Introduction to Modern Imaging Physics and Techniques used in Clinical Neurology

Benjamin M. Ellingson, Ph.D., M.S.
Associate Professor of Radiology, Biomedical Physics, Bioengineering, and Psychiatry
UCLA Neuro-Oncology Program
Director, UCLA Brain Tumor Imaging Laboratory (BTIL)
Depts. of Radiological Sciences and Psychiatry
David Geffen School of Medicine at UCLA

CTSI: Modern Imaging Techniques in Clinical Neuroscience Research
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Overview

- Brief History of Neuroimaging Technology
- Basic Anatomic MRI
  - T2-Weighted MRI
  - T2-Weighted FLAIR
  - Pre- and Post-Contrast T1-Weighted MRI
- Advanced MRI Techniques
  - Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI)
  - Perfusion MRI (DSC and ASL)
  - Functional MRI
  - MR Spectroscopy
- Basic PET Imaging
Brief History of Neuroimaging Technology
Pneumoencephalogram

• 1918 - 1930’s
  • Brain soft tissue is not opaque on x-ray
  • Walter Dandy, 1918
  • Injecting filtered air into ventricular system outlines the ventricles and surface of brain
  • Great advance in neuroimaging - but very dangerous
Cerebral Angiography

• 1930’s - Present
  • Egas Moniz, 1927
  • Injection of positive contrast (iodine) to highlight blood vessels
  • Still used today for certain procedures
Computed Tomography (CT)

• 1970’s - Present

• William Olendorf (1961), Godfrey Hounsfield (1973), and Allan Cormack (1973)

• Collects x-rays at various angles around the body, then reconstructs it in 2D (computed axial tomography, CAT)

• Repeated for multiple slices
Positron Emission Tomography (PET)

- **1973 - Present**
- Developed by Edward Hoffman and Michael Phelps (Wash U, later to UCLA)
- Uses biochemicals labeled with “anti-matter” to image metabolism and/or follow molecular probes
Positron Emission Tomography (PET)

• 1973 - Present

• First human PET scanner was developed by Edward Hoffman and Michael Phelps (Wash U, later to UCLA)

• Uses biochemicals labeled with “anti-matter” to image metabolism and/or follow molecular probes

A. MRI

B. $^{18}$F-FDOPA PET
Magnetic Resonance Imaging (MRI)

- **1977 - Present**
  - MRI uses strong magnetic fields and radio waves to image water protons in the body
  - Magnetic fields cause protons on water molecules to absorb RF energy at a certain frequencies (FM - determined by the Larmor Equation & Gyromagnetic Ratio)
Magnetic Resonance Imaging (MRI)

• **1977 - Present**
  
  • Different tissues then release this RF energy differently (relaxation) depending on local magnetic environment
  
  • The rates at which RF energy are released/dissipate are “T1” and “T2”
Magnetic Resonance Imaging (MRI)

- **1977 - Present**
  - Damadian, *Science*, 1971 - NMR characteristics differ between normal tissue and cancer

**Tumor Detection by Nuclear Magnetic Resonance**

Abstract. *Spin echo nuclear magnetic resonance measurements may be used as a method for discriminating between malignant tumors and normal tissue. Measurements of spin-lattice (T₁) and spin-spin (T₂) magnetic relaxation times were made in six normal tissues in the rat (muscle, kidney, stomach, intestine, brain, and liver) and in two malignant solid tumors, Walker sarcoma and Novikoff hepatoma. Relaxation times for the two malignant tumors were distinctly outside the range of values for the normal tissues studied, an indication that the malignant tissues were characterized by an increase in the motional freedom of tissue water molecules. The possibility of using magnetic relaxation methods for rapid discrimination between benign and malignant surgical specimens has also been considered. Spin-lattice relaxation times for two benign fibroadenomas were distinct from those for both malignant tissues and were the same as those of muscle.*

**Raymond Damadian**

Biophysical Laboratory, Department of Medicine, State University of New York, Brooklyn 11203
Magnetic Resonance Imaging (MRI)

• 1973 - Paul Lauterbur & Sir Peter Mansfield (Nobel Prize)
  first MRI images
Magnetic Resonance Imaging (MRI)

- 1973 - Paul Lauterbur & Sir Peter Mansfield (Nobel Prize) first MRI images
- 1977 - Damadian - First Human Scan Achieved
- Currently used *routinely*

First MRI Scanner

First MR scan, 1977
Why MRI?

