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MRI susceptometry: Theory and robustness of an external phantom method for measuring bulk susceptibility from MRI field echo phase reconstruction maps applied to human liver iron overload

Holt, Randall William, Ph.D.

Case Western Reserve University, 1993

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MRI SUSCEPTOMETRY - THEORY AND ROBUSTNESS OF AN EXTERNAL PHANTOM METHOD FOR MEASURING BULK SUSCEPTIBILITY FROM MRI FIELD ECHO PHASE RECONSTRUCTION MAPS APPLIED TO HUMAN LIVER IRON OVERLOAD

by

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Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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August, 1993
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GRADUATE STUDIES

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(date 8/3/93)

*We also certify that written approval has been obtained for any proprietary material contained therein.
MRI SUSCEPTOMETRY - THEORY AND ROBUSTNESS OF AN EXTERNAL PHANTOM METHOD FOR MEASURING BULK SUSCEPTIBILITY FROM MRI FIELD ECHO PHASE RECONSTRUCTION MAPS APPLIED TO HUMAN LIVER IRON OVERLOAD

Abstract

by

RANDALL WILLIAM HOLT

A novel method for estimating the susceptibility of an object using the MRI field distortions in an external reference water bath next to the object is described. The field measurement is obtained using a MRI phase reconstruction from a Gradient Echo scan. A field model of an arbitrary object in a static magnetic field is discretely calculated using a Fourier convolution method from geometry determined from the magnitude reconstruction. Least squares estimation then yields the susceptibility of the object. Required (and proven) assumptions include; superposition, object homogeneity, negligible higher order field terms, field model accuracy, geometrical model accuracy and correlation of MRI FE phase to field distortion. MRI susceptometry estimation of in vitro phantoms yielded susceptibility estimates which correlated well with known values ($r > 0.9975$). This external reference bath MRI susceptometry method could be used to quantitate iron levels in iron overload patients.

The errors which may occur in MRI susceptometry include field noise, and model errors including; outline error, outline shift, compartment inhomogeneity, volume error and unmodeled sources of field distortion. Ultimately, the model errors can all be treated as unmodeled sources. Simulations and in vitro studies
indicate that expected levels of field noise will not reduce the efficacy of the susceptibility estimations. However, unmodeled sources with relative strengths on the order of an unmodeled lung to a modeled liver of normal iron levels will reduce the efficacy of the fit (for a 22 patient \textit{in vivo} experiment, \( r < 0.6 \)). Filter application will alter the noise model, and improve the fit. Additionally, choosing the data set which lies closest to the organ of interest (i.e. the liver) will also improve the fit. With filtering and data set restriction, the estimates of the \textit{in vivo} patient data were improved (\( r > 0.85 \)). However, correlation of only the normal and low-level iron overload patients was not improved (\( r < 0.5 \)).
DEDICATION

To Linnéa Alice Sheppard,

With love and friendship and a little humor.
PREFACE

While this thesis was completed for the doctorate in Biomedical Engineering at Case Western Reserve University, the work originated at the Department of Radiology of MetroHealth Hospital in Cleveland, Ohio. The work evolved over a period of four years, and was originally intended as a method for linking the liver iron data (which was readily available through this hospital) to MRI. With time and experimentation, it became clear that matching the T2 relaxation to the liver iron was a dead end, and other approaches were attempted. The most successful method transformed into this thesis, a novel method for measuring susceptibility using MRI.

This work assumes a reasonable depth of knowledge of MRI, electromagnetic field theory, and system and filter applications theory. Some physiology is helpful, but not necessary.

The casual reader may wish to read chapters 1-4, and 9 and 10. The reader interested in the in vivo applications is also directed to chapter 8. The remaining chapters - the hard parts - are involved in the theory and robustness of the method.
ACKNOWLEDGEMENTS

"A man's friends are his magnetisms."
Emerson, Conduct of Life: Fate.

This is the place where one is expected to get maudlin or wax philosophical. Not me. Well, maybe a little. I'm still not sure what drove me to produce this pile of paper or seek a sheepskin in science. But, I do want to take a moment and thank all of the people who have made my rites of passage either easier or more interesting, or both.

First and foremost, my wife Linnéa is the one most deserving of thanks and praise. The many nights and weekends that she spent alone are a monument to her love and support. Without question, my life has changed for the better because of you. Through good and bad times, easy and hard, you never gave up, you just found a way to cope with me, and found a way to make it easier for me.

To my parents, Don and Karen Holt, I would like to thank for always believing in me, for never doubting that I would someday reach this goal. To my sibs, Nan, Jeff, Rame, Steph, Bry, Sue, and Marie, I'd like to thank you for the support, the love, and the prayers. And for the occasionally needed dose of hubris reduction - you are the ones who really know me. To my grandmother, Violet Passey, one of the most intelligent people I have ever met, for instilling in me, when very young, the desire to reach high and to make the most of my abilities.

To my research advisor, Pedro Diaz, I'd like to thank for the support, both
financial and intellectual that I have received. As you have often told me, "You can have it good, cheap or fast - pick two." Sometimes you only get to pick one.

I'd like to thank all of the many teachers and mentors who have made their life's work the cultivating of others. Especially, to Ray Gilbert, my high school calculus teacher, who, to the detriment of students everywhere - no longer teaches. I want you to know that you did make a difference, and the math lessons and the lessons in life have always been with me. Also, to H. Steven Wiley, who gave me a love for science and gave me the inspiration to reach for the doctorate, thank you. I'd also like to thank C. Mont Mahoney for imbuing in me survival skills from which I have benefitted in both the outdoor wilderness and in the jungles of academia.

To my "brothers of science and home repair", Drs. Jeff Duerk, Greg Hurst, Lonnie Simonetti, Hua Jianmin and Colin Griffiths, I'd like to extend an exceptionally warm gesture of thanks. The many hours we've spent arguing everything from science to the cinema, from drywall repair to sporting events to world politics were some of the most enjoyable times of my life. A special thanks is due to Jeff, without whom I'd never have finished, for his academic advice, zymurgical critique and more. I'd also like to thank Greg for the invaluable lessons about transverse and longitudinal relaxation, spin space and friendship. A special thanks to Jianmin, for the many discussions on science and the free-market system. Also to Colin, who kept the machines running, from the MRI to
the Evinrude. And finally, to Lonnie Simonetti, who kept me company during the late nights and long weekends, and put up with my imitation of the Annoying Man, always remember that I still hold the record for best control.

I'd also like to thank Errol Bellon and the Edison Biotechnology Center for financial support over the years. To all the wonderful people at the MetroHealth Dept. of Radiology, and especially the MRI group; Beccie, Gigi, Eileen, Ed, Cindy, Ed, Holly, Jan, Helen, Emma, Zhenghong, Walt, Nino, Debbie, Carol and Sarah. Thank you.

To my committee members, Drs. Rudy, Brittenham, Thomas, Duerk and Diaz, who had to suffer through many interminably long meetings, and whose example and exhortations inspired me to work harder and to finish well, thank you. Also, I'd like to thank Dr. Gerry Saidel and the entire CWRU Dept. of Biomedical Engineering, for their guidance and teaching. I'd also like to thank my first friends in Cleveland, my biomed peers, Frank Dexter and Marc Penn, who started with me, and beat me out of here by years.

To my former undergrad roommates and friends, Raj Sharma and Wade Peterson, who bore the brunt of my late night ramblings, thanks for everything. The years at the U, and the experiences we shared will always be a part of me. Hard to believe what young idiots we once were. Now we’re just older fools. To my graduate roommate and friend, Mike Romero, words alone cannot express the
bond I feel for you, and for the great times we have had together. You alone understand the trials and tribulations that a degree from Case can be made to require.

To Jeff Friedman, and his mother Dorothy, who took me in and were always there, I’ll always have a warm spot in my heart for you. To my teacher of the physical and spiritual, Sa Bom Nim Ronald Cechner, Tang Soo! To my Cleveland in-laws, Stan, Carol, Laurel, Leslie and Lucia Sheppard, Mike McSweeney, and Mike Rohde, many thanks for the good times, moral support and excellent company.

Finally, and again, I’d like to thank Linnéa. I’m finally done, and without your help it wouldn’t have happened. By the way, dear, I’m applying to medical school. Just kidding.
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Chapter I - Introduction to MRI Susceptibility and Liver Iron Overload

1.1 Introduction

Iron in the human body includes (i) transport iron in the plasma and extracellular fluid, (ii) functional iron within hemoglobin, myoglobin, heme and non-heme enzymes, and (iii) storage iron sequestered in ferritin and hemosiderin molecules found in virtually all tissues, but primarily localized in hepatocytes, liver macrophages, bone marrow, spleen and muscle (Brittenham, 1992; Harrison, 1974). The amount of iron in the body is normally regulated by controlling uptake of iron through the duodenal mucosa. Various clinical conditions are known to alter the uptake and accumulation of iron. Hereditary (HLA-linked) hemochromatosis is an iron overload syndrome due to a genetic abnormality in the regulation of iron uptake. Chronic blood transfusion, needed in the treatment of refractory anemias, such as beta thalassemia major and other disorders, bypasses the normal iron regulatory pathway and may produce iron overload. Left untreated, iron overload may result in organ damage and death (Powell, 1985). Measurement of increased body iron is important for the clinical management of iron overload.

Currently, the reference method for liver iron measurement in patients with iron overload involves direct analysis of tissue obtained by surgical liver biopsy (Powell, 1985). A variety of other methods which also provide information on iron levels, including serum iron and ferritin assay, chelation tests, computed tomography and dual energy computed tomography, and T2- relaxation using Magnetic Resonance Imaging (MRI) have met with limited success (Brittenham, 1988; Kaltwasser, 1989).
The development of a technique which utilizes a SQUID (Superconducting QUantum Interference Device) magnetometer to perform an external measurement of the internal magnetic susceptibility in an organ of interest has provided an additional tool for the measurement of hepatic iron stores. This technique maps SQUID-measured susceptibility values to hepatic iron concentration using experimentally determined calibration/conversion tables (Brittendenham, 1982; Paulson, 1989). While, this technique has the advantages of being non-invasive and accurate in the measurement of increased hepatic iron stores ($r > 0.95$), the limited availability of the SQUID susceptometer restricts its clinical use. Regardless, none of the other non-invasive measurement techniques mentioned above have resulted in measurements of hepatic iron concentration values which correlate better with those obtained by analysis of tissue obtained using surgical liver biopsy (Powell, 1985).

This thesis proposes a new method for MRI measurement of liver iron levels utilizing a MRI technique. The method estimates the distortion of the Zeeman field of an MR imaging system from a phase map obtained from a field distortion sensitive gradient echo pulse sequence. The field distortion data is then analyzed by performing a linear least squares regression of susceptibility-induced variations predicted from a two compartment model (liver and torso) calculated using a discrete Fourier convolution method. Results of the least squares regression are susceptibility values for the modeled liver and torso. These susceptibility values are significantly correlated with measurements of hepatic iron by magnetic susceptibility studies using the SQUID device as well as with chemical analysis of hepatic tissues obtained by biopsy.
1.2 Tissue Iron

1.2.1 Iron Metabolism and Storage

The iron uptake pathway begins with dietary iron which passes through the brush border in the small intestine, and is then bound to transferrin and distributed throughout the body in the plasma and extracellular fluid (Brittenham, 1992). Iron is delivered by plasma transferrin to the erythroid marrow, where it is incorporated into hemoglobin within red blood cells, the main pathway of iron utilization in normal individuals. Transferrin-bound iron is also transported to all cells in the body. Iron absorbed in excess of the functional needs of the body is incorporated into a storage molecule, ferritin, and eventually into a long term storage form, hemosiderin, principally within hepatocytes and macrophages of the liver, bone marrow and spleen. A small amount of ferritin is also released into the plasma. Eventually, senescent red blood cells are consumed by macrophages which then release catabolized iron to transferrin in the blood. A minor fraction of iron is lost daily via cell sloughing, intestinal and urinary losses, and blood loss and menstruation. Normally, the amount of iron absorbed in the gut is equivalent to the amount which is lost (Brittenham, 1992).

The distribution of iron in the normal human is approximately 80% functional (heme and non-heme proteins) iron and 20% storage iron (ferritin and hemosiderin), with less than 0.5% transport iron available (Powell, 1985). Storage iron exists in virtually all tissues in the body, with the largest portion of the storage iron (approximately one-third) in the liver (ibid). Normal levels of storage iron in the liver range...
from 50-500 ug Fe/mg tissue (wet weight) (ibid). When iron stores are within the normal range, approximately twice as much iron is present in ferritin as in hemosiderin.

I.2.B Iron Overload

Clinical conditions associated with an increase in the body iron are referred to as iron overload syndromes. Patients with iron overload include those with hereditary hemochromatosis, where the body iron increases due to a genetic abnormality affecting the regulation of iron uptake. The number of these patients with the homozygous form of this recessive disorder are estimated at 0.5% of the population in the U.S., or about 1 million patients, of whom about 50,000 are currently being treated (Powell, 1985). Another group of patients consists of those requiring chronic transfusion, such as beta thalassemia major and other refractory anemias. The iron burden in these patients results from repeated blood transfusions required by the disease. These patients number around 50,000 in the U.S. (Gorduek, 1987). Other forms of iron overload include those associated with excess intake of dietary iron, chronic liver disease, iron-loading anemias with increased iron absorption and a number of other rare conditions (Brittenham, 1992).

Storage iron levels are increased in overload syndromes (Powell, 1985). The concentration of plasma ferritin and plasma transferrin-bound iron usually increase non-linearly with overload, reaching plateau levels at early stages of iron overload (Kaltwasser, 1989). Excess storage iron is eventually deposited in all organs, resulting in eventual organ damage, but a principal site of organ damage is the liver where
storage iron can reach concentrations of 20000 ug Fe/ml or more (Brittenham, 1992). In all forms of overload, storage iron is distributed in parenchymal cells of the liver, pancreas, heart and other organs, which is thought to be responsible for tissue damage or in macrophages, where the iron appears to be more innocuous (Kaltwasser, 1989).

1.2.C Diagnosis of Iron Overload

Liver biopsy is the most accurate means for measurement of iron status, as it provides information on both iron levels and cellular deposition of iron in parenchymal or in reticuloendothelial cells. Several other methods are available, but none provide the histologic information available from a biopsy. Measurement of serum transferrin saturation and serum ferritin levels has been proposed for wide spread screening for hereditary hemochromatosis (Edwards, 1993). Edwards suggests that serum transferrin saturation levels be measured, and if positive, be followed by serum ferritin measurement. If serum ferritin is elevated above normal, a liver biopsy would be indicated, followed by immediate treatment. If serum transferrin saturation was high, but serum ferritin was not, then semi-annual repetition of screening is suggested (ibid).

One disadvantage to screening using plasma ferritin, is that inflammation and disease will alter concentrations. Also, during the venesection treatment of hereditary hemochromatosis, serum ferritin and transferrin saturation levels do not always provide reliable estimates of iron stores. As repeated liver biopsy is relatively contraindicated because of risk, it is desirable to develop non-invasive methods for repeated quantitation of liver iron. A non-invasive method would also be useful following
screening procedures. Besides providing clinically useful information on total iron stores, it would be useful to have a non-invasive screening method to identify elevated body iron, prior to the onset of organ dysfunction which accompanies severe iron overload.

As mentioned earlier, SQUID susceptometry would provide a useful intermediate tool for screening and treatment of iron overload, but is limited in availability (currently only three clinical units exist worldwide). Another method, dual energy computed tomography, has shown some promise, but can be considered invasive because of radiation exposure, and is not yet proven to be quantitative. MRI measurements have also been investigated for use in tissue iron measurement. As a primary screening tool, MRI may not be suitable for populations, as cost factors inhibit its use (serum iron levels cost less than one-fifth that of a MRI scan). However, T2 relaxation studies using MRI have not proven accurate over all clinically relevant levels of liver iron (100 to 20000 ug Fe/ml) (Stark, 1985). Table 1-1 summarizes methods for assessment of body iron stores. The ideal method of MRI measurement would be capable of accurate quantitation over the entire range of iron overload. The proposed advantages, disadvantages and availability of this new method are listed in the last row of Table 1-1. This thesis focuses on a new method, utilizing MRI for measurements of the magnetic susceptibility of the liver.
Table 1-1. Advantages and Limitations of Measurements of Iron Stores

<table>
<thead>
<tr>
<th>Advantage/Feature</th>
<th>Biopsy</th>
<th>Plasma Ferritin</th>
<th>Saturation TF</th>
<th>CT</th>
<th>MRI T2</th>
<th>SQUID</th>
<th>MRI X</th>
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<td>Iron Range (μg Fe/ml)</td>
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<td>50</td>
<td>200</td>
<td>200</td>
<td>200</td>
<td>500</td>
<td>?</td>
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<tr>
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<td>20,000</td>
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<td>20,000</td>
<td>20,000</td>
<td>?</td>
</tr>
<tr>
<td>Accuracy</td>
<td>Reference Method</td>
<td>Varies w/ Disease</td>
<td>r &gt; 0.6</td>
<td>r &gt; 0.8</td>
<td>r &gt; 0.95</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Invasiveness</td>
<td>High Occ. Fatal</td>
<td>Low (Venipuncture)</td>
<td>MED (X-Rays)</td>
<td>NONE</td>
<td>NONE</td>
<td>NONE</td>
<td>NONE</td>
</tr>
<tr>
<td>Liver Damage Assessment</td>
<td>Excellent Detection</td>
<td>None</td>
<td>Low Detection</td>
<td>MILD DETECTION</td>
<td>NONE</td>
<td>LOW DETECTION</td>
<td></td>
</tr>
<tr>
<td>Availability</td>
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<td>All Hospitals</td>
<td>All Hospitals</td>
<td>&gt; 3000 Units</td>
<td>3 Units</td>
<td>&gt; 3000 Units</td>
<td></td>
</tr>
<tr>
<td>Approximate Cost</td>
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<td>$80</td>
<td>$300</td>
<td>$800</td>
<td>N/A</td>
<td>$800</td>
<td></td>
</tr>
</tbody>
</table>
1.3 MRI Susceptometry of Liver Iron

Objects placed in a magnetic field will distort that magnetic field (Jackson, 1961). The amount of distortion is a function of the geometry and differential susceptibility of the object. This field distortion is precisely what is measured by SQUID susceptometry, which is fit to an appropriate model (Farrell, 1980; Brittenham, 1982; Fischer, 1989). Assuming that field distortion can be measured in MRI, a similar method might be possible.

Field distortions in a MRI magnet arising from susceptibility effects have long been considered to be a nuisance. A large body of literature exists on the correction and elimination of these susceptibility artifacts (for an excellent and comprehensive review, see Haacke, 1988). Faul and Margosian introduced the concept that these artifacts could be used to make clinical assessments, predicting that phase information of the Gradient Field Echo (GFE) MRI measurement could be used to assess blood clots in cranial hemorrhage (Faul, 1984; Cox, 1986). The extension of this concept to measurements of liver iron makes use of MRI sensitivity to susceptibility artifacts.

This combination leads to the following hypothesis:
"Liver susceptibility can be estimated from MRI GFE phase information when appropriately fit to a field model based on two compartments consisting of the liver and torso."

In this thesis, a method is described for the estimation of liver iron with MRI. The presence of some object, such as the human torso, located inside the magnet of
an MRI system creates distortions in the otherwise homogeneous magnetic field. The level of these distortions can be derived from the phase of the MRI image. A GFE sequence is used to acquire the MR data, due to its inherent phase sensitivity. In the method proposed here, rather than measure iron effects directly in the liver, the effect of the entire iron loaded organ has on the magnetic field in a water bath adjacent to the patient is measured for a number of reasons which are elucidated in the thesis.

In order to estimate susceptibility values from the field distortions in the phase of the MRI signal, a field model must be developed. The field model used here is calculated with a Discrete Fourier Convolution Method which is based on the arbitrary geometry of each patient or object investigated. This geometry can be derived by segmentation of the modeled objects from the magnitude reconstruction of the same GFE data used to provide the phase map field data. The field model and the field data are then fit to obtain the susceptibility of the object under study.

This thesis first discusses the general physiology of the iron-loaded liver and its physical behavior in a magnetic field in Chapter II. Then, a detailed description of the methods used to acquire the MR data, the sensitivity of the method and its validity are presented in Chapter III. The overall algorithm, from MR data gathering and the development and computation of the geometric model and magnetic field model to the method used in performing the data fitting used in generating susceptibility values are detailed in Chapter IV. An in-depth look at the discrete method used to generate the field model is made in Chapter V. A theoretical description of noise and it’s effects on the estimation of susceptibility will be examined in Chapter VI. Potential
sources of experimental and computational error are examined using analytically simulated and experimentally acquired phantom data in order to determine their impact on the susceptibility estimates obtained using this method in Chapter VII. The final test of the hypothesis will be to apply the method to patients, using any information derived in the earlier sections, in Chapter VIII. Finally, an overview of results, conclusions and a summary are presented along with future directions in Chapter IX.

Three short appendices are also attached to provide more in depth information on specific techniques.
Chapter II - Liver Iron Stores Influences in MRI Physics

II.1 Introduction

In this chapter, the general physiology of hemochromatosis, where pertinent to MRI based measurement of the liver, will be discussed. The behavior of iron and iron sequestration as it applies to measurement in a magnetic field will be introduced. Previous attempts of correlating MRI T₂ values to liver iron have been made, and as the basic physics are not altered, it is prudent to investigate these methods for their inadequacies, prior to addressing the MRI susceptibility approach. In fact, it will be seen that the detrimental aspects of MRI T₂ measurement lead directly to the MRI susceptibility approach.

II.2 Ferritin and Hemosiderin Contribution to Liver Iron Stores

As discussed in section I.2, the storage iron in the liver increases with iron overload, and provides a clear diagnosis for overload progression. The storage iron is distributed in ferritin and hemosiderin molecules stockpiled in all organs for future need, with approximately 1/3 of all storage iron located in the liver. The ferritin molecule may exhibit compartment-like aspects, as the iron is sequestered inside the molecule, and is partially crystallized (Harrison, 1974). The ferritin molecule is about 25% crystalline iron by weight, or 2000 iron atoms per molecule, with a maximum of 4500 iron atoms per molecule (Harrison, 1974). At the end of the storage pathway is a long term iron storage molecule, hemosiderin, which may be
formed from the breakdown of ferritin and aggregation into granular form (Harrison, 1974). A histologically based study shows relatively even distribution of iron in the liver (Overmoyer, 1987).

II.3 Iron and MRI Relaxation
II.3.A Paramagnetic Spin-Spin Relaxation

The theory of the behavior of paramagnetic ions, such as Fe$^{3+}$ and Mn$^{2+}$ in solution, on the spin-lattice relaxation ($T_1$) and the spin-spin relaxation ($T_2$) of water molecules in a magnetic field was initially described in the 1950's (Solomon, 1955; Abragam, 1961). A relaxation rate refers to a time constant of the exponential decay of the alignment of a proton in a magnetic field (Bloch, 1946). The theory of paramagnetic spin behavior describes the spin energy exchange between like spins (proton-proton) and unlike spins (proton-paramagnetically relaxed proton) (Solomon, 1955). This theory indicates the presence of multiple relaxation times in solutions, especially the complex biological solutions of human tissue. Differing relaxation rates result from differing degrees of interaction of protons with a) themselves, and b) other ions in solution such as ferric ions (Abragam, 1961). The effective relaxation rate for multiple relaxation times is,

\[ \frac{1}{T_2} = \sum_{i=1}^{n} \frac{C_i}{T_{2,i}} \]  \hspace{1cm} [2.1]

where each relaxation rate would contribute according to the concentration, $C_i$, of each compartment $i$ that it comprised (Mansfield, 1980). Any sum of multiple components of relaxation rate will effectively reduce the relaxation time.
II.3.B Field Gradient Contributions to Relaxation

Field distortions and proton diffusion can also contribute to relaxation rates (Aragam, 1961). The effective $T_2$, which includes field inhomogeneity effects, is usually denoted $T_2^*$. In general, the contributions to the transverse relaxation by iron presence can be described by

$$\frac{1}{T_2^*} = \sum_{i=1}^{n} \frac{C_i}{T_{2,i}} + \gamma \Delta H + D \tau_c \gamma^2 G_z^2 T E^2 \tag{2.2}$$

In this relaxation model (Aragam, 1961), $T_2^*$ is the total relaxation rate of the proton, and $T_{2,i}$ is the relaxation rate of the i-th component, each of which is weighted by $C_i$. In the case of protons interacting with free iron in solution, this weight will be directly proportional to the concentration of the iron (Koenig, 1985). However, for iron-laden ferritin molecules, $C_i$ does not correspond well to the concentration of iron (Koenig, 1986). In the liver, multiple relaxation rates would be expected for water proton-water proton, water proton-ferric ion, water proton-protein proton, water proton-fat proton and many more species interactions. Field inhomogeneity, $\Delta H$, will also reduce $T_2^*$. The field inhomogeneity causes a dephasing as each proton nutates about the imposed magnetic field axis at different effective frequencies, given by the field inhomogeneity times the gyromagnetic ratio ($\gamma$), and is normally corrected for by use of a Spin Echo sequence (Mansfield, 1980). The final term in this model represents a diffusion based relaxivity term, where $D$ is the diffusivity of the proton, $\tau_c$ is a correlation time, $G_z$ is the z-direction gradient of the applied field (the only field component which applies as seen in Appendix A), and $TE$ is the echo time of the MRI sequence.
In addition to the concentration dependent relaxation $T_{2,i}$, the presence of crystalline ferritin and hemosiderin iron in the liver will further reduce the transverse relaxation rate of the liver. These small iron spheres have a magnetic susceptibility that is both paramagnetic and superparamagnetic (Koenig, 1986). The inclusion of these microspheres in tissue of differing susceptibility causes a local distortion in the otherwise nearly homogeneous static magnetic field (Ludeke, 1985; Gillis, 1987). Magnetostatic theory (Jackson, 1961; Edmonds, 1988) predicts the manner of these field distortions. The field inhomogeneity and gradients will be high near the ferritin and hemosiderin granules. Equation [2.2] predicts that $T_2^*$ will be reduced due to the effect of the field inhomogeneity, which may result from background field inhomogeneity as well as iron particle induced field distortion. This term can be quite large in the presence of the particulate iron found in the ferritin and hemosiderin complexes (Majumdar, 1988). This field inhomogeneity will also contribute to the diffusion based relaxation.

II.4 MRI $T_2^*$ Method of Liver Iron Estimation

Based on the relaxation behavior predicted in [2.2], determination of iron levels in vivo would seem to be possible by quantitation of $T_2^*$, and many researchers have made the attempt (Stark, 1985; Hernandez, 1988; Murphy, 1986; Gottshalk, 1991; Gomori, 1988). The MRI $T_2^*$ method acquires image data in the liver at multiple points of the magnetic decay curve and fits these points to an exponential decay to obtain the relaxation rate (Stark, 1985). A Spin-Echo sequence is used, which is known to correct for the field inhomogeneity term in [2.2] (Mansfield, 1980).
In practice, iron quantitation using MRI $T_2^*$ measurement shows high correlation ($r > 0.94$) with biopsy determined iron levels than when measured on patients with normal to low levels (4 x normal) of liver iron (Gottshalk, 1991). However, this correlation is much lower ($r < 0.50$) for concentrations over all physiological ranges (Gottshalk, 1991; Hernandez, 1988; Stark, 1985; Murphy, 1986). As predicted by [2.2], the $T_2^*$ relaxation rate of the excited spins shows an inverse dependence on the amount of iron in the liver, at low levels of liver iron. The diffusion term in [2.2], which is non-linear, may be one reason for this failure, but higher order polynomial fits fail to improve the correlation (Gottshalk, 1991).

