Biomedical Informatics 260: Computational Methods for Biomedical Image Analysis and Interpretation

Class Introduction and Biomedical Imaging Modalities

Lecture 1

David Paik, PhD

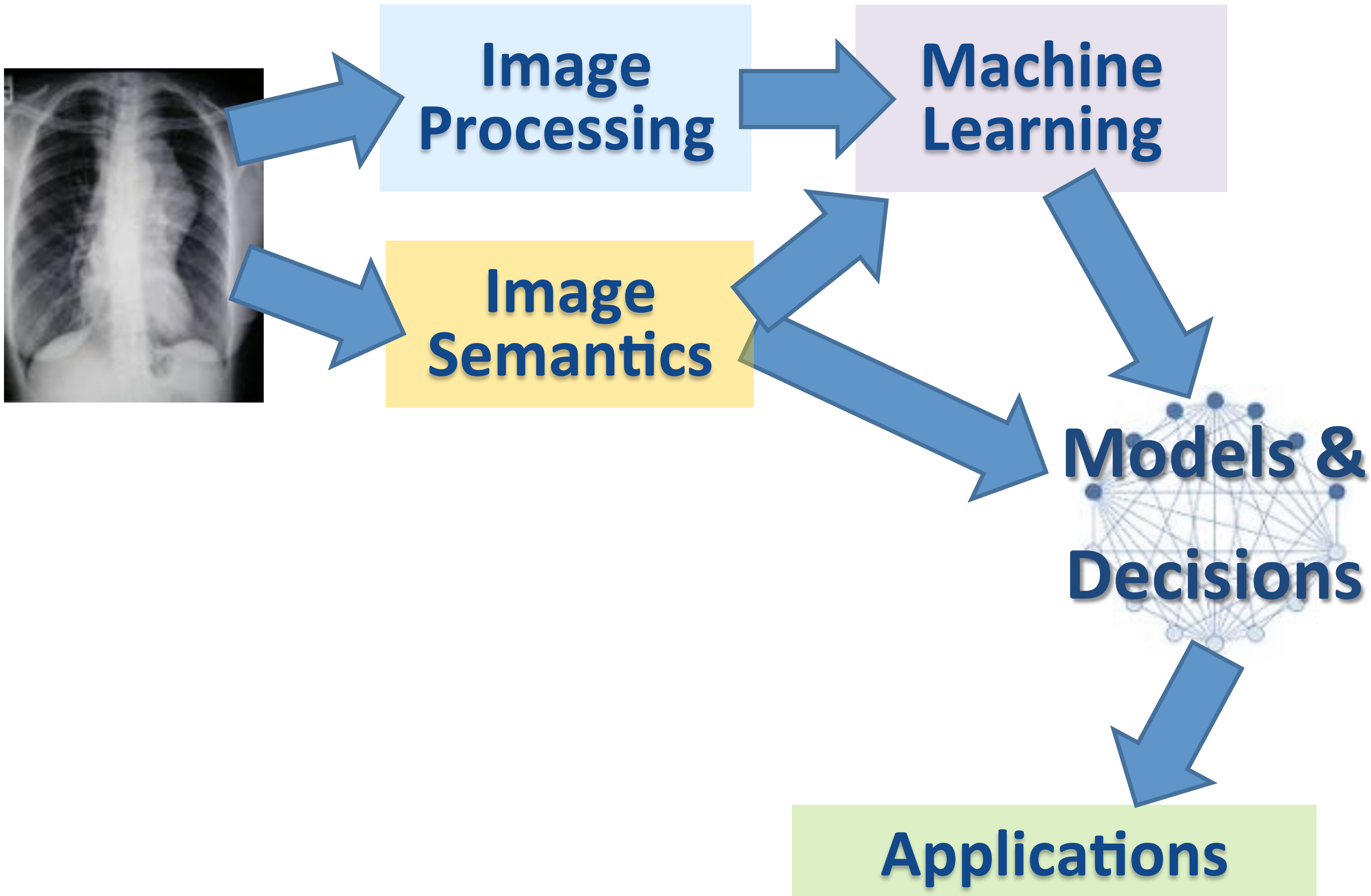
Spring 2017

Class Introduction

Course Learning Objectives

- How images are acquired
- How to extract information from images
- Machine learning over images
- Representation of what we see in images
- Reasoning over images
- Applications of imaging informatics
- *Hands on experience!*

From Images to Understanding



Audience

- Undergraduates
- Graduate Students
- Postdocs
- Medical Students
- Medical Residents and Fellows
- Auditors welcome as active participants

Course Instructors

David Paik, PhD

- Adjunct Lecturer, Radiology
- Industry research director
- Biomedical imaging informatics researcher
- **Research:** visualization, image analysis, molecular imaging, image quantitation, cancer modeling

Daniel Rubin, MD, MS

- Assistant Professor of Radiology
- Biomedical imaging informatics researcher and radiologist
- **Research:** machine processing of image content, image mining, machine learning, decision support with images

Teaching Assistants

Albee Ling

- PhD candidate, Biomedical Informatics

Darvin Yi

- PhD candidate, Biomedical Informatics
- Masters of Medicine program

Pre-requisites

- What you absolutely need to know
  - Programming ability (CS 106A)
  - Basic statistics
  - Basic biology

- Highly recommended
  - Familiarity with Python or Matlab
    - Friday TA-led session on programming in Python

Readings

- **Articles**
  - Assigned with each lecture
  - Links posted on course website
- **Books**
  - Not required
  - Supplement required readings
  - (see course website)

Coursework

- **3 Assignments (involving programming)**
  - Lung Field Segmentation
  - Machine Learning with Mammography I
  - Machine Learning with Mammography II
  - OUT on Friday, DUE on Fridays
- **Midterm**
  - Open notes, during class, 5/15
- **Final project presentations**
  - Project proposal due 4/28
  - Milestone write-up due 5/19
  - Final write-up due 6/12
  - Final presentation on 6/12
- Talking with others acceptable, all work individual
- Submissions on Canvas

Final Project

- A substantive programming project
  - Should utilize both ***image analysis*** and ***image semantics***
- Can be done in groups, up to 4 students
- Written portion
  - Project proposal
  - Milestone write-up
  - Final write-up
- Final presentation
  - Gates B03 ***June 12 at 3:30-6:30pm***

Grading

- **Grade Breakdown**
  - Assignment 1 15%
  - Assignment 2 15%
  - Assignment 3 15%
  - Midterm exam 15%
  - Final project 30%
  - Participation 10%
- **Class participation**: There are many different ways to participate, including but not limited to:
  - Attending class
  - Attending TA sections
  - Asking questions

Resources

- Main website (general info)
  - http://bmi260.stanford.edu
- Piazza (discussion, project teams)
  - http://piazza.com/stanford/spring2017/bmi260rad260
- Canvas (homework submission)
  - http://canvas.stanford.edu

Schedule

- **Lectures**
  - Mon / Wed 1:30-2:50pm, Gates B03
- **Section**
  - Friday 1:30-2:50pm, Gates B03

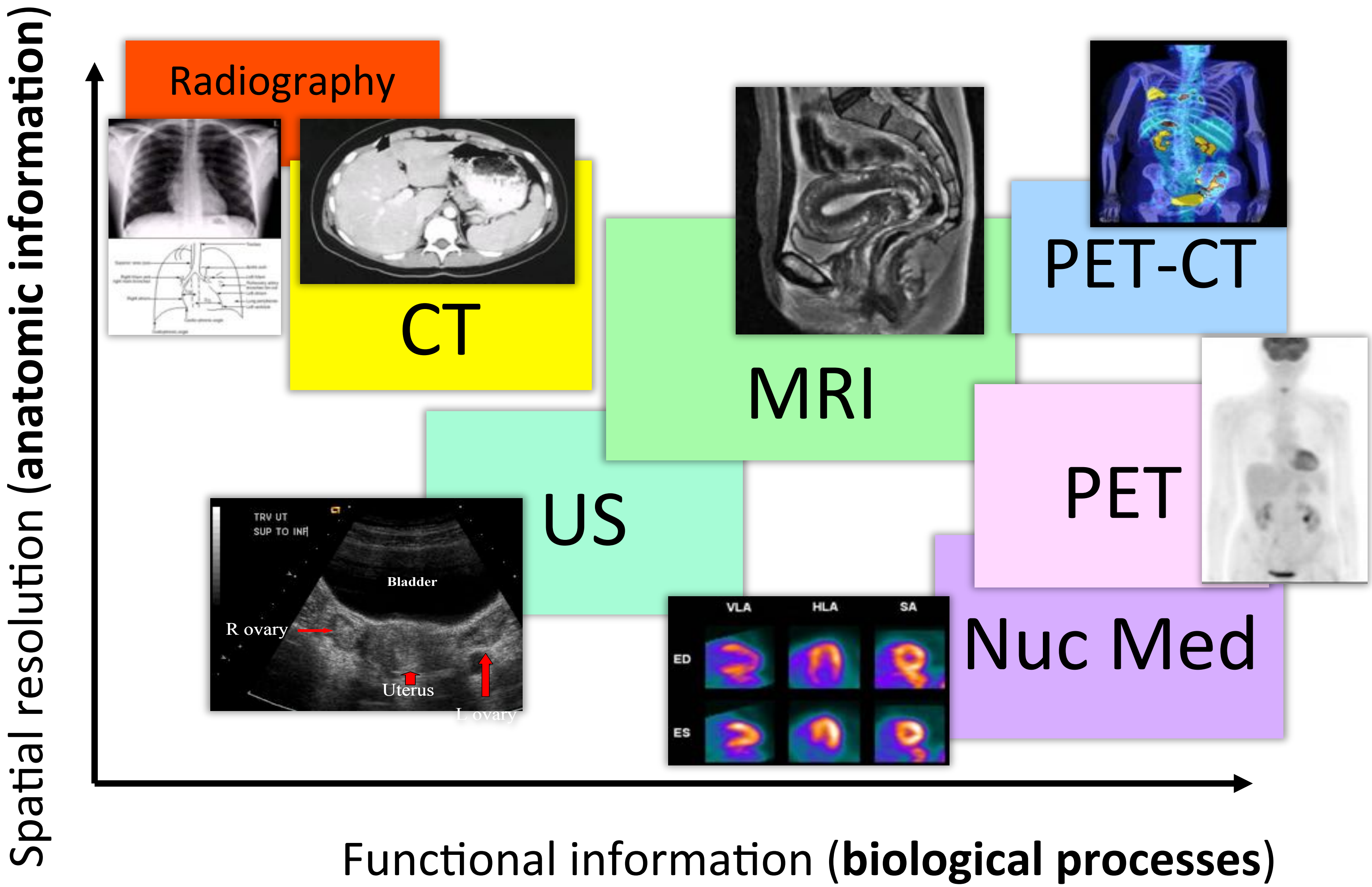
Syllabus

Rubin	
Paik	
TAs	
Guests	

WEEK	Mon		Wed	
1	4/3	Imaging Modalities	4/5	Visualization
2	4/10	Image Segmentation	4/12	Filtering
3	4/17	Geometric Features	4/19	Texture Analysis
4	4/24	Machine Learning Intro	4/26	Evaluation of Machine Learning
5	5/1	Neural Networks	5/3	Convolutional Neural Networks
6	5/8	Machine Learning Research 1	5/10	Machine Learning Research 2
7	5/15	***Midterm***	5/17	Image Registration
8	5/15	Semantic Features Intro	5/24	Natural Language Processing
9	5/29	***Memorial Day***	5/31	Querying Images
10	6/5	Decision Support	6/7	Content Based Image Retrieval
11	6/12	***Final Presentations***		

