Imaging Fundamentals

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So, What is the Interest?

- In 1993, an NIH Study Group chose Medical Imaging as the most important emergent medical technology
  - For the next generation
  - To peak in 15-20 years
  - We are at 15 years and they were right.
- Clinical Trials Registry has 2,239 active clinical trials that include an imaging endpoint
- JSM 2007
  - 23 presentations/papers that dealt with imaging
  - 2 of these covered clinical trials issues

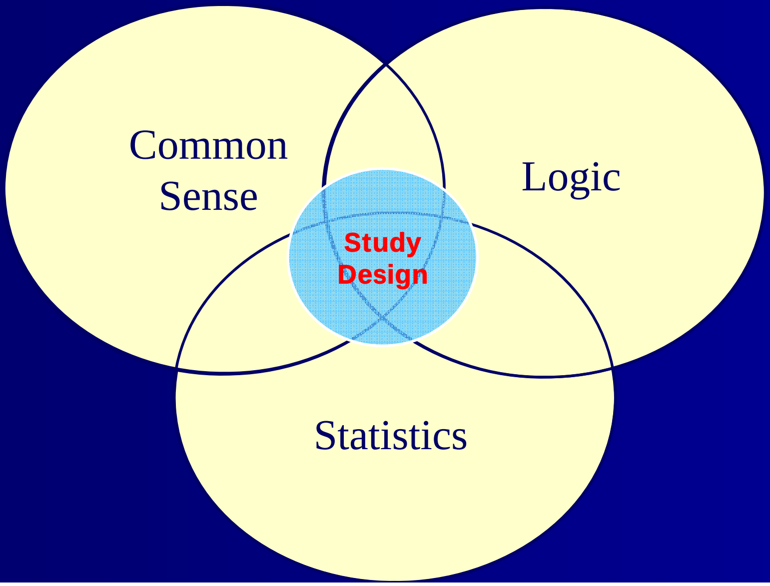
Why Imaging Biomarkers

Imaging Biomarkers are one more step closer to the expressed phenotype of the disease and to the direct causal pathway

- True volume measurements
- Organ-to-cellular-to-molecular function
- Real- or Near Real-time dynamic imaging
- Translational pre-clinical longitudinal measurements
- Sources of error not well-understood
- Missing Data is the rule – and a problem
- Lexicon is very different – and confusing

Tutorial Objectives

Upon completion of this tutorial, the statistician will become familiar with imaging fundamentals at a level of understanding that enhances the statistician's role in the design and analysis of clinical trials that involve medical imaging.

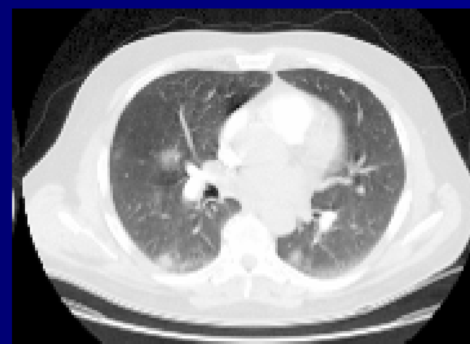


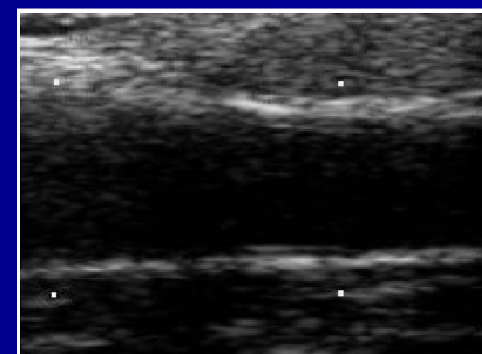
Quantitative Imaging

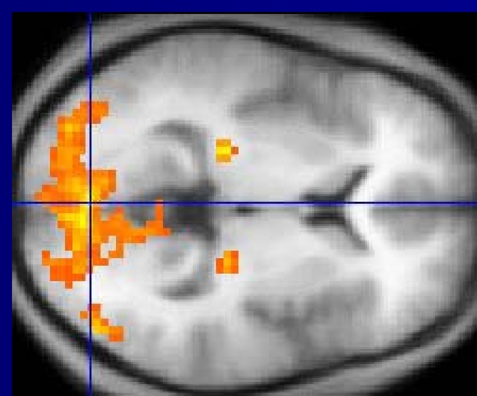
"Quantitative imaging is the development, standardization, and optimization of anatomical, functional, and molecular imaging acquisition protocols, data analyses, display methods, and reporting structures in order to permit the validation of accurately and precisely obtained image-derived metrics with physiologically relevant parameters, and the use of such metrics in clinical research and patient care."

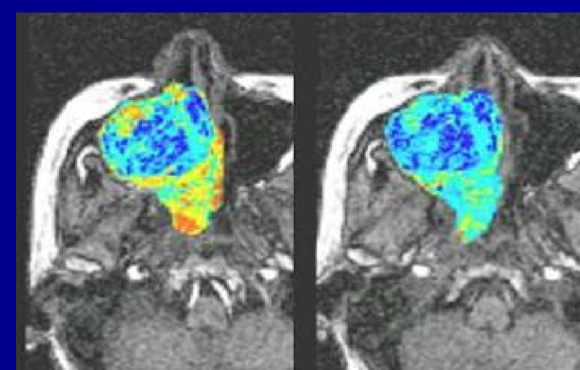
– *(RSNA TQI Draft Definition 2008)*

Examples of Medical Images









What Exactly is an Image?

- Detected Energy
  - Spatial Location → Region of Interest (ROI)
  - Types of Energy
    - electromagnetic (MRI, X-ray/CT and optical)
    - the momentum of a subatomic particle (PET),
    - the energy released from radioactive decay (SPECT) or
    - acoustic (ultrasound).
- Quantitative Measurements
  - Size of ROI
  - Intensity of ROI
  - Change in intensity in ROI

