Imaging Informatics

Ashish Sharma

Agenda

Scope, Benefits and Limitations

Data Standards and Management

Radiology – Modalities

Digital Pathology

Lab

Housekeeping

- http://download.slicer.org

- Download the relevant release (large ~250MB, so start now)

Agenda

- Scope, Benefits and Limitations
- Data Standards and Management
- Radiology – Modalities
- Digital Pathology
- Lab

Imaging Informatics

- Diverse field
- Information theory
- Strategies of image acquisition, processing, warping, spatial normalization, statistical parametric mapping, non-parametric image statistics and data mining
- Image management, data representation, transmission and sharing

Advantages of Imaging

Real time monitoring of disease/response

Little to no tissue destruction

- Minimally invasive

Varying time & size scales

- Millisecond (protein binding) – Years (cancer growth)
- Molecular → Cellular →Organ → Whole Body

Basic Concept of Imaging

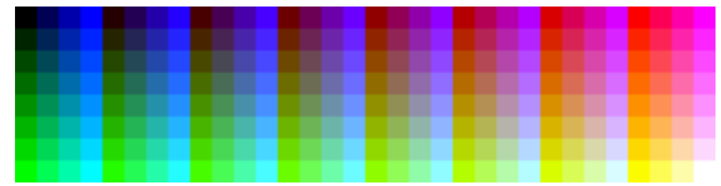
- Imaging is a 2D or a 3D signal
  - Pixel is the 2D atomic unit
  - Voxel is the 3D atomic unit
- In 2D, image is a bit-map (2D array that describes color, intensity – i.e. visual attribute at that point)
- Space (3D)
  - XYZ: left-right, up-down, in-out
- Color (3D)
  - RGB: red, green, blue
  - YUV: luminance, hue, saturation
  - YCrCb: mathematical variation of YUV

Resolution

- Spatial (Sharpness of Image)
  - how much area does each pixel represent
- Temporal
  - minimum time between sequential images
  - maximum time to capture a single image
- Color
  - minimum color difference
- Contrast
  - minimum intensity difference

More Pixels == More Colors == More Information == More Data

- 8 bit (hundreds of colors)
  - magnitude of grayness
    - from black (0) to white (28 = 256)
  - magnitude of color composition
    - 3 bits red, 3 bits green, 2 bits blue, 1 bit black or white
    - 23 x 23 x 22 = 28 = 256



- 24 bit (millions of colors)
  - magnitude of color composition
  - 8 bits [28=256] each for red, green, blue
  - 256x256x256 = 224 = 16,777,216
- 32 bit (24 bit RGB + Alpha channel)

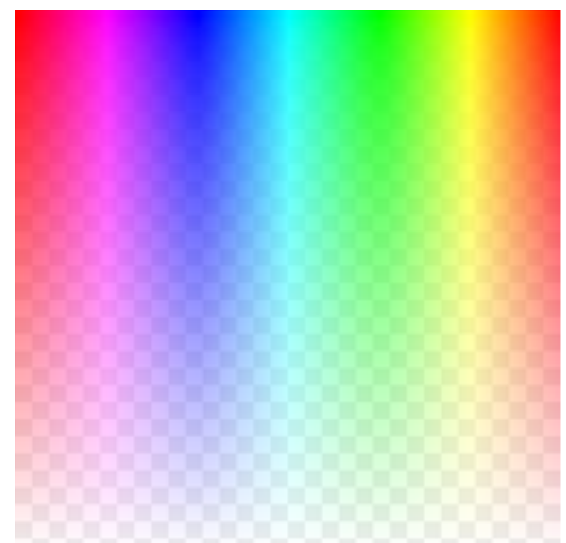


Image Contrast

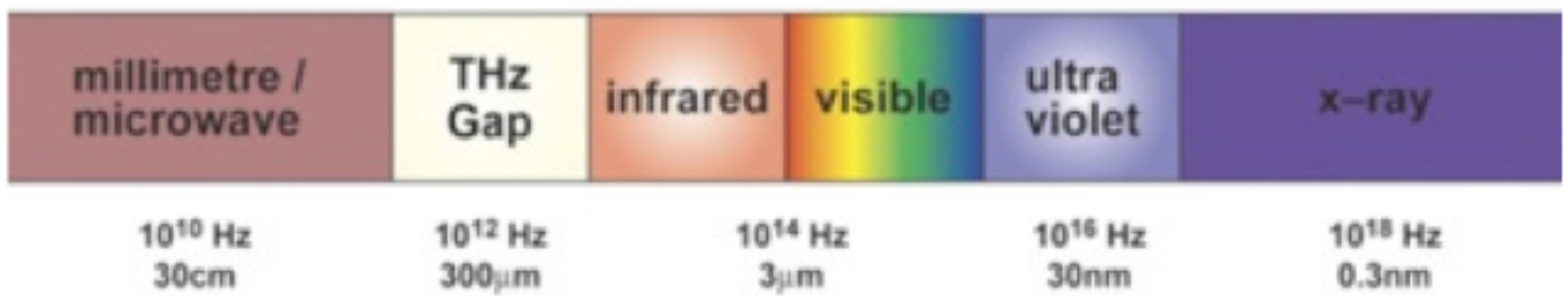
- Contrast due to changes in physical properties of tissue produced by:
  - Internal mechanisms
    - Radiation absorption, reflection and transmission
    - Magnetic properties
    - Oxygenation
    - Mechanical properties
    - …
  - External agents
    - Radiation absorption, reflection and transmission
    - Fluorescence
    - Nanoparticles
    - …

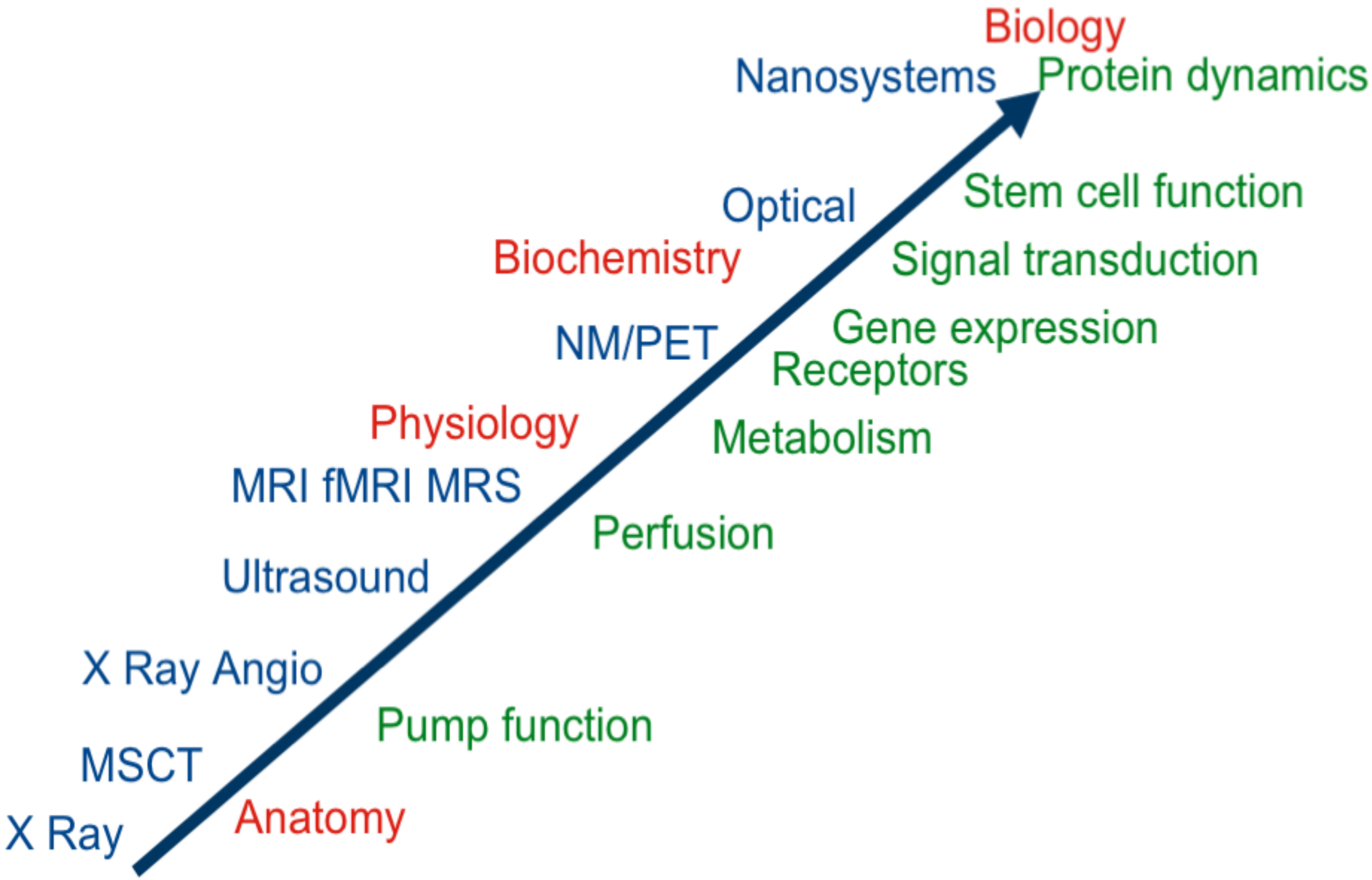
Major Modalities

- Projection based Radiography
  - Digital CR
  - Mammography
- Computed Tomography
- Nuclear Medicine
  - SPECT
  - PET
- Ultrasound
- Magnetic Resonance

Frequency Spectrum

MRI Ultrasound X-Ray, CT PET





Scope and sensitivity of modalities

Agenda

Scope, Benefits and Limitations

Data Standards and Management

Radiology – Modalities

Digital Pathology

Lab

Relevant Standards

- DICOM Digital Imaging and Communication in Medicine
- HL7 Health Level 7
- IHE Integrating the Healthcare Enterprise

DICOM

- Digital Imaging and Communications for Medicine

- A means by which users of imaging equipment may determine whether two devices are able to exchange information, facilitate communication in networked environments, and connection of PACS to specialized information systems such as Hospital Information Systems (HIS) and Radiology Information Systems (RIS)

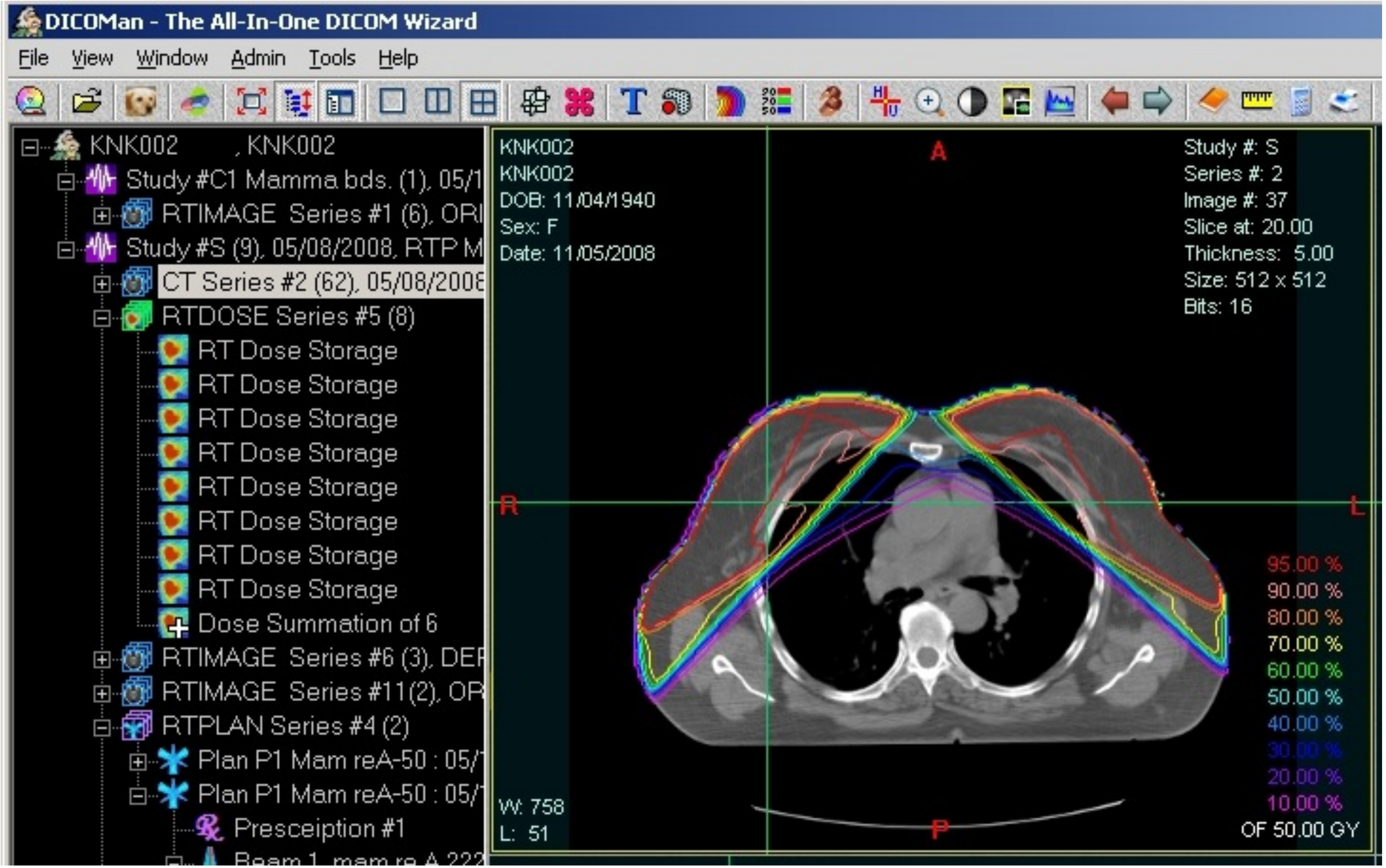
- One of the best examples of models for representation and transfer of digital biomedical image data

Scope of DICOM

DICOM is nearly synonymous with medical imaging

Cardiology
Dentistry
Endoscopy
Mammography
Opthamology
Orthopedics
Pathology
Pediatrics
Radiation therapy
Radiology
Surgery, etc.

Initiatives are underway to add image guided surgery, pathology and veterinary practice

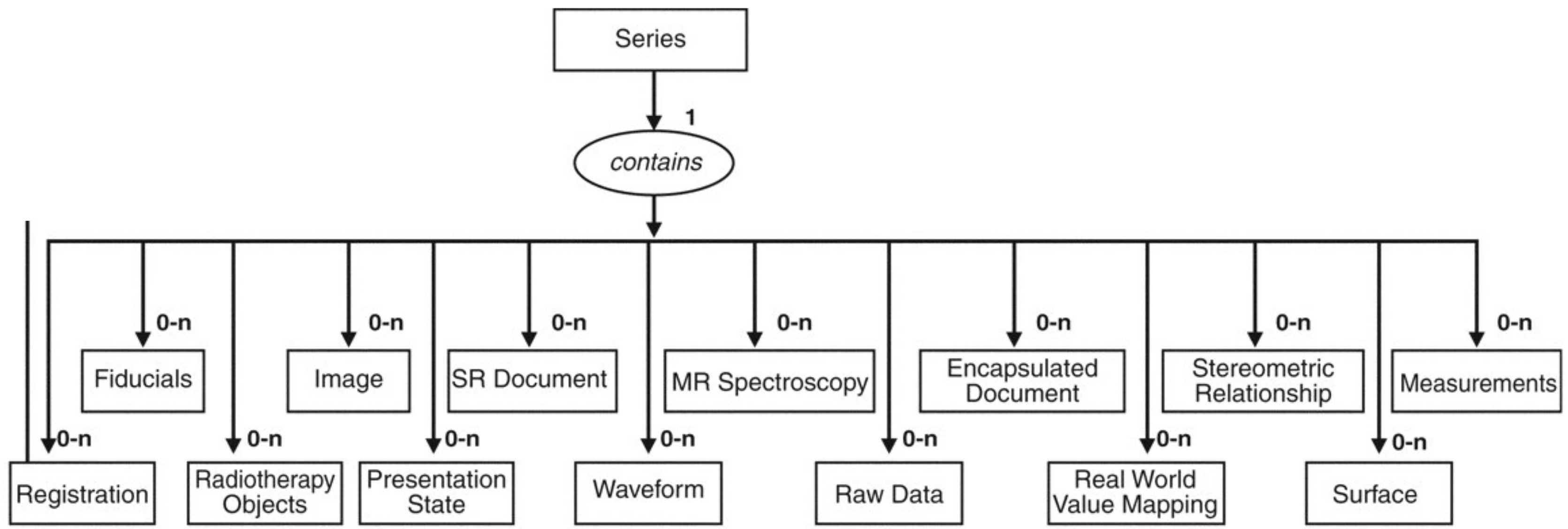


DICOM image sample

DICOM History

- pre-DICOM — vendor defined everything
- The American College of Radiology (ACR) and the National Electrical Manufacturers Association (NEMA) in 1983 formed a joint committee to create a universal standard, resulting in creation of the Digital Imaging and Communications in Medicine (DICOM) work group.
- The DICOM work group's charge was to achieve compatibility and uniformity of header data in medical images regardless of vendor or modality type
- The DICOM Committee has a published standard that continues to evolve to cover other clinical imaging specialties such as pathology, RT etc.