One possible reason for the inaccuracy of the $T_2^*$ method in predicting iron levels at high concentrations may lie in the machine limitations of an MRI system. In normal, or near-normal, levels of liver iron (125-250 ug/ml), the $T_2^*$ is approximately 40-50 ms. As predicted by equation [2.2], the $T_2^*$ is reduced with increasing iron levels, and for levels of liver iron above 4 x normal, the $T_2^*$ is less than 2 ms. In the Spin-Echo measurement, a typical limit of spin-echo time ($TE$) is approximately 6 ms. on commercial MRI systems. In this case, the MRI signal strength will have decayed over three exponential time constants ($T_2^*/TE = 1/3$), or to less than 5% of the maximum signal. This introduces a high variance into the measurement of $T_2^*$. The effect of signal reduction will be compounded by the large susceptibility based magnetic field gradients formed by particulate iron, causing a non-linear term in $T_2^*$ (Majumdar, 1988). This technique is not valid when compared to the high degree of accuracy of surgical biopsy or SQUID estimation, except for low-end stages of iron overload disease.
II.5 Static MRI Field Distortion

These susceptibility-based field distortions can be predicted by Maxwell's equations, as can the behavior of any object placed in a static magnetic field. For regions of differential susceptibility in a homogeneous magnetic field, with no currents present, the magnetic field, $\overline{H}$, is derivable from the vector potential, $\overline{H} = -\nabla \Phi$ (Jackson, 1961). Since the magnetic induction, $\overline{B} = \mu \overline{H}$, is a product of the permeability ($\mu$) and the magnetic intensity, $\overline{H}$, the divergence equation, $\nabla \cdot \overline{B} = 0$, becomes $\nabla \cdot \overline{H} = 0$ to give Laplace's equation,

$$\nabla \cdot \overline{H} = \nabla \cdot (-\nabla \Phi) = \nabla^2 \Phi = 0 \quad [2.3]$$

For objects of simple geometry in a static field, analytical solutions are available. For a perfect sphere of radius $R$, of constant permeability, $\mu$, in a homogeneous external medium, $\mu_n$, with a homogeneous external field, $H_0 \hat{e}_z$, the magnetostatic equations become, in cylindrical coordinates, for the axial component of the field outside the sphere,

$$H_z = H_0 - H_0 \frac{\Delta \chi}{3} R^3 \frac{3 \cos^2 \theta - 1}{(r^2 + z^2)^{3/2}} \quad \text{for} \quad r \geq R \quad [2.4(a)]$$

and for the axial component of the field inside the sphere,

$$H_z = H_0 \frac{2 \Delta \chi}{3} \quad \text{for} \quad r \leq R \quad [2.4(b)]$$

For the radial component of the field outside the sphere,

$$H_\theta = -H_0 \frac{2 \Delta \chi}{3} R^3 \frac{3 \sin \theta \cos \theta}{(r^2 + z^2)^{3/2}} \quad \text{for} \quad r \geq R \quad [2.4(c)]$$

and inside the sphere,

$$H_\theta = 0 \quad \text{for} \quad r \geq R \quad [2.4(d)]$$
For this solution a simplification has been made using an approximation for the differential susceptibility,

\[ \Delta \chi / 3 \equiv (\mu_i - \mu_o)/(2\mu_o + \mu_i) \]

as permeability is defined as \( \mu = 1 + \chi \) and \( \chi << 1 \). The MRI magnetic field is, by convention, defined as a z-axial field, \( H = H_0\hat{z} \). As seen in equation [2.4(a)], the field distortion for \( H_r \) displays inverse r-cubed behavior, as shown in figure 2-1 along both r and z axes.

II.6 Summary of Liver Iron Field Distortion

For the case of a human liver, iron is stored as ferritin and hemosiderin molecules in the liver, with 2000–4500 ferric ions per molecule. On a microscopic scale, these iron-laden molecules will distort a surrounding magnetic field with an intensity that diminishes with distance at an inverse-cubed rate. This field distortion, along with the low signal-to-noise ratio in an iron-loaded liver, preclude accurate estimates of iron from \( T_2^* \) measurements. With large numbers of these molecules, such as are present even in the normal liver, a macroscopic effect will be exhibited (Majumdar, 1988), in that the liver can be treated as a homogeneous compartment with a mean susceptibility, different than that of the surrounding torso (Overmoyer, 1987). Extension of the principles shown in equations [2.3-2.4] imply that this differential susceptibility will distort a field outside of the liver extending infinitely off in space, reduced with inverse cubed distance. SQUID magnetometers function by taking advantage of this bio-magnetic distortion and provide liver iron estimates by correlating the field distortion to the magnetic susceptibility (Farrell, 1980).
Figure 2-1. Analytical Magnetostatic Field solutions for a single sphere in a constant field show the distribution of the vector field, $H$, and $H_r$, along the $y$ and $z$ axes. The field vector aligned with the magnetic field, $H_r$, has a differential field component inside the sphere, which does not exist in the non-aligned field vector, $H_o$. The differential field which extends outward from the object, or sphere, is spatially proportional with inverse cubed distance.
MRI susceptibility method described here performs by virtue of the same phenomenon, by correlating field distortion data to a magnetostatic field model to derive the mean liver susceptibility.
CHAPTER III - Measurement of MRI Field Distortion and Comparison to Analytically Derived Field Distortion

III.1 Introduction

In this chapter, the measurement of field distortion with a MRI scanner is described. The method is based on measuring the distortions in the magnetic field arising from the presence of some object, such as the human torso, located inside the magnet. The level of these distortions can be derived from the phase of the MRI image.

This chapter presents the theory and techniques used to acquire the MR data. The field distortions for a single sphere can be analytically derived from Maxwell's equations. A comparison of measured MRI field distortions and of derived field distortions for a single sphere is made. In addition, the sensitivity of the MRI field distortion method is discussed. Finally, the concept of superposition is introduced and examined for validity in the MRI system.

III.2 MRI Field Distortion

III.2.1 MRI Measurement of Field Distortion

As discussed in Chapter II (equations [2.3-2.4]), inclusion of any object of differential susceptibility into a magnetic field will distort that field. Field distortion data can be acquired in MRI by using the Field Echo Phase Map technique (Faul, 1984; Cox, 1986; Appendix B). When a Field Echo sequence is used to acquire the
MRI data, it can be shown that the phase of the MRI signal at any point, $\Delta \phi(r)$, is related to the z-axis vector distortion of magnetic induction about that point, $\Delta B_z(r)$, by,

$$\Delta \phi(r) = \bar{\gamma} \Delta B_z(r) TE$$  \hspace{1cm} [3.1(a)]

where $\bar{\gamma}$ is the gyromagnetic ratio (Mansfield, 1980; Appendix B). Only the differential phase is represented, as the phase will inherently contain some baseline value, such that $\Delta \phi(r) = \phi(r) - \phi_o$. Only the z-axial component of the distortion affects the phase of the MRI signal (ibid). For any given echo time, $TE$, a direct relationship between the phase and the field distortion can be obtained. Hematoma induced iron localizations in the brain have been identified using Field Echo sequences, based on the distortion in the phase map acquired over the brain (Edelman, 1986; Cox, 1986; Young, 1987; Young, 1989).

The variation in the magnetic induction at any point, $\Delta B(r)$ is the product of the field distortion, $\Delta H(r)$, and magnetic permeability, $\mu(r)$. The magnetic susceptibility of any object is related to permeability by $\mu = 1 + \chi$, so that the field distortion relationship to the MRI phase obtained from a Field Echo sequence and the susceptibility of an object is,

$$\Delta H_z(r) = \frac{\Delta \phi(r)}{\bar{\gamma}(1 + \chi)TE}$$  \hspace{1cm} [3.1(b)]

Susceptibility is a dimensionless parameter usually on the order of parts per million for biological samples. Examples of the susceptibilities of various solutions and biological tissues are provided in table 3-1.
As the field distorting behavior of any object in a field can be predicted by Maxwell's equations ([2.3]), and as the field data can be obtained from the phase image of a GFE scan, then the susceptibility of a given sample can be found by measuring the phase/field map in and around the sample, and fitting that field map to an appropriate magnetostatic model. The magnetostatic model must be based on the specific geometry of each individual case, which will be discussed in turn.

III.2.B Theoretical Sensitivity of the MRI Field Distortion Method

The absolute limits of the resolution of the external phantom MRI field map method can be computed from the theory. Given the equation for phase information due to any field distortion from the gradient field echo sequence (equation [3.1]), where the gyromagnetic ratio constant for hydrogen is $\tilde{\gamma} = 4257.59$ Hz/G, then the smallest relative field measurable is dependent on the variable echo time, $t_e$, and the smallest resolvable phase for the system.

The echo time is dependent on the transverse relaxation time, $T_2$, of the phantom used, the sequence used, and the capabilities of the electronics of the imager. The shortest Gradient Field Echo time possible on the Picker Vista 1.5T in our laboratory, limited mostly by the first order gradient system, is 12 ms (at the time of these experiments), with no theoretical upper boundary. However, the slowest $T_2$ we would expect to measure would be with ultra-pure water, of about 1000 ms. Since the $T_2$ is an exponential decay rate of the signal, up to 3 time constants may pass, with only a 20 fold loss of signal to noise. The imaging system, depending on the sequence used,
has reported signal-to-noise (SNR) values of up to 120, which would be reduced by
signal decay to about SNR = 6 if $TE = 3*T_2 = 3000$ ms. This large of an echo time is
only used to clarify the extreme end of the technique.

The smallest resolvable phase is a function of the maximum range of phase mea-
surable and the digital resolution of the system. The signal is sampled at 16-bits, but
the transmit/receive portion of the system is analog and has a maximum resolution of
about 80 dB, so only 12-bits of signal (approximately 72 dB) are retained (Oppe-
nehmen, 1975). The phase is computed from the arctangent of the orthogonal vectors
of the transverse plane, therefore, the arctangent of any argument will range from $-\pi$
to $\pi$. The final resolution of the phase, or the minimum change of phase that can be
resolved between two pixels is $2\pi$ radians /$(2^{12} - 1)$ pixels = 0.001534 radians/pixel.
For the entire system, taken to extremes, the smallest field measurable is,

$$\Delta B_{\text{min}} = \frac{\Delta \phi_{\text{min}}}{2\pi \tau_E} = \frac{2\pi(2^{12} - 1)\text{rads/pixel}}{2\pi \times 4253\text{Hz}/G \times 3000\text{ms}} = 19.14nG/\text{pixel} \quad [3.2(a)]$$

when $t_E = 3000\text{ms}$. At 1.5 T, this represents a relative sensitivity of $\Delta B/B_0 =$
$1.276 \times 10^{-12}$ per pixel.

For larger order field distortions, the phase signal will repetitively wrap, giving
a 'zebra stripe' effect (more completely discussed in Appendix B). These phase
wrappings can be reliably 'unwrapped' using nearest neighbor (Tribolet, 1977) or cel-
lular automata algorithms (Ghiglia, 1987) as long as the maximum frequency of
phase wrapping is less than $2\pi$ over 4 pixels. This gives $\Delta \phi_{\text{max}} = 2\pi$ radians / 4 pixels,
and at $t_E = 12$ ms, then
\[
\Delta B_{\text{max}} = \frac{\Delta \phi_{\text{max}}}{2\pi \gamma_0} = \frac{2 \pi \text{rads/4 pixel}}{2 \pi \times 4253 \text{Hz/G} \times 12 \text{ms}} = 4.99 \text{mG/pixel} \quad [3.2(b)]
\]

of field can be resolved, or a relative sensitivity of \(\Delta B/B_0 = 3.27 \times 10^{-7}\) per pixel (0.33 ppm). The total range of sensitivity for the this gradient field echo field map system is on the order of \(10^{-11}\) to \(10^{-7}\). For comparison to a similar method, SQUID sensitivities to changes in field range from \(10^{-15}\) to \(10^{-6}\). The field sensitivity needed to accurately quantitate liver iron levels is about \(10^{-10}\) to \(10^{-8}\) (Farrell, 1980) and lie well within the predicted ranges of MRI field maps.

### III.3 Superposition and Background Subtraction

The theory of superposition states that the electromagnetic potential of any group of objects should be equivalent to the sum of the potentials of each object measured individually (Jackson, 1961). For objects of non-ferromagnetic susceptibility in a static field, with no current sources, superposition will also hold for the magnetic fields of each separate object.

The imposed magnetic field inherently contains some small amount of field inhomogeneity (typical manufacturers specifications - less than 4 ppm over 30 cm). The assumption of superposition is of key importance to this method, as it allows background subtraction of the slight field inhomogeneity. The background subtraction method is an important step which renders the MRI field measurement independent of both the background field non-uniformities and the influence of the reference phantom. The absence of external currents is necessary for superposition to hold, and as eddy currents from the gradient fields of an MRI may exist, the principle of super-
position must be tested.

In order to test the applicability of superposition, an in vitro experiment was performed on two spherical phantoms, A and B. If superposition holds, then the field which exists in the presence of both spheres \( \overline{H}_{A+B}(\vec{r}) \) should be equivalent to the sum of the fields for each sphere alone, \( \overline{H}_A(\vec{r}) \) and \( \overline{H}_B(\vec{r}) \),

\[
\overline{H}_{A+B}(\vec{r}) = \overline{H}_A(\vec{r}) + \overline{H}_B(\vec{r}) \quad [3.3(a)]
\]

In practice, the background field, \( H_{BKG} \), must also be considered part of the verification step. As the MRI field data which is actually measured is,

\[
\overline{H}_A(\vec{r}) = \overline{H}_{A+BKG}(\vec{r}) - \overline{H}_{BKG}(\vec{r}) \quad [3.3(b)]
\]

\[
\overline{H}_B(\vec{r}) = \overline{H}_{B+BKG}(\vec{r}) - \overline{H}_{BKG}(\vec{r}) \quad [3.3(c)]
\]

\[
\overline{H}_{A+B}(\vec{r}) = \overline{H}_{A+B+BKG}(\vec{r}) - \overline{H}_{BKG}(\vec{r}) \quad [3.3(d)]
\]

then superposition would be expected to hold if,

\[
\overline{H}_{A+B+BKG}(\vec{r}) - \overline{H}_{BKG}(\vec{r}) = \overline{H}_{A+BKG}(\vec{r}) + \overline{H}_{B+BKG}(\vec{r}) - 2\overline{H}_{BKG}(\vec{r}) [3.3(e)]
\]

was true.

III.4 Measurements of Field Distortions and Verification of Superposition

III.4.A Materials and Methods

In order to examine the field distribution in MRI, a single sphere was placed over a water bath and the field was measured as in equation [3.1]. The background field in the bath is also measured and subtracted from the combination of sphere and bath. An analytical simulation of a single sphere in a field was created from equations [2.4] and comparisons made between the analytical and in vitro field distortions.
III.4.4 In Vitro Phantoms

A uniform in vitro phantom comprised of a large cylindrical vessel (D = 30 cm, h = 20 cm) was filled with double distilled water (Resistivity = 18 M Ohm) and is placed in the isocenter of the MRI field. Separate spherical phantoms (volume = 12.5, 25, 50 and 100 +/- 0.1 cubic centimeters, and radius = 1.34, 1.87, 2.27, and 2.51 +/- 0.05 cm, respectively) were constructed from stiff, thin membrane surgical latex balloon provided by excising the finger of a surgical glove. The latex was washed in a light acid (0.01 mM HCl) to remove any trace residue of iron. The spherical phantoms were filled with solutions of aqueous Iron Chloride (Fe2Cl3-6H2O, Sigma) (12.5 uM, 25 uM, 50 uM and 100 uM +/- 2.5 %), made from serial dilutions. Absolute susceptibility for iron chloride solutions can be predicted from physical constant formulae (Weast, 1982) for use in the analytically derived comparisons to the estimated susceptibility. The iron-chloride filled balloon was suspended in the cylindrical water bath at room temperature, as shown in figure 3-1. The suspension apparatus is a structure of thin wooden rods that have been submerged in a weak acid (0.01 mM HCl) solution to remove trace metals. The suspension structure is kept saturated with water to eliminate any air pockets which would cause a field distortion. A residual field distortion from the supporting structure will persist.

The MRI data of the water bath and balloons, as well as a background scan of the water bath alone, were acquired on a Picker Vista 1.5T magnet using a TE = 15.3 ms, TR = 500 ms, Field Echo scan, with two signal averages. Up to 64 transverse slices (0.5 cm) were acquired using 256 phase encode steps and 256 read encode steps over a field of view of 30 cm x 30 cm. Each voxel (or data point) measured
In Vitro Phantom

Figure 3-1. The in vitro spheres filled with FeCl3 are placed above a water bath reference phantom for MRI FE measurements of the phase reconstruction/magnetic field.
with these protocols has dimensions of 1.17 x 1.17 x 5 mm³, over which the phase reconstruction is the mean of the phase of all spins in the volume (Mansfield, 1980). For simplicity, the data are compared only along the y-axis below the sphere (figure 3-1). The phase data was unwrapped in order to correct for arctangent induced phase-wrapping (Tribolet, 1977; Appendix B). The phase unwrapped background scan was then subtracted to correct the minor field inhomogeneities as well as the influence of the reference bath. The spatial positioning of the spheres in each experiment was obtained from the MRI magnitude reconstruction with a spatial resolution of +/- 0.69 mm along the x and y axes.

III.4.A.ii Analytical Simulation of Single Sphere Field Distortion

The analytical spheres field solutions for each sphere measured can be calculated for any combination of spheres using equation [2.4] and the principle of superposition (equation [3.3]), which allows the overlaying of potential fields in magnetostatics (Jackson, 1961). To make these field simulations, the parameters for the sphere radius, the differential susceptibility of contents of the spheres and air and a series of coordinates for each point the field is desired are needed (in these cases along the y-axis below the sphere).

III.4.B Superposition and Background Subtraction

To obtain the in vitro field data, two spherical phantoms were placed in the water bath as in the inset of figure 3-4, where Sphere A is filled with 50 cc of 25 uM FeCl₃, and Sphere B filled with 50 cc of 50 uM (B). A Field Echo MRI scan for each
sphere (A or B) alone, for both spheres together (A and B), and for no spheres at all (BKG) was acquired. With both spheres present, the separation of the two spheres was less than 2 mm. Care was taken to replicate the exact positions of each sphere within the field of view from scan to scan (+/− 1.8 mm). The phase of each signal was unwrapped, and the background field was subtracted from each scan (A, B, A and B).

III.4.C Statistics
Correlation of any measured and derived fields is calculated by;

\[ r = \sqrt{\frac{\frac{1}{N} \sum_{i=1}^{N} (\chi_{i,1} - M_1)(\chi_{i,2} - M_2)}{\sigma_1 \sigma_2}} \]  \[3.4(a)\]

where,
the mean over a data range is defined as,

\[ M_x = \frac{1}{N} \sum_{i=1}^{N} \chi_i \]  \[3.4(b)\]

and the variance over a single data set is defined here as,

\[ \sigma^2 = \frac{1}{N} \sum_{i=1}^{N} (\chi_i - M_x)^2 \]  \[3.4(c)\]

III.5 Results and Discussion
III.5.A In Vitro Spheres - Susceptibility Estimation

The FE MRI phase measurement and field model fit can be verified using in vitro phantoms. An in vitro phantom for a single sphere was constructed, measured and fit as described above. The phase reconstruction at a transverse slice through
such an in vitro experiment is shown in figure 3-2(a). The background of the water bath without a sphere present is shown in figure 3-2(b). The phase of the signal is seen to fall off with distance from the sphere, as shown in the axial projections along both x and y axes through the center of the sphere (figure 3-2(c)), although the phase as shown is phase-wrapped. The MRI phase reconstruction data was phase unwrapped and the background field was subtracted as described above.

In figure 3-3(a), a comparison of 110 unwrapped, background corrected y-axial field data and derived analytical solutions is made for spheres of varying volume ($V = 25, 50$ and 100 cc) and fixed contents (FeCl3 = 50 µM). The analytical solutions predict the field distortion well ($r > 0.9977$ for all cases). The effect of varying susceptibility (FeCl3 = 12.5 µM, 25 µM, 50 µM, 100 µM - see table 3-1 for susceptibility values) for a fixed volume ($V = 50$ cc) is shown in figure 3-3(b). As expected from the analytical equations for single spheres, the field distortion predicted for each is proportional to susceptibility.

These comparisons show that the field distortion data can be well predicted by analytical solutions of perfect spheres phantoms, as shown by the similarity of curves and the high degree of correlation between MRI data and analytical models in figure 3-3.
Table 3-1 Calculation of Susceptibility

Some equivalent susceptibilities and molarities are:

<table>
<thead>
<tr>
<th>$\chi$ (x10^6)</th>
<th>[AMI-25] µM</th>
<th>[FeCl3-6H2O]µM</th>
<th>Hepatic Fe (µg Fe/cc)</th>
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</thead>
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<tr>
<td>9</td>
<td>58.6</td>
<td>1683</td>
<td></td>
</tr>
<tr>
<td>-4.5</td>
<td>125</td>
<td>3591</td>
<td></td>
</tr>
<tr>
<td>-2.25</td>
<td>158.2</td>
<td>4546</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>191.4</td>
<td>5500</td>
<td></td>
</tr>
<tr>
<td>+2.25</td>
<td>224.6</td>
<td>6454</td>
<td></td>
</tr>
<tr>
<td>+4.5</td>
<td>257.8</td>
<td>7408</td>
<td></td>
</tr>
<tr>
<td>+9</td>
<td>324.2</td>
<td>9317</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>[FeCl3-6H2O]µM</th>
<th>$\chi$ (x10^6)</th>
<th>[AMI-25] µM</th>
<th>Hepatic Fe (µg Fe/cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>10.6</td>
<td>44.2</td>
<td>1016</td>
</tr>
<tr>
<td>-8.18</td>
<td>12.5</td>
<td>88.4</td>
<td>2032</td>
</tr>
<tr>
<td>-3.38</td>
<td>25</td>
<td>177</td>
<td>4063</td>
</tr>
<tr>
<td>+6.19</td>
<td>50</td>
<td>354</td>
<td>8127</td>
</tr>
</tbody>
</table>

Susceptibility is given by $\chi = \chi_m \times 4\pi \times M$, where $\chi_m$ is molar susceptibility, $\chi$ is bulk susceptibility, and $M$ is molarity. $\chi$ and $\chi_m$ are expressed as cgs units X10^6.

Hepatic Iron is related to susceptibility by,

$$\text{Hepatic Iron} = \left( \frac{\chi}{\chi_{water}} + 1 \right) \times 5500 \mu \text{g Fe/cc}$$

The susceptibility values used here are:

<table>
<thead>
<tr>
<th>Substance</th>
<th>$\chi$ (x10^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
H2O       -12.97
FeCl3-6H2O +15250
AMI-25     +5393
Figure 3-2. a) Phase/Field scan of one sphere (denoted sphere A) in the reference water bath b) Phase Field of the second sphere (usually denoted sphere B) in the reference bath c) Background phase scan of the water bath alone. d) Phase reconstruction image of both spheres A and B in the water bath.
Figure 3-3. a) Y-Axial Field data of several spheres, volume = 50 cc. [FeCl₃] = 12.5, 25, 50 and 100 μM compared to the analytical equations for field distortion based on identical spheres. b) Same as (a), but for constant [FeCl₃] = 25 μM and varying Volume = 25, 50 and 100 cc.
III.5. B Superposition

A 2-D mesh plot of each sphere individually, and of both spheres together is shown in figure 3-4(a-d), where the data appear to be superposable. 2-D mesh plots are useful for this sort of visual inspection, but for a more quantitative analysis, the z-axial data from the line closest to the spheres is shown in figure 3-5. The summation of the single sphere fields (A&B = superposed) is observed to be nearly equal to the field induced by both spheres (A+B = measured together). A small amount of error over the entire data set is observed (less than 1% at any point), which is consistent with normal amounts of noise in the phase reconstruction (which will be discussed in Chapter VI), except at the point exactly between the spheres, which diverges slightly (up to 10% error). It is uncertain whether this larger error is due to the effect of eddy currents which can reach as much as 30% of the field signal (Boesch, 1990), and which would not be superposable, or to error in the relative alignment of each sphere, when taking the measurements. A slight (sub-pixel) shift of position or volume error might be enough to account for the less than 5% error seen, but this geometry would not be recoverable from the magnitude reconstruction data (similar to partial volume uncertainty). However, artificial shifting of the relative positions of the two data sets of sphere A and sphere B was unable to recover a better fit than is seen in figures 3-4 and 3-5. The overall correlation between A&B and A+B was $r > 0.999$ over the slice in figure 3-4, and $r > 0.995$ over the single axis lines in figure 3-5, even with the difference of fit below the nexus of the spheres. The conclusion can be drawn that the assumption of superposition is valid.
Superposition of Two Spheres for XZ-Plane Data

Figure 3-4. 2-D meshes of the yz-plane below the spheres background corrected Field Data below spheres to display the ability to superpose spheres. a) sphere A alone, b) Sphere B alone, c) Sphere A and Sphere B Measured together, and d) Superposed Fields of Sphere A and Sphere B which is similar to figure 2(c) ($r > 0.9975$).
Figure 3-5. Z-axial data taken from figure 3-4, directly below each sphere, both spheres, and the superposition of both spheres shows that superposition is valid over most of the data space ($r > 0.999$). The small difference between $A+B$ and $A&B$ is not resolvable, but displayed for the worst case over all of the data space.
III.6 Summary

To summarize the method, magnetic fields are measured from the phase reconstruction of a MRI Field Echo scan. The magnetic fields can also be predicted for perfect spheres and compared to measured fields. The experimental results and high correlation of simulated and measured fields of the single sphere estimations suggest that the external phantom MRI method for measuring susceptibility induced field distortion is sound.

The high correlation of the superposition test indicates that superposition will hold, and that the background field can be corrected for. The small amount of field difference seen between the measurement (A+B) and superposition (A&B) suggests that a small amount of eddy current field has not been ruled out. However, the field difference is small (< 5 % of error at any one point), and over the entire data space, the two fields are well correlated.

Given that the measurement of the fields can be reliably made, a method for deriving the susceptibility of an arbitrary object of known geometry and unknown susceptibility will now be tendered.
CHAPTER IV - Overall Algorithm for Measurement, Modeling and Susceptibility Estimation of MRI Field Distortion

IV.1 Introduction

In this chapter, the method of estimating the susceptibility parameter is introduced. In Chapter III, the MRI field data was compared to analytically derived fields. In practice, the arbitrary geometry of each patient will not be analytically derivable. However, in order to estimate susceptibility values from the field distortions in the phase of the MRI signal, a magnetic field model unique to the geometry of the MRI experiment must be developed. The field model is obtained from patient geometry using the Discrete Fourier Convolution (DFC) Method (which will be examined in detail in Chapter V). This geometry can be obtained from the 2DFT magnitude reconstruction of the acquired FE data, the same data which provided the phase image used to measure the field distortions. The field model and the field data are used in a parameter estimation to obtain the susceptibility of the object under study.

This chapter presents the theory and techniques used to acquire the MR data, to generate and compute the geometric model and magnetic field model, and to perform the data fitting used in generating susceptibility values. Although a detailed description of the DFC method will be presented in Chapter V, the basic theory behind the DFC will be presented (in abbreviated form) to aid the continuity of this chapter.
IV.2 General Algorithm for Liver Iron Estimation

The procedure used to estimate susceptibility is shown in figure 4-1. The first step is to obtain an MRI data set using a Gradient Field Echo (GFE) scan. A magnitude image and a phase image are reconstructed from the MRI data. The magnitude image is passed to both the geometry extraction routine and the phase image is passed to the phase extraction routine. The MRI phase image is used in a routine which uses it to calculate the magnetic field (Field Data). The MRI magnitude images is used to generate a geometric model of the object under study, which is then used to calculate the field distortion (Field Model) expected for that specific geometry. Both the Field Data and the Field Model are passed to a linear Least Squares Estimation routine to determine the susceptibility of the object. A general overview of each step in the susceptibility algorithm is presented below, followed by detailed descriptions of the theory and method behind each step, along with the expected errors and difficulties encountered in implementation.

IV.3 MRI Measurement of Field Distortion in an External Phantom Reference Bath

For human subjects, relating the phase to the field by means of equation [3.1] is a challenging task. Field distortion measurements in the torso are complicated by the large number of interfacing tissue types, such as fat, water, bone and connective tissue. Each of these tissues have varying susceptibility, and as seen in equation [2.4], differential susceptibility interfaces ($\Delta \chi$) will induce field distortions. Chemical shift artifact, often observed in tissues (Axel, 1988), will also distort the magnitude and phase image inside the patient torso. In chemical shift artifacts, a proton associated
MRI External Reference Method for Susceptibility Estimation

Field Echo Scan of Patient → MRI Magnitude Reconstruction → Geometry Segmentation → Field Model Calculation → Least Squares Fit → Susceptibility Parameters

Background Scan ← MRI Phase Reconstruction

Field Data ← Analytical Simulation

Figure 4-1. The General Algorithm for MRI Susceptibility begins with acquiring patient and background data from a GFE MRI scan. The Phase reconstruction is corrected for background to provide the Field Data. The Magnitude reconstruction is segmented into geometrically separate compartments, which are used in the DFC calculation of the Field Model. The susceptibility parameters are estimated from the field data and field model using Least Squares Estimation. For regularized geometries, such as perfect spheres, the analytical solutions may be substituted for the MRI-derived field data.
with a fat molecule will be spatially shifted in the magnitude and phase reconstruction with respect to a water bound proton. The chemical shift will alter the baseline phase of the phase related field distortions (equation [3.1]).

In order to obtain field data points which are unaffected by local susceptibility variations, or local chemical shift variations an external reference bath is used (figure 4-2). A field measurement which is not affected by local proton densities from tissue variations can be obtained inside the reference phantom, as the contents of the bath will, by definition, be uniform.