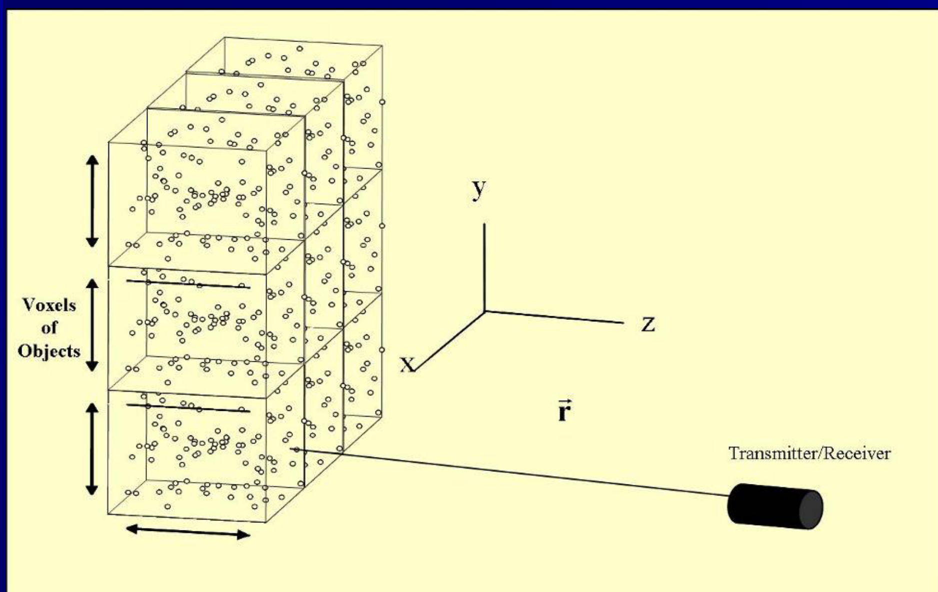
A Basic Imaging System

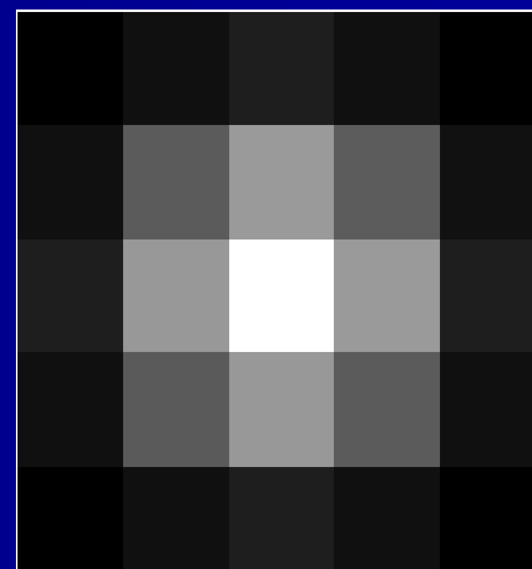
Pixel – PI(x)cture ELement

- Intensity Q total pixel energy within the imaged volume

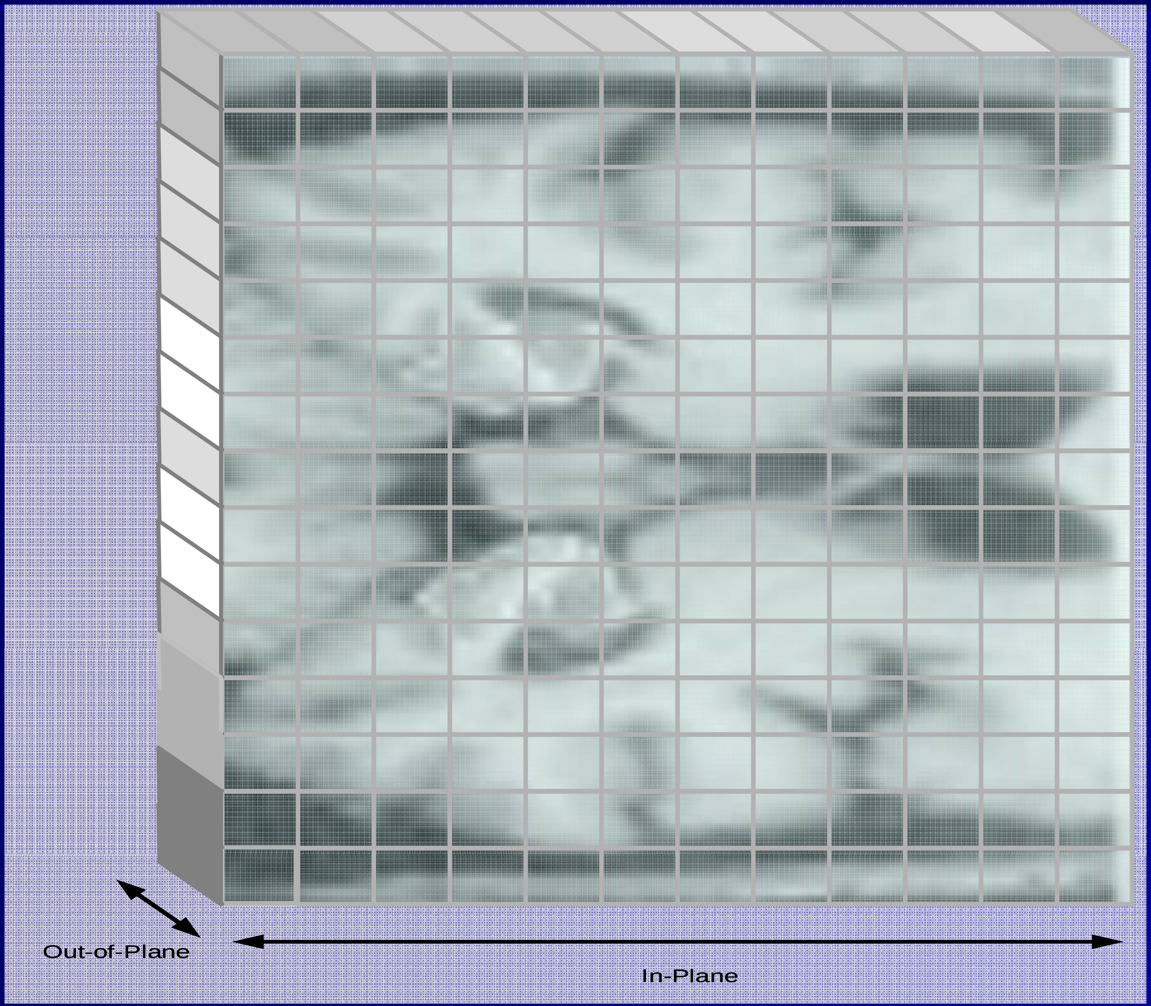
Voxel – VO(x)lume Element

- Intensity Q total energy within imaged volume





Medical Image
Matrix of Pixels

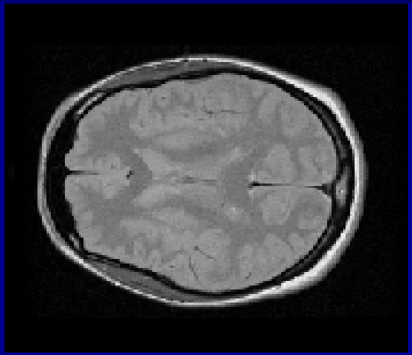


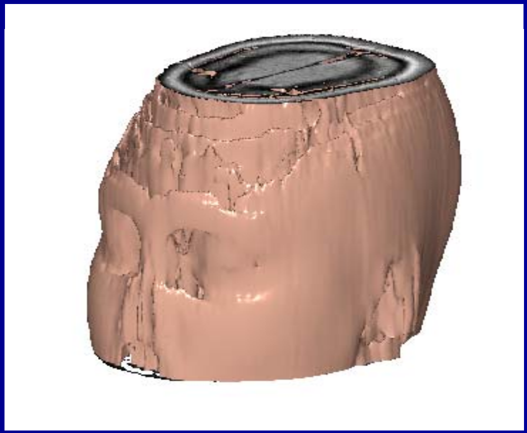
From Voltage to Images

- MRI
  - Computed reconstruction
  - Slices of the imaged tissue are constructed
- PET / SPECT
  - Computed reconstruction using EM algorithm or Filtered Backprojection
- X-ray/CT
  - Plate exposure for single image X-ray
  - Computed reconstruction for CT
- Ultrasound :
  - Time gated and direction of arrival from reflected acoustic pulses

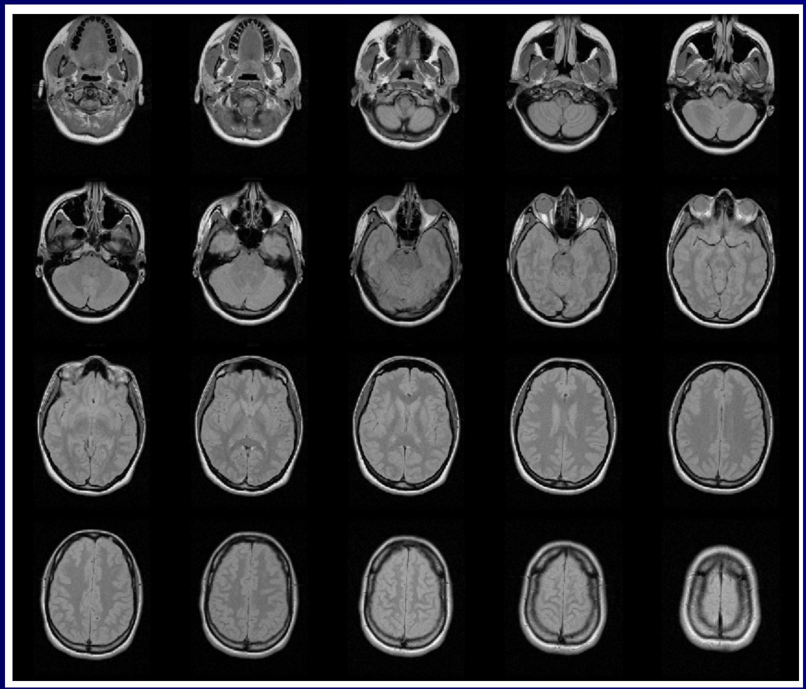
From 2-D to 3-D Images Stacking Pixel Matrices

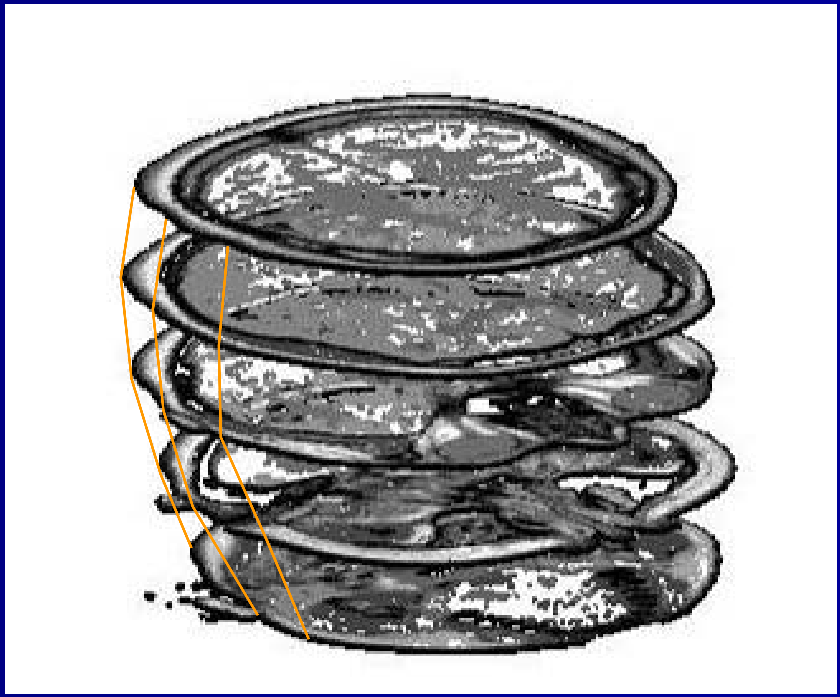
- All modalities have 3-D Capability
- Stacked Slices of Images
  - Connections by interpolation algorithms
- Slices
  - Acquired as slices of the image
  - Result of back projection reconstruction
  - MRI, PET, CT and Ultrasound
- Slice Properties
  - Thickness
    - Thin slices for resolution
  - Separation
    - Small separation for precise volumes