Entity-relationship diagram illustrates the DICOM real-world model, in which a Patient has one or more Studies and each Study contains one or more Series.



Kahn C E et al. Radiographics 2011;31:295-304

RadioGraphics

Data Management

- Picture Archiving and Communication System
  - An underlying database the stores the images and the tables
  - A DICOM communication layer that understands composite messages
    - C_FIND
    - C_GET / C_MOVE
    - C_STORE
  - A web based image delivery system
    - WADO — Web Access to DICOM Persistent Objects
    - Vendor specific proprietary solution
  - DICOMWeb — REST for DICOM
    - Accepted specifications and APIs to access PACS

Data Delivery and Analysis

- Data sizes are growing rapidly
- PACS counter this by staging the data on a local system from the archive
  - Good for local, high-speed, network
  - Remote users?
- Server-Side Rendering (teleradiology)
  - not Citrix
- Computational Power needed to compute various analysis metrics
  - CAD; Image Segmentation, 3D Registration, Visualization
  - Use GPUs, FPGAs, Cell (PS3), Clusters and Clouds

Data Sharing

- Raw Image Data or Derived Data?
- An image is acquired at say the imaging center or hospital, read by the radiologist and they create a report.
  - The ordering physician might need access to the image
  - A specialist hospital might need it
- or, prevent redundant imaging and reduce exposure
- or submitted for QA in clinical trials
- CDs are primary means (Quality, Hospital security, no workstations, long term provenance)

Structured Content

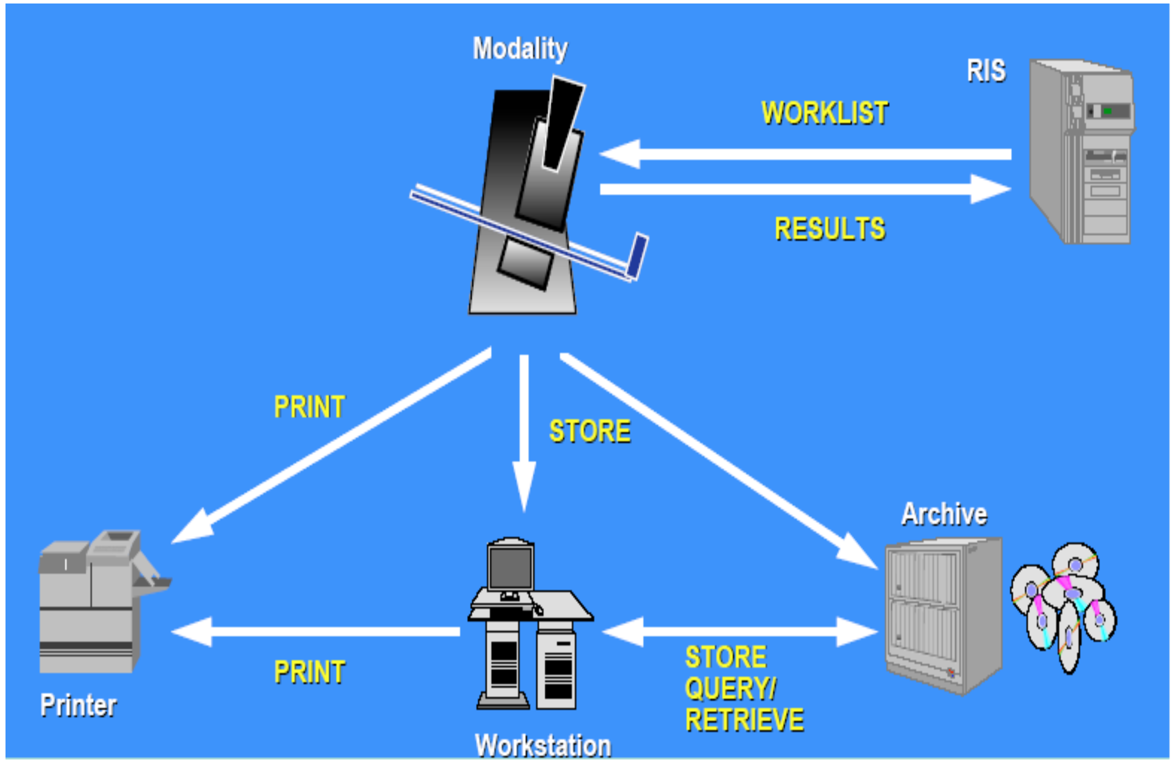
- DICOM Structured Report
  - Standardize data and clinical observations
  - Capture both acquisition and analysis information
  - Extremely flexible
    - Hierarchical; Utilize Coded Nomenclature
    - SR Templates
- Query the content of an image not the metadata and not the findings in the radiology report
  - DICOM SR
  - AIM (Annotation and Image Markup)
  - PAIS

DICOM issues

- a number of issues hamper DICOM scalability within distributed organizations in biomedical informatics research
- the first step in sending a DICOM image is to establish data connections between the two machines for the negotiation of the details of the image transmission, with security mechanisms between communication networks configured to allow passage of information between the sites; this naturally does not scale well
- since DICOM is specified in terms of individual components, when two systems support sending DICOM images, but neither knows how to receive and store them, then these devices will have trouble interconnecting, let alone interoperating.

Technology Overview

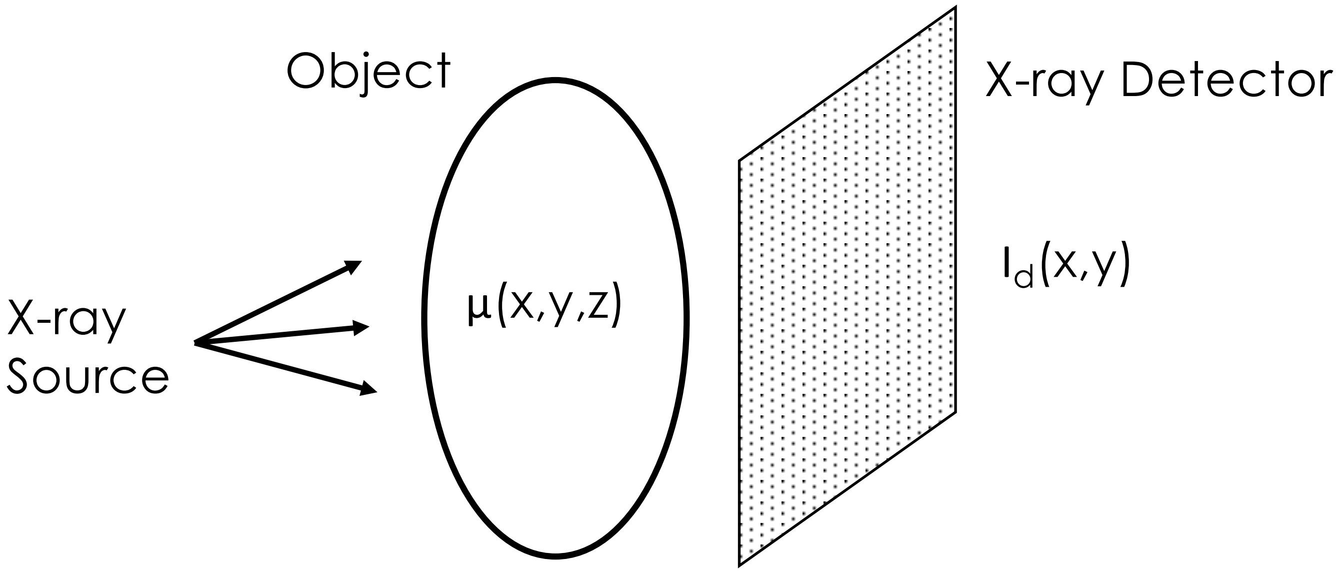
- DICOM Functionality: Service Classes
- Archive/Transfer Images: Store (across network)
- Archive/Interchange Images: Media Storage
- Query for Information & Retrieve Images
- Make Hardcopies: Print Management
- Patient, Study & Results Management
- RIS-Modality: Worklist Management
- Test Connectivity: Verification



Agenda

- Scope, Benefits and Limitations
- Data Standards and Management
- Radiology – Modalities
- Digital Pathology
- Lab

Projection Based Radiography – X-Ray

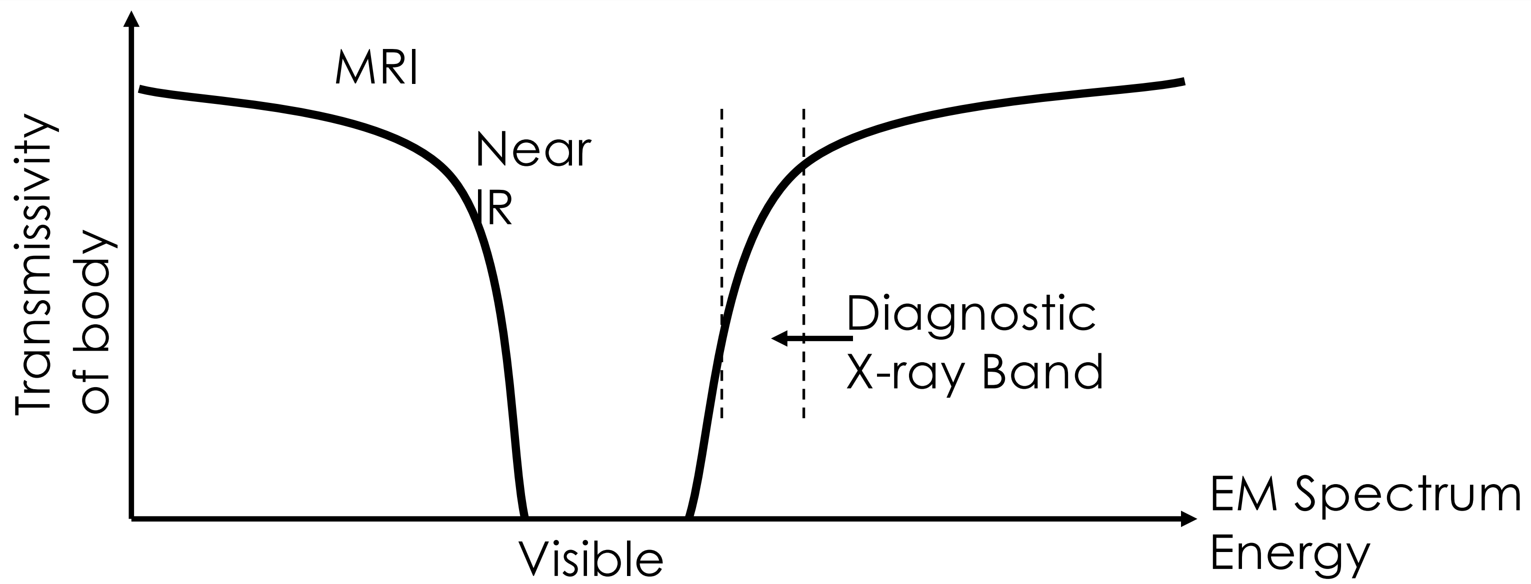


- Image records transmission of x-rays through object

$$I_d(x,y) = I_0 \exp(-\int \mu(x,y,z)dl)$$

- The integral is a line-integral or a "projection"
- $\mu(x,y,z)$ – x-ray attenuation coefficient, a tissue property, a function of electron density, atomic #, …

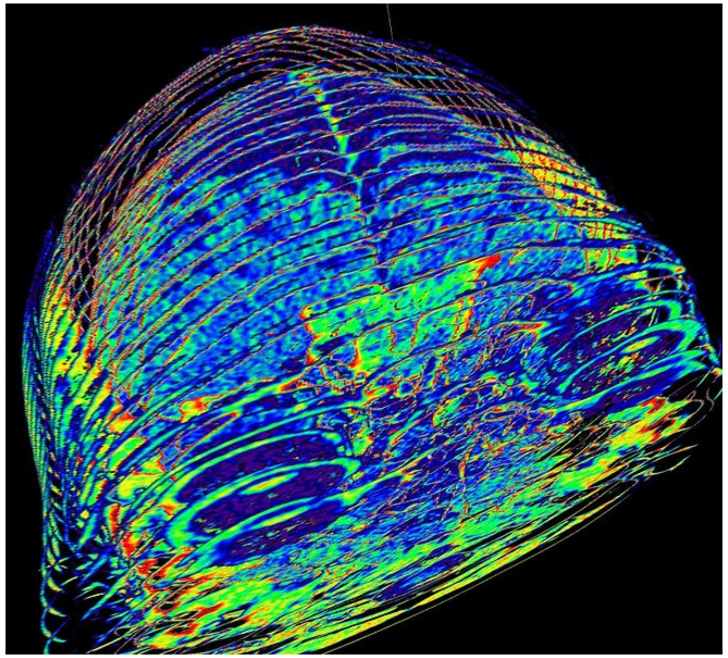
Attenuation Rates and Uses



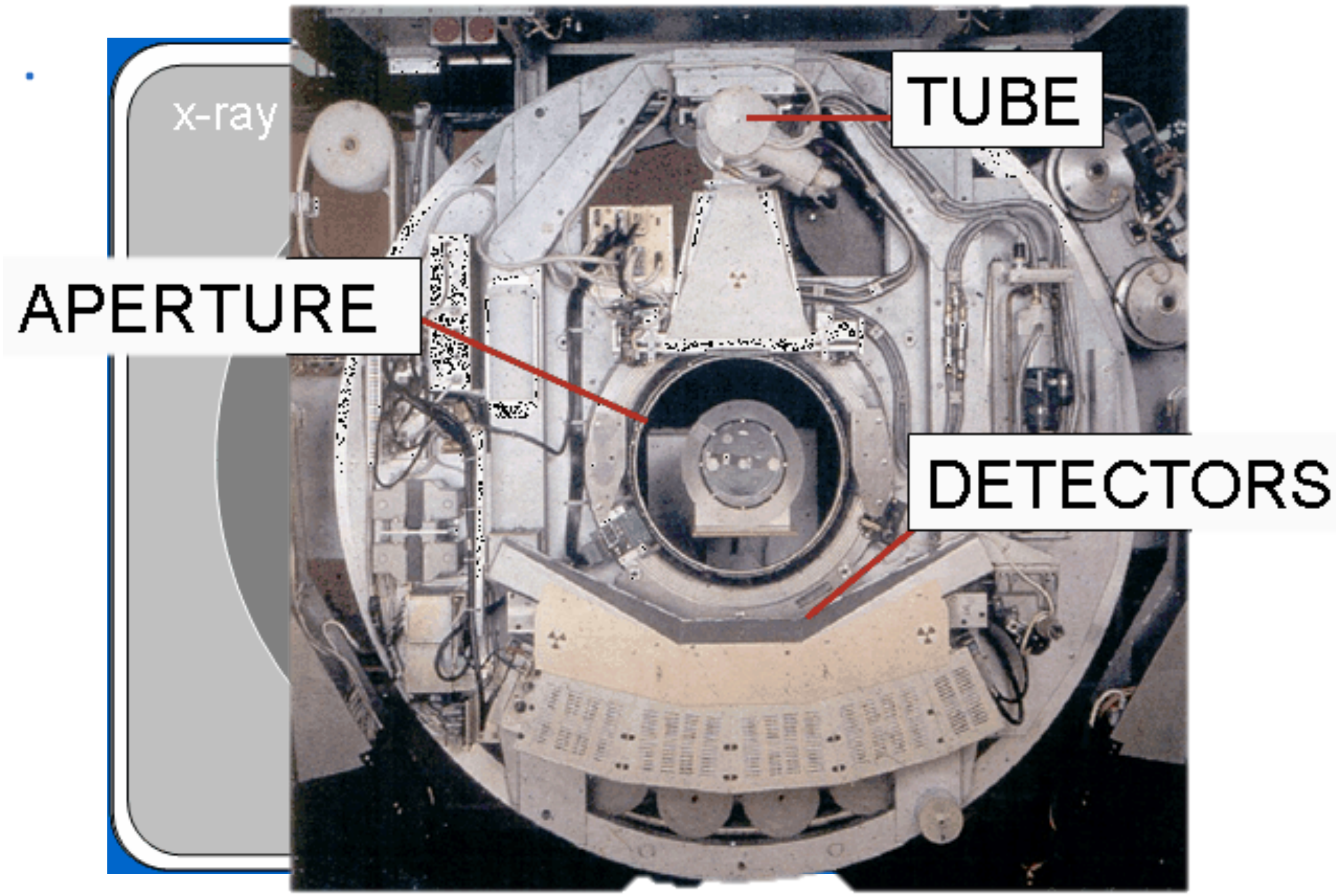
- X-ray imaging requires interactions of x-ray photons with object – work in a specific energy band
  - Above this band – body is too transparent
  - Below this band – body is too opaque
  - Well below this band – wavelengths are too long
- One problem with x-ray imaging: no depth (z) info