An added benefit is that motion artifacts can also be minimized by use of the external reference bath as the bath itself is stationary. In addition, the GFE scan phase-encoding axis is chosen to be from left to right so that patient motion is not ghosted into the bath. Also, the contents of the reference bath can be adjusted to provide an optimal MRI signal. Furthermore, due to short $T_2$ values, the MRI image of the liver of an iron-overload patient is often degraded below system noise levels, a phenomenon known as "black liver" (Stark, 1985). Using the external reference bath alleviates the need to directly measure the field inside the black liver.

IV.4 Field Model Calculation

IV.4.1 Geometry Model

The analytically derived solutions, while providing suitable field models for simple geometry, such as perfect spheres, do not apply to arbitrary objects such as the human torso and liver. A field model generator which will calculate the magnetic
Figure 4-2. An external reference bath, placed below the patient liver is required to allow for background correction, as well as to improve the S/N of the measured Phase image.
field solution for any arbitrary geometry is therefore required.

The first step is to specify the geometry for the model. For cases of known geometry, such as analytical simulations or specially constructed phantoms, this is a trivial step. For unknown geometry, as is the case for human torso studies, the geometry can be obtained from the same MRI GFE scan that provided the field data information (as described by figure 4-1).

The MRI magnitude reconstruction of the GFE data provides the exact torso and liver position in the magnetic field at the time of field data acquisition. The geometry of the subject can be segmented from the magnitude reconstruction. Automated segmentation algorithms proved inadequate for this step (Appendix C), forcing an operator-interactive outlining step utilizing a trackball. The operator must outline model compartments, to be passed on to the field model generator.

The number of separate compartments used in the model is a somewhat flexible parameter. A higher correlation between SQUID susceptibility data and liver biopsy has been found using a two compartment model, consisting of a liver and a torso, rather than a single liver-torso susceptibility compartment (Fischer, 1989). Additional compartments of interest, besides torso and liver, may be the heart, lungs, stomach and bowel. As in any modeling situation, the fewest number of necessary compartments is desired to simplify the parameter estimation routine. The reduction or addition of number of model compartments is a subject which will be discussed in more detail in Chapter VII.
In addition to the manual outlining of the objects of interest, the boundaries of
the reference bath may also be extracted in the geometry specification step. As men-
tioned in the previous section, the field in the reference phantom will be the data of
interest, due to the minimization of noise and artifact there. The reference phantom
geometry is passed on to the Least Squares estimation step (figure 4-1).

IV.4.B Field Model - Field Calculation

While many computationally intense methods for the solution of an arbitrary
gometry in a field are available (Borup, 1987), a Discrete Fourier Convolution
(DFC) magnetostatic solution method which is simple and fast was used. This
numerical solution consists of a discrete convolution method that can rapidly calcu-
late the fields associated with an arbitrary object placed in a static, homogeneous
field. The DFC method will be examined in detail in the following chapter, but, to
provide a continuous flow to the description of the overall algorithm, the basic theory
behind the DFC method is stated below.

From Maxwell’s equations, when a static field, \( \vec{H}_o(\vec{r}) \), acts upon an object of
some susceptibility, \( \chi(\vec{r}) \), the resultant field is,

\[
\vec{H}(\vec{r}) = \vec{H}_o(\vec{r}) - \frac{1}{4\pi} \nabla \cdot \int_{\mathcal{V}} \vec{M}(\vec{r}') \cdot \frac{1}{|\vec{r} - \vec{r}'|} d^3 r'
\]

which is also known as the integral solution to Laplace’s equation (equation [2.3]).
As the object is assumed to be some combination of paramagnetic, diamagnetic or
superparamagnetic materials, and, as the principle of superposition holds for the solu-
tions to any Laplacian problem, then the magnetization vector is expected to be linear
with the applied field, \( \overline{M}(\vec{r}) = \overline{\chi}(\vec{r})\overline{H}(\vec{r}) \). The field vector is a combination of the imposed (background) field vector and the distortion field vector

\[ \overline{H}(\vec{r}) = \overline{H}_0(\vec{r}) + \Delta\overline{H}(\vec{r}) \]

The effect of the distortion term on the magnetization vector is negligible with respect to the background field vector (\( \Delta H/H \ll 0.0001 \)), and may be omitted from the magnetization term (as shown in Chapter V), so that,

\[ \overline{M}(\vec{r}) = \overline{\chi}(\vec{r})\overline{H}_0(\vec{r}) \]  \[ 4.2 \]

For a constant field, \( \overline{H}_0(\vec{r}) = H_0\hat{k} \), the limits of the integral (equation [4.1]) can be incorporated into the susceptibility vector, and the integral limits can be extended to infinity,

\[ \overline{H}(\vec{r}) = \overline{H}_0(\vec{r}) - \frac{H_0}{4\pi} \nabla \cdot \int_{-\infty}^{\infty} \overline{\chi}(\vec{r})\hat{k} \cdot \frac{\vec{r} - \vec{r}'}{|\vec{r} - \vec{r}'|} d^3r' \]  \[ 4.3 \]

When the dot product in [4.3] is multiplied through, and the sign of the dipole function is switched, this function becomes a three-dimensional convolution of the form,

\[ \overline{H}(\vec{r}) = \overline{H}_0(\vec{r}) + \frac{H_0}{4\pi} \nabla \cdot \left[ \overline{\chi}(\vec{r})\hat{k} \right] \left[ \frac{z}{|\vec{r}|^3} \right] \]  \[ 4.4 \]

This convolution can be now be evaluated by transforming its \( \overline{\chi}(\vec{r}) \) and \( z/|r|^3 \) into the Fourier domain, performing a simple multiplication, and inverse transforming the result back into the real domain. As the static field computation is a form of convolution, a spatial filtering by the Green's function \( (z/|r|^3) \) on the susceptibility vector will result. The discrete Fourier transform nature of the filter application will induce Gibbs artifact ringing in the field model as well as smooth the sharp edges (i.e. high spatial frequencies) of the geometrical model and will be discussed in later chapters.

This method is not as fast or accurate when solving magnetodynamic field solutions as are the Finite Element Method or the Boundary Element Method, as shown
by Borup. However, as will be shown in the following chapter, for the magnetostatic field solutions, the DFC method is as accurate, and considerably faster, because of the inherent speed factor of fast Fourier transforms (FFTs).

IV.5 Parameter Estimation Method

IV.5.A Susceptibility Estimation

In order to estimate susceptibility, it is helpful to separate the susceptibility parameter from the field model. The susceptibility vector, \( \chi(\vec{r}) \), represents some mean susceptibility value at each position. The susceptibility value can be separated from the positional information by allowing the object in the field to be represented by separate compartments, with the volumetric geometry described by a three dimensional step function (or volume function), \( V_i(\vec{r}) \), as in figure 4-3(a). We make the assumption that the susceptibility of any compartment of the model is uniform within that compartment. Iron deposits have been shown to be uniformly distributed throughout the liver in iron overload syndromes (Overmoyer, 1987).

As superposition holds in the absence of external sources or currents, the susceptibility vector, \( \chi(\vec{r}) \), can be represented as the linear combination of the mean compartment susceptibility \( \chi_i \) and the compartment volume function, \( V_i(\vec{r}) \), to give

\[
\chi(\vec{r}) = \sum_i \chi_i V_i(\vec{r}) = \chi_{\text{torso}} V_{\text{torso}}(\vec{r}) + \chi_{\text{liver}} V_{\text{liver}}(\vec{r}) + \chi_{\text{lungs}} V_{\text{lungs}}(\vec{r}) + \ldots \tag{4.5(a)}
\]

The model as described in equation [4.5] would be represented by a solid torso volume, with void spaces where the volume of each organ is, as shown in figure 4-3(a). This can be rearranged to simplify the geometrical representation of the torso, by
assuming the torso to be solidly filled, and using the differential susceptibility of each compartment (figure 4-3(b)) in the field calculation, as follows,

\[
\bar{\chi}(r) = \chi_{\text{torso}}(V_{\text{torso}}(r)) + V_{\text{liver}}(r) + V_{\text{lungs}}(r) + ... \\
+ (\chi_{\text{liver}} - \chi_{\text{torso}})V_{\text{liver}}(r) + (\chi_{\text{lungs}} - \chi_{\text{torso}})V_{\text{lungs}}(r) + ... \quad [4.5(b)]
\]

The new volume and differential susceptibilities are represented as,
Methods of Compartmentation

Absolute Susceptibility

\[ V_{\text{torso}} - V_{\text{liver}} \]

\[ \chi_{\text{torso}} \]

\[ \chi_{\text{liver}} \]

Differential Susceptibility

\[ \chi_{\text{torso}} \]

\[ V_{\text{torso}} \]

\[ \chi_{\text{torso}} - \chi_{\text{liver}} \]

\[ V_{\text{liver}} \]

Figure 4-3. The geometry of one object inside of another can be viewed as a summation of two objects which either (a) are volumetrically separate, with absolute susceptibility, or (b) volumetrically dependant with differential susceptibility. DFC calculation using the second method reduces edge and partial volume errors, but requires that $\chi_{\text{torso}}$ be estimated in order to determine $\chi_{\text{liver}}$. 
\[ \chi'_{\text{tissue}} = \chi_{\text{tissue}} \]
\[ V'_{\text{tissue}}(\mathbf{r}) = V_{\text{tissue}}(\mathbf{r}) + V_{\text{tissue}}^2(\mathbf{r}) + \ldots \]
\[ \chi'_{\text{Liver}} = \chi_{\text{Liver}} - \chi'_{\text{tissue}} \]
\[ V'_{\text{Liver}}(\mathbf{r}) = V_{\text{Liver}}(\mathbf{r}) \]
\[ \chi'_{\text{Lungs}} = \chi_{\text{Lungs}} - \chi'_{\text{tissue}} \]
\[ V'_{\text{Lungs}}(\mathbf{r}) = V_{\text{Lungs}}(\mathbf{r}) \]

and so on, for each compartment. Combining equations [4.4] and [4.5], the final field result of the multi-compartment model in the presence of a constant background field, \( H_0 \), will be

\[ \Delta \mathcal{H}_i(\mathbf{r}) = \mathcal{H}(\mathbf{r}) - H_0(\mathbf{r}) = H_0 \sum_i \frac{\delta}{\delta z} \left[ \chi'_i V'_i(\mathbf{r}) \left( \frac{z}{|\mathbf{r}|^3} \right) \right] \]  

[4.6]

summed over each compartment, \( i \). Only the field distortion parallel to the imposed field along the \( k \)-vector, \( \Delta \mathcal{H}_z \), is needed for this method, as that is the component provided by the phase/field map (Appendix A). Note that the field distortion described by the right hand summation term is independent of imposed background field distortion. For the field model determination, this is based on the assumption of negligibility in equation [4.2]. In the MRI data measurements (equation [3.1(b)]), the background field is corrected with the background phantom scan, by virtue of the assumption of superposition. The assumption of superposition was shown to be reasonable in Chapter III.

If the volumetric function, \( V'_i(\mathbf{r}) \), is known, for any compartment \( i \), the field can be estimated,

\[ \Delta \mathcal{H}_{z,i}(\mathbf{r}) = \frac{H_0}{4\pi \delta z} \left[ \chi'_i V'_i(\mathbf{r}) \left( \frac{z}{|\mathbf{r}|^3} \right) \right] \]  

[4.7]

As the susceptibility is assumed to be a constant value across the compartment, then the susceptibility parameter can be brought outside of the partial derivative,
\[ \Delta H_{t_i}(\vec{r}) = \chi' \frac{H_o}{4\pi \delta z} \left[ V'_{i}(\vec{r})^* \left( \frac{z}{|\vec{r}|^3} \right) \right] \]  \hspace{1cm} \text{[4.8]}

The induced field can now be calculated independent of the susceptibility,

\[ \Delta \vec{H}_{t_i}(\vec{r}) = \frac{\Delta H_{t_i}(\vec{r})}{\chi'_{i}} = \frac{H_o}{4\pi \delta z} \left[ V'_{i}(\vec{r})^* \left( \frac{z}{|\vec{r}|^3} \right) \right] \]  \hspace{1cm} \text{[4.9]}

where \( \vec{H}_{t_i} \) is the k-vector field component of the field due to compartment \( V'_{i} \), normalized for the differential scalar susceptibility, \( \chi'_{i} \). The field distortion due to compartment \( i \), becomes,

\[ \Delta H_{t_i}(\vec{r}) = \chi'_{i} \Delta \vec{H}_{t_i}(\vec{r}) \]  \hspace{1cm} \text{[4.10]}

The total field will be the sum of the field due to each compartment, as in figure 4-3(b),

\[ H_{t}(\vec{r}) = H_o + \sum_{i} \chi'_i \Delta \vec{H}_{t_i}(\vec{r}) \]  \hspace{1cm} \text{[4.11]}

The differential susceptibility of each compartment, \( \chi'_{i} \), can be estimated by using a linear least-squares estimation (LSE) (Press, 1989) of the modeled field (equation [4.11]) to the MRI phase/field map data generated from the MRI Field Echo acquisition. The LSE fit begins with arbitrary initial susceptibility values and iteratively adjusts the susceptibility values until the smallest absolute error between the modeled field and the acquired field data is found. The final susceptibility must be calculated from the differential susceptibility, \( \chi'_i = \chi_i + \chi_{soro} \).

\textbf{IV.5.B Linear Least Squares Estimation}

In any comparison of models to data, some error will occur,
\[ e(\bar{r}, \bar{\chi}) = \Delta H_{MRI\ Field\ Data}(\bar{r}, \bar{\chi}) - \Delta H_{Field\ Model}(\bar{r}, \bar{\chi}) \]  \[4.12\]

where the field data is obtained as in equation [3.1(b)] and the model data is as given in equation [4.11]. The least squares fit minimizes this error with respect to the susceptibility,

\[ \bar{\chi} = \min_{\bar{\chi}} \sum_{k=1}^{N} e_k(\bar{r}, \bar{\chi})^2 \]  \[4.13\]

The data points, \( k \), over which the least squares fit is made are restricted to the region within the external phantom.

**IV.6 Experimental Estimation of Susceptibility**

**IV.6.A Materials and Methods**

The application of the general algorithm was tested using the system of in vitro spheres described in Chapter III for which DFC field models from the sphere geometry were examined and susceptibility estimated as in equation [4.13].

In vitro phantoms constructed as in Chapter III were measured above a reference water bath. Separate spherical phantoms (volume = 50 +/- 0.1 cc, and radius = 2.27 +/- 0.05 cm) were filled with solutions of aqueous Iron Chloride (Fe2Cl3-6H2O, Sigma) (20.7 uM, 44.2 uM, 55.9 uM, 67.7 uM, 79.4 uM, 91.2 uM, 114.6 uM +/- 2.5%), made from serial dilutions. Absolute susceptibility for iron chloride solutions can be predicted from physical constant formulae (Weast, 1982) for comparison to the estimated susceptibility (c.f. Table 3-1). A second set of spheres of equivalent
susceptibility were filled with a super-paramagnetic iron solution (AMI-25, Biomagnetics) (58.6 nM, 125 nM, 158.2 nM, 191.4 nM, 224.6 nM, 257.8 nM and 342.2 nM). The concentrations were chosen to give differential susceptibility equivalent to the Iron Chloride solutions. Similar to the procedure in Chapter III, the MRI data of the water bath and balloons, as well as a background scan of the water bath alone, were acquired.

The spatial positioning of the spheres in each experiment was obtained from the MRI magnitude reconstruction with an spatial resolution of +/- 0.69 mm along the x and y axes, and the DFC field was calculated individually for each compartment. The susceptibility of these spheres were estimated using the LSE fit described above in equations [4.12-13].

For these experiments, a region of fit was chosen which reflects the method of data collection for the in vivo method. That is, for the in vivo measurements, the fit must be made in the external phantom located underneath the liver (as in figure 4-2). For consistency, the fits of in vitro fields were made in the same relative region respective to the spheres, that is, in the data space which lies directly beneath, but not overlapping, the modeled spheres (figure 4-3).

IV.6.B Statistics

The correlation between two data sets was defined in equation [3.4].
IV.7 Results and Discussion

IV.7.1 In Vitro Spheres - Susceptibility Estimation

The susceptibility estimation method (figure 4-1) was applied to a set of in vitro phantom spheres for which MRI measured field data and DFC modeled field data. The relationship between the MRI estimated and known susceptibility values is shown in figure 4-4, for which an excellent correlation is observed ($r > 0.9975$) for all data.

While the similarity of curves between MRI data and analytical models in Chapter III indicated that the field distortion data could be predicted and measured, the application of the susceptibility estimation algorithm shows that an unknown parameter can be resolved from this data.

IV.8 Summary

To summarize the method, susceptibility is estimated by fitting magnetic field data to a magnetic field model. The magnetic field data is obtained from the phase reconstruction of an MRI GFE sequence, and may be influenced by systemic MRI noise. The magnetic field model is generated by a DFC field calculation on the geometry of the objects of interest. The geometrical model is obtained by segmentation of the magnitude reconstruction of the same GFE sequence which provided the field data.

The basic premise of measuring field distortion in the MRI was investigated in
Correlation of Susceptibility and MRI Estimates

![Graph showing correlation between MRI susceptibility estimate and susceptibility](image)

$Y = 0.03 + 0.99 X$

$r > 0.997$

Figure 4-4. The MRI susceptibility LSE method is tested with 6 spheres of differing susceptibility and paramagnetic contents (FeCl$_3$ and AMI-25) by measuring the fields, DFC modeling the fields and LSE fitting the susceptibility. The known susceptibility is computed from CRC and compared weel to the MRI susceptibility ($r < 0.999$).
Chapter III and shown to be sound. The estimation method has now been shown to be adequate to provide accurate results for in vitro measurements of simple geometry. Other assumptions made in this chapter that need to be tested are the neglect of higher orders of field distortion, the assumption of compartment homogeneity, and the effect of experimental error on the susceptibility estimation.

Introduction of experimental error or noise into this method will effect the estimation of susceptibility. The various forms of error, such as inherent MRI field noise, or error in the geometrical model, and their consequences are discussed in Chapter VII. The restriction of the number of model compartments and the choice of points which are included in the Least Squares fit must also be tested for boundaries of use. To make these tests, analytical and DFC numerical solutions, as well as in vitro and in vivo MRI experiments will be used. The choice of the region of fit and the effects of noise will be discussed in Chapter VI. In the next chapter, an in depth examination of the DFC method the application is made.
Chapter V Magnetostatic Field Calculation of Arbitrary Geometry using a Discrete Fourier Convolution Method

V.1 Introduction

The MRI susceptibility estimation method, which measures the magnetic field external to the subject and could be used to estimate the bulk magnetic susceptibility of the liver was proposed in Chapter IV. This method requires that the magnetic fields induced by a human torso placed in the magnetic field of the MR imager be known. This chapter presents a discrete convolution method to compute the fields induced by an arbitrary object placed in a static, homogeneous field, and provides examples of its applicability and accuracy when applied to the MRI field mapping problem.

The rapid calculation of the static field associated with a SQUID device measurement has been discussed by Hoare and co-workers (Hoare, 1988). That work shows the results for Discrete Summation (DS) method of solution of the magnetostatic equation in comparison to a reciprocity solution method which is suitable for the SQUID measurement. A Reduced Discrete Summation (RDS) method was also introduced by Hoare which takes advantage of approximations to the magnetostatic solutions for an object in a field. The RDS (a modified DS method) is applicable to the case of MRI measurements, although the computation time required to obtain solutions for intricate arbitrary objects (i.e., the human torso) remains high.

The analysis of the magnetostatic equations for the problem of an arbitrary
object in a magnetic field, and the nature of the MRI measurement has resulted in the Discrete Fourier Convolution (DFC) solution method presented in this chapter. This method can reduce the computation needed for solution by large factors over the DS and RDS methods. The approach is similar to an iterative convolution solution to time-varying potentials (Borup, 1987). However, due to the static nature of the MR magnetic field problem and the small susceptibility values of the human torso, it can be implemented in a single iteration.

The DFC method presented is analogous to the development and analysis of a three-dimensional filter problem using Fourier transforms (FTs). To examine the behavior of the DFC method, the behavior and validity of the FT of the filter function specific to the DFC problem must be determined. The discrete FT of this filter function must also be examined for unacceptable behavior. The accuracy of the method is assessed by comparing it to the results obtained using analytical solutions for a model of perfect, concentric spheres.

Finally, it is shown that the DFC method can be used to estimate the magnetic susceptibility of multi-compartmental objects of arbitrary geometry. Possible sources of error in this method are examined for their effect on the parameter estimates. The results indicate that the method may be used in bio-magnetic susceptibility estimation problems, such as in liver iron overload diseases, where susceptibility measurements correlate with in vivo iron levels.
V.2 Magnetic Scalar Potential Evaluation

Magnetostatic theory provides a general solution for the action of a field $\vec{H}(\vec{r})$ upon a magnetized object $\vec{M}(\vec{r})$ as described by Maxwell’s equations for a magnetic field,
\begin{align*}
\nabla \times \vec{H}(\vec{r}) &= 0 \quad [5.1(a)] \\
\nabla \cdot \vec{H}(\vec{r}) &= -4\pi \nabla \cdot \vec{M}(\vec{r}) \quad [5.1(b)]
\end{align*}

These equations show that $\vec{H}(\vec{r})$ is derivable from a potential, much like an electrical potential, and that $-\nabla \cdot \vec{M}(\vec{r})$ acts as a magnetic charge density. Thus, with the field-potential relationship,
\begin{equation}
\vec{H}(\vec{r}) = -\frac{1}{4\pi} \nabla \Phi(\vec{r}) \quad [5.1(c)]
\end{equation}

we have a Poisson equation,
\begin{equation}
\nabla^2 \Phi(\vec{r}) = 4\pi \nabla \cdot \vec{M}(\vec{r}) \quad [5.2]
\end{equation}

The potential at any point, $\vec{r}$, will be influenced by all source points, $\vec{r}'$, which are in contained within the volume, $V'$, of the magnetized object, $\vec{M}(\vec{r}')$ (figure 5-1(a)).

This influence will decrease with distance, by way of the dipole function operator $\frac{1}{|\vec{r} - \vec{r}'|}$. The relationship between the source point, $\vec{r}'$, and the point at which the potential is desired, $\vec{r}$, is shown in figure 5-1(a), where $\vec{r} = xi + yj + zk$. From general texts on electrodynamics, (i.e., Jackson, 1961), the solution to [5.2] for the static case can take the form,
\begin{equation}
\Phi(\vec{r}) = \int_{V'} \vec{M}(\vec{r}') \cdot \nabla \left( \frac{1}{|\vec{r} - \vec{r}'|} \right) d^3r' \quad [5.3]
\end{equation}

The field generated by the magnetized object can be derived from the gradient of the scalar potential (equation [5.1(c)]) is,
Figure 5-1. (a) The magnetic potential at any point $\vec{r}$ due to an object $V'$. 
\[
\overline{H}(\vec{r}) = -\frac{1}{4\pi} \nabla \cdot \Phi(\vec{r}) = \overline{H}_o(\vec{r}) - \frac{1}{4\pi} \nabla \cdot \int_{\vec{r}'} \overline{M}(\vec{r}') \cdot \nabla' \frac{1}{|\vec{r} - \vec{r}'|} d^3r' \quad [5.4]
\]

where the additional background term of the static field, \(\overline{H}_o(\vec{r})\), appears as a constant of integration. For the remainder of this discussion both the scalar potential and the field vector will be referred to interchangeably, as the field vector can easily be established from the scalar potential.

When current-based field sources are negligible (i.e. no sources), then the principle of superposition holds, and the resulting magnetization vector is linear with the applied field, \(\overline{M}(\vec{r}') = \chi(\vec{r}') \overline{H}(\vec{r}')\). In this analysis, it is assumed that the susceptibility, \(\chi(\vec{r})\), of all objects is composed of some combination of paramagnetic, diamagnetic or superparamagnetic materials. Ferromagnetic objects are not considered in this model. Expressing the field vector as the applied field plus the induced field, \(\overline{H}(\vec{r}) = \overline{H}_o + \Delta \overline{H}(\vec{r})\) leaves

\[
\overline{M}(\vec{r}') = \chi(\vec{r}') \overline{H}_o(\vec{r}') + \chi(\vec{r}') \Delta \overline{H}(\vec{r}')
\]

By noting that the induced field distortions are on the order of \(\Delta \overline{H}(\vec{r}) = \overline{H}_o \Delta \chi_{\text{max}}\), which are on the order of +/-10 parts per million (ppm) in the human torso, then the magnetization vector becomes,

\[
\overline{M}(\vec{r}') = \chi(\vec{r}') (\overline{H}_o(\vec{r}') + \chi_{\text{max}}(\vec{r}') \overline{H}_o(\vec{r}'))
\]

\[
= \chi(\vec{r}') \overline{H}_o(\vec{r}') (1 + \chi_{\text{max}}(\vec{r}'))
\]

\[
= \chi(\vec{r}') \overline{H}_o(\vec{r}')
\]

as \(1 + \chi_{\text{max}}(\vec{r}') \approx 1\). This assumption will be discussed in greater detail later (section V.7.F). With this simplification, after applying the gradient operation on the dipole function in the scalar potential equation [5.3], results in,
\[ \Phi(\tilde{r}) = - \int \chi(\tilde{r}') \overline{H}_o(\tilde{r}') \cdot \frac{\tilde{r} - \tilde{r}'}{|\tilde{r} - \tilde{r}'|^3} d^3 r' \]  

which must now be evaluated.

V.3 Discrete Summation Methods

A discrete approach to the solution of equation [5.6] discretizes the vector space into LxMxN volume elements, or voxels, as in Figure 5-1(b) (Hoare, 1988). With the same assumptions that led to equation [5.6], but by applying discrete summation rather than integration, arrives at a potential given by,

\[ \Phi(\tilde{r}) = -V \sum_{\tilde{r}'} \chi(\tilde{r}') \overline{H}_o(\tilde{r}') \cdot \frac{\tilde{r} - \tilde{r}'}{|\tilde{r} - \tilde{r}'|^3} \]  

[5.7(a)]

Hoare introduces a RDS approximation that takes advantage of the large fall-off of the inverse cubed Green’s function (the furthest right component of equation [5.7(a)]). They note that any contribution to the scalar potential by a magnetized human torso will be negligible at a distance greater than twice the radius of the torso.

The RDS method is made by reducing the number of points which are included in each summation step of equation [5.7(a)],

\[ \Phi(\tilde{r}) = -V \sum_{i=M/2}^{M/2} \sum_{j=N/2}^{N/2} \sum_{k=N/2}^{N/2} \chi(i, j, k) \overline{H}_o(i, j, k) \cdot \frac{\tilde{r} - \tilde{r}(i, j, k)'}{|\tilde{r} - \tilde{r}(i, j, k)'|^3} \]  

[5.7(b)]

The number of discrete sums which contribute to each potential is reduced to 

\((L + 1)(M + 1)(N + 1)\) summations at each point \(\tilde{r}\). Hoare, et. al., suggest that summation of 13 \(1\text{-cm}^3\) elements along each x, y, and z direction is sufficient to provide a magnetic field representation of the human torso. They do not examine in detail the
nature, or extent of, the error which either method introduces into the potential solution.

The major drawback to these approaches are the large computation time required in order to achieve adequate resolution. Computation of the DS method for an object of 16 voxels in diameter located in a 32x32x32 voxel space requires at least $2^{32}$ floating point operations ($4*(2^5)^3$ operations at each of $(2^5)^3$ points or 4 GFlop, where 1 GFlop = $2^{30}$ Flop), which requires up to 240 minutes on a 20 MHz personal computer. The RDS method applied to the same object reduces computation to under 32 MFlop. For the MRI problem, field distortion data from MRI phase information can provide spatial data consisting of up to 256x256x64 points, requiring 64 TFlops ($4*(2^8*2^8*2^6)$ operations at each point, where 1 TFlop = $2^{40}$ Flop) to solve using the DS method. Using Hoare's RDS method, this would reduce to about 64 GFlops ($4*(13^3)$ operations at each point). In order to make routine measurements of susceptibility using MRI data a less computationally intensive solution is desired.

