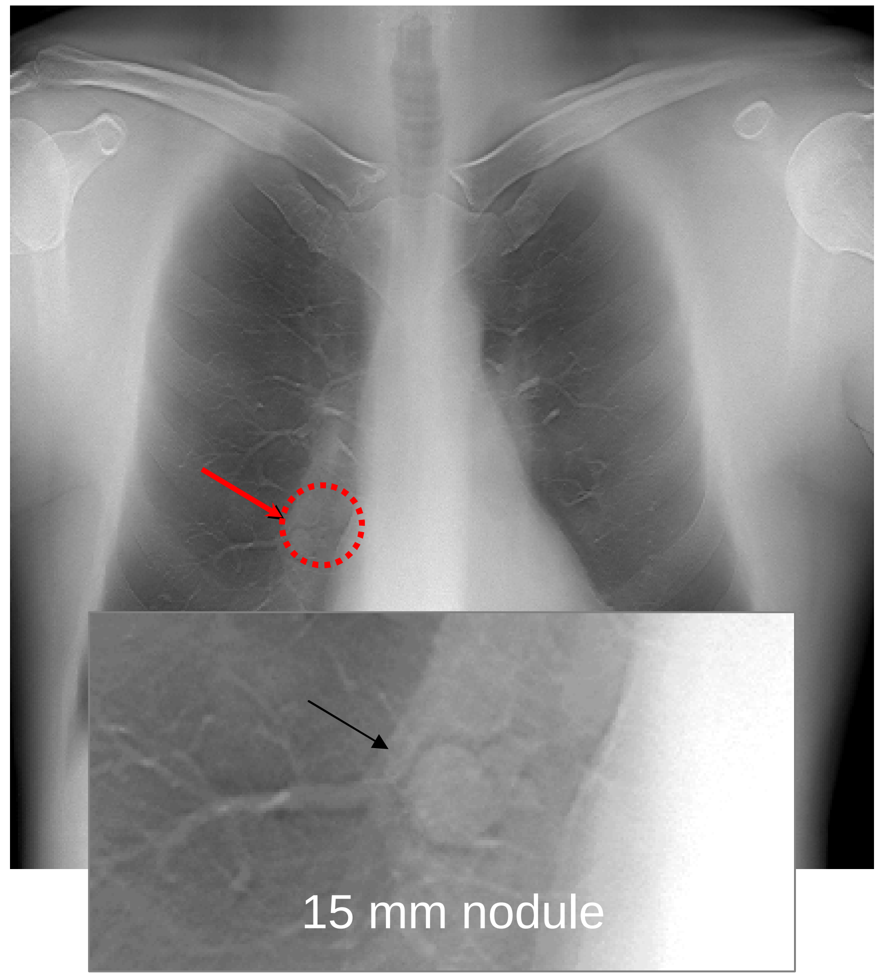


Chest Tomosynthesis Clinical Example

15 mm hilar nodule not visible in projection image

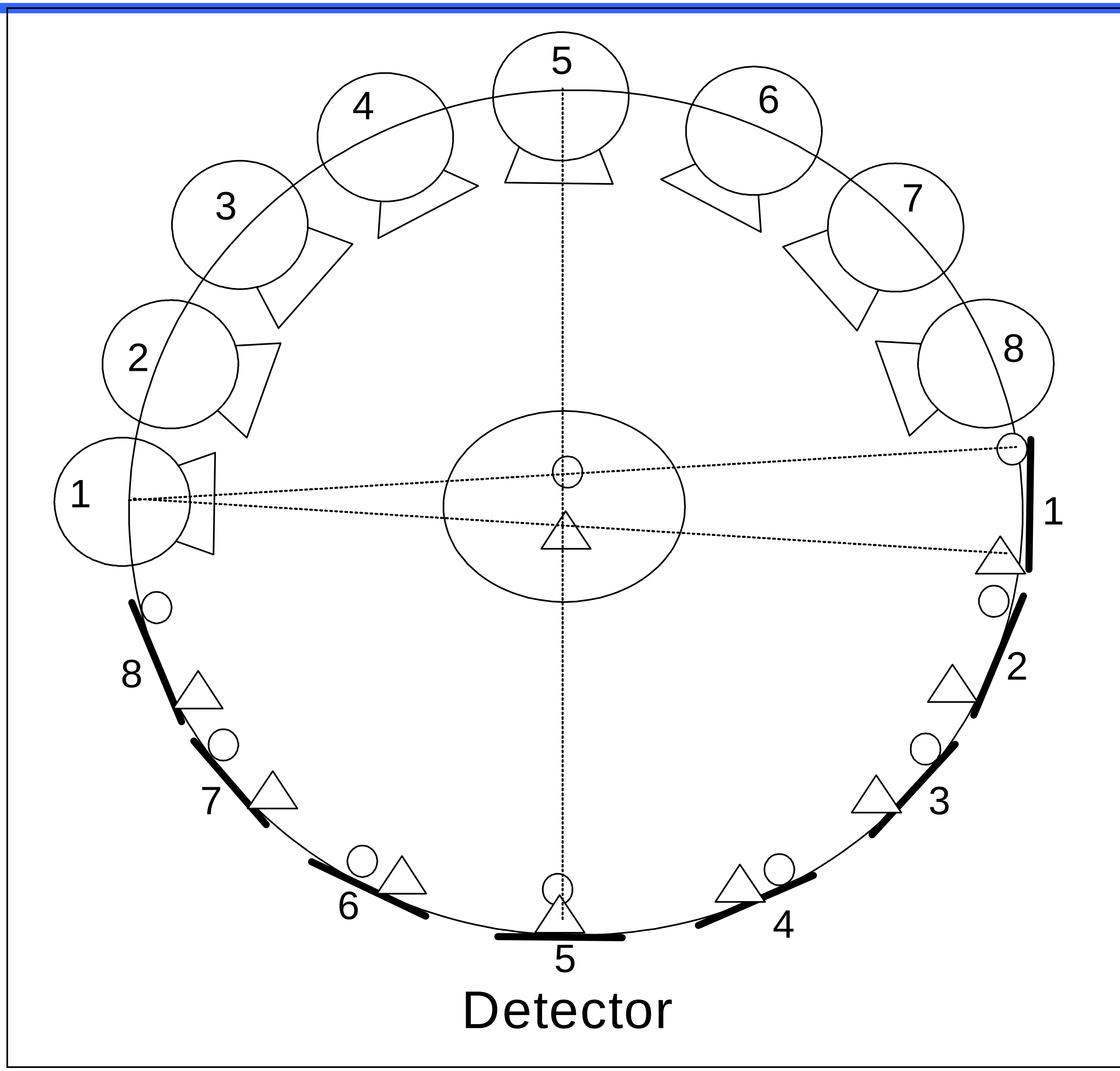
16-degree tube angle, 61 projection images, 5 mm slice spacing
Total tomo exposure ≈ Lateral image exposure (screen film)



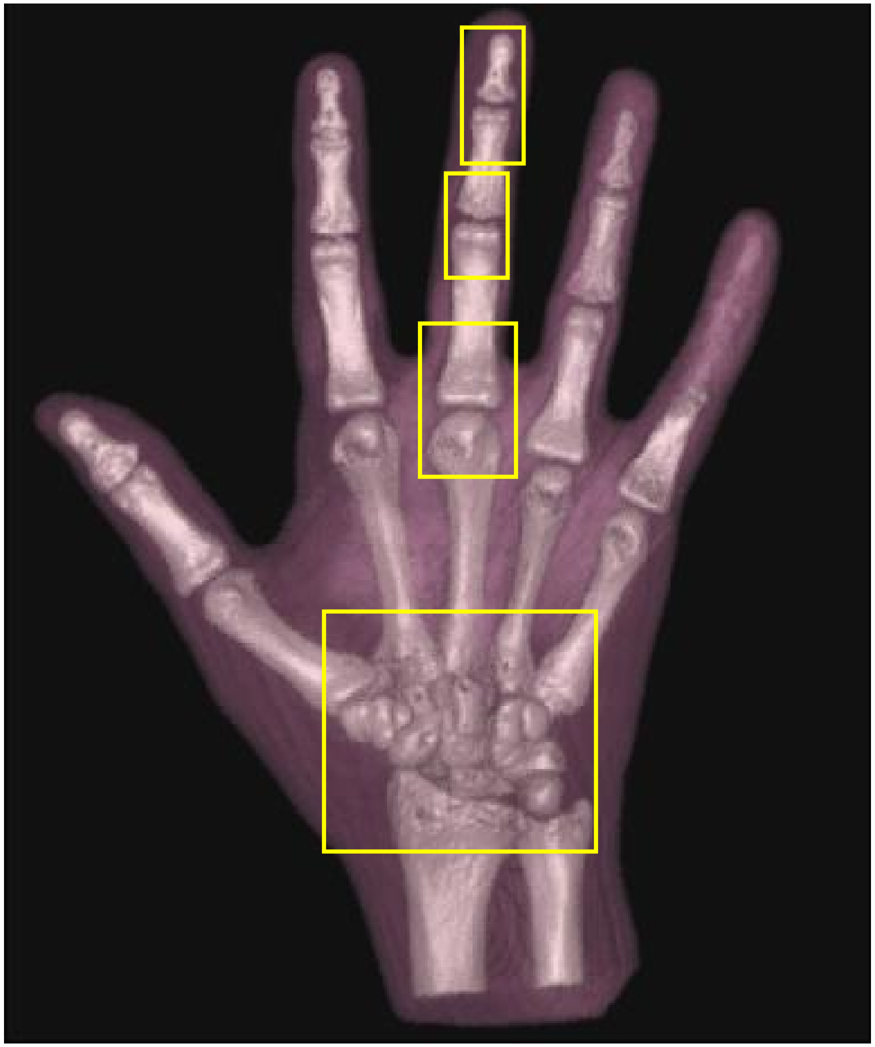


(Courtesy: James Dobbins, PhD, Duke University Medical Center)

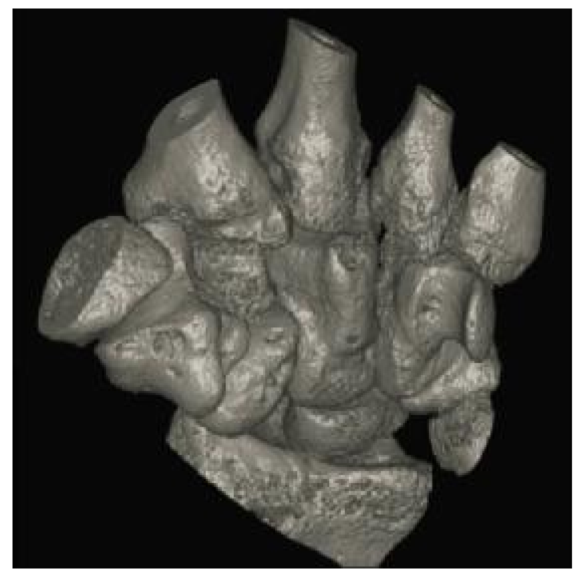
Flat-panel “Cone Beam” CT



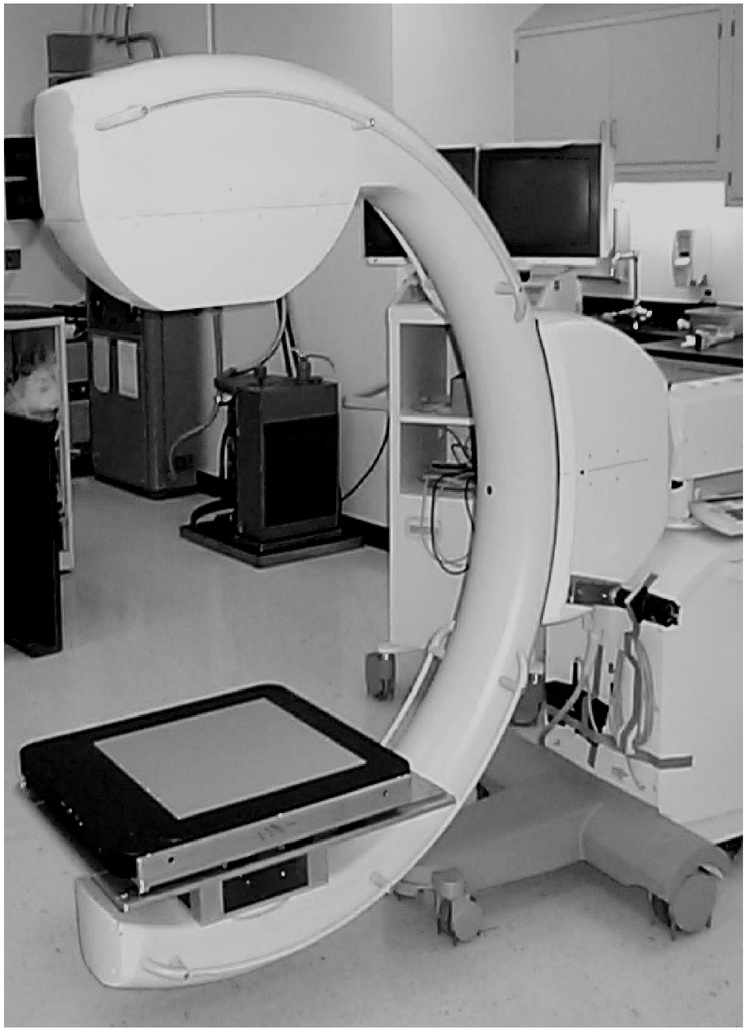
CBCT Spatial Discrimination

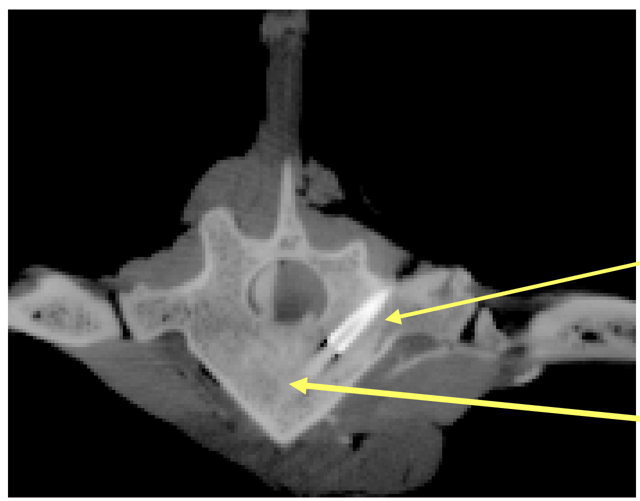


- Isotropic resolution
- Patient dose << CT
- Some soft tissue vis.



CBCT Image Guidance

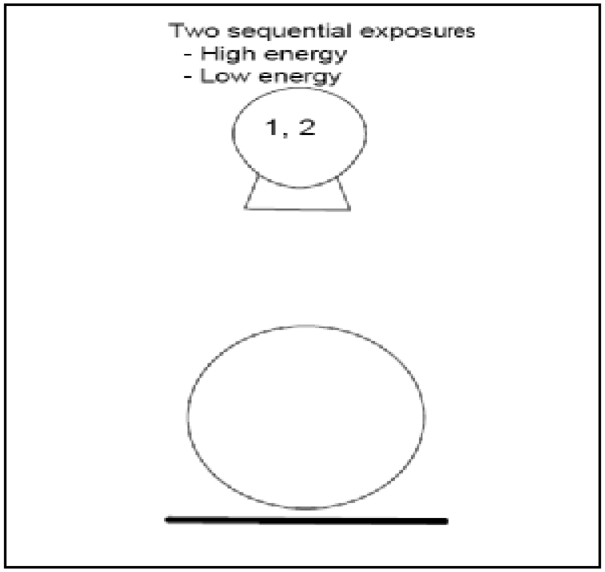




(D. A. Jaffray and J. H. Siewerdsen, Princess Margaret Hospital , University of Toronto)

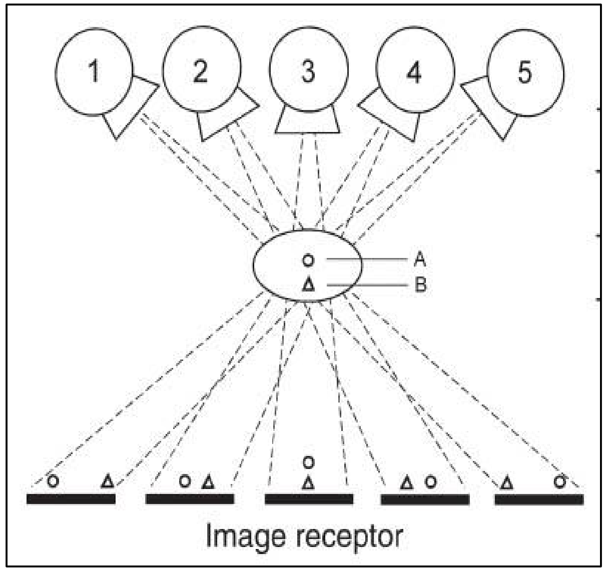
Advanced Imaging Modality Requirements

Dual Energy



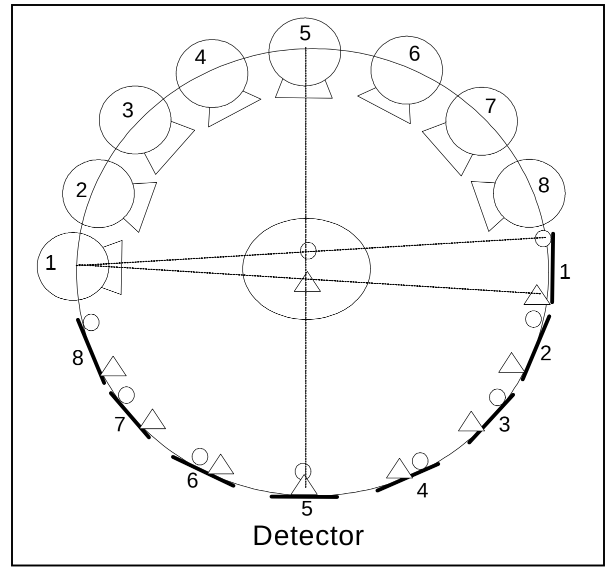
Number of images	2
Total dose	1X
Dose per image	50%
Frame rate	~5 fps

Tomo-Synthesis



Number of images	~20 -100
Total dose	1X-5X
Dose per image	10%
Frame rate	~5-30fps

Cone-beam CT

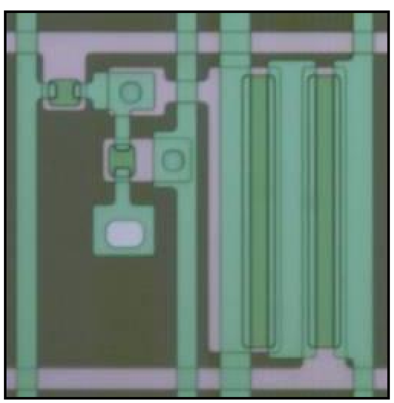


Number of images	100's
Total dose	1X - 10X+
Dose per image	1 % – 5 %
Frame rate	~30 fps

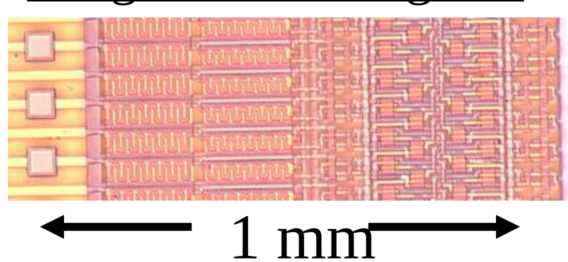
Key Vectors for Radiographic Detector Development

- 2-D Projection Radiography
  - Cost (on-glass electronics, digital lith. & fab-less design)
  - Robustness & weight (robust plastic/metal substrates)
- Advanced Applications (Dual energy and 3D modalities)
  - Improved sensitivity (SNR) at low exposure ("smart" pixels)
  - Improved spatial resolution (improved x-ray converters)
  - High frame-rate readout (on-glass electronics)

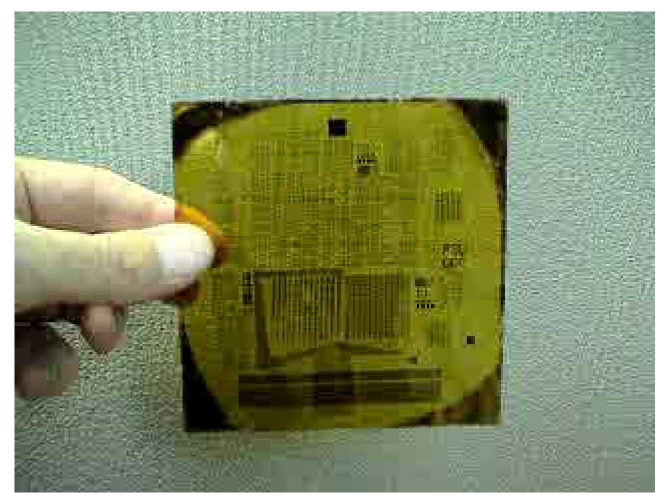
Active Pixel Design



On-glass Shift Register



Flexible Substrate

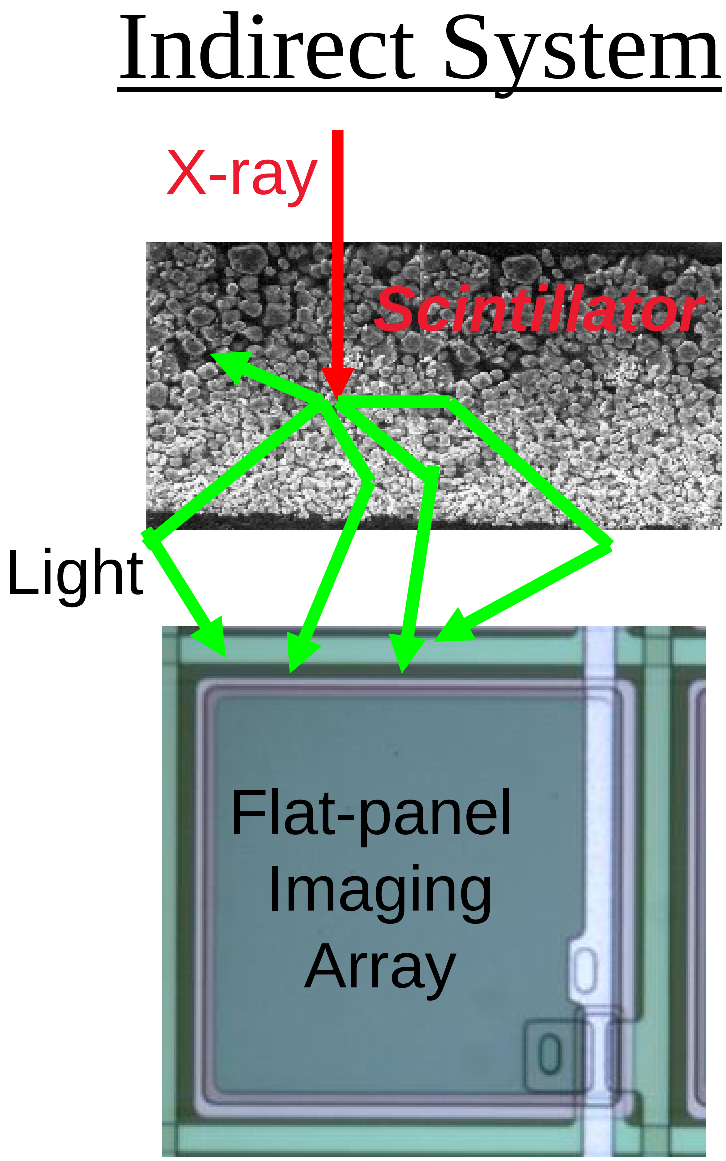


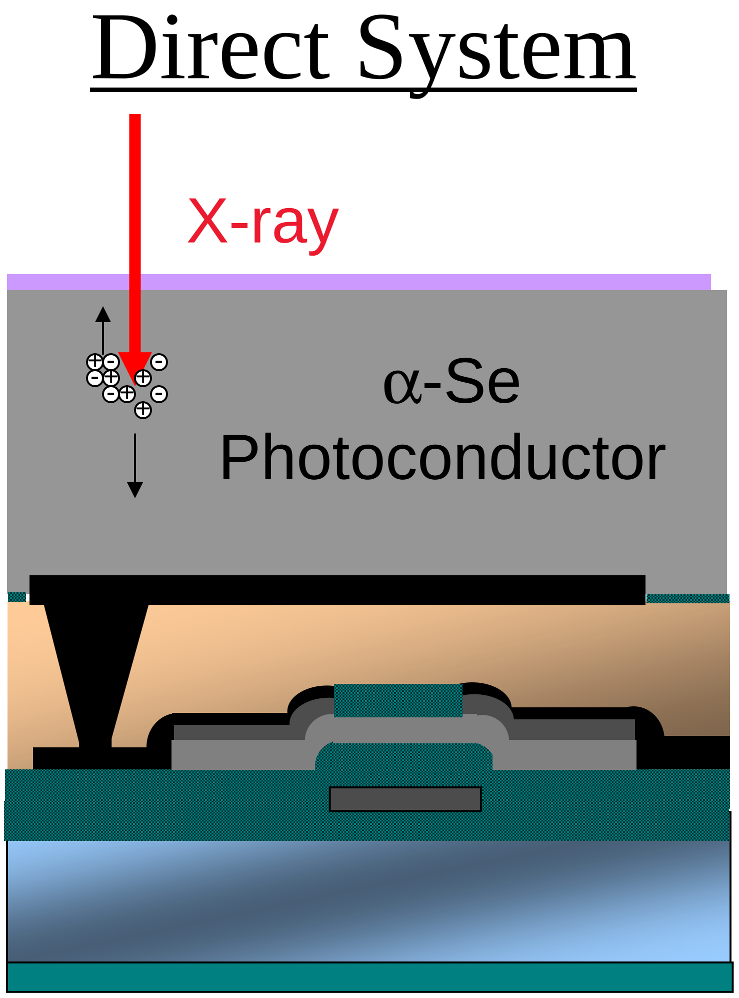
(Courtesy Dr. T.Jackson PennState)