Why move to CT

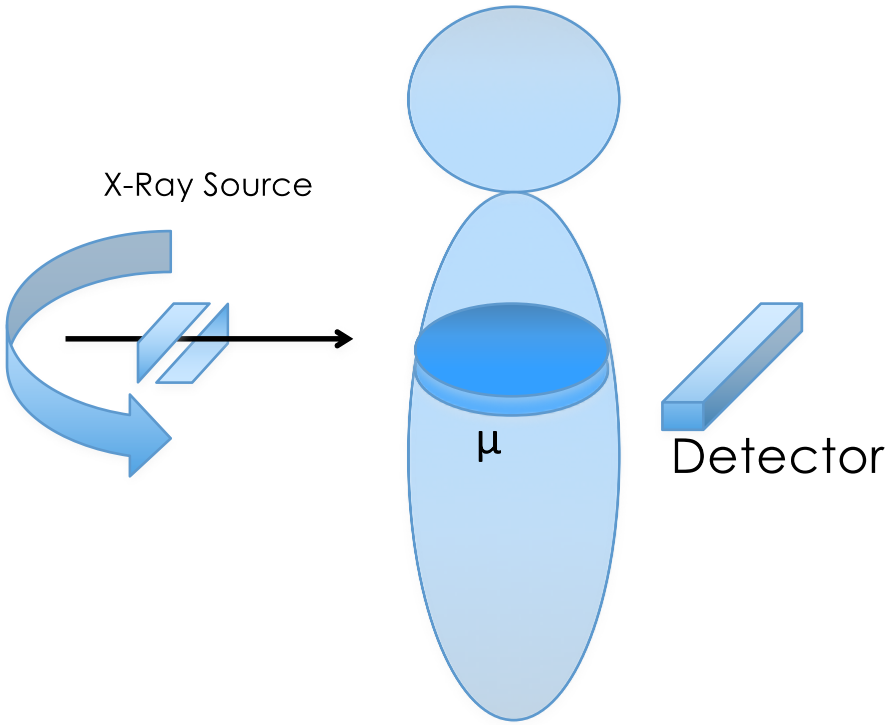
- It's 2D
- Very good structural imaging technique
  - High contrast resolution allowing you to detect subtle changes in tissue/structure



CT Scanner



Data Acquisition



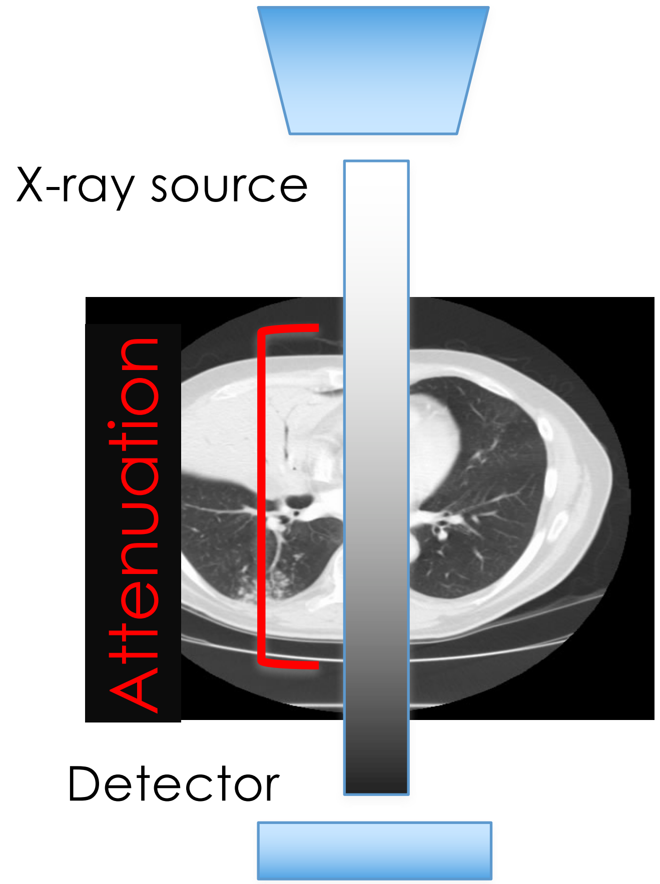
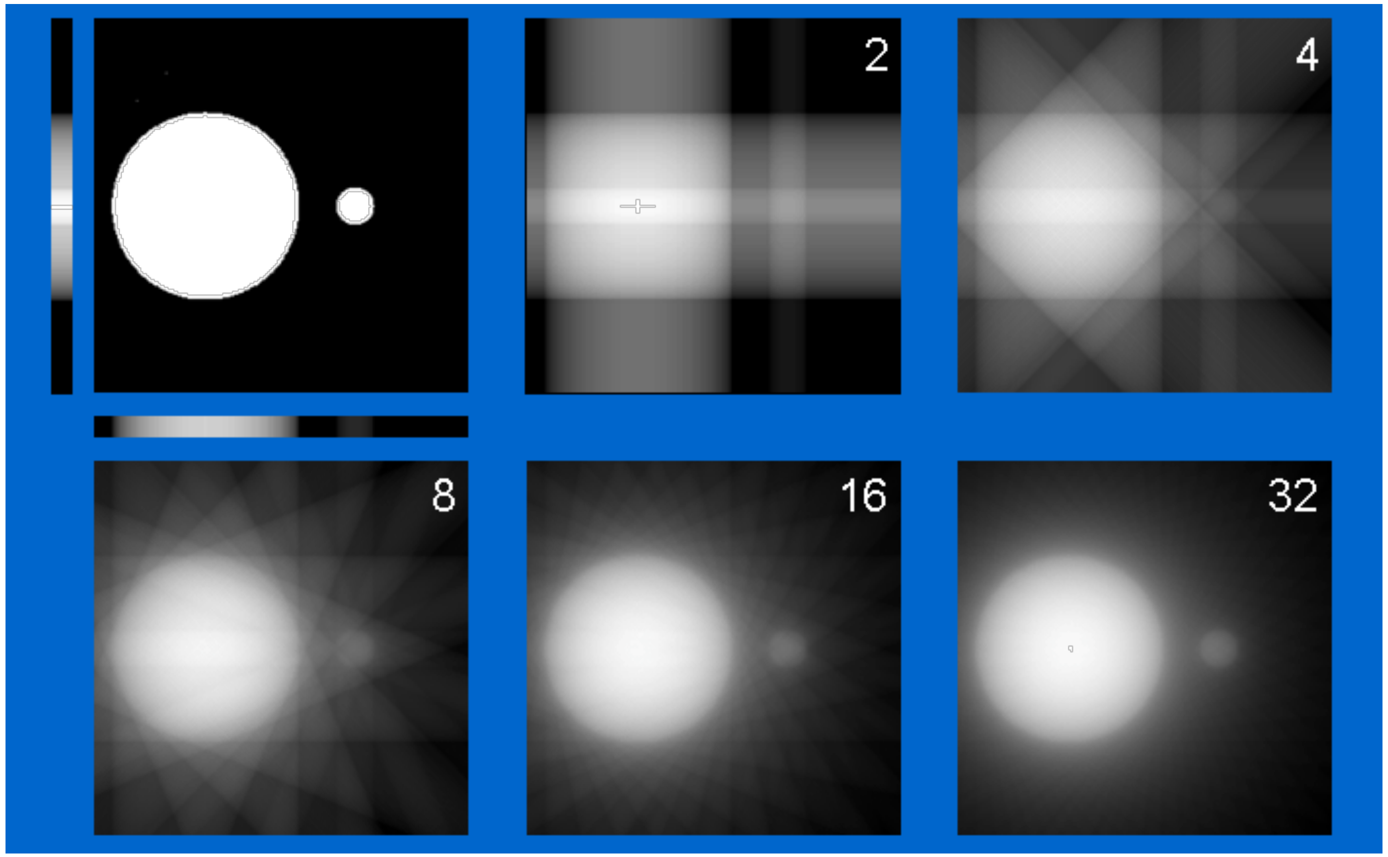
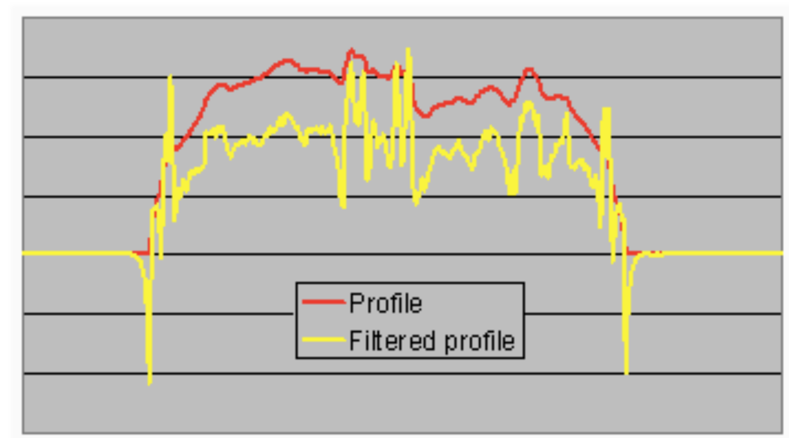
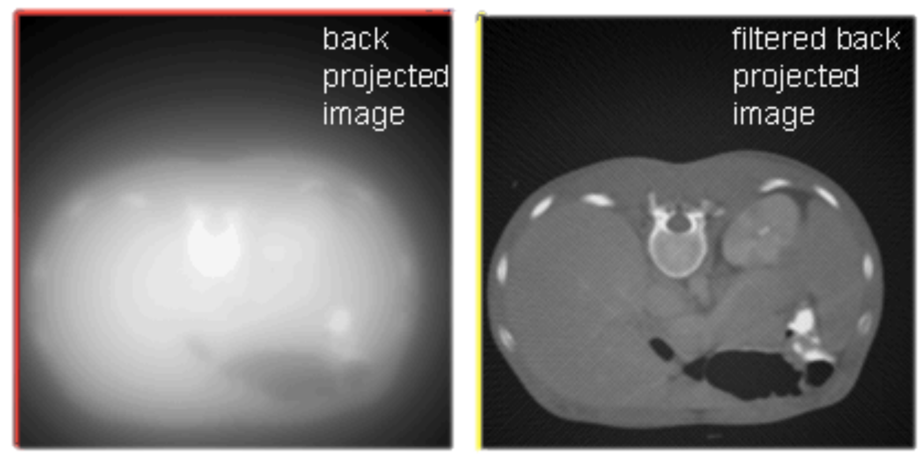


Image Reconstruction



From impact course on Principles of CT





Scanner Parameters

- Collimators: Radiation beam is emitted using special diaphragms. Controls amount of dose delivered. A 5mm collimator == 5mm slice thickness

- Increment: Determines the distance between images reconstructed from data volume. How much overlap between successive slices

- Pitch: The larger the table feed, the faster (i.e. with fewer rotations) a body region can be scanned. However, if the table feed is too large, image quality will be impaired.
  - pitch = table feed per rotation/collimation

Scanner Parameters

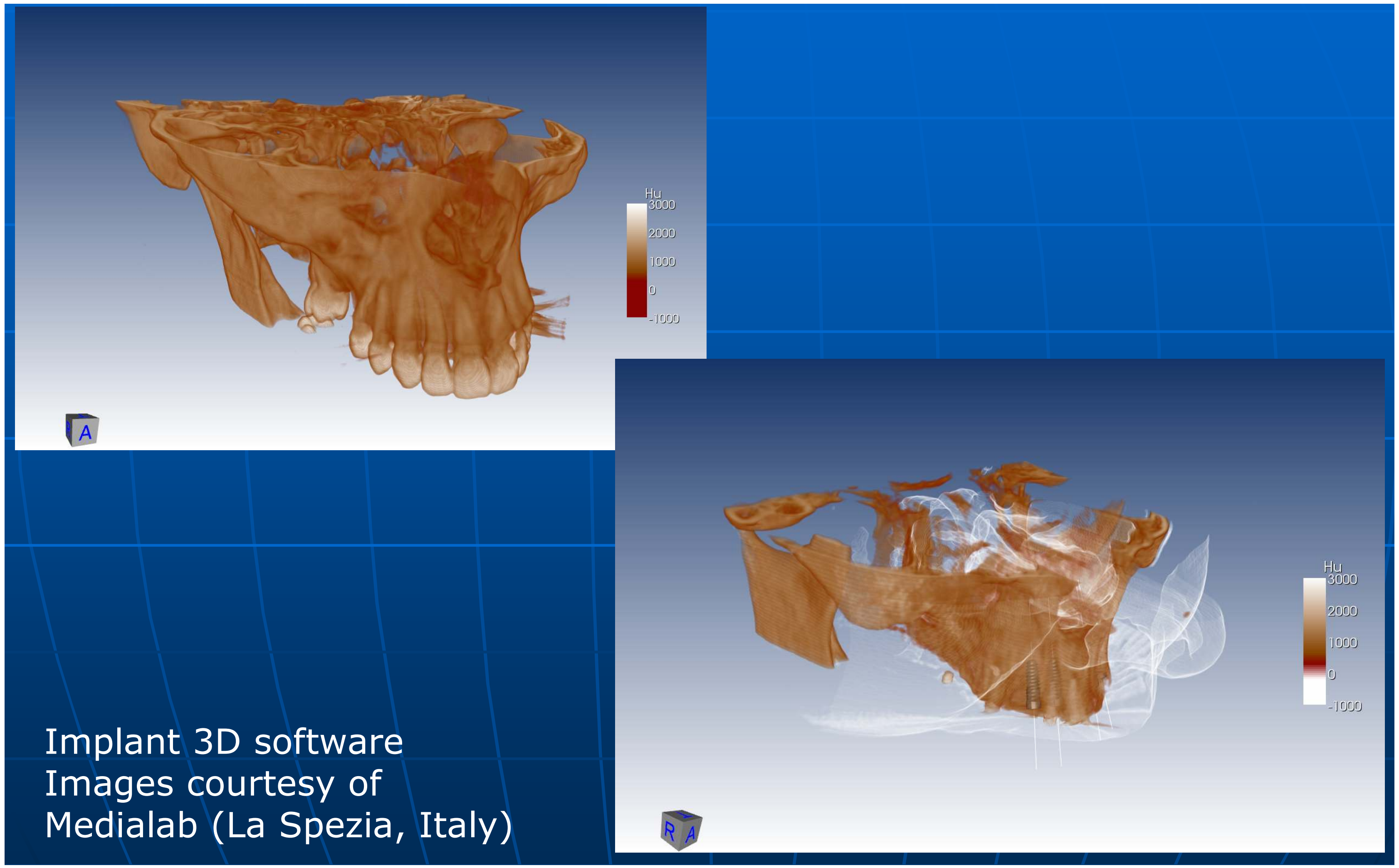
- Rotation Time: Rotation time is the time interval needed for a complete 360° rotation of the tube-detector system around the patient. 0.4s per rotation

- mAs: The mAs value (e.g. 100 mAs) is the product of the tube current (e.g. 200 mA) &the rotation time (e.g. 0.5 s).
  - The selected mAs and tube voltage determine the dose. The mAs value selected depends on the type of examination. Higher mAs values reduce the image noise, thus improving the detectability of lower contrasts.