V.4 Discrete Convolution Method

A similar approach can be developed using FTs. Given any two arbitrary functions, $a(r)$ and $b(r)$, for which the Fourier integrals exist, $A(\omega) = \mathcal{F}[a(r)]$ and $B(\omega) = \mathcal{F}[b(r)]$, the convolution property of the FT states that the multiplication of two Fourier space functions is equivalent to their convolution in real space (Papoulis, 1962; Rabiner, 1975; Oppenheim, 1975),
Discrete Method for Field Calculation

Voxel space (V) with object (V')

\[
\mathbf{r} = \hat{x} \mathbf{i} + \hat{y} \mathbf{j} + \hat{z} \mathbf{k}
\]

\[
\mathbf{r'} = \hat{x} \mathbf{i} + \hat{y} \mathbf{j} + \hat{z} \mathbf{k}
\]

\[
H(i) = H_0 i - \frac{V}{4 \pi} \sum_{V'} X(i) H_o(i') \cdot \frac{(i - i')}{|i - i'|^3}
\]

Discrete magnetostatic equation

Figure 5-1. (b) In the Discrete Method for Field Calculation the field is computed for each point \( \mathbf{r} \) by summation of each point \( \mathbf{r}' \) of the product of Magnetization \( (\chi(\mathbf{r}')H(\mathbf{r}')) \) and Green's Vector \( (\mathbf{r}' - \mathbf{r} \mid \mathbf{r}' - \mathbf{r}) \). Inspection of the summation reveals a convolution, which is the basis for the DFC method.
\[ a \ast b = \mathcal{F}^{-1}\{\mathcal{F}(a \ast b)\} = \mathcal{F}^{-1}\{\mathcal{F}(a) \cdot \mathcal{F}(b)\} = \mathcal{F}^{-1}\{A \cdot B\} \quad [5.8] \]

This property holds in the case of n-dimensional convolutions. The use of FFT algorithms makes Fourier-Space convolution significantly faster than traditional real space convolution (Brigham, 1974). To use this property, the scalar potential solution equation [5.6] can be arranged into a 3-D convolution. Since superposition holds for this problem, then;

1) The axes are chosen so that the applied field is constant along \( z \), so
\[
\vec{H}_o(\vec{r}) = H_o \hat{k}.
\]

2) Without altering the potential, the limits of the integral can be incorporated into the susceptibility function, and the limits of integration can be extended to infinity. So [5.6] becomes,
\[
\Phi(\vec{r}) = -H_o \int_{-V}^{V} \tilde{\chi}(\vec{r}') \hat{k} \cdot \frac{\vec{r} - \vec{r}'}{|\vec{r} - \vec{r}'|^3} d^3r' \quad [5.9]
\]

where the susceptibility vector is now,
\[
\tilde{\chi}(\vec{r}') = \begin{cases} 
0 & \text{for } |\vec{r} - \vec{r}'| > V \\
\chi(\vec{r}') & \text{for } |\vec{r} - \vec{r}'| \leq V
\end{cases}
\]

3) The dot product in [5.9] is multiplied through, and the sign of the dipole function is switched, to give,
\[
\Phi(\vec{r}) = H_o \int_{-V}^{V} \tilde{\chi}(\vec{r}') \frac{z' - z}{|\vec{r}' - \vec{r}|^3} d^3r' \quad [5.10]
\]

4) Now, by examination of [5.10] it can be seen that this function is a 3-D convolution of the form,
\[
\Phi(\vec{r}) = H_o \tilde{\chi}(\vec{r}) * \left( \frac{z}{|\vec{r}|} \right) \quad [5.11]
\]
The vector function on the far right of equation [5.11] is a combination of the uniform, single vector applied field \( (H_o \hat{k}) \) and the vector dipole Green’s function inherent to the magnetic scalar potential solution. This function will be referred to as the "field-dipole" function.

Equation [5.6] may now be evaluated by taking the 3D-FT of both the susceptibility function and the field-dipole function, multiplying them together, and inverse transforming them, to give,

\[
\overline{H}(\vec{r}) = H_o \hat{k} + \frac{1}{4\pi} \nabla \cdot \left( [\tilde{\chi}(\vec{r})] H_o \hat{k} \cdot \left[ \frac{\vec{r}}{|\vec{r}|^3} \right] \right) \\
= H_o \hat{k} + \frac{H_o}{4\pi} \nabla \cdot \left( \mathcal{F}^{-1} \mathcal{F}^l \tilde{\chi}(\vec{r}) \cdot \mathcal{F} \left[ \frac{z}{|\vec{r}|^3} \right] \right) \tag{5.12}
\]

This DFC method has altered the form of the field solution from an integration solution to a filter application, with an input of the susceptibility vector, operated on by the field-dipole filter, resulting in an output of the magnetostatic potential. The magnetostatic potential is then further operated on by a gradient operator and scalars to arrive at the field vector solution.

The DFC method reduces computations to about 16 MFlops for the 32x32x32 volume space and requires less than 200 seconds to solve. The DFC offers potential improvements in calculation speed (up to 72-fold) at the expense of only a small potential error. The ratio of improvement in computation time for the DFC versus DS method follows the familiar \( N \log_2(N) \) rule (Brigham, 1974). In addition, for any particular voxel set of \( L \times M \times N \), the FFT of the field-dipole function need be generated only once.
V.5 Field-Dipole Function Evaluation

At the beginning of the previous section, it was stated that two functions may be convolved in Fourier space, provided that Fourier integrals exist for each function. In this section, the filter function will be examined to ensure that it is well-behaved in frequency space. In particular, the field-dipole function is discontinuous at zero, and may not be accurately represented following Discrete Fourier transformation. The field-dipole function is,

\[ f(\vec{r}) = \frac{z}{|\vec{r}|^3} = \frac{z}{(x^2 + y^2 + z^2)^{3/2}} \]  

[5.13]

Concerning the existence of a Fourier transform for any function, Papoulis states,

"If \( f(t) \) is absolutely integrable in the sense

\[ \int |f(t)| \, dt < \infty \]  

[5.14]

then its Fourier integral \( F(\omega) \) exists."

It should be noted that this is a sufficient, but not necessary condition. This can be extended to multiple dimensions, where if,

\[ \int |f(\vec{r})| \, d\vec{r} < \infty \]  

[5.15]

then the Fourier integral \( F(\vec{\omega}) \) will exist. Then, the integrability of [5.15] is

\[ \int |f(\vec{r})| = 2 \int_0^\infty \int_0^\pi \frac{z}{(x^2 + y^2 + z^2)^{3/2}} \, dz \, dy \, dx \]  

[5.16]

where the absolute value of the function has altered the limits of integration along \( z \). Introducing the transformation of variables \( x = a \cos \theta, \ y = a \sin \theta \) and

\( dx \, dy = ada \, d\theta \), with appropriate integral limits altered to also reflect the coordinate
change as well as the imposed absolute values ([5.15]), leads to

\[
\int f(\vec{r}) \, d\vec{r} = 4 \int_0 ^{\infty} \int_0 ^{\infty \frac{a \sqrt{2}}{(a^2 + z^2)^{3/2}}} d\theta \, dz \, da
\]

\[
= 4\pi \int_0 ^{\infty \frac{-a}{(a^2 + z^2)^{1/2}}} \left| \frac{1}{a^2} \right| da
\]

\[
= 4\pi \int_0 ^{\infty \frac{a}{(a^2)^{1/2}}} da
\]

\[
= 4\pi a \left| \int_0 \right.
\]

\[
= \infty \quad [5.17]
\]

so that the condition stated in equation [5.15] doesn’t insure that a Fourier integral exists.

Another conditional test of the Fourier integrability of a function (paraphrased) from Papoulis, is that;

"If \( f(t) \) is a monotonically decreasing function and if, for \( t \geq 0 \), the function \( f(t)/t \) is absolutely integrable, then \( F(w) \) exists."

By limiting the integrability of the function to non-zero values, \( a \geq 0, \, z \geq 0 \), then the lower limits of integration will be \( a = \eta, \, z = \nu \) which are values infinitesimally larger than zero. In this case, testing the integrability of \( f(\vec{r})/\vec{r} \)
\[ \int \frac{f(r)}{r} \, d\bar{r} = 4 \int \int_{\eta} \int_{\eta} z^2 \frac{a^2}{(a^2 + z^2)^{3/2}} \, d\theta \, dz \, da \]

\[ = 4\pi \int_{\eta} \int \frac{-3a}{(a^2 + z^2)^{3/2}} \int_{-\nu}^{\nu} da \]

\[ = 12\pi \int_{\eta} \frac{a}{(a^2 + \nu^2)^{3/2}} \, da \]

\[ = 12\pi \frac{-1}{(a^2 + \nu^2)^{1/2}} \int_{\eta} \]

\[ = \frac{12\pi}{(\eta^2 + \nu^2)^{1/2}} \quad |\eta|, |\nu| > 0 \quad [5.18] \]

As the function does decrease monotonically, then a Fourier transform can be certain to exist, and it will be well-behaved over all frequency space. This is an important conclusion, for it verifies that the field-dipole function may be used as a convolution filter. This does not imply that the transform will be analytically solvable, but this is not required for it's use as a filter, particularly in the discrete case used in this analysis.

V.6 Discrete Field-Dipole Filters

In practice, the transform of the Green's function is not used. Rather, a discretely sampled version is. The discrete form of the field-dipole function will be noted by

\[ h(l, m, n) = \{ f(x, y, z) \} \quad [5.19] \]
The stability of this function when used as a discrete multiple dimension filter must be examined. The stability criterion of a discrete filter is similar to the Fourier transform existence theory [5.14]. If in one dimension

\[ \sum_{n=-\infty}^{\infty} |h(n)| < \infty \]  \hspace{1cm} [5.20]

then the discrete filter is said to be stable (Rabiner, 1975; Oppenheim, 1975). For a finite impulse response (FIR) filter of three dimensions, where the filter is bounded in space by the windows,

\[
L_{\text{min}} \leq l \leq L_{\text{max}} \\
M_{\text{min}} \leq m \leq M_{\text{max}} \\
N_{\text{min}} \leq n \leq N_{\text{max}}
\]  \hspace{1cm} [5.21]

the stability condition is

\[ \sum_{l=L_{\text{min}}}^{L_{\text{max}}} \sum_{m=M_{\text{min}}}^{M_{\text{max}}} \sum_{n=N_{\text{min}}}^{N_{\text{max}}} |h(l,m,n)| < \infty \]  \hspace{1cm} [5.22]

Any FIR filter will be stable as, by definition, a finite number of terms are included, each of which must be finite in value. However, when discretely sampling the field-dipole function, a discrete sample taken at the origin will yield \( h(0,0,0) = +\infty \). This singularity at the origin can be adjusted, by forcing the point at the origin to \( f(0,0,0) = 0 \) as in figure 2(a). This may have the effect of adversely altering the filter function beyond the desired response. No concrete reason exists to require sampling at the center point of the coordinate system. However, as the field dipole filter is odd-wise symmetric about zero, the window boundaries must extend equally to either side of the origin, \( L_{\text{max}} = -L_{\text{min}}, M_{\text{max}} = -M_{\text{min}}, \) and \( N_{\text{max}} = -N_{\text{min}} \) in order to make the filter zero-gain (recall that there are no sources in this system, so
that no net change of energy should occur). It is also necessary that the number of points in any one direction be of the form \(2^j\) in order to benefit from the computational speed improvement of the FFT. These requirements force the window boundaries to be

\[
-(L - 1)/2 \leq l \leq (L - 1)/2 \quad L = 2^a \\
-(M - 1)/2 \leq m \leq (N - 1)/2 \quad M = 2^b \\
-(N - 1)/2 \leq n \leq (M - 1)/2 \quad N = 2^c \quad [5.23]
\]

where the power factors \((a, b, c)\) are chosen to match the available input. This choice of window boundaries fortuitously avoids sampling at the origin (figure 2(b)). One important note on the choice of the window boundaries on spatially varying functions, is that if the window boundaries of the filter are shifted in space with respect to the input function, then the output function will also be shifted in space (Lim, 1990). When applying the field-dipole function as a filter, the same region of space must be used in the discrete input vector \((\tilde{\chi}(\vec{r}))\) and the filter in order to observe the output over that region of space. If the input and the filter are spatially shifted with respect to each other, then the output will also be spatially shifted. Therefore, the same window boundaries ([5.23]) must also be applied to the susceptibility vector.

Although the filter has been shown to be well behaved, there will always be some loss of high frequency (HF) signal in a discrete sampling of information (Oppenheim, 1975). This loss will occur for both the susceptibility vector and the field-dipole filter, and will appear in the output as edge ringing, known as Gibb’s artifact. The effect of this ringing, or HF loss, can be observed by comparing analytically derived solutions of a field to DFC derived field solutions.
Figure 5-2. After taking the dot product of the magnetization and the Green's Function, a single dimensional 'field-dipole' vector will result, $z/| \vec{P} - \vec{r} |^3$ (a) The representation of the 'field dipole' vector along the xz-plane through $y=0$, where the indeterminate point at the origin has been artificially set to zero. (b) Forcing the data window to make avoid the zero-point sampling.
V.7 Comparison of Discrete Summation, Discrete Fourier Convolution and Analytical Solutions

V.7.1 Methods

The major advantage of a discrete approach is that field distortions due to arbitrary geometries may be computed, whereas analytical solutions to the magnetostatic equation are limited to cylindrical and spherical harmonic techniques based on symmetrical, regularizable shapes, such as spheres, ovoids, or cylinders. To compare these techniques, two concentric spheres of radius $R_a$ and $R_b$, with $R_a < R_b$, are positioned in the uniform field (figure 5-3) and examined with analytical and discrete methods while the radii of the spheres are altered. The concentric spheres model provides a good test for the sensitivity of the discrete methods for separating the field effects of several objects and object parameters (Rudy, 1979). The magnetostatic fields can be obtained from the well-known analytical solutions for these concentric spheres in a constant external field (Jackson, 1961). The analytical solution of the magnetic field for the concentric spheres in a vacuum with a static background field applied, as in figure 5-3, is,

$$H_x(\vec{r}) = -3\alpha \frac{z^2}{r^3}, H_y(\vec{r}) = -3\alpha \frac{x^2 y}{r^3}, H_z(\vec{r}) = H_0 - \alpha \frac{(2z^2 - x^2 - y^2)}{r^3} \quad r \geq R_b \quad [5.24(a)]$$

$$H_x(\vec{r}) = -3\beta \frac{x^2}{r^3}, H_y(\vec{r}) = -3\beta \frac{x^2 y}{r^3}, H_z(\vec{r}) = \beta - \gamma \frac{(2z^2 - x^2 - y^2)}{r^3} \quad R_b > r \geq R_a \quad [5.24(b)]$$

$$H_x(\vec{r}) = 0, H_y(\vec{r}) = 0, H_z(\vec{r}) = \delta \quad R_a > r \quad [5.24(c)]$$

where,
\[
\alpha = H_0 \left[ R_b^3 - \frac{R_a^3 (2 \mu_b - \mu_a) - R^3 b^3 (\mu_b - \mu_a)}{(2 - \mu_b) (2 \mu_b + \mu_a) R_b^3 + (1 - 2 \mu_b) (\mu_b - \mu_a) R_a^3} \right]
\]

\[
\beta = H_0 \left[ \frac{-R_b^3 (2 \mu_b - \mu_a)}{(2 - \mu_b) (2 \mu_b + \mu_a) R_b^3 + (1 - 2 \mu_b) (\mu_b - \mu_a) R_a^3} \right]
\]

\[
\gamma = H_0 \left[ \frac{-R_b^3 R^3_a (\mu_b - \mu_a)}{(2 - \mu_b) (2 \mu_b + \mu_a) R_b^3 + (1 - 2 \mu_b) (\mu_b - \mu_a) R_a^3} \right]
\]

\[
\delta = H_0 \left[ \frac{-3 R_b^3 \mu_b}{(2 - \mu_b) (2 \mu_b + \mu_a) R_b^3 + (1 - 2 \mu_b) (\mu_b - \mu_a) R_a^3} \right]
\]

for \( \mu_b = 1 + \chi_b \) and \( \mu_a = 1 + \chi_a \).

**V.7.B Partial and Discrete Voluming**

The DS, RDS, and DFC solutions can then be obtained for the same radii and susceptibility parameters as the analytical solution. The discrete convolution method is solved over 32x32x32 voxels using concentric spheres that are either partially-volumed or discretely volumed. A partially volumed sphere assigns analog values to each voxel based on the fractional volume of boundary voxels which are occupied by the sphere. A discretely volumed sphere is either one susceptibility value or the other, dependent on the percent volume of the boundary voxel occupied by the sphere. The first option is more reflective of real situations, particularly MRI, where an effective integration over a sampling volume is performed by a sensor device. It is, however, useful to make clear this distinction for those who may wish to duplicate this work.

The effect of partial voluming was first investigated using the DFC method. When discretely sampling a sphere volume, the edge of the sphere is chosen to lie
Figure 5-3. The Analytical Solution of Concentric Spheres is used to evaluate the field solutions of the discrete solutions methods, DS, RDS and DFC. The susceptibilities used ranged over 0, 0.5 and 1 x 10^6 cgs units. The relative radii ranged over 0.5, 0.9 and 0.9. The following field plots are shown along the x or z axis through the origin. Y-axial solutions are equivalent to the x-axial solutions due to cylindrical symmetry, and need not be shown.
either inside or outside of the radial boundary of the sphere. This sampling introduces a small error at the surface boundary. A partially volumed sphere is one in which the value of the voxel is chosen to reflect the volume of the voxel which lies within the sphere. Partial voluming is like applying an optimal smoothing filter to a boundary descriptor (Lim, 1990). In figure 5-4 the k-vector component of the field, $H_z$, is shown along the $z$-axis for a single sphere of 8 pixels in radius for the analytical solution, and DFC solutions of a discretely volumed sphere and a partially volumed sphere. The discrete volume approach shows much higher error compared to the analytical solution, especially at the object edge, than does the partial-volume approach. In practical applications, a sensor device (such as MRI) will sample a voxel as the integrated value of the volume in that voxel, which is the partial volume case. But, with partial voluming a good approximation of the field is achieved as in figure 5-4. Partial voluming will be used when solving discrete solutions of the concentric spheres geometry for the remainder of this paper.
Comparison of Analytical, Partially Volumed DFC and Non-Partially Volumed DFC Solutions at x=y=0, for R = 4

Figure 5-4. The effect of discrete sampling is observed by comparing partially volumed geometry and non-partially volumed geometry. (a) The use of partial-volume corrected geometry decreases the error to less than 15%, and only for 1 or 2 points on either side of the sphere edge. (b) The non-partially volume corrected solutions have edge error, as expected in any Fourier method, of up to 20%, but also have reduced volume which appears as a thinner object in cross-section.
Figure 5.4. (c, d, e) 2D-mesh plots of the Analytical solution, DFC Partial Volume corrected solution and DFC Non-Partial Volume corrected solutions show the qualitative effect of partial voluming. The boundary of the analytical solution is sharp, and for either DFC method, the boundary is less defined. The cross-sections of the DFC-calculated spheres show reduced width, which is improved in the partial volume corrected DFC method.
V.7.C Variation of Susceptibility and Volume with Field Estimation Technique

The $H_1$ field vectors along the x and z-axes for the analytical solutions are shown with three discrete solutions, DS, RDS and DFC in figures 5-5 to 5-11. Each series of figures includes mesh plots through the xz plane of the (a) Analytical solution, (b) DFC solution, (c) DS solution, and the (d) RDS solution, as well as the comparison of each discrete method along the x and z axes for (e) DFC vs. Analytical, (f) DS vs. Analytical and (f) RDS vs. Analytical solutions. Relative susceptibilities of $\chi_a/\chi_b = 0, 0.5$ and 0.9 were computed, while varying the relative radii of $R_a/R_b = 0$ (i.e. single sphere), 0.5 and 0.9. A summary of the radii and susceptibilities modeled are shown in Table 5-1 for clarity. All $H_1$ field vector components are displayed in as a normalized term, $H_1' = (H_1 - H_o)/H_o$. The $H_x$ and $H_y$ vector components of the field are present in the solutions, but need not be shown to make the point. The y-axis results of $H_1$ are not shown as the x-axis and y-axis results are equivalent, due to cylindrical symmetry. The susceptibility of the external medium was set to zero, or vacuum. The radii in figures 5-5 to 5-11 of the outer sphere was 8 pixels in a field of view of 65x65x65 voxels, and the radii of the center spheres of were 0, 4 and 7.2 pixels, respectively. These examples were all partially volumed.
Table 5-1 Analytical Sphere Parameters used in figures 5-5 to 5-11

<table>
<thead>
<tr>
<th>$R_s/R_b$</th>
<th>0</th>
<th>.5</th>
<th>0.9</th>
</tr>
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<tbody>
<tr>
<td>$\chi_s/\chi_b$</td>
<td></td>
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</table>

0  | l | Figure 5-5 | Figure 5-6 | Figure 5-9 |
0.5 | l | * | Figure 5-7 | Figure 5-10 |
0.9 | l | * | Figure 5-8 | Figure 5-11 |

* = same as Figure 5-5, which is a single sphere case
Figures 5-5. The 2-D mesh plots along the yz-plane (x=0) for (a) analytical, (b) DS, (c) RDS, and (d) DFC for $R_a/R_b = 0$, and $X_a/X_b = 0$.
Figures 5-5. The y and z axial comparisons of the analytical solutions with solutions using the (e, f) DS, (g, h) RDS and (i, j) DFC methods are shown along with the difference of each method with the analytical solutions for $R/R_s = 0$, and $\chi_e/\chi_s = 0$. 
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Figures 5-6. The y and z axial comparisons of the analytical solutions with solutions using the (e, f) DS, (g, h) RDS and (i, j) DFC methods are shown along with the difference of each method with the analytical solutions for $R_b/R_a = 0.5$, and $\chi_0/\chi_a = 0$. 

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Figures 5-7. The 2-D mesh plots along the yz-plane (x=0) for (a) analytical, (b) DS, (c) RDS, and (d) DFC for R_a/R_b = 0.9, and X_a/X_b = 0.
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Figures 5-9. The 2-D mesh plots along the yz-plane (x=0) for (a) analytical, (b) DS, (c) RDS, and (d) DFC for $R_a/R_b = 0.5$, and $\chi_a/\chi_b = 0.9$. 
Figures 5-9. The y and z axial comparisons of the analytical solutions with solutions using the (c, f) DS, (g, h) RDS and (i, j) DFC methods are shown along with the difference of each method with the analytical solutions for \( R_2/R_s = 0.5 \), and \( \chi_s/\chi_s = 0.9 \).
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Ra/Rb = 0.9, Xa/Xb = 0.5

Figures 5-10. The 2-D mesh plots along the yz-plane (x=0) for (a) analytical, (b) DS, (c) RDS, and (d) DFC for R_2/R_1 = 0.9, and \chi_1/\chi_2 = 0.5.
Figures 5-10. The y and z axial comparisons of the analytical solutions with solutions using the (e, f) DS, (g, h) RDS and (i, j) DFC methods are shown along with the difference of each method with the analytical solutions for $R_s/R_i = 0.9$, and $\chi_s/\chi_i = 0.5$. 
Figures 5-11. The 2-D mesh plots along the yz-plane (x=0) for (a) analytical, (b) DS, (c) RDS, and (d) DFC for \( \frac{R_s}{R_b} = 0.9 \), and \( \chi_a/\chi_b = 0.9 \).
Figures 5-11. The y and z axial comparisons of the analytical solutions with solutions using the (e, f) DS, (g, h) RDS and (i, j) DFC methods are shown along with the difference of each method with the analytical solutions for $R_a/R_b = 0.9$ and $\chi_y/\chi_z = 0.9$. 
The field derived by the discrete method is similar to the analytical field, with some error seen at the edges of the spheres, where the error is defined as the difference between the discrete and analytical solutions (all figures 5-5 through 5-11 (e, f and g)). The RDS approximation method described by Hoare et al., is prone to error (up to 150% error at the edges). Although the general shape is correct, this shape similarity will give isogauss contour plots that can disguise the total error, an interpretation which is not distinguished by Hoare. The results of the DFC method are almost identical to the DS method results, except at sphere boundaries and at the edges of the window, where the error appears to increase. For the DFC method, which is a filtering approach, an overshoot of the expected field at the edges of the object are seen, similar to Gibbs artifact of a low-pass filtered step function. This edge error can be as large as 50% at the edges, although this does not reflect the overall error, which will be examined later as correlation of the two field solutions. The filtering or aliasing effects are also investigated later. With very thin outer shells of less than one full voxel in width ($R_d/R_b = 0.9$, as in figures 5-9, 5-10 and 5-11), the DFC field estimation less accurately reflects the expected field in the outer layer, especially in the case where the interior susceptibility is near that of the external susceptibility ($\chi_d/\chi_b = 0.9$, figure 5-11). For very large edge differential, as in figure 5-9 ($R_d/R_b = 0.9, \chi_d/\chi_b = 0$), the field of the outer shell is effectively smoothed to half of the field value expected. When modeling thin shells, and/or large susceptibility differentials, the smoothing effect must be taken into consideration.

V.7.D Discrete Sampling

The error in the DFC method at the edge of the field of view window, suggested
that aliasing in the spatial domain may be responsible. Aliasing is a "folding-over" of information which has been excluded by the discrete windowing process and can occur in either the spatial or frequency domains (Bracewell, 1978; Oppenheim, 1975). Aliasing in the spatial domain can be reduced by increasing the window size relative to the object, or conversely, reducing the object size relative to the window (although the latter will introduce larger amounts of edge ringing error). The analytical and DFC solutions for single spheres of radii 8, 4, and 2 pixels in a field of view of 32x32x32 pixels are shown for z axis projections, along with a difference plot in figures 5-12(a, b and c). The error at the edge of the field-of-view is seen to quickly reduce when the ratio of window size to sphere size is increased from 5-12(a) through 5-12(c). Another detail which appears in this figure is an edge overshoot which increases as the samples per sphere are reduced. This type of overshoot, or ringing, is consistent with Gibb's artifact. This is an important result as it implies that near-edge field estimation of smaller arbitrary objects will be less accurate than of larger objects, when sampled at the same spatial frequencies. These sampling errors can be avoided with over-sampling and the choice of a field-of-view at least 4 times larger than the object being modeled.

The aliasing artifact can be explored further by "folding over", or artificially aliasing, an analytical solution of the $H_z$ field for a single sphere, which is compared to the DFC solution in figure 5-13. From this, it can be concluded that most of the window edge error in the DFC method is due to aliasing. The slight loss of less than 1 percent of field accuracy inside the sphere due to artificial "aliasing", is not seen in the DFC solution of the same diagram, but the cause of this discrepancy is unknown.
Figure 5-12. The effect of sphere radius relative to the 32x32x32 point volume computed is examined by reducing the radius of a single sphere to (a) 2, (b) 4 and (c) 8 pixels. The edge error in the R=2 sphere of (a) is twice the error in either the 4 or 8 pixel spheres of (b) and (c). Another effect is manifested as the diameter of the sphere increases, an error appears at the edges of the sampling window as in (c).
Comparison of DFC Solution and Aliased Analytical Solution, R=4

Figure 5-13. The window-edge error observed in figure 5-12(c) can be simulated by artificially aliasing the analytical solution by folding it over on itself. Comparison of the aliased analytical and DFC solutions indicate the likelihood of aliasing to be the cause of window edge error.
V.7.E Correlation of Discrete to Analytical Solutions

To relate the absolute difference between the FFT method to the analytical solution a correlation coefficient \( R \) is computed as,

\[
R = \frac{\sum_{i=1}^{n} (A_i - \mu_A) (D_i - \mu_D)}{\sqrt{\left( \sum_{i=1}^{n} (A_i - \mu_A)^2 \right) \left( \sum_{i=1}^{n} (D_i - \mu_D)^2 \right)}}
\]  \hspace{1cm} [5.25]

where \( A_i \) and \( D_i \) are the respective analytical and discrete solutions at each point \( i \). \( R \) is calculated over all \( n \) points in the 32x32x32 volume, with \( \mu_A \) and \( \mu_D \) computed as the mean field value for the entire volume for each respective solution method. This correlation coefficient was obtained for the analytical and partially-volumed DFC methods with 16 equally spaced points ranging over \( 0 \leq R_s/R_s < 1 \), with \( \chi_s = 10 \text{ppm} \) and 16 equally spaced points over \( 0 \leq \chi_s < 10 \text{ppm} \), and is graphically displayed in figure 5-14(a). This figure indicates that a high degree of correlation between analytical and discrete solution is present (\( R > 0.992 \)), but also indicates that higher susceptibility differential and thinner shell layers will contribute to the error.

As previously noted, there is a small aliasing artifact seen at the volume boundaries. By restricting the computation of the correlation coefficient to be only inside the magnetized object an even higher correlation coefficient (\( R > 0.9988 \)) over the same parameter set is observed (figure 5-14(b)). The discrete convolution method works best away from the borders of the sample space window. Higher correlation coefficients can be achieved by increasing the size of the sample space volume with respect to the magnetized object or by increasing the number of samples over the same space, reducing aliasing or Gibb's artifact error respectively, as shown in figure
Figure 5-14. Overall error is measured by correlation of the solution methods over all space. The worst case, where $R > 0.9925$ occurs when the differential susceptibility is highest, and when the outer sphere shell is thinnest.
5-12.