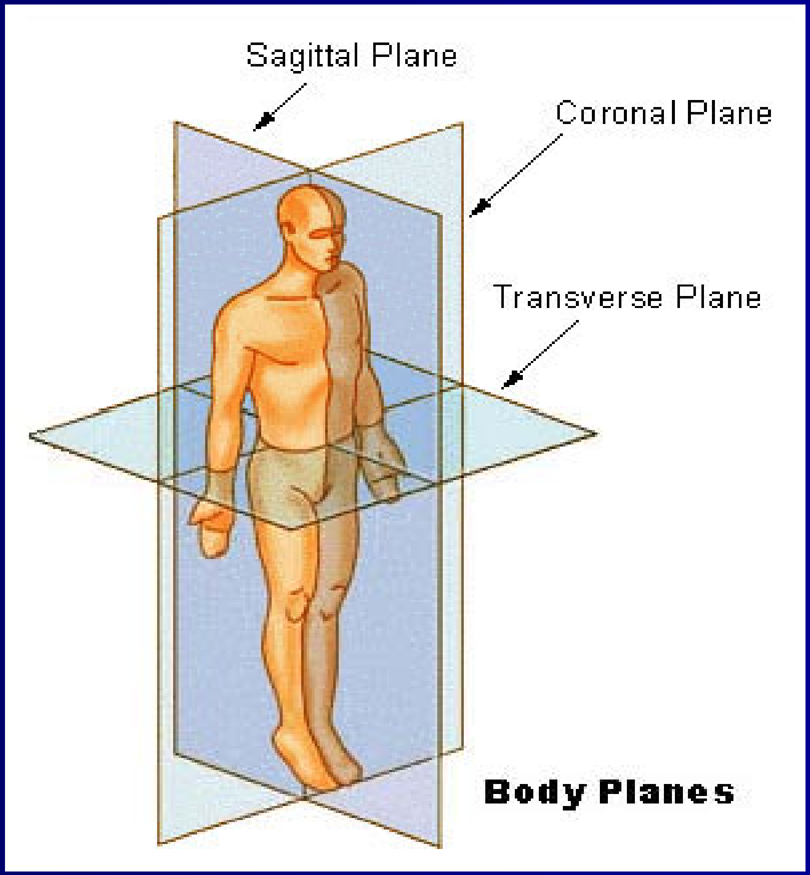


Slice Mosaic and Selected Slice Stacked View





Viewing Planes



Viewing Platforms

- Two Primary types
  - Cathode Ray Tube (CRT)
  - Liquid Crystal Display (LCD)
- Properties Required for Medical Grade Viewing
  - Brightness and Contrast generally preferred
  - Ambient light features
  - Flicker-free
  - Wide Viewing Angle
- Laptops are generally not acceptable and not used by imaging CROs

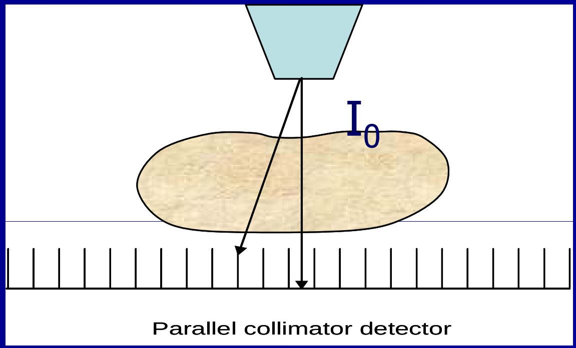
Imaging Modality Basics

Types of Medical Imaging Modalities

- X-Ray / Computed Tomography (CT)
- Ultrasound
- Magnetic Resonance Imaging
- Positron Emission Tomography
- Others
  - SPECT
  - Optical
  - Near infra-red

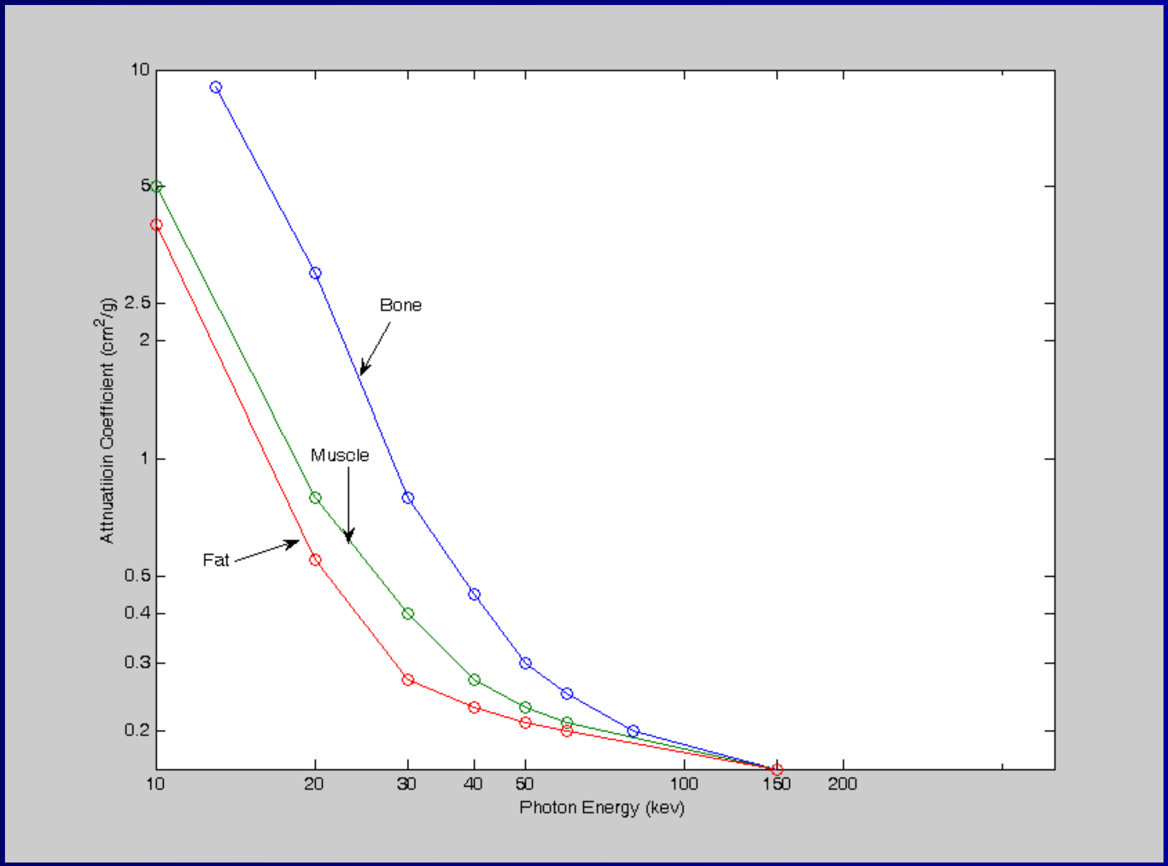
X-Ray

- Concept:
  - High Energy X-rays are transmitted through entire tissue and collected on the other side
  - Different energies for different features
- Limitations
  - Soft-tissue is relatively transparent
  - Occluded features (Shadow effect)
  - Radiation Exposure
- Resolution
  - 50 µm



$$I = I_0 \exp\left(-\int \mu(x,y)\,ds\right)$$

X-Ray Principles
Attenuation for Tissue



Data derived from Macovski 1994

X-Ray
Clinical Endpoints

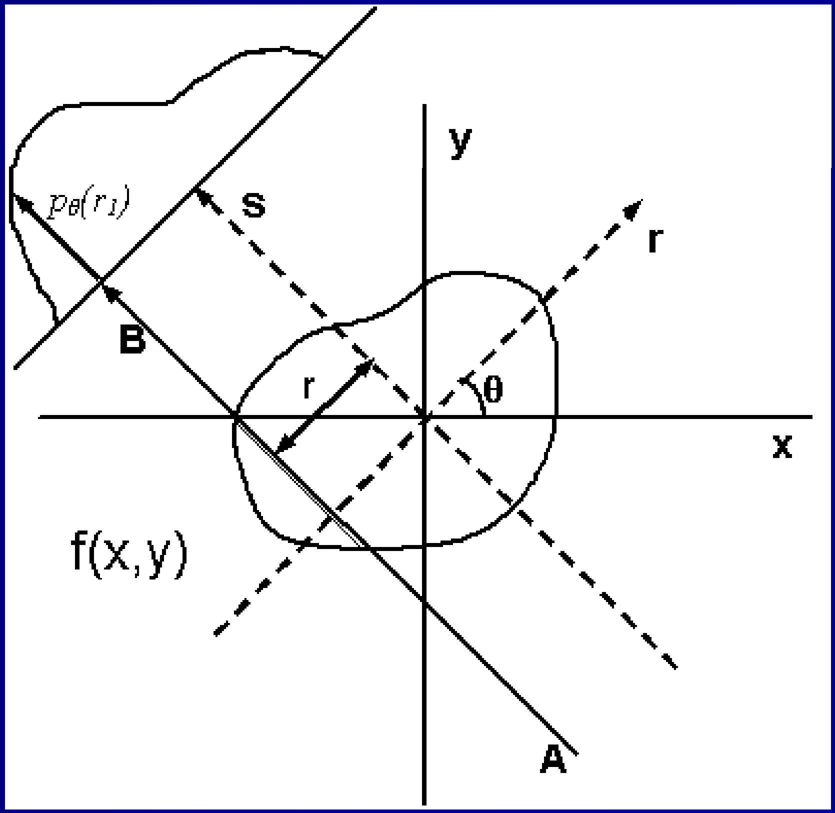
- Oncology
  - Detection
  - Tumor Size Assessment – RECIST
- Osteoarthritis
  - Spine, peripheral joints
  - Osteophytes and joint erosion
- Bone healing
  - Fractures: Detection and measurement
  - Dual Energy X-ray Absorptiometry (DXA)
    - Osteoporosis
    - Gender and Age specific
- Angiography
  - Use opaque contrast

X-ray
Computed Tomography (CT)

- Concept:
  - Revolving X-Ray
  - 3-D Reconstructed image with no shadows or occluded features
- Advantages
  - High signal / Low Noise
  - No occluded features
- Limitations
  - Soft-tissue characterization is limited
  - Radiation Exposure can be high
- Resolution
  - 10 µm