How to visualize

- CT Number
  - each voxel of the volume of interest is expressed by a number called the CT Number
  - The scale of CT numbers is specific for each equipment, and even for each modality therein
  - CT numbers correlate to gray levels, or gray shades, when the volumetric dataset is visualized

Example of CT Number in action



Implant 3D software
Images courtesy of
Medialab (La Spezia, Italy)

Hounsfield Unit Scale

- The Hounsfield Unit (HU) scale is a linear transformation of the linear attenuation coefficient measurement into one in which the radiodensity of distilled water (at standard pressure and temperature) is defined as zero HU, while the radiodensity of air at STP is defined as - 1000 HU. For a material X with linear attenuation coefficient µX, the HU value is therefore given by

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

Computed Medical Imaging
Nobel Lecture, 8 December 1979 Godfrey N. Hounsfield
J Radiol. 1980 Jun-Jul;61(6-7):459-68

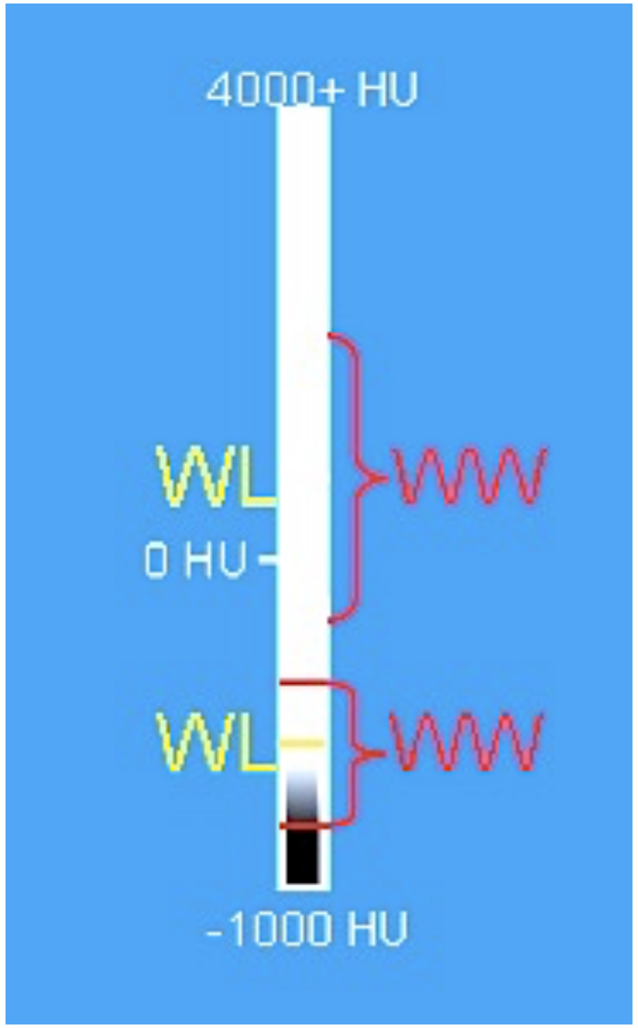
Hounsfield Units

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

Air = -1000
Fat = -120
Water = 0
Blood = +30 to +45
Bone > 400

- An Image can be displayed with user defined brightness and contrast
- Use window level (WL) and window width (WW)
- Dictated by clinical needs

- Osirix Demo



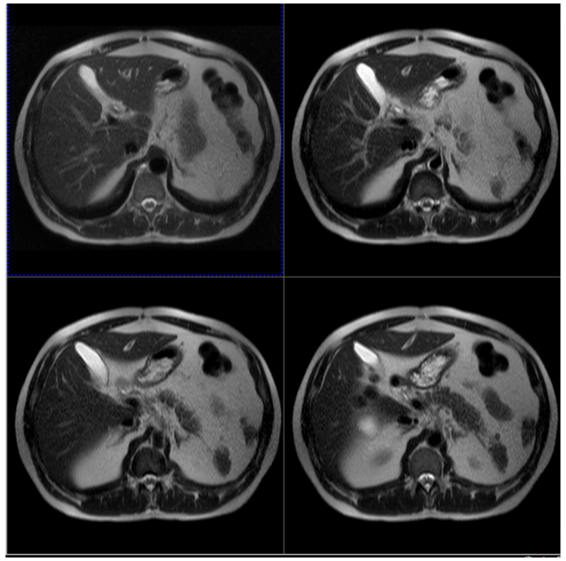
Practical Purpose of HU

- Identification & characterization of tumors in soft tissues (HU in the range 0 – 100) was the main focus in the early times of CT development, when the HU scale was defined
- Therefore the HU scale was conceived to be most effective in the short range of soft- tissues radiodensities

Magnetic Resonance Imaging

- In Vivo Imaging Technique that relies on Nuclear Magnetic Resonance
- Used in a wide variety of specialties
  - High Contrast
  - Non ionizing
  - Arbitrary scan planes
- Cost
  - >$1M equipment
  - Capital costs

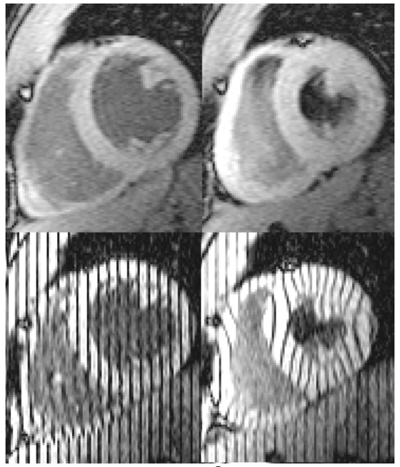
Brain



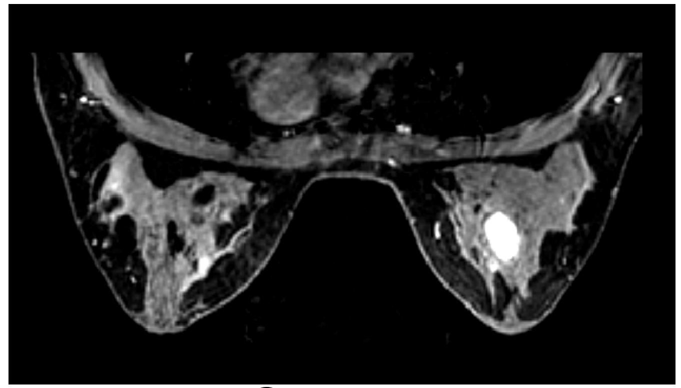
Abdomen

MRI

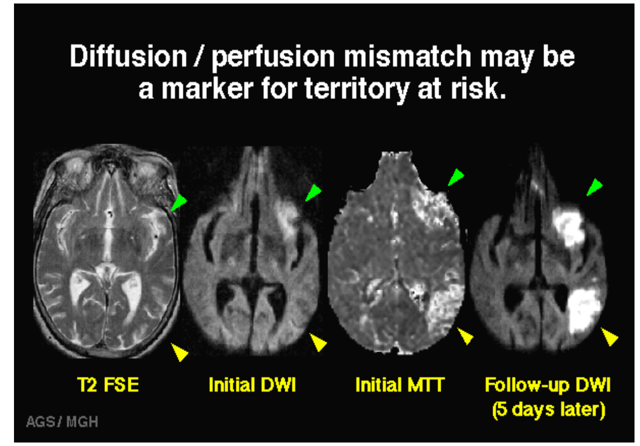
- Excellent tissue contrast with high resolution
    - The contrast comes from a combination of density of nuclear spins of stimulated protons, relaxation time of magentized tissue, and other contrast enhancing agents
- Permits oblique cuts
- no ionizing radiation



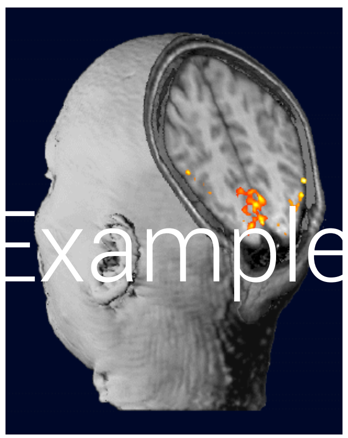
Cardiac



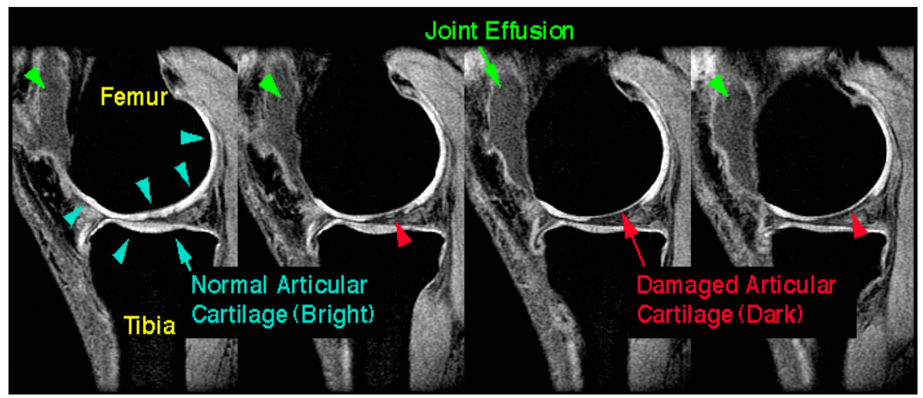
Cancer



Stroke



Neuro Function



Joint

Lung

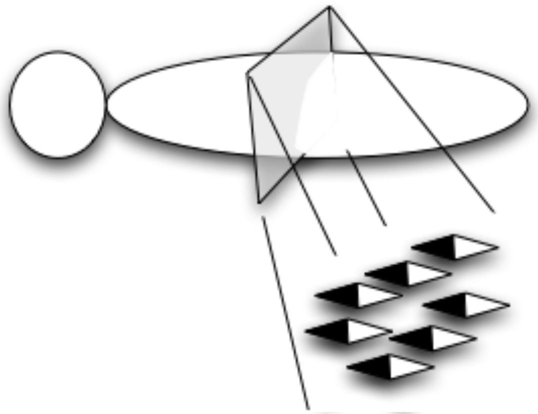
Examples

MR Physics

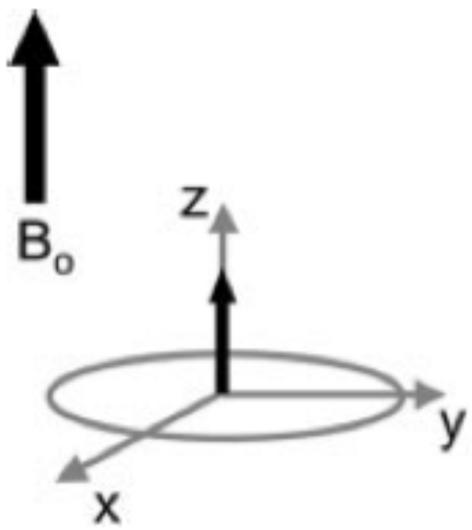
- SPIN: a pure quantum characteristic of atomic building blocks.
- Nucleus = Proton + Neutron
- Both have spins
- Uneven number of protons or neutrons = nuclear spin. ^{13}C, ^{23}Na
- Even number of protons or neutron = no nuclear spin, magnetically neutral. ^{16}O, ^{12}C

Driving Principle:
Nuclear Magnetic Resonance

- Human body is largely water
- Magnetic moments of H+ will align in a field
  - Produces net magnetic field
  - MRI signal source
- Coordinate System:
  - Z: Head → Foot
  - X: Left → Right
  - Y: Anterior → Posterior

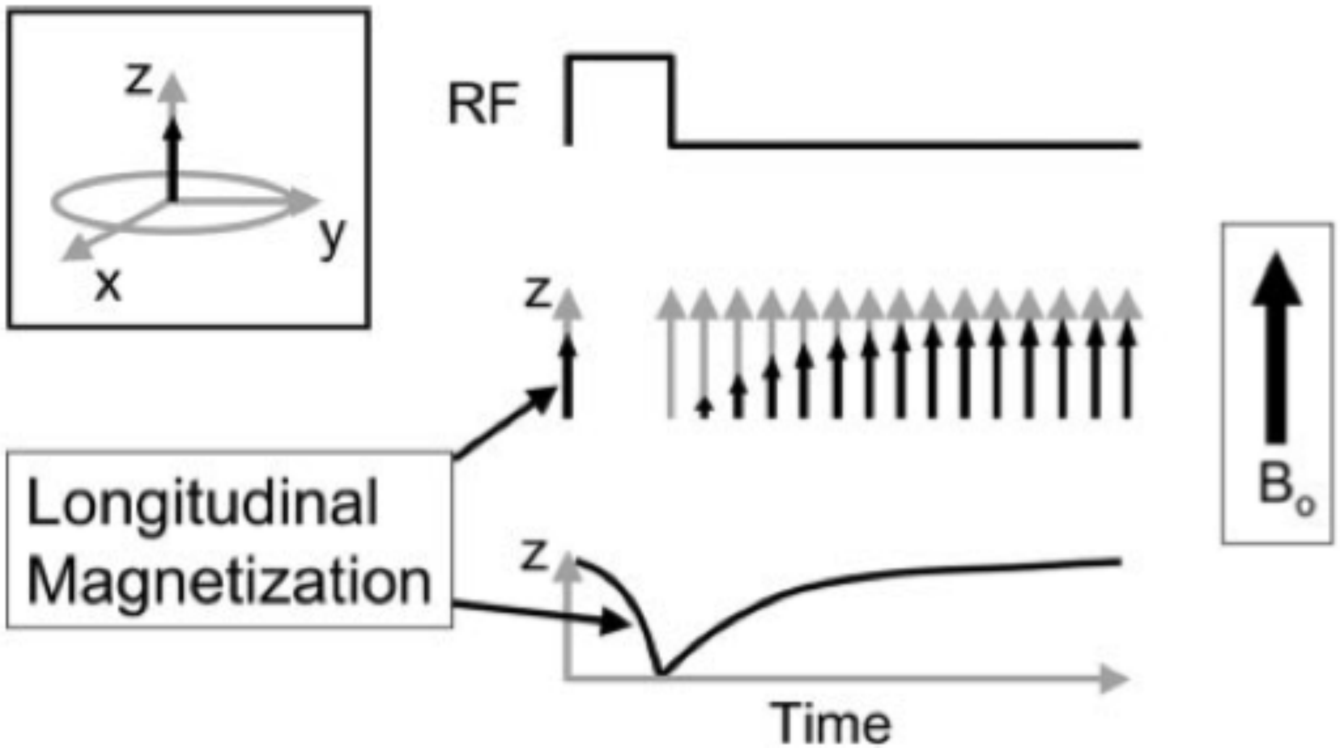


RF Signal to Image



- Aligned protons subjected to RF excitation
- Absorb energy and change direction
- Ends up emiting energy at a resonant frequency:

RF Signal to Image



Longitudinal Magnetization — T1

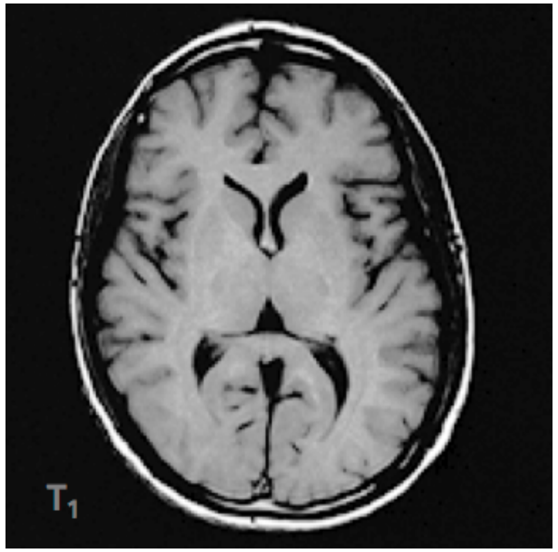
- LONGITUDINAL MAGNETIZATION M_z is the portion of the vector in the z-direction, that is, along the external magnetic field.
- The recovery of the longitudinal magnetization is an exponential process, known as LONGITUDINAL RELAXATION.
- After T1, the longitudinal magnetization M_z has recovered to approximately 63 % of its final value. After 5 T1 times, recovery is complete

T_1 constants (in ms)

	0.2 Tesla	1.0 Tesla	1.5 Tesla
Fat		240	
Muscle	370	730	863
White matter	388	680	783
Gray matter	492	809	917
CSF	1,400	2,500	3,000

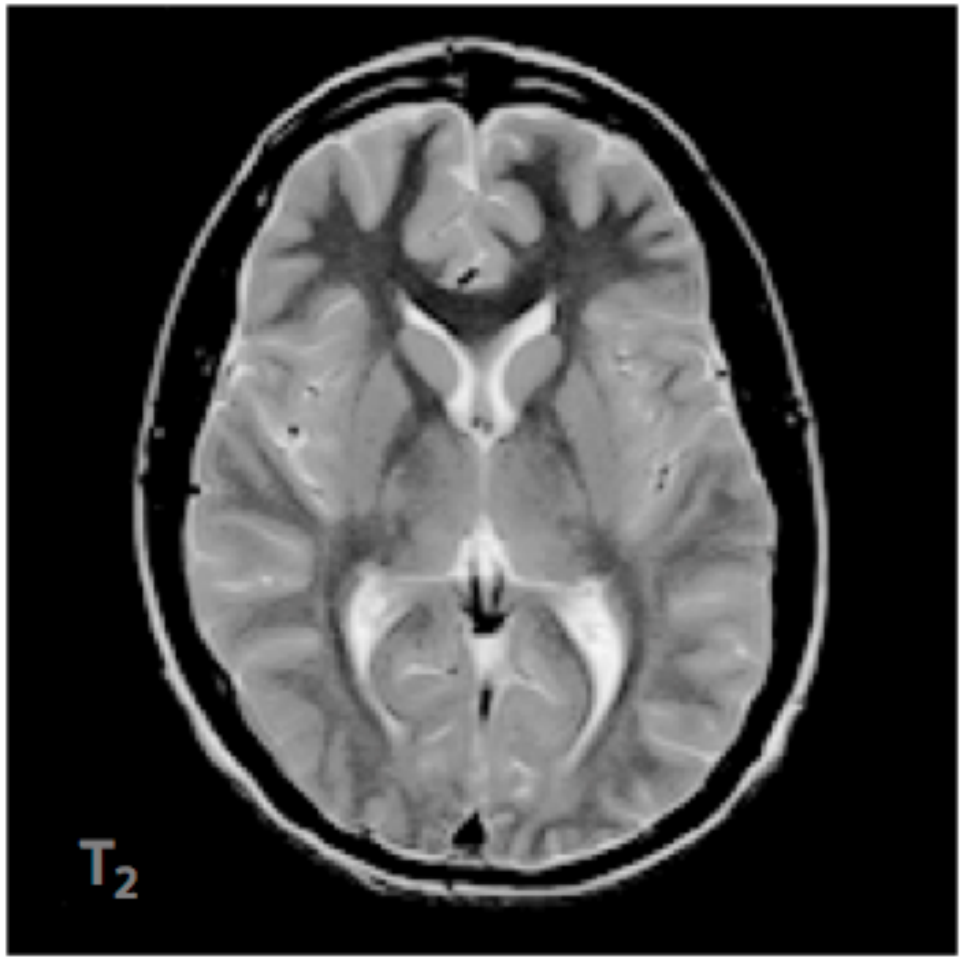
T1 MR Image

- pathological tissue shows a different concentration of water than the surrounding tissue—and this means a different relaxation constant. The difference in relaxation is visualized as contrast in the MR image
- Fat → short T1 → Bright Areas
  - Fat, subacute hemoorrhage, protien rich fluid…
- Water → long T1 → Dark Areas
  - Tumor, inflammation, flow voids…
-