**V.7.F Higher Orders of Field Distortion**

The assumption made in equation [5.5] that higher orders of field do not significantly contribute to the potential was also tested. Recall that the magnetization of the object was given as $\bar{M}(\vec{r}) = \bar{\chi}(\vec{r}) \bar{H}(\vec{r})$. It was assumed that if the field vector is described as the applied field plus the induced field, $\bar{H}(\vec{r}) = \bar{H}_o + \Delta \bar{H}(\vec{r})$, then for $\bar{H}_o \gg \Delta \bar{H}(\vec{r})$ the magnetization will not be dependent on the field distortion $\Delta \bar{H}(\vec{r})$. A more accurate field solution can be obtained using an iterative convolution approach (Borup, 1987). Using this iterative method, beginning with an initial guess of $H^0(\vec{r}) = H_o \hat{k}$, a concentric spheres problem will converge after only 1 iteration, for convergence criteria of $10^{-5}$. The only difference in these iterations is that all three orthogonal field vectors are now present, so equation [5.12] becomes for each iteration $i + 1$,

$$\bar{H}^{(i+1)}(\vec{r}) = H_o \hat{k} + \frac{1}{4\pi} \nabla \cdot \left( [\bar{\chi}(\vec{r}) \bar{H}^i(\vec{r})] \star \left[ \frac{\vec{r}}{|\vec{r}|^3} \right] \right)$$

[5.26]

The 3D convolution term on the right side of [5.26] can be evaluated by separating into vector components,

$$[\bar{\chi}(\vec{r}) \bar{H}^i(\vec{r})] \star \left[ \frac{\vec{r}}{|\vec{r}|^3} \right] = [\bar{\chi}(\vec{r}) \bar{H}_x^i(\vec{r})] \star \left[ \frac{x}{|\vec{r}|^3} \right]$$

$$+ [\bar{\chi}(\vec{r}) \bar{H}_y^i(\vec{r})] \star \left[ \frac{y}{|\vec{r}|^3} \right] + [\bar{\chi}(\vec{r}) \bar{H}_z^i(\vec{r})] \star \left[ \frac{z}{|\vec{r}|^3} \right]$$

[5.27]

Using the iterative solution, the computed field distortion did not change by more than a factor of 10 ppm, as shown in figures 5-15(a,b) for a single sphere case ($\chi_o = 10 \times 10^{-6}$) and for concentric spheres, $R_o/R_s = 0.5$, and $\chi_a = 0$, $\chi_b = 10 \times 10^{-6}$. 
Examination of equation [5.26] shows that the error of any iteration will be proportional to the susceptibility, \( \chi(r) \). In the case of biological experiments, the maximum susceptibility differential will be that of an air-water interface, \( \Delta \chi = 10 \times 10^{-6} \). As seen in figure 5-15, the difference between the initial and first iterations are on the same order as the susceptibility differential. This justifies the assumption that \( H_o \approx \Delta H(r) \), and that equation [5.5] is reasonable. In cases where a very large susceptibility differential exists, such as with superparamagnetic materials (\( \chi > 2000 \times 10^{-6} \)), then larger, non-negligible fields may be produced which will require this iterative approach for higher accuracy. But, as seen in Table 3-1, the differential susceptibility expected in a human subject is less than +/- 10 ppm, so that the iterative method is not likely to be required. This approach will increase computation time at least four-fold for each single iteration. The iterative approach can be used to solve time-varying magnetodynamic problems, or problems with sources present, such as eddy-currents or ferromagnetic materials (Borup, 1987).

\section*{V.8 Discussion}

The application of the convolution method to the magnetostatic equation works well, as long as the maximum dimension of the susceptibility function is small relative to the window size of the entire sampled space to reduce aliasing. Except for the aliasing artifact, the results of the DFC are equivalent to the DS method. As the RDS method is an approximation of the DS method, and is known to have to reduced accuracy (Hoare, 1988), it is not surprising that the accuracy of both the DFC and the DS methods are greater than the RDS method.
Figure 5-15. a, b) Iterative improvement is possible using the DFC method. The initial and first iteration solutions are shown for (a) $\text{Ra/Rb} = 0$, $X_a/X_b$ = arbitrary, (b) $\text{Ra/Rb} = 0.5$, $X_a/X_b = 0.9$, and on the next page (c) $\text{Ra/Rb} = 0.5$, $X_a/X_b = 0.5$, and (d) $\text{Ra/Rb} = 0.5$, $X_a/X_b = 0$. For the static problem, iteration does not improve the estimate by more than 10 ppm per iteration.
Figure 5.15. c, d) See previous page for legend.
The field-dipole function goes to infinity at \( r = 0 \), which is avoided by shifting the axis of the field-dipole function. In doing so, the high frequencies of this function in Fourier space will be reduced, resulting in a small loss of accuracy. This error can be minimized by restricting the use of this technique to objects which have little high frequency spatial components as in the case of the human torso.

Comparison of the DFC method with the analytical extraction of the transformed field-dipole function shows that it is well-behaved, and may be used without restriction other than the spatial sampling shift. The overall error is seen as the smoothing that accompanies both the discrete sums method and the FFT convolution method. The reduced spatial summation method introduced by Hoare does not give accurate results when compared to the analytical solution comparable to expected biologic conditions. Aliasing due to the Fourier space windowing can be avoided by increasing the size of the field of view relative to the object. The high degree of correlation between discrete convolution and analytical solutions validates its use in practice. The large order reduction of computation time further justifies the use of the DFC method.

In conclusion, the DFC has been shown to reliably, accurately and quickly compute the static magnetic field of an arbitrary non-ferromagnetic object in three dimensions. The overall accuracy of the DFC solution is high in comparison to analytical solutions, is of equivalent accuracy to the DS method, is superior to the RDS method, and can be used in model predictions and measurements where spatially dependent three dimensional field signals can be obtained, such as in 3D-MRI.
Chapter VI - Least Squares Estimation of Magnetic Susceptibility in the Presence of Random and Biased Noise in the Field Data

VI.1 Introduction

In chapter IV the MRI Susceptometry method which required the generation of a field model via MRI which was LSE fit to MRI phase generated field data was introduced. In this chapter, an investigation will be made on the effect of noise and other parameters on the goodness of fit of a least squares estimation of susceptibility over a sub-space region near the object of interest. The purpose of this section is to examine the ability to estimate \( \chi \) in the presence of random noise and biased noise using the DFC and the LSE discussed in chapter IV. This chapter will form a basis for guiding the choice of position and size of the data examined in the LSE fit of either in vitro or in vivo experimental data. The factors which affect the field distortion, and the factors which can be altered to optimize the fit will be examined. In particular, the behavior of a LSE fit along the y-axis of a single sphere in a static field when altering the number of points in the fit \( n \), the sampling distance between points \( \Delta y \), and the position of the data set with respect to the modeled compartment \( \gamma_o \) will be examined. The effect of non-random error and subsequent filtering the data with either the random noise or biased error will also be investigated. Finally, the choice of the region of fit is examined for fields due to imperfectly spherical or arbitrary shapes.
VI.2 Random Noise

VI.2.1 Signal-to-Noise

For this chapter it is convenient to treat the magnetostatic field as a signal which varies in space, and make comparisons to classical signal theory (Oppenheim, 1975; Ljung, 1987). The estimation method used is the LSE (equations [4.12-4.13]), where error is defined as the difference between the field data and the field model. The error which will be examined in this section is limited to random, zero-mean, Gaussian noise of specific variance which is present in the field data, due to the MRI system. Later in this chapter non-random noise will be examined.

The S/N of the measurement can be defined by the ratios of variances,

\[
S/N = \frac{\sigma_{\text{noise + signal}}^2}{\sigma_{\text{noise}}^2}
\]  \hspace{1cm} [6.1]

where,

\[
\mu_x = \frac{1}{N} \sum_{i=1}^{N} x_i
\]  \hspace{1cm} [6.2]

\[
\sigma_x^2 = \frac{1}{N} \sum_{i=1}^{N} (x_i - \mu_x)^2
\]  \hspace{1cm} [6.3]

As the field strength is spatially dependent (i.e. a non-stationary probability density function), then the variance will also be influenced by its spatial position. The variance of any signal is a representation of the sum of the power spectra, and therefore reflects the strength of the signal in space (Oppenheim, 1975). Therefore, the S/N describes the relationship of the power of the signal to the power of the noise. For
random noise, the noise variance is assumed to be uncorrelated with the signal variance, so that,

\[
S/N = \frac{\sigma_{\text{noise}}^2 + \sigma_{\text{signal}}^2}{\sigma_{\text{noise}}^2} = 1 + \frac{\sigma_{\text{signal}}^2}{\sigma_{\text{noise}}^2}
\]  \hspace{1cm} [6.4]

An important effect of noise (or error) in LSE methods is that the larger the variance of the noise with respect to the variance of the model, the less accurate the estimate. That is, the larger the S/N, the better the fit.

If it is assumed that the differences between two objects are reflected in the field distortions, then the S/N is a function of background noise variance and total field distortion variance. For example, the S/N defined above will be larger for a data set which produces the highest field distortion. Any implications of improved S/N due to increased phase wrappings are absorbed in the overall field distortion inherent to the object under study. However, the distinction between whether low noise or high signal is the cause of the improved fit is unclear when the goodness-of-fit is based solely on S/N.

VI.2.B Noise in the Field Measurement

Conturo has shown that MRI phase noise differs from MRI magnitude noise by a scalar applied over the entire image (Conturo, 1990). The reason for introducing the scalar, is that the phase image is inherently phase wrapped due to the arctangent function (Appendix B). Following unwrapping, the variance is improved over the MRI magnitude variance by \( n \times 2\pi \), where \( n \) is the number of phase unwrappings.
VI.2.C LSE Model Variance

The LSE method (equations [4.12-4.13]) can be measured for "goodness-of-fit" by examining the sum of the squares of the error model,

\[ V_N = \sum_{i=1}^{N} e^2 = \sum_{i=1}^{N} (H_{\text{field, model}}(r_i) - H_{\text{field, data}}(r_i))^2 \]  \[ 6.5 \]

where the error model is the difference between the measured data and the modeled data. The LSE fit minimizes \( V_N \) with respect to the model parameters (in this case, susceptibility) (equation [4.13]).

As this LSE is quadratic, a fit is always found. But the concept of the goodness-of-fit is still in question. The model variance \( V_N \) is a quantitative measurement of the error, and is proportional to the product of the number of points and the noise variance, provided that the model is correct and only Gaussian, white noise is present,

\[ \sigma_n^2 = \frac{1}{N} \sum_{i=1}^{N} (H_{\text{model}}(r_i) - H_{\text{data}}(r_i) - \mu_n)^2 = \frac{1}{N} \sum_{i=1}^{N} (H_{\text{model}}(r_i) - H_{\text{data}}(r_i))^2 = \frac{V_N}{N} \]  \[ 6.6 \]

Separate identities for the noise variance and the model variance are needed for those cases when the system noise is non-random or non-stationary. If \( V_N \) is low, the model error is low, and the fit is good, and so forth. Conversely, increased noise reduces the quality of fit. Again, this only examines the effect of the noise or error on fit, and not the effect of the model itself, or the effect of S/N.

VI.2.D LSE Covariance as a measure of Goodness-of-Fit

A qualitative measurement of the goodness of fit which includes model error, data noise and model signal variation is the asymptotic covariance matrix of the
model (Ljung, 1987). The covariance matrix of the parameter set \( \overline{\Theta} \) estimated over \( N \) points is defined (Ljung, 1987) as,

\[
Cov\overline{\Theta}_N = \frac{1}{N} P_\Theta = \frac{1}{N} \frac{V_N}{E[JJ^t]} \tag{6.7}
\]

where the Jacobian is,

\[
\overline{J}_i = \delta \overline{e}(r_i, \Theta_N)/\delta \overline{\Theta}_N \tag{6.8}
\]

and the expected value of the Jacobian is

\[
E[JJ^t] = \frac{1}{N} \sum_{i=1}^{N} \overline{J}_i \overline{J}_i^t \tag{6.9}
\]

The Jacobian of the error model is

\[
\overline{J}_i(r_i, \Theta_N) = \frac{\delta e(r_i, \Theta_N)}{\delta \Theta_N} = \frac{\delta[H_{\text{field data}}(r_i) - H_{\text{field model}}(r_i, \Theta_N)]}{\delta \Theta_N} = \frac{-\delta H_{\text{field model}}(r_i, \Theta_N)}{\delta \Theta_N} \tag{6.10}
\]

When examining the perfect spheres model for a single sphere (from equation [5.24]), the parameter set is a scalar, \( \overline{\Theta}_N = \Delta \chi \), and the Jacobian becomes,

\[
\overline{J}_i(r_i, \Theta_N) = -\frac{\delta H_{\text{field model}}(r_i, \Theta_N)}{\delta \Theta_N} = -\frac{\delta}{\delta \Delta \chi} \left[ \frac{H_d R_d^3 \Delta \chi (2z_i^2 - x_i^2 - y_i^2)}{3(x_i^2 + y_i^2 + z_i^2)^{3/2}} \right]
\]

\[
= \frac{H_d R_d^3 (2z_i^2 - x_i^2 - y_i^2)}{3(x_i^2 + y_i^2 + z_i^2)^{3/2}} \tag{6.11}
\]
This Jacobian at any point \( r_i \) is independent of susceptibility, but dependant on field strength, sphere size and the point at which the measurement is made. The asymptotic covariance is then,

\[
\text{Cov}(\hat{\theta}_N) = \frac{\sigma_N}{\sum_{i=1}^{N} J_i(r_i, \hat{\theta}_N)^2}
\]

for all \( N \) points \( r_i \) which are measured and modeled.

The covariance matrix is related to the variance, and therefore to the correlation coefficient by definition. As a general measure of model fit, the lower the asymptotic covariance, the better the model fit. Note that any increase in the Jacobian will reflect a decrease in the covariance, and imply a better fit.

**VI.2.E LSE Covariance as a Function of the Choice of Data Set**

The design parameters which will alter the covariance matrix have been mentioned, in particular; object volume, field strength, and the choice of the points which are measured. The choice of points contains several options; the number (\( N \)) of points sampled, the distance (\( \Delta r \)) between points, and the distance (\( r_o \)) from the center of the object where the points are taken. For this chapter, as a matter of convenience, examination of the model behavior will be restricted to the \( y \)-axial data of the field distortion of a perfect sphere, for \( n \) points, sampled at \( \Delta y \) intervals beginning at point \( y_o \). Also, the radius size \( R_a \) influences the location of the points in the fit, so that any vector point that will be examined is defined by \( r_i = y_i = R_a + y_o + i^* \Delta y \). The sampling choices of point number, location
Parameters which affect LSE Fit

Number of Points in Fit, n

Data Offset from edge of Sphere, yo

Sampling Distance, dy

Figure 6-1. Without spatially biased noise (or $\sigma = \text{constant}$), the Jacobian term ($E(J^TJ)$) in the denominator dominates the asymptotic covariance. The Jacobian, and therefore the covariance are affected by A) choice of number of points fit, $n$. B) the distance, $y_o$, from the object and C) the sampling width, $dy$, between each point.
and sampling interval are shown in figure 6-1 for a field distorted by a sphere. Without spatially biased noise (or stationary noise, with \( \sigma = \text{constant in space} \)), the Jacobian term \( (E[\mathbf{J}]) \) in the denominator dominates the asymptotic covariance.

Closer examination of the covariance matrix ([6.12]) predicts the effect of each parameter on the fit. The increase in \( n \) will increase the expectancy of the Jacobian, and should decrease the covariance.

Other effects can just as readily be identified from the equations. Increasing sphere size will increase the Jacobian, as shown by examining the equations for \( \overline{J}_i(r_i) \),

\[
\overline{J}_i(r_i) = -\frac{H_o R_a^3 (2z_i^2 - x_i^2 - y_i^2)}{3 \left( x_i^2 + y_i^2 + z_i^2 \right)^{3/2}} \tag{6.13}
\]

If the equations are examined only along the y-axis

\( (x = z = 0, r_i = y_i = R_a + y_o + i \Delta y) \), then

\[
\overline{J}_i(y_i) = -\frac{H_o}{3} \frac{R_a^3}{(y_o + i \Delta y + R_a)^3} \tag{6.14}
\]

where the y position must be offset by the sphere size \( R_a \), then the effect of increasing \( R_a \) will have cubic effects on both the numerator and denominator. Rearranging,

\[
\overline{J}_i(y_i) = -\frac{H_o}{3} \frac{1}{\left( 1 + \frac{y_o + i \Delta y}{R_a} \right)^3} \tag{6.15}
\]

shows that any increase in \( R_a \) (or in the initial point of measurement, \( y_o \)) will decrease the denominator, and increase the value of the Jacobian. Extending the model to three dimensions has the same effect, although slightly more complex.
Similar to sphere size, an increase in field strength will improve the fit by reducing covariance by way of increasing the Jacobian. In practice, the geometry of the sphere (or patient liver) is fixed, while the field strength is restricted; in this project to 1.5 T.

Another effect can be observed from the single axis model, that of the best place to measure any data point or the entire data set. If we wish to maximize the Jacobian with respect to an inverse power function \( r \), then \( r \) should be minimized. For the single axis model, \( y_i = R_a (y_o = 0) \) will be the best point of measurement, as it is the nearest point to the center of the sphere which is possible to sample. This would be expected as the spatially varying S/N is largest at this point.

Changing the values of the sampling distance \( \Delta y \) has a similar result on the Jacobian. As the Jacobian should be maximized for best fit, then the sampling distance should be as small as possible to place the samples as near the sphere as possible.

VI.2.F Simulations of Random noise and Signals

These three sampling parameters, \( n \), \( \Delta y \) and \( y_o \) were examined for an analytically modeled sphere, and the Jacobian was calculated. The noise was assumed to be Gaussian and white, with a fixed variance, so examination could be restricted to only the Jacobian, which, in turn, will reflect the changes to the asymptotic covariance. The Jacobian as \( n \), \( \Delta y \) and \( y_o \) vary are shown in figure 6-2.
As predicted the Jacobian is shown to increase with $n$ (figures 6-2(a), and 6-2(b)). Increasing the Jacobian matrix will decrease the covariance, which implies a better fit. Therefore, for any given $\Delta y$ (6-2(a)) and $y_o$ (6-2(b)), increasing the number of points will improve the fit, by up to 4-fold for any particular set of sample width or offset. The saturation of these curves can be attributed to the inverse-distance oriented reduction of the magnetic field (and therefore the Jacobian) away from the sphere. For any of the sets shown here, the Jacobian is within 90% of the eventual maximum within $n = 32$ points.

Observation of the changes in the Jacobian with offset $y_o$ (figure 6-2(c)) or sampling width $\Delta y$ (figure 6-2(d)) as the other parameters vary show that minimizing both $\Delta y$ and $y_o$ will maximize the Jacobian. An improvement of up to 8-fold can be observed for any set. This follows from equation [6-11], as distance from the sphere will reduce the modeled (or measured) field, thus reducing the Jacobian. Increases in offset or sampling width will increase the average distance of the entire measurement from the sphere. The entire sampling window for the Jacobian is $n*\Delta y$ (figure 6-2(e)), over which a much more marked change occurs in the Jacobian than in the previous graphs indicating a much stronger preference for minimizing the sampling resolution as well as the offset. The Jacobian reaches 90% of its eventual maximum for all data sets within $y_o + n*\Delta y < 2*R_s$. As this ratio is inherent to the Jacobian (equation [6.15]), the restriction of the LSE data set to within two radii of the sphere will not detract from the LSE fit for perfect data and Gaussian, white noise.
Figure 6-2. a) The effects of $y_0$ on the Jacobian.
Figure 6-2. b) The effects of $\Delta y$ on the Jacobian.
Figure 6-2. c) The effects of $y_o$ on the Jacobian.
Figure 6-2. d) The effects of sampling width Δy on the Jacobian.
Figure 6-2. e) The effects of the sampling window $n \Delta y$ on the Jacobian.
To summarize the theoretical effects of the estimation method in the presence of random noise;

- Increased number of points gives less biased noise.
- Increased number of points increases the Jacobian and decreases covariance.
- Increased sphere size and field strength increase the Jacobian and decrease covariance.
- Decreased $y_c$ increases the Jacobian and decreases covariance.
- Decreased $\Delta y$ increases the Jacobian and decreases covariance.
- Restriction of the data set so that $y_i < 2R_s$ will not reduce the overall Jacobian.

**VI.3 Influence of Arbitrary Field Behavior on Signal Strength and Fit**

**VI.3.A Prolate/Oblate Spheroids**

When moving from the radial symmetry discussed so far to the more arbitrary geometry of the in vivo case, the advantage of the radial perfection of spheres will vanish. However, from equation [3.11] it is expected that the fields due to any source will still follow some variant of the inverse cubed law. The modeled object signal versus the unmodeled source noise would still be expected to peak as near the object as possible. This can be examined for regularized objects such as oblate or prolate spheroids.

The field solutions for oblate/prolate spheroids were generated using the method of transformation of variables (Plonsey, 1961). The perfect spheres field solution in
equation [3.2] can be elongated or contracted along any axis, and any angular rotation can be applied. The x-axial signals which lie in the xz-plane directly beneath the spheroids (see inset figure 6-3) were calculated for spheroids of fixed x and y dimensions (a = 1, b = 1), and varied z dimension (c = 1/4 (oblate), 1/2 (oblate), 1 (sphere), 2 (prolate) and 4 (prolate)). Each set of spheroids is allowed to rotate about either the x-axis (θ = 0, 15, 30 degrees) or y-axis (θ = 0, 15 and 30 degrees). As expected, the field distortion signal peaks nearest the center of the spheroid, except when the object is angularly rotated with respect to the field. In these cases, seen in figure 6-3, the field will peak somewhere between the axial projection of the center of mass and the point of the object nearest to the study plane.

**VI.3.B Signal Strength Based Data Set Restriction**

As this exercise shows, with more geometrically complex objects, the choice of region of fit will become more complex. However, the basic conclusions will hold, that the goodness-of-fit will be improved by minimizing the covariance by maximizing the Jacobian. The Jacobian can be maximized by simply choosing the data set to include those points for which the magnetic field is strongest. As the field model (ideally) should reflect the spatial distribution of the field data, then it is reasonable to expect that a data set restriction based on the field model would improve the goodness-of-fit. As will be seen for fits in the presence of spatially correlated noise, utilization of more data points includes increasing amounts of non-random noise in the fit. Depending on the object of interest, and the unmodeled sources present, some form of data restriction will reduce the uncorrelated noise, yet reduce the effect of random noise.
Field Distortion for Oblate and Prolate Spheroids with Angular Distortion

Figure 6-3. Field Distortions caused by oblate and prolate spheroids are examined along the x-axis for varying elongations ($a = x$ elongation, $b = y$ elongation, $c = z$ elongation) as the spheroid is rotated about the $y$-axis (theta) or the $z$-axis (phi). The field distortions of non-perfect spheres or arbitrary objects will not maintain field symmetry, and must be analyzed from the DFC modeled field distortions.
One form of data restriction can be based on the magnitude of the induced field distortion. The magnetic field distortion of an object will be largest nearest the object. This implies that the data space nearest the object will be less influenced by random or non-random noise. The data can be restricted to the data points nearest the modeled object, based on the calculated field model for that object,

\[ k \in \{ \Delta H_{FieldModel,k} > \eta \Delta H_{FieldModel,\text{maximum}} \} \quad 0 < \eta \leq 1 \quad [6.16] \]

for some threshold value \( \eta \). For a set of spheres in a field, the inverse r-cubed nature of the field implies that this would be equivalent to restricting the data by some threshold based on radial distance from the sphere. Less regularized objects will have similar inverse r-cubed field strength behavior, but will not have the spherical symmetry. The choice of threshold value \( \eta \) may need to be made experimentally, due to the absence of a priori knowledge concerning the noise sources, but based on the information gleaned earlier in this chapter, it is likely to have some relationship to the mean object radius.

VI.4 Non-stationary Noise

VI.4.A Non-stationary Noise effect on S/N and Covariance

For non-stationary noise, the basic assumptions change little. One difference is that, if the noise varies in space, it may not be uncorrelated with signal of the field. In this case, the signal to noise from equation [6.4] is,

\[
\frac{S}{N} = \frac{\sigma_{\text{signal}}^2 + 2\sigma_{\text{noise}} \sigma_{\text{signal}} + \sigma_{\text{signal}}^2}{\sigma_{\text{noise}}^2} = 1 + 2 \frac{\sigma_{\text{signal}}}{\sigma_{\text{noise}}} + \frac{\sigma_{\text{signal}}^2}{\sigma_{\text{noise}}^2} \quad [6.17]
\]
For both random and non-random noise, the S/N varies spatially. However, the
model variance \( V_n \) will not be constant in space, so that equation [6.6] does not hold
and covariance must be considered from equation [6.7] and not equation [6.12]. In
the previous section the covariance could be examined by the behavior of the Jaco-
bian alone; in the presence of non-random noise, the entire covariance term of equa-
tion [6.7], including the model variance, must be observed.

**VI.4.B Biased Ring Error from the Discrete Fourier Convolution**

One assumption made in section VI.2 and equation [6.6], is that the field model
is correct. In actual use, the precision of the field model is based on the ability of the
DFC method to generate the correct field for a given geometry. As seen in chapter V,
some edge error is introduced by the DFC method (Gibb's artifact). A spatially
biased noise addition will alter the previous conclusions of figure 6-2, and ringing
error will increase the variance and also alter the Jacobian. The effect of model ring-
ing error must be examined for it's influence on the goodness-of-fit for each measure-
ment parameter.

The ring error due to the loss of high frequency (HF) information following dis-
crete windowing (chapter V) is shown in figure 6-4, where a band-width limiting win-
dow applied in the frequency domain will result in ringing in the spatial domain.
HF-limiting filters (HF frequencies eliminated = 1/32, 1/8, 1/4 and 3/4) were applied
to the spherical field, and increased the ringing respectively (figure 6-5(a)). The ring
error (the filtered field less the unfiltered field) is shown for the HF filters above (fig-
ure 6-5(b)). The error is most pronounced at the edge of the sphere, where the
Figure 6-4. Introduction of random noise into the asymptotic covariance will not affect the model-based Jacobian, but may affect the standard deviation. The windowing method is shown in this figure, where a band-width limiting window applied in the frequency domain will result in ringing in the spatial domain.
Figure 6-5. a) Several HF filters (HF=1/32, 1/8, 1/4 and 3/4) are applied to the spherical field, and increase the ringing respectively. b) The Ring Error (ringing field - Hz) is shown for the HF filters above.
Figure 6-5. c) The standard deviation of the above ring error as a function HF filtered BW show that the elimination of the highest frequencies (BW < 1/2) have little effect on the STD, and therefore on the COV.
previous zero noise examination indicated the optimal fit. In figure 6-5(c), the standard deviation (STD = square root of the variance) of the Ring Error in 6-4, as a function of filtered HF, show that the elimination of the highest frequencies (BW < 1/2) have little effect on the STD, and therefore on the covariance (COV).

VI.4.C Model Covariance with DFC Ring Error

Ring Error was introduced into the same simulation method from figure 6-2, where the effects of HF filtering, $n$, $\Delta y$, and $y_0$ on the covariance are shown in figure 6-6. In figure 6-6(a), the covariance as a function of $n$, $\Delta y$, and $y_0$ and HF shows that for any amount of ring error, the covariance increases with number of points, the opposite of the error free cases in figure 6-2. This is a result of the ring error diminishing less with distance than the Jacobian does, so that increasing $n$ will increase the total variance more than the increase in the Jacobian. For low ring error (HF = 0.015) the covariance remains less than 0.001, and less than 0.002 for mid-level ring error (HF = 0.125). For larger ring error (HF = 0.75) the covariance jumps to as much as 0.5. The variation of offset within individual plots shows that minimizing $y_0$ will minimize covariance, similar to the noise free model, except within the first three points of mid-range ring error. However, the covariance at this HF is still below 0.0005. Generally, increasing $y_0$ only one point will increase the covariance by two to ten-fold for any set.
Unsmoothed (m=1) Covariance with n, varying yo, dy, and HF

\( dy = 1 \) \hspace{2cm} \( dy = 2 \) \hspace{2cm} \( dy = 8 \)

\( HF = 0.0150 \)

\( HF = 0.125 \)

\( HF = 0.75 \)

\( n \)

\( y_o = 1 \)

\( y_o = 2 \)

\( y_o = 3 \)

\( y_o = 4 \)

Figure 6-6 a) Covariance as a function of \( n \), varying \( y_o \), \( \Delta y \) and HF.
Figure 6-6 b) Similar to figure 6-6(a), but with sample width $\Delta y$ varied within each sub-plot, and plotted over $n^*\Delta y$. 
Unsmoothed (m=1) Covariance with Offset (yo), varying n, dy, and HF

dy = 1


dy = 2


dy = 8

HF = 0.0152

HF = 0.125

HF = 0.75

\[ \text{yo} \]

\[ \text{n = 1} \]
\[ \text{n = 8} \]
\[ \text{n = 16} \]
\[ \text{n = 32} \]

Figure 6-6 c) Similar to figure 6-6(b), but versus yo.
Figure 6-6(b) is similar to 6-6(a), but with sample width $\Delta y$ varied within each sub-plot, and plotted over $n*\Delta y$. For low-level ringing, similar to figure 6-2(e), the covariance is least for a minimized $n*\Delta y$. However, for higher levels of ringing, the large ring error nearest the sphere will bias the covariance. Minimizing $\gamma_o$ will minimize the covariance, but the spatial bias of the ring-error indicates that a few points over a fixed distance will have lower covariance than many points over the same space. That is, for $n*\Delta y = 32$, the covariance is lower for $n = 4, \Delta y = 8$, than for $n = 32, \Delta y = 1$, which is opposite of the case for unbiased error. As for the Jacobian of the unbiased noise (figure 6-2(e)), the covariance of the biased noise will reach a maximum level, over which additional data has no effect. Unlike the unbiased noise set, maximizing covariance is not desirable, so that restricting $\gamma_o + n*\Delta y < R_o$ will ensure the minimization of the covariance.

