Small Animal Magnetic Resonance Imaging: Current Trends, Challenges and Perspectives for Pathological Imaging

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Outline

• Why image animals?
• MRI review
• Clinical versus animal imaging
  (A Day in the Life of a Lab Rat)
• Current trends
• On the horizon

Why Image Animals?

• Serial evaluation of preclinical disease models
  – Morphological (size, location)
  – Functional (blood flow, metabolism)
  – Cellular/Molecular
• Drug Screening
• Validation (characterization) of novel imaging methods
  – Biophysical basis of contrast mechanisms
Why Use MRI?

<table>
<thead>
<tr>
<th>Technique</th>
<th>Resolution</th>
<th>Depth</th>
<th>Time</th>
<th>Cost</th>
<th>Uses (animals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>10-100 µm</td>
<td>No limit</td>
<td>Min-Hrs</td>
<td>$$$</td>
<td>High contrast, physiology, cell tracking</td>
</tr>
<tr>
<td>CT</td>
<td>50 µm</td>
<td>No limit</td>
<td>Min</td>
<td>$$</td>
<td>Lung/Bone tumor Imaging</td>
</tr>
<tr>
<td>PET/SPECT</td>
<td>1 - 2 mm</td>
<td>No limit</td>
<td>Min</td>
<td>$$-$$</td>
<td>Metabolism of molecules/probes</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>50 µm</td>
<td>mm</td>
<td>Min</td>
<td>$$$</td>
<td>Vascular, Gross Morphology</td>
</tr>
<tr>
<td>Optical</td>
<td>1 - 2 mm</td>
<td>cm</td>
<td>Sec-Min</td>
<td>$$</td>
<td>Molecular, gene expression</td>
</tr>
</tbody>
</table>


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Cancer Imaging at VUIIS

MicroCT   Bioluminescence
Doppler US Fluorescence
MCES      MRI
MRA

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Imaging Across Scales

1) tumor size
2) tumor morphology
3) vascularity
4) cell proliferation
5) cell density
6) apoptosis
7) cell surface receptors
8) extracellular milieu

anatomical/physiological
cellular
molecular

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Basis of NMR

Hydrogen nuclei are small magnets. Normally they point in all different directions.

MRI Review

Magnetization

Precession

Relaxation to Equilibrium

Localization

Disturb with RF energy
Transverse and Longitudinal Magnetization

Net Magnetization: \( B_0 \)

Transverse Magnetization: \( M_T \)

Longitudinal Magnetization: \( M_Z \)

\[ T_1 \]

\[ T_2 \]

Relaxation Contrast

Different tissues have different \( T_1 \) and \( T_2 \) values

\[ T_1 \text{ Contrast} \]

Different weighting, different contrast

Diagrams of MRI images showing different tissue contrast.
Other Ways to Generate Contrast

• Alter T₁ and T₂ with paramagnetic contrast agents
  – Non-Targeted (permeability, blood flow)
  – Targeted (cellular and molecular imaging)
• Diffusion weighting
• Flow contrast
• Susceptibility weighting
• ... 

Clinical vs. Animal MRI SNR

• Resolution (↑Resolution ↓SNR)
  – Human ~ 100 kg: 10 mm³ (1 x 1 x 10 mm)
  – Rat ~ 300 g: .03 mm³ (310 x 310 x 310 μm)
  – Mouse ~ 25g: .0025 mm³ (165 x 165 x 165 μm)
• Imaging time
  – To maintain SNR: t α 1 / x²
• Magnetic field strength (↑T ↑SNR)
  – Clinical (1.5T - 3T)
  – Animal (1.5T - 11.7T)
• RF coil (↓Size, better coupling, ↑SNR)


Clinical vs. Animal MRI (2)

Practical Aspects (or my soap box)

• Commercially available animal MRI systems come with very basic software packages
• Typically poor QC and QA
• Necessitates a dedicated MRI physicist/programmer/engineer for pulse programming, software debugging and hardware development. (need a job?)
  VUIIS: 2 MRI physicists and 1 engineer for 4 dedicated animal MRI systems
• Hardware → clinic to lab
Data Issues

- Processing/Storing three-dimensional volumetric datasets (multi-modal and multi-parametric) is challenging.
  - 1 animal / 1 session ~ 1 - 5 GB
- Quantitative metrics, image fusion
- Screening, High throughput studies?
- Automation

Animal Handling

Day 0: Animals Delivered
Days 1-7: Animal acclimation
Day 8: Tumor Inoculation
Day 13: Catheters implanted
Days 14-35: Imaging Studies
Days 14-35: Treatment Application

Imaging Issues (2)

- Tune/Matching
- Shimming
- Respiratory / Cardiac Gating
  - Human RR ~ 20 breaths / minute
  - Mouse RR ~ 160 breaths / minute
- Human HR ~ 72 beats / minute
- Mouse HR ~ 632 beats / minute
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Current Trends

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- anatomical/physiological
  DCE-MRI, BOLD-MRI, ASL,
- cellular
  Diffusion, Spectroscopy
- molecular

Anatomical Localization/Size

• Rat glioma model
• Anti-angiogenic therapy
• T_1-Weighted Images after Gd-DTPA injection

Vascular Properties: DCE / DSC MRI

Interaction

Direct ($T_1$)

- Increase MRI Signal
- Dynamic Contrast Enhanced (DCE) MRI

Field ($T_2, T_2^*$)

- Decrease MRI Signal
- Dynamic Susceptibility Contrast (DSC) MRI

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DCE-MRI: Physiological Parameters

Physiological parameters that influence the temporal distribution of this contrast agent:

- Blood volume: $BV$ (units: $ml \cdot g^{-1}$)
- Extravascular extracellular (EES) volume fraction: $v_e$
- Vascular permeability: $P \cdot S$ (units: $ml \cdot g^{-1} \cdot min^{-1}$)
- Blood flow: $F$ (units: $ml \cdot g^{-1} \cdot min^{-1}$)

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Quantitative Analysis

Using a Compartmental Model

Knowns:
- $C_p$, $C_t$

Unknowns:
- $K_{trans}$, $v_e$

Note:
$K_{trans}$ related to $F$ and $PS$
Physiological parameters that influence the temporal distribution of this contrast agent:

- **blood volume** \( BV \) (units: \( ml \cdot g^{-1} \))
- **blood flow** \( F \) (units: \( ml \cdot g^{-1} \cdot min^{-1} \))
- **transit times** (sec)
DSC MRI: Preclinical Studies


BOLD MRI

- Blood oxygen level-dependent MRI
- MRI signal intensity reflects oxygenation status of hemoglobin
  - deoxyhemoglobin (Fe²⁺) is in a paramagnetic high spin state
  - Affects $R_2^{*}$ ($1/T_2^*$) transverse relaxation rates of water in blood and in the tissue surrounding the blood vessels
  - Potentially useful for predicting response to oxygen enhancing therapeutics (e.g. changes in hypoxic fraction or responsiveness to radiation treatment)

BOLD MRI

- Compared BOLD and radiation response in GH3 and RIF-1 tumor models while animals breathed air or carbogen

L.M. Rodrigues, JMRI 2004
Validation of CR-BOLD Contrast

![Graph showing ΔOXYGEN at 15% for different inhaled gas percentages.]

Arterial Spin Labeling

*Used to quantify tissue perfusion*
1. Acquire a “control image”
2. Tag Inflowing blood using selective RF pulse
3. Acquire the “tag image”

![Images of brain sections showing CBF.]

Image source: http://www.umich.edu/~fmri/asl.html

Rodent ASL Issues

- Human studies typically employ a single coil for labeling and imaging
- Difficult in rats/mice because labeling and imaging plane are in close proximity
  - RF irradiation for labeling can saturate the magnetization of macromolecules within the imaging plane (*magnetization transfer*)
  - Results in loss of water signal intensity

![Diagram showing labeling coil, detection coil, and labeling plane.]
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- cellular
  - Diffusion, Spectroscopy
- molecular

Diffusion

- B. Ross, Mol Can Ther, 2003
Spectroscopy

- Non-invasive assessment of tissue specific metabolites
- Lactate - evidence of increased glycolysis
- Choline - shown to be useful for malignant diagnosis, treatment planning and monitoring treatment response

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Spectroscopy

Matsumoto, J Clin Invest, 2008
Hot Topics

• Sodium Imaging
• pH Imaging
• Cell Tracking
• Molecular Imaging

$^{23}$Na MR Imaging

• Cell division and the acidic extracellular microenvironment of tumors cells are associated with an increase in intracellular $^{23}$Na concentration.

VD Schepkin, NMR in Medicine, 2006
Na MR Imaging

- Cell division and the acidic extracellular microenvironment of tumor cells are associated with an increase in intracellular Na concentration.

VD Schepkin, NMR in Medicine, 2006

pH Imaging

- Development of pH sensitive MRI contrast agents is a highly active area of research.
- Two strategies
  - Act as a T1 agent (Gd-based)
  - Directly image the agent using spectroscopy

ML Garcia-Martin, Cancer Research, 2001

Imaging

- pH sensitive MRI is a highly active area
• Development of pH sensitive MRI contrast agents is a highly active area of research.

• Two strategies:
  – Act as a T1 agent (Gd-based)
  – Directly image the agent using spectroscopy

Z. Bhujwalla, NMR in Biomedicine, 2002

Cell Tracking (1)

• Bone marrow derived neural precursor cells incorporate into growing tumor vessels.
• Can be labeled with MRI-visible iron oxide nanoparticles and injected systemically
• Study - Image 10 days after injection of labeled cells

S. Anderson, Blood 2005
Cell Tracking (2)

- Neural precursor cells also colocalize within Multiple Sclerosis lesions.
- Can be labeled with MRI-visible iron oxide nanoparticles and injected systemically
- Study - Image 24 hours after injection of labeled cells

L. Pololi, Stem Cells 2007

Cell Tracking (2)

L. Pololi, Stem Cells 2007

$\alpha_\nu\beta_3$ Integrin Imaging

- Angiogenesis depends on adhesive interactions of endothelial cells
- $\alpha_\nu\beta_3$ is an important adhesion receptor integrin and has been imaged by many modalities
- Study: Compared non-targeted and targeted Gd-loaded liposomes

DA Sipkins, Nature Medicine, 1998
Integrin Imaging

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Her-2/neu Imaging

- The HER-2/neu receptor is an important target for tumor prognosis and therapy
- It is overexpressed in approximately 25% of human breast cancers
- HER-2/neu expression correlates with poor prognosis for breast and other forms of human cancer

D. Artemov, Cancer Research 2003
Her-2/neu Imaging

- The HER-2/neu receptor is an important target for tumor prognosis and therapy.

D. Artemov, Cancer Research 2003

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Conclusions

- Animal MRI Advantages: High contrast, sensitive to many physiological and biochemical tissue characteristics
- Animal MRI Disadvantages: Costly, time consuming, requires substantial infrastructure
- Derived metrics useful for disease characterization, treatment planning and monitoring
- Serves as a screening process for clinically relevant tools
Acknowledgements

- Tom Yankeelov
- Mark Does***
- Chris Wargo
- Daniel Colvi
- Noor Tantaway

*** Hates that I exported his fancy and neat Keynote slides into Powerpoint