• No radiation (only magnetic fields and radio waves)
• Better soft tissue contrast
• More detailed anatomy of the brain
• Multiple ways to acquire images (flexibility)
• Physiologic imaging
Basic Clinical Neuroimaging Protocol

- T2-Weighted MRI
- T2-Weighted FLAIR MRI
- Pre- and Post-Contrast T1-Weighted MRI
Basic Clinical Neuroimaging Protocol

- **T2-Weighted MRI**
  - Related to *rotational mobility* of water molecules

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**Shorter T2**

Free Mobile Water

Structured water

Hydrophobic surface

Rotationally bound (dipolar)

Bound water

Rotationally bound (ionic)

Irrotationally bound (dipolar)

Irrotationally bound (ionic)

---

Darker the Image on T2-Weighted MRI
Basic Clinical Neuroimaging Protocol

• **T2-Weighted MRI**
  - Related to **rotational mobility** of water molecules
  - Mobile water = **Long T2** = Bright on T2w

\[
\frac{M_{xy}}{M_0} = e^{-\frac{TE}{T_2}}
\]

Long T2 = More Signal = Bright

T2-Weighted MRI
Basic Clinical Neuroimaging Protocol

• **T2-Weighted MRI**
  • Sensitive to general pathology (non-specific)
Basic Clinical Neuroimaging Protocol

• **T2-Weighted “FLAIR” MRI**
  - “Fluid Attenuated Inversion Recovery” = FLAIR
  - Uses a RF pulse to “null” signals from CSF
  - Results in T2-weighting, but dark CSF
Basic Clinical Neuroimaging Protocol

- **T2-Weighted “FLAIR” MRI**
  - Sensitive (but not specific) to pathology
Basic Clinical Neuroimaging Protocol

- Pre-Contrast T1-Weighted MRI
  - Also related to water mobility
  - Short T1 = Bright on T1-Weighted MRI
  - Blood products = shorten T1 on pre-contrast (bright)
• **Post-Contrast T1-Weighted MRI**
  • Tumor vasculature causes contrast agent to leak into the brain
  • Contrast agents shorten T1 (bright on T1w)
• **Post-Contrast T1-Weighted MRI**
  - Tumor vasculature causes contrast agent to leak into the brain
  - Contrast agents shorten T1 (bright on T1w)

---

**Basic Clinical Neuroimaging Protocol**

**Pre-Contrast T1-Weighted**

**Post-Contrast T1-Weighted**

*Gadolinium Contrast Injected into Veins*
Basic Clinical Neuroimaging Protocol

• T2 vs. FLAIR
Basic Clinical Neuroimaging Protocol

• T1 vs. T2

Pre-Contrast
T1-Weighted

T2-Weighted

Edema

Tumor
Basic Clinical Neuroimaging Protocol

• Pre and Post-Contrast T1

Pre-Contrast T1-Weighted

T2-Weighted

Edema

Tumor
Basic Clinical Neuroimaging Protocol

• High-Resolution 3D T1-Weighted Images
  • Used for brain morphometry (e.g. cortical thickness, tumor volume, etc.)