The data are re-plotted along $\gamma_o$ in figure 6-6(c). Note the periodic nature of the ringing as the sample window is shifted through the cyclically biased error, and is much more noticeable with fewer points in the fit. The worst case (in the lower right-hand corner at $\Delta y = 8, HF = 0.75, \gamma_o = 28$) amplifies the covariance to 84, four orders of magnitude larger than for $\gamma_o = 1$. Neglecting the cyclic anomalies, $\gamma_o$ will minimize the covariance.

Overall, the addition of biased ring error to the model indicate that restriction of the offset to as near the sphere as possible is desirable. If an acceptable level of covariance for this problem is designated at $COV = 10^{-3}$, then, for low to medium level ringing, restriction of the sample window to $\gamma_o + n*\Delta y < R_o$ is acceptable ($R_o = 16$). From equation [6.15], the ratio of the data set to sphere radius will hold
over any sphere size, so the larger (or smaller) the sphere size, the larger (or smaller) the acceptable data set will be. For the higher levels of ringing shown, (neglecting the periodic dips in covariance) no clear restriction is notable, suggesting that error reduction methods must be examined.

DFC error affects the model as well as the error, but the model is implicitly assumed to be correct in asymptotic covariance calculations, so a biased model, such as the DFC model, will skew the results of the covariance measurement. This means that hard conclusions based on the Jacobian are only valid so far as the skewed model may be trusted. Based on the nature of ringing error, the model is more accurate over many points, but not over the first few points, and not for large amounts of ring error.

**VI.5 Filter effects on noise**

**VI.5.1 Filtering random and non-random noise in LSE models**

The linear least squares fit routine described by equations [4.12-4.13] is based on the assumption that the error, $\epsilon$, is random and uncorrelated to the field data or the model. Addition of spatially correlated noise due to unmodeled sources may skew the susceptibility estimation of the LSE fit.

Ljung proposes a filtering method to reduce the effect of spatially correlated noise. As Ljung states,

"The effect of [a filter] is to allow extra freedom in dealing with non-momentary properties of the prediction errors. Clearly, if the predictor is linear and time invariant, and [the input] and [the output] are scalars, then the result of filtering $\epsilon$ is the same as first filtering the input-output data and then applying the filters."
He later states, that,

"The effect of pre-filtering is thus identical to changing the noise model...". According to this, when applying filters to the MRI field data and the field model, if the error is random, stationary white noise, then application of filters designed to reduce white noise will improve the fit. An averaging (or low-pass) filter is one such example (Oppenheim, 1975).

Introduction of colored noise into the model usually reduces the ability of the LSE to correctly estimate model parameters. Pre-filtering can also be used with colored noise, but with less effect (Ljung, 1987). Any a priori information which can be determined about the noise model should be utilized during the pre-filtering step (ibid). So far, only DFC colored noise has been considered, but, as will be seen in the next chapter, field sources which have not been modeled will also contribute spatially varying noise to the LSE fit.

VI.5.B Low Pass Smooth Filtering of DFC Ring Error

A generalized 3-D space filter applied as an averaging filter (i.e. low-pass filter) over the data error set (equation [4.12]) is,

$$
\varepsilon_f(x, y, z) = \frac{1}{LMN} \sum_{i=1}^{L} \sum_{j=1}^{M} \sum_{k=1}^{N} \varepsilon(x + i, y + j, z + k) \quad [6.17]
$$

for all data points (x, y, z) which lie in the phantom or data space under the sphere.

The LSE (equation [4.13]) is then applied over the reduced number of filtered points.

Pre-filtering the data will alter the error model as well as the Jacobian. Theoretically (as stated by Ljung), the LSE of pre-filtered data will be the same as the non-
filtered data, provided the noise is Gaussian and white. This can be seen as averaging over \( m \) points will reduce the variance by a factor of \( m \), but, reduction of number of points in the Jacobian by \( m \) will reduce that by a factor of \( m \) also, resulting in an unchanged asymptotic covariance. For the case of biased noise, this will not hold.

Filter operations on biased error will preferentially change the model variance and Jacobian. The real-space and frequency space effects of filtration are diagrammed in figure 6-7. The model and the data must both be filtered before the fit, so that the error-free model will also be filtered. The gain of a group of \( m \)-point filters (\( m = 1, 3, 7, 15, 31 \) and 63) over a 64-point window. (i.e. \( m/\text{window} = .015, .046, .125, .25, .5 \) and .985) is shown in figure 6-8. Many other filter options are available, such as those which minimize high frequency lobes or maintain linear phase characteristics (Oppenheim, 1975), but the \( m \)-point averaging filter is sufficient for this example.
Smoothing of Ringing by m-point Convolution

Figure 6-7. Ringing can be reduced by post-filtration of the ring-error. The model and the data are both filtered before the fit.
Figure 6-8. the gain of an m-point filter \((m=1,3,7,15,31\text{ and }63)\) over a 64-point window. (i.e. \\
m/window = .015, .046, .125, .25, .5 and .985).

Figure 6-9. the full-width half maximum of any m-point filter is loglog related to \(m\).
Neglecting the minor lobes in the frequency response of these filters, the cutoff points of the major LF lobe can be characterized by the frequency at which each filter has gain of 0.5, known as the Full Width Half Maximum (FWHM). The FWHM is a log-log function of the number of points averaged over, as shown in figure 6-9.

Application of an m-point smoothing filter to varying amounts of ring error (BW = 1/64, 1/2, 5/8, 13/16, 7/8, and 61/64) will reduce the ring artifact, and will reduce the variance of the ring error (figure 6-10). Application of filters of similar FWHM and BW ring reduced std by 8-fold or more. This may improve the covariance (and therefore the fit), but will also reduce HF information of the model and data. For the magnetostatic problem, this poses little concern, as the field is inherently low in HF information chapter V). In essence, the degree of ringing error can be used as a priori information when choosing an appropriate filter.

VI.5.C Model Covariance Following Low Pass Smooth Filtering of DFC Ring Error

For this section, it is more interesting to investigate the effect of post-filtering of biased noise on the choice of fit parameters, \( n \), \( \Delta y \), and \( y_o \). The same data from figure 6-6 was smoothed by \( m = 3 \) and \( m = 9 \) point filters and shown as a function of \( n \) (figures 6-11(a) and 6-11(b) respectively), \( y_o \) (figures 6-12(a) and 6-12(b) respectively), and \( \Delta y \) (figures 6-13(a) and 6-13(b) respectively), all of which show expected reduction of covariance.

As a function of \( n \), for the worst case examined (HF = 0.75, \( y_o = 8 \), \( \Delta y = 8 \), in the lower right-hand sub-plot figures 6-11(a) and 6-11(b)) the covariance was reduced from 0.4 with no filter, to 0.06 with a 3-point filter, and further to 0.006 with a
Figure 6-10. The STD of several levels of induced ring error (by bandlimited HF filter) is reduced by applying m-point filters.
Smoothed (m=3) Covariance with n, varying y0, dy, and HF

Figure 6-11. a) Filtering the same data as in figure 6-6 for m = 3 filters.
Figure 6.11. b) Filtering the same data as in figure 6-6 for m = 9 filters.
9-point filter, approximately an m-squared improvement in covariance. The 3 and 9 point filters have FWHM of 0.8 and 0.3 respectively. From figure 6-10, an effective filter would have a FWHM of 0.25 (1 - BW), so the choice of a 9 or 11 point filter will eliminate most of the ringing artifact. Even with smoothing, the rate of increase in the Jacobian with increasing \( n \) does not outweigh the increase in the variance, so that the covariance shows a general \( \sqrt{n} \) increase with \( n \), except for a few initial points closest to the sphere. This suggests that, contrary to expectations, reducing \( n \) will improve the fit. However, addition of unbiased random, white noise to the model will restore the benefits of larger \( n \), effectively reducing the variance (equation [6.5]) by \( n \) so that smoothed covariance (equation [6.7]) will improve by \( n \). Applying the criteria of acceptable limits for covariance to be less than \( 10^3 \), the 9-point smoothing filter will allow the offset to be as large as \( y_o = 4 \) for HF =0.75.

Examination of the covariance as a function of \( n \) *dy (figures 6-12(a) and 6-12(b)) shows that minimizing \( \Delta y \) is will minimize covariance, and with the same improvement due to filtering seen in figure 6-11. Similar to figure 6-6(b), the large ring error nearest the sphere will bias the covariance. Again, the spatial bias of the ring-error indicates that a few points over a fixed distance will have lower covariance than many points over the same space, even following smoothing operations. Apparently, the filtering step does not reduce the ring error bias enough to restore sampling width \( \Delta y \) sensitivity to the fit. Applying the acceptance criteria of COV < \( 10^3 \) to the HF = 0.75 case, then \( m = 3 \) is not enough smoothing, but any combination of fit parameters are acceptable for \( m = 9 \). In general, reduction of \( y_o \) will reduce covariance.
Smoothed (m=3) Covariance with Position (n*dy), varying n, yo, and HF

\[ yo = 1 \quad yo = 2 \quad yo = 8 \]

\[ HF = 0.0152 \quad HF = 0.125 \quad HF = 0.75 \]

\[ n \times dy \]

---

Figure 6-12. a) Similar improvements with \( n \times dy \) are seen for \( m = 3 \) filters.
Figure 6-12. b) Similar improvements with $n \cdot \Delta y$ are seen for $m = 9$ point filters.
Figure 6-13. a) The application of \( m = 3 \) point filters are most noticeable when viewed while varying \( y_o \).
Smoothed (m=9) Covariance with Offset (yo), varying n, dy, and HF

\( dy = 1 \quad dy = 2 \quad dy = 8 \)

HF = 0.0152

HF = 0.125

HF = 0.75

yo

---

n = 1
n = 8
n = 16
n = 32

Figure 6-13. b) The application of \( m = 9 \) point filters are most noticeable when viewed while varying \( y_o \).
The application of m-point smoothing filters for covariance as a function of $y_0$ (figures 6-13(a) and 6-13(b)) show that minimizing $y_0$ is preferential. Additionally, the large periodic covariance is decreased from 84 to 10 to .01 (in the worst case - lower right corner), but not eliminated. For the acceptance limit of COV < $10^{-3}$, then restriction of the offset to $y_o < R_o$ for the case of HF = 0.75 is indicated similar to the conclusions reached in the non-filtered case. While the period does not alter, the initial point of minimal covariance is shifted from 8 to 11 to 17, which follows the degree of smoothing m = 1, 3, and 9. As an m-point convolution will enlarge an object by m-points, this may be the cause of the shift.

Finally, the effect of smoothing is examined for each group in figure 6-14, as a function of n. In each case filtering reduces COV, reinforcing the use of filtering of biased noise. Other than what has been previously noted, for an acceptance level of COV < $10^{-3}$, for the HF case where $y_o = 1$, then smoothing by m = 5 is sufficient to reduce the ring error bias. However, from figure 6-13(b), for $y_o = R_o = 16$, then smoothing of m = 9 is needed.

VI.6 Discussion and Summary

When LSE fits are made on the fields due to a sphere in a static background field, the choice of parameters affects the goodness of fit. In the case of unbiased error, the goodness of fit, or covariance, is improved by minimizing the sample width ($\Delta y$) and offset ($y_o$) from the center of sphere, and maximizing the number of points (n) in the fit.
Figure 6-14. The effect of varying levels of smoothing are examined for varying $\Delta y$ and $n$. 
In the presence of biased ring-error, then, minimizing $y_o$ will still minimize the covariance, but the spatially biased nature of the ring error reverses the effects of $\Delta y$ and $n$. In addition, large amounts of ring error will skew the covariance such that reliability of the LSE fit would be in question.

The biased ring error can be reduced by filtering the model, where filter theory suggests that a smoothing filter with a FWHM cutoff close to the cutoff of the ring-inducing filter will most effectively reduce the variance of the ring error. Examination of the covariance of the smoothed ring error model shows that this holds. Additionally, restricting the offset to $y_o < R_o$ will reduce the covariance to acceptable limits. The smoothing had no effect on the reversal of effects of $\Delta y$ and $n$ for biased ring error. In fact, increasing $n*\Delta y$ increased the covariance by approximately $\sqrt{n*\Delta y}$. However, for unbiased error the covariance will reduce linearly with $n$, so that combination of both unbiased error and biased ring error would show an overall change in covariance based on the variance,

$$\sigma_{overall}^2 = \frac{\sigma_{random}^2}{n} + \sigma_{biased}^2 \sqrt{n} = \sigma_{random}^2 \left( \frac{1}{n} + \frac{\sigma_{biased}^2}{\sigma_{random}^2} \sqrt{n} \right) \quad [6.18]$$

For $n < 100$, provided that $\sigma_{biased}^2/\sigma_{random}^2 < 0.1$, then the unbiased error will dominate, and increasing $n$ (up to 100 points) will improve the covariance.

In practice, the standard deviation of the DFC induced error is less than $10^{-4}$, similar to the mid-level ring HF=1/8, described above. The unbiased noise in the MRI has variance of about 0.03, so that the need to reduce the effect of unbiased noise by increasing $n$ outweighs the ring error increase of covariance with $n$. How-
ever, a small amount of smoothing would be indicated by the presence of mid-level ring as shown by figure 6-14. In addition, it is clear that the offset should be minimized, (i.e. $y_0 < R_e$) and $\Delta y$ should be minimized.

Finally, this technique must be applied to fields of arbitrarily shaped objects, which, as shown in this chapter, will not always be symmetrical, but can be modeled with the DFC calculator. The concepts that the goodness-of-fit for arbitrary fields might be examined over localized spaces, and that data set restriction could be based on the field model were introduced.
Chapter VII Examination of the Robustness of the External Phantom MRI Susceptibility Estimation Method using Analytical Simulations and In Vitro Data

VII.1 Introduction

In chapters III and IV the physical theory behind the external phantom method was described. At each point in the method, systemic noise or modeling error may occur. In this chapter, the sensitivity of the method to error and noise will be examined. Methods of least squares estimation which can reduce error using filtering or data restriction techniques will also be discussed, and then investigated. Potential sources of experimental and computational error are examined using analytically simulated and experimentally acquired phantom data in order to determine their impact on the susceptibility estimates obtained using this method.

Following the examination of the specific methodological sources of error, the LSE fit of spheres in the presence of colored noise in the form of unmodeled sources will be examined. The effect of random and non-stationary noise on the goodness-of-fit (i.e. covariance) was examined in chapter VI. In this chapter the effect of random and colored noise will be examined on the LSE fit itself, rather than the Jacobian or covariance for reasons that will become clear.

VII.2 Random and Non-Random Error

VII.2.A Expected Sources of Methodological Error

The sources of error which might be expected to arise can be determined by
examining the susceptibility estimation procedure for points of uncertainty or outright introduction of error. Each of the subsections in the general algorithm (Figure 7-1): Field Data Acquisition (including Background Field Subtraction), Geometrical Model Extraction, Field Model Generation and Least-Squares Susceptibility Estimation are potential sources of error. The specific types of error, and their potential effect on susceptibility estimation using the MRI reference phantom method are the experimental focus of this chapter.

VII.2.B *Methodological Error as Colored Noise*

As discussed in chapter VI, the model error takes the form of either random, uncorrelated noise or non-stationary colored noise. Of the types of error investigated, only the field noise is expected to be random. Because the MRI susceptibility estimation method is based on a non-stationary process (i.e. varies in space), model based error will always be colored to some extent, although the degree to which it is colored may be a random process. As for chapter VI, the amount of influence an error source has on the LSE is related to the Jacobian, which is only slightly more complex with more than one compartment. Recall from chapter VI that the Jacobian is

$$J(r_i, \theta_i) = \frac{\delta H(r_i)}{\delta \theta_i}$$

From superposition, the field $H(r_i)$ at any one point $r_i$ is composed of separate components (as in equation [5.7]), each based on the susceptibility of that compartment,

$$H(r) = \Delta X_1 \tilde{H}_1(r) + \Delta X_2 \tilde{H}_2(r) + \ldots$$
Figure 7.1. The MRI Susceptibility method may be sensitive to methodological Error, which are indicated at the points of introduction in the General Algorithm, and discussed in the text.
where $\tilde{H}(r)$ is the geometrical contribution to the field distortion independent of $\Delta \chi$.

As the parameter vector is, $\tilde{\theta} = [\Delta \chi_1, \Delta \chi_2, \ldots]$, then for a two compartment model, the Jacobian becomes

$$J(r_i) = \begin{bmatrix} \frac{\delta \tilde{H}_1(r_i)}{\delta \Delta \chi_1} & \frac{\delta \tilde{H}_2(r_i)}{\delta \Delta \chi_2} \end{bmatrix}$$  \hspace{0.5cm} [7.1]$$

and the expectation of the Jacobian is,

$$E[J^T J] = \begin{bmatrix} \sum_{i=1}^{N} \tilde{H}_1(r_i)^2 & \sum_{i=1}^{N} \tilde{H}_1(r_i)\tilde{H}_2(r_i) \\ \sum_{i=1}^{N} \tilde{H}_1(r_i)\tilde{H}_2(r_i) & \sum_{i=1}^{N} \tilde{H}_2(r_i)^2 \end{bmatrix}$$  \hspace{0.5cm} [7.2]$$

so that the asymptotic covariance is,

$$Cov = \begin{bmatrix} V_N & V_N \\ \sum_{i=1}^{N} \tilde{H}_1(r_i)^2 & \sum_{i=1}^{N} \tilde{H}_1(r_i)\tilde{H}_2(r_i) \\ V_N & V_N \\ \sum_{i=1}^{N} \tilde{H}_1(r_i)\tilde{H}_2(r_i) & \sum_{i=1}^{N} \tilde{H}_2(r_i)^2 \end{bmatrix}$$  \hspace{0.5cm} [7.3]$$

For this model, each covariance term depends on the strength of the modeled field for any model compartment in $E[J^T J]$, and they all depend on the variance of the measured data $V_N$. From this description of goodness-of-fit, the model will behave in a similar fashion as described in chapter VI for random and colored noise and their inverse r-cubed relationships to data space restriction, except that the goodness-of-fit for one parameter may be higher than the goodness-of-fit for the second compartment based on the strength of the field model. For the case of concentric spheres, as the inner sphere is inherently further from the data set (so that it’s data set $r_i$ is further from the data space than the outer sphere), and for the outer sphere the covariance
will be smaller and the goodness-of-fit will be better. The cross-covariance term (either second term, first row or first term, second row of [7.3]) is a representation of the goodness-of-fit for both terms together.

The covariance implies some things that the model will be sensitive to, such as data space restriction (discussed in chapter VI). But, knowledge of the covariance does not aid in testing the resistance of the LSE fit to colored noise. Based on superposition, each of the model methodological errors can be treated as a single source of undefined shapes and strengths which have not been included in the model. So that, eventually, the examination of the error model will become an examination of the model in the presence of unmodeled sources. Until then, it is beneficial to gauge the extent of each of these model errors which will result in colored noise, by examining a macroscopic (non-data restricted) set of simulated errors. The extent of each of these types of error to alter the LSE fit, compared to the likelihood that any of these types of error will occur, will indicate the overall amount of colored noise that might eventually be expected and unavoidable.

Following the examination of the LSE and model-based noise, the conclusions made in chapter V about data space restriction can be translated to their application for colored noise models. The examination of the methodological error is followed by an examination of the variation over space of the LSE when colored noise is present, and then of the reduction of colored noise using data space restriction and filtering methods.
VII.3 Sources of Methodological Error

VII.3.A Field Noise

MRI system noise may influence the ability of this method to provide estimates of susceptibility. Field data obtained with the FE sequence will contain some amount of noise, based on the noise of the phase reconstruction. If the magnitude image has random uncorrelated noise, then the phase image (and therefore the field data) will also have random uncorrelated noise (Conturo, 1990).

The investigation of noise can be made on either MRI field data to which uniform white noise has been added, or on simulated field data to which similar noise is added. The simulated field data can be generated by the analytical solution for a perfect sphere (equation [3.1]). This analytical solution can be substituted for MRI field data (as in figure 7-1), and uniform white noise can be added to simulate MRI system noise. In order to compare simulated field data to analytical field data, the field data of a set of spherical phantoms of varying size and susceptibility will be acquired using the Field Echo sequence.


Three major types of error may be introduced during the object segmentation procedure if the outline is not accurate. Random, zero-mean outline error will result in a jittery outline. Random, non-zero-mean outline error will effectively shift the center of mass of the object. Finally, non-random, zero-mean error may increase or
decrease the volume of the sphere. These types of error can be investigated by cor-
rupting the geometrical models of either analytically derived simulations or specially
constructed spherical phantoms.

Outline jitter can be simulated by adding white noise to the outline of the geo-
metrical model, where the noise is manifested as a random error in both the x and y
spatial coordinates at any one point. Similarly, outline shift can be simulated by
adding random value to all points in both x and y coordinates. This constant error at
each point results in a spatial shift of the entire compartment. Volume error will
result if the outline is consistently larger or smaller than the actual outline, a form of
non-random error. The volume error may result from consistently over-estimating or
under estimating the size of the sphere.

Another form of error which may accrue during the outlining step is known as
pixelation. An uncertainty of +/- 1/2 pixel results from the discrete resolution of the
magnitude image used in deriving the arbitrary object compartmentation. This error,
common to many forms of discrete signal analysis, is a uniformly distributed, zero-
mean error (Oppenheim, 1975), and can be lumped in with the outline jitter error
mentioned previously.

VII.3.C Compartment Homogeneity Error

Two major assumptions were made in Chapters III and IV in order to make a
linear least squares method applicable to these fits. First, the principle of superposi-
tion is implied (equation [3.5]), and secondly the susceptibility of each compartment
is assumed to be homogeneous (equation [4.7]). The assumption of superposition is of key importance to this method, as it allows compartment separability. Additionally, as shown in figure 7-1, the background field, and the field distortion due to the reference bath are both corrected for by subtraction of the background field data. As shown in figures 3-4 and 3-5, and discussed in chapter IV, this is a reasonable assumption.

In equation [4.7], the compartmental susceptibility was assumed to be homogeneous across the volume, which may be justified, but almost certainly isn’t true for the in vivo cases and must be tested for the extents of its error limits. Compartment inhomogeneity can be simulated at equation [3.13], where instead of defining a constant volumetric object, \( V(r) \) is allowed to randomly vary over the volume. This would simulate the textural nature of tissue, and can be quantitated by its mean and uniform variance. For ease of computation, the mean would be set to unity, and for a variance of 1/2 would describe an object which ranged from 1 +/- 1/2. Note that a negative value for an object would not be physically real, and the maximum texture would be 1 +/- 1. In this manner, the effect of compartment texture can be examined with the analytically simulated models and spherical phantom models as the other forms of error are examined.

**VII.3.D Complete and Incomplete Geometrical Model - Unmodeled Sources as Colored Noise**

The model used to fit the in vivo measurements should include geometry which accurately reflects the anatomically separate regions of susceptibility. Model accu-
racy is necessary, as the magnetic field is deployed over the entire torso, and the field distorting effects of tissues near the liver may interfere with the field distortion of the liver. Besides liver and torso, separate compartments representing the heart, spleen, skin, gut, bone and lungs may require representation in the model.

On the other hand, it is obviously best to utilize only as many compartments as are required for an accurate measurement. In practice, a small number of compartments is desirable in order to simplify the segmentation procedure and reduce computation. Objects which are present in the magnetic field, but which are excluded from the model, will contribute a form of noise to the field data which is spatially correlated (again following the inverse cubed law). The effect of spatially non-stationary noise was considered in chapter VI, where it was determined that some colored noise could be tolerated, provided the LSE data set is appropriately restricted. The presence of unmodeled sources may need to be accounted for, or corrected for, in the estimation routine.

VII.3.E Summary of Experimental Errors

Field noise will inevitably occur in an MRI system (despite the claims of some manufacturers) and must be examined for its effect on the estimation method. Errors which may influence the geometric model include outline jitter, outline shift and volumetric error. The field model assumes compartment homogeneity of the geometric model. The field model also assumes superposition to be valid. The geometric model need not necessarily include all compartments or magnetic sources that are present in
the magnet, if appropriate steps are taken to minimize correlated noise. Methods which may reduce spatially correlated error include field model based restriction and pre-filtering with appropriately chosen filters.

The MRI susceptibility estimation method was tested for its veracity and eventual applicability to in vivo situations using analytical simulations and in vitro measurements of spherical phantoms. The types of error (field data, geometrical outline, compartmental homogeneity, and unmodeled source) which are expected were simulated, and the susceptibility was estimated using the LSE technique described in equations [4.12-4.13] and [6.20-6.21] as applicable. The expected outcome of these simulations and experiments are to determine which of the sources of noise, if any, are likely to influence the outcome of the estimation. In addition, insight into the LSE method which may provide the best estimates for this model will be obtained.

VII.3.F Data Set Restriction and Pre-Filtering

For the cases investigated, a region of fit was chosen which reflects the method of data collection for the in vivo method. That is, for the in vivo measurements, the fit must be made in the external phantom located underneath the liver (as in figure 4-2). For consistency, the fits of simulated fields were made in the same relative region respective to the spheres, that is, in the data space which lies directly beneath, but not overlapping, the modeled spheres (figure 7-2). The spatial frame of reference used in analytical simulations was adjusted to match either the in vitro experiments or to (roughly) simulate in vivo geometries.
Geometry for Dual Spheres

Sphere B (modeled or unmodeled)

Sphere A (Always Modeled)

y axis

Fit over all points under sphere

z axis

Figure 7-2. The data space may be restricted by choosing a subset underneath the spheres, in a space corresponding to a water bath.
As determined in chapter VI, in the presence of random, white noise, a better LSE fit will result from fitting as many data points as possible. But with spatially correlated noise, utilization of more data points includes increasing amounts of non-random noise in the fit. Depending on the object of interest, and the unmodeled sources present, some form of data restriction will reduce the uncorrelated noise, yet reduce the effect of random noise.

Also noted in chapter VI (equation [6.20]), one form of data set restriction that will minimize the covariance of the estimation fit requires that the data points at maximum signal strength be used, where these data points can be chosen from the field model. In equation [6.21], a method was introduced which allows the examination of the LSE in the presence of colored noise, by examining the fit over small regions over the entire a data set. This examination of small subsets of localized fit can substitute for the examination of the covariance made in chapter VI, which are used to analyze the efficacy of the LSE. These small-region localized fits may yield insight into the influences of the colored-noise over the entire data space, which can then be used in refining the restriction or filter treatment of the fit.

One method of reducing colored noise influence discussed in chapter VI involved the use of pre-filtering the data. As seen, the filter altered the noise characteristics without altering the data and model characteristics. Little a priori information about the colored noise exists to guide the choice of filters, except that the unmodeled noise will be strongest near the region of the unmodeled sphere. This information suggests that a filter which is preferentially oriented along the axes transverse to the unmodeled source may have some beneficial effect on the fit.
VII.4 Analytical and In Vitro Studies of Methodological Error

VII.4.A Materials and Methods

In order to investigate the effects of different noise sources and errors, a series of analytical and in vitro data are examined. The experimental analysis tools for simple geometries which we used in this study were: Analytically simulated perfect MRI data, DFC modeled perfect spheres and in vitro MRI sphere measurements. For more complex in vivo geometry, no analytical solution is available, and the DFC modeled torso field and the in vivo MRI data will be examined in a later companion paper.