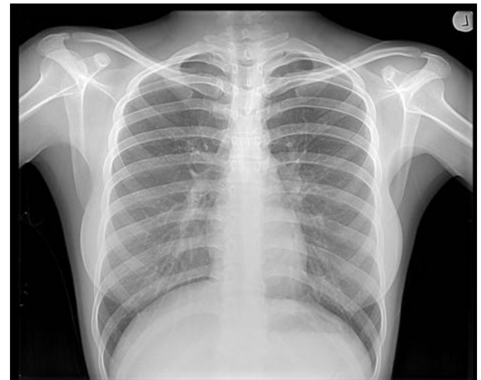
Imaging Modalities

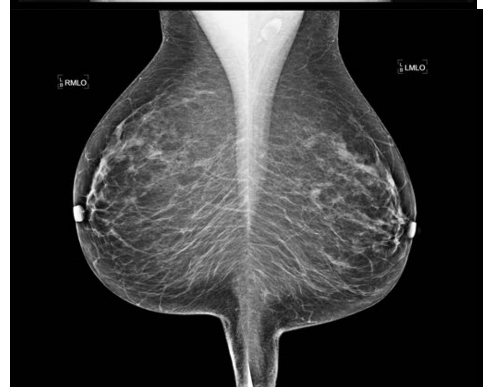
Medical images show us different kinds of information about disease

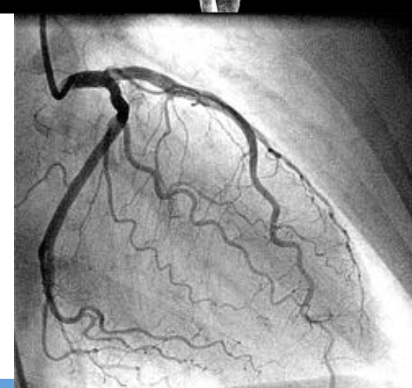


Radiography/Fluoroscopy (X-ray)

Imaging Modalities:
Radiography / Fluoroscopy

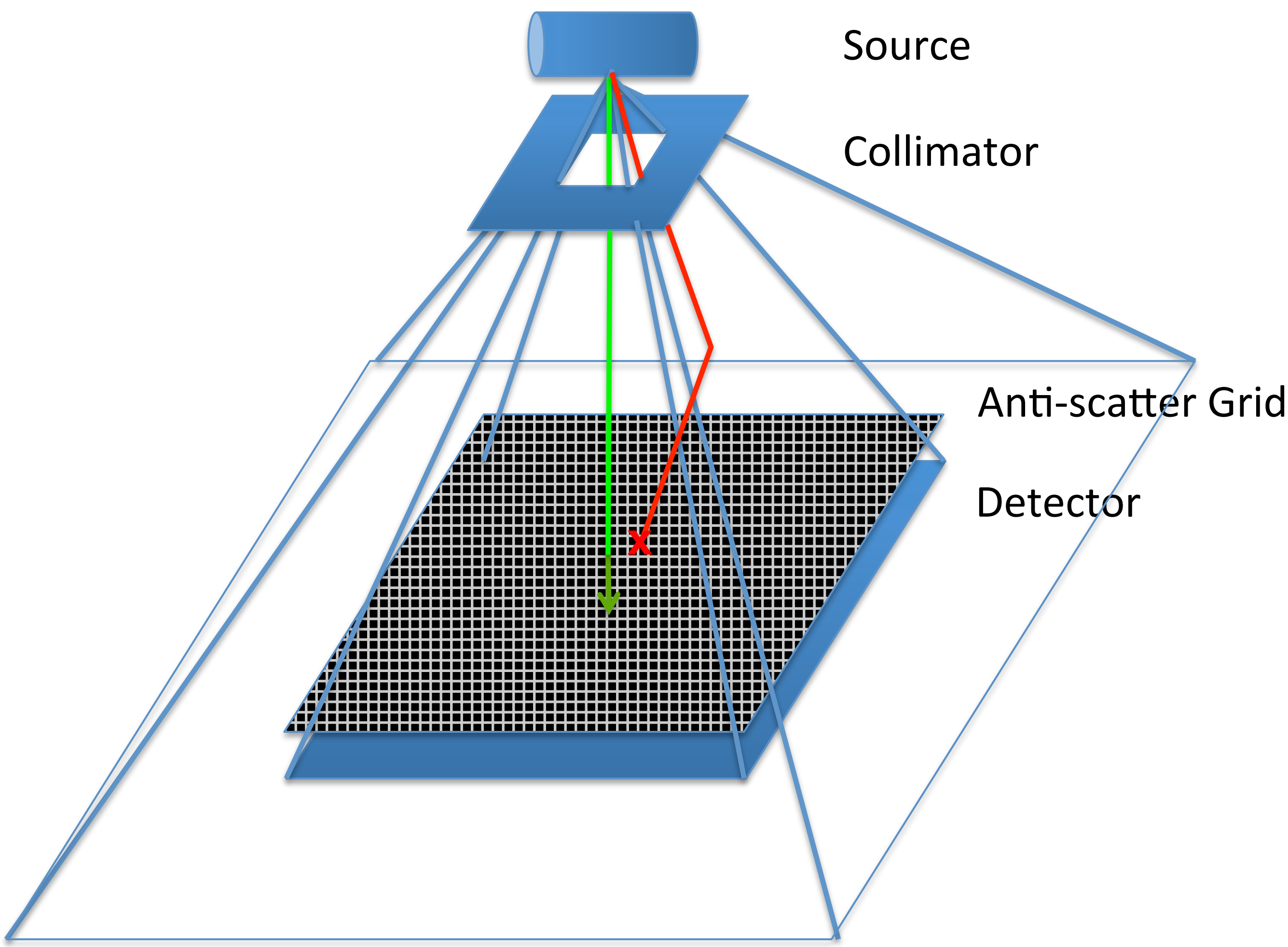


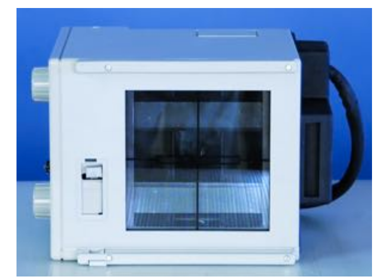


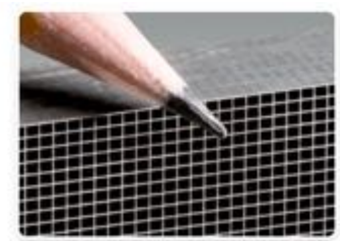


X-Ray

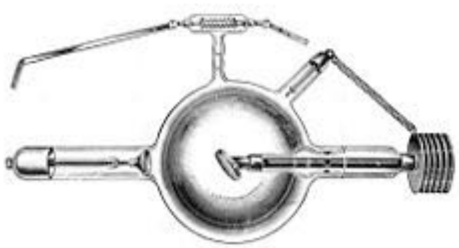
Radiography Hardware







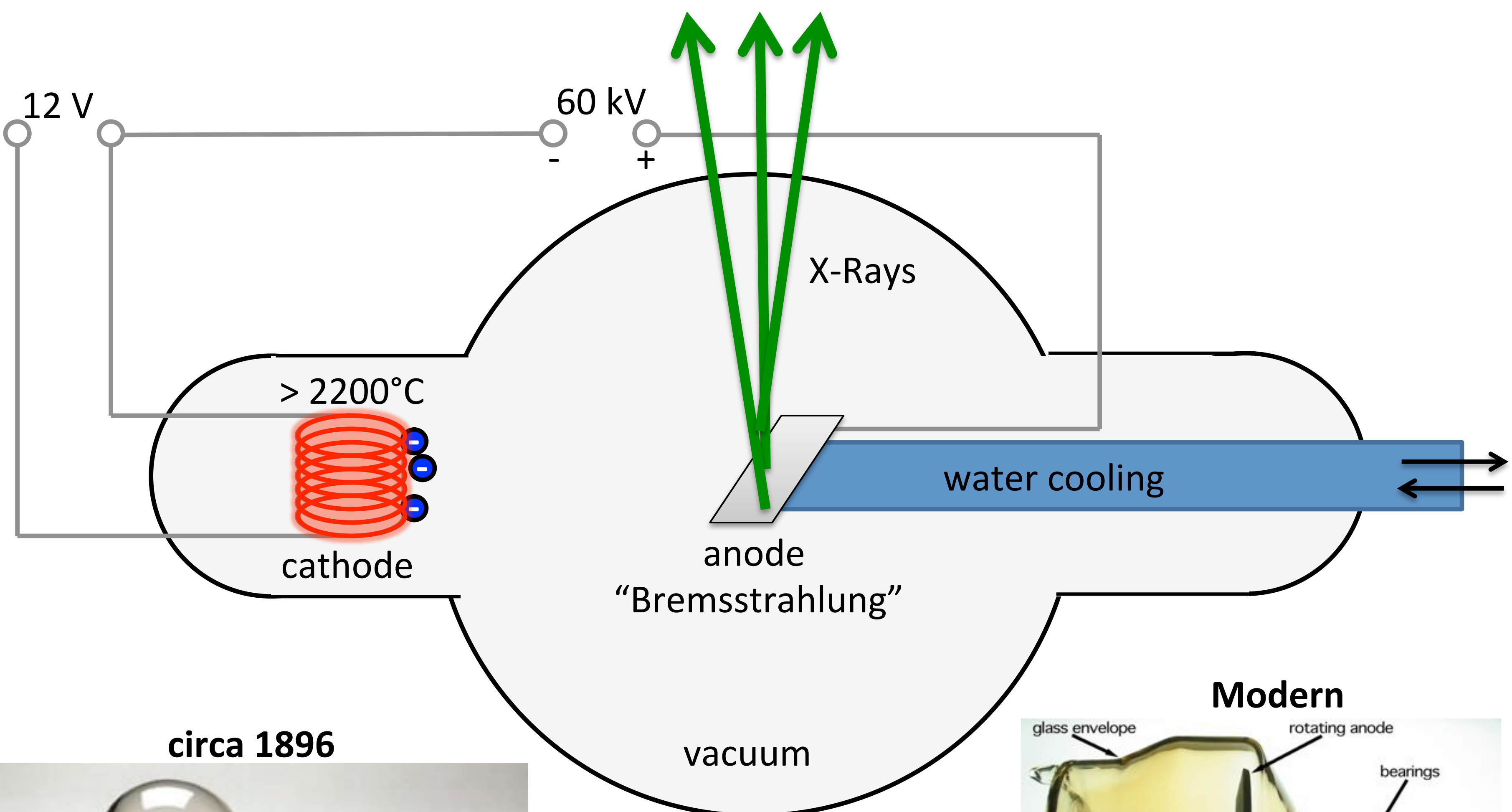
History of the X-Ray



Wilhelm Röntgen
1895 discovered X-rays
1901 Nobel Prize in Physics
(first Nobel Prize!)

Recommended reading on history of medical imaging:
Naked to the Bone by Bettyann Kevles