With T1 contrast
CSF appears dark

T2 Contrast Image



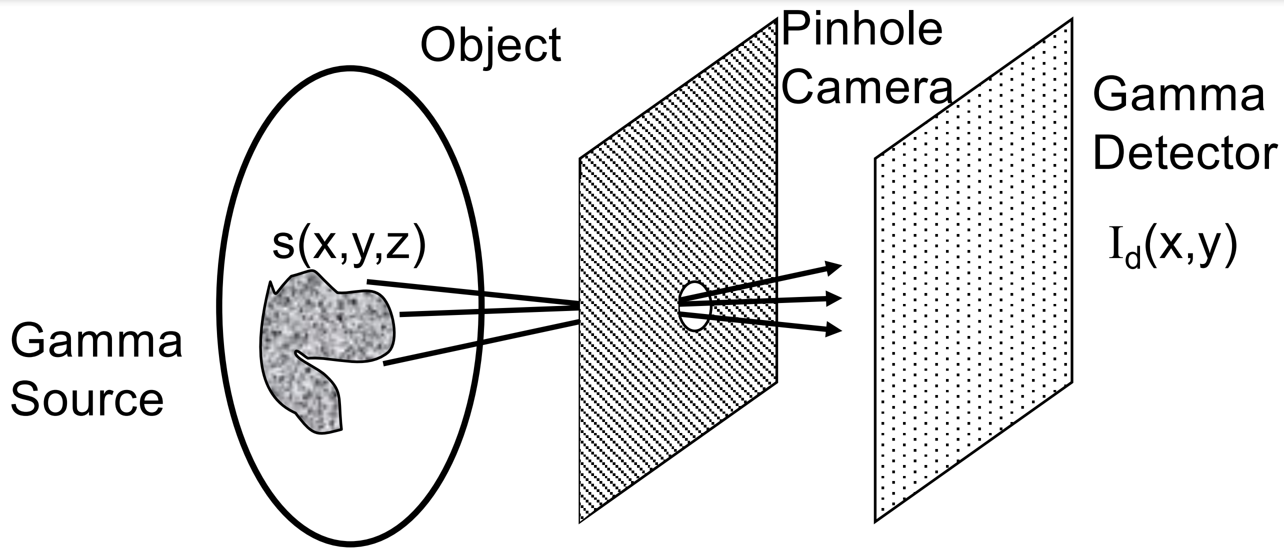
T_2 contrast shows CSF as bright in the MR image—opposite to T_1 contrast

Nuclear Medicine

Nuclear Medicine

- CT & MRI give high quality structural information
- Functional – Use contrast agents
  - Nuclear Medicine
    - Scintigraphy (2D)
    - SPECT (3D)
    - PET (3D)

Scintigraphy

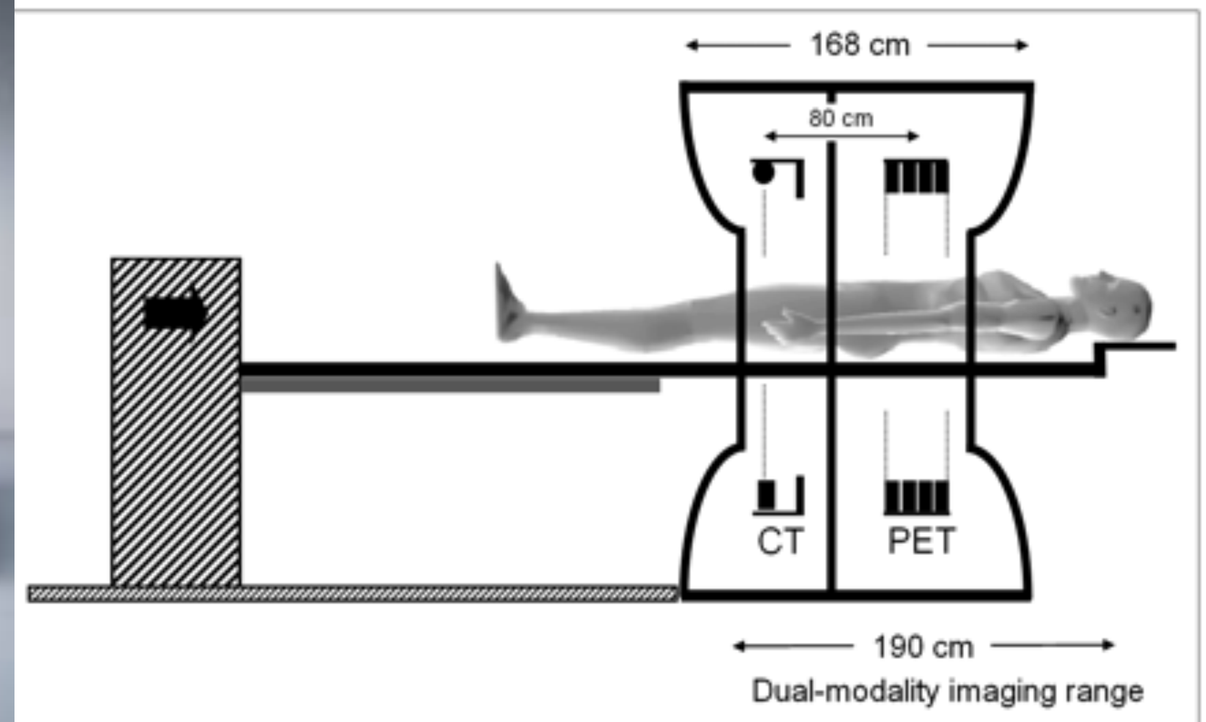


$$I_d(x,y) = \int s(x,y,z)\,d\vec{l}\,)$$

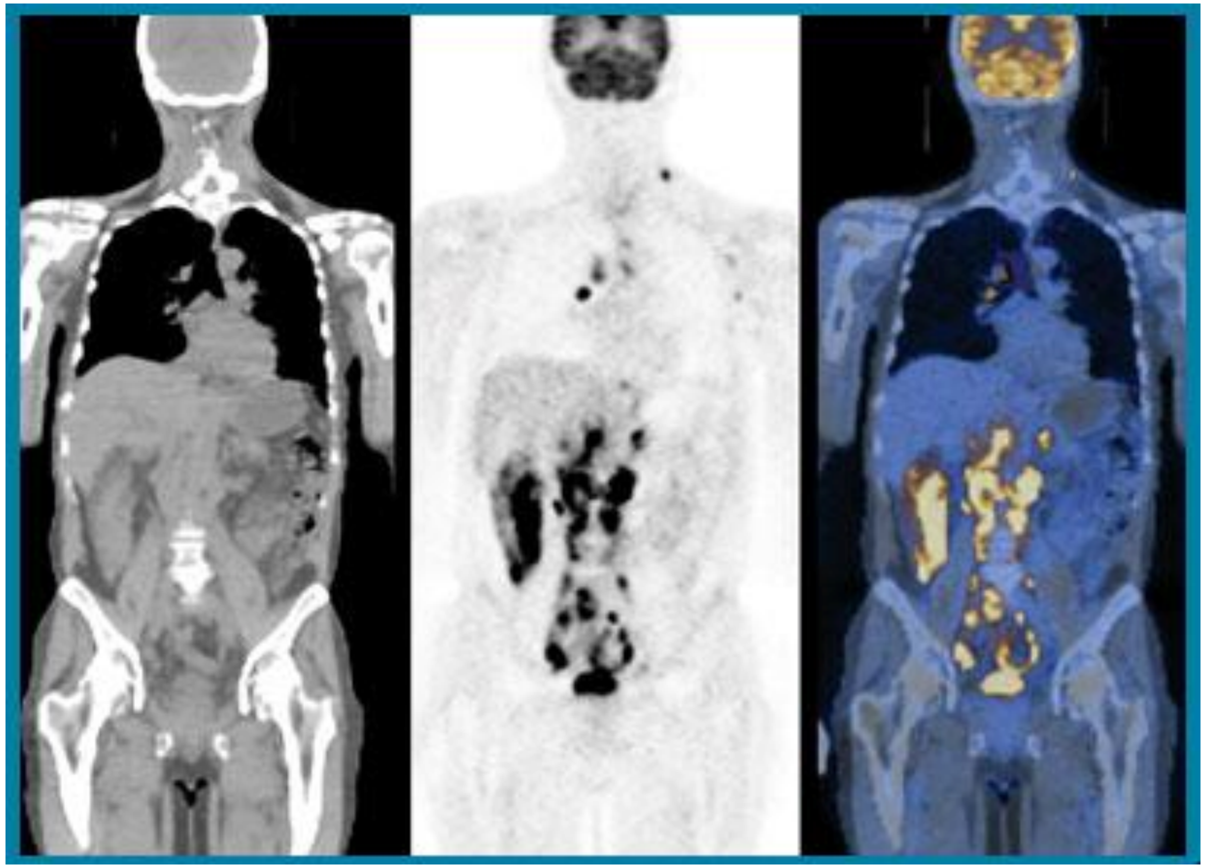
PET

- Positron emission tomography
- Unlike Scint, this provides 3D Info
- Operation:
  - Inject a short-lived radioactive tracer isotope
  - The tracer is chemically incorporated into a biologically active molecule
    - fluorodeoxyglucose (FDG)
  - radioisotope undergoes positron emission decay which eventually results in gamma radiation
  - detected when they reach a scintillator

PET-CT Scanner



PET-CT Scan



Anatomy Function Both

Agenda

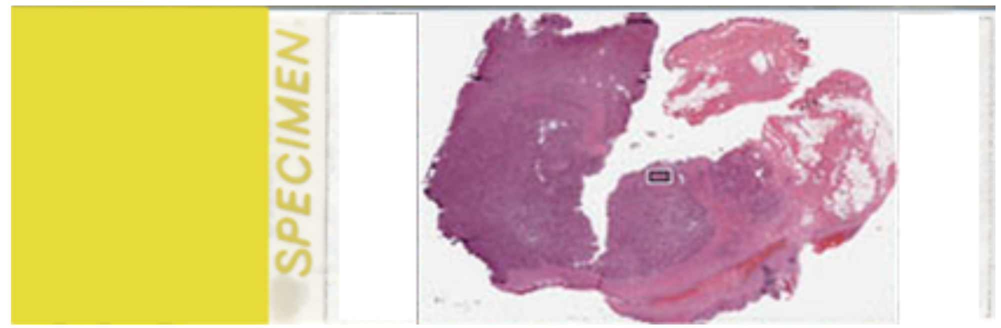
- Scope, Benefits and Limitations
- Data Standards and Management
- Radiology – Modalities
- Digital Pathology
- Lab

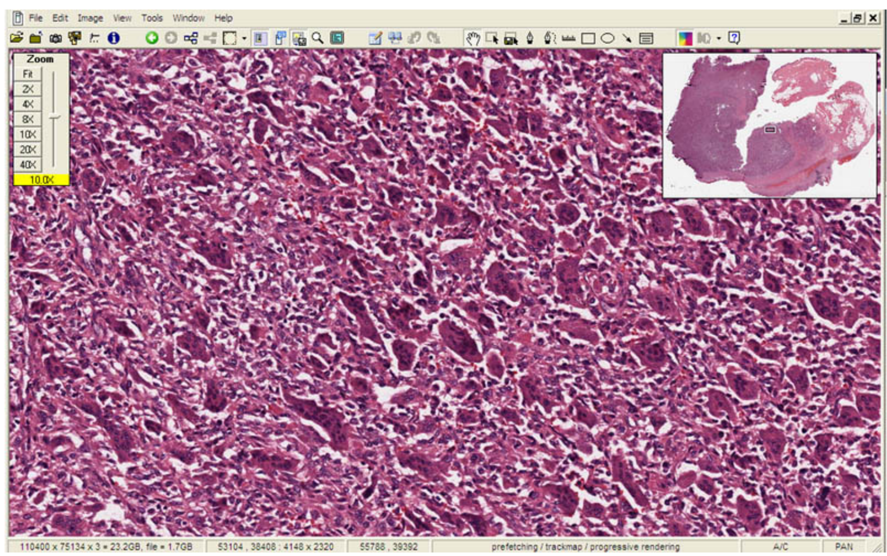
Year	Advance
1590	Zacharias Janssen, Dutch spectacle-maker, discovers the principles of the compound microscope
1665	Robert Hooke publishes *Micrographia*,
1858	Joseph von Gerlach differentially stains the nucleus and cytoplasm using carmine dyes
1873	Camillo Golgi devises the silver stain
1871	Adolf von Bayer uses the first fluorescent dye
1873	Ernst Abbe, with Carl Zeiss and Otto Schott, devise the diffraction limit theory
1896	Paul Mayer applies the hematoxylin and eosin stain
1911	Oskar Heimstädt develops the first practical fluorescence microscope
1965	In an era of increasing growth of digital technology, Gordon Moore predicts the exponential growth of computing power
1967	Morris Karnovsky develops peroxidase methods for microscopically detecting antigens
1986-1987	"Telepathology" appears in literature [1, 2]
1990s	CCD & CMOS sensors achieve common use in microscopy, allowing widespread digital use in pathology
2000s	Whole slide imaging becomes more widespread

Origins

Scope

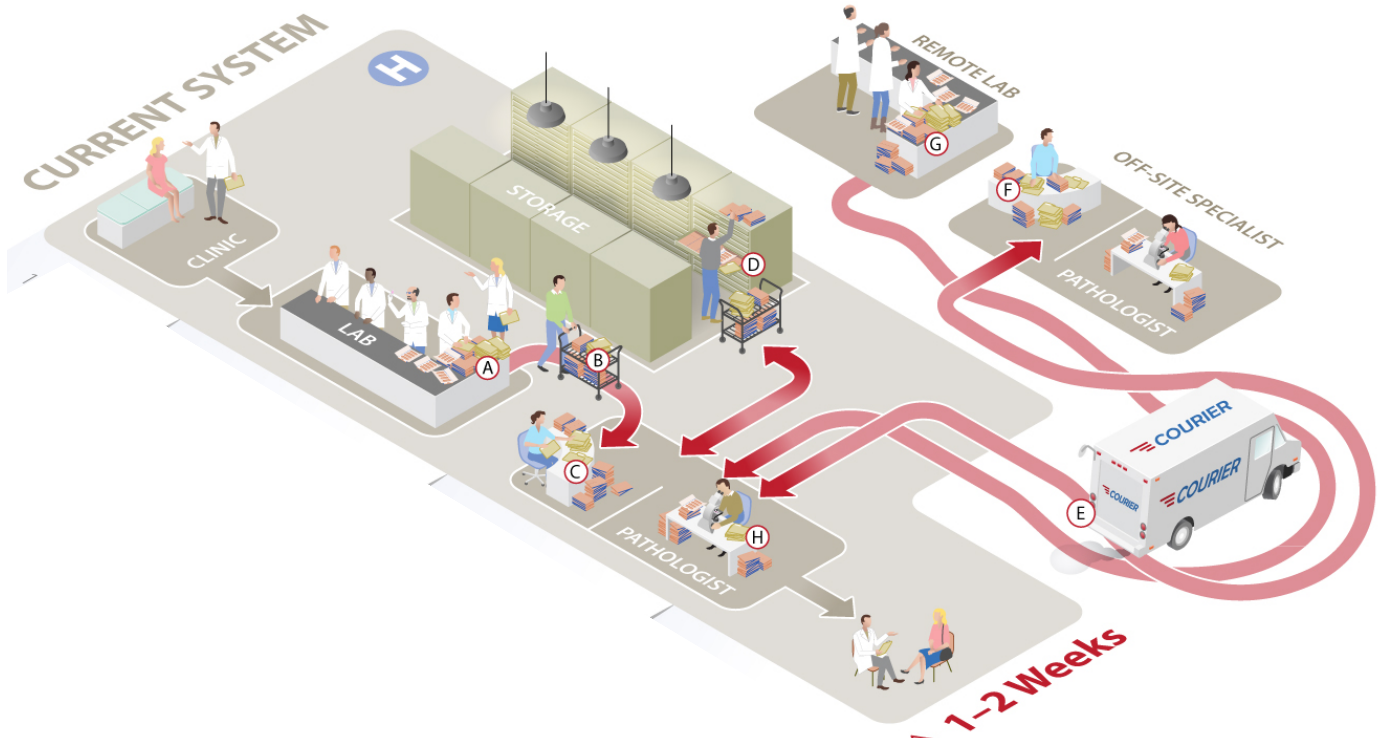
- Pathos (feeling, suffering) + logia (the study of)
- A core subspecialty in medicine
  - Clinical Pathology
  - Anatomic Pathology
- Primary means for diagnosis