VII.4.B Analytical Simulations of Magnetostatic Fields

The analytical simulations were computed as described in Chapters III and IV. The field data was either simulated using a concentric/eccentric geometry in equations [5.24] or taken from in vitro data. All orientations can vary in volume (inner sphere proportional to $R_a^3$, outer sphere to $R_b^3$) and susceptibility $X_a, X_b$ of the sphere.

For eccentric and concentric spheres simulations (figure 7-3(inset), the differential susceptibility method of compartmentation was used (figure 4-3(b)), which simplifies the analytical solution, as superposition can be used. In keeping with this definition of susceptibility, the internal sphere was modeled with a relative differential susceptibility defined as $d\chi = (\chi_a - \chi_b)/\chi_b$. For non-overlapping multiple sphere models (figure 7-2), the effects of relative absolute susceptibility, $\chi_a/\chi_b$, was examined, as the simplification of superposition is not required.
Figure 7-3. The MRI method is examined for sensitivity to field noise by examining the LSE fit for eccentric/concentric spheres with simulated random noise added. The more concentric the spheres, the less accurate the estimation of internal sphere susceptibility, $\chi_i$. Smaller $dX/\chi_a$ and smaller $R_i/R_a$ result in larger errors in estimation. Increased noise (or decreased S/N) also increases error. The expected noise performance of an MRI system is on the order of 30:1, for which the maximum error is less than 5%.
VII.4.C In Vitro Phantoms

When available (i.e. for the studies not requiring concentricity), in vitro data was also used in the investigation of the sensitivity of the MRI susceptibility estimation method to noise and model error. As detailed in Chapters III and IV, a series of iron-cholride solutions in spherical phantoms were placed above a uniform in vitro reference bath. The MRI FE was obtained as described (chapter III) and magnitude and phase image reconstructions obtained and passed into the Estimation Algorithm for phase unwrapping and DFC Field Modeling.

VII.4.D DFC Field Models and LSE of Susceptibility

A discretized volumetric model for each spherical geometry was used to generate the field model using the DFC method. The results of the analytically simulated field data and the DFC generated field model were then least squares fit to the field model to estimate susceptibility as in equation [4.12-4.13].

VII.4.E Methodological Error Simulation

The different types of noise or error that were used to corrupt the data are discussed at the beginning of each subsection below. In order to keep each simulation separate, the error generation method and simulation conditions will be stated at the beginning of each experimental results group.

VII.4.F Data Set Restriction and Pre-Filtering
For the cases investigated, a region of fit was chosen which reflects the method of data collection for the in vivo method. That is, for the in vivo measurements, the fit must be made in the external phantom located underneath the liver (as in figure 4-2). For consistency, the fits of simulated fields were made in the same relative region respective to the spheres, that is, in the data space which lies directly beneath, but not overlapping, the modeled spheres (figure 7-3, inset). The spatial frame of reference used in analytical simulations was adjusted to match either the in vitro experiments or to (roughly) simulate in vivo geometries.

A generalized 3-D space filter applied as an averaging filter (i.e. low-pass filter) over the data set is,

$$
\epsilon(x, y, z) = \frac{1}{LMN} \sum_{i=1}^{L} \sum_{j=1}^{M} \sum_{k=1}^{N} \epsilon(x + i, y + j, z + k)
$$

[7.4]

for all data points (x,y,z) which lie in the phantom or data space under the sphere (see figure 7-13, later in this chapter). The LSE (equation [4.12]) is then applied over the reduced number of filtered points. For pre-filtering data and noise two types of filters were examined, cubic and rectangular. The cubic filter has L = M = N = \{1, 7, 13, 19\}. The rectangular filter used had N = 1 and L = M = \{1, 7, 13, 19\}. These two filters will differ in that the cubic filter will include data averaging along the all axes, but the rectangular filter will only filter along the x and y axes, not incorporating any error which may lie preferentially along the z-axis.
VII.4.G Statistics

Statistical parameters used in this study are estimate mean, estimate variance and estimate correlation, all of which are used to determine the Confidence Interval of the data.

The confidence interval (CI) is defined as the allowable deviation from the mean under which some $\alpha$-percent of the data points should lie, provided the error can be attributed to normally distributed noise. Or,

$$CI(\alpha) = +/- t_{1-\alpha} \sigma/\sqrt{n}$$  \[7.5\]

where $n$ are the number of points in the sample, $\sigma$ is the standard deviation (equation [3.4(c)]), and $t$ is the t-test distribution at $1-\alpha$ (two-tailed).

The correlation $r$ between two data sets was defined in equation [3.5(a)].

VII.5 Results and Discussion

VII.5.A Effects of MRI Field Noise

As noted in the initial descriptions of this method (chapter IV), several types of noise or error may influence the ability of the external phantom method to correctly estimate susceptibility. MRI system noise which would appear in the field data is one possible noise source. The expected in vitro Signal to Noise Ratios (S/N) of magnitude reconstruction images are on the order of 30:1 for the Field Echo sequence described above. The S/N of phase reconstruction images are increased over the magnitude reconstruction images due to phase unwrapping (Conturo, 1990). The
actual S/N for MRI field data will depend not only on the MRI magnitude S/N, but on the number of phase wraps. The number of phase wrappings depends on the magnitude of the field distortion. However, the phase wrapping improvement of S/N will never be lower than the S/N of the magnitude reconstruction (ibid). For the paper, it is easiest to look at the overall magnitude of the field distortion signal, specifying S/N as

$$\frac{\sum_{i=1}^{N} (H_{\text{field data} + \text{noise}})^2}{\sum_{i=1}^{N} (H_{\text{noise}})^2} - 1 = \frac{\sigma_{\text{field data}}^2 + \sigma_{\text{noise}}^2}{\sigma_{\text{noise}}^2} - 1 = \frac{\sigma_{\text{field data}}^2}{\sigma_{\text{noise}}^2}$$  \[7.6\]

for uncorrelated noise and field data. The subtraction of 1 in the definition is made for convenience in representing just the relative power of the field data versus the power of the noise.

VII.5.B Phase Data Noise - Concentric and Eccentric spheres

When multiple objects are present the field distortion of one object may overwhelm the field distortion of another. In order to examine the ability of the external phantom method to accurately estimate susceptibility in these cases, a set of concentric and eccentric spheres was examined. Given the inverse r-cubed nature of the fields, it would be expected that the closer an internal object is to the region of fit data space, the larger the field source strength of that object will be. Therefore, the more eccentric the spheres, the more accurate the estimation of the internal sphere.

Due to the difficulties of construction of concentric/eccentric spheres, the field data for these estimations were simulated analytically. Uniform white noise of vary-
ing strength (as above) was added to the analytical field solution for concentric and eccentric spheres, and LSE fit (figure 7-1) to the DFC calculation of the field of that sphere over the aforementioned in-vitro restricted data space. The effect of field data noise on estimations of eccentric objects must also be measured to insure that, as in the previous results, susceptibility may be estimated in the presence of random noise.

The eccentric spheres model is shown in figure 7-3 (inset), where the $R_o$ parameter signifies the eccentricity of the central sphere. Field solutions for the eccentric spheres model were generated analytically using equations [2.4] and [5.24]. Since superposition applies, the field for each sphere was computed separately and subsequently added to give the entire field. The differential relative susceptibilities used were $d\chi/\chi_s = 1/32$, 1/4, and 1, using a fixed $\chi_s = 1$, where $d\chi = \chi_o - \chi_s$. The region of fit of the model was restricted to the 3-D rectangular region of 32x32x32 units of length below the sphere. Note that arbitrary units of length may be used in the analytical simulations, to which any real value may be assigned, lending a wide degree of applicability to the simulations. $R_b$ was fixed to 16 units with $R_a = 8$, 11 and 14 length units, so that the relative internal versus external radii were, $R_o/R_b = 0.5$, 0.7 and 0.9. The eccentricity of the central spheres used in simulation ranged over $R_o/R_{o\text{max}} = 0, 1/8, 1/2$ and 1, where $R_{o\text{max}} = R_b - R_a$ is the maximum amount of eccentricity possible. The simulations ranged over $S/N = 100, 50, 25, 12.5, 6.25, 3.13, 1.52, 0.78$ and 0.39. The simulation parameters are summarized in Table 7-1.

The estimations for the effect of noise in the MRI field/phase data are shown in figure 7-3 for all cases of the internal sphere estimation. In each case, the higher the
S/N, the more closely the estimates for each $\chi_a$ were to the normalized values of 1. Also, with increasing differential susceptibility and increasing relative volume, the estimation of $\chi_a$ improves.

To relate any of these values to human proportions, the normal human liver is approximately 1/8 of the volume of the torso (or $R_o/R_s = 0.5$), with a differential susceptibility of about 1/32 relative to the torso. With an average liver size of roughly 10-12 cm in diameter, which lays beneath the skin at about 2 cm, this translates to an eccentricity of at least $R_o/R_{\text{max}} > 1/2$. At these values, the $\chi_a$ estimation is within 10% at a S/N = 12.5. The in vitro MRI scans examined in this study have S/N of approximately 30:1, well above the needed S/N for a good estimate of the 1/2 eccentric spheres. For much less eccentricity, however, the estimates of $\chi_a$ were in error by up to an order of magnitude, which would be predicted by the inverse cubed nature of the field distortion equations. A summary of internal sphere estimations at S/N = 25 is arranged in Table 7-2(a).

High levels of liver iron can be as large as $d\chi/\chi_s = 2$ (where liver iron is greater than 12000 ug/ml) before the patient succumbs, and it can be seen in figure 7-3, and Table 7-2(a) that the field distortion of $d\chi/\chi_s = 1$ estimated $\chi_a$ better than 0.5% for all cases of S/N > 12.5. However, some patients may have more concentrically located livers, such as in highly obese patients. At levels of $d\chi/\chi_s = 1/32$ and $R_o/R_s = 0.5$, an eccentricity of $R_o/R_{\text{max}} = 1/8$ estimated $\chi_a$ near -2 at S/N = 12.5 (a 300 % error). Larger patients, with more centrally located livers, may not be well suited for this examination.
Accurate estimation of $\chi_b$ is necessary to determine $\chi_a$ from the value of $d\chi/\chi_b$, as it is $d\chi/\chi_b$ which is actually estimated. The estimates for $\chi_b$ for the same simulations are shown in figure 7-4. Summary results for external sphere estimates for the cases where S/N = 25 are shown in Table 7-2(b). In the most difficult case to estimate the central sphere, $d\chi/\chi_b = 1/32$, $R_a/R_b = 0.5$, eccentricity = 0 and S/N = 25, the $\chi_b$ estimate of the outer sphere was within 2%. This would be expected, as the field distortion signal of the internal sphere would be less likely to overshadow the field of the external sphere. It follows, then that the higher the field distortion of the internal sphere, the less accurate the external sphere estimate will be. For this case, where $d\chi/\chi_b = 1$, $R_a/R_b = 0.9$, and low S/N the $\chi_b$ estimate was still within 3%, although the increase in relative susceptibility had little effect on the external sphere estimations.
Table 7-1  Eccentric Sphere Study Parameters

**Common Parameters**

$\chi_b = 1, R_b = 16$

$\chi_s/\chi_b = 1/32, 1/4, 1, and 4.$

$R_s/R_b = 0.5, 0.7$ and $0.9$

$R_{o_{\max}} = R_b - R_s$

$R_s/R_{o_{\max}} = 0, 1/8, 1/2$ and $1$

**Study Parameters**

Field Noise

S/N = .39, .78, 1.52, 3.13, 6.25, 12.5, 25, 50, 100

**Compartment Homogeneity**

S/N = 1, 2, 4, 8, 16, 32, 64, 128, 256

**Outline Jitter**

S/N = .39, .78, 1.52, 3.13, 6.25, 12.5, 25, 50, 100

**Outline Shift Error**

$R_{\text{shift\_error}}/R_s = +/- 0, 1/8, 1/4, 1/2, 1$

**Volume Error**

Volume Error = -38%, -17%, -9.9%, -4.6%, 0, 4.7%, 9.7%, 20% and 42%.
Table 7-2(a) $\chi_a$ Estimates for Field Noise, S/N = 25

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<th>$R_a/R_b$</th>
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<th>1/2</th>
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<td>.998</td>
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Table 7-2(b)  $\chi_b$ Estimates for Field Noise, S/N = 25

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</table>
Figure 7-4. Estimation of $\chi_a$ for the same method as figure 7-4 shows similar sensitivity to concentricity, relative to differential susceptibility, relative radii and S/N. At expected noise levels the maximum error is less than 0.1%.
VII.5.C Compartment Inhomogeneity

A simplification was made in equation [3.9] by assuming homogeneity across each compartment. If this is not the case, incorrect estimations may result. To examine the effect of inhomogeneity on the method for a set of concentric and eccentric spheres, the analytical spheres field solution is fit to DFC generated fields based on sphere models for which the uniform compartment model is corrupted by inhomogeneity. Compartment inhomogeneity (chapter IV) was simulated by adding uniform, white noise to the geometrical descriptors $V(r)$ of both spheres, and is defined as the the mean compartment value versus the variance of the compartment,

$$\text{Compartment Homogeneity} = \frac{M}{\sqrt{\frac{1}{N} \sum_{i=1}^{N} (V(r_i) - M)}}$$

where $M = \frac{1}{N} \sum_{i=1}^{N} V(r_i)$ [7.7]

In this description of a 3-D geometrical object, a compartment homogeneity less than 1 has no physical meaning, and was not simulated.

Susceptibility estimations were made for compartment homogeneity ranging from 1 to 256 using eccentric and concentric spheres with the set of $R_o$, $R_a/R_b$ and $d\chi/\chi_b$ as summarized in Table 7-1. The results of the compartment inhomogeneity study are shown in figure 7-5 for the internal sphere estimates and in figure 7-6 for the external sphere estimates. As in figures 7-3 and 7-4, with lower $R_a/R_b$ and $d\chi/\chi_b$, the accuracy of the estimate was reduced. A summary of estimates for each study at compartment homogeneity = 100 is given in tables 7-3(a) and 7-3(b). Compartment homogeneity of 100 indicates a uniform variance across the sphere within +/- 10% of
the mean compartment value. For the both the internal and external spheres, the susceptibility is always estimated within 5% as long as the homogeneity S/N is above 100.

In normal and iron-loaded patients, the iron levels (and therefore the susceptibility) in the liver exhibit uniform variance of less than 10% over the entire organ (Overmoyer, 1987). The ability of the model to accurately estimate the susceptibility of inhomogeneous objects may lie in the spatial filtering nature of the DFC field generator (equations [4.4] or [5.12]). This equation indicates that small, uniform variances may be smoothed over by convolution of the volumetric function by the Green’s function. However, a caveat must be made for in vivo examinations other than the liver, as the compartment variance may not have the uniformly random spatial distribution assumed for these simulations.
Table 7.3(a) \( \chi \) Estimates for Compartment Homogeneity S/N = 100

<table>
<thead>
<tr>
<th>( R_a/R_b )</th>
<th>( \chi_a/\chi_b )</th>
<th>( R_a/R_a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>1/32</td>
<td>1</td>
</tr>
<tr>
<td>0.9</td>
<td>1/4</td>
<td>1</td>
</tr>
<tr>
<td>0.9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.7</td>
<td>1/32</td>
<td>1</td>
</tr>
<tr>
<td>0.7</td>
<td>1/4</td>
<td>1</td>
</tr>
<tr>
<td>0.7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0.5</td>
<td>1/32</td>
<td>1</td>
</tr>
<tr>
<td>0.5</td>
<td>1/4</td>
<td>1</td>
</tr>
<tr>
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<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 7-3(b) \( \chi_b \) Estimates for Compartment Homogeneity \( S/N = 100 \)

<table>
<thead>
<tr>
<th>( R_a/R_b )</th>
<th>( \chi_a/\chi_b )</th>
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<th>1/8</th>
<th>1/2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>1/32</td>
<td>.960</td>
<td>.960</td>
<td>.961</td>
<td>.965</td>
</tr>
<tr>
<td>0.9</td>
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<td>.980</td>
<td>.980</td>
<td>.981</td>
<td>.983</td>
</tr>
<tr>
<td>0.9</td>
<td>1</td>
<td>.993</td>
<td>.990</td>
<td>.990</td>
<td>.991</td>
</tr>
<tr>
<td>0.7</td>
<td>1/32</td>
<td>.959</td>
<td>.959</td>
<td>.960</td>
<td>.964</td>
</tr>
<tr>
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<td>.980</td>
<td>.980</td>
<td>.982</td>
</tr>
<tr>
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<td>1</td>
<td>.958</td>
<td>.990</td>
<td>.990</td>
<td>.991</td>
</tr>
<tr>
<td>0.5</td>
<td>1/32</td>
<td>.990</td>
<td>.958</td>
<td>.959</td>
<td>.962</td>
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<tr>
<td>0.5</td>
<td>1/4</td>
<td>.979</td>
<td>.979</td>
<td>.979</td>
<td>.981</td>
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<tr>
<td>0.5</td>
<td>1</td>
<td>.989</td>
<td>.989</td>
<td>.990</td>
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</tr>
</tbody>
</table>
Inhomogeneous Compartments Effect on \(X_a\) Estimation

varying \(R_a/R_b\), \(dX/X_b\) and Eccentricity

Figure 7-5. The effect of compartment homogeneity was investigated by adding compartment error to both spheres of an eccentric/concentric spheres set. For \(X_a\) estimation, decreasing inhomogeneity increase the error in the estimates. Contrary to the noise results in Figures 7-3 and 7-4, the effect of increasing relative susceptibility and decreasing relative radii is to increase the error. Similar to the noise results, decreasing \(dX/X_a\) increases the error in estimation. Expected compartment homogeneity S/N levels are on the order of 100:1, for which maximum error is less than 5%.
Inhomogeneous Compartments Effect on Xb Estimation varying Ra/Rb, dX/Xb and Eccentricity

Figure 7-6. The estimates of $\chi_a$ are also affected by compartment homogeneity for the same simulations of figure 7-3. The sensitivity of differential susceptibility is similar to figure 7-3, but opposite for eccentricity and is not affected by relative radii. Maximum error at expected homogeneity is less than 0.1%.
VII.5.D Outline Error - Jitter, Shift and Volume Error

Three types of error may be introduced during the object segmentation procedure if the outline is not accurate. Random, zero-mean outline error will result in a jittery outline. Random, non-zero mean outline error will effectively shift the center of mass of the object. Finally, non-random, zero-mean error may increase or decrease the volume of the sphere. The expected degree of error by the operator-interactive outlining of the compartments are discussed in Appendix C.

VII.5.D.i Jitter Error

Outline jitter results from imprecise segmentation of an object, such that the segmented outline has additive random error along each axis. It would be expected that the spatial smoothing property of the DFC field generator (equations [4.4] or [5.12]) will reduce the effects of the random spatial noise of outline jitter on the field model and therefore on susceptibility estimation.

The effects of outline jitter were examined on the eccentric spheres model for the simulation parameters \(R_a, R_b/R_a, \) and \(d\chi/\chi_a\) which are shown in Table 7-1. Outline jitter was modeled by adding zero-mean, Gaussian white noise to the outline of the central sphere, where the noise is manifested as an error in both the x and y spatial coordinates. Outline Jitter S/N is defined as,

\[
\text{Outline Jitter S/N} = \frac{\sum_{i=1}^{N} [(x_i + x_{i,\text{noise}})^2 + (y_i + y_{i,\text{noise}})^2]}{\sum_{i=1}^{N} [x_{i,\text{noise}}^2 + y_{i,\text{noise}}^2]}
\]

The susceptibility was then fit as usual (figure 7-1).
The susceptibility estimates for simulated outline jitter are shown in figure 7-7, for the same values of eccentricity, radius and susceptibility as above, as a function of jitter error. For reference, outline S/N = 100 corresponds to random error in the outline of a unit circle of up to +/- 10% at each point, and outline S/N = 1 is error of up to 100%. The model appears to be highly insensitive to outline jitter. The least accurate case was that of a large internal sphere, \( R_e/R_b = 0.9 \), and low relative differential susceptibility, \( d\chi/\chi_b = 1/32 \), where the estimation was off by 8% at minimum outline jitter S/N (i.e. maximum outline jitter error). The minimum outline jitter S/N, however, represents an unlikely case of very poor segmentation. As shown in Appendix C, the amount of error associated with an experienced operator segmenting a clearly defined image is less than +/- 1% of the radius (of a 64 pixel in diameter object). A summary of each simulation set at this level of outline jitter is shown in Table 7-4.

One of the physical scan parameters which also contributes to the outline error is the minimum pixel resolution inherent to any digital image. An uncertainty in the outline of any object for the geometrical model of +/- 1/2 pixel will always exist, but will be zero-mean and uniformly distributed over the outline (Oppenheim, 1975). For an image of an average sized liver of 50x100 pixels, this is at most 2% error, or outline jitter S/N = 2500, and will have little or no effect on susceptibility estimation.

As mentioned, the insensitivity of the method to outline accuracy may partly be due to the filtering nature of the DFC method, as seen by the convolution term in equations [4.4] or [5.12], as well as the effect of randomness over the entire surface. That is, random outline error is just as likely to increase the field distortion as to
decrease it, and for a large surface area, this effect will be cancelled out at a distance. It is interesting, but predictable from the inverse-cubed nature of the field, that this filtering advantage increases as the central sphere gains distance from the reference data, as it becomes more like a point source.
Table 7-4  \( \chi_a \) Estimates for Outline Jitter S/N = 100

<table>
<thead>
<tr>
<th>( R_a/R_b )</th>
<th>( \chi_a/\chi_b )</th>
<th>0</th>
<th>1/8</th>
<th>1/2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>1/32</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.9</td>
<td>1/4</td>
<td>.9999</td>
<td>.9999</td>
<td>.9999</td>
<td>.9999</td>
</tr>
<tr>
<td>0.9</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.7</td>
<td>1/32</td>
<td>.9996</td>
<td>.9998</td>
<td>.9999</td>
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<tr>
<td>0.7</td>
<td>1/4</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.7</td>
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<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>0.5</td>
<td>1/32</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.5</td>
<td>1/4</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>
Figure 7-7. Noisy compartment segmentation outlines were simulated by corrupting the outlines of the concentric/eccentric spheres models used in figure 7-3. $\chi_a$ estimation suffers only slightly from outline error, with error increasing as $dX/d\chi_a$ decreases, $R_a/R_b$ increases, eccentricity increases, and Outline S/N decreases. Expected outline S/N is 10 for which the maximum estimation error is less than 0.5%.
VII.5.D.ii Shift Error

When segmenting the geometric model of the objects, if the segmentation algorithm or the operator performing the outline procedure has a consistent error, then a spatial shift of the object may result. More precisely, outline shift will occur with an addition of random, non-zero mean error along either the x or y axis. The outline shift can be quantitated by the shift of the center of mass. Due to the inverse r-cubed nature of magnetic fields, a small spatial shift in the geometric model, will result in a much larger error following DFC field generation, which will reduce LSE fit reliability.

A series of eccentric and concentric spheres was estimated, using the parameter set defined in Table 7-1. Outline shifts relative to the internal radius size $R_{shift error}/R_a = +/- 0, 1/8, 1/4, 1/2$ and 1 were simulated and the susceptibility fit as usual was performed (figure 7-1). In order to provide a more physically meaningful simulation, zero-mean, Gaussian white noise was added to the analytical simulations of the eccentric and concentric spheres field data (S/N = 30:1, as for in vitro data). Without this field data noise, the data point for zero shift can have no error in the fit, and therefore no relevance.

The effect of an outline shift induced error is seen in figure 7-8. The model is very sensitive to shift in the center of mass. For the concentric sphere, with $R_{shift error}/R_a = 1/8$, the estimate of the internal sphere is off by 100%. This could be predicted by the sensitivity of the estimations to eccentric spheres, as the inverse r-cubed law applies here also. For the more eccentric cases, the error is not as rapid,
but is still present, with no more than 4% error in susceptibility estimation for cases of 1/2 eccentricity and $R_{\text{shift \, error}}/R_a = 1/8$. A summary set of shift error at $R_{\text{shift \, error}}/R_a = 1/8$ is given in Table 7-5.

As minimum pixel resolution is defined as zero-mean error, it should not contribute to outline shift. However, "zero-mean" is a theoretical concept, and in practice, a small amount of mean digitization error may creep into the object outline. As in the case for outline jitter, this shift would not be more that +/- 1 pixel, or an outline shift error of 2% for a normal human liver outline, and the error in estimation will be less than 5% for 1/2 eccentric spheres. Center of mass shift is less than 0.1% of the radius of an equivalently sized and sampled object, for an experienced operator (Appendix C). However, the sensitivity of the model to center of mass shift indicates that the operator must be careful during the outlining procedure to accurately depict the boundaries of the object.
Table 7-5  $\chi_a$ Estimates for Sphere Shift Error $R_{shift \; error}/R_a = 1/8$  

<table>
<thead>
<tr>
<th>$R_d/R_b$</th>
<th>$\chi_d/\chi_b$</th>
<th>0</th>
<th>1/8</th>
<th>1/2</th>
<th>1</th>
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<tr>
<td>0.9</td>
<td>1/32</td>
<td>.010</td>
<td>.750</td>
<td>.974</td>
<td>.992</td>
</tr>
<tr>
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<td>.777</td>
<td>.982</td>
<td>.995</td>
</tr>
<tr>
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<td>1</td>
<td>.019</td>
<td>.780</td>
<td>.983</td>
<td>.996</td>
</tr>
<tr>
<td>0.7</td>
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<td>.945</td>
<td>.994</td>
<td>.998</td>
</tr>
<tr>
<td>0.7</td>
<td>1/4</td>
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<td>.967</td>
<td>.998</td>
<td>.999</td>
</tr>
<tr>
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<td>.163</td>
<td>.970</td>
<td>.998</td>
<td>.999</td>
</tr>
<tr>
<td>0.5</td>
<td>1/32</td>
<td>.148</td>
<td>.950</td>
<td>.995</td>
<td>.999</td>
</tr>
<tr>
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<td>1/4</td>
<td>.331</td>
<td>.984</td>
<td>.999</td>
<td>.999</td>
</tr>
<tr>
<td>0.5</td>
<td>1</td>
<td>.351</td>
<td>.988</td>
<td>.999</td>
<td>.999</td>
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</table>
Figure 7-8. Shift error in compartment outlines were modeled by spatially displacing the geometrical models of the same simulation of figure 7-3. The method is very sensitive to outline shift, but less so for more eccentric spheres. Concentric and eccentric spheres have differing sensitivities to relative radii and susceptibility. Expected shift due to operator error and discrete sampling error (pixelation) is less than 2%, for which the maximal error of the 1/2 eccentric spheres were less than 5%.
VII.5.D.iii Volume Error

During the segmentation procedure, if the outline is consistently larger or smaller than the actual outline, the volume of the compartment will be in error. This non-random, zero-mean error would be expected (from equation [2.4]) to have a linear influence on the susceptibility estimate.

A set of eccentric and concentric spheres (as in Table 7-1) was simulated, with volume error in the geometric model, and the susceptibility was estimated as usual. The radius of the spheres simulated in the geometrical model, $R_{error} = R_a*(1 + \text{RadiusError})$, had error relative to the internal sphere radius which ranged over $\text{RadiusError} = +/- 0, 1/64, 1/32, 1/16$, and $1/8$ (resulting in relative volume errors of -38%, -17%, -9.9%, -4.6%, 0, 4.7%, 9.7%, 20% and 42%).

The influence of volume error on internal sphere estimation is shown in figure 7-9. In each case, regardless of the differential susceptibility, the relative volume ratios or the amount of eccentricity, the error in susceptibility estimation is linear with the volume error. From Appendix C it would not be expected that this type of error would be likely nor large, but we note here that every percent of non-random outlining error will result in an equivalent percent of error in susceptibility estimation. The most likely error in this case would result from partial voluming, which results from the same minimum digital resolution in an object outline as discussed in outline jitter. Up to 3% error in volumetric determination can be expected due to partial voluming on objects of this size (Park, 1987), which would cause a 3% error in estimation of susceptibility. Park proposes a 3-D Fourier Descriptor (FD) method for
Volume error effect: Eccentric Spheres $X_a$
Estimate with Noise varying $Ra/Rb$ and $dX/Xb$

![Graphs showing the relationship between $Ra/Rb$ and $X_a$ estimate for different values of $dX/Xb$.](image)

Figure 7-9. Volume error was modeled by altering the volume of the spherical compartments and the estimating susceptibility similar to figure 7-3. The effect of volume error was linear and nearly identical for all estimations. Expected volume is less than 0.01% following operator sampling and FD smoothing, for which a 0.01% error may be expected.
improving volume estimates to within less than 0.1%.