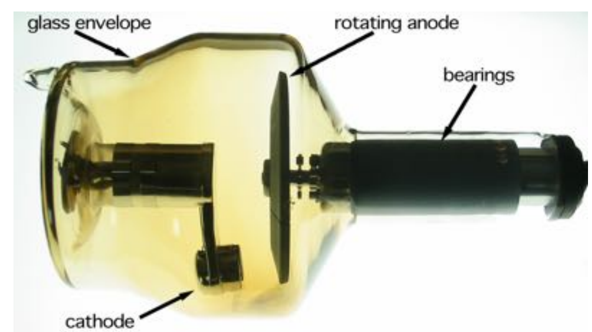
X-Ray Tube



circa 1896

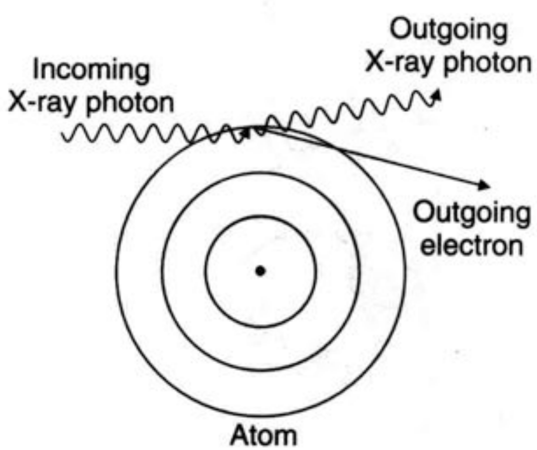
www.sciencemuseum.org.uk

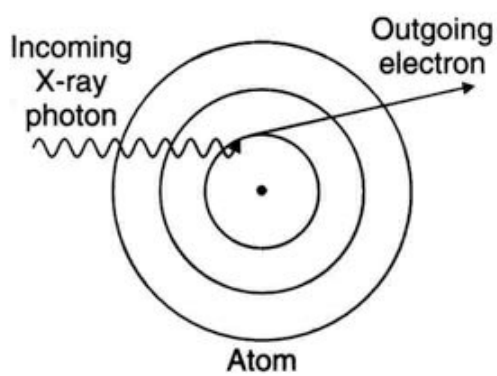
Modern



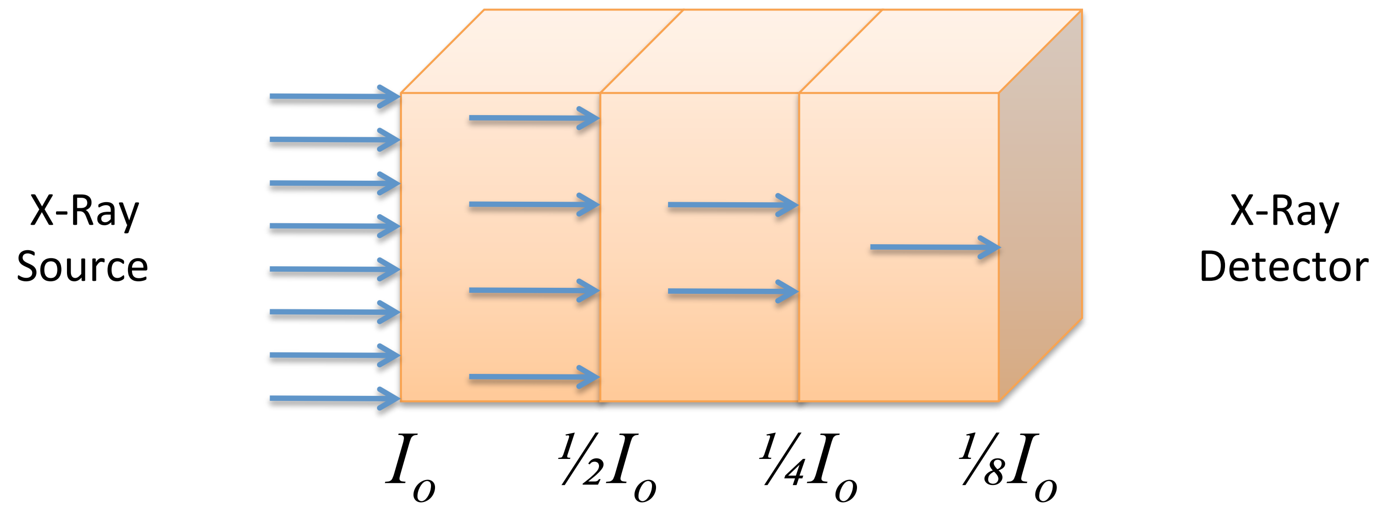
X-Ray Interactions with Matter

- **Penetrate (no interaction)**
- **Scatter**
  - *Rayleigh scattering*
    - *Elastic, no energy deposition, <u>low probability in diagnostic imaging</u>*
  - **Compton scattering**
    - **Inelastic, valence electron ejected**
    - **Ionizing radiation**
- **Absorption**
  - **Photoelectric absorption**
    - **Inner electron ejected, photon absorbed, outer electron fills vacancy**
    - **Ionizing radiation**
  - *Pair production*
    - *Photon interacts with nucleus to produce e^- + e^+, <u>low probability in diagnostic imaging</u>*





X-Ray Contrast



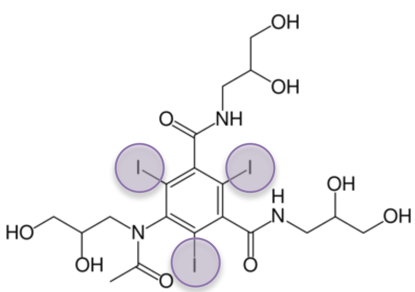
$$I = I_O e^{-\mu x}$$

Half photon penetration depth ($\ln(2)/\mu$) to 0.5 – 5.0 cm depending on X-Ray energy and tissue density

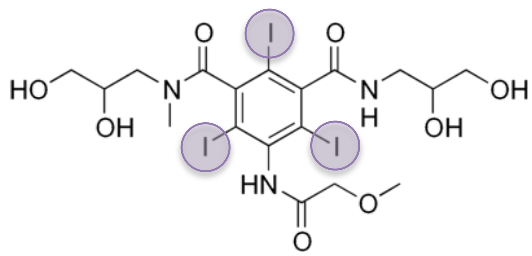
X-Ray pixel value represents μ integrated through the body depends on X-Ray energy, tissue density, ***and on thickness of body***

X-Ray Contrast Agents

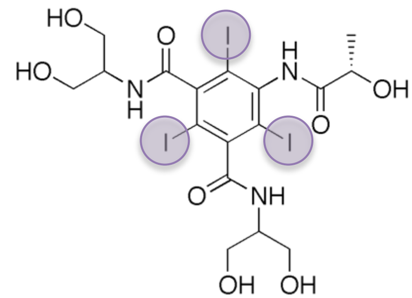
- Iodinated compounds



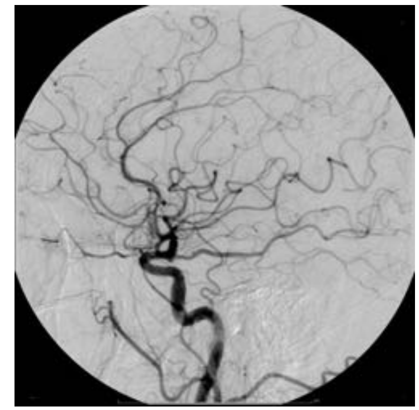
Omnipaque



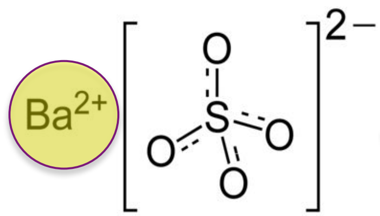
Ultravist

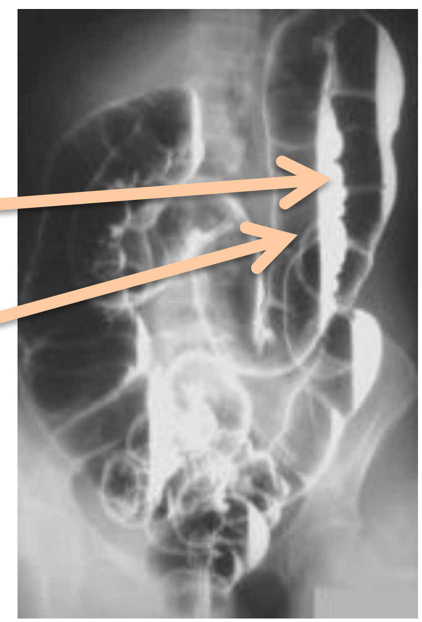


Isovue



- Barium Sulfate

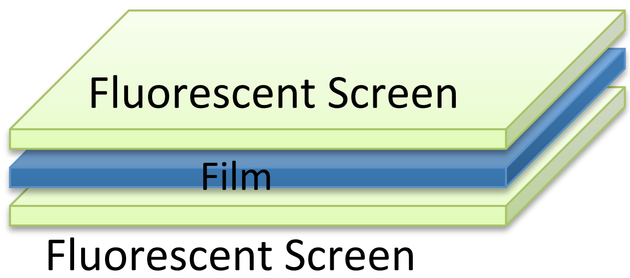




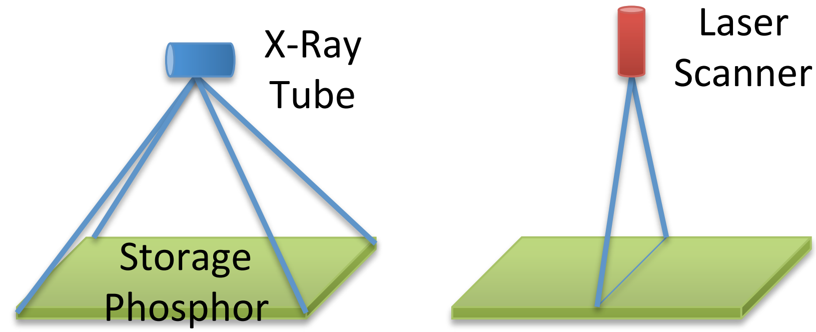
- Air (negative contrast)

(high attenuation sometimes visualized as white, sometimes black)

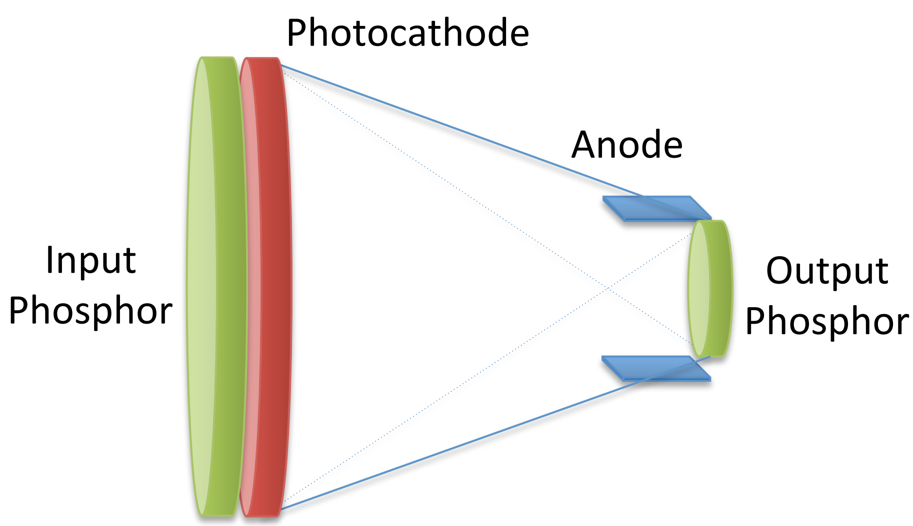
X-Ray Detection



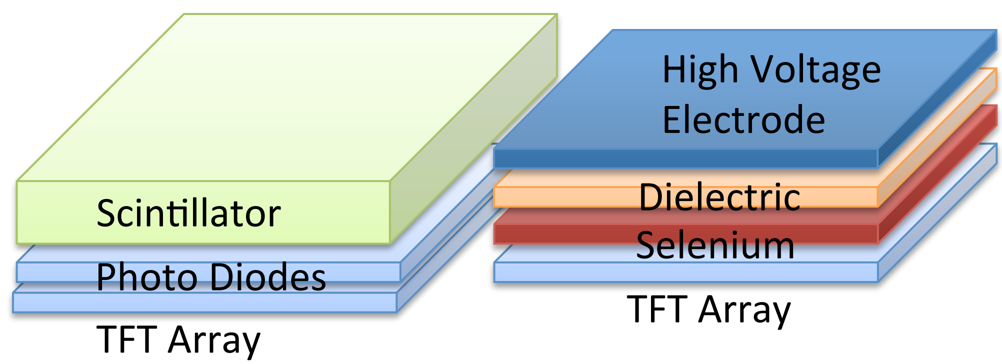
Film



Computed Radiography



Fluoroscopy



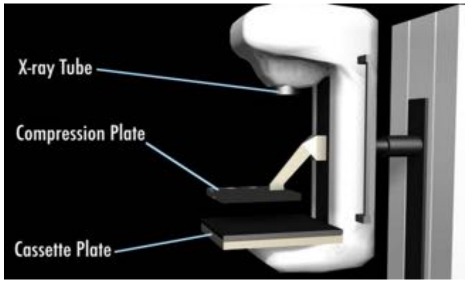
Indirect
X-ray → light → electron

Direct
X-ray → electron

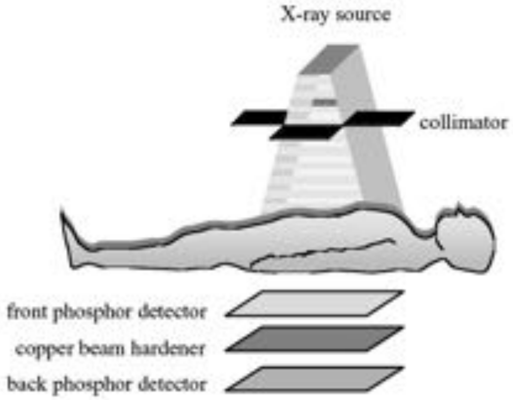
Digital Radiography

Some Radiography Variants

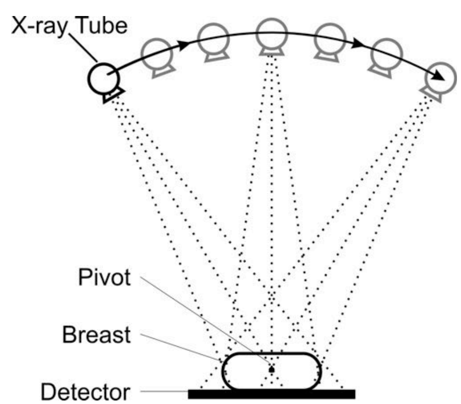
- Mammography
  - Highly regulated by Mammography Quality Standards Act (MQSA)



