Mouse Imaging with Whole-Body MRI Scanners

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Abstract

Magnetic Resonance Imaging has been used in clinical applications for several decades. It offers a physician excellent anatomic detail and tissue characterization. Within the past decade, advances in MRI allowed us to image with a sub-millimetre in-plane resolution. Achieving such reduction in voxel volume require novel technological developments in every aspect of the MRI acquisition process: RF and gradient hardware and pulse sequence software.

At the same time there is growing interest in Magnetic Resonance Microscopy studies of small animal models of human disease. In general MR microscopy studies can be done exclusively on a specialized imager equipped with a small bore gradient coil.

We have developed new techniques for inserting a custom designed and built, high-strength gradient coil into an existing clinical MR imager. Such inserts can produce strong gradient fields that lead to maximum spatial resolution and excellent signal sensitivity. We describe the interfacing and calibration methods that we developed for our custom inserts in both 1.5T and 3T General Electric MR scanners. We show that all tests have met the specifications of the clinical gradient coil. The implementation of our method allow for switching between clinical and research modes without having to purchase and maintain another MR system.
Introduction

A Magnetic Resonance Imager uses a combination of a static magnetic field, local variations of this magnetic field (magnetic field gradients) and RF pulses, to generate signal and images. To accomplish these goals, a MRI system must include the following components:

- Magnet for generating the static field
- Magnetic field gradient system
- RF amplifier and RF transmit coil for production of pulses to excite the nuclei.
- RF receive coil and one or more preamplifiers to detect re-emitted signals from the nuclei
- Signal acquisition system

Commercial whole body magnets are available in field strengths ranging from low field (<0.5T) to high field (>3T). By comparison, the earth’s magnetic field varies between 20 and 70 µT. In addition to magnetic field strength, magnetic field homogeneity is an important parameter in the magnet system. Optimal field homogeneity is crucial to generating images free from distortion and with the maximum possible signal-to-noise ratio.

For the high range of magnetic field strengths, superconductive magnets are used, which have magnetic coil windings cooled to the temperature of liquid helium.

Magnetic field gradient systems consist of a gradient amplifier and gradient coils. The gradient coils produce three mutually orthogonal fields, which add to or subtract from the static magnetic field, permitting the possibility of encoding spatial information from the nuclei within an imaged tissue. The electrical currents pulsed through these gradients coils are in the range of several hundred Amperes. Because these gradient coils sit in the strong static field produced by the main magnet, large mechanical forces act on the gradient coil and mechanical supports, producing the acoustic noise characteristic of MR imaging.

Typical clinical whole-body MRI scanners are shown in Fig.1 and Fig.2. Scanners similar to these are available to many researchers around the world.
Development of High-Strength Gradient Hardware

There is great interest in the use of MRI for the non-destructive study of specimens and small animal models of human disease. This has led to the development of the field of magnetic resonance microscopy (MRM), which is the use of MRI for making images at spatial resolution of 100µm or better. Continuing technological advances in MRM and a focus on ex vivo specimen imaging have led to an emphasis on “MR histology” as a new tool for the pathologist. These high-resolution techniques permit a non-destructive evaluation of tissue, both in vivo and ex vivo. The requirement for very high spatial resolution places extreme demands on the MR gradient hardware, most often exceeding the gradient coil capabilities of existing clinical MR scanners. So even though the rest of the clinical MR system may be very suited to small animal and specimen imaging, including main magnet and RF / data acquisition systems, the gradient system is the dominant limiting factor for using whole-body MRI systems for MRM and MR histology.

Typically, dedicated small animal MR imagers with high gradient field strengths and optimised bore sizes are utilised to achieve maximal image quality and spatial resolution. Unfortunately, many investigators do not have access to such facilities and, therefore, clinical scanners are often used for small animal studies. However as mentioned above, these MRM studies being limited by suboptimal spatial resolution.

Our group has developed new tools for the design and implementation of custom-built high-strength gradient coil inserts into clinical MR scanners. Such inserts have been shown to produce an order of magnitude stronger gradient fields than those provided by the whole-body gradient system, and in a strength and slew rate range suitable for high quality MRM and MR histology.