Outline

- Introduction to medical imaging modalities
  - X-ray, CT, MRI, SPECT, PET, Ultrasound, Endoscope, NIRS
- Radiography
  - Introduction to digital radiography
  - Clinical challenges
  - Amorphous silicon imaging arrays
  - LTPS silicon imaging arrays
  - Silicon Imaging arrays
- Molecular Imaging
- Applications for Quantum Limited Detectors

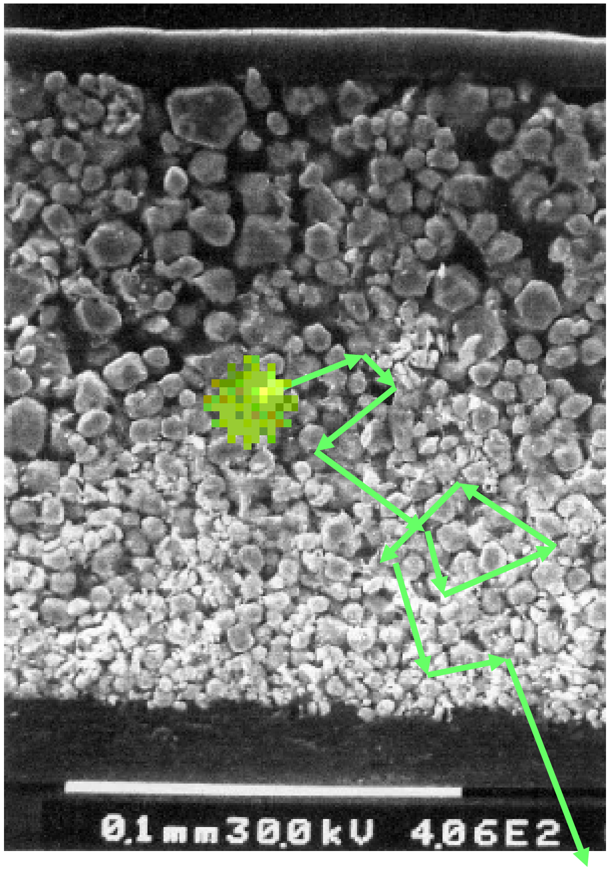
DR X-ray detection



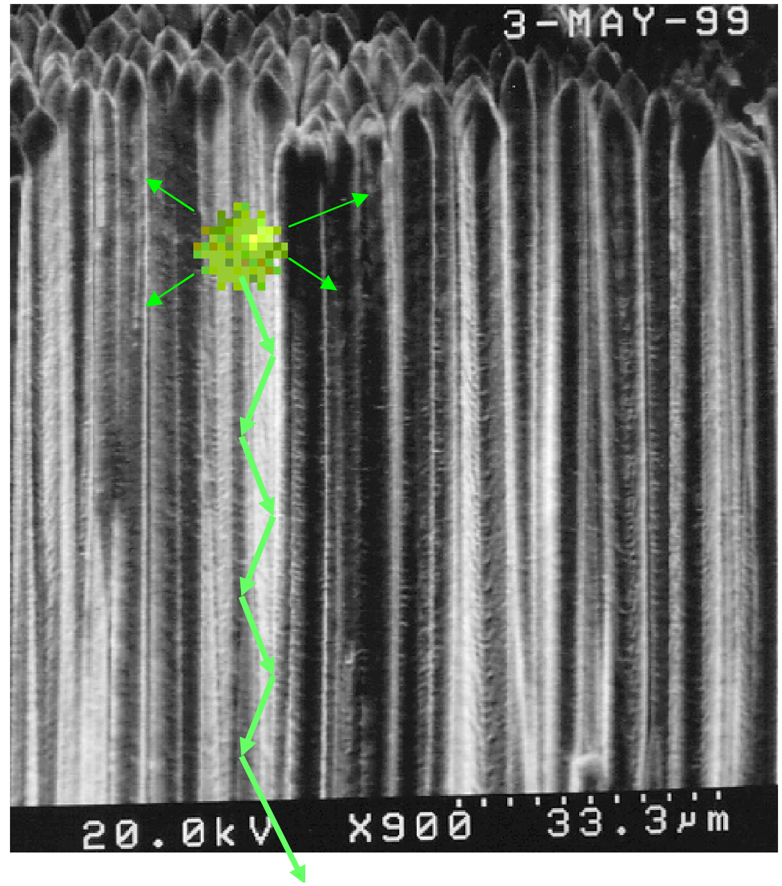


X-Ray Converter

Powdered Phosphor

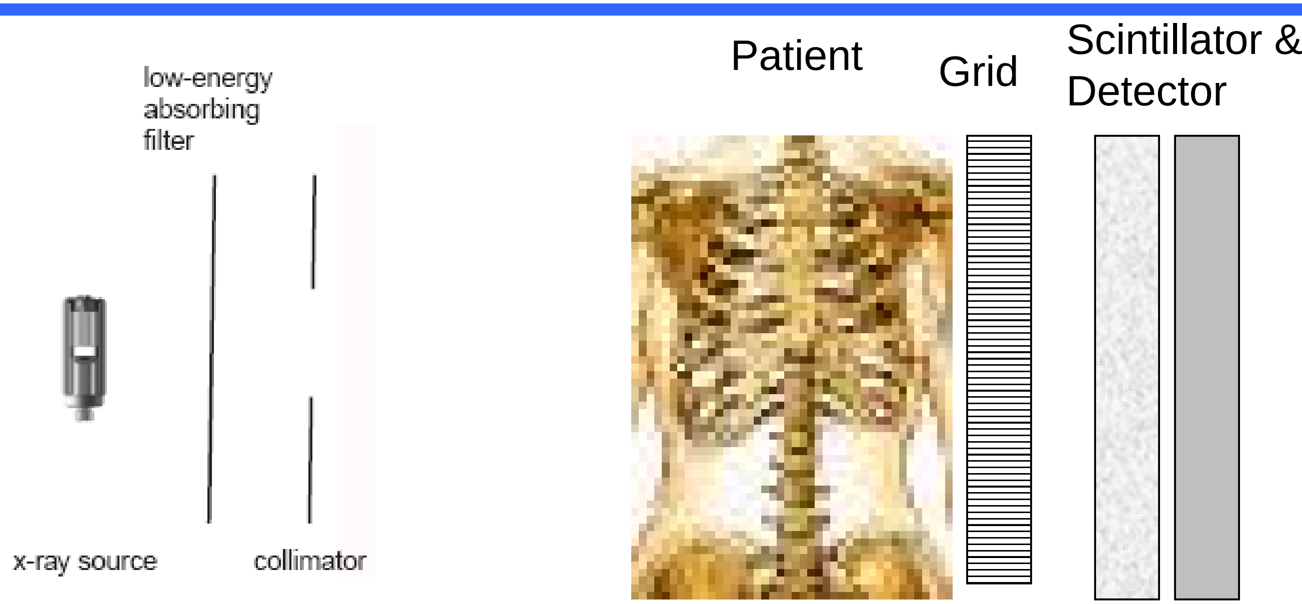


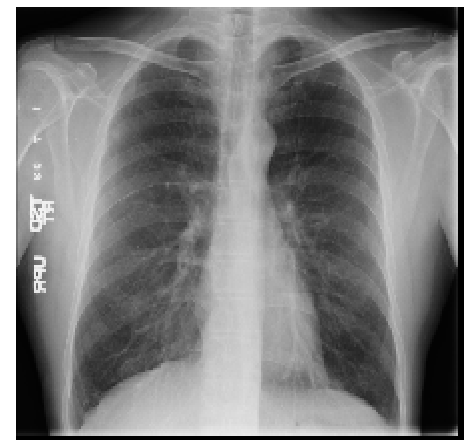
Structured Phosphor (CsI)



- Structured phosphor maintains spatial resolution
- Photoconductor internal field functions similarly

Signal and Noise: Chest Radiograph
140 μm pixel dimension

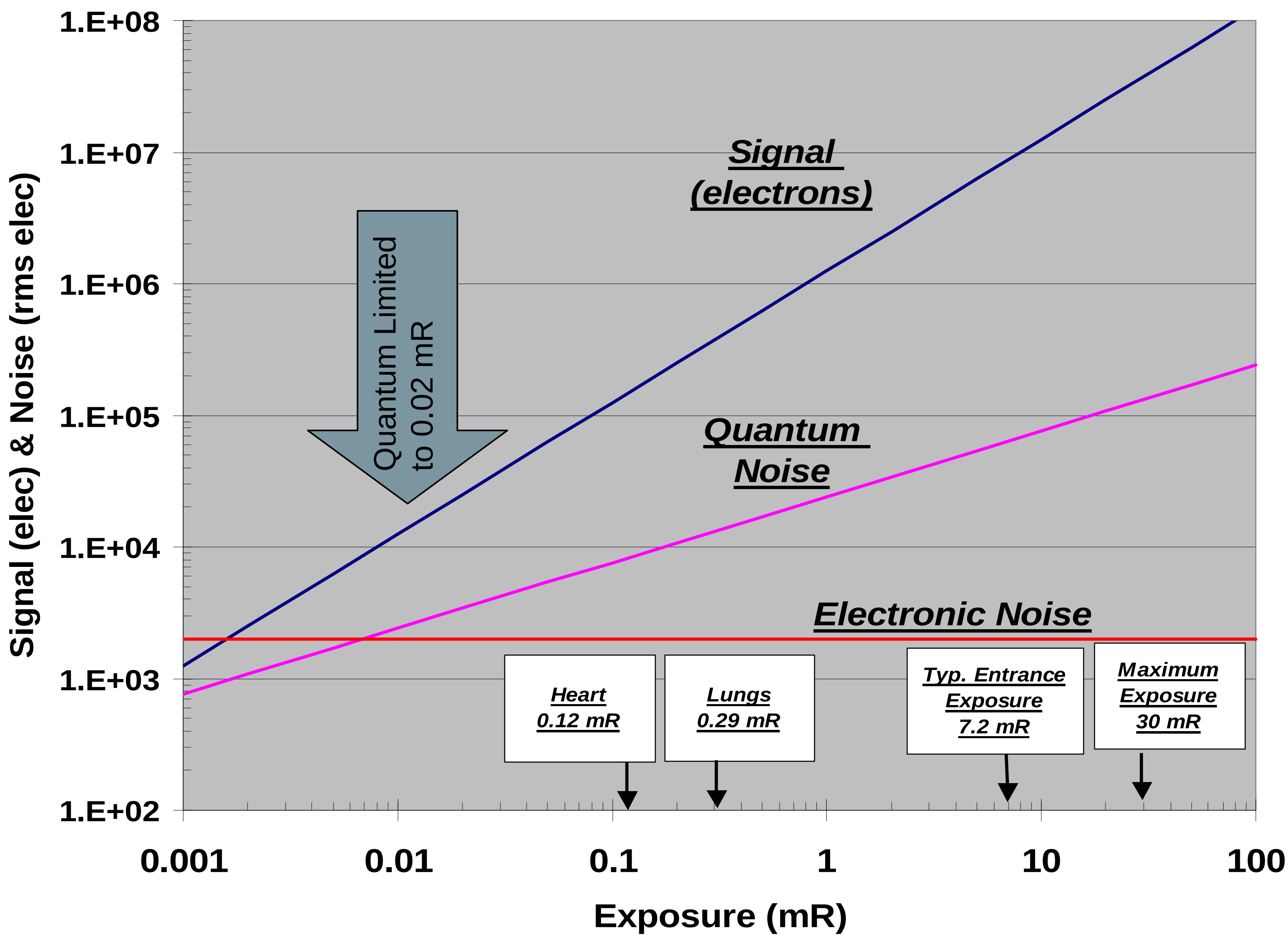




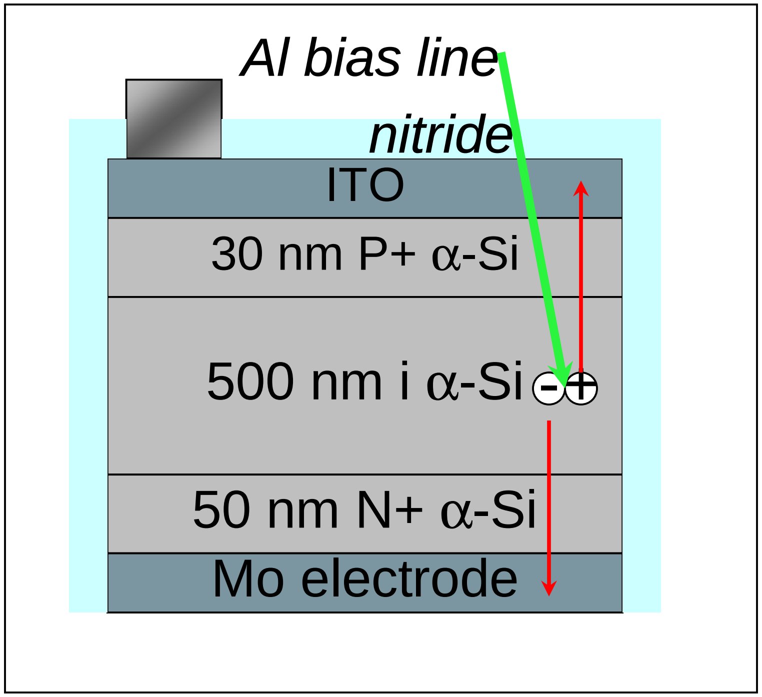
	X-ray exposure Per pixel	X-rays to scintillator Per pixel	Photons from scintillator Per pixel	Electrons collected Per pixel	Quantum Noise Per pixel
Outside Chest	142,000	142,000	88,750,000	31,808,000	84,410
Ribs	142,000	426	266,250	95,424	4,623
Ribs	142,000	426	266,250	95,424	4,623
Lungs	142,000	~ 1,420	887,500	318,080	8,441
Mediastinum	142,000	142	88,750	31,808	2,669
Heart	142,000	< 142	< 88,750	< 31,808	2,669

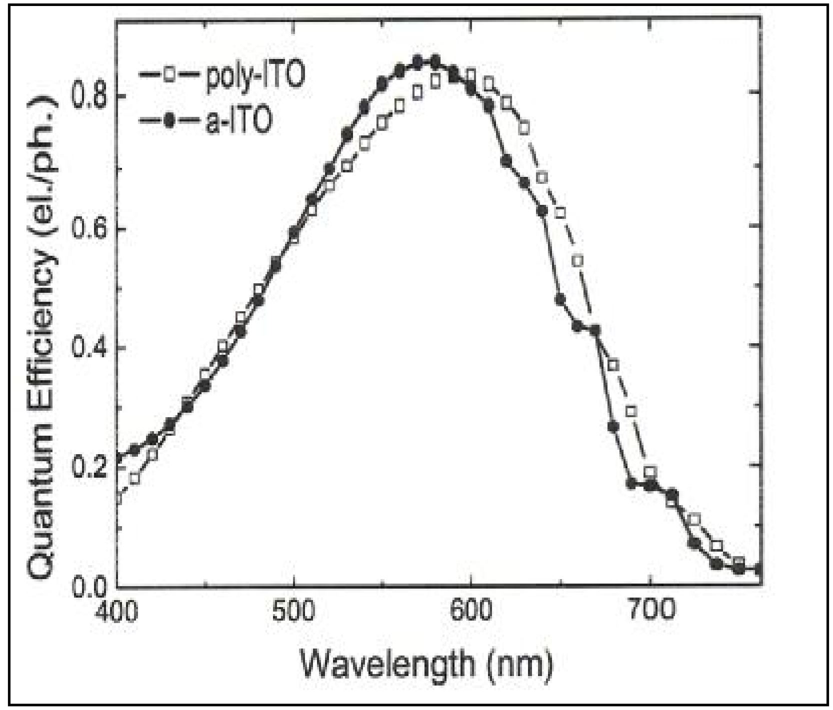
Signal and Noise vs. Exposure

Projection radiography: chest



Photosensors for Indirect Radiographic Detectors
PIN Photodiodes



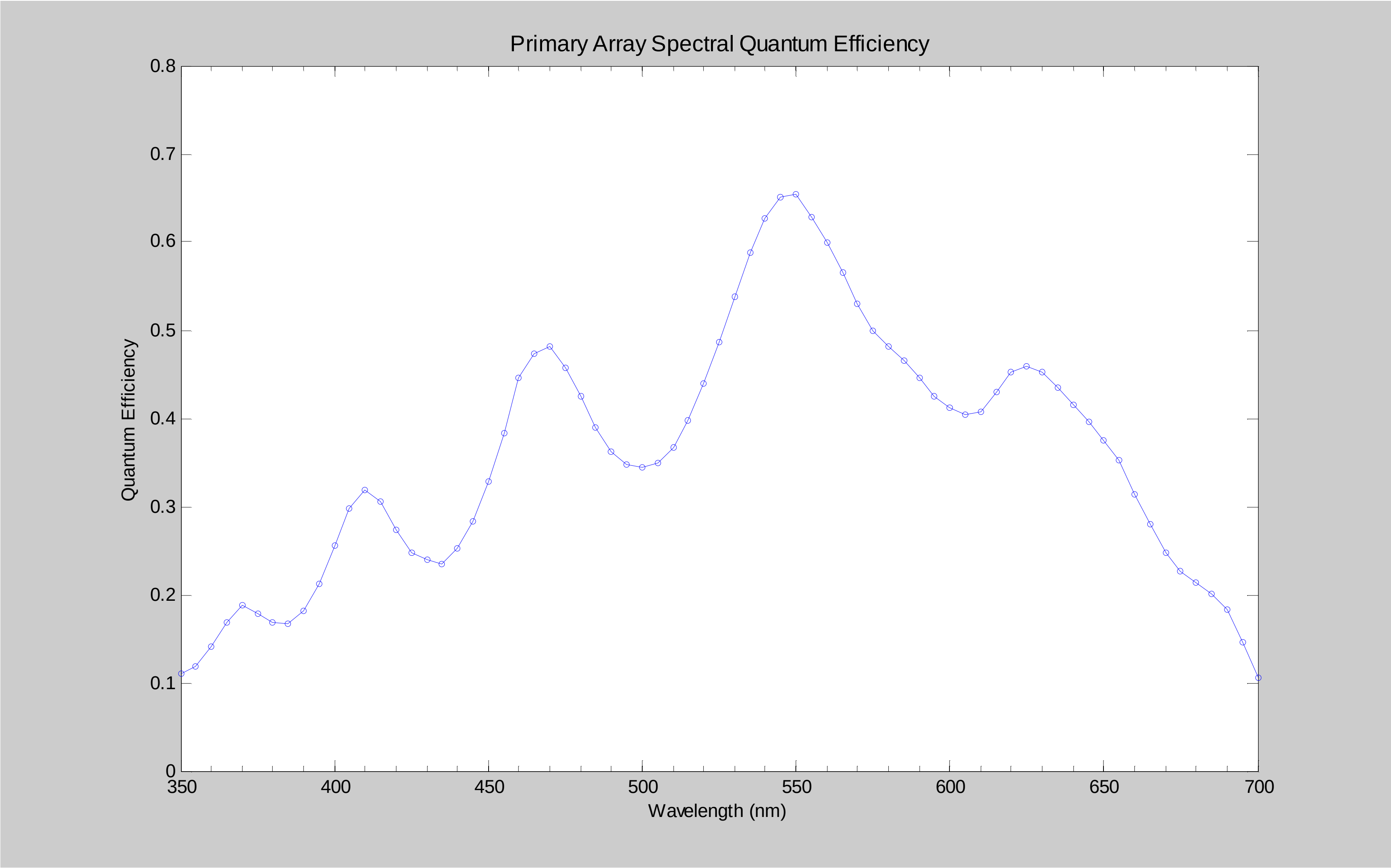


Advantages
- High quantum efficiency
- Low dark current
- Operated steady-state (no transient)

Disadvantages
- P+ not widely available – requires special process capability

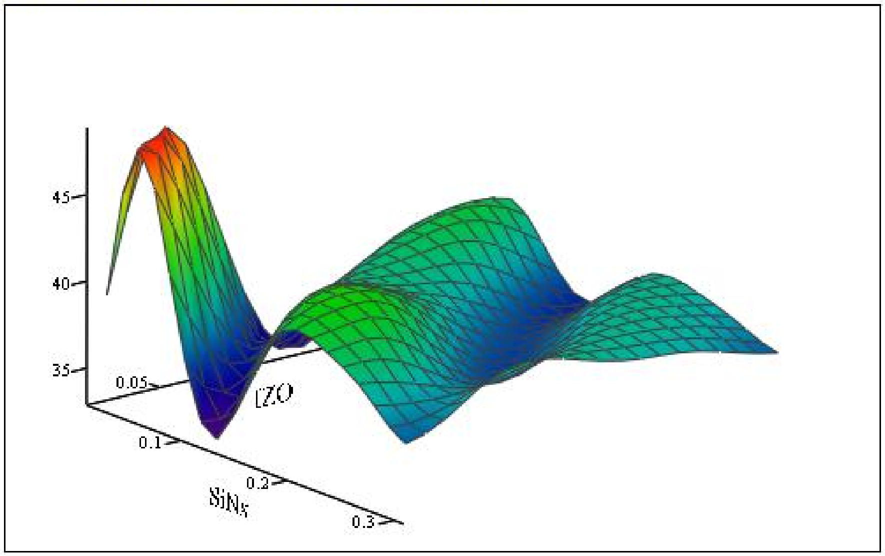
Quantum Efficiency
- 85% quantum efficiency in green
- QE drops in blue due to absorption in P+
- QE in red decreases due to band edge

PIN Photodiode in DR Array
Spectral Quantum Efficiency

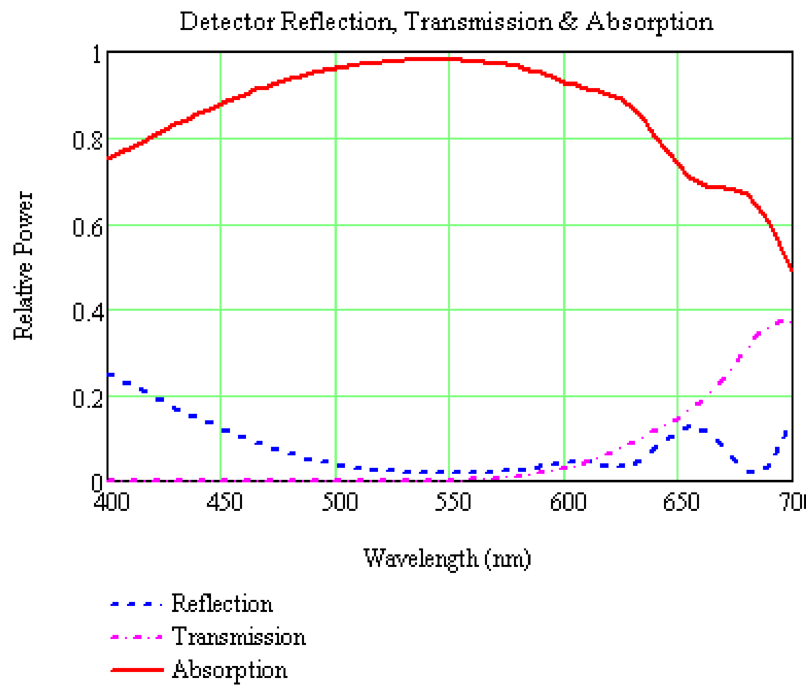


Reducing the interference, reflection losses
Optimization of layer thicknesses

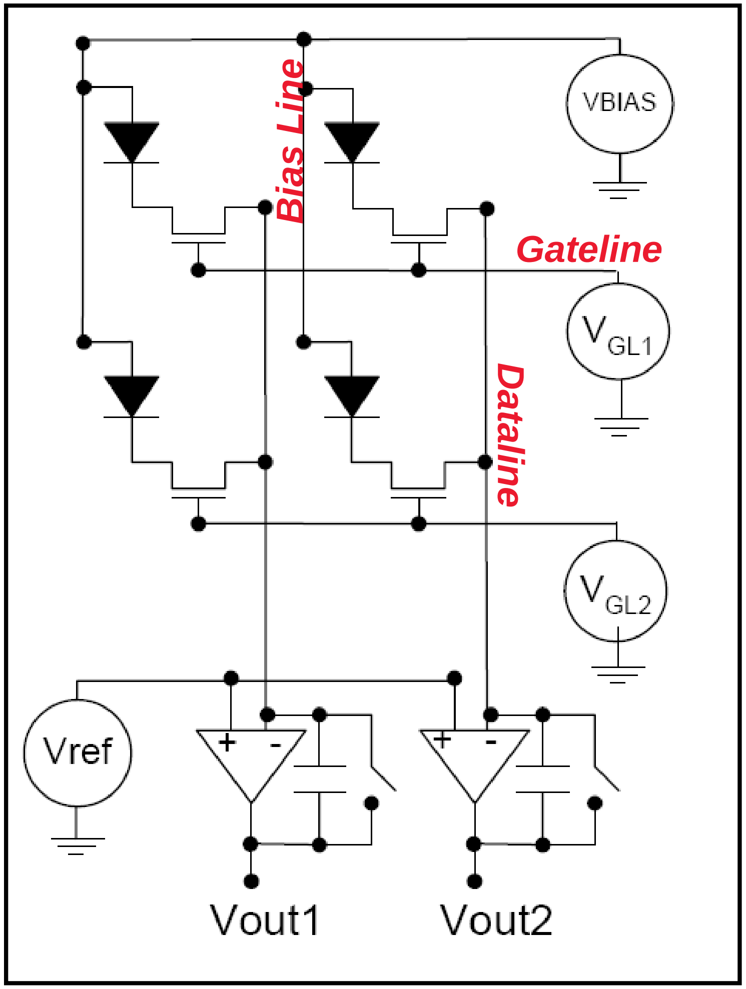
Merit Function versus SiNx and IZO layer thickness