- DXA – Dual-energy X-ray Absorptiometry
  - Measures Bone Mineral Density (BMD)
  - Either two different tube voltages are used OR a beam hardener is used between two stacked detectors



- Tomosynthesis
  - Combining views from multiple angles to selectively blur all but one plane



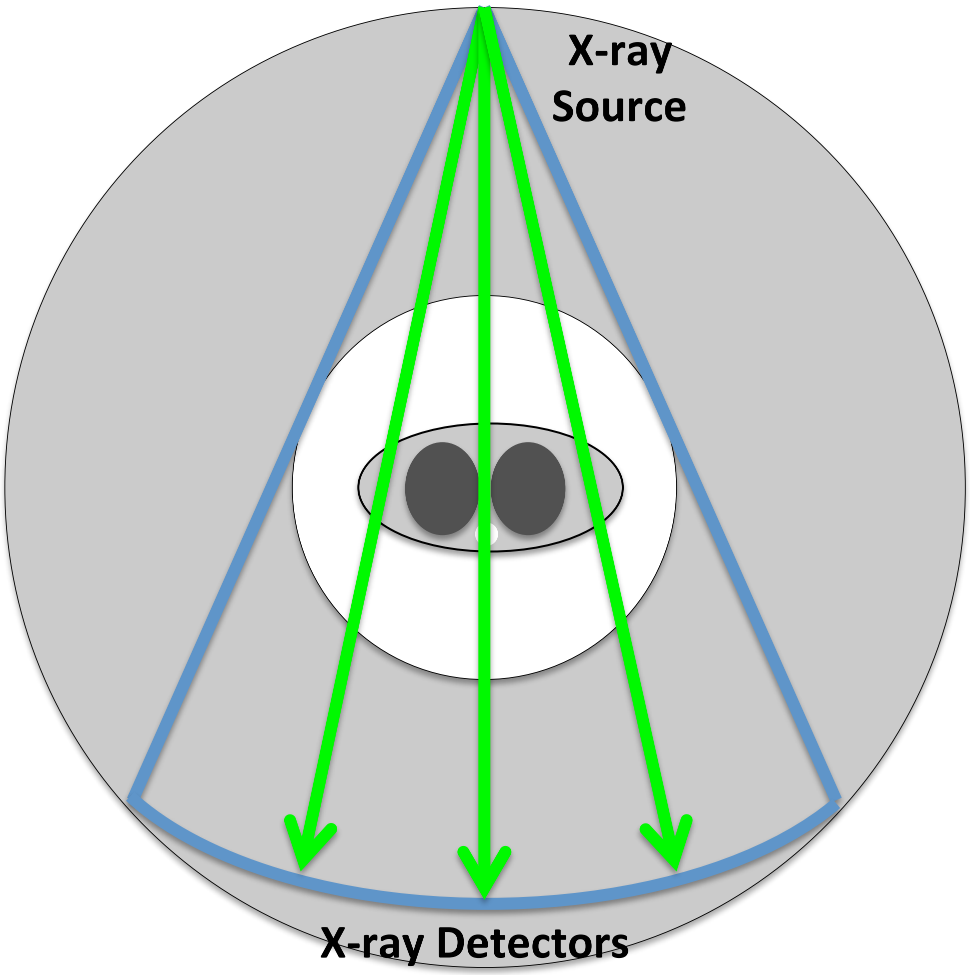
http://media.wiley.com/product_data/excerpt/63/04712376/0471237663.pdf
Yaffe, Breast Cancer Research 2008

Computed Tomography (CT)

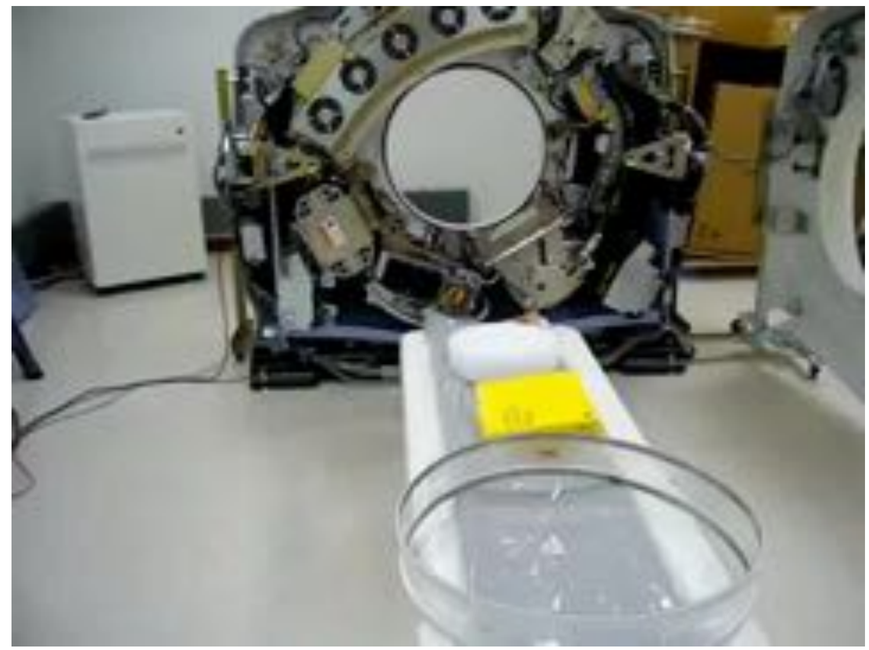
Imaging Modality:
CT (Computed Tomography)

Tomos – Greek word for cut or slice
(e.g., atom, anatomy)

CT Scanner Geometry



0.25s rotations typical

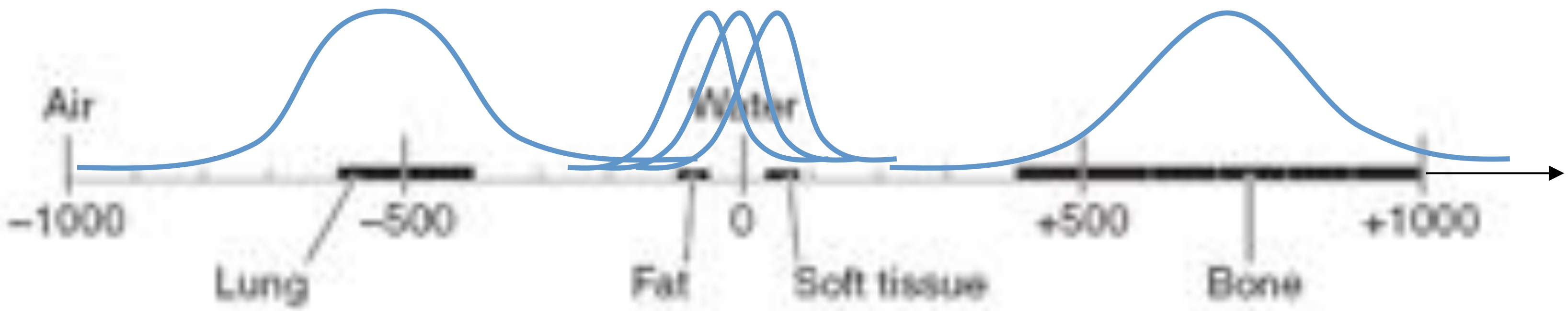


wikipedia.org

Patient translated through the scanner during gantry rotations (i.e., helical CT)

[Video of Rotating CT Scanner]

CT Contrast



$$I = I_O e^{-\mu x}$$

$$HU = \frac{\mu - \mu_{water}}{\mu_{water} - \mu_{air}} \times 1000$$

Bone	+400 → +1000
Soft tissue	+40 → +80
Water	0
Fat	–60 → –100
Lung	–400 → –600
Air	–1000

http://www.odec.ca/

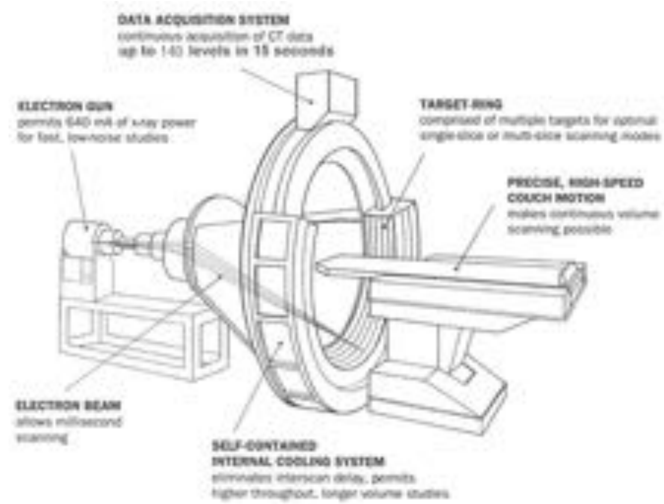
Hounsfield Units (HU) provide a quantitative measure from CT

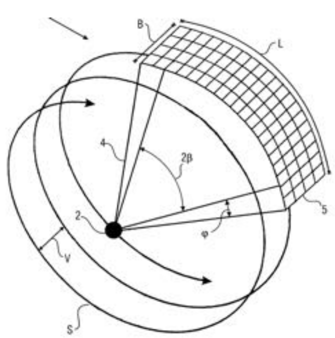
Differences in HU are roughly proportional to differences in material density

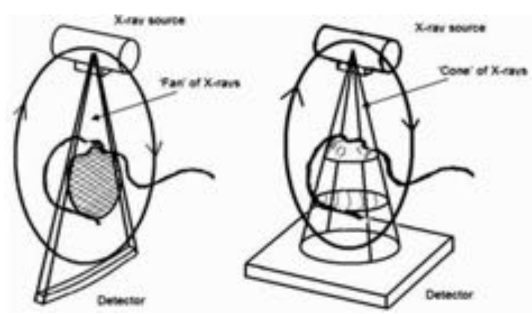
Contrast agents generally same as in radiography

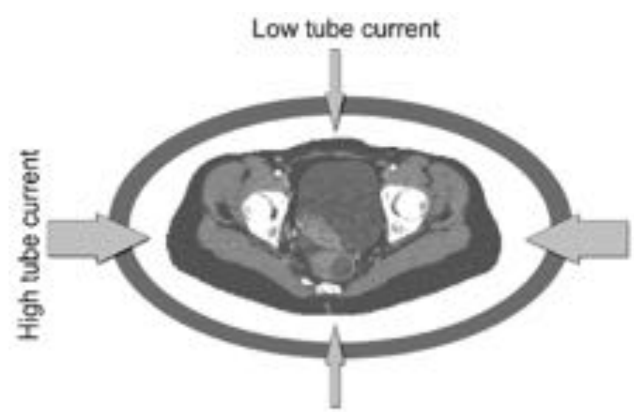
Some CT Variants

- MDCT – Multi-Detector CT
  - 2D grid of detector elements
- Cone Beam CT
- EBCT – Electron Beam
- Cardiac-gated CT
- Tube current modulation