Advanced MRI

- T1 and T2 characteristics do not tell us everything
  - Physiologic Imaging - Tells us about *function*

![Diagram showing Advanced MRI features: Cell Density and Proliferation, Metabolism, Signaling, Perfusion]
Advanced MRI

• Routine Advanced MRI at UCLA:
  • Diffusion MRI - Microstructure & location/density of axon tracts
  • Perfusion MRI - Vascularity, blood flow
  • Functional MRI - Brain function & reorganization
  • MR Spectroscopy - Brain metabolite concentrations
Diffusion MRI
Diffusion MRI

Restricted Diffusion

B.M. Ellingson, Ph.D., Dept. of Radiological Sciences, David Geffen School of Medicine at UCLA, 2016
Diffusion MRI
• **Diffusion MRI in Neuro-Oncology**

  • Apparent diffusion coefficient (ADC) and tumor cell density are **negatively correlated** (Sugahara, 1999; Lyng, 2000; Chenevert, 2000; Gaurain, 2001; Nonomura, 2001; Guo, 2002; Chen, 2005; Hayashida, 2006; Manenti, 2008; Kinoshita, 2008; Ellingson, 2010)

  \[
  \downarrow \text{ADC (or mean diffusion)} = \uparrow \text{cell density ("hypercellularity")}
  \]

  \[
  \uparrow \text{ADC} = \downarrow \text{cell density ("hypocellularity")}
  \]
Diffusion MRI
Diffusion MRI

ADC Before Radiation

ADC After Radiation
Diffusion MRI

• Diffusion MRI in Acute Stroke
  • Intracellular water diffusivity is slower than extracellular water diffusivity
  • Ischemia results in swelling of intracellular volume
    • Increased DWI signal, decreased measured ADC
Diffusion MRI

• Diffusion MRI in Acute Stroke

Courtesy of Jeff Alger, UCLA Brain Mapping Center
Diffusion MRI

• Diffusion MRI in Acute Stroke

Courtesy of Jeff Alger, UCLA Brain Mapping Center
Diffusion *Tensor* Imaging (DTI)

- Measure diffusion in many directions
- ADC perpendicular to white matter tracts is low
- ADC parallel to white matter tracts is high
Diffusion Tensor Imaging

• Fiber Tractography

• Create “pseudoaxons” in the direction of largest ADC

\[
\frac{d\bar{r}(s)}{ds} = \bar{v}_1(\bar{r}(s))
\]

Fiber Tracking
Diffusion Tensor Imaging

• Fiber Tractography

• Create “pseudoaxons” in the direction of largest ADC

\[
\frac{d\vec{r}(s)}{ds} = \vec{v}_1(\vec{r}(s))
\]

Fiber Tracking
Diffusion Tensor Imaging

• DTI Tractography
  • Used for pre-surgical planning to avoid cutting important parts of the brain
Diffusion Tensor Imaging

• DTI Tractography
  • Deterministic vs. Probabilistic Tractography

Deterministic
One Streamline per seed voxel

Probabilistic
A probability distribution (sum of all streamlines from all seed voxels)

Courtesy of Anastasia Yendiki, MGH/Harvard, Martinos Center
Diffusion Tensor Imaging

• DTI Tractography
  • Used to understand the strength of connections between brain regions

Courtesy of McGill University

Courtesy of Human Connectome Project
Perfusion MRI

• Dynamic Susceptibility Contrast (DSC)-MRI
  • Acquire *dynamic* MR images *during* injection of contrast
  • Acquired *between* pre and post-contrast T1-weighted images

Pre-Contrast T1-Weighted  

*Dynamic Perfusion MRI*

Post-Contrast T1-Weighted

Gadolinium Contrast Injected into Veins
Perfusion MRI

• **Dynamic Susceptibility Contrast (DSC)-MRI**
  - Acquire *dynamic* MR images *during* injection of contrast
  - Models the “first pass” of contrast through the vessels
Perfusion MRI

- **Dynamic Susceptibility Contrast (DSC)-MRI**
  - Add up all contrast that passes through vessels = Blood Volume

![Diagram of Dynamic Susceptibility Contrast (DSC) MRI](image)
Perfusion MRI

• Dynamic Susceptibility Contrast (DSC)-MRI
  • Acquire *dynamic* MR images *during* injection of contrast
  • Models the “first pass” of contrast through the vessels

Raw Dynamic Data | Post-Contrast T1-Weighted | Cerebral Blood Volume
Perfusion MRI