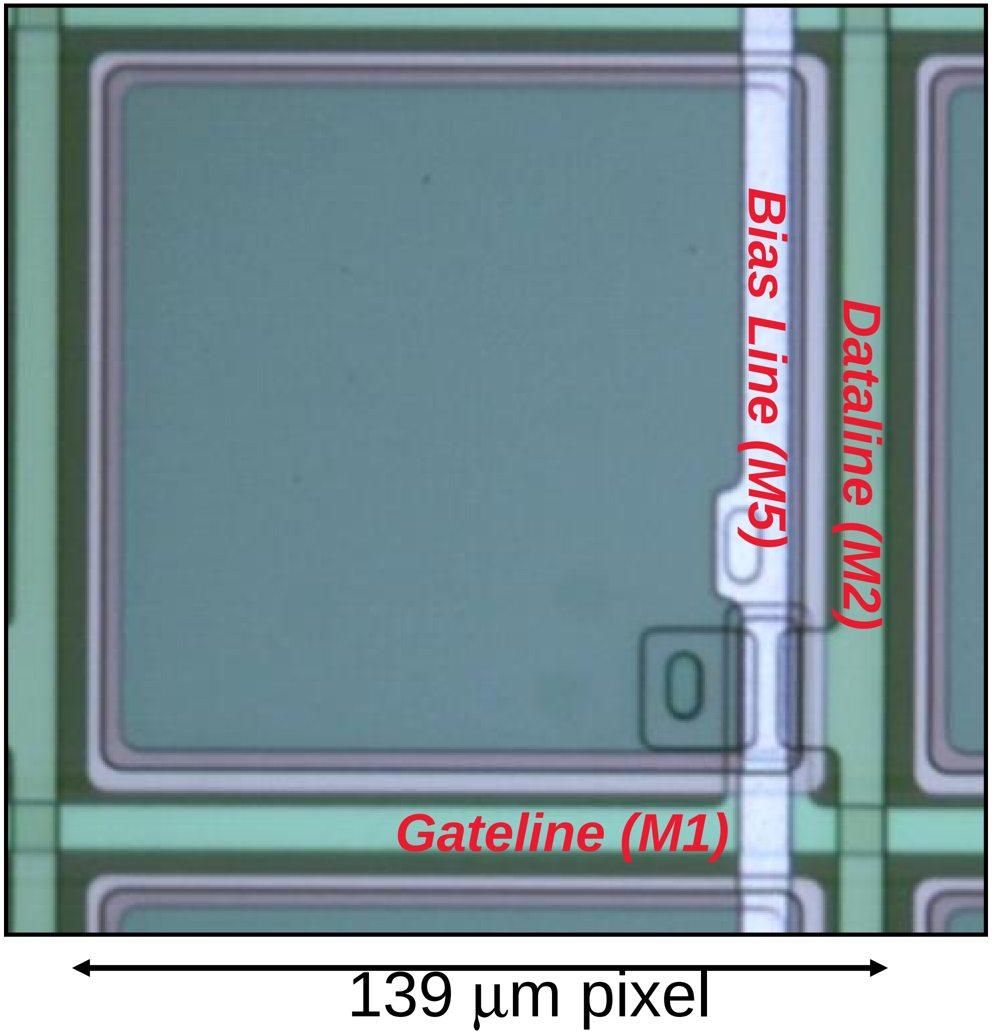


mmf

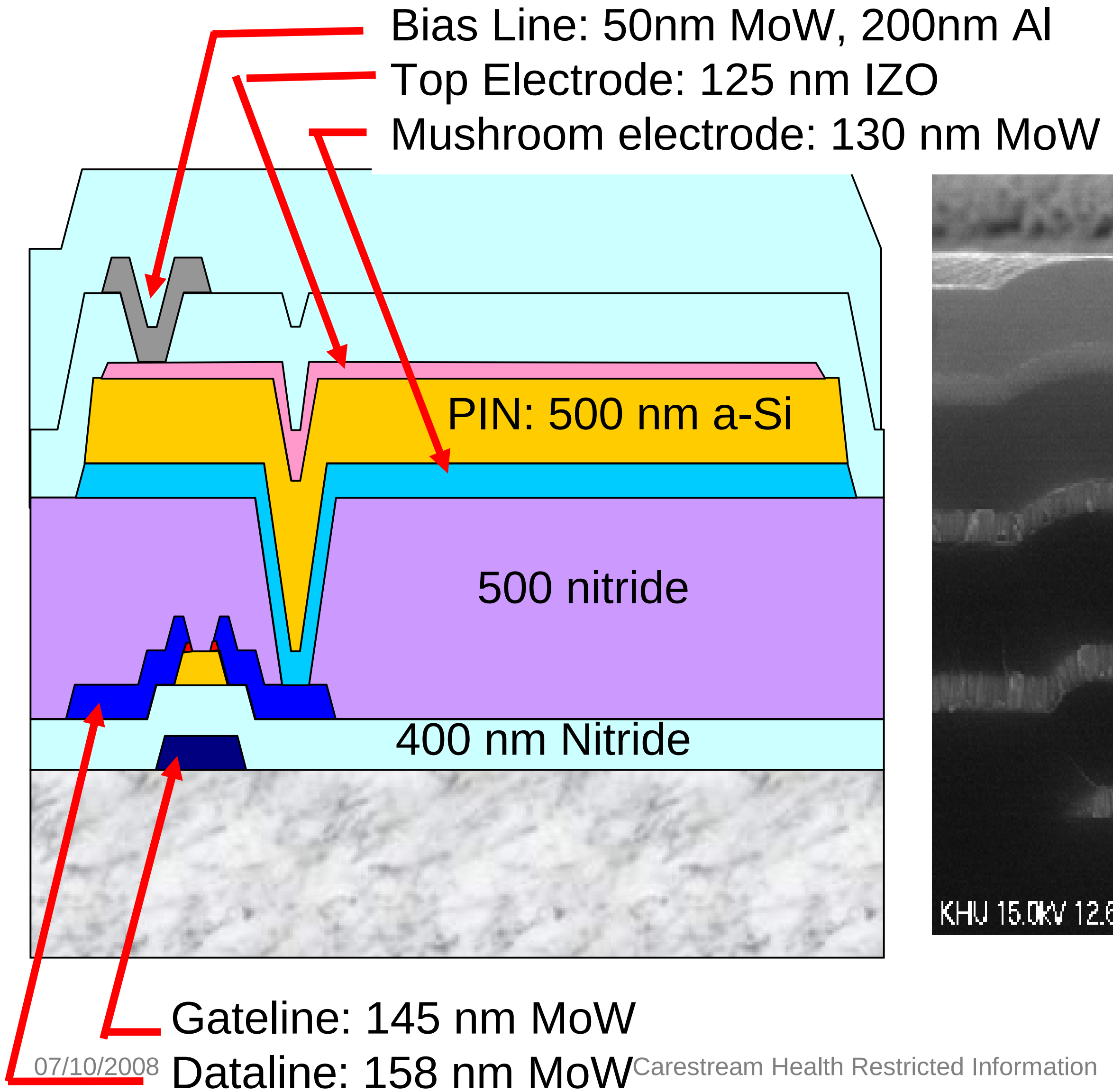


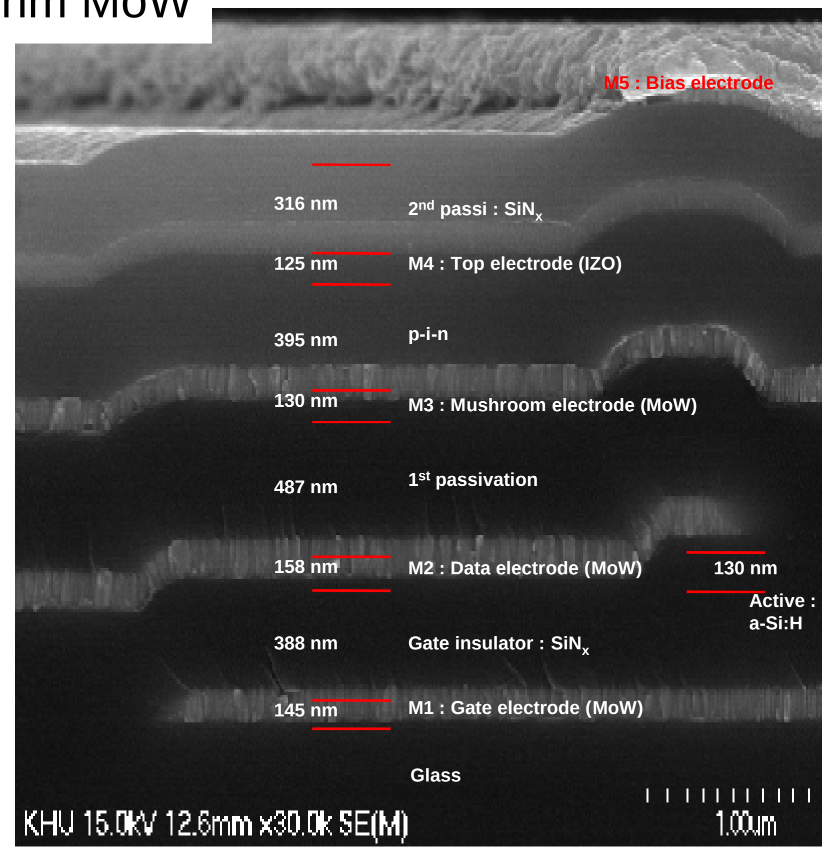
a-Si Detector Arrays
Passive Pixel Design



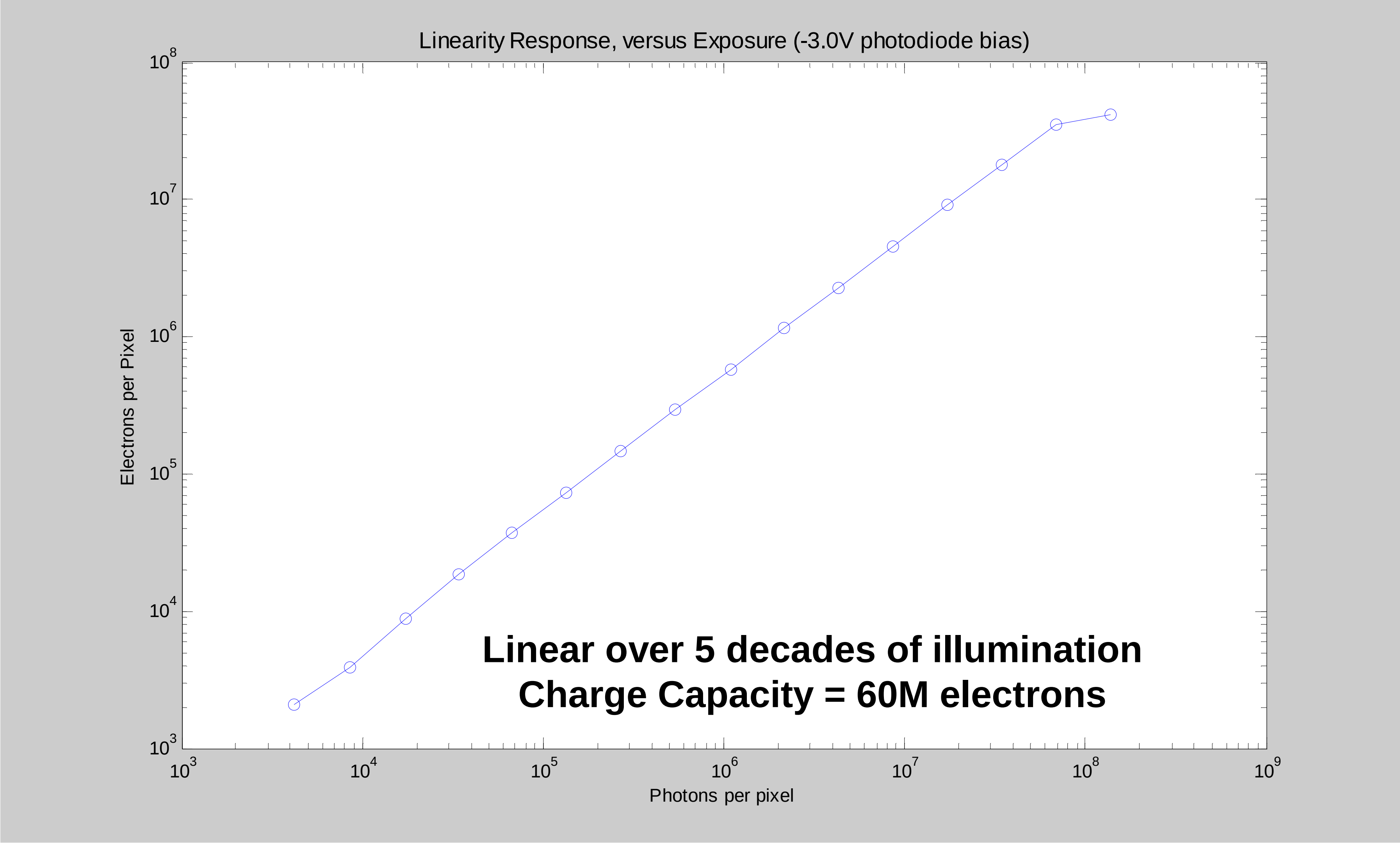


Cross-section of Vertically Integrated DR Array





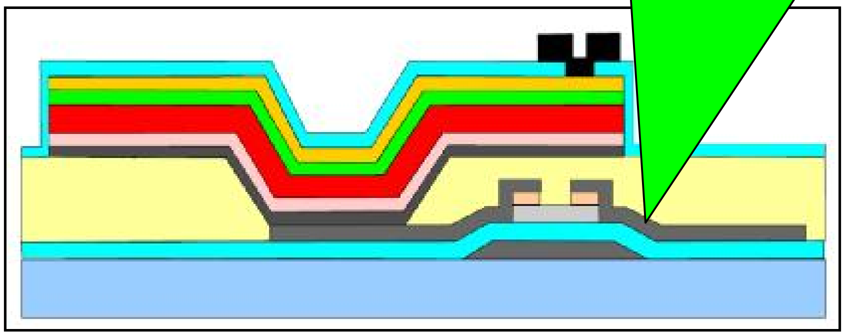
ARIA 1 Performance Verification
Linearity (uncorrected)

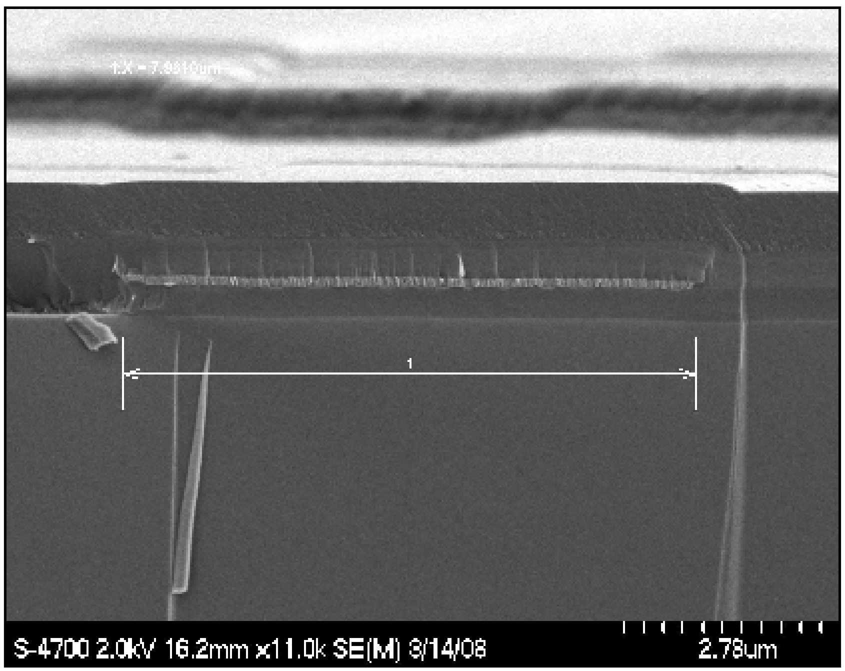


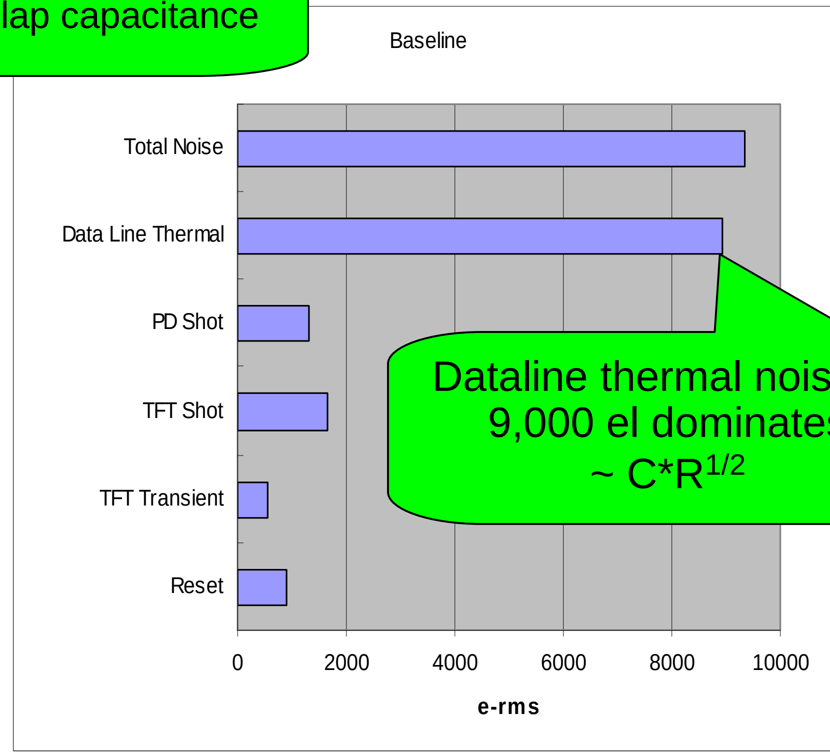
Noise in Amorphous silicon passive pixel array

Dataline thermal noise dominates

- High M2 dataline resistance
- High M1-M2 overlap capacitance (500 nm nitride)





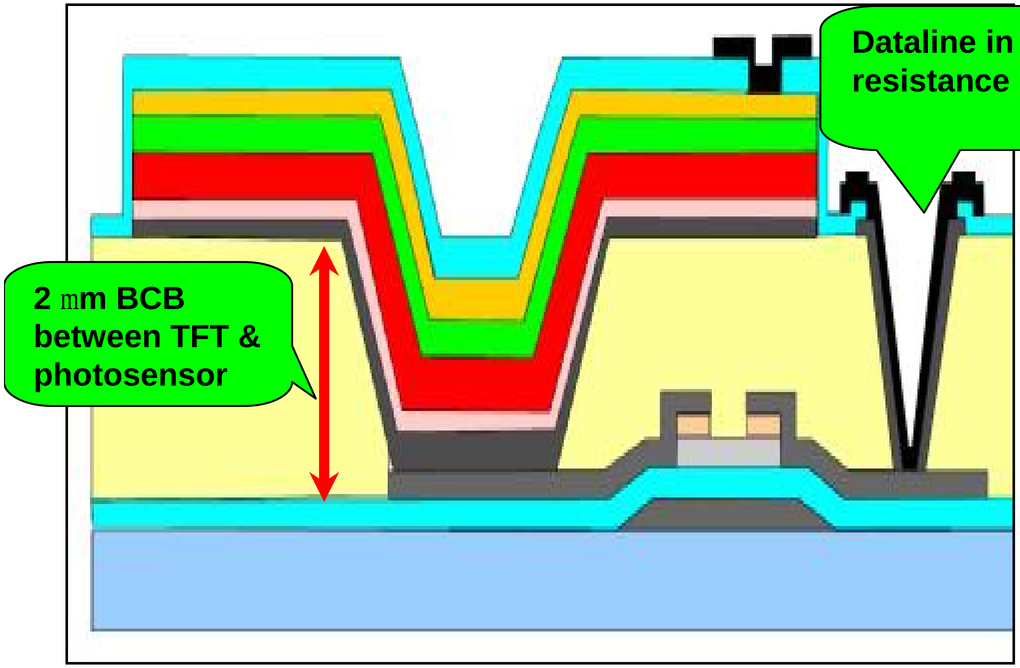


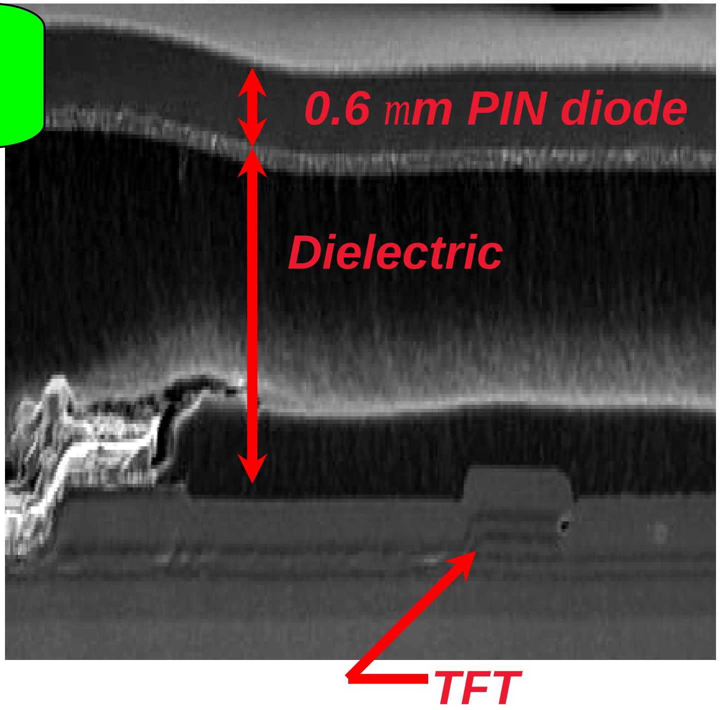
Dataline thermal noise at 9,000 el dominates $\sim C^*R^{1/2}$

- Dataline is in Metal 2, gateline in metal 1 with 500 nm inter-layer dielectric
- Dataline thermal noise $\sim C^*R^{1/2}$ is the largest contributor with 9,000 electrons noise
- Next largest noise source is < 2,000 electrons