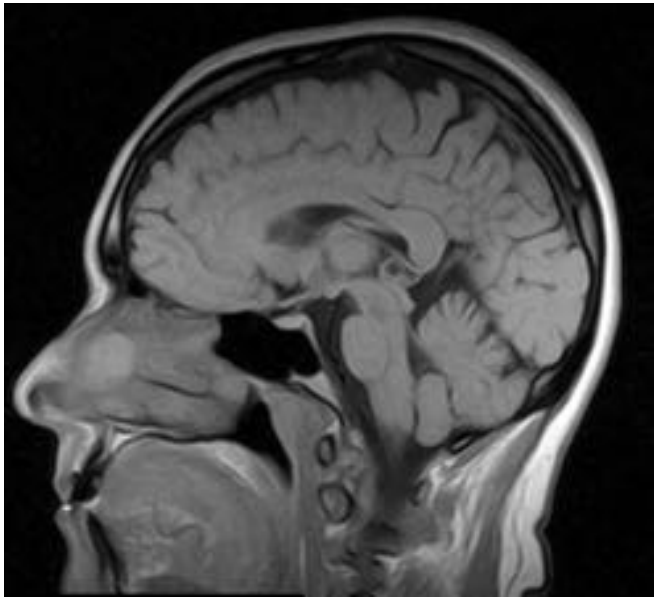


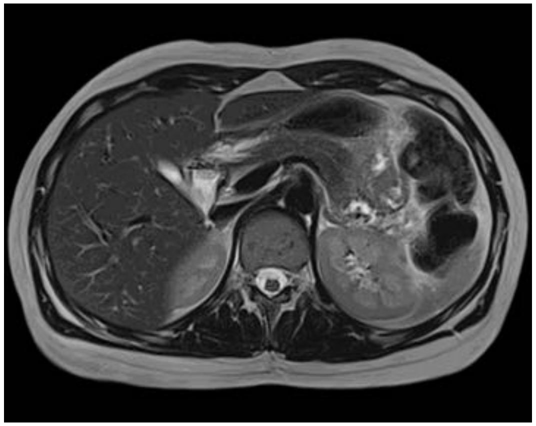


Kalra et al, Radiology 2004

Magnetic Resonance Imaging (MRI)

Imaging Modality:
MR (Magnetic Resonance)

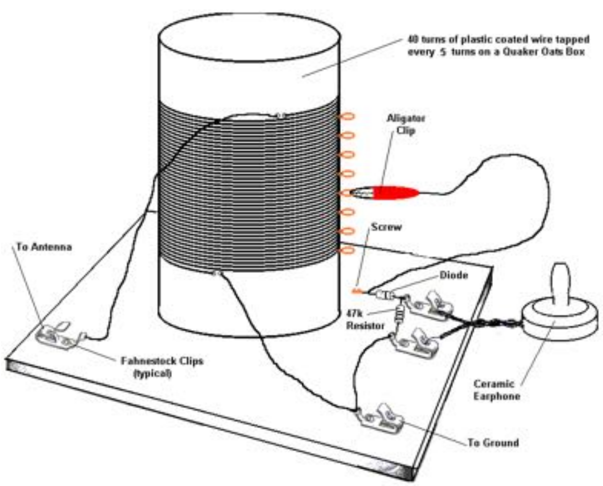




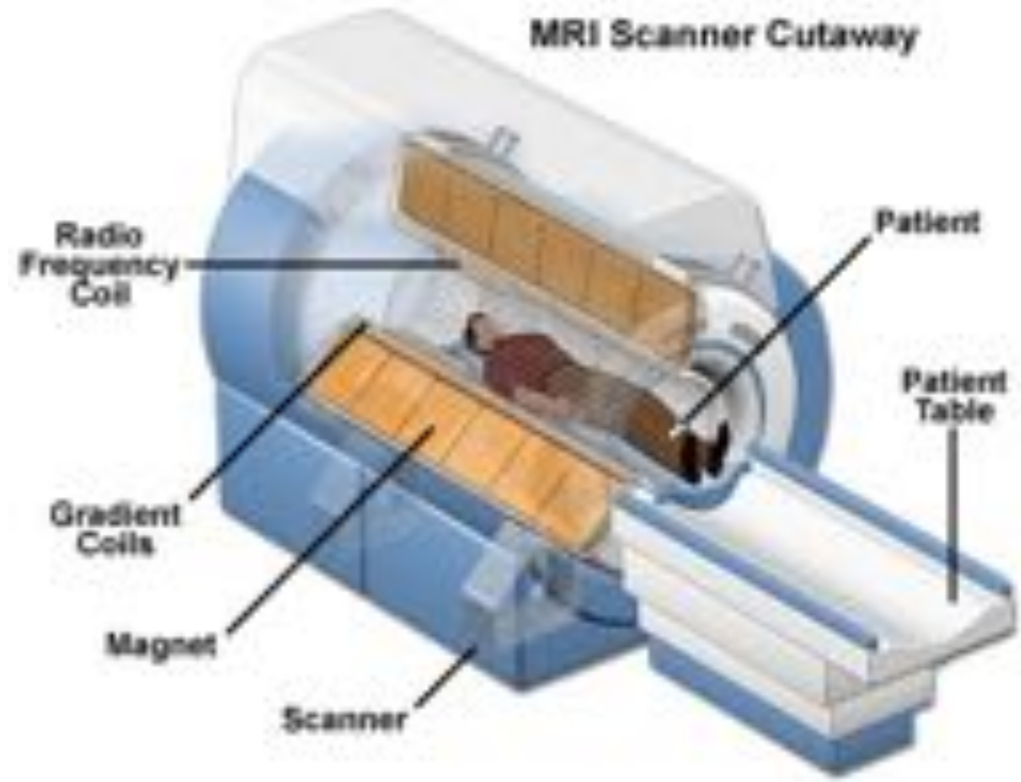
www.magnet.fsu.edu
siemens.com

MR Scanner Hardware

Simple electromagnet



Simple radio receiver



MR Scanner with
liquid helium cooled
superconducting magnet

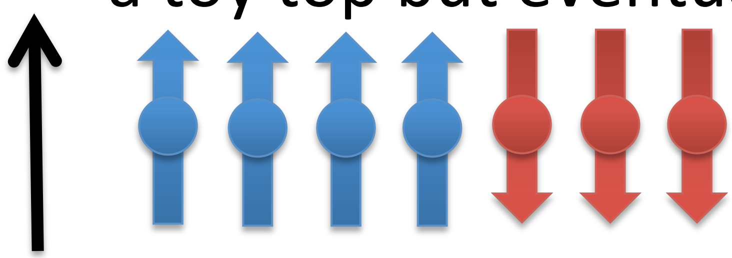
1.5 T, 3.0 T magnet strength (100,000x Earth's mag field)

MR Scanner Hardware

Safety demonstration with 4T MRI

MR Physics

- Nuclei with odd number of protons and/or neutrons have a magnetic moment with non-zero quantum mechanical up or down "spin"
  - e.g., ^{1}H, ^{13}C, ^{19}F, ^{31}P
- In a magnetic field, they line up to be parallel or antiparallel with the field with a tiny preference for parallel (lower energy)
  - If "knocked over" they will wobble or precess like a toy top but eventually recover

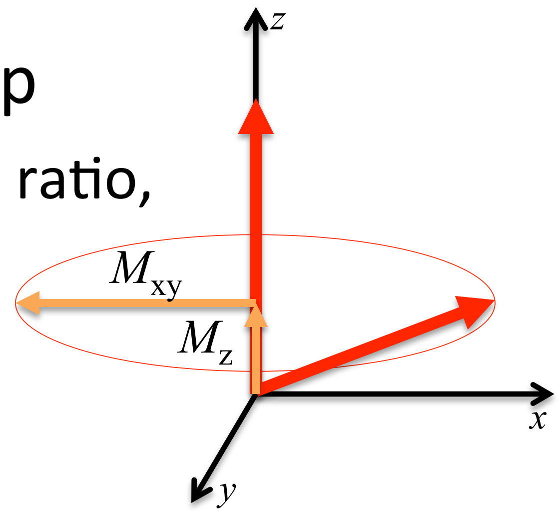


More MR Physics

- Larmor equation says a specific radiofrequency pulse will "tip" the top
  - f is frequency, γ is nucleus gyromagnetic ratio, B is external magnetic field strength

$$f = \frac{\gamma}{2\pi} B$$

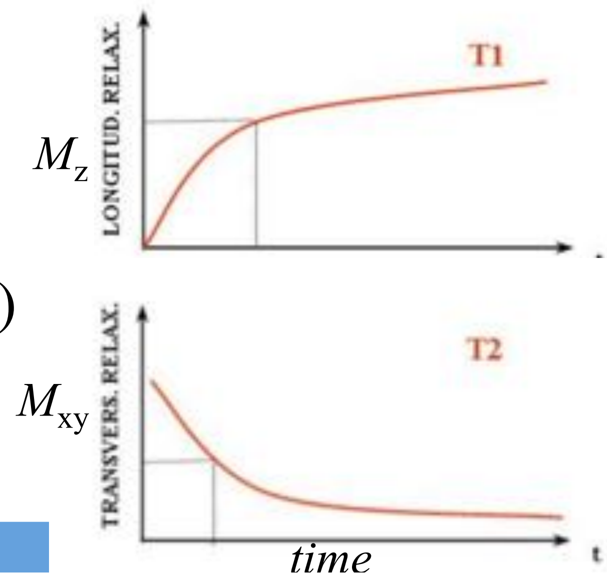
  - For ^1H, $\frac{\gamma}{2\pi} = 42.576 \frac{MHz}{T}$



- For a 90° pulse,

$$M_z(0) = 0 \quad M_z(t) = M_{z,eq}(1 - e^{-t/T_1})$$

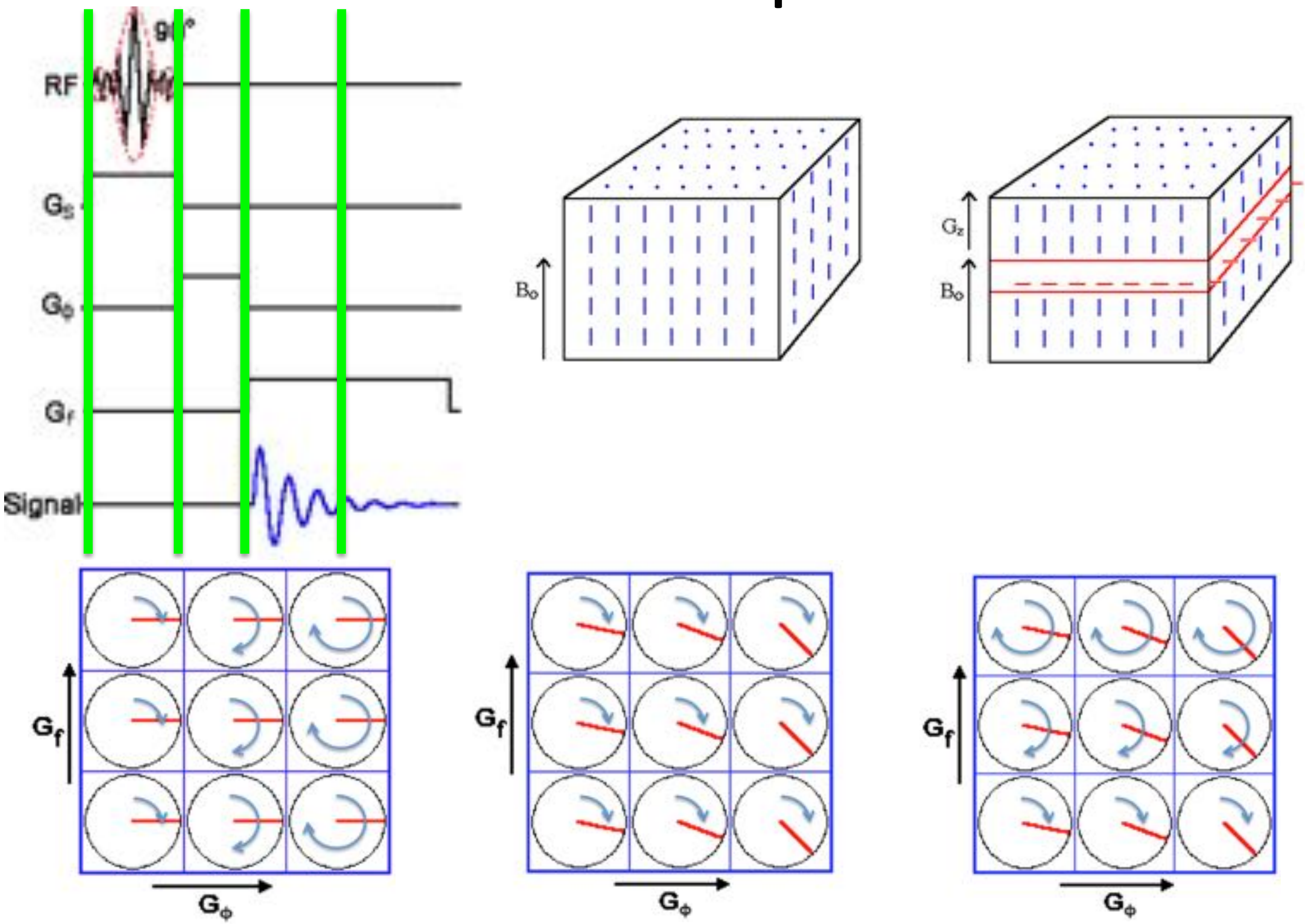
$$M_{xy}(t) = M_{xy}(0)e^{-t/T_2}$$



MR Pulse Sequence

- Slice selection
  - A magnetic field gradient (spatial variation) in Z is used during a radiofrequency (RF) pulse at a single frequency that will only tip the spins in a thin slice tuned in to that particular frequency
- Phase encoding
  - After RF pulse, a brief gradient in X is used to add a position dependent phase shift in X
- Frequency encoding (readout)
  - After phase encoding, a gradient is applied in Y to encode a position dependent frequency shift in Y
  - The free induction decay is listened for with a quadrature detection coil to determine both phase and frequency