Anatomic Pathology Workflow

- Pathology workflow starts with a specimen
- Dissection
- Chemical processing
- Cut thin sections and place on glass slides
- Stain with a variety of techniques
    - Chemical
    - Immunochemical
    - in-situ hybridization

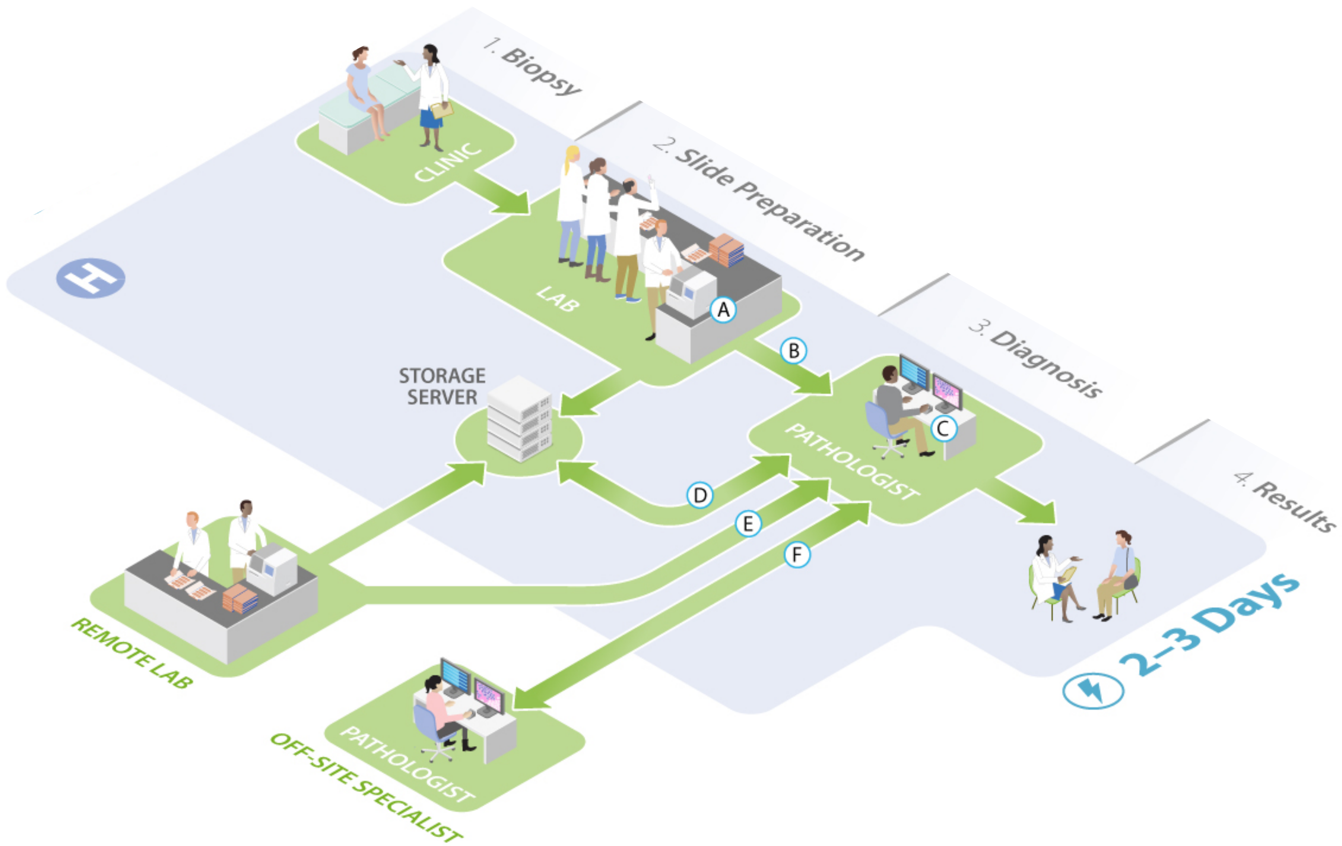


Slide from GE and Omnyx product literature

Current Workflow

Why Move To Digital Imaging?

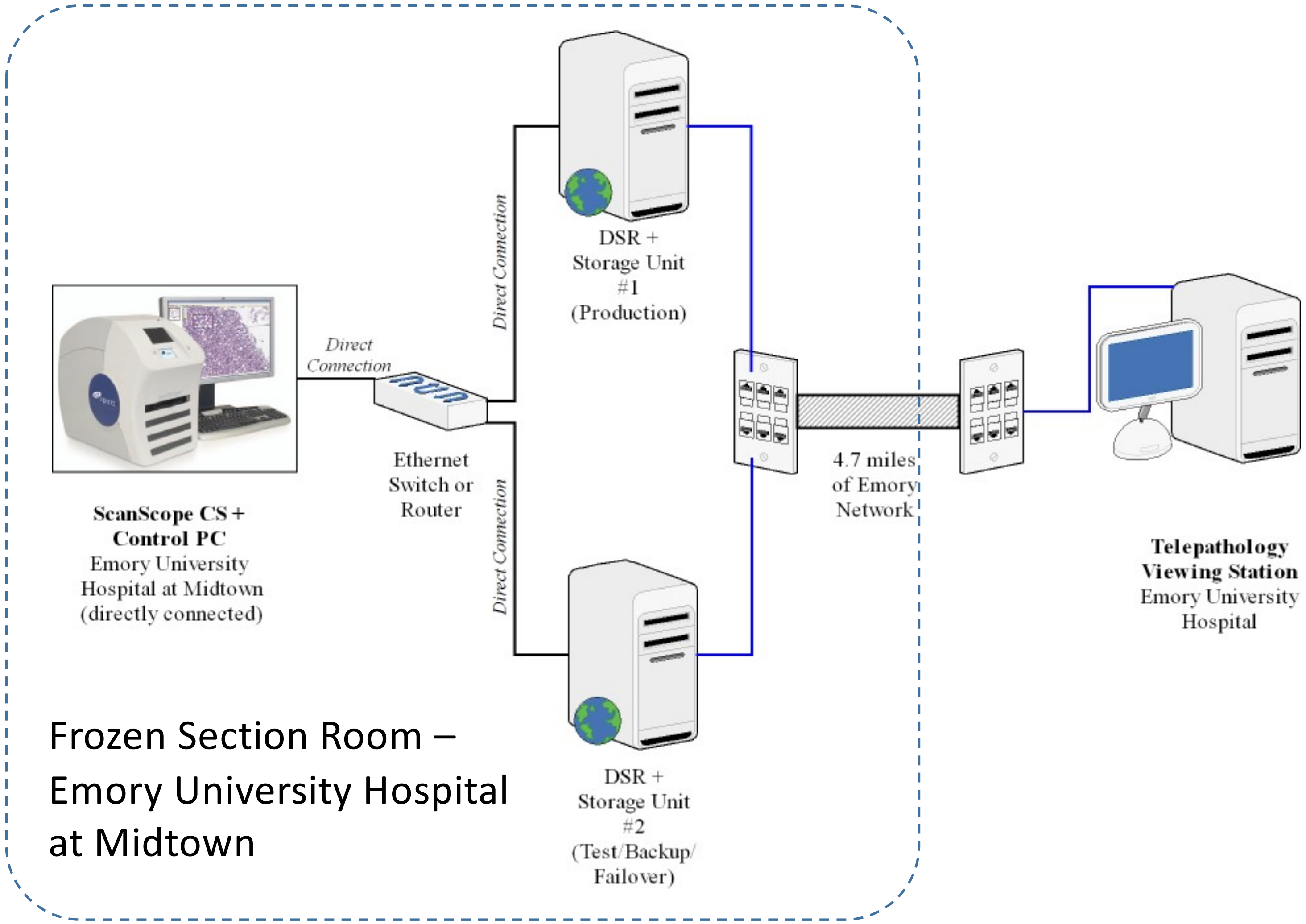
- Location independence
- Sharing of images with clinicians
- Enables new analysis techniques
  - Computerized screening of pap smears
  - Image analysis for quantitation of special stains
  - Computer aided diagnosis for other specimens



Slide from GE and Omnyx productliterature

Digital Pathology Workflow

Digital Pathology @ Emory



Comparison of Digital Imaging

Radiology

- Digital acquisition
- Manageable file size
- Many clinician interpretable
- Cost savings compared to analog
- Computer aided detection for mammograms

Pathology

- Mainly analog data which is digitized
- Very large file size in pathology
- Some clinician interpretable
- Incremental costs in addition to analog
- Computer assisted screening for pap smears

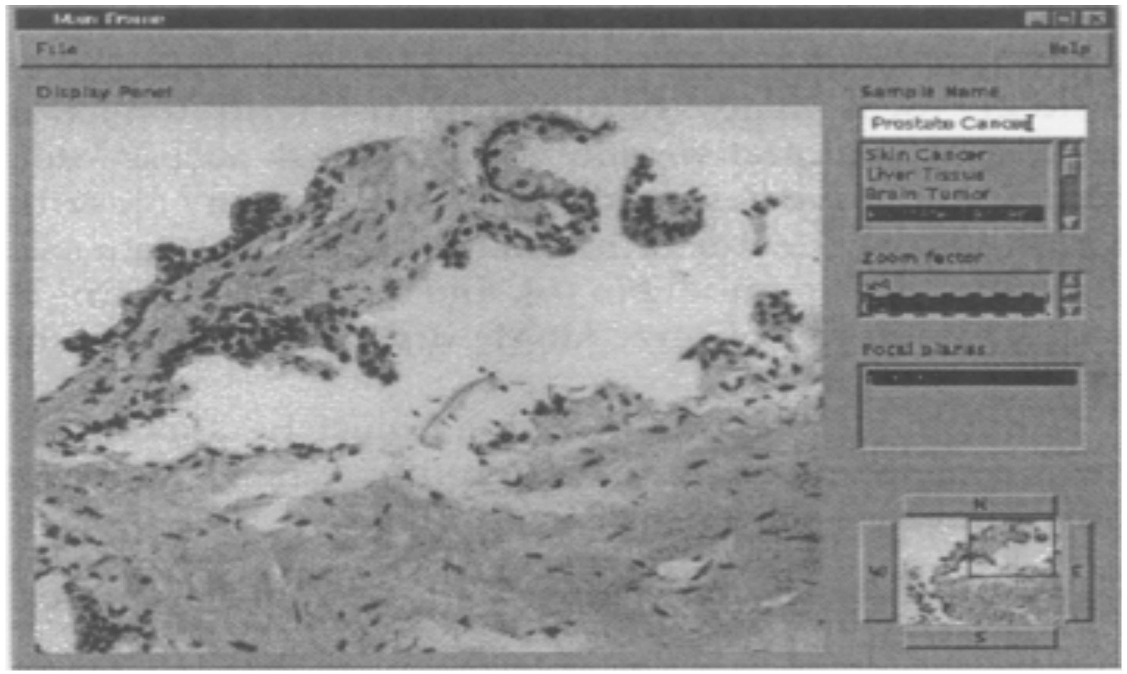
Challenges with Digital Pathology

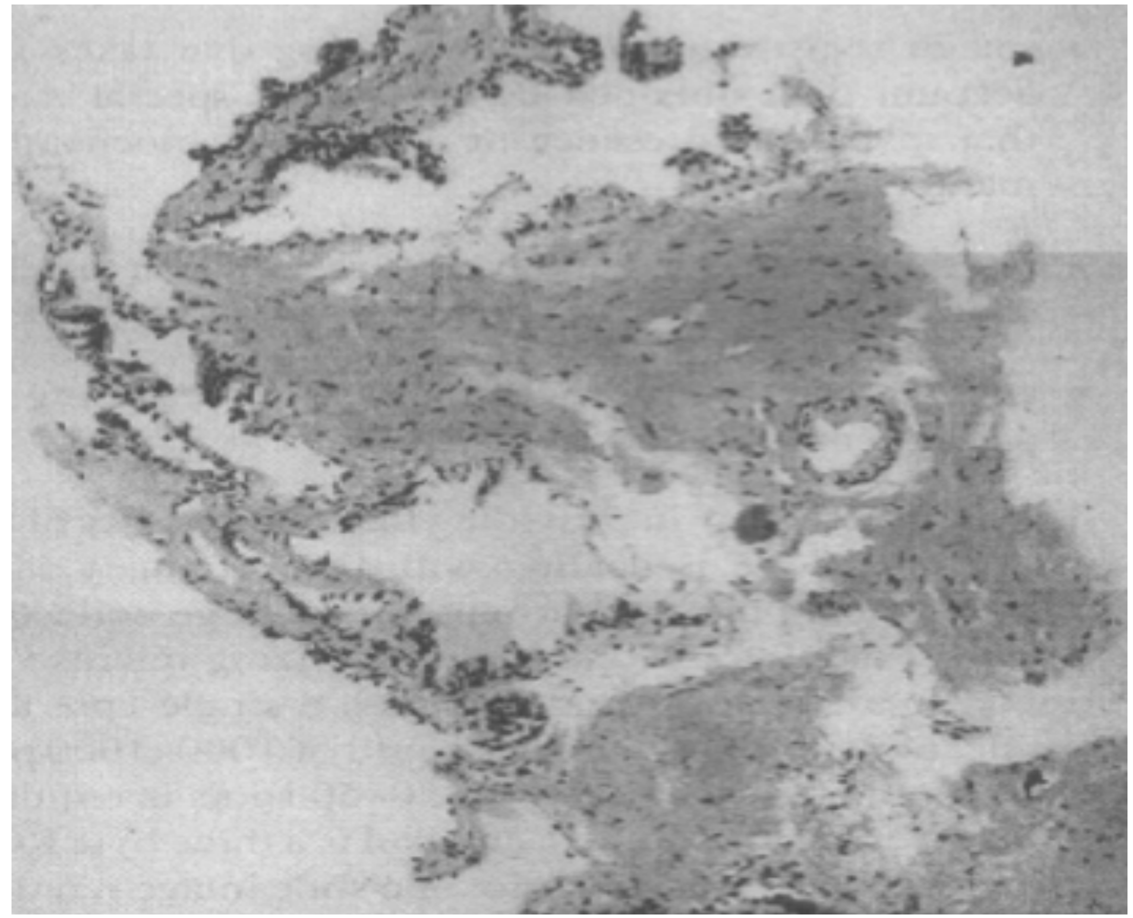
- Scan time
- Image Size
- Low-latency access
- Image compression

Scan Time

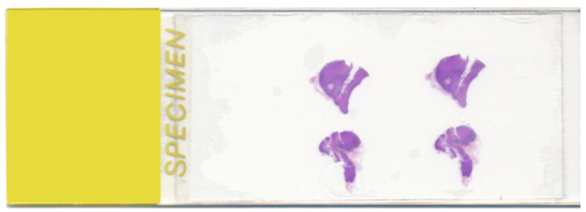
	8 hrs per day*	16 hrs per day*
Average Pathology Practice $\frac{80{,}000 \text{ slides/yr}}{250 \text{ days/yr}}$ = 320 slides/day	1.5 min per slide	3 min per slide
Large Pathology Practice $\frac{320{,}000 \text{ slides/yr}}{250 \text{ days/yr}}$ = 1380 slides/day	21 s per slide	42 s per slide

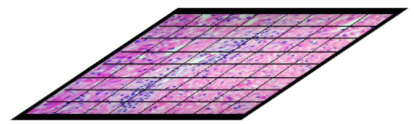
Virtual Microscope (Saltz et. al, 1997)