Experimental a-Si Passive Pixel

Reduced dataline thermal noise

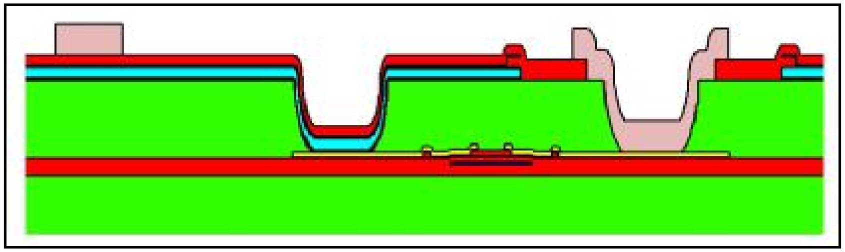


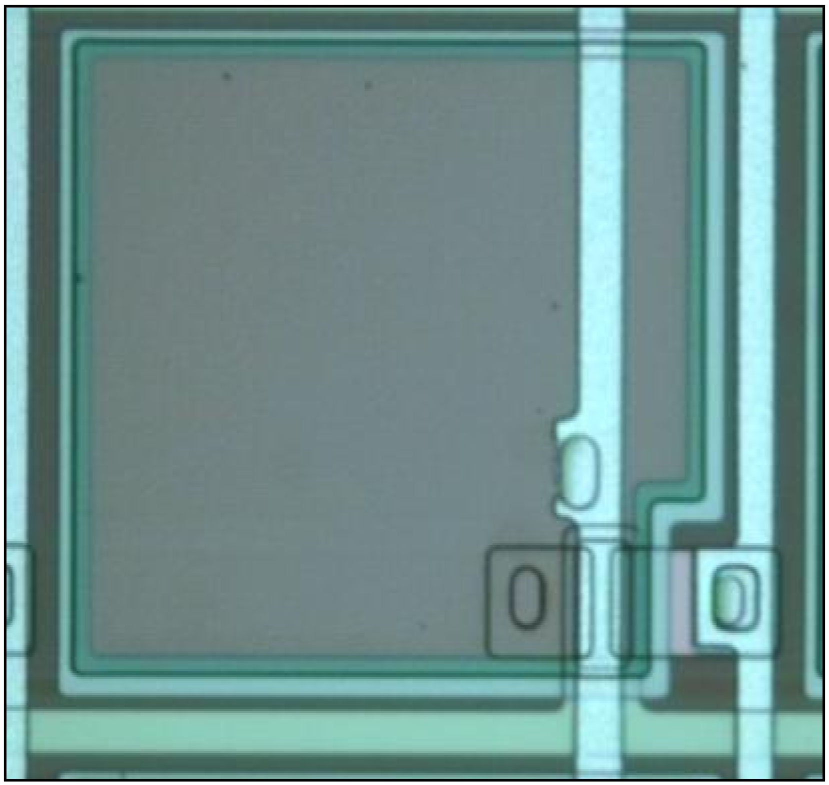


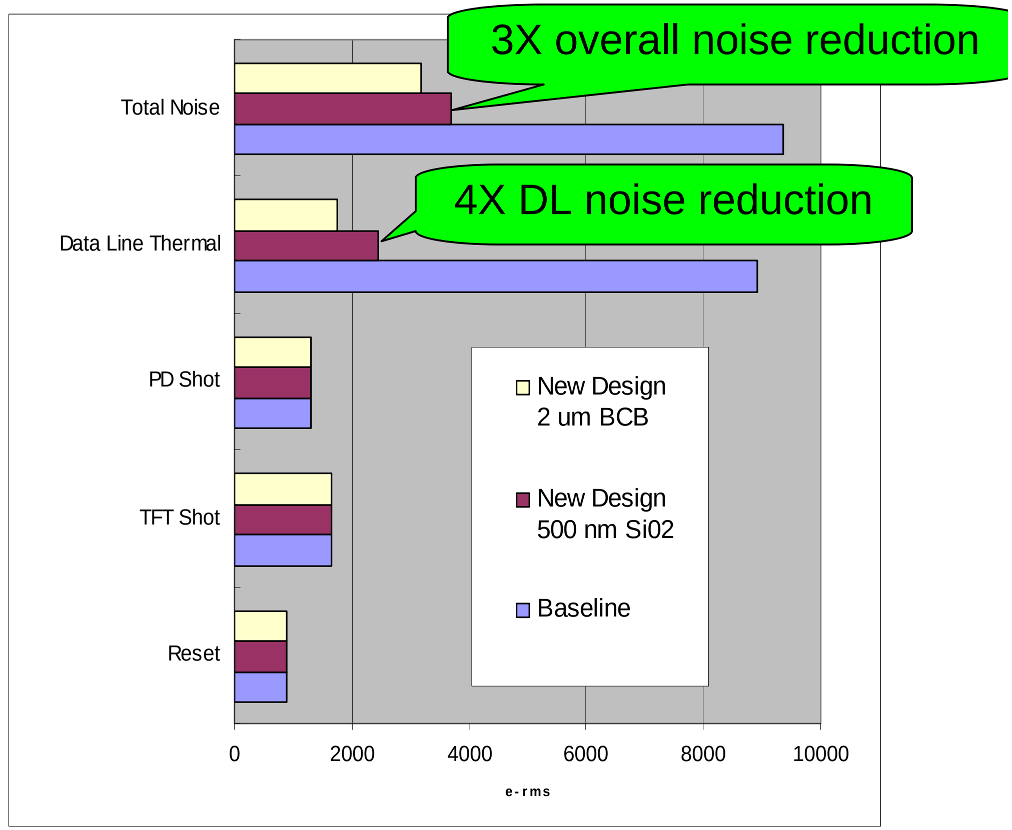
- 2 µm thick BCB layer or thick nitride dielectric between TFT plane and photosensor plane
  - Planarization of topography
  - Reduced overlap capacitance
- Dataline in metal 5
  - 500 nm Al for low resistance
  - 2,000 nm BCB + 400 nm nitride dielectric for reduced overlap capacitance

Experimental a-Si Passive Pixel

3X Noise Reduction in Passive a-Si Arrays

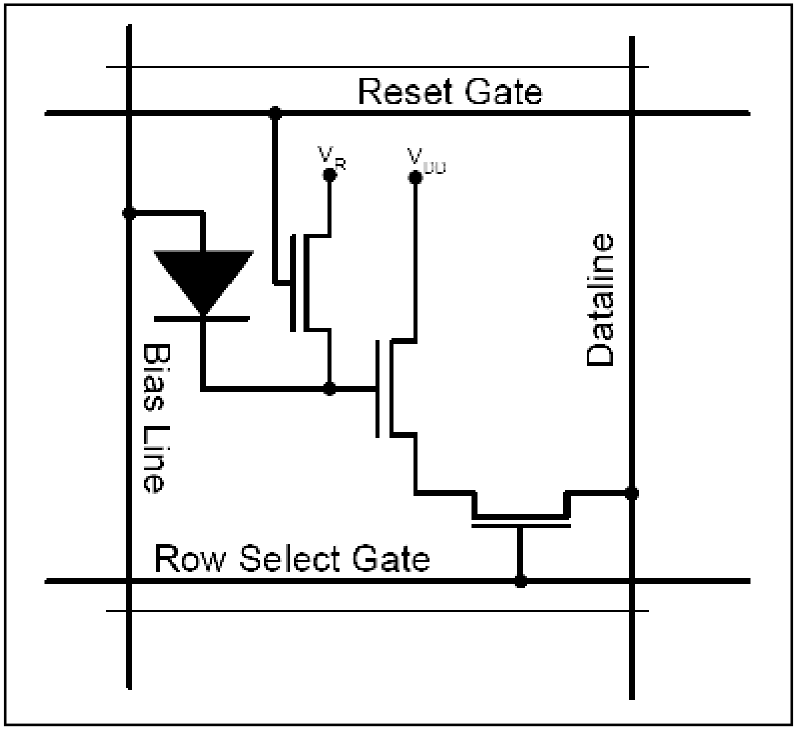


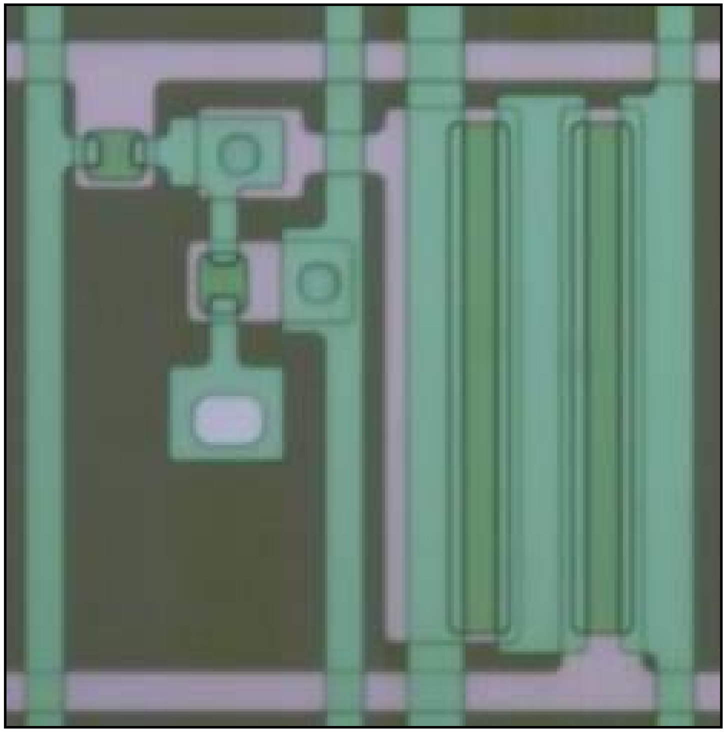




- ~40% Reduction in C_{DL}
- ~90% Reduction in R_{DL}
- 4X reduction in data line thermal noise

Advanced a-Si arrays
Active pixel designs

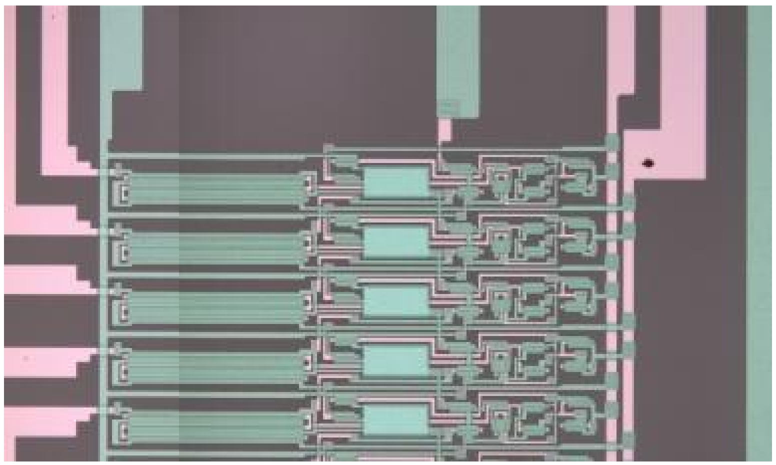


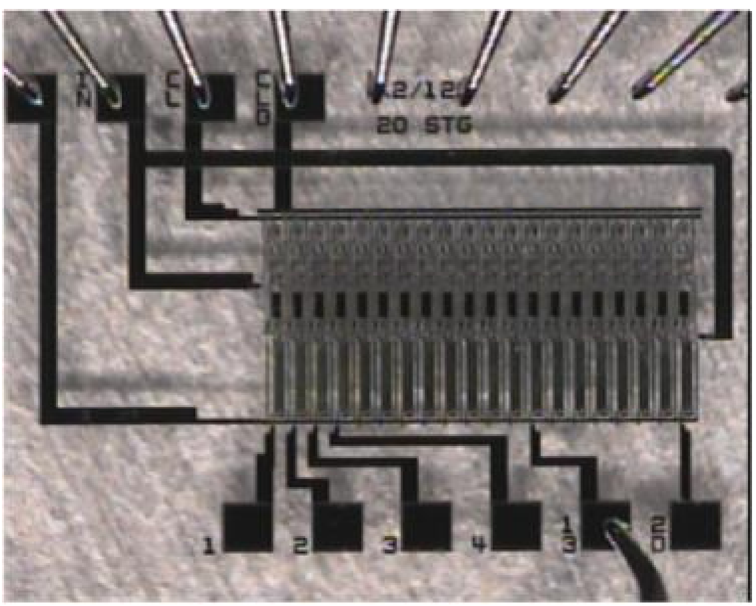


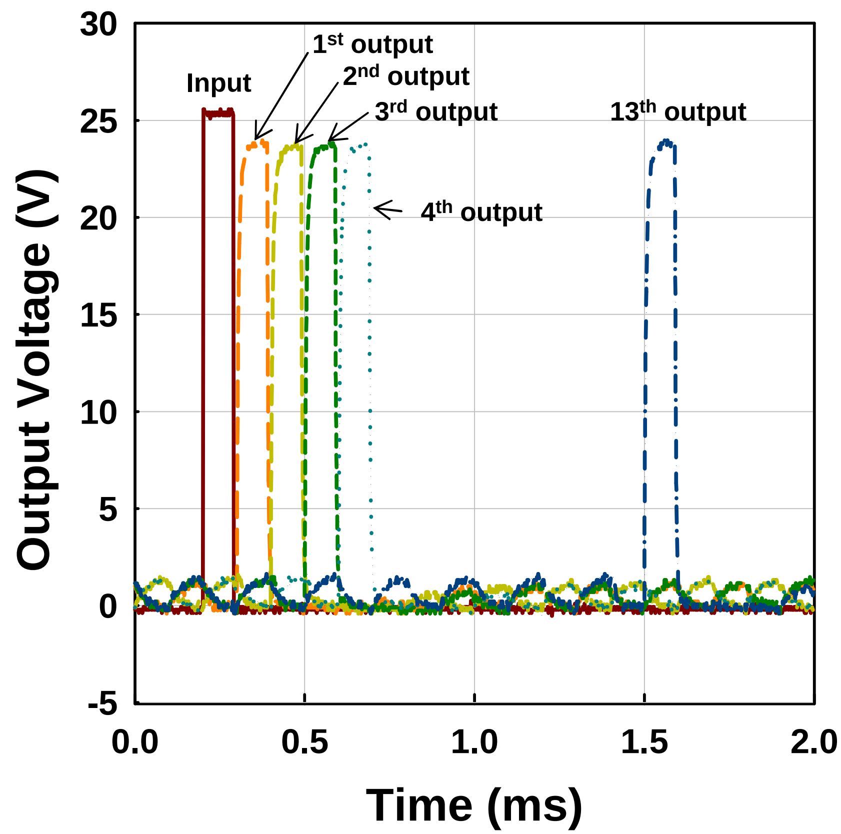
- Advantages
  - **Noise Reduction**: Dataline thermal noise reduced by charge gain of pixel amplifier (>10X)
  - **Speed Increase:** 10X or more reduction in dataline setting time due to active amplifier
- Disadvantages
  - **Yield:** 9X increase in transistor area and ~ 3 additional bias and clock lines
  - **Linearity:** Smaller linear range of output vs. exposure
  - **Stability:** TFT threshold voltage shift with aging – TFT is amplifier, not a switch

Amorphous Silicon Shift Register for Active Pixel Array

120 um pitch a-Si:H shift register

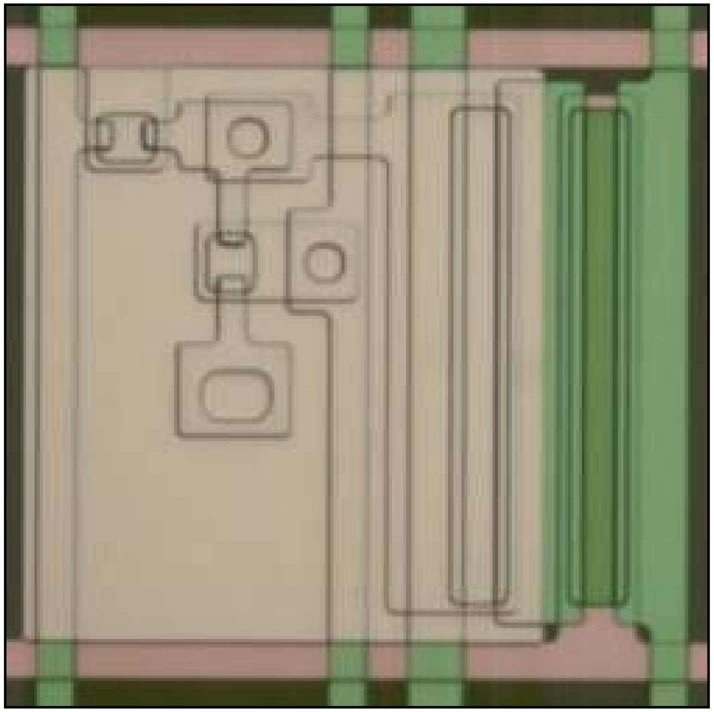


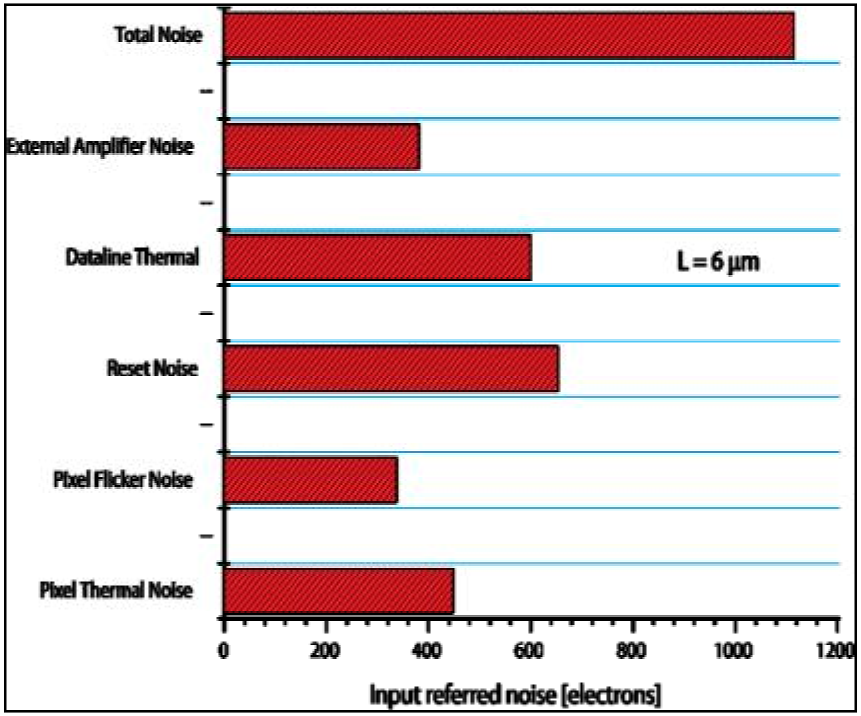




Advanced a-Si arrays

Active pixel designs

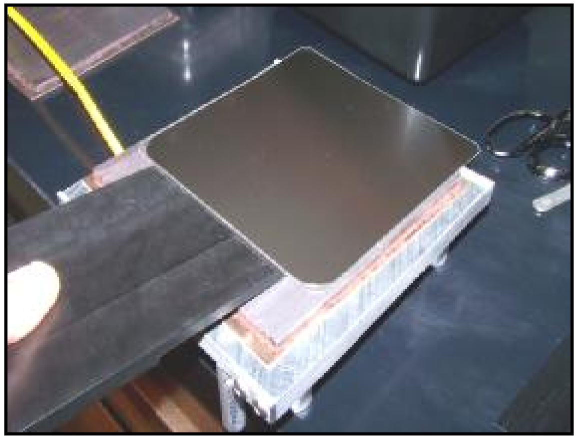




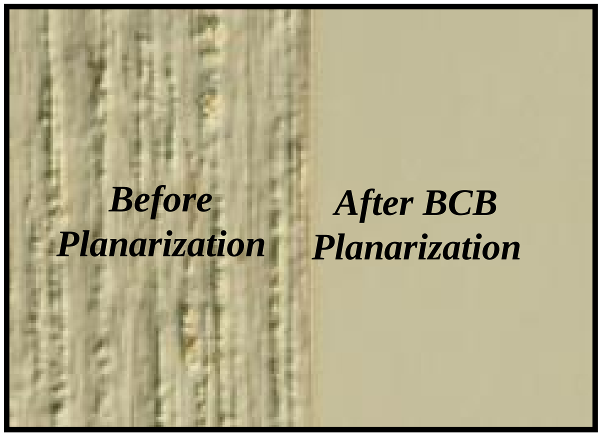
- Dataline thermal noise reduced 5X by charge gain of pixel amplifier
- External amplifier noise reduced 5X by charge gain of pixel amplifier
- Largest remaining noise source is reset noise of the photodiode – can be further reduced by thicker intrinsic amorphous silicon

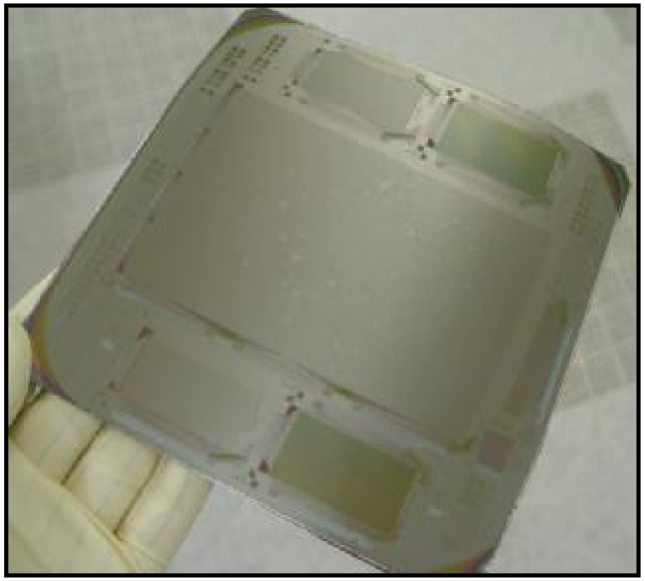
Fabrication of DR Array on Metal Foil

Laminate to Glass

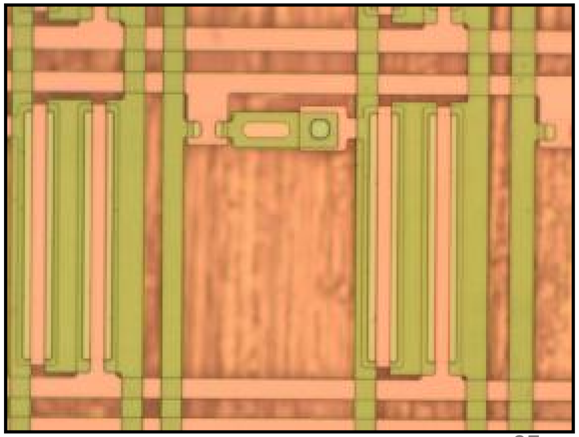


Planarize

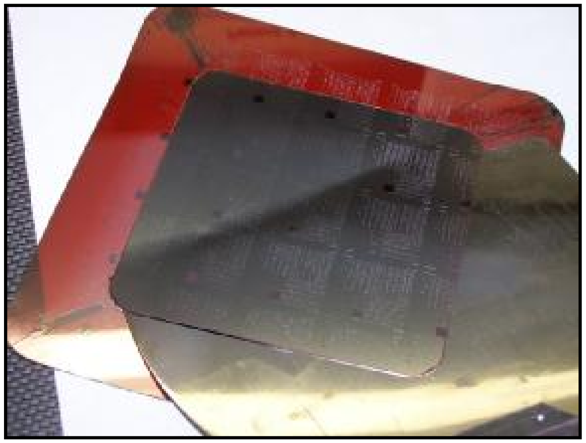




Fabricate Array



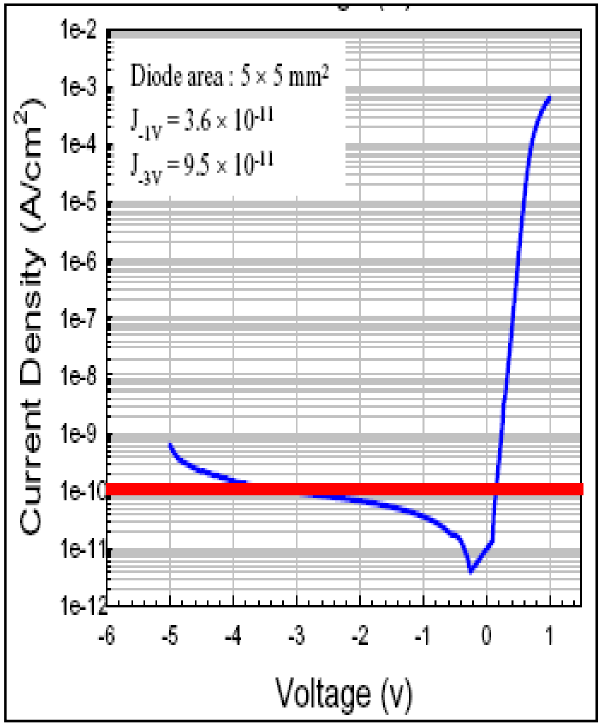
Release

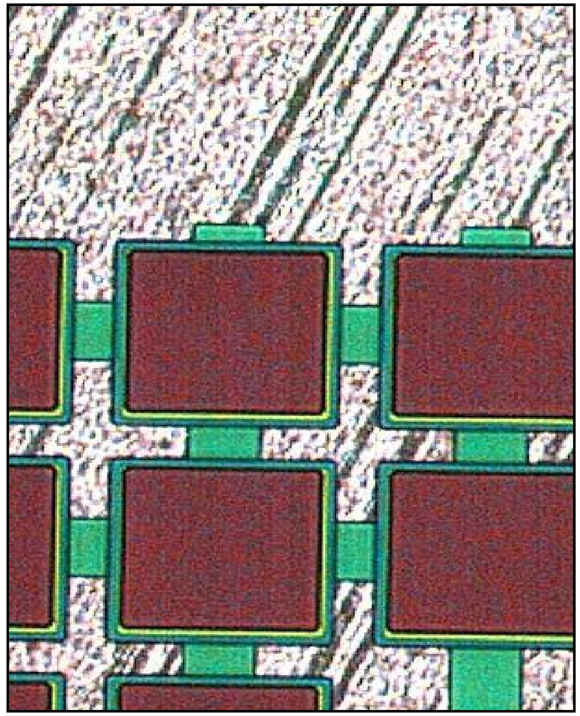


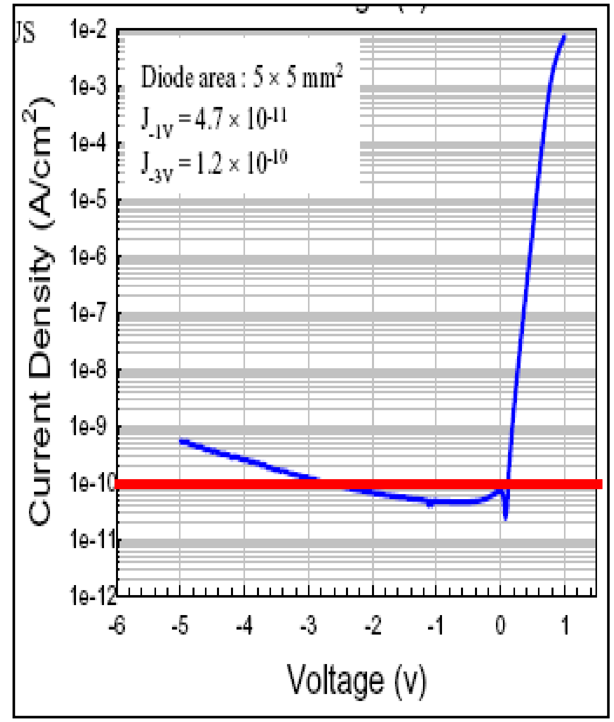
PIN photodiodes on stainless steel substrates