• **Dynamic Susceptibility Contrast (DSC)-MRI**
  • Acquire *dynamic* MR images *during* injection of contrast
  • Models the “first pass” of contrast through the vessels

![Raw Dynamic Data](image1)

![Post-Contrast T1-Weighted](image2)

![Cerebral Blood Volume](image3)
Perfusion MRI

• DSC-MRI in Stroke

\[ MTT = \frac{CBV}{CBF} \]

Copen, Neuroimaging Clin N Am, 2011
Perfusion MRI

• DSC-MRI in Stroke

\[ MTT = \frac{CBV}{CBF} \]

Arterial Spin Labeling (ASL)

- No Contrast
- Uses magnetically “tagged” or “labeled” blood

Courtesy of JJ Wang, UCLA Brain Mapping Center
Arterial Spin Labeling (ASL)

- No Contrast
- Uses magnetically “tagged” or “labeled” blood

Zaharchuk, MRM, 1999
Arterial Spin Labeling (ASL)

- No Contrast
- Uses magnetically “tagged” or “labeled” blood

Bokkers, *Stroke*, 2012
Functional MRI

- Changes in brain function cause a change in the amount of oxygen in blood
- Hemoglobin = molecule that carries oxygen, contains iron (magnetic)
Functional MRI

- Changes in brain function cause a change in the amount of oxygen in blood
- Hemoglobin = molecule that carries oxygen, contains iron (magnetic)
- Changes in oxygenation cause a change in MRI

97% Oxygen - 3% Halothane

0% Oxygen - 100% Nitrogen

Ogawa, PNAS, 1990
Functional MRI

- Perform a series of tasks - finger tapping, language, etc.
- Used for surgical planning - avoid important areas of the brain
Functional MRI

• Resting-state fMRI - No Tasks
• Signal fluctuates over time in sync with other areas of the brain “networks”

Fox, Front Syst Neurosci, 2010
Functional MRI

• Resting-state fMRI
• No Tasks
• Signal fluctuates over time in sync with other areas of the brain “networks”

Xuan, PLoS One, 2012
MR Spectroscopy

- Water protons far outnumber other protons in the body.
- With MR Spectroscopy we can suppress water protons and examine other biochemicals within the brain.

### Observable Proton Metabolites

<table>
<thead>
<tr>
<th>ppm</th>
<th>Metabolite</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9-1.4</td>
<td>Lipids</td>
<td>Products of brain destruction</td>
</tr>
<tr>
<td>1.3</td>
<td>Lactate</td>
<td>Product of anaerobic glycolysis</td>
</tr>
<tr>
<td>2.0</td>
<td>NAA</td>
<td>Neuronal marker</td>
</tr>
<tr>
<td>2.2-2.4</td>
<td>Glutamine/GABA</td>
<td>Neurotransmitters</td>
</tr>
<tr>
<td>3.0</td>
<td>Creatine</td>
<td>Energy metabolism</td>
</tr>
<tr>
<td>3.2</td>
<td>Choline</td>
<td>Cell membrane marker</td>
</tr>
<tr>
<td>3.5</td>
<td>myo-inositol</td>
<td>Glial cell marker, osmolyte hormone receptor mechanisms</td>
</tr>
<tr>
<td>1.2</td>
<td>Ethanol</td>
<td>Triplet</td>
</tr>
<tr>
<td>1.48</td>
<td>Alanine</td>
<td>Present in meningiomas</td>
</tr>
<tr>
<td>3.4&amp;3.8</td>
<td>Glucose</td>
<td>Increased in diabetes</td>
</tr>
<tr>
<td>3.8</td>
<td>Mannitol</td>
<td>Rx for increased ICP</td>
</tr>
</tbody>
</table>

*Courtesy of MGH/Harvard Radiology*  
*Courtesy of Hesselink, UCSD*
MR Spectroscopy

- Water protons far outnumber other protons in the body
- With MR Spectroscopy we can suppress water protons and examine other biochemicals within the brain