The Image Size Challenge



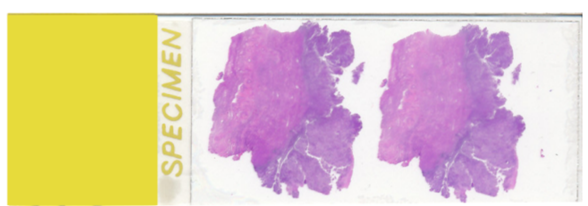


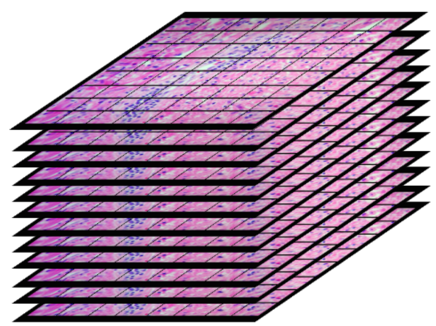
1 focal plane

24 bit color

40x magnification

15 Gigabytes





10 focal planes

24 bit color

40x magnification

3.75 Terabytes

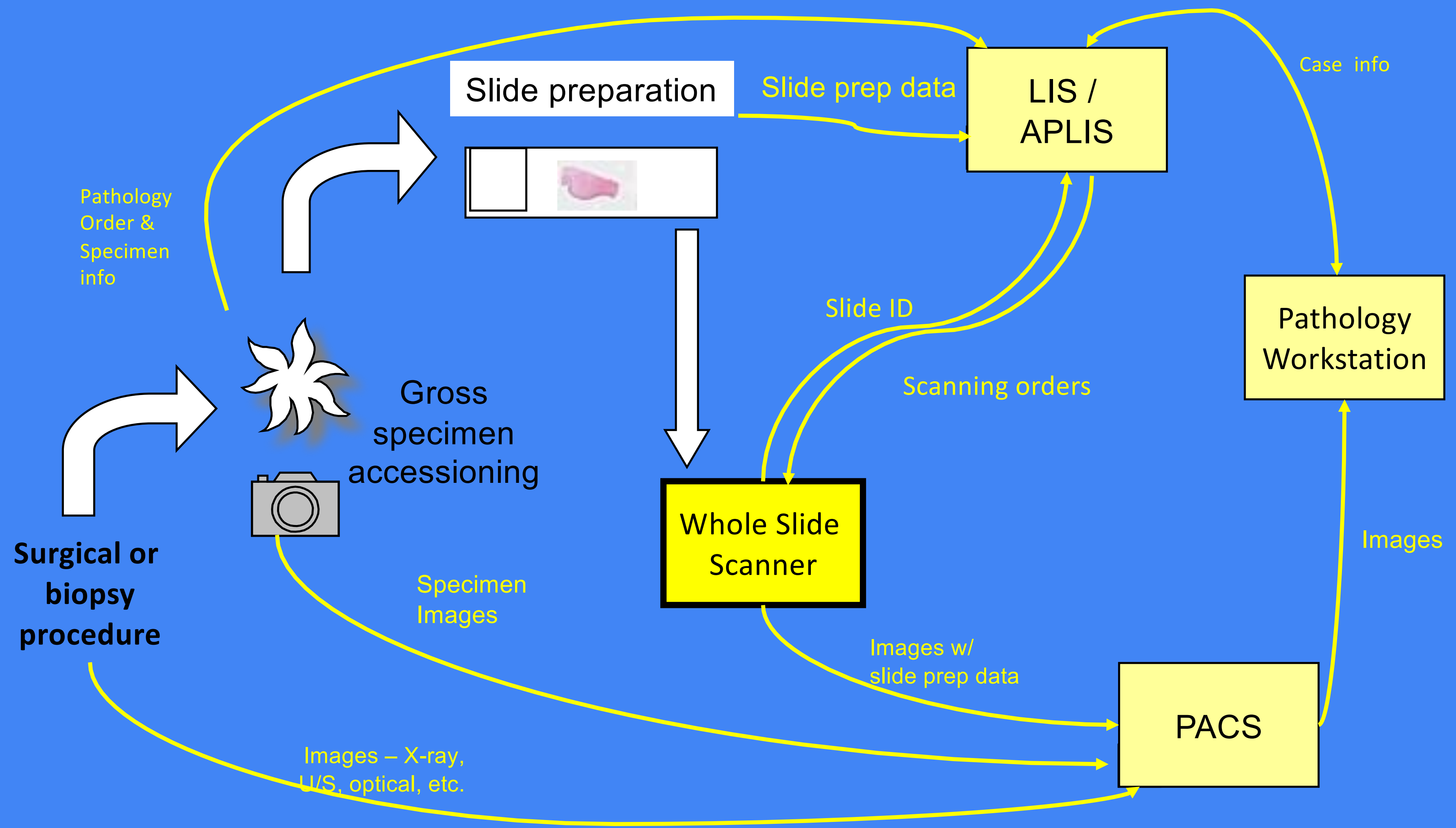
PACS for Pathology

- DICOM needs work to support digital pathology use case
  - specimen identification
  - large image encoding
  - large image access
  - coded vocabulary for processing
- DICOM originally designed for
  - store and forward
  - multiple modest size images
    e.g., early (1999) Sup 15 VL SM, GM IODs

WG-26 Goals

- Initial goals:
  - Extend minimal capabilities to describe specimens in DICOM
  - Create a mechanism to allow exchange and use of whole slide microscopic images within DICOM
- Long term goals:
  - Other imaging modalities, such as multi-spectral images, electron microscopy, flow cytometry, clinical lab images

Pathology Imaging Workflow



Adapted from H Solomon GE

DICOM and Digital Pathology

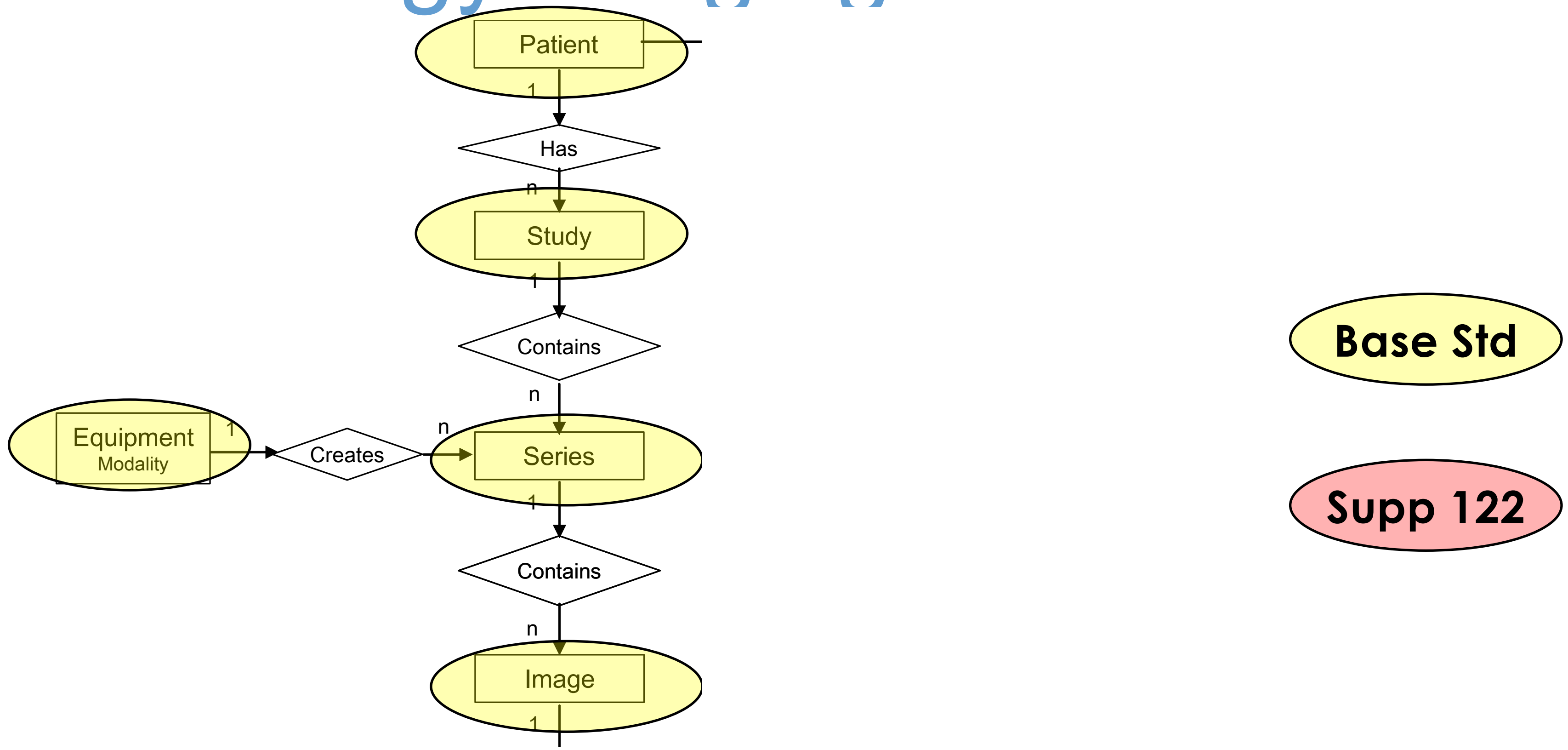
- Sup 122 – Specimen Identification
- Sup 145 – Whole Slide Image
- Sup 61 – JPEG 2000
- Sup 106 – JPEG Interactive Protocol
- Sup 119 – Frame Level Retrieve

- DICOM WG 26 Pathology
- IHE Anatomical Pathology Domain

Specimen Identification

- Specimen identification
- Specimen description
- Processing description
- multiple steps
  - Staining
  - coded vocabulary
- Anatomic location (within patient)
- Location within container

Pathology Imaging in DICOM



Integration Issues

- Supp 122 has the needed data elements,
  BUT most AP LIS Systems don't have these data at the SPECIMEN level, if at all
  - Unique slide ID may not be explicitly present
  - No ability to identify subregions of a slide/block
  - Staining and fixation information often co-mingled
  - Specimen descriptions difficult to parse out from large text blocks
  - Dictionaries may be poorly implemented

DICOM and Digital Pathology

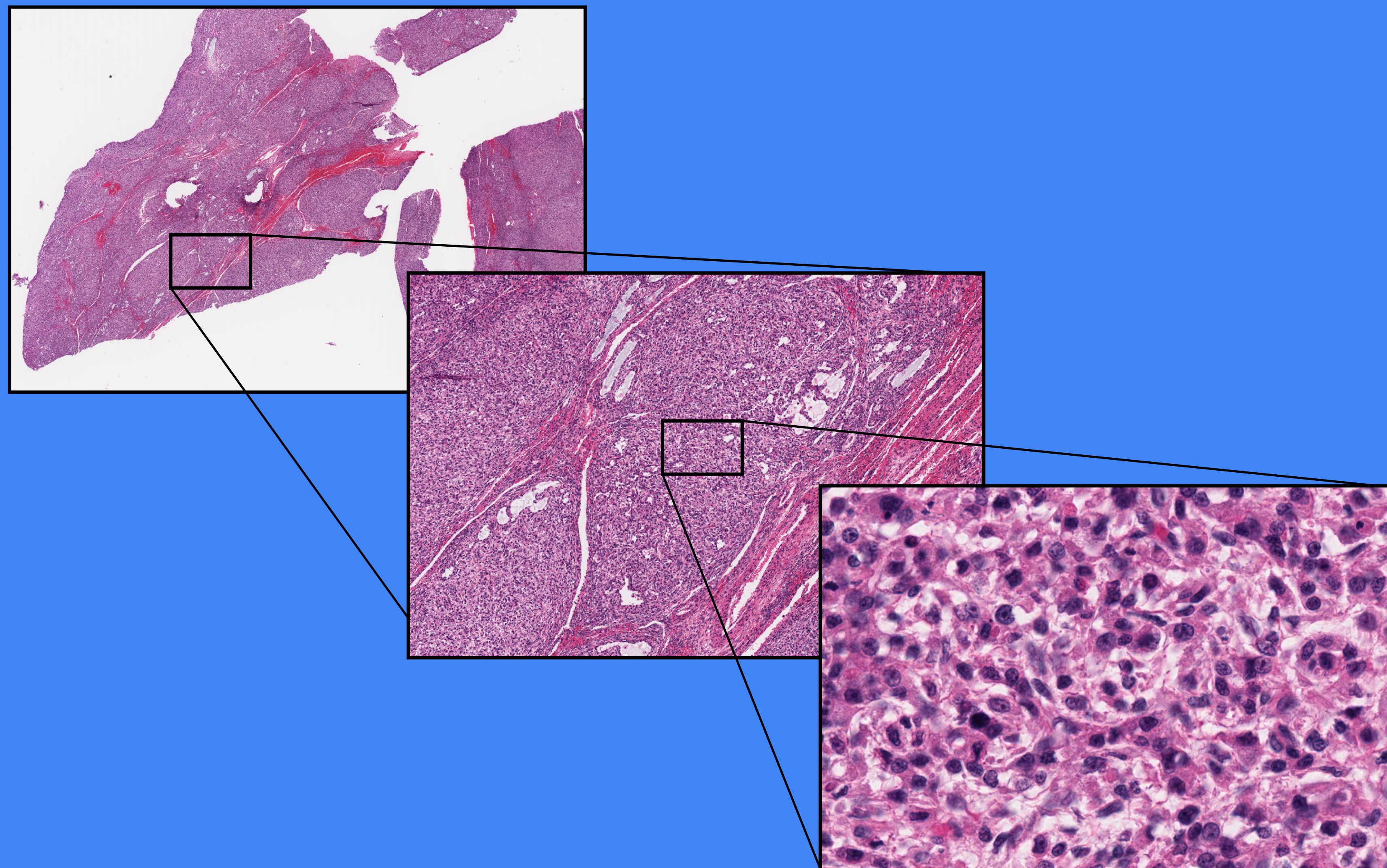
- Sup 122 – Specimen Identification
- Sup 145 – Whole Slide Image
- Sup 61 – JPEG 2000
- Sup 106 – JPEG Interactive Protocol
- Sup 119 – Frame Level Retrieve

- DICOM WG 26 Pathology
- IHE Anatomical Pathology Domain

Supplement 145 –
Whole Slide Images

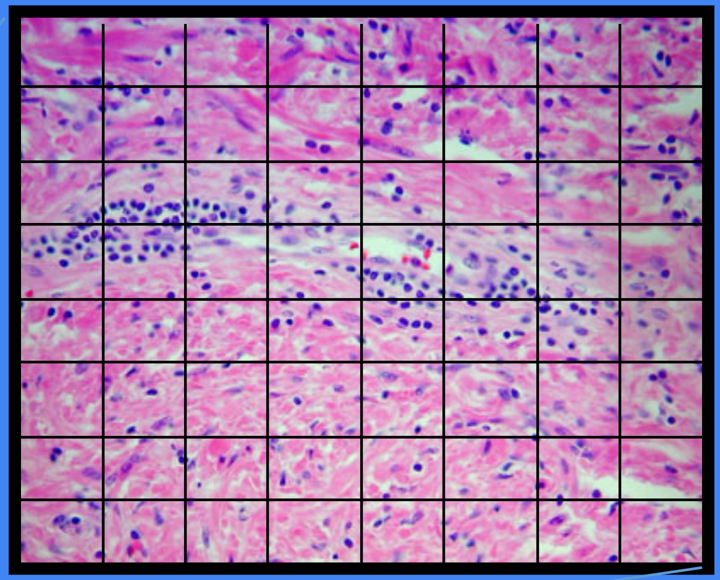
- Need a new DICOM Image Object Definition
- Challenges
  - Vast size
  - Need for intuitive and fast viewing interface
- DICOM specific issues
  - Image pixel dimensions limited to 64k x 64k
  - Image size description limited to 4GB
  - Desirable to be backwards compatible
  - Efficient sub-region access
  - Most DICOM services assume entire image transmission