CT Principles

- X-Ray acquistions from many angles
- Line integrals are the basis behind a single X-ray
- Radon Transform
- Images formed by backprojection to resolve separate voxels



Clinical Trials Endpoints Computed Tomography

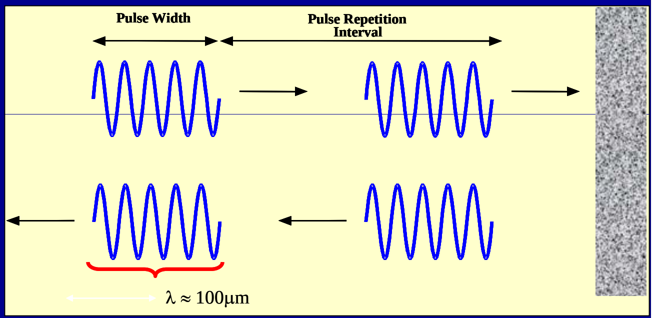
- Bone Health (Quantitative CT – QCT)
  - Bone Mineral Content, Volume and Density
- Osteoarthritis
  - Joint Space Width
  - Cartilage volume
- Cancer Detection and Measurement
  - 3-D RECIST/WHO
  - Tumor Volume, Cavitation
  - PET Registration
- Lung and Airway Disease
  - Obstructions, Emphysema, Lesions
- Cardiac imaging
  - Motion correction
  - Fast Cardiac gating
- Abdominal and Pelvic
- Extremities

Ultrasound

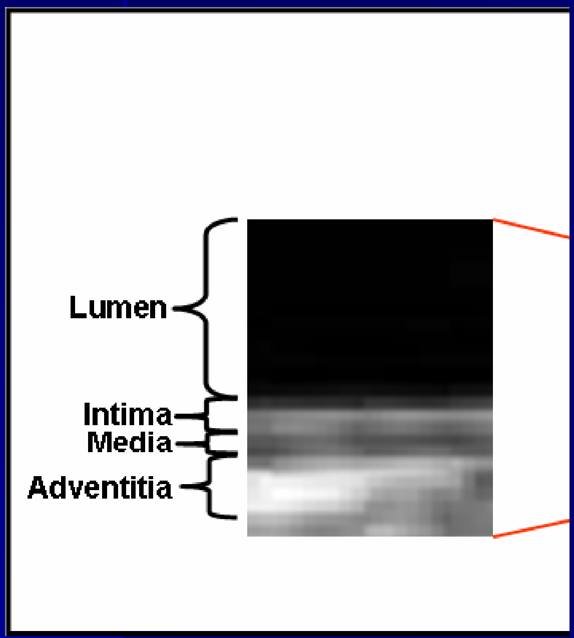
- Concept:
  - High Frequency acoustic reflection
  - Typically hand operated
- Advantages
  - Real-time images
  - Non-ionizing and Safe
- Limitations
  - Dense materials create shadows
  - Very noisy images Limited penetration
  - Limited resolution
  - Sensitive to Operator Expertise
- Resolution
  - 80 μm

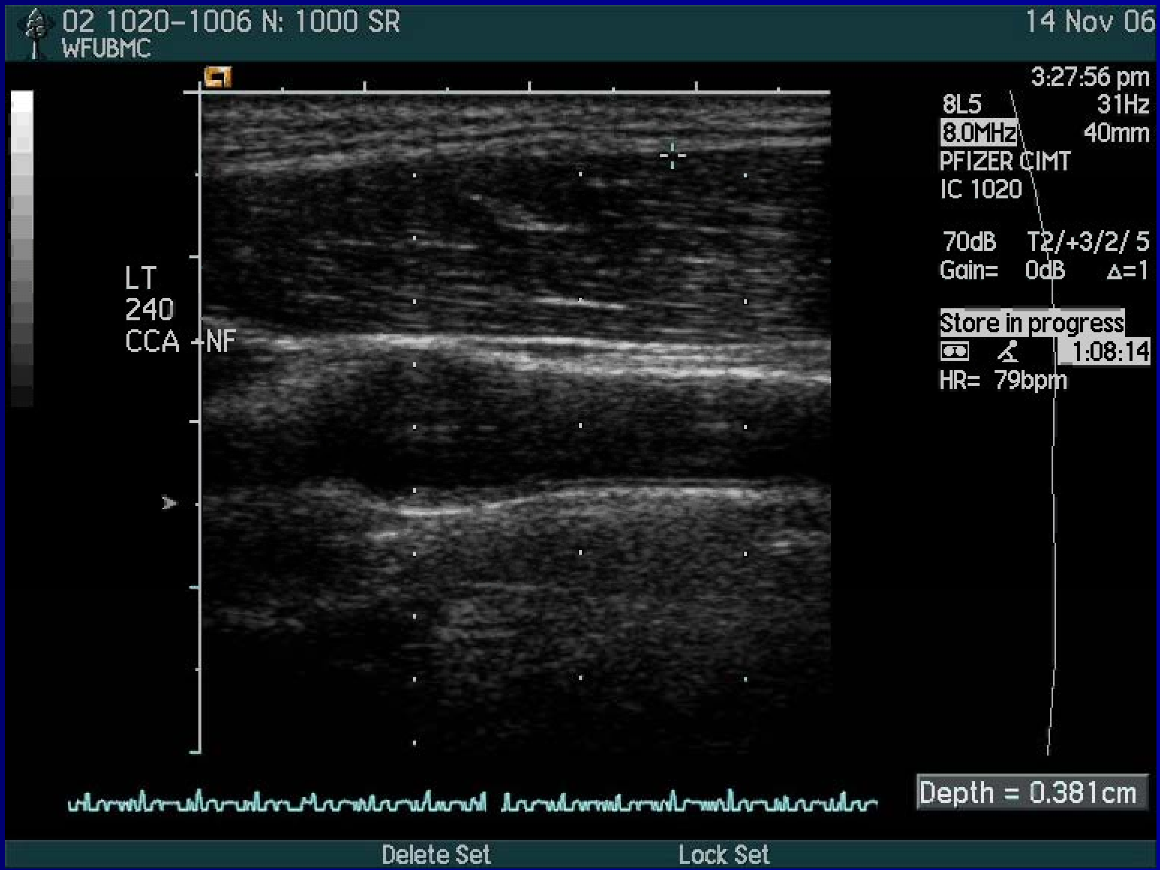
Ultrasound Principles

- Pulses of high frequency acoustic energy reflect at tissue boundaries
  - 150k – 40 MHz
  - Higher Frequency → Higher resolution
  - Higher frequency → Lower penetration
  - Reflections interfere with each other → Speckle
    - Compounding reduces speckle
- Location
  - Time of Arrival provides depth
  - Direction of Arrival provides x-y location
- Movement
  - Changes in Frequency provide velocity