Scaling Law

To collect in-vivo data in a 30-g mouse using an imager designed for 70-kg human, the field-of-view (FOV) needs to be scaled down by a factor of approximately 10 [1]. Given constant gradient power and coil inductance, a scaling law for gradient coil radius reduction versus FOV reduction can be derived as follows:

\[ \frac{a}{a_0} = \frac{1}{r^{0.4}} \]

\( a \) – insert coil radius
\( a_0 \) – clinical coil radius
\( r \) – FOV reduction factor

A typical clinical whole-body gradient coil has minimum inner radius of 30cm. The above scaling law tells us that the maximum coil radius for factor-of-10 FOV reduction, typical for mouse imaging, is 12cm.

Gradient Design Tools

Our group has developed gradient design tools, such as the Constrained Current Minimum Inductance Target Field method [2]. These tools have been refined and utilized for the design of very high strength (up to 2000mT/m), multi-layer gradient coils suitable for small animal studies. We have also worked on the practical construction and interfacing of a number of high performance gradient inserts into whole-body clinical MRI systems for principally small animal studies.

2000mT/m Mouse Gradient Coil

Early in our program development, we were interested in producing a very high strength coil capable of handling a mouse-size object. Using gradient scaling theory, we determined that a typical whole body coil design of radius 30cm, producing 20mT/m (I=200A) with L=1200mH could simply be scaled down to a radius of 3cm and produce 2000mT/m with L=120mH; however, the wire density would increase by ten times and the operating temperature by one thousand times.

For this reason we decided to use a multi-layer design, with more than one layer of wiring per axis. The optimal five-layer configuration for this application was chosen to be a layer ordering of XYZYX. Although several kW of power per axis may be dissipated during extreme applications, this can be handled with a forced water cooling system [3].

Fig. 3. High performance mouse gradient coil (15cm OD, 5 cm ID, 1cm side-wall aperture)
**600mT/m Mouse/Rat/Rabbit Gradient Coil**

Several designs of three-layer gradient coils with between 9 and 12 cm bore radius have been designed and built in our lab to explore the gradient size range that would handle mouse, rat and up to rabbit-size objects. These coil have been designed to produce up to 600mT/m gradient strength at 320A current, which was approximately 15 times stronger than the maximum strength possible on a typical clinical MR system.

These gradient coils have been designed in such a way that their effective inductance matched that of the whole-body coil inductance (1000-1400µH). This has made the job of rapid switch-over and matching of gradient driver to gradient coil easier.

Our coils have all been constructed with rectangular compacted litz wire and encased in thermally conductive epoxy resin. Thin walled copper or plastic tubing has been embedded in the epoxy-filled spaces between each layer to provide forced water cooling.

Figs. 4, 5 and 6 show details of construction of this class of insertable gradient coil.

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**Fig. 4.** Wire pattern of the 600mT/m gradient coil (left: z-axis, middle, right: transverse axes)

**Fig. 5.** Cooling channels placed on and between wire layers of 600mT/m gradient coil.

**Fig. 6.** Completed 600mT/m gradient assemblies (left: front view, right: rear view showing electrical and cooling connections).
Interfacing Methods

An interfacing mechanism was developed to place our insert gradient coils into GE clinical MR scanners. Cable switching mechanisms were designed and built to bypass the built-in system gradient coils and to connect the custom insert gradient coil to the clinical gradient drivers. Fig 7 shows the schematic diagram for this switching mechanism.

![Gradient coil switch mechanism](image)

Fig. 7. Gradient coil switch mechanism

We have developed simple but safe procedures for easy transition between clinical configuration with the whole body gradient coil and research configuration with a small bore custom gradient insert. Fig. 8 shows the procedure of sliding the insert gradient into position in the bore of the clinical MRI system. Attachment of insert gradient cables to a custom cable interface box occurs at the back of the magnet.

![Gradient insert being placed in the bore of clinical GE MRI scanner](image)

Fig. 8. Gradient insert being placed in the bore of clinical GE MRI scanner.

Configuration files were created to contain tuning/calibration parameters specific to the insert coil. Simple-to-use Unix scripts were created and validated for rapid switching between the insert-customized and the clinical configuration files. We conducted hardware/imaging calibrations and functional checks using standard service tools provided by GE Healthcare.

Results: Installation and Calibration

The time required for mechanical and software installation / switching of the insert into the clinical scanner by one person is typically 10 minutes. All calibration and performance results met the specifications set by the vendor for the clinical whole-body gradient coil system.

We have encountered some difficulties achieving optimal gradient driver tuning. Since our gradient coil are fabricated with litz wire, their resistance vs. frequency characteristics are different than that of typical whole-body gradient coils. We developed a simple manual tuning procedure to overcome this problem, and more recently have developed more sophisticated tools for gradient driver parameter optimization [4].