Comparison of 280 C PIN diodes on glass and on free-standing Stainless foil

280 C PIN on Glass	*PIN Diodes on Stainless*	*280 C PIN on Stainless*







J_D(-1V) = 36 pA/cm²	*125 mm stainless foil* *3 mm BCB planarization* *8 nm rms roughness*	*J_D(-1V) = 47 pA/cm²*

Outline

- Introduction to medical imaging modalities
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  - LTPS silicon imaging arrays
  - Silicon imaging arrays
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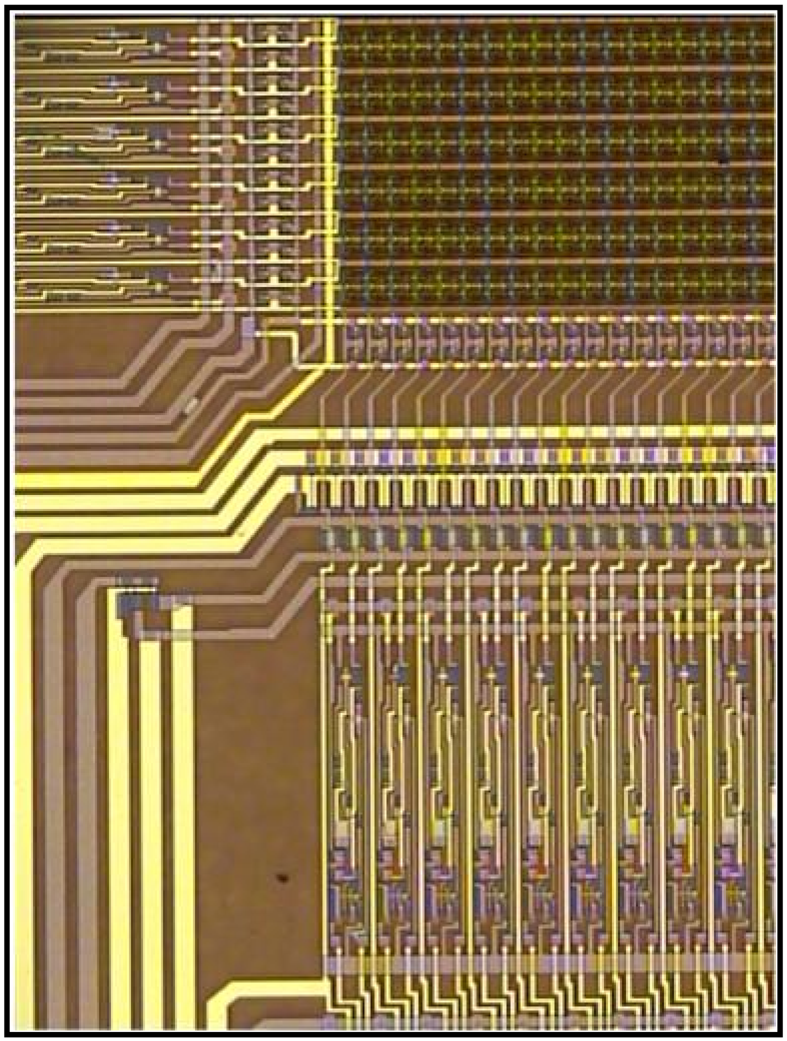
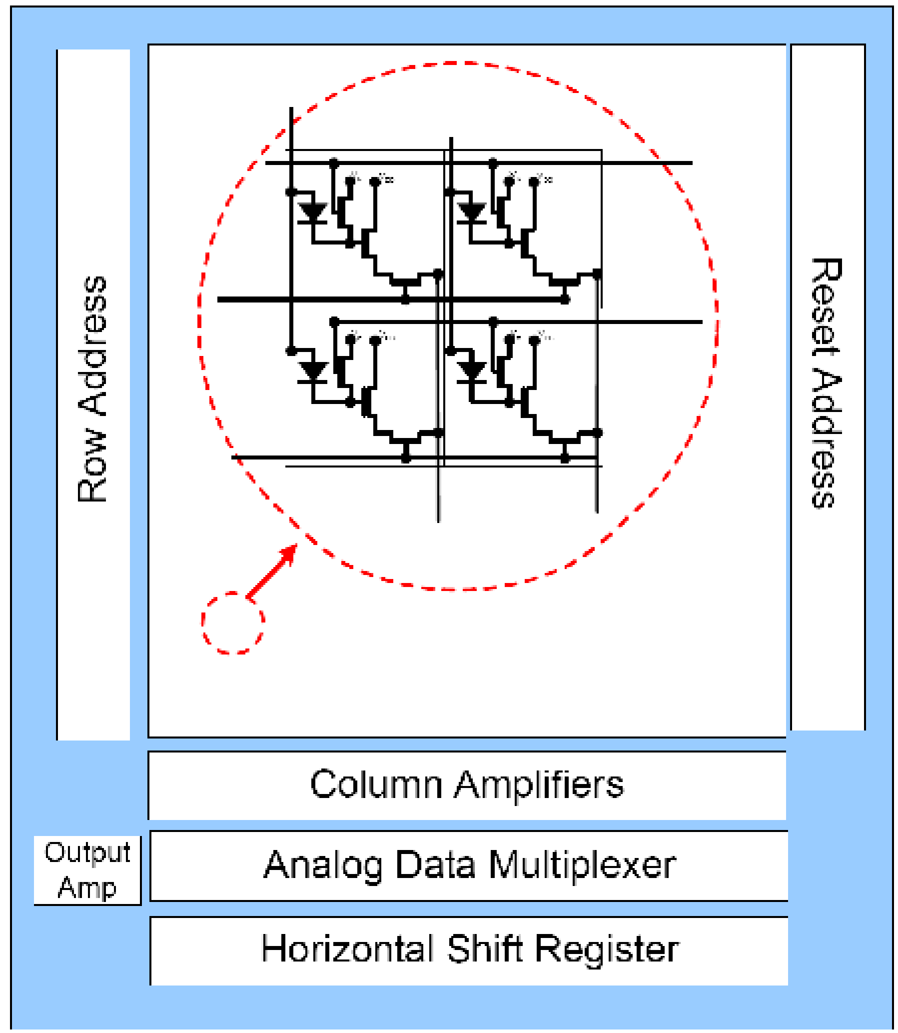
- Applications for Quantum Limited Detectors

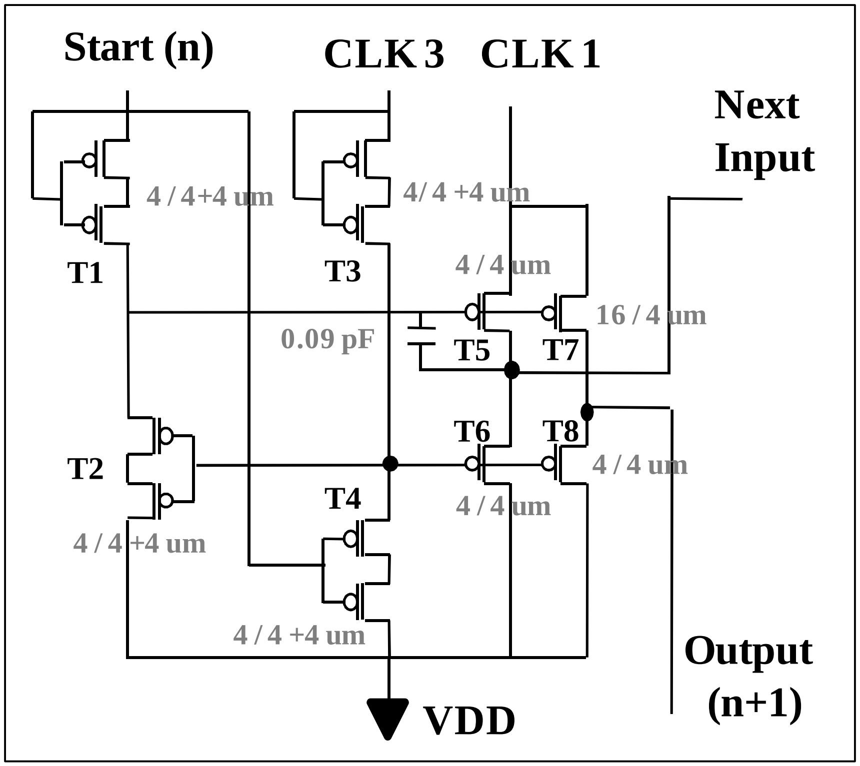
LTPS imaging array with peripheral circuits

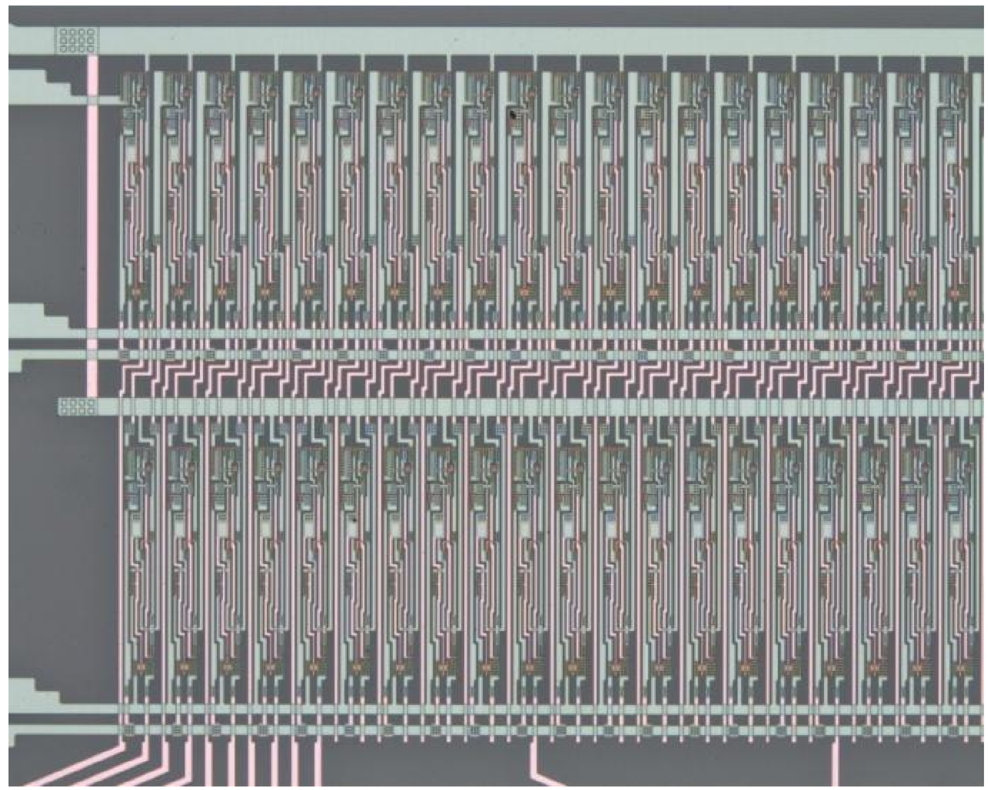




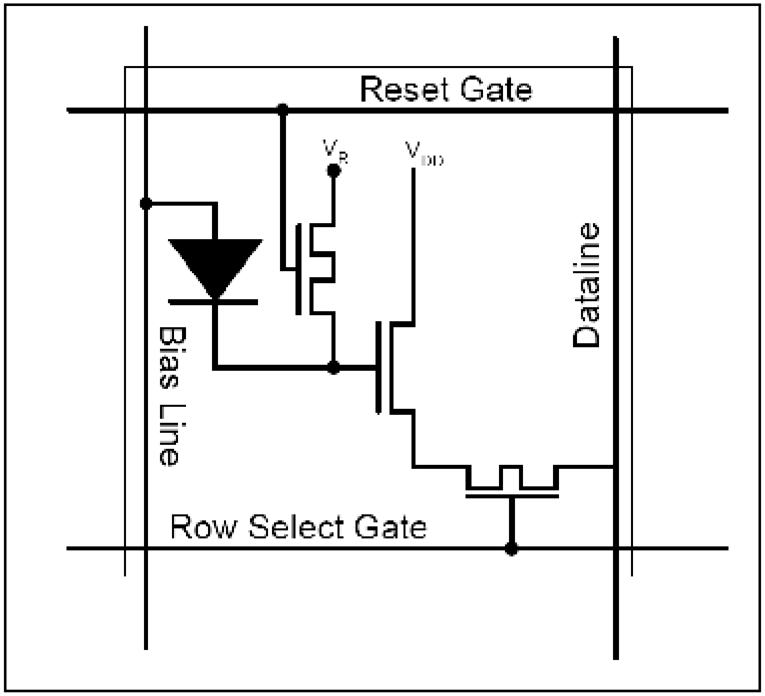
LTPS imaging array with peripheral circuits

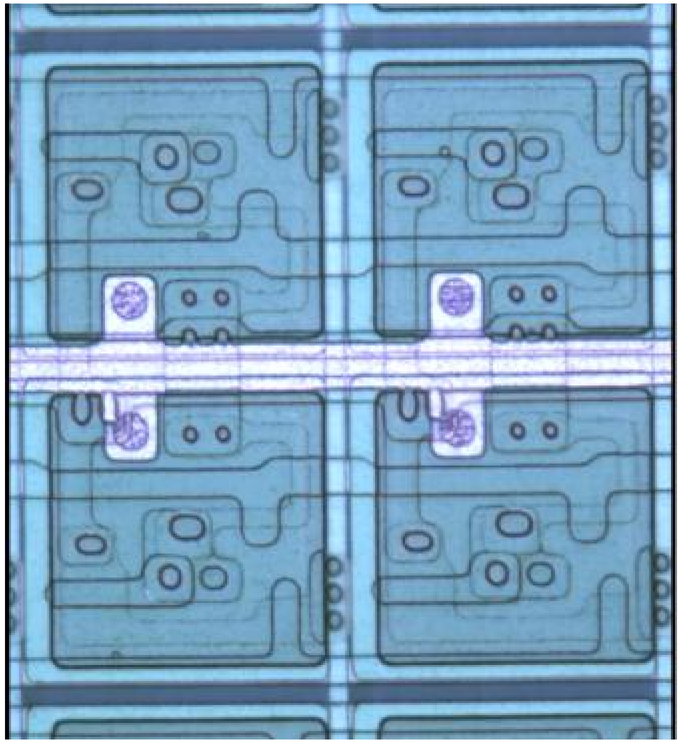
PMOS LTPS Shift Register

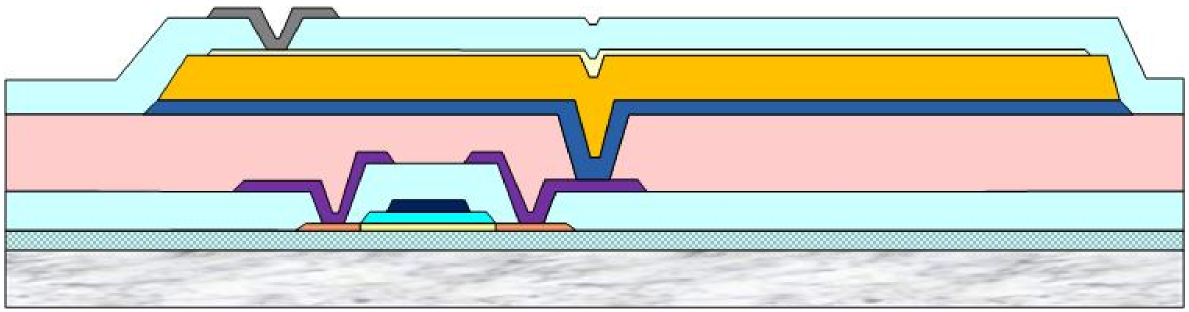




Pixel of LTPS Imaging Array with a-Si PIN photodiode

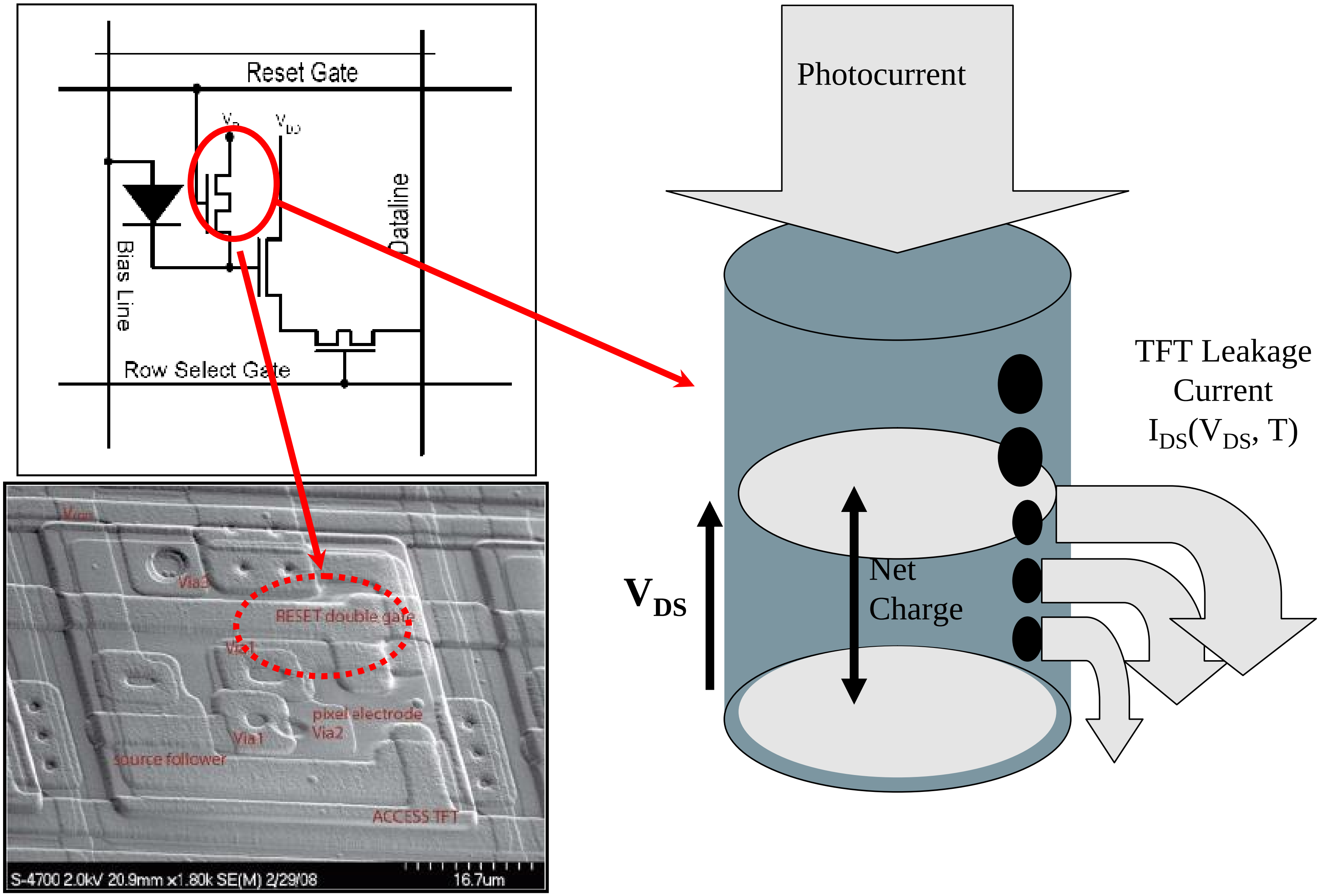






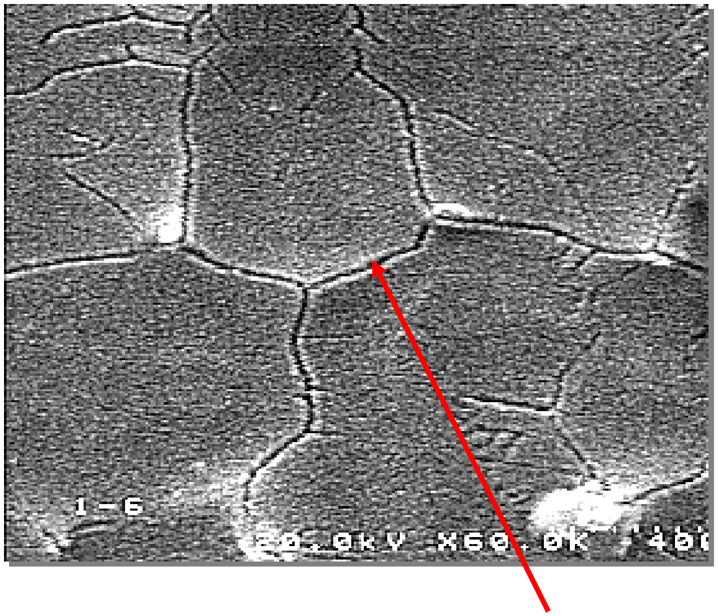
Key Challenges for LTPS Imaging Arrays

Reset TFT leakage current: siphons off photo-charge



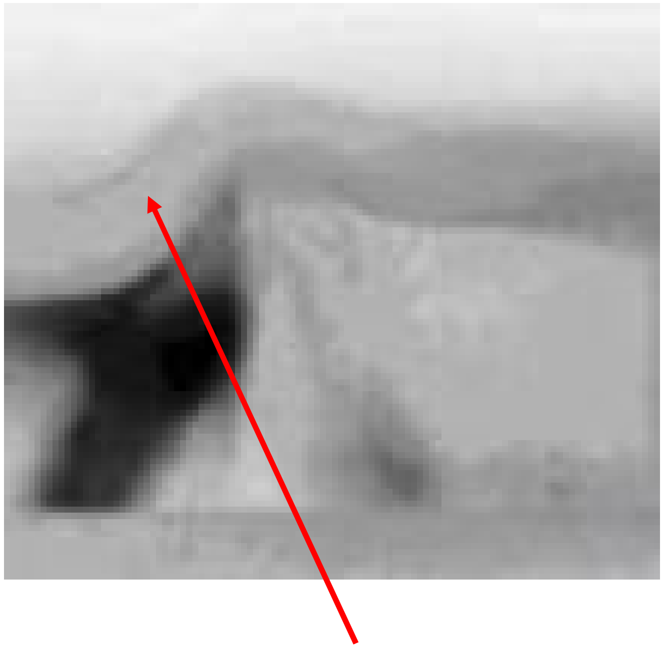
Sources of Leakage in LTPS TFT's

TFT Channel Leakage At Grain Boundaries



- Generation current at grain boundaries results in TFT leakage
- Gate-to-drain field enhances leakage current, resulting in exponential increase in leakage with gate voltage, even band-band tunneling
- Variable from TFT to TFT

Gate Oxide Leakage at Grain Boundaries

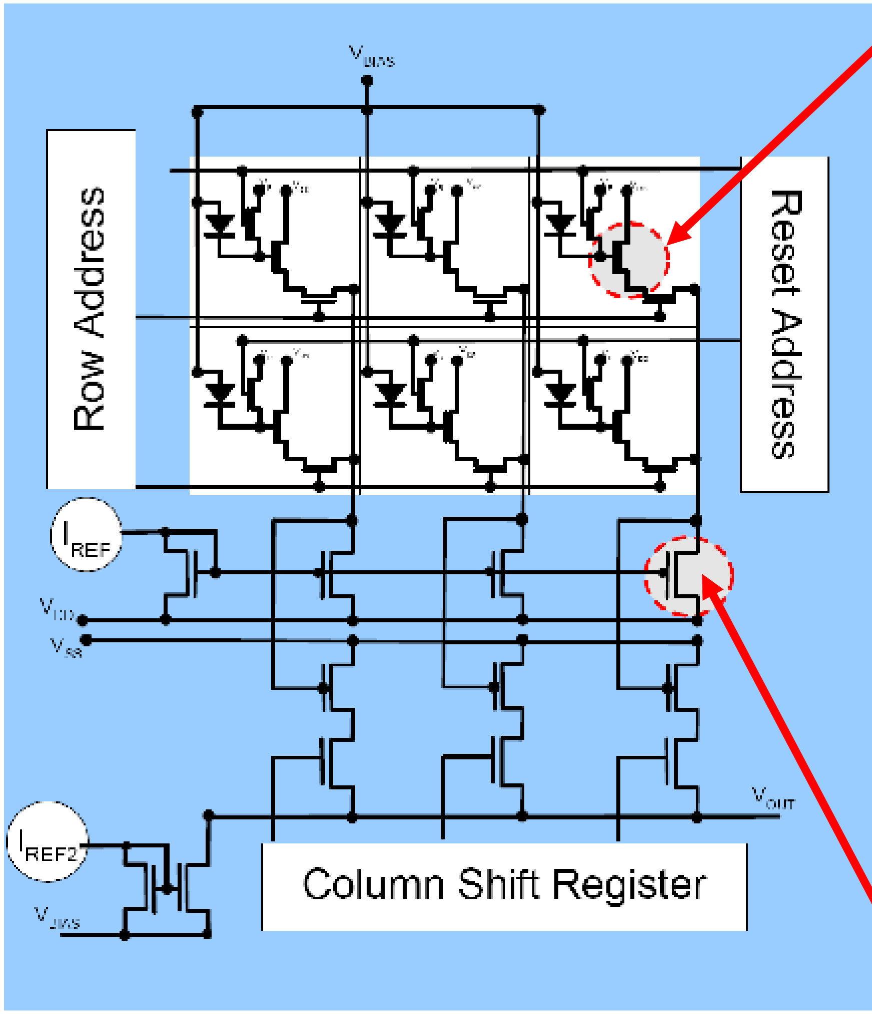


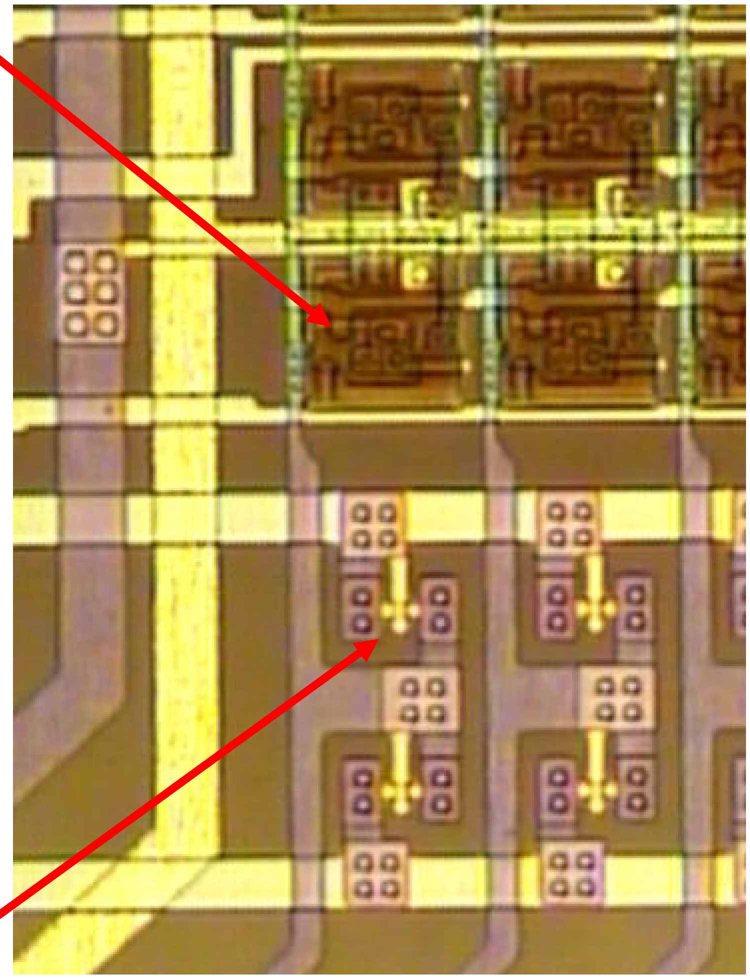
- Surface topography at grain boundary edges causes gate oxide leakage
- Variable from TFT to TFT