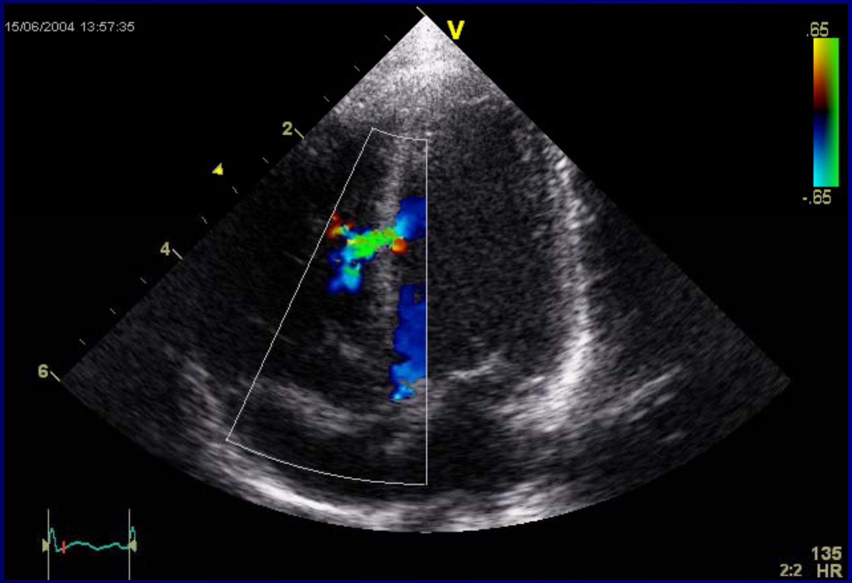


Ultrasound Example Cine

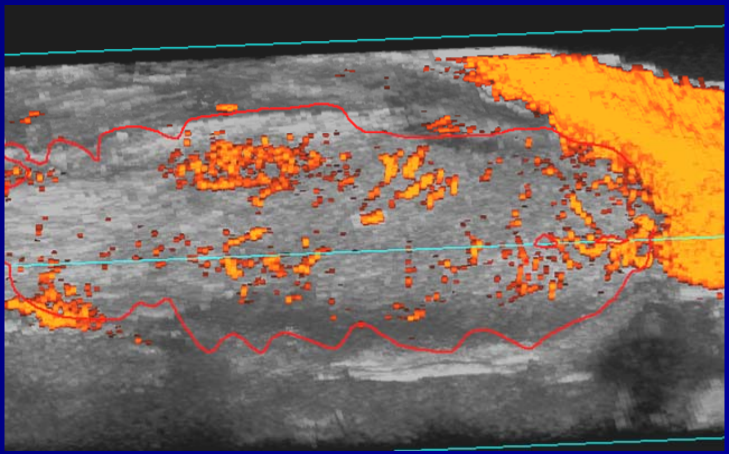




Ultrasound Example Doppler



Color Doppler - Echo Cardiography



Power Doppler Tumor Angiogenesis

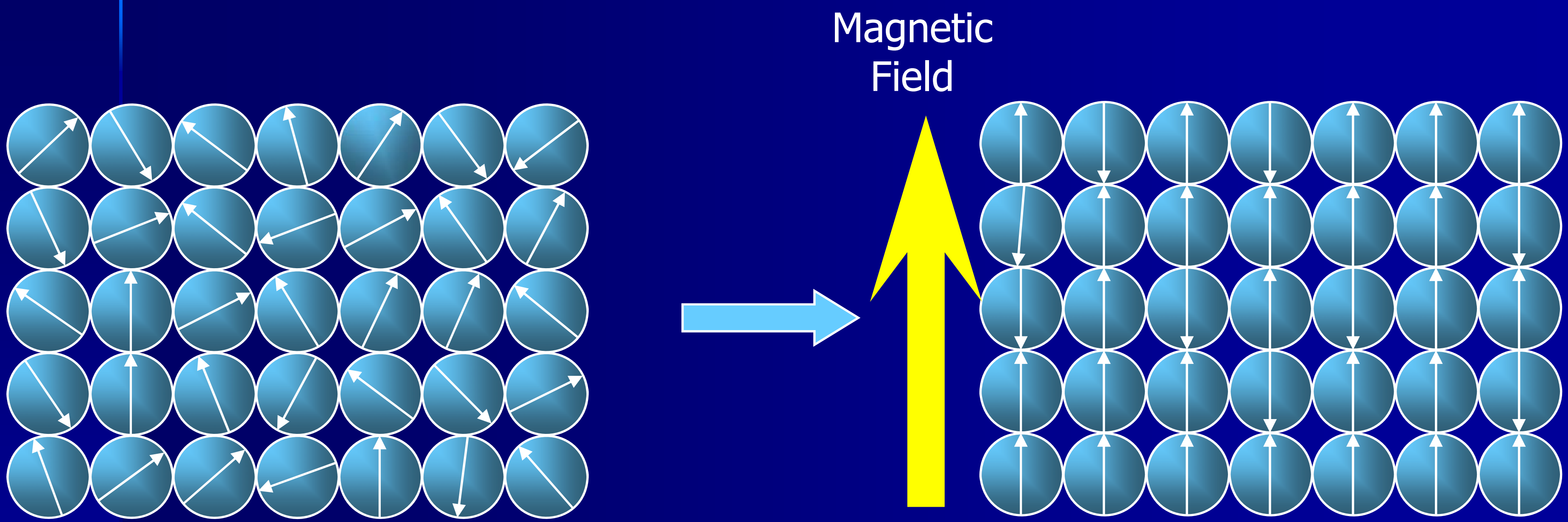
Clinical Trials Endpoints Ultrasound

- Cardiac and Vascular Health
  - Arterial Wall measurements
    - Carotid (Intima Media Thickness – cIMT)
    - Coronary plaque (IMT, volume)
      - Intravascular Ultrasound (IVUS)
  - Arterial and Venous Elasticity (Modulus of Elasticity)
  - Thrombosis and Stenosis – Doppler Ultrasound
  - Ejection Fraction (EF), Valve insufficiency
- Oncology
  - Detection, tissue characterization, size, blood flow
- Brain
  - Blood flow for stroke

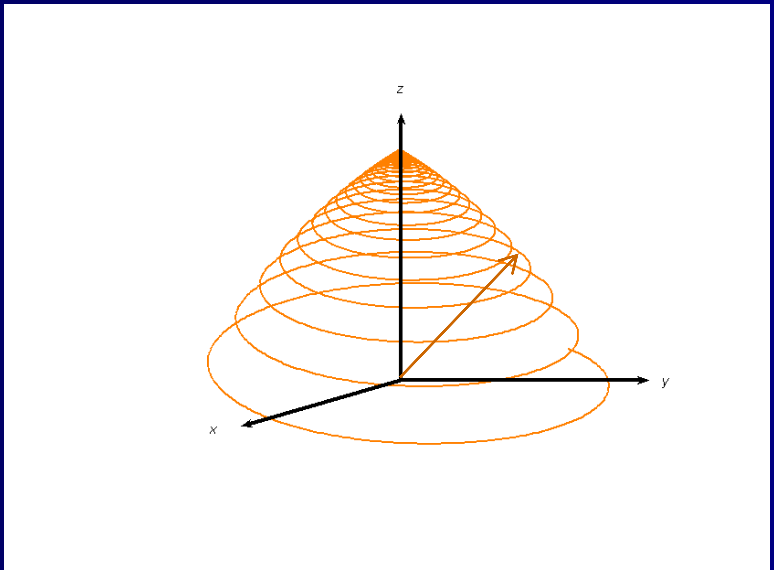
Magnetic Resonance Imaging (MRI)

- Concept:
  - Atomic resonance to an excitation magnetic field
- Advantages
  - Tissue Differentiation
  - Functional imaging
  - Nonionizing
- Limitations
  - Patient limitations
  - Long Acquisition time
- Resolution
  - Depends on the mode, magnet and scanner and tissue
  - Down to 90 nm

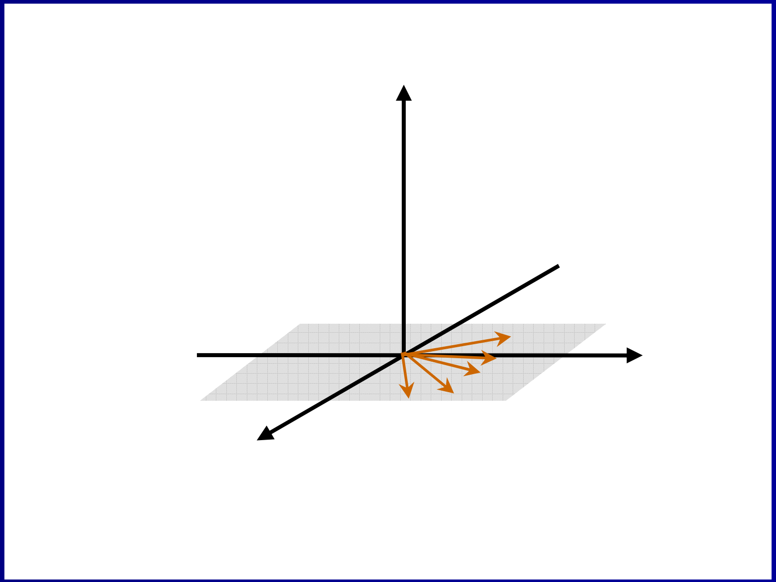
Bulk Magnetization



What is Meant by T1 and T2 Relaxation



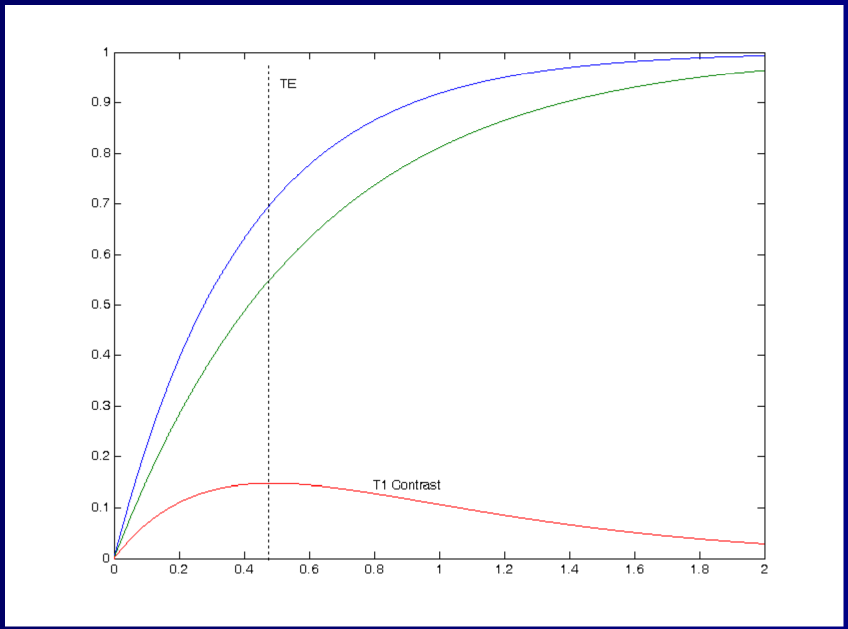
T1-Relaxation – Rate at which magnetization recovers