![Spectroscopy Images](source: Semin Neurol © 2008 Thieme Medical Publishers)
MR Spectroscopic Imaging (MRSI)

• Fast MRS technique to create an “image” of metabolites
MR Spectroscopic Imaging (MRSI)

- Fast MRS technique to create an “image” of metabolites

Lipids/Lactate  
NAA  
Choline
Positron Emission Tomography (PET)

- Uses biochemicals labeled with “anti-matter” to image metabolism and/or follow molecular probes
Positron Emission Tomography (PET)

- Uses biochemicals labeled with “anti-matter” to image metabolism and/or follow molecular probes

Fischman et al., Clin Pharmacokinet, 2002

Fig. 6. Model for ligand transport and binding. This formulation illustrates the interaction of labelled and unlabelled ligand. Although unlabelled ligand concentrations are not directly measurable by positron emission tomography, the concentration of specifically bound unlabelled ligand affects the local concentration of free receptors and thus binding of labelled ligand. B = bound ligand in tissue; $B_{\text{max}}$ = local concentration of unoccupied receptors; F = free ligand in tissue; $k_\text{on}$ = rate constant for specific binding; $k_\text{off}$ = rate constant for dissociation of specific binding; $K_1$ = rate constant for flux of ligand into tissue; $k_2$ = rate constant for escape from tissue; $k_3$ = rate constant for nonspecific binding; $k_4$ = rate constant for dissociation of nonspecific binding; NS = nonspecifically bound ligand; P = free ligand in plasma; SA(t) = specific activity at time t.
Positron Emission Tomography (PET)

- Brain Tumor Recurrence

<table>
<thead>
<tr>
<th>Date</th>
<th>T1+C</th>
<th>FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Surgical (9/21/10)</td>
<td><img src="image1" alt="Brain MRI Pre-Surgical" /></td>
<td><img src="image2" alt="Brain MRI FLAIR Pre-Surgical" /></td>
</tr>
<tr>
<td>Post-Surgical (9/24/10)</td>
<td><img src="image3" alt="Brain MRI Post-Surgical" /></td>
<td><img src="image4" alt="Brain MRI FLAIR Post-Surgical" /></td>
</tr>
<tr>
<td>10/5/10</td>
<td><img src="image5" alt="Brain MRI 10/5/10" /></td>
<td><img src="image6" alt="Brain MRI FLAIR 10/5/10" /></td>
</tr>
<tr>
<td>11/3/10</td>
<td><img src="image7" alt="Brain MRI 11/3/10" /></td>
<td><img src="image8" alt="Brain MRI FLAIR 11/3/10" /></td>
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<tr>
<td>Recurrence (12/28/10)</td>
<td><img src="image9" alt="Brain MRI Recurrence" /></td>
<td><img src="image10" alt="Brain MRI FLAIR Recurrence" /></td>
</tr>
</tbody>
</table>
• Brain Tumor Recurrence
18F-FDOPA PET
Overview

• Brief History of Neuroimaging Technology

• Basic Anatomic MRI
  • T2-Weighted MRI
  • T2-Weighted FLAIR
  • Pre- and Post-Contrast T1-Weighted MRI

• Advanced MRI Techniques
  • Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI)
  • Perfusion MRI (DSC and ASL)
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• Basic PET Imaging
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UCLA Brain Tumor Imaging Lab (BTIL)
Depts. of Radiological Sciences and Psychiatry
David Geffen School of Medicine
University of California - Los Angeles
bellingson@mednet.ucla.edu

American Cancer Society Research Scholar Grant
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University of California Cancer Research Grant
National Brain Tumor Society Research Grant
Siemens Healthcare Research Grant
Genentech/Roche Research Grant
Art of the Brain
Ziering Family Foundation in memory of Sigi Ziering
Singleton Family Foundation
Clarence Klein Fund for Neuro-Oncology
UC Cancer Research Coordinating Committee Grant
UCLA Jonsson Comprehensive Cancer Center Grant
UCLA Institute for Molecular Medicine Seed Grant
UCLA Radiology Exploratory Research Grant