Key Challenges for LTPS Imaging Arrays

Threshold voltage variability

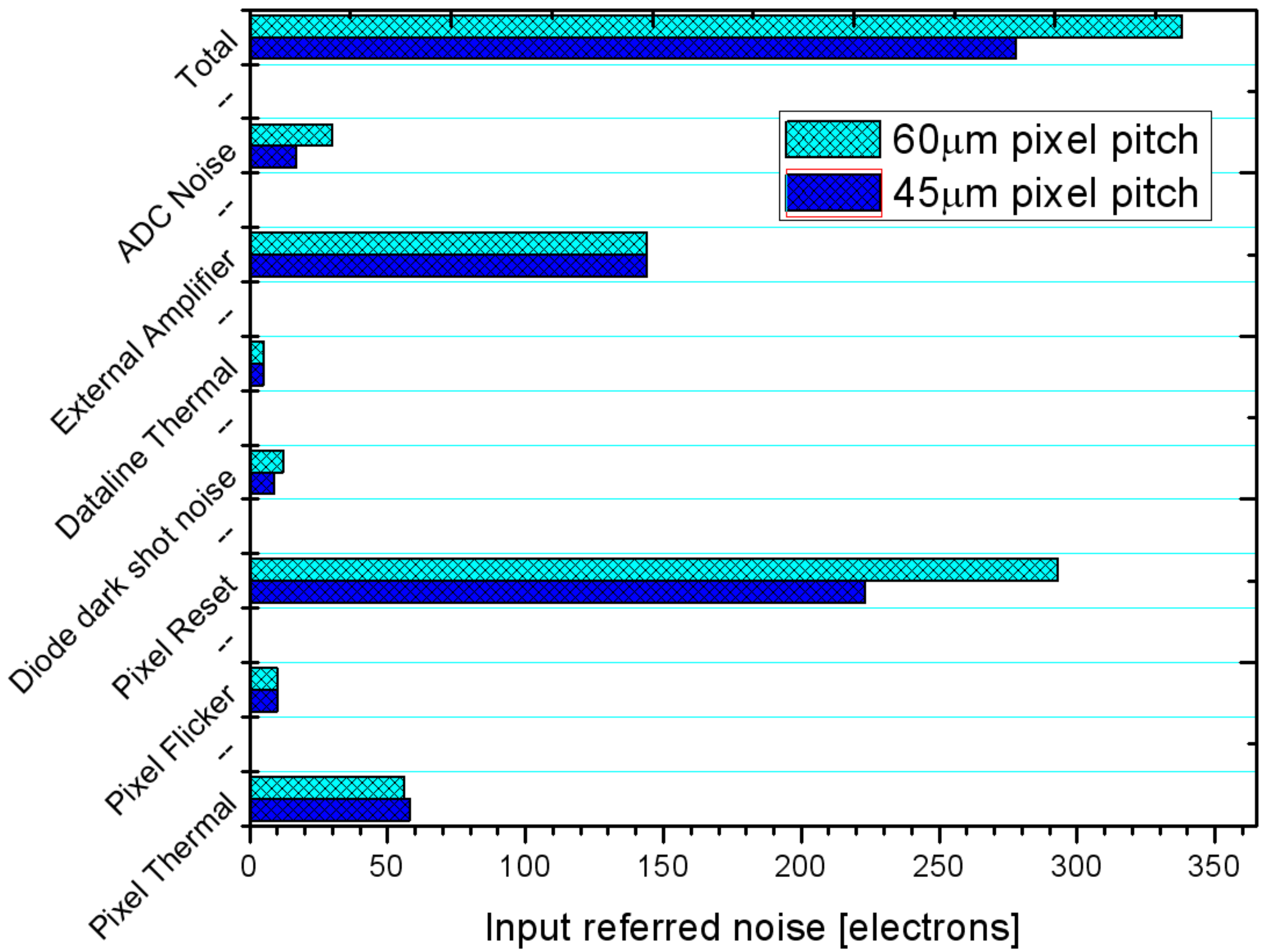
Pixel Amplifier TFT





Current Mirror Column Amplifier TFT

Noise in LTPS Imaging Arrays



Summary

Directions for radiographic detector development

2-D Projection Radiography

- **Robustness, weight** → ***Detector arrays on metal foil & plastic***
- **Cost** → ***Fabless model (utilize display fabs)***

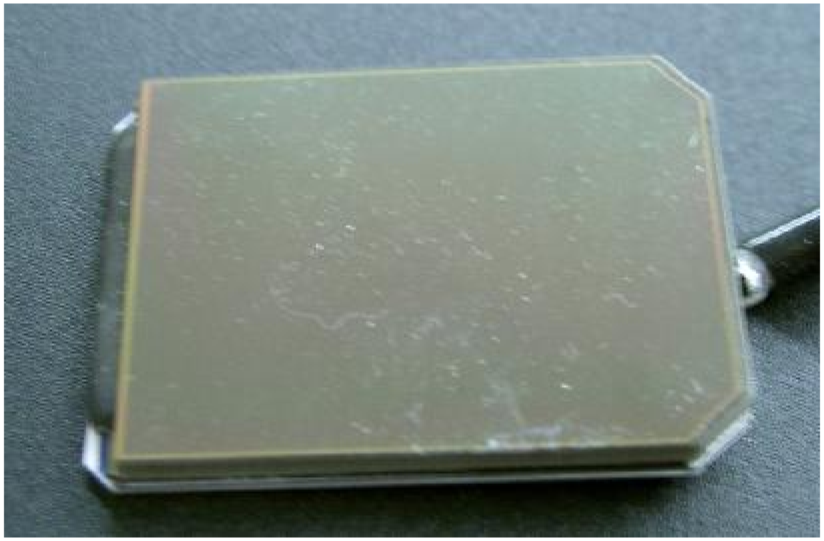
Advanced Applications (Dual energy and 3D)

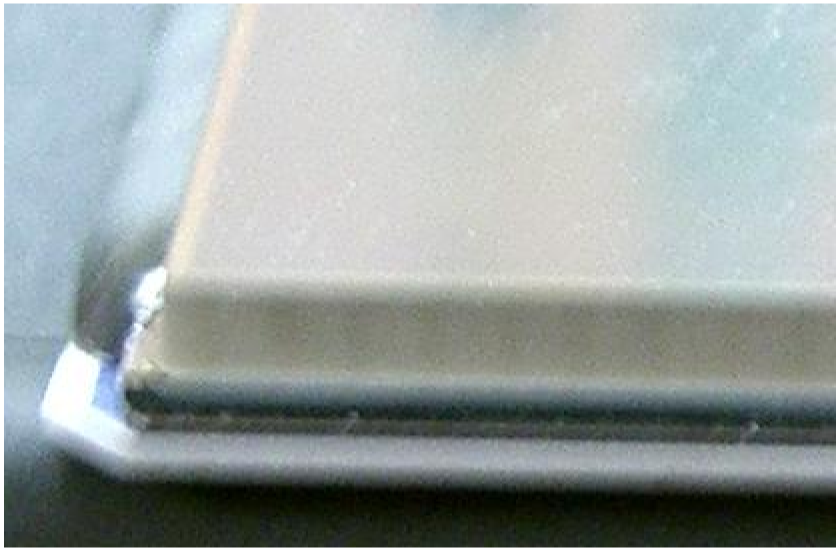
- **Improved sensitivity** → ***Improved passive pixel designs***
  Active pixel a-Si arrays
  Active pixel LTPS
- **Improved resolution** → ***Structured phosphors***
  Direct detection
  Active pixel LTPS with peripheral circuits
- **High frame rate** → ***Active pixel a-Si arrays***
  Active pixel LTPS

Outline

- Introduction to medical imaging modalities
  - X-ray, CT, MRI, SPECT, PET, Ultrasound, Endoscope, NIRS
- Radiography
  - Introduction to digital radiography
  - Clinical challenges
  - Amorphous silicon imaging arrays
  - LTPS silicon imaging arrays
  - Silicon Imaging arrays
- Molecular Imaging
- Applications for Quantum Limited Detectors

Carestream Dental Array

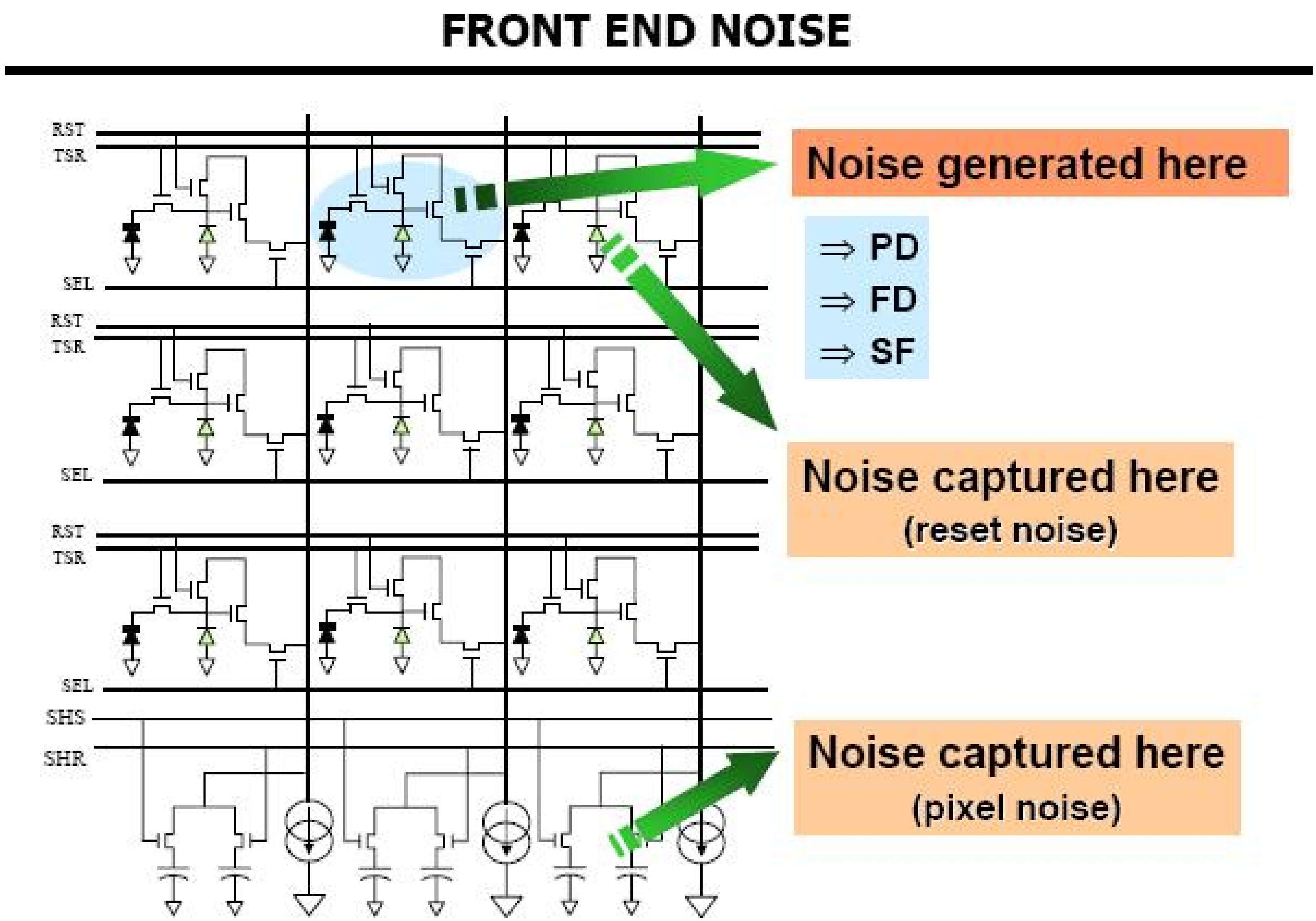




Typical characteristics of CMOS Imagers for Dental

Parameter	Typical values
Pixel dimension	18 μm
Array size	~ 27mm x 36mm
Pixels	1,440 x 1,920
Quantum Efficiency	~ 50% at 550 nm
Fill factor	40%
Saturation charge	~ 500K electrons
Noise	50 - 100 rms electrons
Dynamic range	5,000:1

Noise in CMOS Image Sensors



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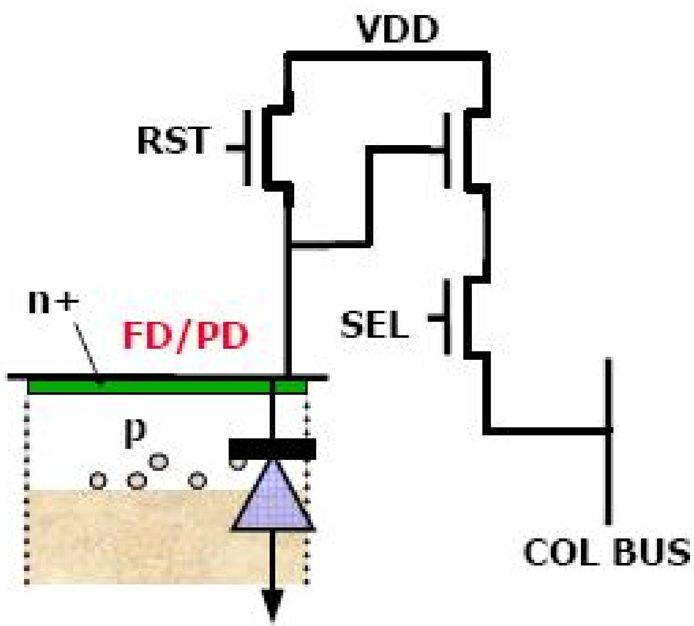
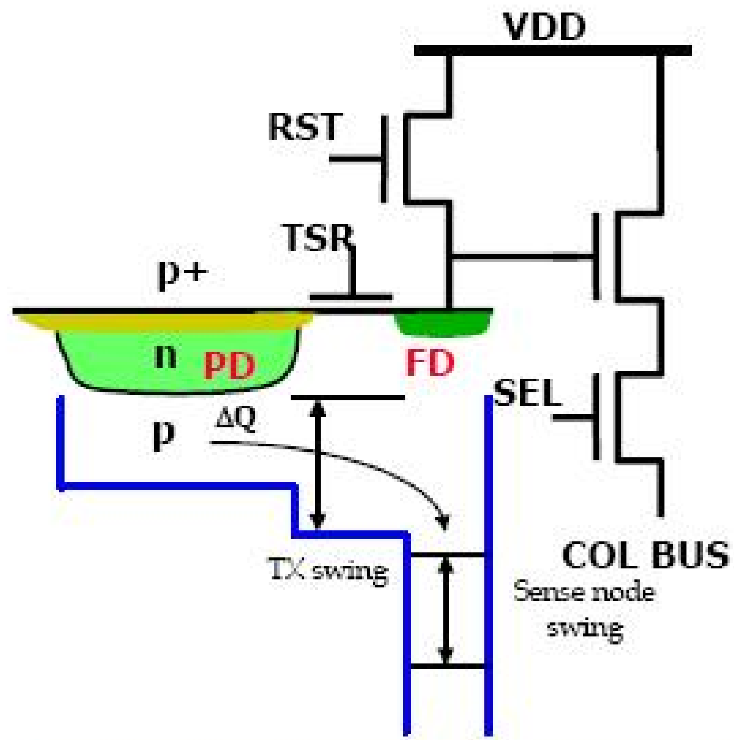
Photodiodes for CMOS image sensors
P-N junction and Pinned Photodiode

P-N Junction Photodiode



Photodiode CMOS pixel

Pinned Photodiode



Pinned photodiode CMOS pixel

- Buried diode can be used with "3T" or "4T"
- Reduces dark current (surface component)

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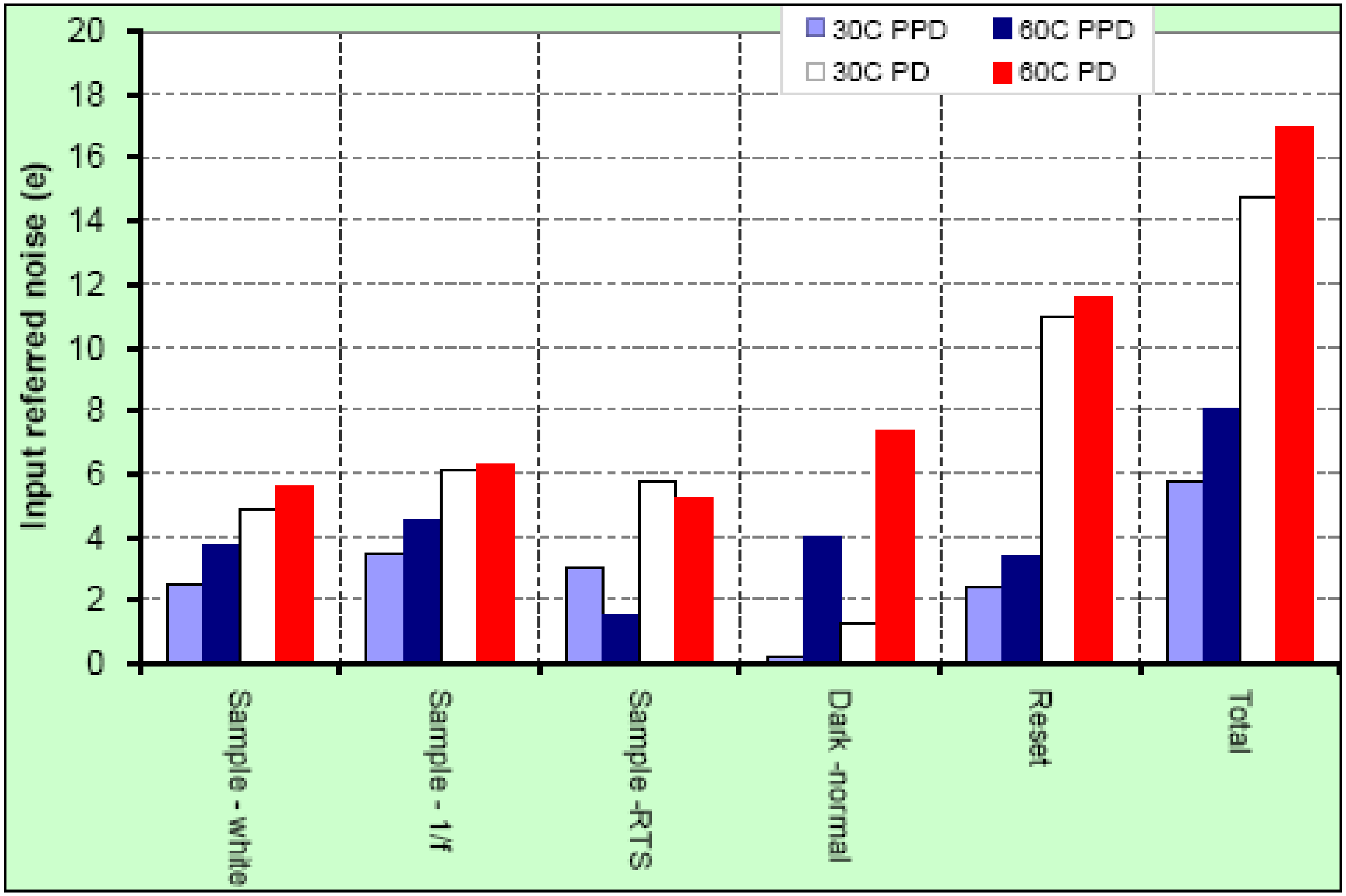
Noise in small-pixel CMOS image sensors



- **PD:** *higher max SNR, lower DR, higher FW, higher noise*
- **PPD:** *lower max SNR, higher DR, smaller FW, lower noise*

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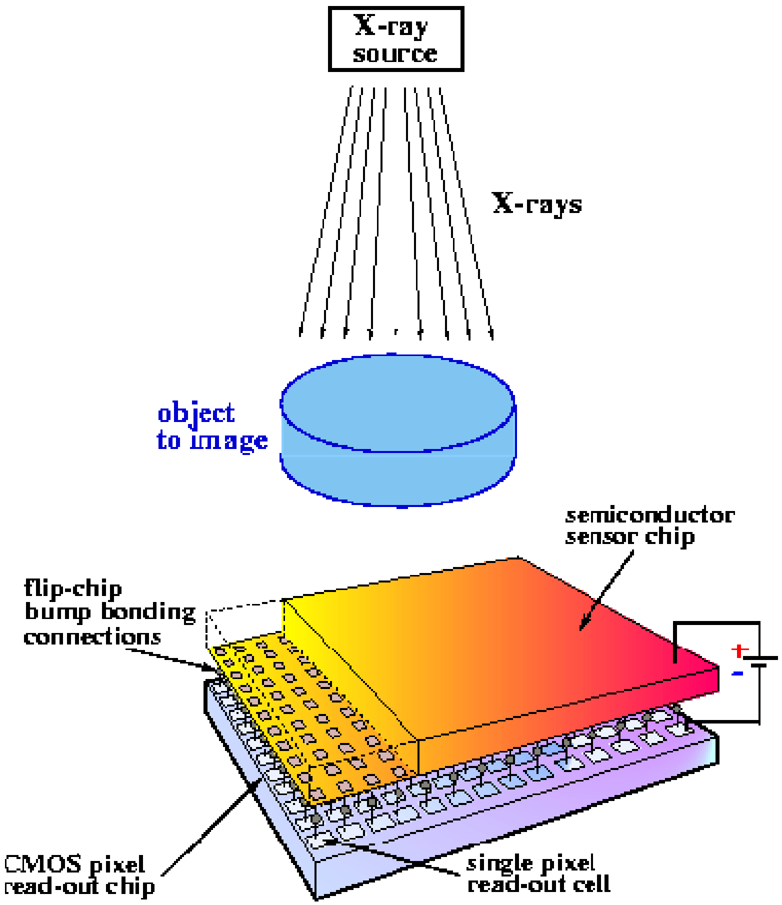
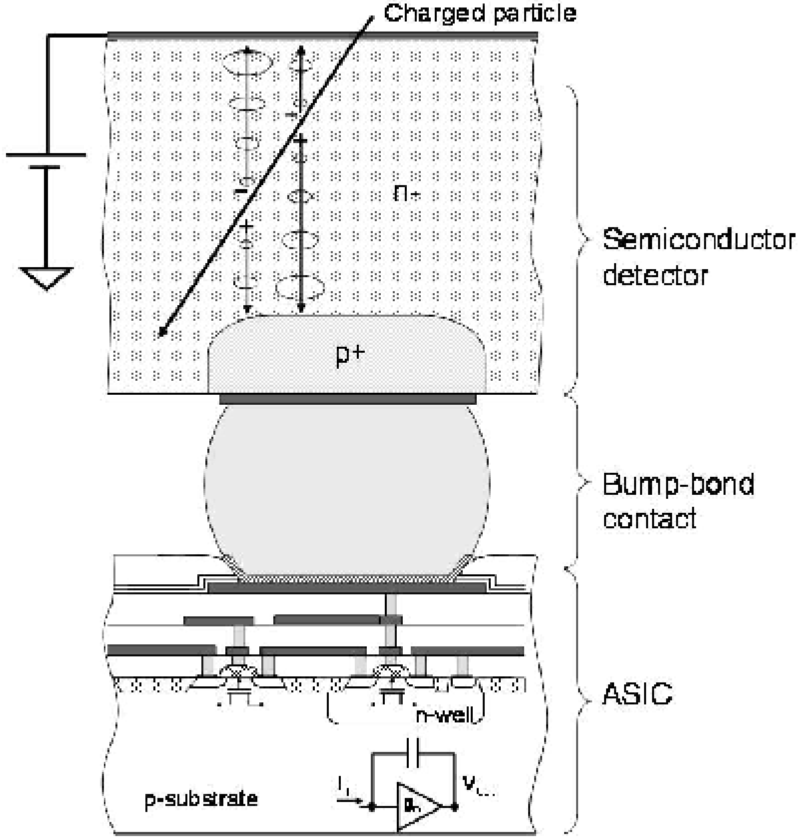
Photon Counting Arrays for Medical Imaging
Medipix Project



- Collaborative European program
- Goal is to develop a photon-counting CMOS-Si backplane modules
- Interconnect to a variety of sensor chips
  - Bump-bonded to CdTe and CdZnTe
  - GaAs
  - Si
- 4-side tiling for large-area detector arrays

Photon Counting Arrays for Medical Imaging
Medipix 2 and Medipix 3 chip



- Medipix 2
  - 55 µm square pixels can accept positive or negative charge
  - 256x256 array for a 14mm x 14mm image area
  - 3-side buttable
  - Adjustable upper and lower detection thresholds
  - 13-bit counter in each pixel
  - Up to 100 kHz count rates
- Medipix 3
  - 4-side buttable with 55 µm pixels
  - 2 counters per pixel (for simultaneous read-write)
  - Dual-energy mode with two threshold levels
  - Can operate either in photon counting or in integration mode

Comparison of Medical Imaging Array Technologies

	Silicon		Flat Panel	
	Photon counting	Integrating	LTPS	A-Si
Imager Area	0.5”	< 1” typical ~ 4” max	4” – 14”	14” - > 25”
Cost/area	> \$ 200.00/in^2	\$ 40.00/in^2	\$ 1.00/in^2	\$ 0.50/in^2
Pixel dimension	200 μm	2-40 μm	40-400 μm	40-400 μm
Quantum Efficiency	70% * gain	70%	70% with a-Si PIN	
Noise	1 el	5-100 el	100-500 el	1,000-5,000 el
Medical Applications	Molecular Imaging	Dental Molecular Imaging Endoscopy	Radiography Molecular Imaging?	