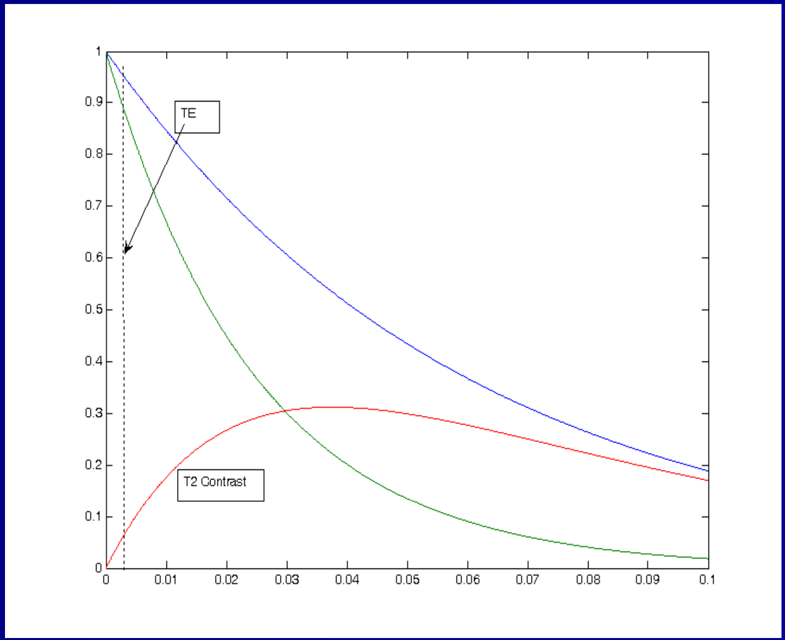


T2-Relaxation – Rate at which magnetization decays

T1 and T2 Tissue Differences and Signal Intensity

$$M_{xy} = M_0\left(1 - e^{-TR/T_1}\right)e^{-TE/T_2}$$





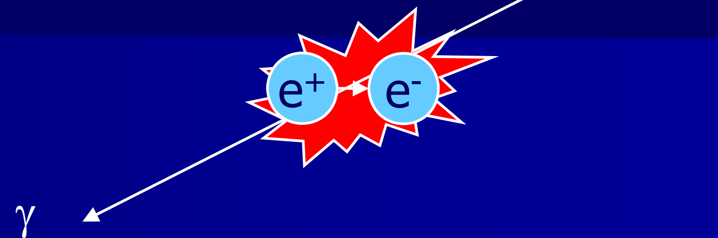
Functional MR Imaging

- Contrast Agents
  - Increase signal
  - Gadolinium is the primary contrast agent
- Dynamic Contrast Enhanced (DCE)
  - Principle: Transfer of contrast through capillaries to interstitial space
  - Purpose: Vascular permeability
- Functional MRI (fMRI)
  - Principle: Detect regions of biological activity
  - Purpose: BOLD and ASL – Detect regions of brain activation through increased oxygen uptake and response
  - Caution: The lexicon for fMRI is derived from statistical lexicon but often does not have the same meaning!

Clinical Trials Endpoints MRI

- Oncology
  - Vascular Permeability (DCE-MRI)
    - Ktrans and IAUC90
  - Tissue Differentiation
- Brain
  - Region Activation –(BOLD/ASL fMRI)
  - Volume (structural MRI, Freesurfer, BBI)
- Osteoarthritis
  - Joint Space Width (JSW)
  - Cartilage Volume
- Cardiovascular
  - Plaque volume, CIMT

Positron Emission Tomography (PET) Imaging

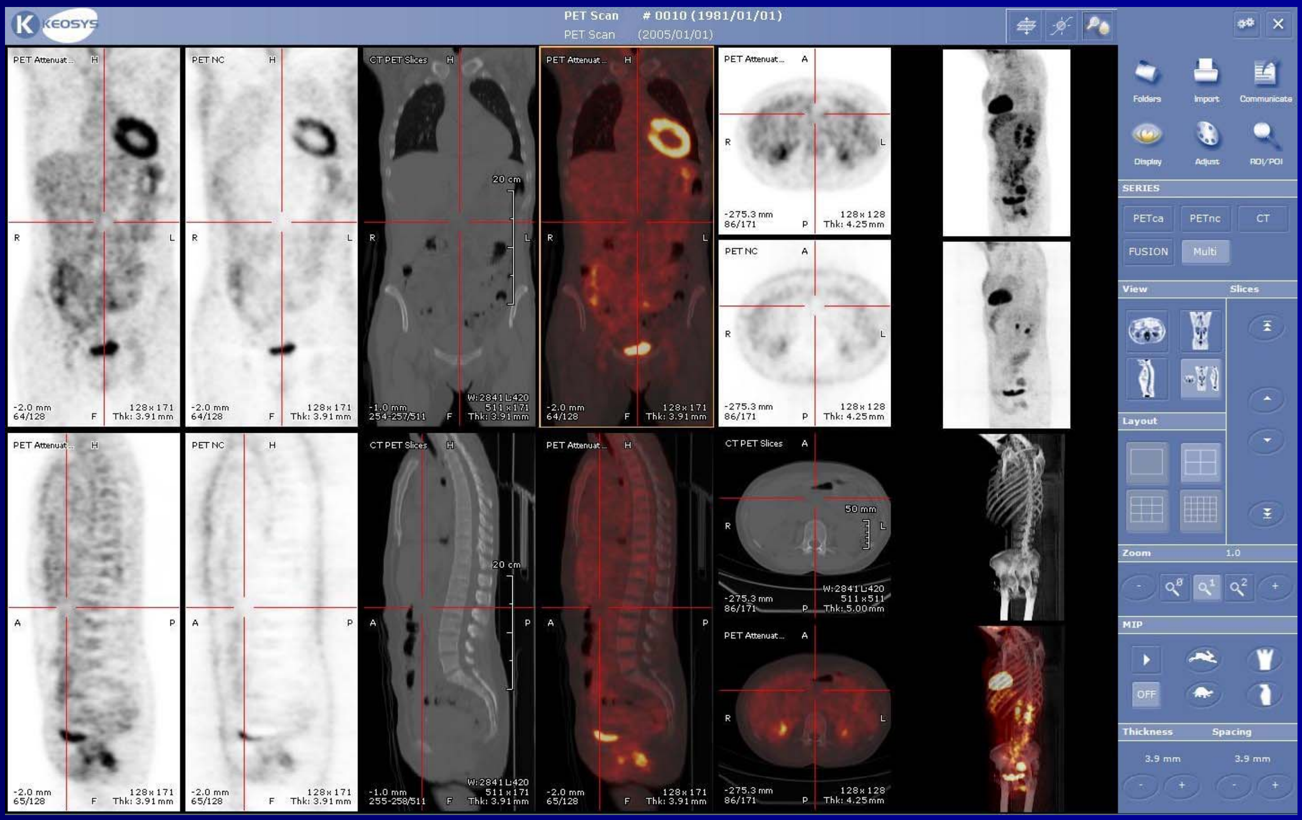


- Concept:
  - Radioactive decay of neutron released
  - positron → electron→ annihilation
  - 2 photons in opposite directions
- Advantages
  - Radioisotope labeling
  - Cellular / Molecular function
- Limitations
  - Low Resolution
  - Registration to anatomic feature
  - Radioactive exposure
- Resolution
  - Very poor
  - Good when combined with CT

Common Radioisotopes

Radionuclide	$T_{1/2}$
Fluorine-18	110 min
Nitrogen-13	10 min
Carbon-11	20 min
Oxygen-15	2 min

Example: Whole Body PET



from http://en.wikipedia.org/wiki/PET_scanner

Clinical Trials Endpoints PET Imaging

- Receptor Occupancy (RO)
  - Radiolabel a ligand with known affinity
  - Administer test compound
  - Measure displacement
- Metabolism (FDG)
  - Voxelized measure uptake (SUV) of 18F-2-fluoro-2-deoxy-D-glucose
  - Dynamic or Single point modeling
- Cellular Proliferation (FLT)
  - Voxelized measure uptake (SUV) of 18F-3′-fluoro-3′-deoxy-L-thymidine

Image Quality
Why It Matters in Clinical Trials

- Impact of Image Quality
  - Desired image signal
  - Background noise and discrimination ability
  - Image integrity – Distortion
- Image Quality Assessment
  - Peak Signal to Noise Ratio (PSNR)
  - Just Noticeable Difference (JND)
  - Contrast to Noise Ratio (CNR)
  - Reviewer comments are most useful

Random Factors that Affect Image Quality

- Patient Movement
  - All modalities
  - MRI is most susceptible and can render the image unusable
  - Bulk movement of the entire patient
  - Breathing or cardiac movement
- Background noise
  - Most prominent with low intensity signals
  - Filters and processing helps

Controllable Factors that Affect Image Quality

- Aliasing
  - Incorrect sampling of the data
  - Much like interactions and incomplete factorial designs
- Operator Error / Noise
  - Also include protocol violations
  - Ultrasound operator (Ultrasonographer)
- Imaging Modality Problems
  - Incorrect calibration
  - Machine settings
  - Resolution