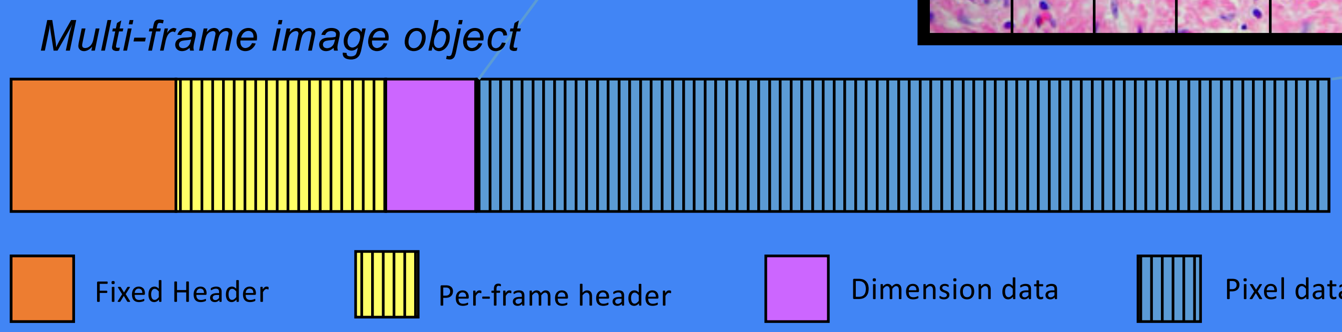
Resolution Challenge



Tiling and Multi-frame encoding

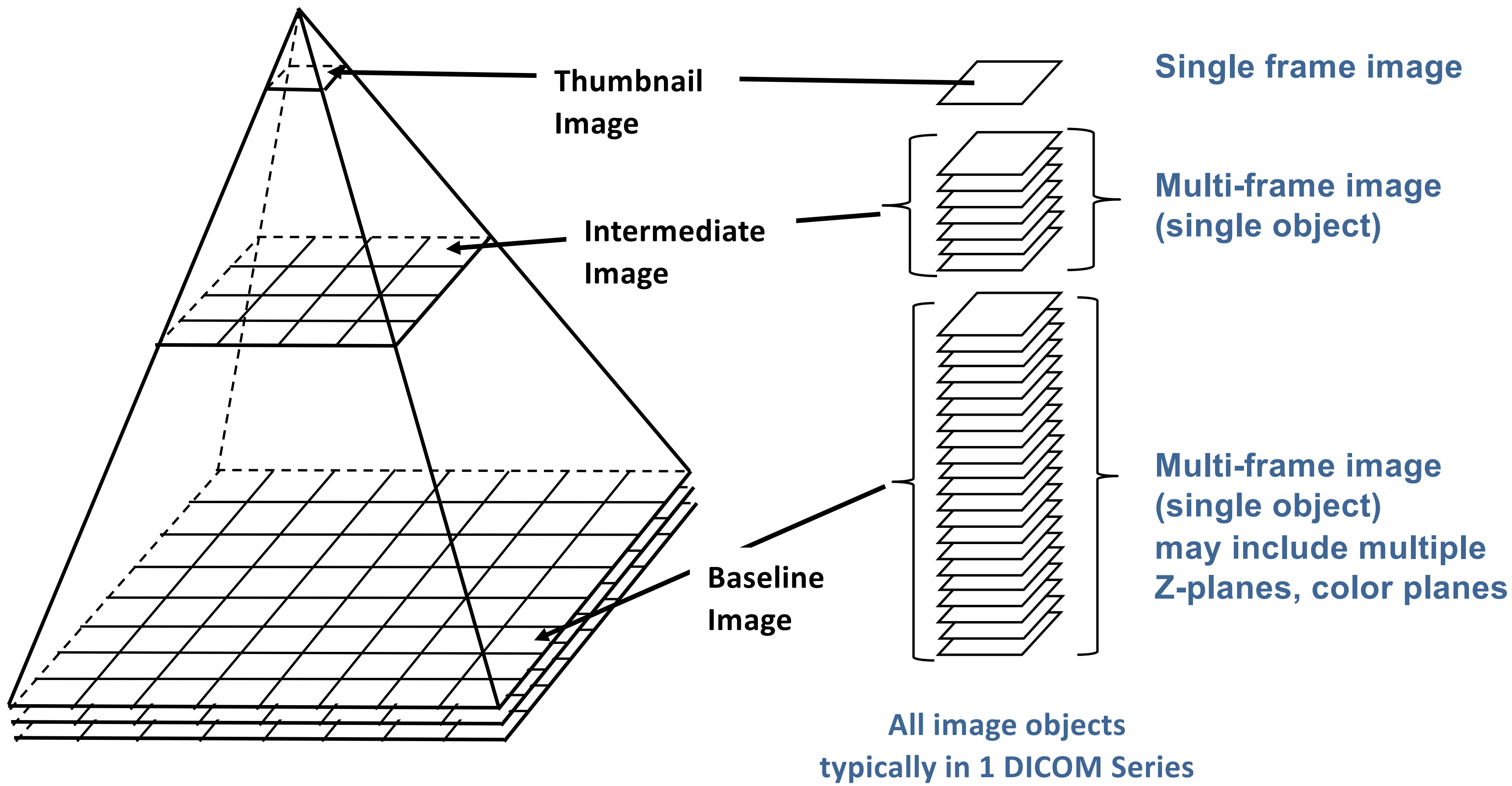
- Whole Slide Image divided into tiles
- Each tile encoded into a frame of multi-frame image object
- Per-frame header gives spatial location for each tile: X, Y, and Z (focal plane)





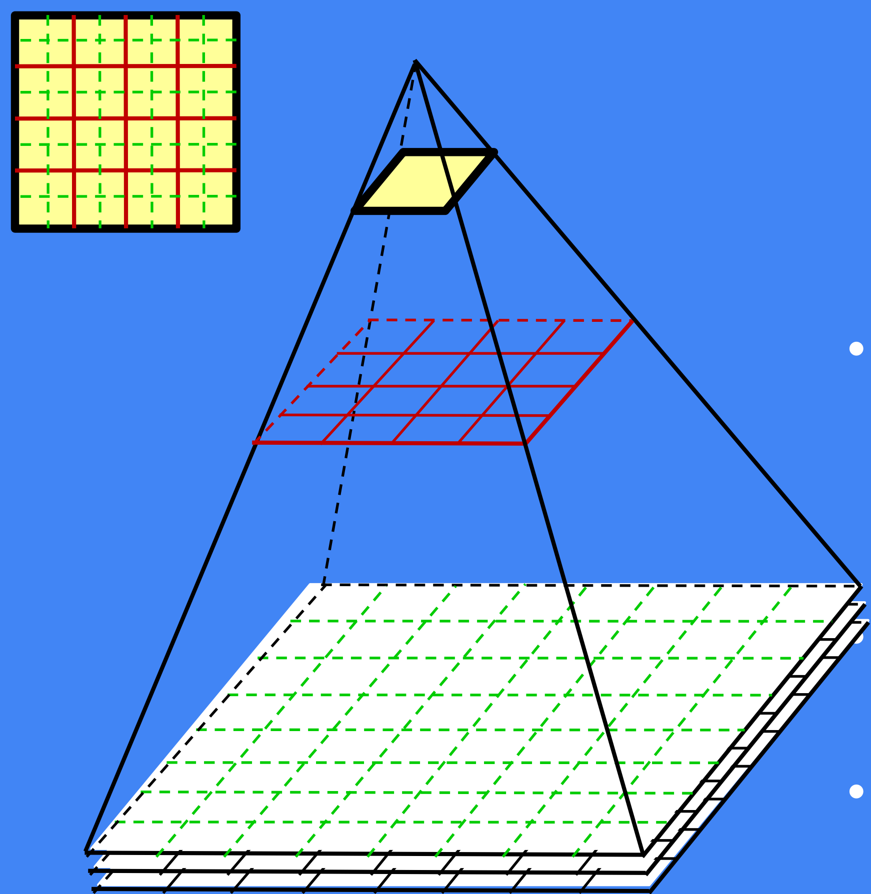
H Solomon GE

Image Pyramid



H Solomon GE

Localizer image "flavor"



- Thumbnail image (single frame) plus navigation links to each frame at each resolution
  - Each tile of other resolution images has its corresponding area identified in thumbnail
- Full description of target tiles
  - Object Unique ID and frame number
  - Resolution
  - Z-plane, color
- Multiple target frames can overlap
  - Different resolution, Z-plane, color, etc.
- Presentation and any interactive behavior is not defined in standard

Image Sharing

- Currently some pathologists include snapshots in reports
  - Tumors, specimen margins, unusual findings, etc
- WSI allows ability to review slides remotely with clinicians
- The ability to correlate slides with other images would be useful
  - Gross specimen images
  - Endoscopy images
  - Radiology images

Challenges to Wider Adoption

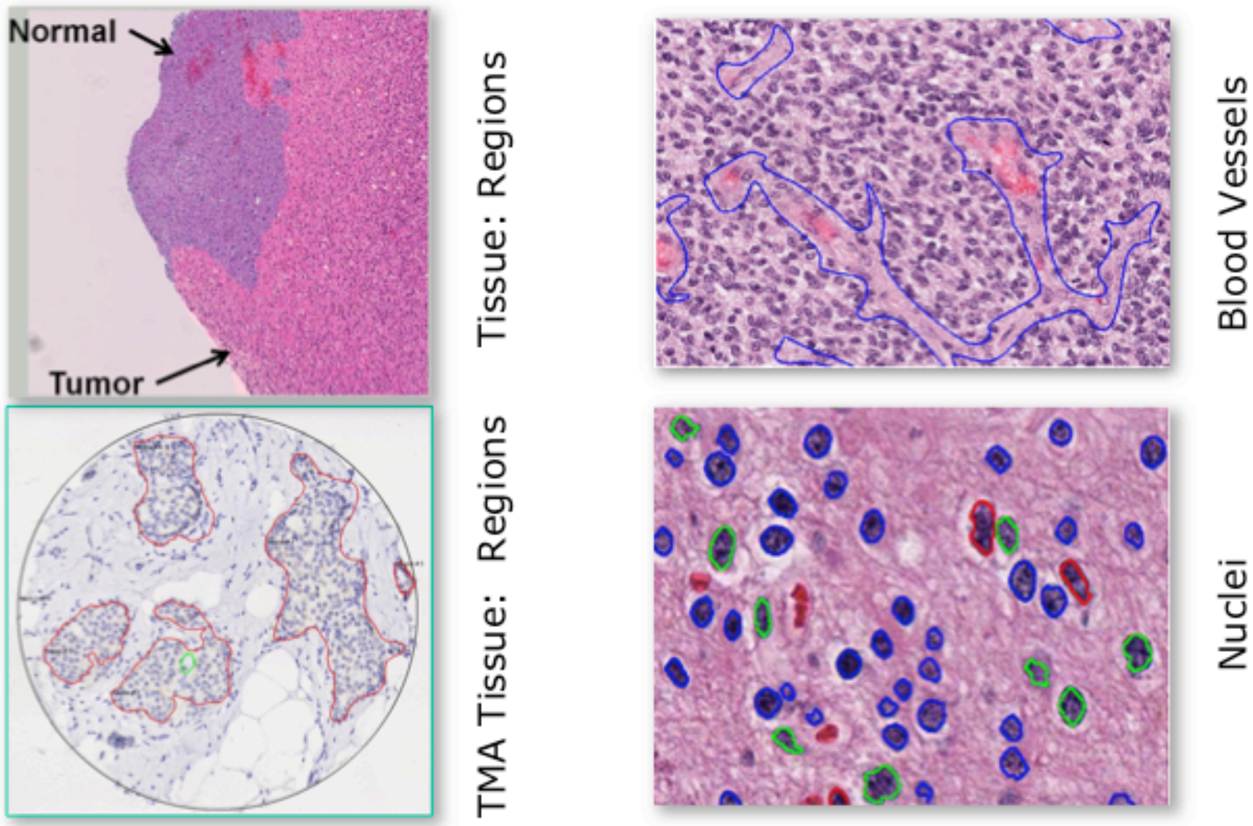
- Storage and bandwidth
  - PACS storage is relatively expensive
  - Don't want to transfer entire huge files
- Pathology systems need to become more image centric (as opposed to report centric)
- EMR's need to be able to accept or connect to images and display correctly
  - Security, credentialing, optimized viewers, etc

Digital Pathology in Action

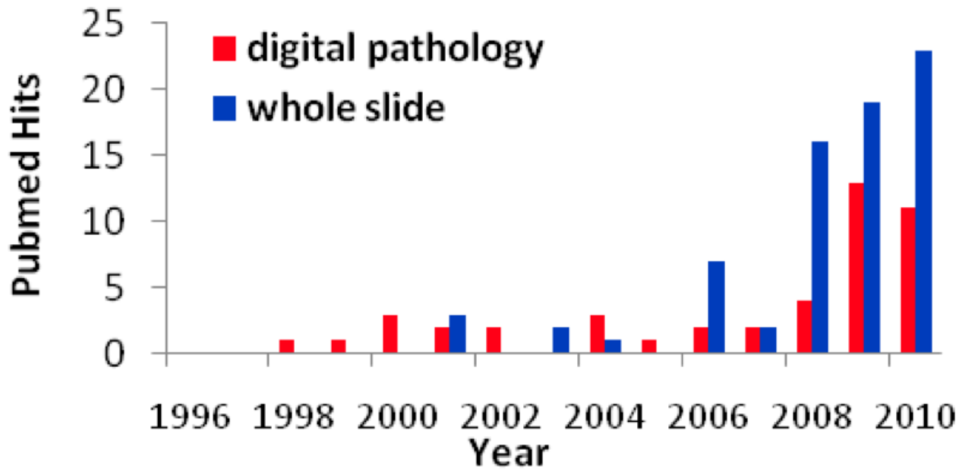
- Quantification of antibodies
- Object Segmentation
- Region Segmentation
- Feature Extraction
- Classification
- Registration

Structured Information

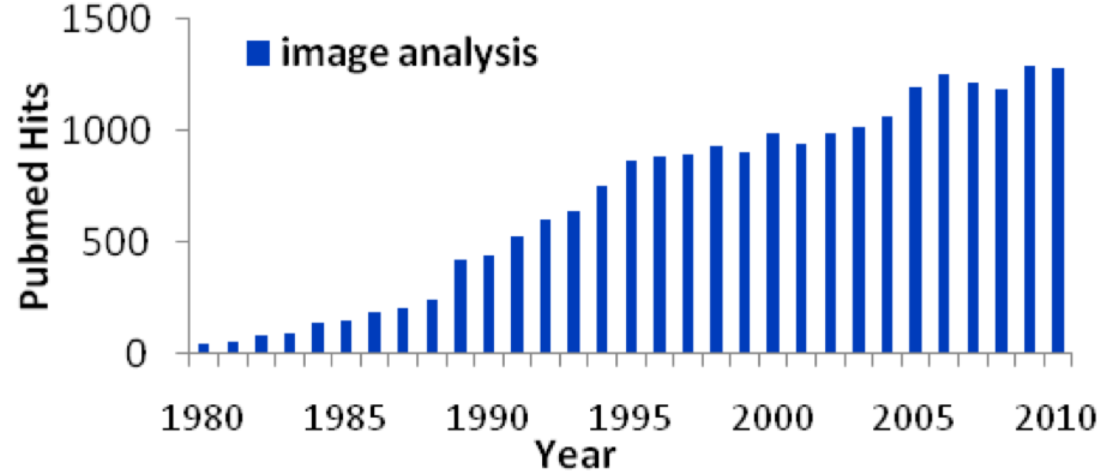
- Pathology images contain rich information, including markups and annotations, by humans or algorithms



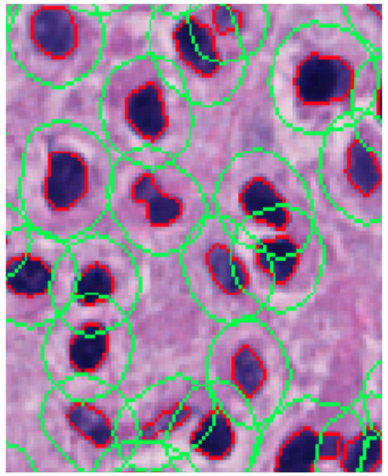
Future



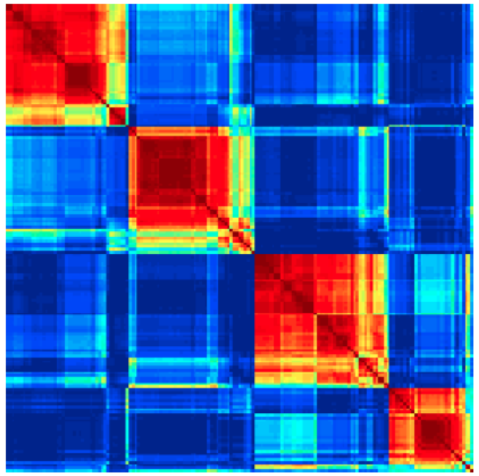
Pubmed Hits
25
20
15
10
5
0
digital pathology
whole slide
1996 1998 2000 2002 2004 2006 2008 2010
Year

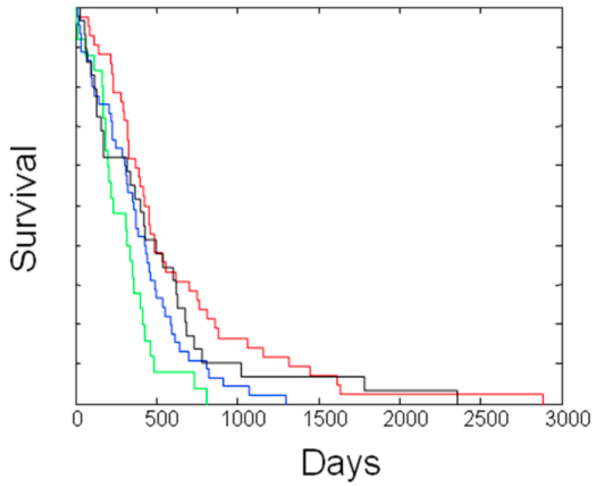


Pubmed Hits
1500
1000
500
0
image analysis
1980 1985 1990 1995 2000 2005 2010
Year



$E\{f_i\}$





Survival
0 500 1000 1500 2000 2500 3000
Days

Agenda

Scope, Benefits and Limitations

Data Standards and Management

Radiology – Modalities

Digital Pathology

Lab

3DSlicer

Platform for analysis and visualization
for quantitative imaging

- Introduction
- 4Minute Quickstart
- Quantitative Imaging Tutorial

Scope of the Lab

http://wiki.slicer.org/slicerWiki/index.php/Documentation/4.4
(slicer.org → Training → Change version to 4.4 in URL)

1. Get familiar with 3DSlicer (Slicer Welcome Tutorial)
2. Quickstart (Slicer4Minute Tutorial)
3. Slicer4 Quantitative Imaging Tutorial
   (Part 2 – Volumetric Changes)