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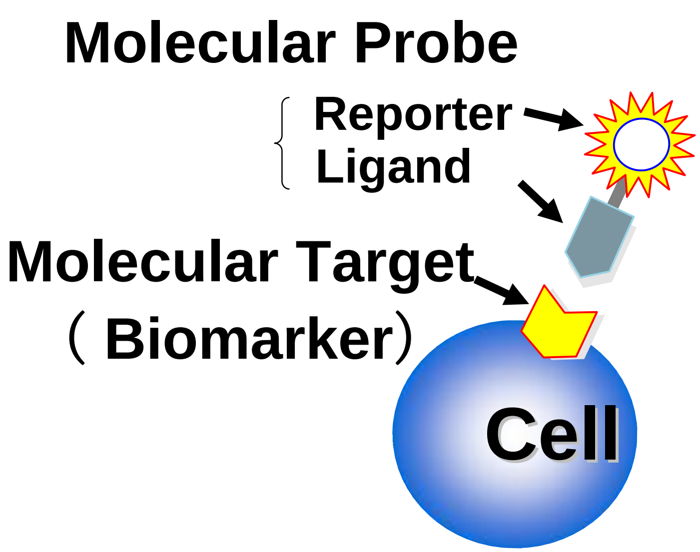
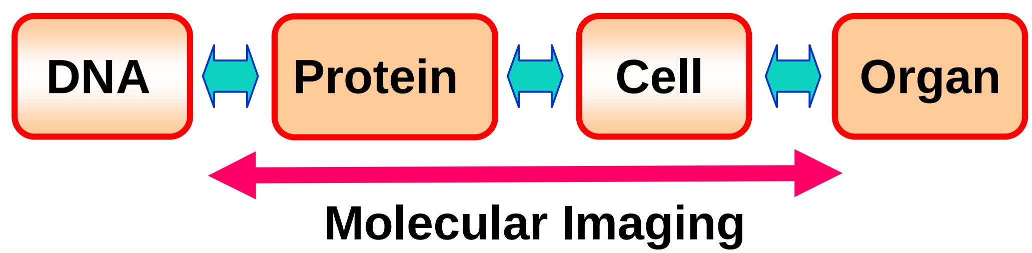
Molecular Imaging

"MI techniques directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications."

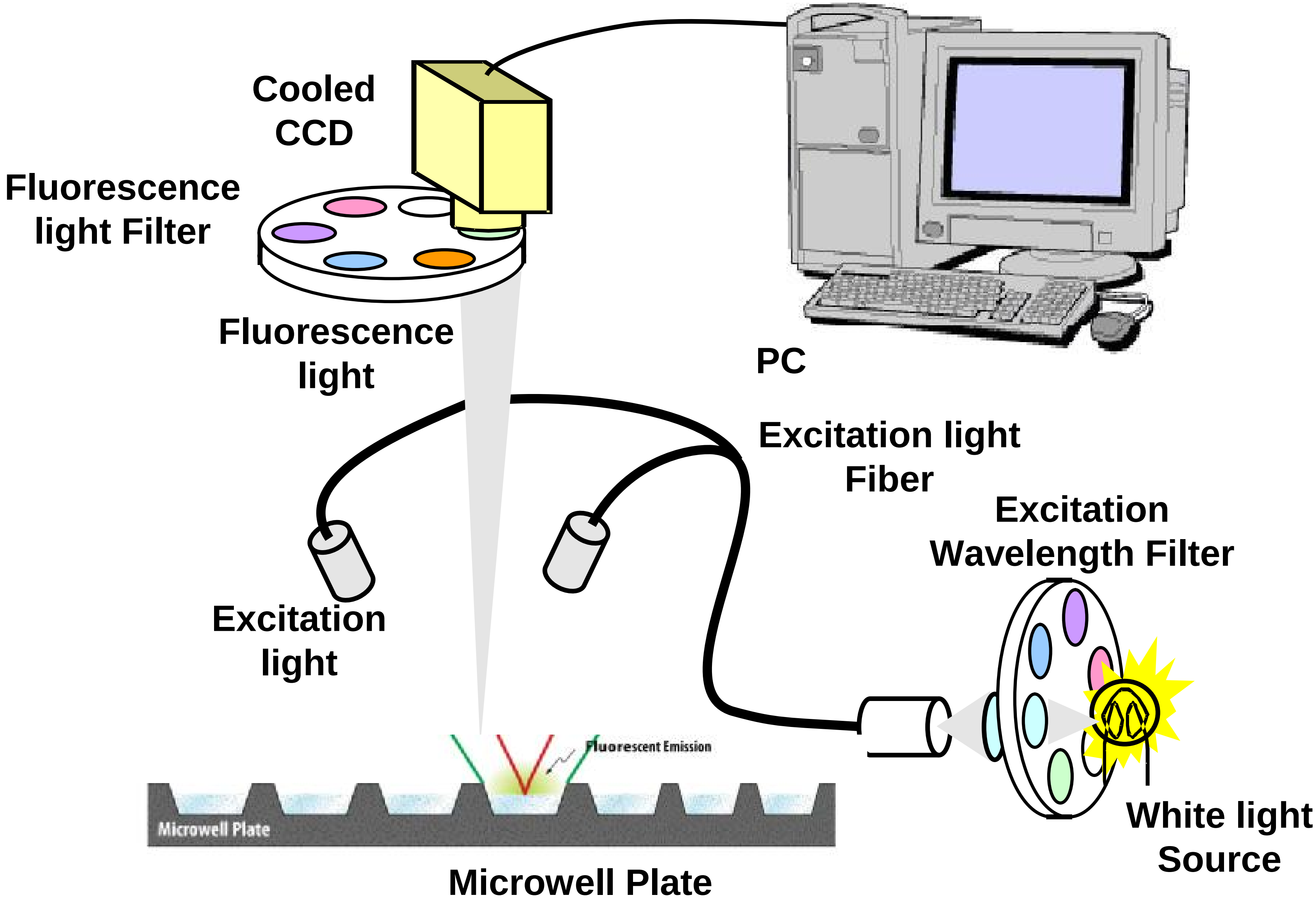
"Report of a Summit on Molecular Imaging" Radiology 2005



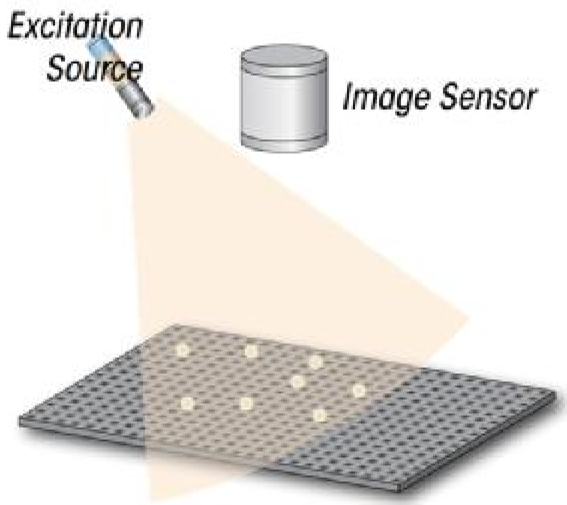
- *in vivo*
- *cellular or molecular level*
- *imaging*

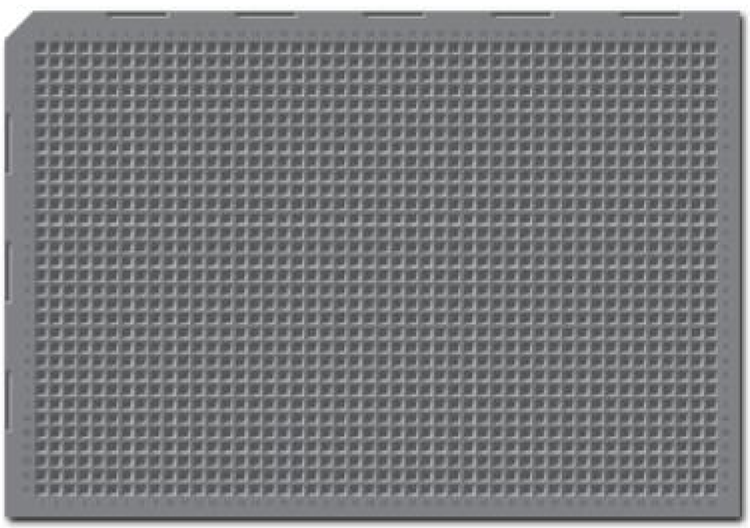


Fluorescence Imaging



Molecular Imaging – Microplates





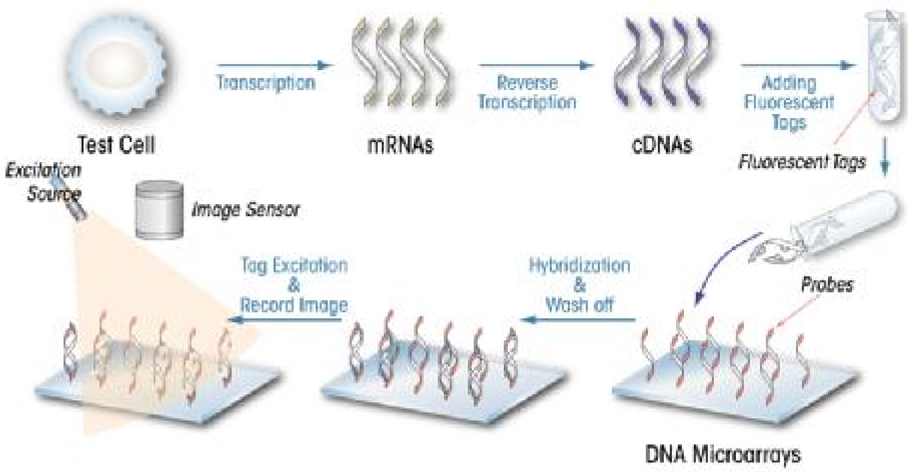
Typical photon flux in the range of 10^3–10^6ph/mm²/sec

For larger molecules or tissues immersed in aqueous solutions, microwells are typically used instead of microarrays.

1. Features of known concentration are usually fixated on the surface of the wells.
2. Sample tissues with labeling fluorophores are dispensed in the well.
3. Only certain samples will bind to the wall and upon excitation, these sites would be identified.

The detection process is similar to those presented for microarrays where low-noise and high-sensitivity detectors are required aside from micro-liter dispensers etc. The plate area is comparatively large and typically requires multiple scans for each microplate.

Molecular Imaging – DNA Microarrays



Gene expression profiling with DNA microarrays.

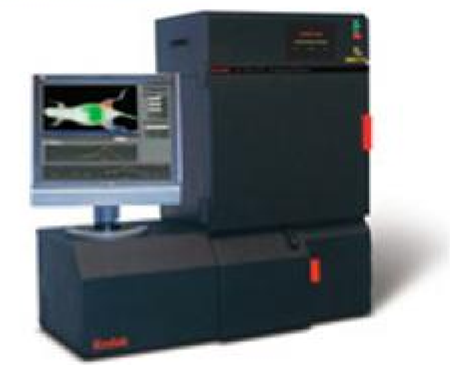
DNA microarrays can be used to measure changes in the expression levels of genes.

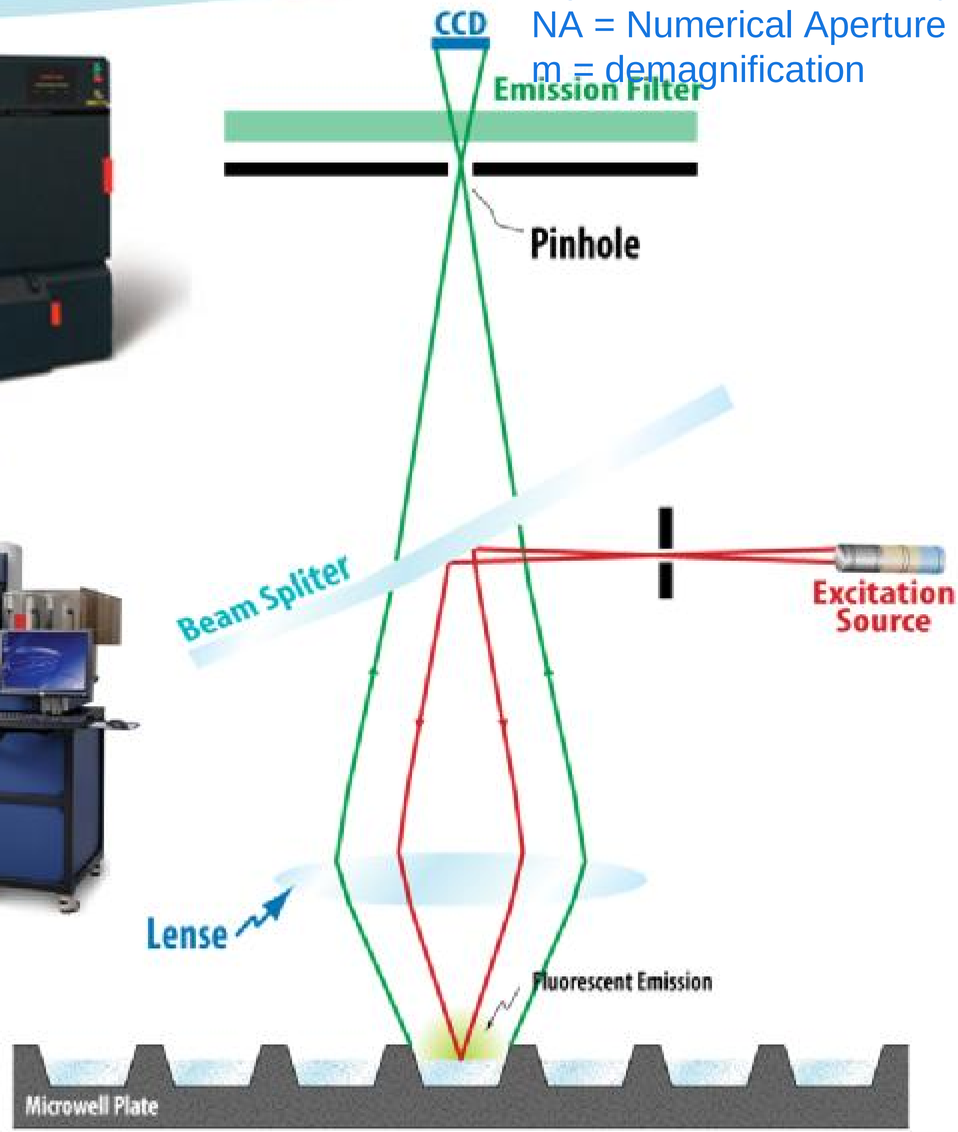
1. The microarray itself contains a 2D array of equally spaced features, each containing a specific DNA sequence that are covalently bonded to a solid substrate such as glass.
2. Test samples are transcribed to unstable messenger RNAs and reverse transcribed to the more stable complementary DNAs.
3. The cDNAs are labeled with fluorophores and are introduced to the microarray.
4. A number of features on the microarray will hybridize to the labeled samples.
5. A light source is used to excite the fluorescent labels.
6. A detector is used to sense the emission form the labels and gauge the degree of hybridization.

This application requires low-noise detectors aside from mechanical and optical assembly needed to position and focus the sample.

Detection with cooled CCD cameras

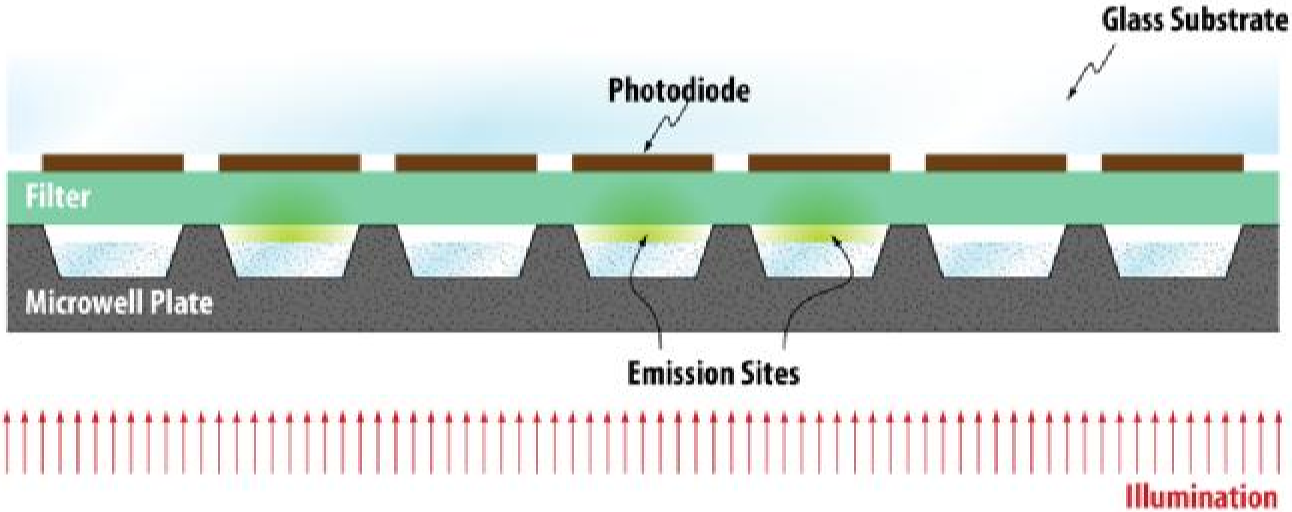
Light Collection Efficiency ~ $NA/(m^2+1)$ is < 1%
NA = Numerical Aperture
m = demagnification





- In current detection technology, CCDs are employed as the underlining sensor. These sensors are cryogenically cooled to lower dark noise.
- The detector assembly usually follows the confocal microscopy design where each feature site is scanned sequentially.
- The fluorescent emissions are discriminated using an emission filter that cross match with the emission wavelength of the labels.

Contact-type Flat-panel Imaging Arrays

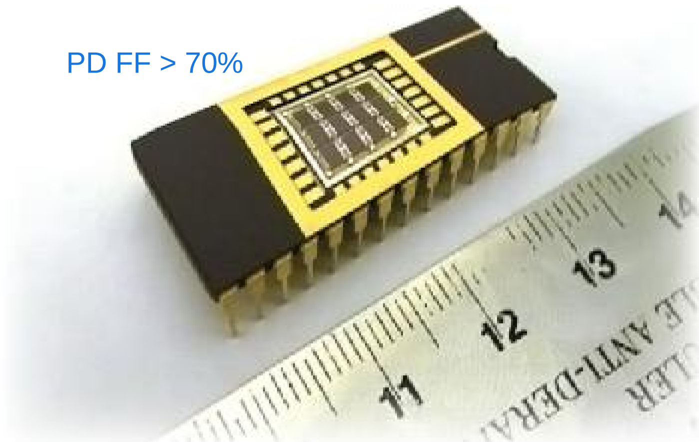


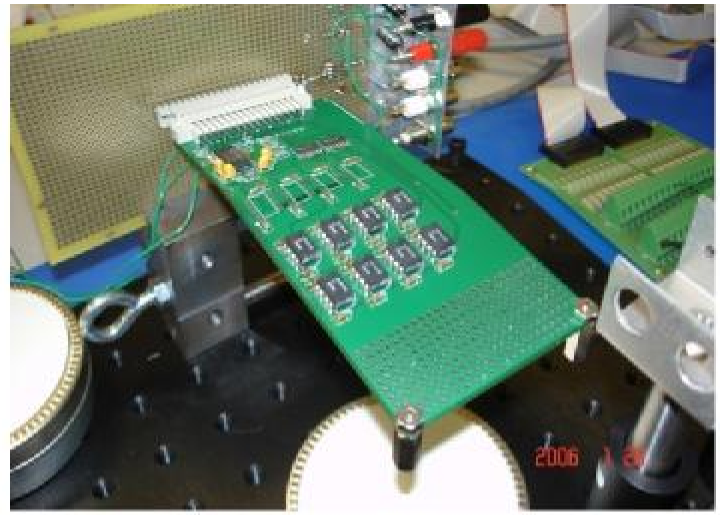
1. The fluorescent tags are excited by high energy beam (usually near UV). Sensors are forward biased to bleed excess charge.
2. Light source is turned off. Sensor is reverse biased to integrate emissions from each well site simultaneously. Typical fluorescence time is below μsec range and decays exponentially.
3. Signal stored in each sensor is read out sequentially.