Example of Image Quality Problems

MRI Motion Artifacts

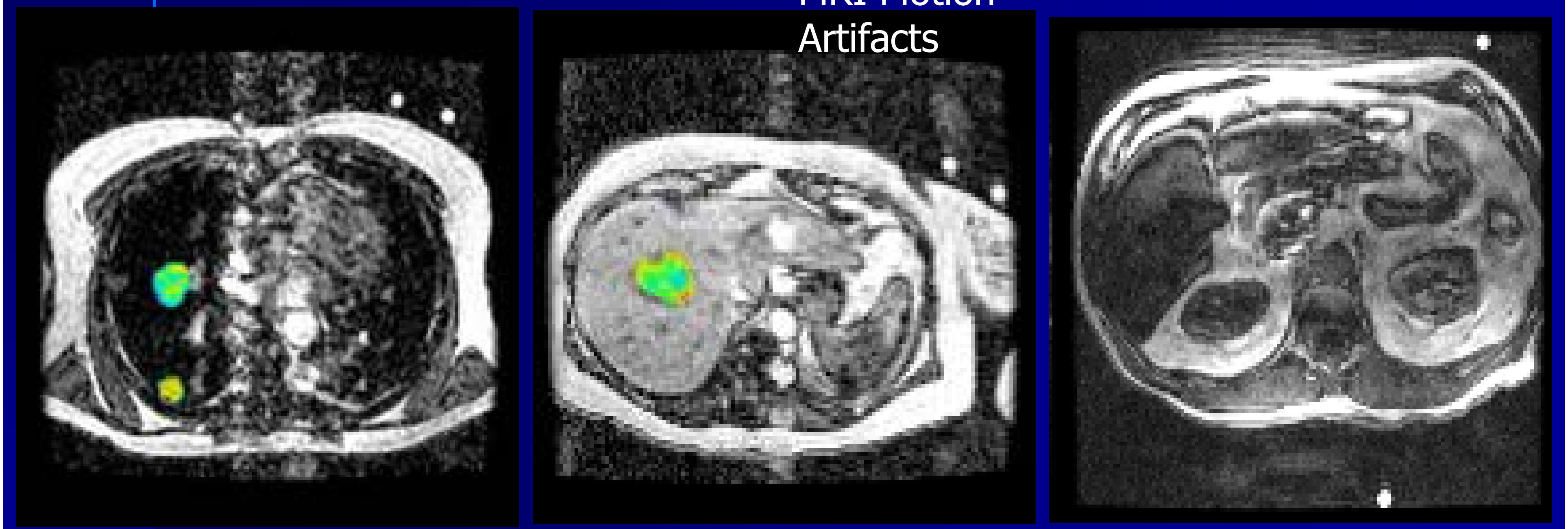


Image Analysis

Image Analysis Characteristics

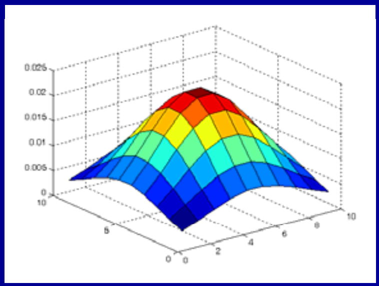
- Image Enhancement
- Edge Detection and Object Segmentation
  - Deterministic
  - Statistical
    - Multispectral (otherwise known as multivariate)
    - Random Fields
- Registration
- Compression
- Measurement

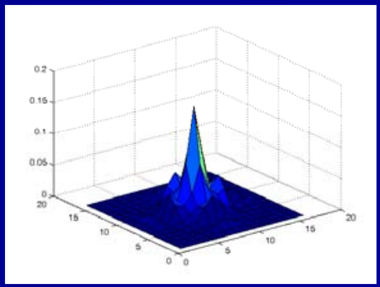
Image Enhancement

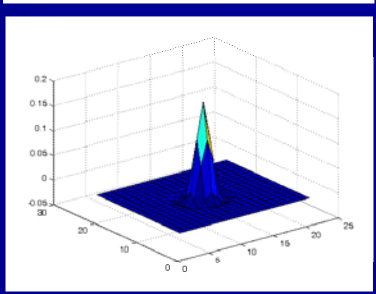
- Noise Filtering
  - Filters out white and non-white noise
  - Whole image
  - Neighborhood (Adaptive Weiner) noise filter
- Intensity Histogram Equalization
  - Critical for X-ray images
  - MLE, MMSE or Adaptive transform to a desired intensity histogram
  - Changes contrast and brightness

Image Filtering

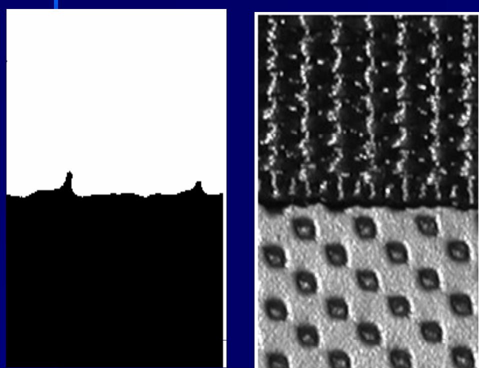
- Averages out noise
  - Gaussian Kernel (also known as a mask)
  - Finite Impulse Response (FIR)
  - Weiner
- Delete isolated bad pixels
  - Median Filter
  - Tophat / Bottomhat
- Eliminate outlier pixels
  - Denoising using Wavelets
- Deblurring
  - Inverse Filter
  - Removes some motion blurring
- Isolate certain features
  - Matched Filter for patterns
  - Texture
  - Directional



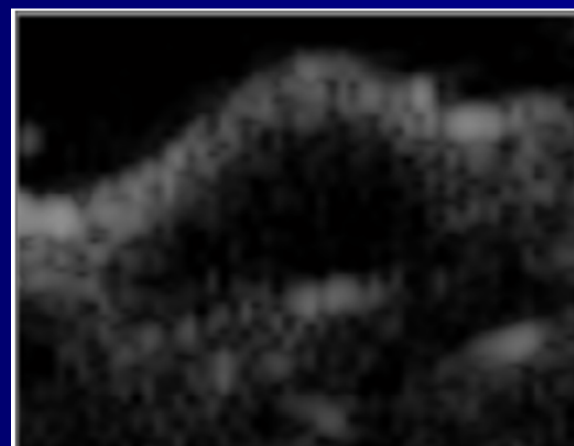




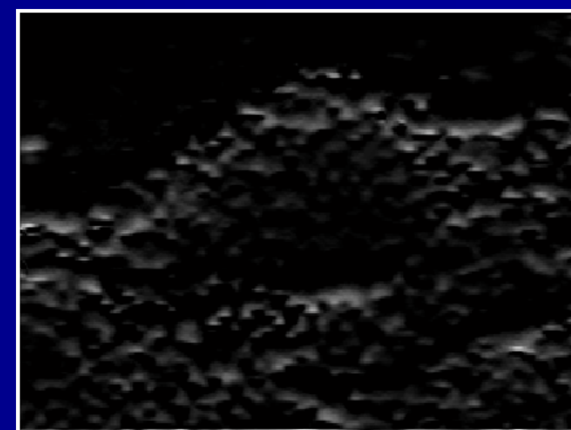
Some Filtered Images



Entropy Filter to detect changes in texture

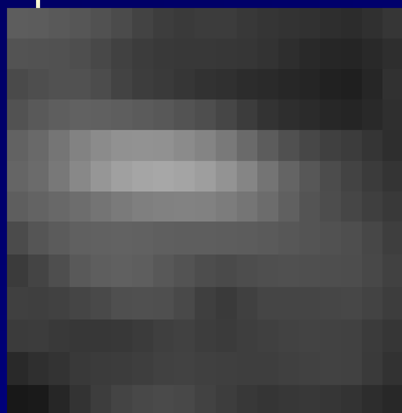


Smoothed (Blurred) previous lesion

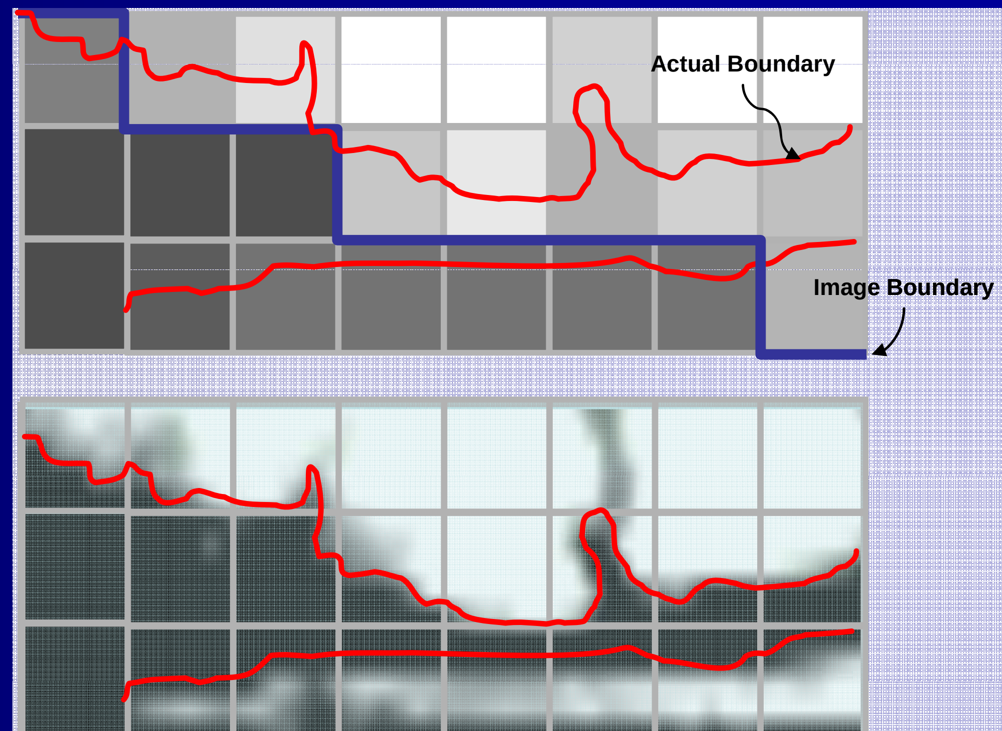


Filtered out vertical edges from previous lesion

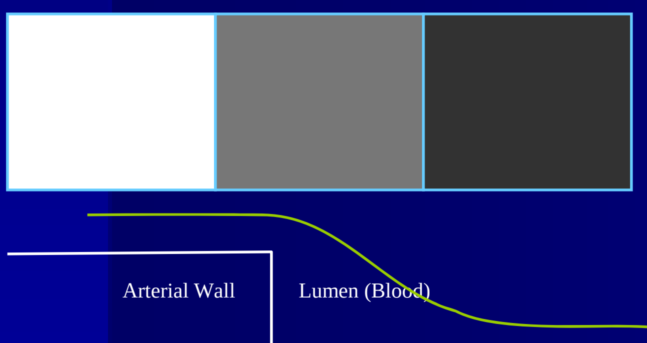
Edges and Partial Volume Effects



Brain White Matter Boundary



Neighboring Pixels



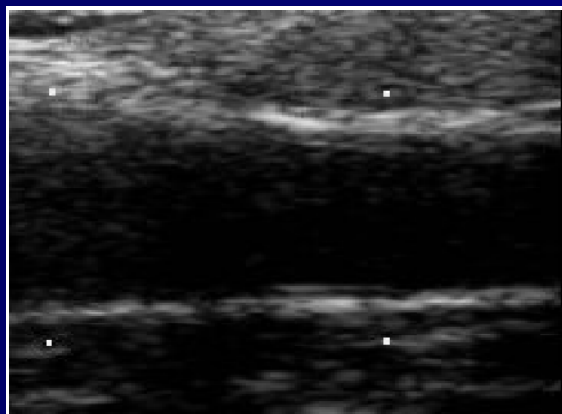
Edge Detection Example Human Xenograft Melanoma