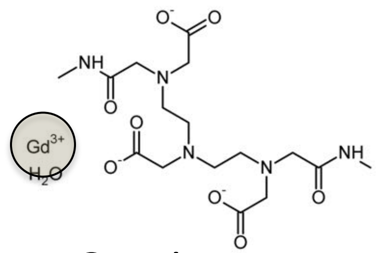
MR Pulse Sequence



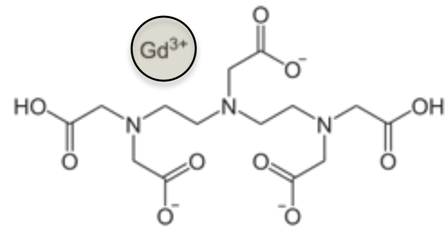
Adapted from http://www.cis.rit.edu/class/schp730/

MR Contrast Agents

- Gadolinium chelates (decrease T1)



Omniscan

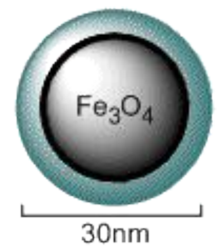


Magnevist

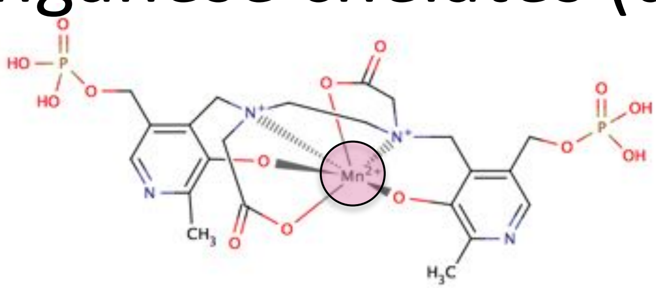
- Iron oxides (decrease T2)

SPIO
Superparamagnetic Iron Oxide
300-3000 nm

USPIO
Ultrasmall SPIO
10-50 nm

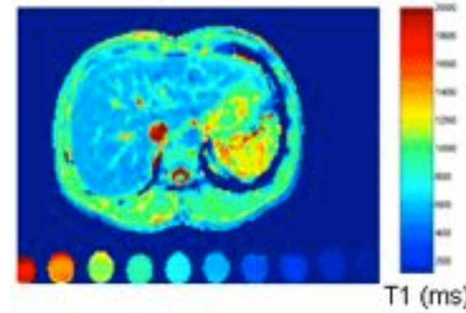


- Manganese chelates (decrease T1)

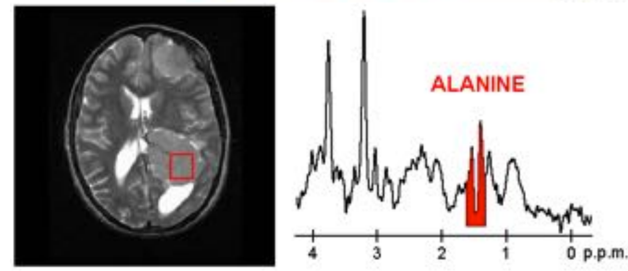


Mangafodipir

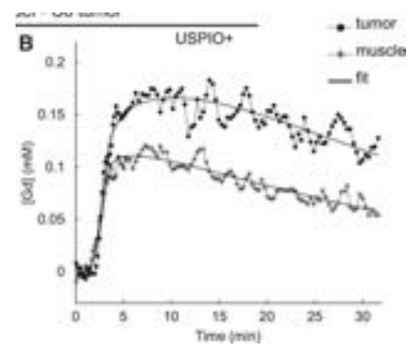
Some MR Variants



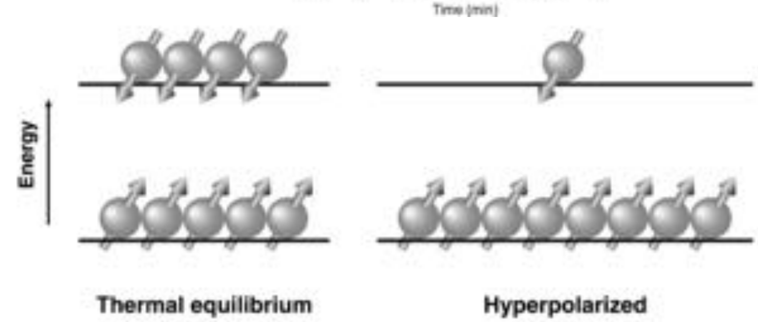
- T1 or T2 Mapping
  - Most MR pixel values are arbitrary units but…
  - Estimate tissue parameters from multiple images



- MR Spectroscopy
  - Uses chemical shift to identify different chemical species



- DCE-MRI
  - Quantify wash-in and wash-out of contrast to infer pharmacokinetics
- Hyperpolarized ^{13}C
  - Induce non-equilibrium spins



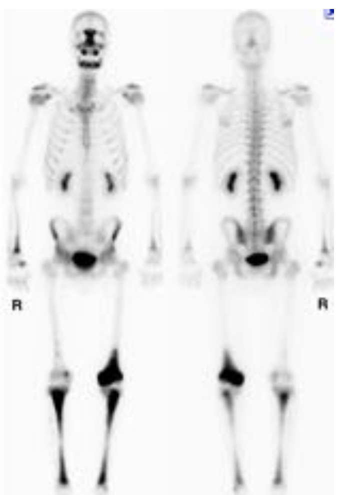
http://www.radiology.northwestern.edu/research/triog/research/trip/
Beaumont et al, J Cer Bl Flow and Metab 2009
Golman et al, BJR 2003

Nuclear Medicine:
Positron Emission Tomography (PET)

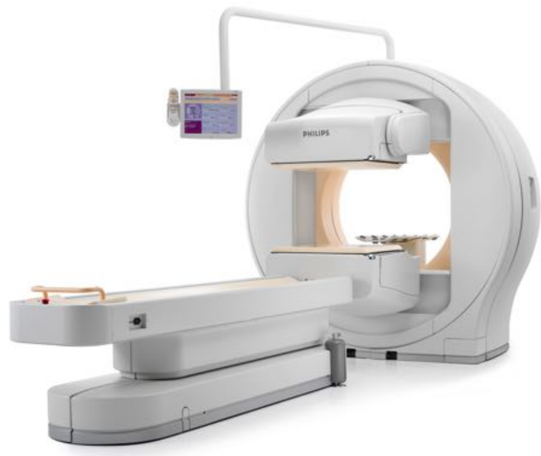
Imaging Modalities:
Nuc Med: Scintigraphy, SPECT, PET

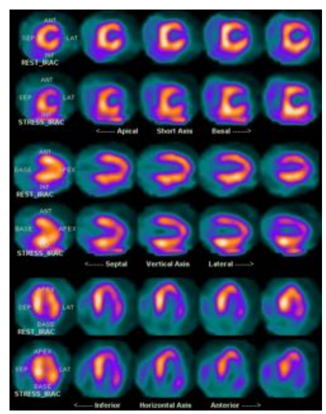
- Signal comes from injected radioactively labeled pharmaceuticals rather than external radiation source
  - Radioactivity must be generated locally/regionally or delivered quickly
  - Physiological function is depicted rather than anatomy
- Diagnostic nuclear medicine scans
  - Scintigraphy
  - SPECT
  - PET

Nuclear Medicine

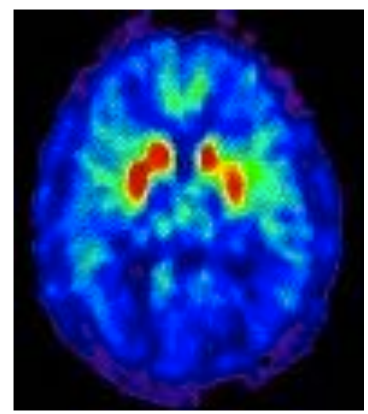


Gamma Camera
(Scintigraphy)



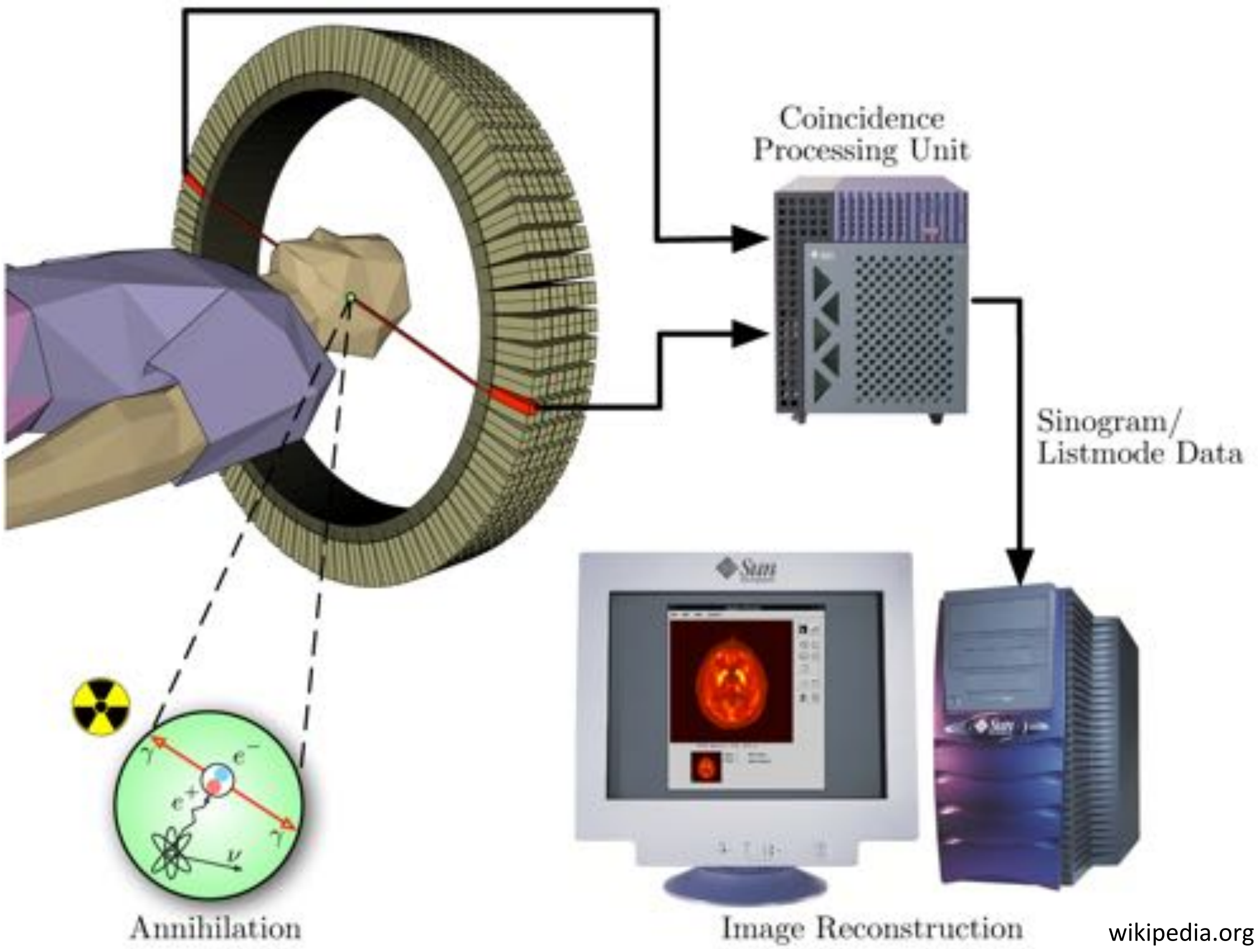


SPECT
(Single Photon Emission
Computed Tomography)