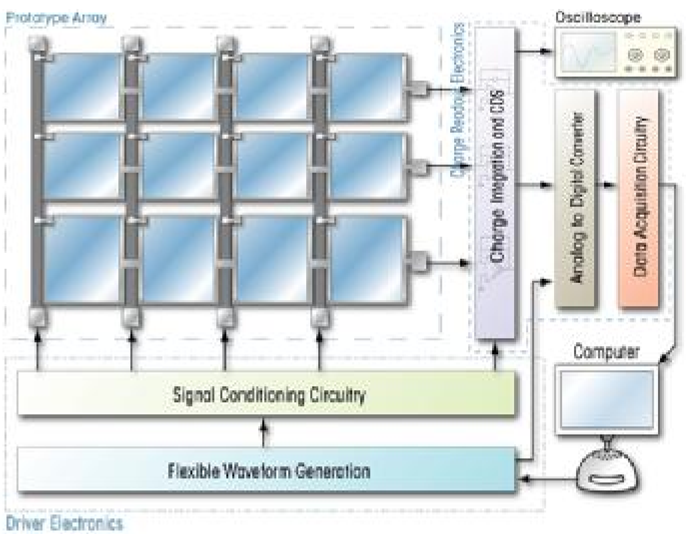
- allow large number of sites per image
- optical coupling efficiency improves >80% with reduced cross talk
- no need for cryogenic cooling due to improvement in SNR
- rejection of excitation beam either by optical filtration or temporal discrimination
- sensor is built with anti-reflection coating and moisture barrier
- sensor speed is not critical

Sample amorphous silicon molecular imaging array

PD FF > 70%





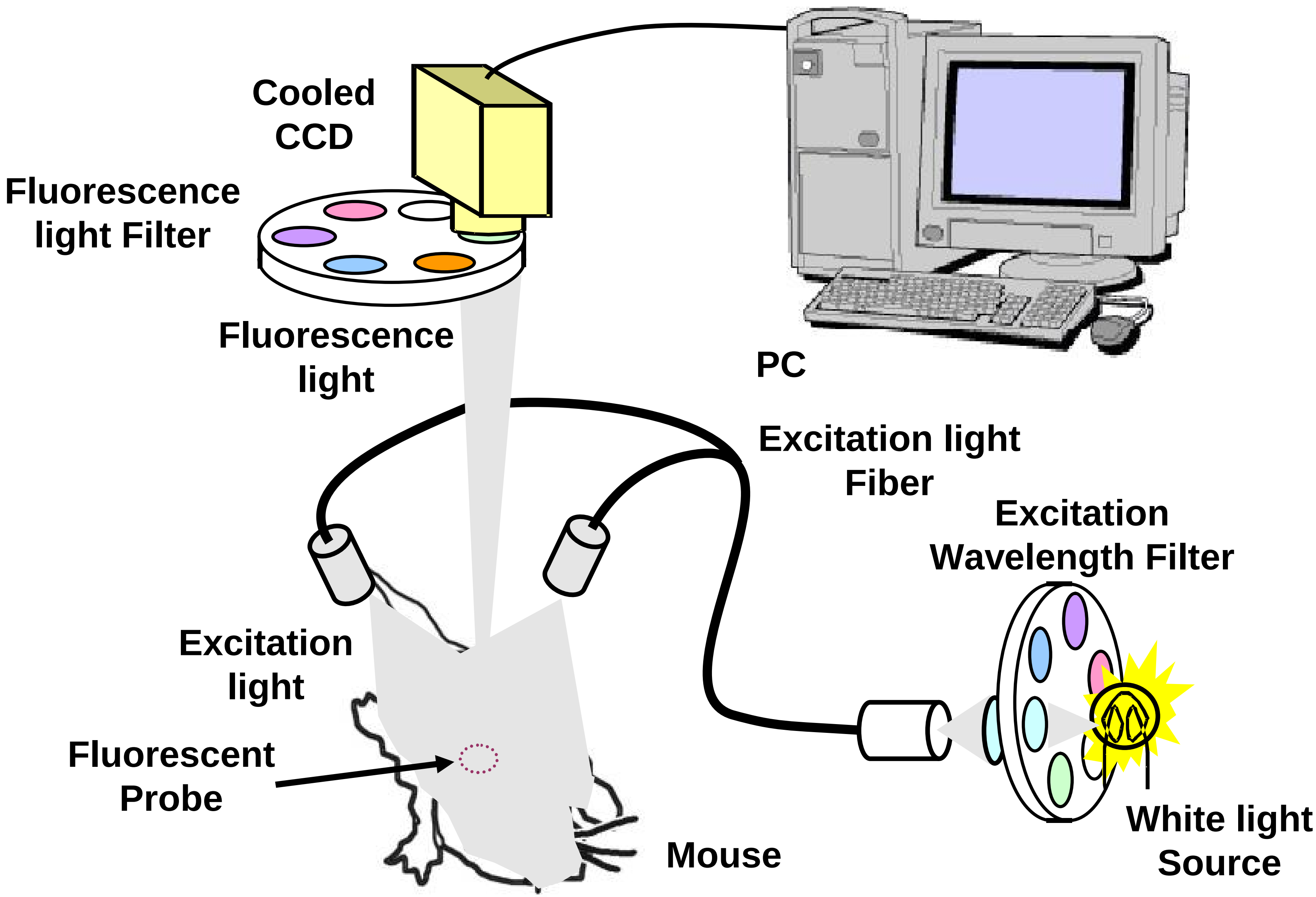


We've built a 3×4 imaging array sample with low-noise readout electronics. The sample employed heterojunction a–Si:H *n–i–p* photodiodes with optimized dark characteristics and quantum efficiency.

Comparison Between Optical and Contact Type Sensors

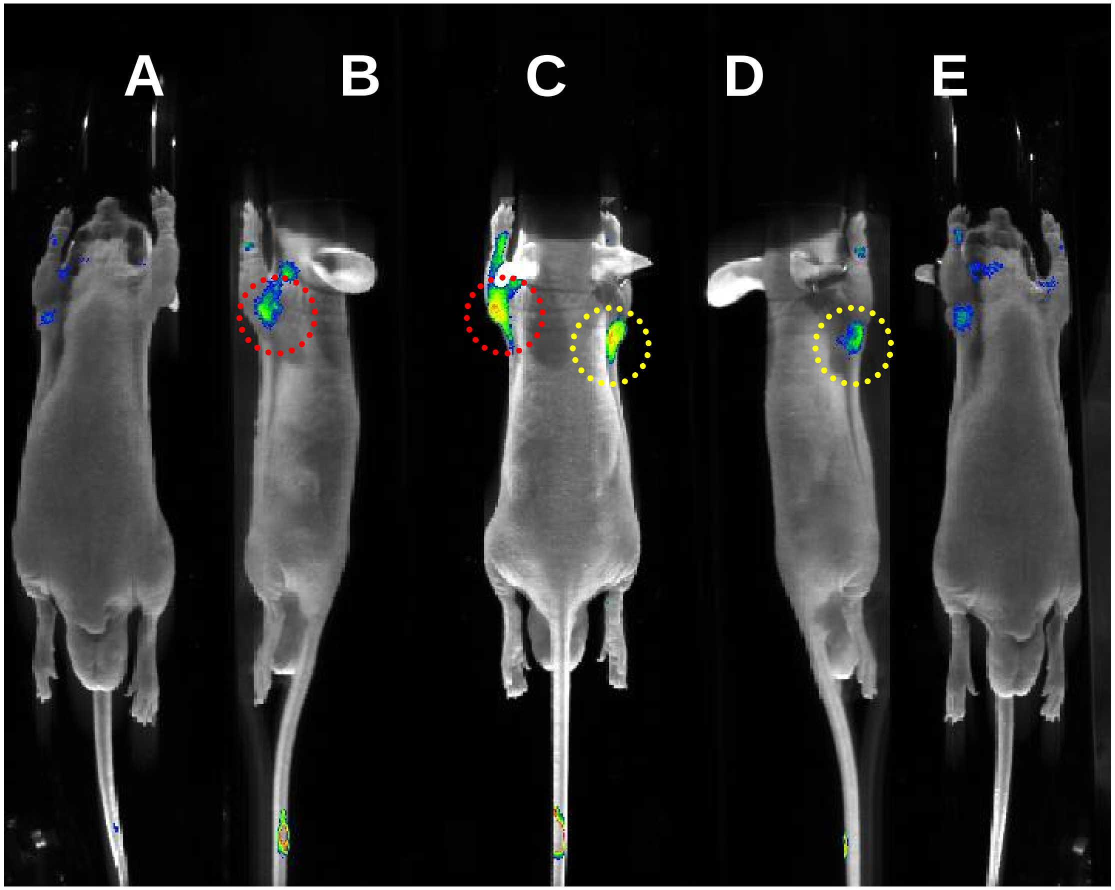
	Cooled CCD	a–Si:H Contact Sensors
Throughput	• Multiple shots may be required per sample plate.	• Slower sensor, but can whole plate is imaged at once.
Cost	• Higher cost per unit area for sensor. • More complex mechanical assembly. • May require cooling equipment depending on application.	• Lower sensor cost with volume. • May be viable as disposables. • Low dark current at room temperature. • No optical lens assembly.
Efficiency	• High loss through optical assembly (over 99% loss)	• Higher optical coupling efficiency (over 80%) and lower cross talk. • Higher QE for common dye wavelength. • Charge loss through trapping in defects.

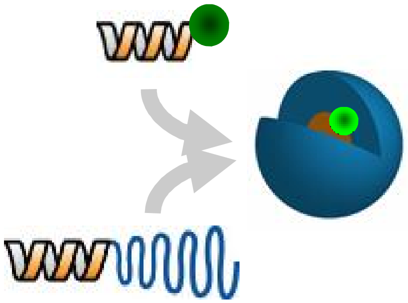
In-Vivo Fluorescence Imaging

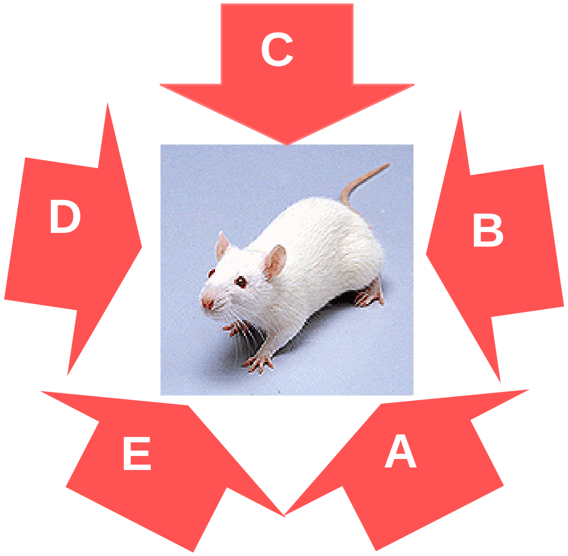


Fluorescence Imaging of Tumor-bearing Mouse

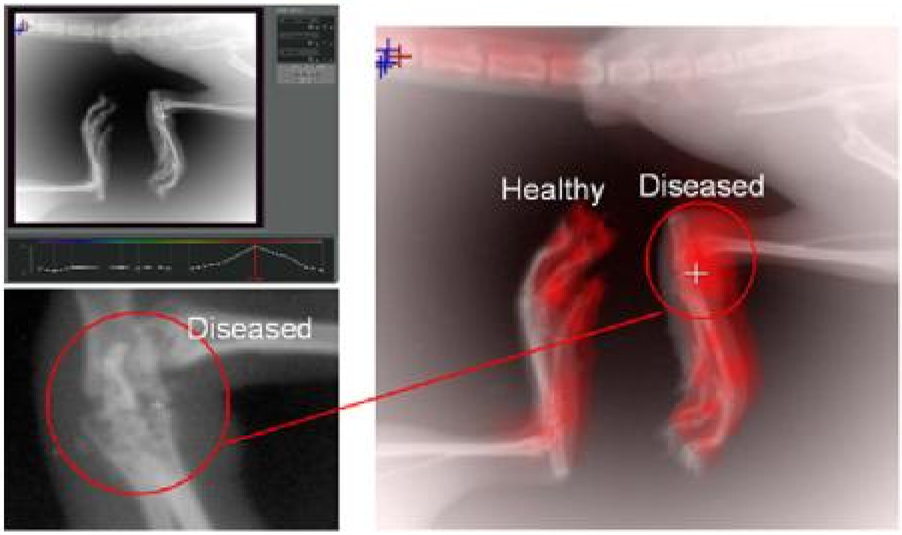
ICG-labeled Nano-particle

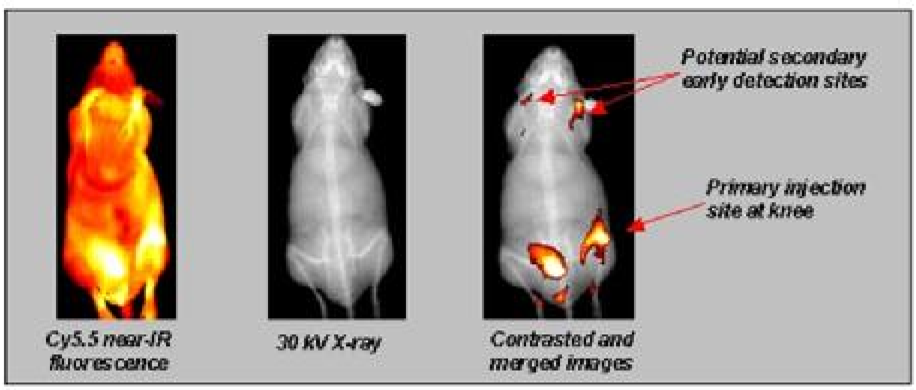






In vivo Molecular Imaging



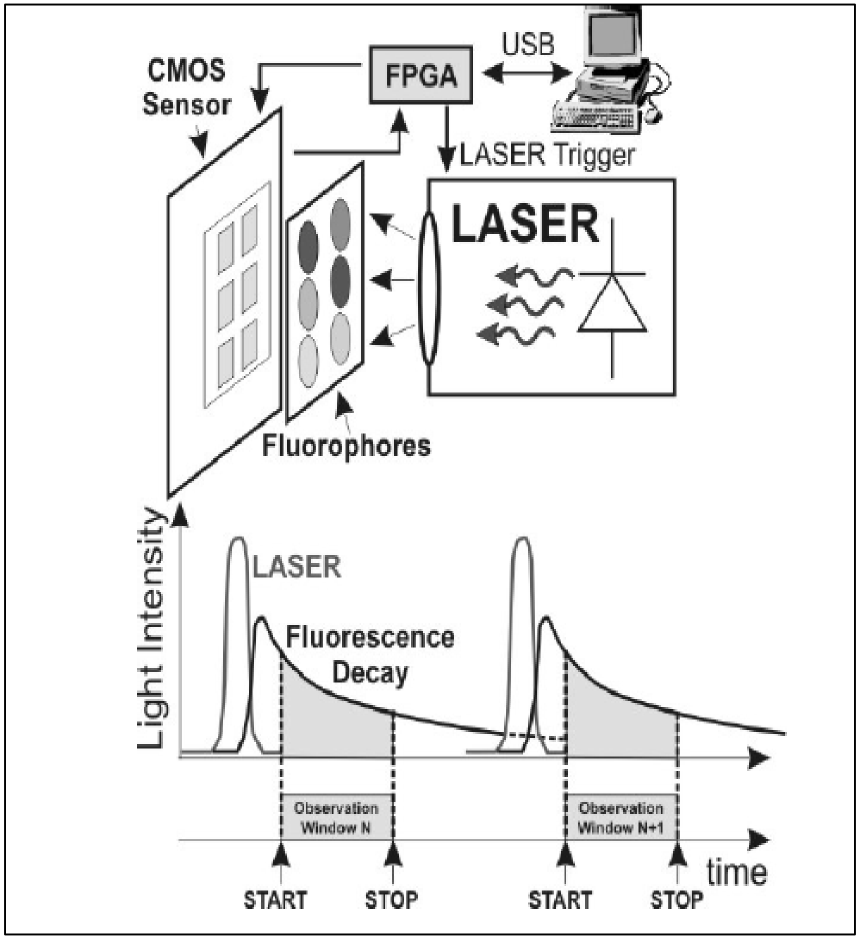


Combination of X-ray imaging and fluorescence imaging provides dynamic view of reactions occurring inside samples. The concept of using contrasting agent is no different than those mentioned previously.

1. Agents with biomarkers are introduced to the test subject.
2. Multiple images are taken at specific intervals with excitation to examine their migrations.
3. Results are superimposed into X-ray images revealing site locations of interest.

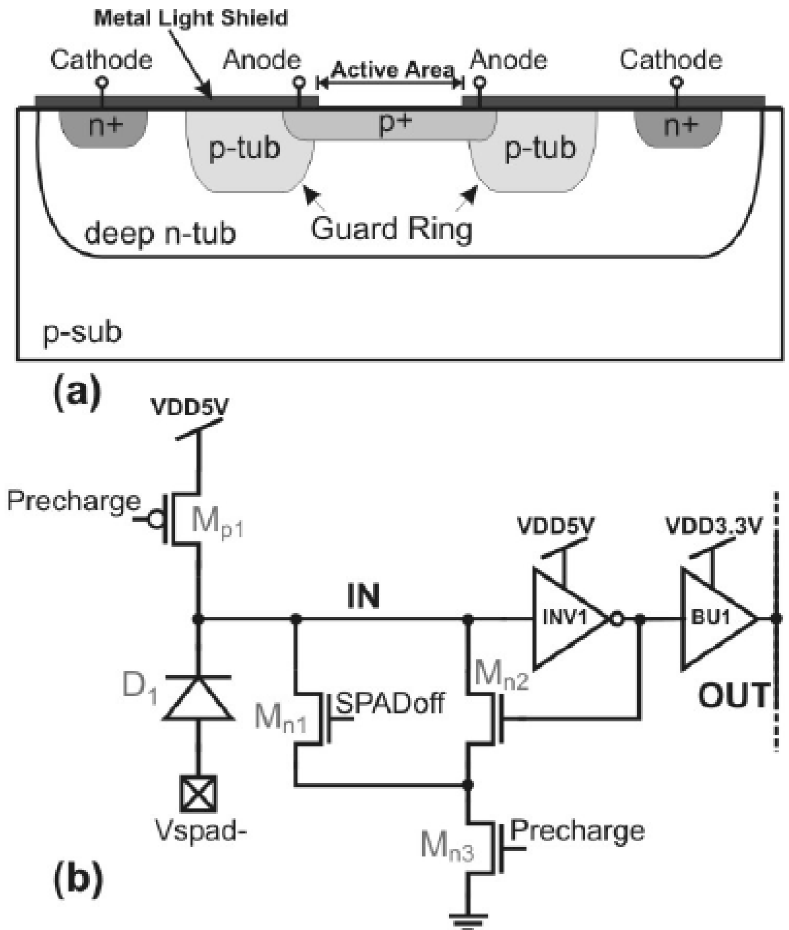
This application requires detectors with dual mode operations. The required imaging area is also relatively large.

Avalanche photodiode array for fluorescence imaging

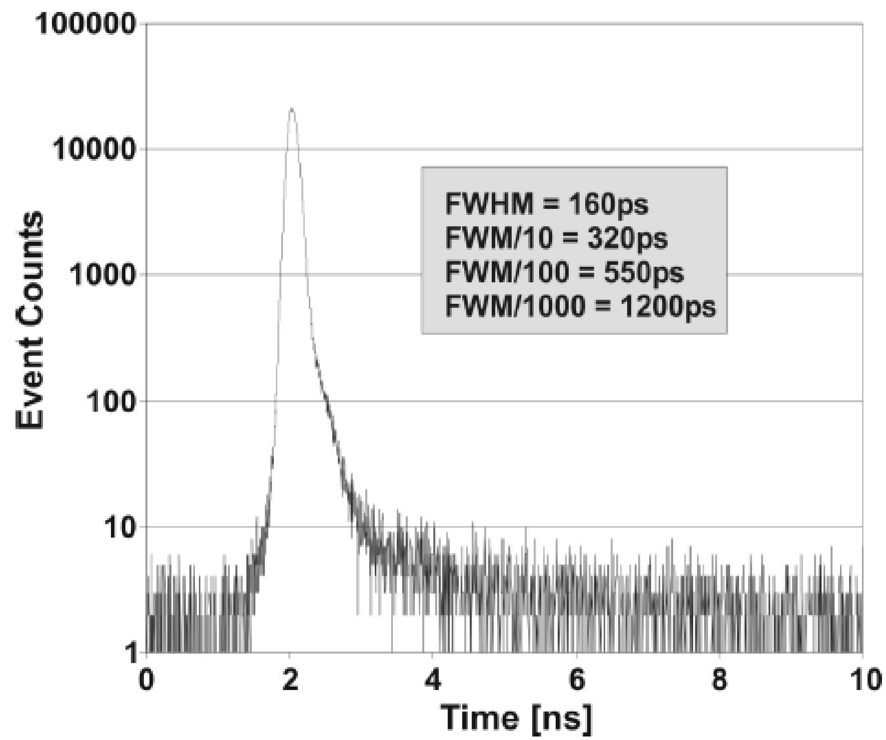


F. Borghetti et. Al., A CMOS Single-Photon Avalanche Diode Sensor for Fluorescence Lifetime Imaging
2007 International Image Sensor Workshop

Avalanche photodiode array for fluorescence imaging



150 ps time resolution



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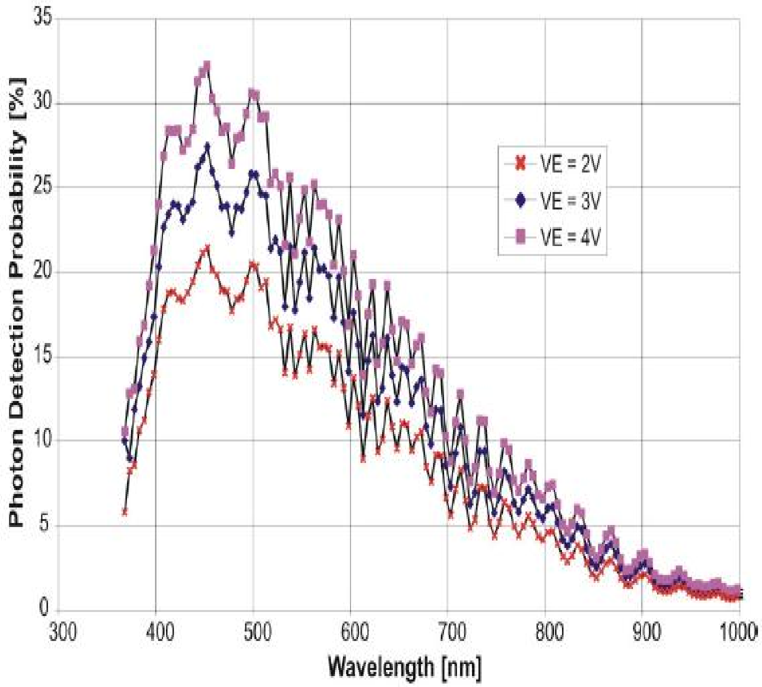
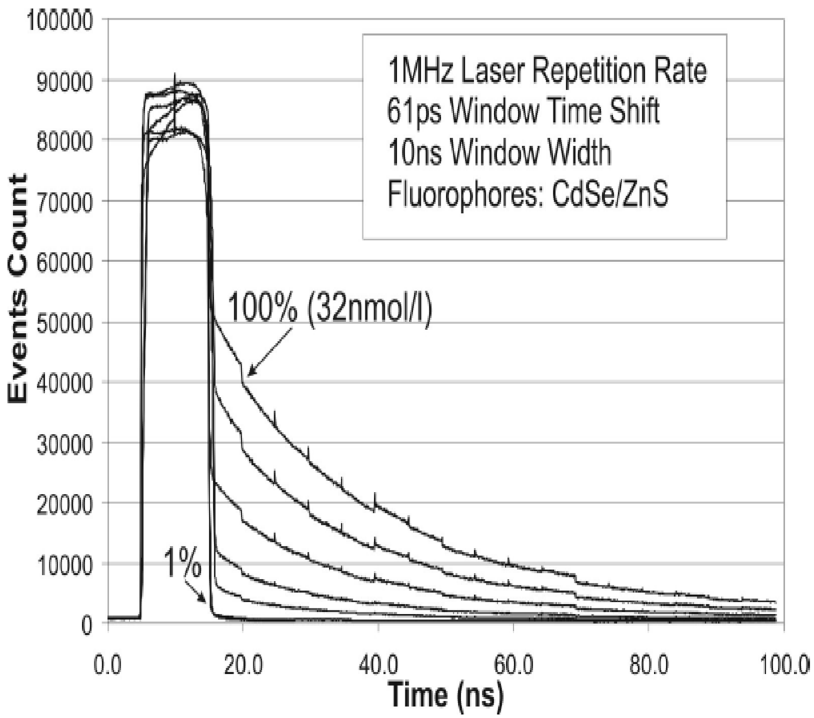
Avalanche photodiode array for fluorescence imaging
Photon detection probability and sensitivity





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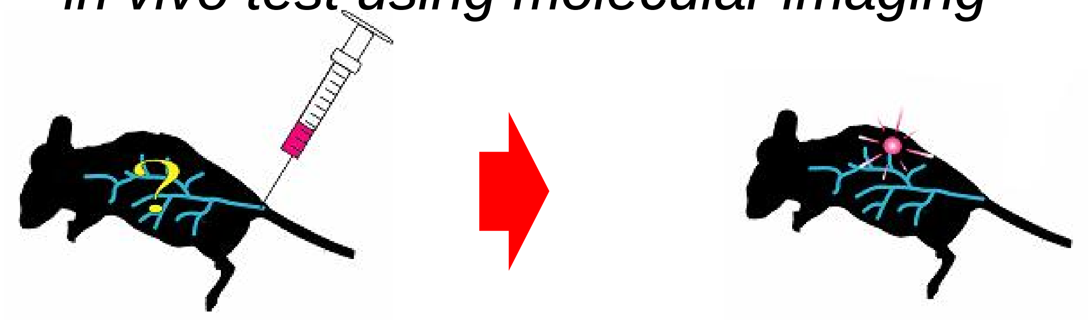
Small Animal Imaging System for Preclinical Research

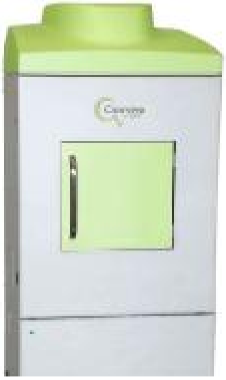
in vivo test using molecular imaging



PET

CT

Optical



Accelerating Basic Research/Drug Development

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Excitation Sources

Light Sources	Description	Advantages	Disadvantages
Gas Laser	■ Electric current is discharged through gas to produce light ■ Helium-Neon, 635nm	■ Commonly available ■ Available in specific wavelengths	■ Large, hot, and fragile
Solid-state and Semiconductor Laser	■ A laser that uses a solid crystal as the gain medium ■ Fixed wavelength ■ Yttrium Aluminium Garnet (YAG), 532nm	■ Small, efficient, and controllable ■ Long life	■ Wavelength choices are restricted to a limited set
White Light Source	■ Xenon arc light source ■ Range of wavelengths from 350nm to 750nm or more	■ Single source is adequate for multiple excitations	■ Large, hot and fragile ■ Needs filters to isolate wavelengths ■ Lower intensity than laser source

Excitation Strategies

Excitation Strategy	Description	Advantages	Disadvantages
Simultaneous Excitation	■ Light sources excite multiple dyes in the same pixel at the same time	■ Increased scanning speed	■ Increased crosstalk ■ Reduced SNR
Pixel Shifting	■ Light sources excite multiple dyes at different pixels at the same time	■ Reduced crosstalk ■ Increased SNR	■ Misalignment ■ Require image registration
Fiber Optics	■ Fiber optic cables direct light from external light source to scanning optics	■ Allow large lasers and alternative light sources	■ Reduced optical power delivery ■ Reduced resolution
Gated Laser	■ Light sources are toggled ■ One light source excite one pixel at a given time	■ Laser lifetime extended ■ Eliminated crosstalk	■ Reduced scanning speed