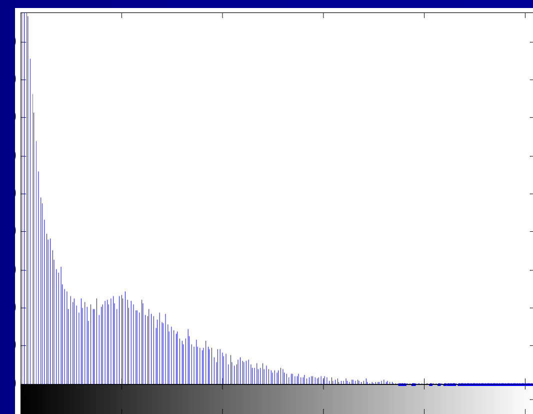
Original Image

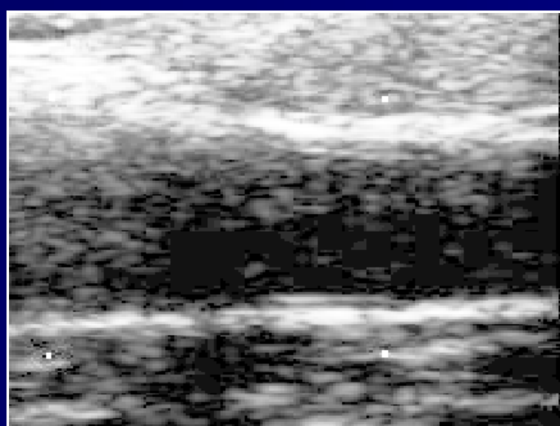
Sobel Edge Detection

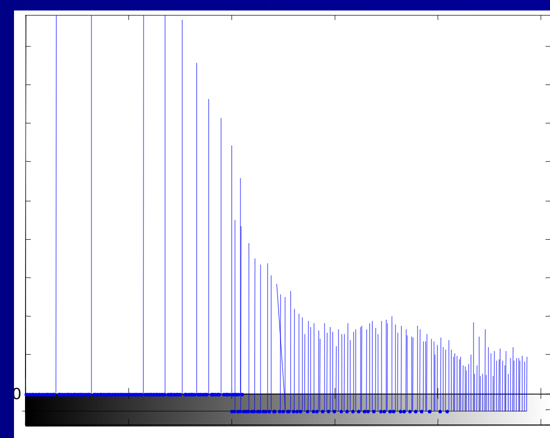
Canny Edge Detection

Example Histogram Equalization
Carotid Artery









Registration Example: Brain Registration to an Atlas

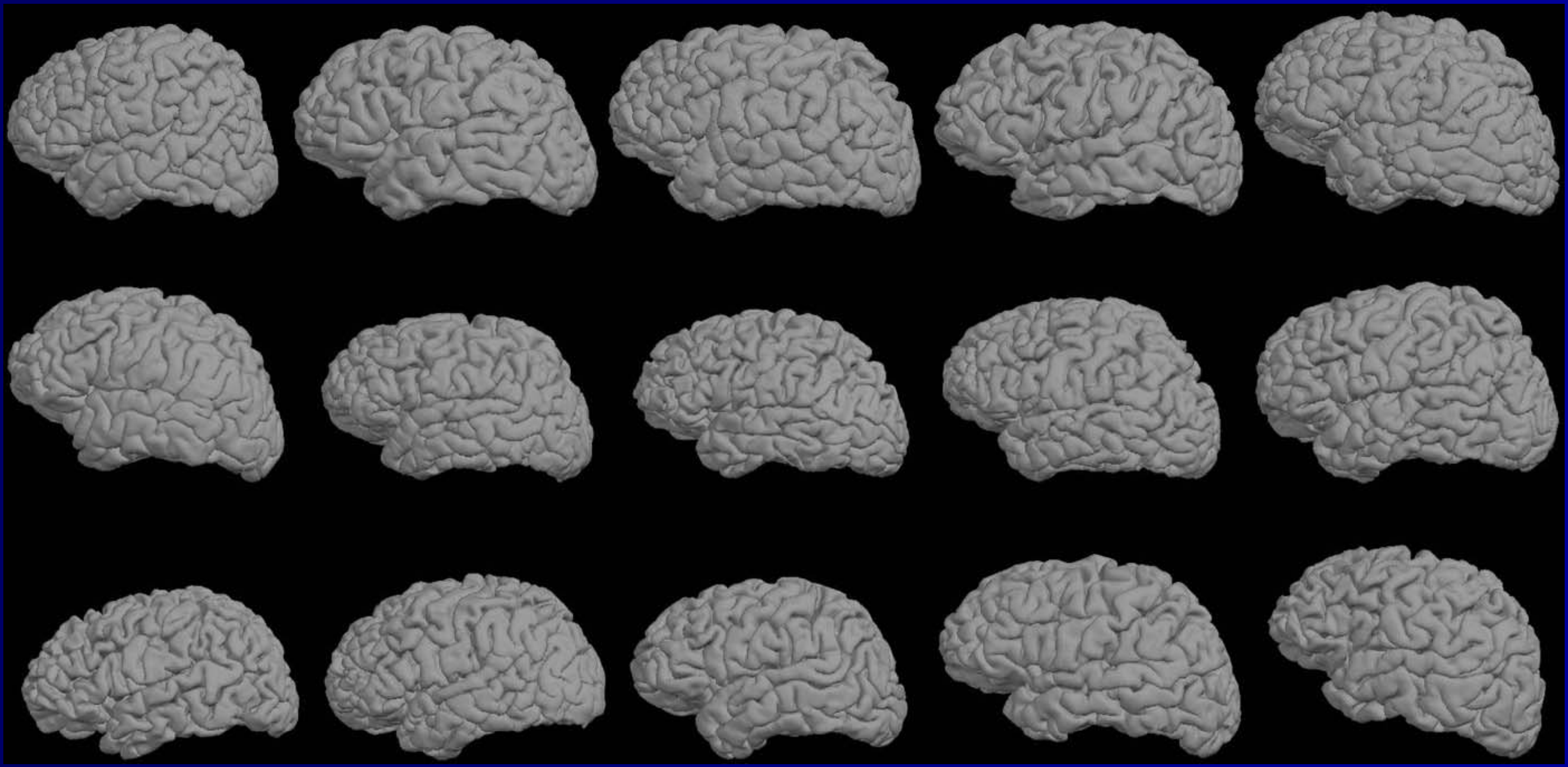
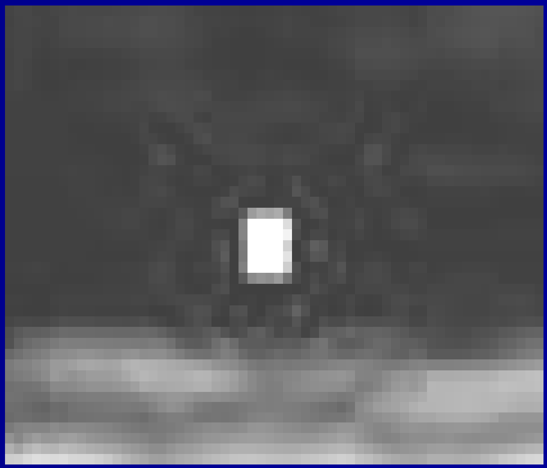


Image Compression

- A means of reducing the size of an image for transmission or storage
- Lossy Compression
  – Deletes changes in intensity based on a measure of importance
  – Most Compression
  – Can result in artifacts
  – JPEG/JPEG2000, TIFF, GIF, Wavelet, DCT, …
- Lossless
  – No loss of information



Compression ringing at a sharp edge

Summary

Modality	Concept	Advantage	Limitation	Clinical Applications
X-ray	Attenuation	Simple, Fast, Inexpensive, High resolution	Soft Tissue, Shadowing, Radiation	Oncology Bone Angiography
CT	Attenuation	High resolution 3-D High contrast	High radiation	Bone, Osteoarthritis, Oncology Lung/Airway, Cardiac Abdominal
MRI	Atomic resonance	High resolution Tissue segmentation, 3-D, Functional Imaging	Patient limitations, long acquisition time	Brain function and structure, Oncology, OA, cardiovascular
PET	Radioactive decay	Radionuclide labeling of ligands, cellular/molecular function	low resolution, radiation exposure, only images where radionuclide is	Receptor occupancy, cellular metabolism, cellular proliferation rate
Ultrasound	Acoustic Reflection	Inexpensive, Safe, versatile, real-time	Image noise Air and Bone Intestine	Oncology Cardiovascular Blood flow

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