PET
(Positron Emission Tomography)

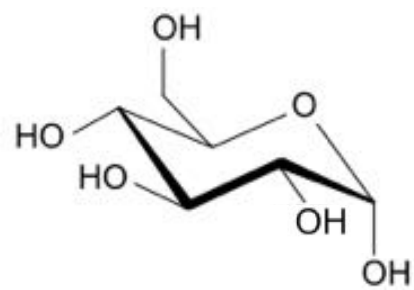
PET Geometry



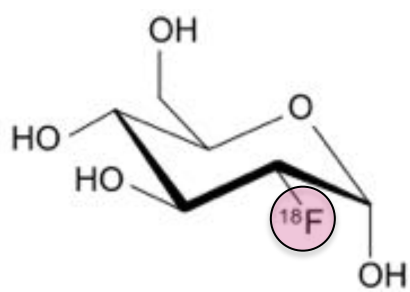
wikipedia.org

Pixel values are counts per unit time per unit volume
Can be normalized to injected dose (and body weight)
Pharmacokinetic parameters can be modeled and derived

FDG as a PET Radiotracer

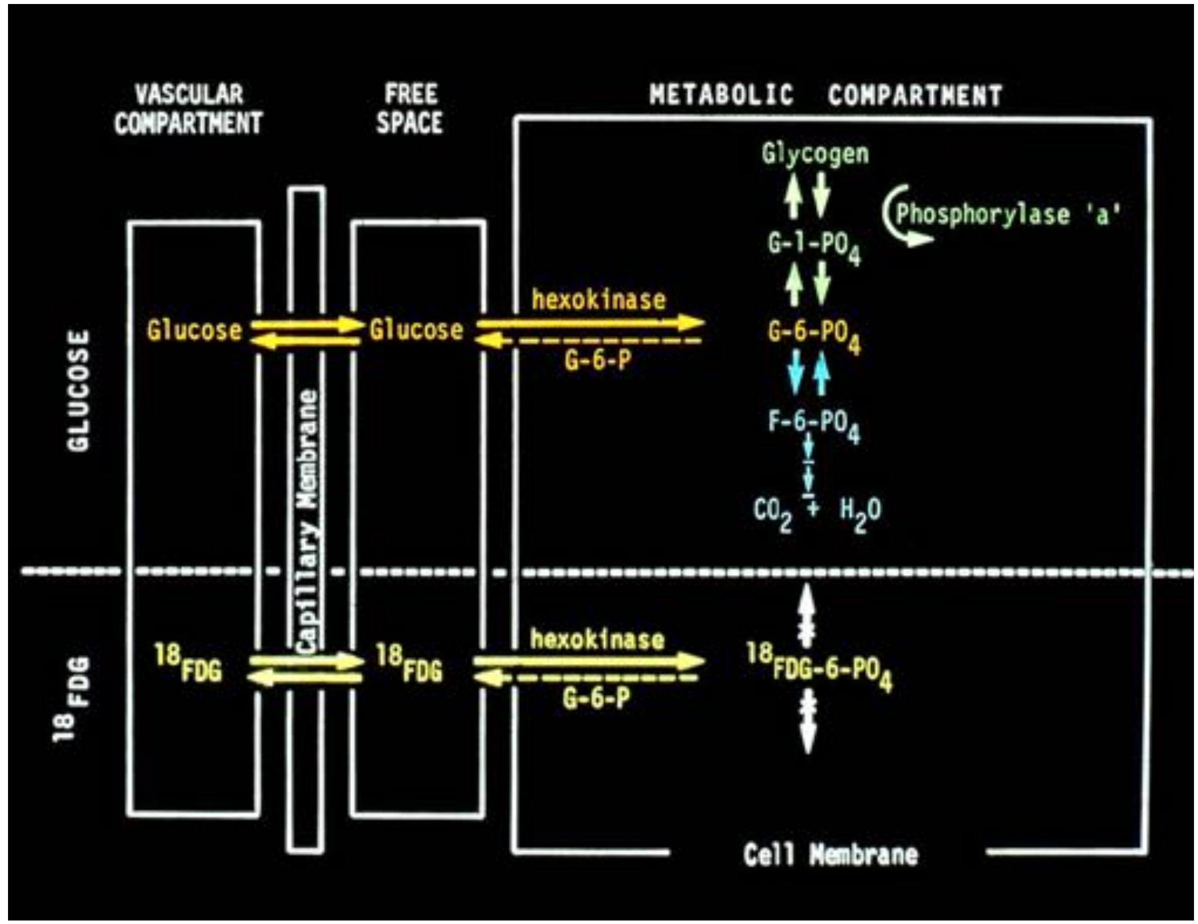


glucose



2-deoxy-2-(^{18}F)fluoro-D-glucose
"FDG"

^{18}F half life is 110 minutes



Hoffman and Gambhir, Radiology 2007

FDG is metabolized similarly to glucose

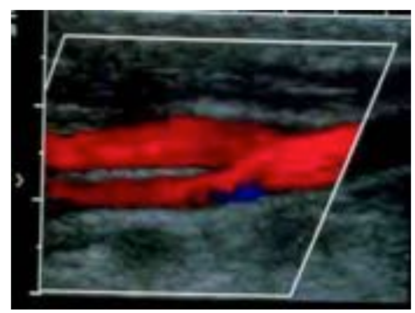
- Transported into cells by glucose transporters
- Trapped in cell after phosphorylation
- But can't enter glycolysis so ^{18}F doesn't leave cell

Some PET Variants

- 2D vs. 3D PET
  - Remove septa (collimator) to allow full 3D coincidence events
- Time of Flight (TOF) PET
  - 300 ps time resolution of coincidence events to place decay on line of response
- Corrections
  - Dead time correction, detector normalization, scatter correction, attenuation correction

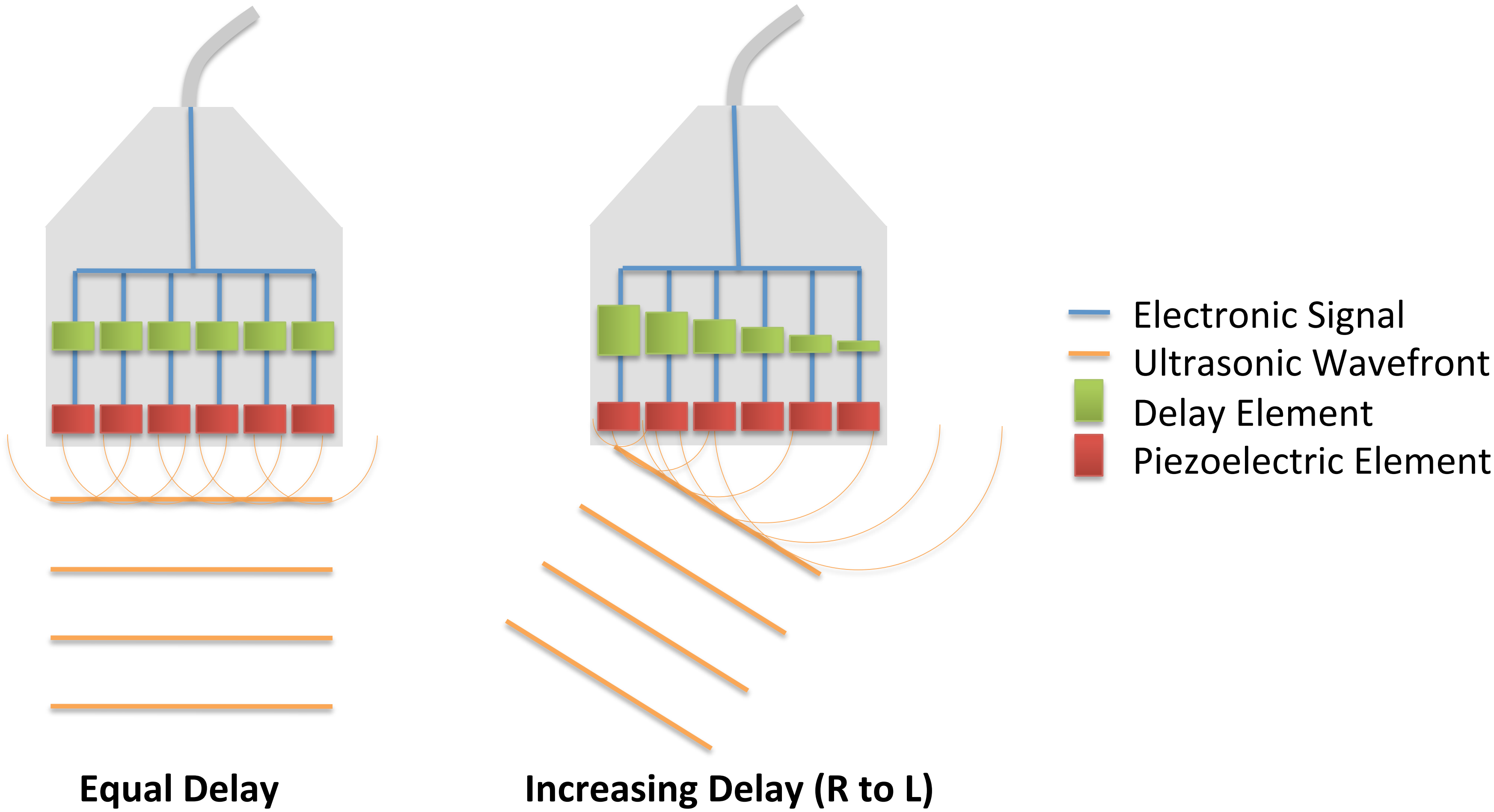
Ultrasound (US)

Imaging Modality:
Ultrasound



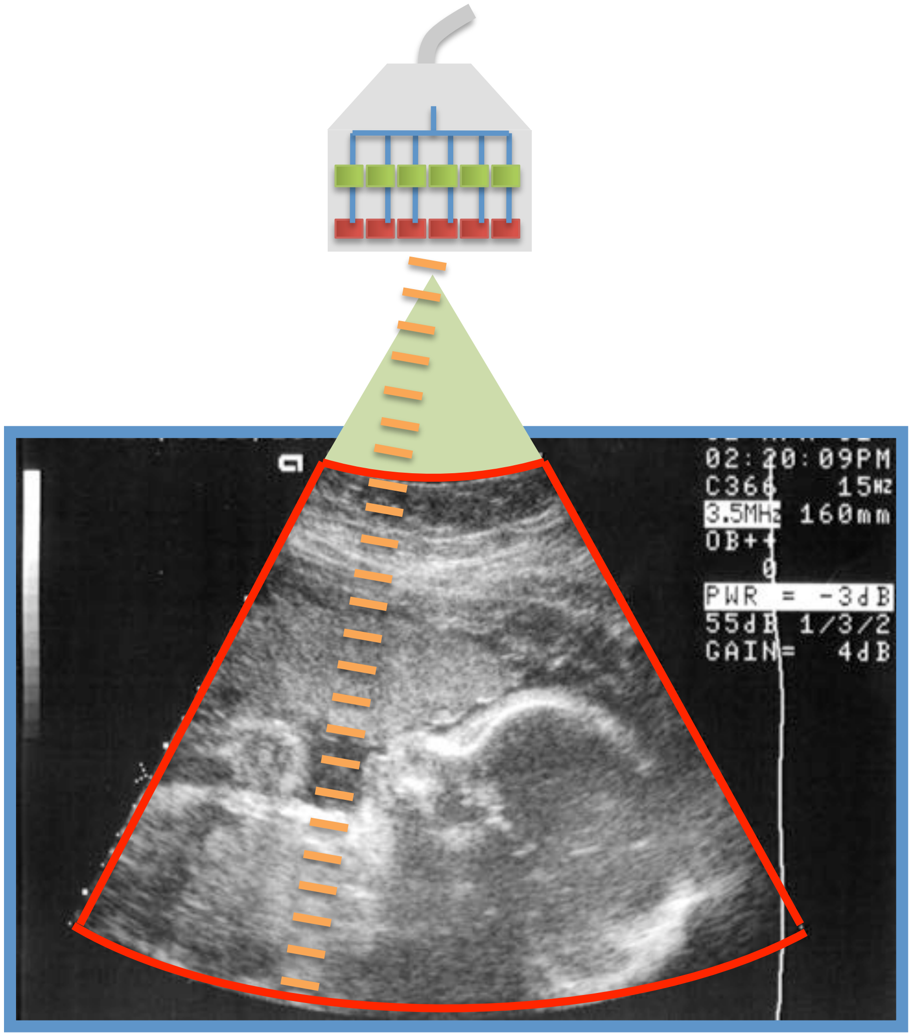
US

Phased Arrays



- Frequencies in 2-20 MHz range
- Speed of sound in water is 1500 m/s (~3000 mph)
- 25 cm round trip takes ~300 µs