Eddy current compensation was done using the vendor’s recommended procedure, using the standard service tools provided for this task, and results are shown in Table 1.

<table>
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<th>Time (ms)</th>
<th>Linear Long Constants</th>
<th>B0 Time Constants</th>
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</thead>
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<td></td>
<td>Max. Deviation(%)</td>
<td>Spec (%)</td>
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<td>-0.008</td>
<td>&lt;0.09</td>
</tr>
<tr>
<td>10.0-100.0</td>
<td>-0.007</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>100.0-2000.0</td>
<td>-0.004</td>
<td>&lt;0.018</td>
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Results: Imaging

MRI was conducted on a 3T scanner (GE Signa HD) with the addition of an insertable gradient coil with inner diameter of 17.5cm and operated at maximum gradient strength of 500mT/m and slew rate 1500T/m/s. A custom-built solenoidal RF coil (2cm diameter x 2cm length) designed for mouse head imaging was used. For in vivo imaging, the mice were anaesthetized using isoflurane and body temperature was maintained by circulating warm water. Ex vivo scanning was performed on fixed heads bathed in Fluorinert™ (3M) with the skull intact.

A balanced steady-state free precessing (bSSFP) sequence was used for mouse brain imaging, as this sequence has been shown by our group to be highly SNR-efficient as well as demonstrated strong sensitivity for iron detection, a major advantage for conducting cell tracking and other forms of cellular MRI.

The conventional bSSFP phase cycling regime available on the GE scanner, consisting of 2 phase cycles and maximum intensity projection (MIP) reconstruction, was
compared to approaches using multiple phase cycles (up to 16) with both MIP and sum-of-squares (SOS) reconstruction in terms of band reduction and SNR efficiency. The resolution was 100μm isotropic in all cases and the NEX and FOV were adjusted to keep the scan time relatively constant to allow visual interpretation.

A dual-contrast bSSFP protocol was developed for imaging ex vivo iron-loaded tumours. The scanning parameters for this dual-contrast protocol were 1) for tumour visualization: 100μm isotropic resolution, 40° flip angle, TE/TR = 3ms/6ms, 21kHz bandwidth, and 16 phase cycles for a scan time of 30 mins, and 2) for sensitive iron-loaded cell detection: 66μm x 66μm x 100μm resolution, 20° flip angle, TE/TR = 11ms/22ms, 15kHz bandwidth, and 10 phase cycles for a scan time of 127 mins. The two flip angles were chosen based on calculations of white matter-gray matter contrast at 3T using T1 and T2 value estimates to calculate bSSFP signal intensity over a range of flip angle. With a flip angle of 20°, white matter-gray matter contrast is minimal, whereas with a flip angle of 40°, maximal white matter-gray matter contrast is obtained. Development of this protocol was conducted ex vivo using mouse heads, 18 days post tumour cell injection and included tumours containing high or low level iron-loaded cells in the proportions mentioned above. The acquisition times were chosen to obtain an SNR of 50 for both scans.

Examples of the images achieved using this dual-contrast bSSFP protocol are shown in Fig. 11.

![Fig. 11. Dual-contrast bSSFP protocol for tumour visualization and high sensitivity to iron contrast. (a) and (b) unlabelled tumour 18 days post cell injection. (c) and (d) tumour containing 25% cells labelled with SiMag beads at 5pg Fe/cell 18 days post cell injection.](image)

These results show great potential for conducting very high resolution MRI and cell tracking in small animal models. Images with good contrast and SNR, for a small volume sample, can be acquired within an hour, even at field strengths as low as 1.5T. In addition, preclinical research results can be translated more easily to clinical research protocols, since a clinical MRI scanner is being used as the base imaging platform. Results achieved in our group and elsewhere show new opportunities for high-performance small animal imaging.

**Conclusion**

The results show the feasibility of inserting high-strength gradient coils into clinical scanners. The electrical and mechanical modifications to the scanner system are simple and cost effective. The system calibration can be done using the existing, vendor-supplied service tools. Successful calibration is important for maintaining high image quality (SNR, anatomical and biological accuracy, etc.). The results of this preliminary work convince us that high-strength gradient inserts will one day become powerful and commonly exploited tools for MR Microscopy research. The authors believe that in the nearest future custom-built gradient coils may be used as routinely as custom-built RF coils are used today.

**References**


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