Ultrasound Image Formation



Depth of reflecting object depends on echo delay

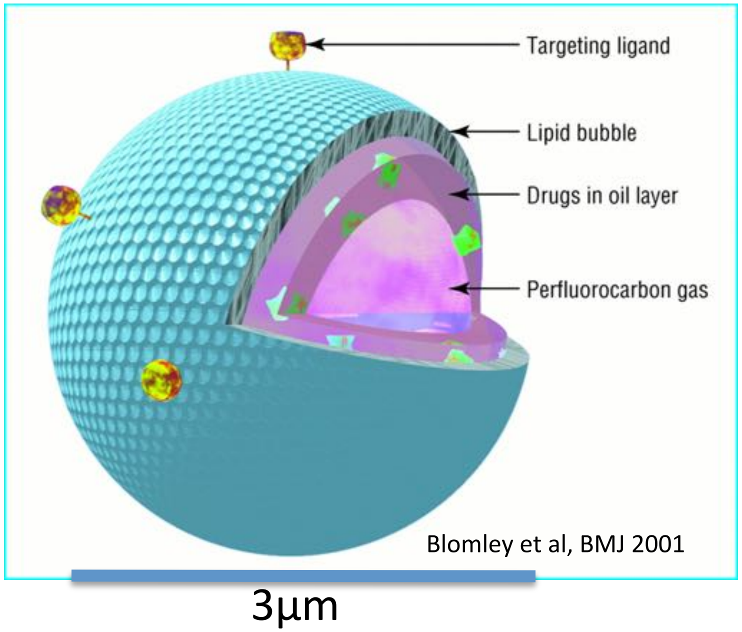
Strength of signal depends on reflectivity and attenuation

Pixel values have *very arbitrary units*

Depth Gain Compensation

Ultrasound Contrast

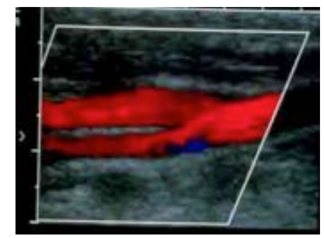
- Inherent contrast
  - Reflections caused by differences in acoustic impedance (a function of density)
- Microbubble contrast agents
  - Injected intravenously
  - Gas bubbles resonate at ultrasonic frequencies increasing reflectivity several thousand fold
  - Bubbles can be destroyed with high intensity signal



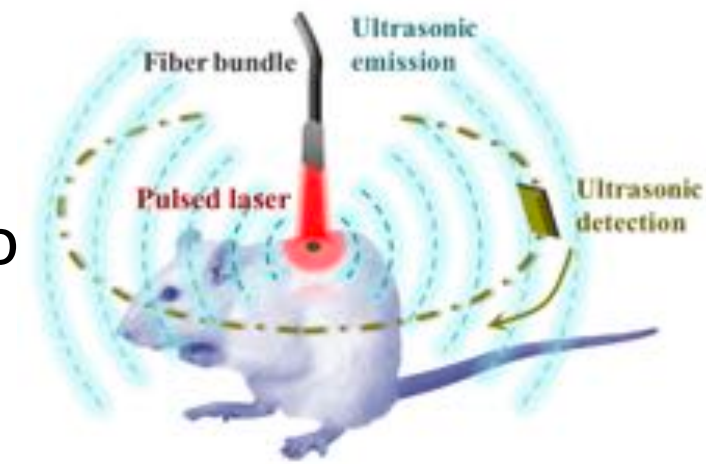
Blomley et al, BMJ 2001

Some Ultrasound Variants

- Doppler Ultrasound
  - Frequency shift indicates motion toward/away from transducer



- Photoacoustic imaging (aka thermoacoustic)
  - MHz laser pulses heat tissue and cause expansion leading to ultrasonic vibrations



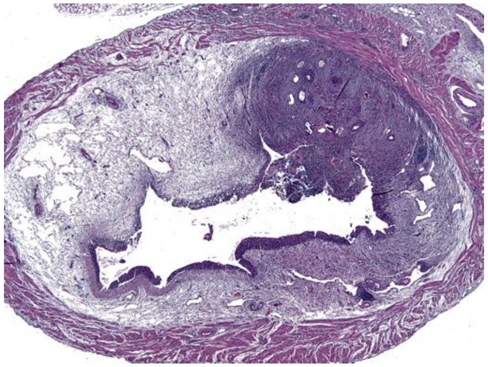
http://www.biophotoacoustics.com/

Optical Imaging

Clinical Imaging Modalities:

http://www.dermatology.ucsf.edu/

http://uti.stanford.edu/



https://e-enm.org

White Light Photography

- Sizing hard due to perspective
- Color important

Endoscopy

- Sizing hard due to perspective
- Color important
- Video analysis

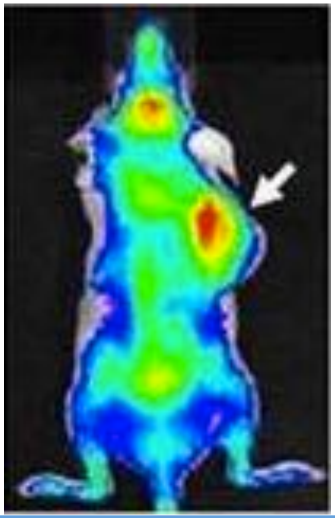
Microscopy

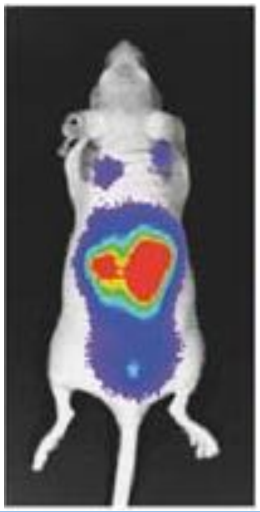
- *ex vivo* changes in tissue
- Choice of stain important
- Can be very large images (e.g. 50k X 50k)

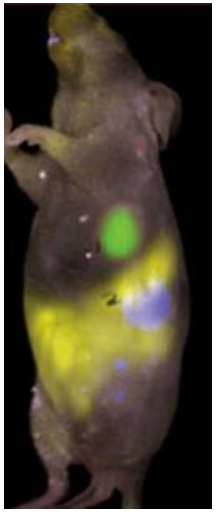
Optical

Pre-clinical Imaging Modalities:

Fluorescence and Bioluminescence Imaging



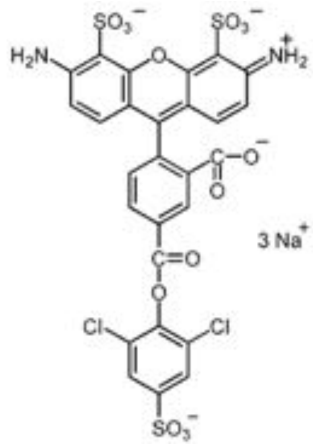




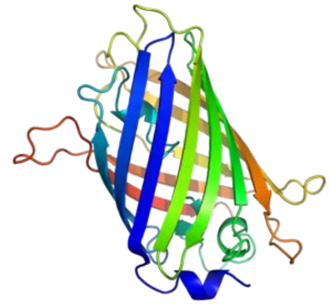
Gao et al, WMIC 2009

Optical

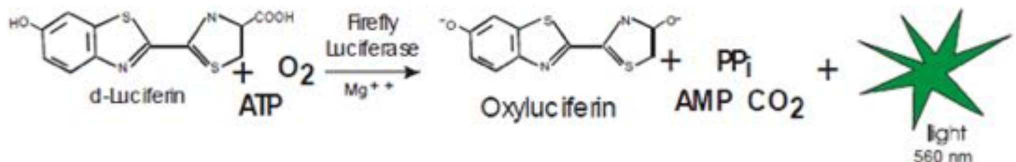
Imaging Probes



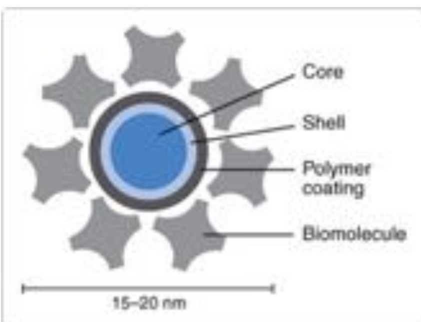
Fluorescent Molecules



Fluorescent Proteins

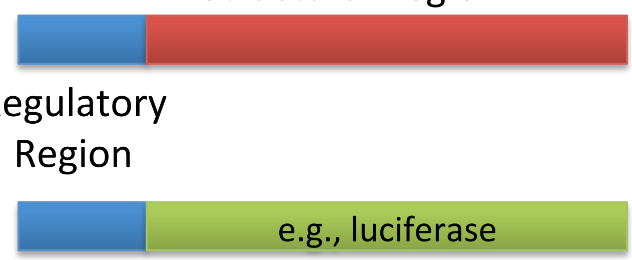


Luciferase/Luciferin



Quantum Dots

Structural Region



Regulatory
Region

e.g., luciferase

Reporter Gene

Reporter Gene Assay

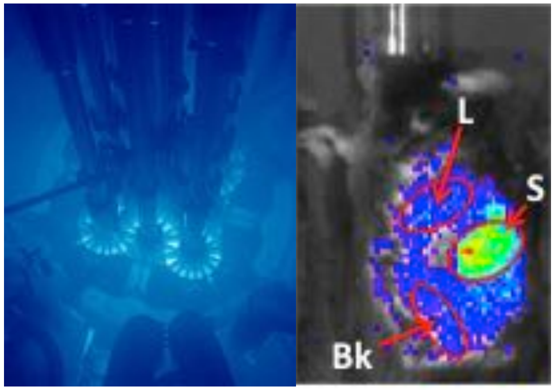
Xing et al, Nat Prot 2007

Some Optical Imaging Variants

- 3D tomography
  - 360 degree views

- Spectral imaging
  - Liquid crystal tunable filter

- Cerenkov Radiation Imaging
  - Emitted positrons traveling faster than speed of light in that medium lose energy as optical photons



http://graphics.tudelft.nl/Projects/BioluminescenceImaging
http://www.cri-inc.com/
Credit: F. Habte, et al.

What does it mean for you?

- Many different imaging modalities
  - Radiography, fluoroscopy, CT, MR, PET, SPECT, scintigraphy, ultrasound, fluorescence imaging, bioluminescence imaging
  - Almost all modalities have small animal equipment for basic biology and pre-clinical research
- Combined modalities are very useful
  - PET/CT, PET/MR, MR/X-ray, SPECT/CT
- Anatomy vs. Function
- **Now you understand what pixel values mean!**
- Next: we can start visualizing the images