VII.5.F Summary of Methodological Errors

The effect of methodological errors at expected levels of noise/error are summarized in Tables 7-2 through 7-5. The degree of error for each type is summarized in Table 7-6 where it is compared to real-life values.

VII.5.F Unmodeled Secondary Sources

As stated before, the model used to fit the field data must include geometry which accurately reflects the anatomically separate regions of susceptibility. It is best to utilize only as many compartments as are required for an accurate measurement. In practice, a small number of compartments is desirable in order to simplify the segmentation procedure and reduce computation. Too few compartments may reduce the accuracy, as the influence of unmodeled secondary sources may contribute to the field data. However, each of the methodological errors may be represented as an unmodeled source error (i.e. colored noise). This is slightly different than the biased noise from DFC-induced ringing examined in chapter VI, as the noise source is no longer correlated to the model. The remainder of this chapter will examine the spatial effect of colored noise on the the LSE fit.

To study the effect of an unmodeled source, a two sphere model as in figure 7-2 was used. In this analysis, sphere B was deliberately omitted from the geometrical
model (and subsequently the field model). The susceptibility of sphere A was estimated on the set of in vitro field data specified in Table 7-7. Note that the relative susceptibility \( \chi_A \chi_b \) is now expressed as absolute rather than differential susceptibility \( d\chi/\chi_b \), as the two objects already comprise separate physical compartments. The susceptibility difference between the spheres and the water bath phantom is accounted for in the background subtraction step justified by superposition.
### Methodological Fit Error Summary

<table>
<thead>
<tr>
<th>Error</th>
<th>Acceptable Limits</th>
<th>Expected Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field Noise</td>
<td>S/N &gt; 10</td>
<td>MRI S/N &gt; 30</td>
</tr>
<tr>
<td>Outline Jitter</td>
<td>V. Large</td>
<td>Operator Error &lt; 1%</td>
</tr>
<tr>
<td>Outline Shift</td>
<td>&lt; 5 % shift</td>
<td>Operator Shift &lt; 1%</td>
</tr>
<tr>
<td>Compartment Inhomogeneity</td>
<td>S/N &gt; 100</td>
<td>S/N ~ 1000</td>
</tr>
<tr>
<td></td>
<td>10% variance</td>
<td>3% variance</td>
</tr>
</tbody>
</table>
Table 7-7  Unmodeled Sphere Parameters

Common Parameters
\[ \chi_b = 1, \ R_b = 16 \]
\[ \chi_a / \chi_b = 1/32, \ 1/4, \ 1, \text{ and } 4. \]
\[ R_a / R_b = 0.5, \ 0.7 \text{ and } 0.9 \]

Representative Parameter Set (Figures 7-14, 7-16, 7-17)
1. \( \chi_a / \chi_b = 1, \ R_a / R_b = 1. \)
2. \( \chi_a / \chi_b = 1/32, \ R_a / R_b = 0.5. \)
Figure 7-10. For LSE fits described in figure 7-2, the estimates are more sensitive to decreases in relative radii and increases in relative susceptibility. Maximal error is greater than 3000%.
Least-Squares estimates were obtained using all of the data in a rectangular region (64x32x64 data points, each of 1.17mm x 4.7mm x 5mm in size) underneath the spheres (as in figure 7-2). The normalized values of the susceptibility estimates of sphere A are shown in figure 7-10. Except for very small $\chi_a/\chi_b$, the susceptibility estimates of sphere A are in error by up to an order or two of magnitude.

For reference to the in vivo situation, the susceptibility of the lungs are about 32 times that of the liver, and the volume of the lungs are two to three times that of the liver. Therefore, reducing the complexity of the model by omitting the lung compartment from the model would not be feasible using this approach. In fact, omitting any nearby object of appreciable susceptibility, such as bowel or rib cage, would not be practical. On the other hand, due to the potentially large number of compartments in a human subject, it is not practical to identify and include every separate source of field distortion in the model. As noted in the theoretical section, data restriction methods may overcome the unmodeled source problem.

VII.5.F.i LSE Data Set Restriction

VII.5.F.i.a Radial Restriction

The radial field distortion of each sphere (predicted by equation [2.4] and shown for in vitro data in Section III.4.A.ii, figure 3-4) suggests that the unmodeled sphere will behave as a source of field data error which varies with distance. The magnitude of the field distortion of the modeled source also varies with distance. The appropriate choice of the region of fit would emphasize the modeled field data, and de-emphasize the unmodeled field error. One method is described in equation [6.20]
which is based on the field of the modeled object only. For a spherical object, the
erestriction in equation 6.20 is equivalent to a radial restriction \((R_{fi}/R_a)\) of the data set
(figure 7-11(inset)).

Using the radial restriction method, the susceptibility values for both in vitro and
analytical unmodeled sources were re-estimated, for the same parameter set of Table
7-7, and shown in figure 7-11. For both sets, the estimation of \(\chi_a\) improves as the
region of fit is increasingly restricted. However, for the noisy in vitro model, as the
region of fit is restricted to as few as one point very near sphere A, the advantage of
numbers is reduced, and the estimate becomes sensitive to the random background
noise (similar to chapter VI, but only along one axis) This perception is verified in the
difference plot of figure 7-11, as the random noise (presumably the only difference
between the analytical and in vitro field data sets) increasingly affects the fit as fewer
points are included. As shown in chapter VI, when biased and random noise is pres-
ent, some balance between too many and not enough points must be found. The max-
imum LSE error was off by as much as 27-fold.

**VII.5.F.i.b Examination of the Confidence of the Unmodeled Source Fit**

From figure 7-11(column 3), the differences between the unmodeled source
error fits of the noisy in vitro data and the noise-free analytical spheres data, should
be due only to the random noise in the MRI data measurement. In figure 7-11, as the
radial region of fit increases, the number of points in the fit will increase, and the
error in the fit would be expected to decrease, assuming normal random error is
involved. One way to verify this, is to observe the behavior of the noise as a function
Effect of Radial Region of Fit on \(X_a\) Estimate varying \(R_a/R_b\) and \(X_a/X_b\)

![Graphs showing analytical and in vitro differences](image)

**Figure 7-11.** Radial variation in field strength is used to restrict the data of figure 7-10, as \(R_{fit}/R_a\) increases, the number of points will increase cubically (inset). Radial data restriction for the perfect, field noise-free analytical (column 1) and the in vitro obtained data (column 2) shows that the radius of fit decreases the estimation for all cases. The difference between the analytical and in vitro methods should, theoretically, only be due to the field-noise inherent to the MRI measurement. As the radial fit size is decreased, the number of data points is decreased, and the noise insensitivity of the method is decreased.
of the number of points used in the fit, as shown in figure 7-12(a). If the noise is
normally distributed, then 50% of the points should lie on either side of the 50% CI,
with a 90/10 distribution of the points for the 90% CI, and so on. As seen in figure
7-12(a), this is approximately the distribution seen, verifying that the residual error is
due to normal white noise.

The CI method can be extended to the examination of the unmodeled sources
error fits. For these fits, the problem of determining a reasonable radial restriction of
fit presents itself as the error varies with increased number of points fit. The radial
cutoff can be defined from the statistics of the CI, as the number of points in the fit
for which the error remains within the CI (figures 7-12(b) and 7-12(c)). For the series
of fits of unmodeled sources (figure 7-11(columns 1 and 2)), the maximum $R_{fit}/R_a$ for
each unmodeled source strength within a CI, is shown in figure 7-12(d). The number
of points is also shown on the right hand abcissa. As the overall source strength is
proportional to the susceptibility and the volume of a sphere, then the relative unmo-
deled source strength of sphere B vs. sphere A is $X_B/X_A = V_B/V_A$. As seen in 7-12(d),
the larger the unmodeled source strength, the smaller the tolerable region of fit $R_{fit}/R_a$.
This will be graphically illustrated in the contour plots of the unmodeled sources (fig-
ures 7-14 and 7-17), and can now be related to the statistical confidence of the fit. In
addition, two levels of confidence are displayed, 50% and 90%, where the 50%
confidence levels allow more points to be used in the fit at any particular unmodeled
source strength. The CI provides a clear acceptance or rejectance of a fit, as well as
method for determining efficacy of additional filtering or model adjustment.

VII.5.F.ii Rectangular Subfits
Confidence Intervals of Analytical and In Vitro Fits with Unmodeled Sources

![Graphs showing error with confidence intervals and analytical simulations.](image)

Figure 7-12. Confidence Intervals based on normally distributed error decrease with increasing number of points. A 50 % CI should contain 50 % of the data points, and a 90% CI should encompass 90% of the points. a) Comparison of all of the residuals from column 3 of figure 7-11 shows that the error displays a normal probability density function. The CI can be used as a gauge for acceptance or rejection of a fit. If the error in the estimate for an unmodeled source over a specified number of points lies outside of the predicted CI, then for that degree of unmodeled source, no confidence exists in the fit. b) and c) The CI levels compared to the unmodeled sources estimates made on analytical simulations in columns 1 and in vitro estimates in column 2 in figure 7-11 as the number of points in the fit increase. d) The maximum number of points which could be included in the estimate which did not exceed the CI boundary of figure (b), as a function of the relative strength of the unmodeled source. At the largest levels of unmodeled source strength, the fit is unacceptable under any conditions.
The spatial variations due to the unmodeled sphere suggest that some specified region of interest, directly underneath the modeled sphere would be best suited to improve the modeled source signal versus the unmodeled source noise. As in equation [6.21], subregions of fit can be made over the entire data space, with susceptibility estimations calculated for each subregion of LxMxN data points (figure 7-13). For this method, each possible complete subregion within the data space was fit.

Initially, a completely modeled version of the in vitro data set from Table 7-7 was fit with 1x1x2, 7x7x7, 13x13x13 and 19x19x19 data points for a single sphere and for a dual sphere experiment. Note that for two compartments, at least two data points must be used to uniquely measure susceptibility. As shown in figure 7-14, for each subregion type, the error increases with radial distance from the spheres, which is the behavior expected for a complete model, with some level of field data noise (as before, S/N = 30:1).
Figure 7-13. The effect of unmodeled compartments on the model are simulated by measuring the field data for two spheres, of varying radii and susceptibility, and leaving out one of the spheres in the geometrical model when DFC calculating the field model. Initially, the LSE fit is made over all data which lies underneath both spheres.
Restricted Region of Fit for In Vitro Single and Dual Spheres

Single Sphere
Ra=15, Xa = 1

Dual Sphere
Ra/Rb = 1/2, Xa/Xb = 1/32

Figure 7-14. Estimations on two-sphere model with both spheres included in the field model, with region of fit restrictions over 1x1x2, 7x7x7, 13x13x13 and 19x19x19 subsets show the effects of spatially varying nature of random white noise versus field model strength on the LSE fit.
Effect of Increasing Size of Region of Fit for Unmodeled Sources

Ra/Rb = 1, Xa/Xb = 1

Ra/Rb = 1/2, Xa/Xb = 1/32

Figure 7-15. Rather than radial restrictions, make the fits over cubic restrictions. For 1, 7, 13, and 19 cubic areas of fit, for two levels of unmodeled source strength, all of the data space under the spheres is shown. As expected, a radial pattern in the estimate is seen, and the larger the unmodeled source strength, the larger the maximal error.
The same series of regional subfits were made for an analytically simulated unmodeled source fit for the parameter set in Table 7-7 over 1, 7, 13 and 19 cubic regions (figure 7-15). As expected, the first simulation, \( R_d/R_b = 1, \chi_d/\chi_b = 1 \), has a higher accuracy near the sphere due to it's larger degree of field distortion. It is not surprising that the larger the region of fit, the less variation across the fit space, as the larger fit area behaves as a smoothing filter, but that the larger the fit space, the more likely that error from the unmodeled sphere is included in the fit. This error is clear in both 19x19x19 cases of figure 7-15, manifested as a relative minimum that does not exist in the single point fit. (Note that an LSE fit over a single point is valid as the model has but a single compartment, in contrast with the necessary two points to fit a complete model of two compartments in figure 7-14).

A wider range parameter sets of analytically simulated field data (Table 7-7) are shown in figure 7-16 for the 1x1x1 sub-region fits of an unmodeled source, displayed only at the slice which bisects sphere A. In the case of the (relatively) weakest unmodeled source, \( (R_d/R_b = 2, \chi_d/\chi_b = 4) \), the fit surface varies by less than 1 % over the slice shown, predicting that the method will be robust for most of the minor tissue differences in the torso. The opposite is true for the strongest case, where \( R_d/R_b = 1/2, \chi_d/\chi_b = 1/32 \), a situation not unlike that of the liver in the presence of an unmodeled lung compartment. However, the single point fit is accurate close to the modeled sphere, where the worst case (upper right) is within 60%, and the best case (lower left) is within 0.01%, at least in this random-noise-free analytically simulated case. Due to the normal 30:1 field noise in the in vitro data set, a 1x1x1 fit is too noisy for this form of display, nor does it allow the examination of only the unmodeled source error. This single point, nearest to the modeled sphere, is the same
Figure 7-16. 12 sets of 1x1x1 subfits - For 12 levels of unmodeled source strength, the distribution of 1x1x1 subfits varies according to strength of model error.
single point shown at the minimum of the radial restriction set of figure 7-11, and the radial distribution of the unmodeled sources error which led to the CI data set restriction is also seen.

VII.5.F.ii.a Unmodeled Source Noise Asymmetry

The restriction of the region of fit region becomes further complicated as the spatially correlated error, while radial in character with respect to the unmodeled source, will not be radial with respect to sphere A. Where the DFC ring error investigated in chapter VI was correlated to the modeled spheres, the spatial variation of an unmodeled source will not be symmetrical about the modeled source, and then will not correlate to the modeled source. This effect is seen in figure 7-17 for 1x1x1 data fits at several slices along the z-axis under sphere A (z = 0, +/- 4, +/- 8, see inset figure 7-17) of an unmodeled source simulation for the parameter set in Table 7-7. Again, the fit is best nearest the modeled source (at slice z = 0), at the same points noted in figure 7-16, with radial degeneration of fit. Comparison of the slices nearer to (z = 4, 8) and farther from (z = -4, -8) the unmodeled source shows the anisotropic influence of the unmodeled source on the fit. Also, for the second case ($R_e/R_b = 1/2, \chi_e/\chi_b = 1/32$), a semi-circular region exists near the top of the data set in both slice (-8) and slice (+8) where the spatially distributed error destructively interferes with modeled source, and results in an ill-conditioned fit. This ill-conditioned fit occurs when the field data is many orders of magnitude less than the field model, and can be avoided by increasing the number of data points in the region of fit.
Figure 7-17. Z-axial distribution of 1x1x1 subfits shows the asymmetry due to the unmodeled source expected along the z-axis. Z-axial estimates (at single points) for large unmodeled source strength are in error up to 250-fold.
VII.5.E.iii Pre-Filtering of Unmodeled Source Noise

The noise model can be altered by pre-filtering as discussed in chapter VI (equation [6.19]). In this method, a filter is separately applied to the field model and the field data, and the LSE is estimated as usual with varying sizes of restricted data set. In figure 7-18, the effect of pre-filtering the data and model using LxMxN-point averaging filters is shown with similar data set subregion fits. The filter sizes used in this figure set were 7x7x7 and 13x13x13. While the estimate data seen in figure 7-18 are similar in nature and magnitude, they are not equal. Theoretically, if the noise sources were spatially random, then the two methods would be equivalent, but the unmodeled sources are non-randomly distributed. Qualitatively, the pre-filtered fits have less slope near the modeled source and may represent a method for acquiring reasonable fits. The point at which the error is a minimum is, again nearest the modeled sphere, and for the 7 and 13 point cubic filters used, was 6% and 2% for un-filtered fits versus 0.5% and 0.2% for the 7 and 13 point sets shown.

The pre-filtering method allows weighting of the model error, which can be chosen to reflect the a priori knowledge of the system (Ljung, 1987), which in this case is limited to the z-axial asymmetry. For instance, if an LxMx1 filter (a planar filter rather than a cubic filter) is first applied to the data, the resulting susceptibility fit will not be influenced by the z-axis asymmetry of the unmodeled source (as it is in figure 7-17). Pre-filtering with a planar LxMx1 filter over a radially restricted region effectively transforms that region into an elliptically restricted region, as in figure 7-19.
Figure 7-18. Cubic 7 and 13 point pre-filters of the same space, LSE fit with a single point show different behavior than the fits over 7x7x7 and 13x13x13 shown in figure 7-14. Due to the spatially varying noise, the otherwise linear and associative process is not equivalent.
Effect of Pre-Filtering with $L = M$ Filter

Data Space

Filter

Results in reduction of data space by filter size

Subsequent Fit with Radial Restriction

Actually covers elliptical region over original data set

Figure 7-19. Choosing a square $L \times M \times 1$ filter followed by a radial restriction will preferentially exclude $z$-axial data, resulting in an effectively elliptical region of fit.
VII.5.E.iv Confidence Intervals of Pre-Filtered Unmodeled Source Noise

While the contour plots of pre-filtered noise indicate that the spatially colored noise is reduced, the usefulness of pre-filtering the data needs to be clarified. The CI method described in equation [7.2] and figure 7-12 was applied and the maximum $R_{fl}/R_a$ (or the maximum number of points) for which the CI is not exceeded for each unmodeled source strength are shown in figure 7-20. Pre-filtering the data has the effect of increasing the number of points in which can be used in the fit. At lower levels of unmodeled source strength ($\chi_a/\chi_s * V_s/V_a < 2$) the region of fit $R_{fl}/R_a$ increases by up to four-fold. At the lowest levels of unmodeled source noise (.03 to .3), the maximum $R_{fl}/R_a$ is 3, restricted by the size of the data volume under the spheres. At larger levels of unmodeled source strength, the number of points in the fit go below $n = 1$, indicating that the unmodeled source strength could not be measured with statistical relevance, even with the fewest points possible. When the error of the unmodeled source fit does not intersect the CI, then the number of points is set to $n = 0.1$ (which is a physically meaningless number, as at least one point must be measured). For some levels of unmodeled source strength, the pre-filtering increased the number of points tolerated by as much as 10 fold. At the highest levels of unmodeled source strength, this resulted in an un-fittable model becoming fittable.

VII.6 Summary

The robustness of the LSE of susceptibility from field distortion data obtained in an external MRI phantom has been examined. Noise or error result from model error or data noise. The data noise has been shown to be random, gaussian white. The
Maximum Rfit/Ra with Pre-Averaged Colored Noise, CI=50%

Maximum Rfit/Ra with Pre-Averaged Colored Noise, CI=90%

Figure 7-20. The confidence intervals of 'elliptical' fits, pre-averaged over 1, 5, 13 and 19 points show some improvement in the acceptance levels of estimates in the presence of unmodeled sources. In particular, the number of points allowed in the fit increase by a factor of up to 10 over non-filtered (1x1x1) data. In the cases of the maximal unmodeled sources, the 13 and 19 point filters make unacceptable fits acceptable.
methodological model errors can all be treated as the biased/colored/non-stationary noise of unmodeled sources. This is useful, as only the general set of unmodeled noise need then be examined. However, each of the potential sources of model error are first examined to show where the estimation method is most sensitive to error.

As summarized in Table 7-6, the susceptibility estimation method is sensitive to MRI noise for concentric spheres, but not for eccentric spheres. Outline jitter and compartment inhomogeneity have little effect for the analytical simulations, while the sensitivity to outline shift is more noticeable. Examination over a physiologically relevant range of unmodeled sources indicated that data restriction was necessary to obtain a good fit, but not sufficient for all levels of unmodeled source error/noise. Then pre-filtering was examined and found to be useful to increase the tolerable unmodeled source noise by a factor of 10. It is quite likely that other filters, designed specifically for a predictable range of noise distributions would further improve the fit. It is also possible that some reduction of the unmodeled source by placement of a point source of field distortion, would reduce the unmodeled source strength sufficiently to enable a fit within the confidence levels.

The CIs allow an interpretation of these results. However, the CI is based on a priori knowledge (that of the susceptibility), and would not be useful without some means of comparing the estimates to known values. If the strength of the unmodeled source was not known, then no useful information would be gained from this test. The CI test of fit acceptance is similar to a (crude) predictor error method, where the desired response of a system is compared to the actual system response, and the system is adjusted accordingly (Ljung, 1987).
VII.7 Conclusions

This study shows that a high degree of accuracy for liver iron estimation could be achieved if all of the sources could be accurately modeled. As the geometrical modeling can tolerate much larger degrees of error than are expected in real measurements, then the geometrical representation step can be treated as an unmodeled source of weak strength. The estimation error in the presence of field noise and DFC ringing are negligible when the eccentricity of the spheres range from fully eccentric to 1/2 eccentric, which is within the expected values for liver and torso placement.

Unmodeled sources will pose the largest problem since all forms of non-random error can be collated into this category, and from the CI analysis, susceptibility measurements of normal level liver iron patients should not lie within the CI. But, when the data is pre-filtered with a filter chosen to preferentially exclude the z-axial data, then the CI analysis suggests that estimations can be made even on normal patients with a small number of points located as close to the patient as possible.

One weakness in the unmodeled sources analysis is that multiples of unmodeled source error were not examined. It would be convenient to claim that by virtue of superposition, any group of unmodeled sources can be approximated by a single unmodeled source, but this is not entirely true. The basic principles of data space restriction and filtering will still hold, however, the simplest method for examination the effect of multiple unmodeled sources is to proceed directly to the in vivo liver iron patients.
Chapter VIII - In Vivo MRI Liver Iron Estimates

VIII.1 Introduction

In the previous chapter, the effects of noise and error were investigated on the MRI external susceptibility estimation method using analytical simulations and in vitro experimental data. In this chapter the method will be applied to in vivo experimental data, and where appropriate, compared to the previous results.

Also, the consistency of the noise error with in vitro results will be examined. LSE fits of the lungs using specific data set restrictions will be used. Pre-filtering the data before the LSE fit will be examined and evaluated using CIs. Following the retrospective examination of pre-filtered patient data, the method will be applied prospectively to a data set in a double blind protocol.

VIII.2 Liver Iron Estimation

VIII.2.A Random and Non-stationary Noise and Data Restriction

In chapters VI and VII, the effects of various types of noise and error were examined for their influence on the goodness of fit of the MRI phase/field to the modeled field. The types of error included; MRI phase noise, compartment outline error (shifted outline, noisy outline and over/under estimation of volume), compartment inhomogeneity, the assumption of superposition and the effect of unmodeled sources of magnetic distortion.
In this chapter, the effect of different sources of noise is examined for in vivo cases. Noise sensitivity is investigated by artificially altering the segmentation data or the MRI data to simulate noise. To examine the effect of the estimation method for more realistic geometry, a representative patient is chosen, and the susceptibility estimation method is performed as outlined above. The effects of noise and geometrical parameters is examined by altering the segmentation data or the field data and comparing it to the original model. Where applicable, the analytical and in vitro experiments for the same parameter perturbations from chapter VII will be compared.

VIII.3 Materials and Methods

VIII.3.A In Vivo MRI Data Acquisition

MRI FE images were acquired using a Picker Vista II HPQ 1.5 T MR Imaging system, using a standard transverse FE/500/15 sequence of 16 slices of 1 cm thick with 64 Phase encode views and 256 frequency encode data points. No signal averaging was performed. Data centering was performed to ensure that no linear shifts in k-space are applied as this will result in an unwanted linear phase component. Patient motion was reduced by requesting patient to breath-hold during the 32 second scan. The field data was then treated as for the in vitro experiments in chapter VII.

VIII.3.B External Reference Phantom

For in vivo experiments, a cylindrical external reference phantom (d = 35 cm, h = 10 cm) was constructed from acrylic plastic which has zero susceptibility, and filled
with deionized double distilled water. Doped water may be used if signal saturation is a concern, but ultra-pure water has the advantage of being less sensitive to eddy current induction due to the high impedance (18 M ohm). The patient is positioned face-down with the liver located approximately above the center of the phantom (figure 8-1(a)). The phantom is recessed in a patient table (figure 8-1(b)) constructed from 6-inch thick high-density extruded polystyrene (standard construction-grade insulating styrofoam), and padded for patient comfort.

VIII.3C Compartment Segmentation

Because the magnetic field is deployed over the entire torso, the effects of all thoracic tissues may need to be considered in the torso model for a high degree of accuracy. However, one of the goals of this study was to determine if the liver susceptibility could be estimated with only two compartments; the torso and the liver. Segmentation of these compartments, $V'_{\text{Liver}}(\mathbf{r})$ and $V'_{\text{Torso}}(\mathbf{r})$, were made on the magnitude reconstruction images of the MRI FE scan data. Exact patient geometry at the time of the MRI field map is available, as the magnitude and phase scans are acquired simultaneously.

The magnitude images were analyzed on a graphics-capable, unix-based, 25 MHz, 80386 driven computer, with a trackball user interface. The geometrical parameters were measured from the image using an interactive program which prompts for anatomical landmarks, and translates trackball entries into the correct spatial units. Segmentation of the torso is made by a nearest approximation of ellipses on a slice by slice basis (appendix C). In order to avoid edge effects in the
Figure 8-1 a). Patient position over water bath b) styrofoam bath holder placed on MRI system patient table.
magnetic field model, the torso compartment is extended from 16 slices to 32 slices by extrapolating the torso for 8 slices on each end. The liver is manually segmented by trackball outline for each slice. The liver outline is smoothed slightly using a Fourier Descriptor method (Park), where the manually selected data points are interpolated to 1024 points, and then low-pass filtered to 13 spectral components. The presence of high frequency noise in the object outline has been shown to have little effect on the fit of the field model to the MRI data (chapter VII). Outline smoothing is necessary to provide a compartment which is of closed form and can be easily modeled (as \( V'(\vec{r}) \) of equation [3-8]).

**VIII.3.D Iron Estimation of Iron Overload Patients**

For the retrospective study, MRI scans were acquired in vivo for 4 normal and 19 iron elevated patients of both sexes, ranging in age from 12 to 65 years, with a median age of 25 and median patient weight of 148 lbs. The overload patients have well characterized iron burdens, by both SQUID and liver biopsy. Original hepatic iron levels in the iron elevated patients ranged from 178 to 6200 ug Fe/cc. Concurrent measurements were made on a SQUID magnetometer, within four hours of the MRI measurement. For the prospective study, MRI susceptometry data was obtained on a second set of 29 beta thalassemia major patients, all of whom had liver biopsies with 1 week of MRI measurement. The overload patients had a median age of 17 and a median weight of 134 lbs. Hepatic iron levels in the second set of patients ranged from 226 to 5878 ug Fe/cc. Each patient was required to fill out volunteer patient release forms before imaging may begin, as per hospital and NIH protocol.
The in vivo magnitude scans were segmented as above into compartments. A Field Model was generated for each compartment using the DFC method (chapter V). The susceptibility of the torso and liver were then estimated as described by the overall algorithm in figure 7-1. As described by equation [3.9], the model is based on the differential susceptibility, and the final liver iron concentration is $\chi_{\text{liver}} = \chi_{\text{torso}} + \chi'_{\text{liver}}$. A units conversion is made from susceptibility to iron concentrations per gram of wet weight using known calibration curves (Brittenham, 1982; Table 3-1). The entire algorithm requires 70-80 minutes of computation for the 256x256x32 voxel space on the 25 MHz 386 computer.

The regions of fit, restricted by the liver field model (equation [4.1]) were used in the LSE estimation. The liver iron estimates were made from the field model and field data as in equation [3.16-17], for unfiltered and pre-filtered data (equation [4.3]). For the retrospective study, MRI-susceptometry measured iron levels were compared to SQUID-susceptometry measured iron levels. For the prospective study, MRI-susceptometry measured iron levels were double blindly compared to liver biopsy measured iron levels.

VIII.3.E Analytic Simulations

The torso and liver compartments of a normal patient ([Fe] = 200 ug/ml) and a 10x overload patient ([Fe] = 2000 ug/ml) were segmented as described, and a liver susceptibility was estimated. The region of fit, as in equation [3.16-17], was $\eta = 0.75$. The values of liver iron initially estimated were then used as a normalizing reference, before investigating the noise characteristics or geometrical errors.
The effect of field noise was simulated by adding uniform random noise to the MRI field data. The effect of compartment outline shift was simulated by shifting the outline before the DFC field calculation. The compartment homogeneity was also corrupted by adding noise to $V_{\text{aver}}(r)$ before the DFC field model was calculated. The analytical simulations for equivalent parameter perturbations on comparable eccentric spheres models from chapter VII are compared to the results of the in vivo cases.

**VIII.3 F Statistics**

The clinical measurements will be compared to the SQUID and surgical biopsy results using the correlation of two data sets described in equation [4.7]. The method for CIs was described in equation [7.3] where the relative unmodeled source strength (used as the abscissa values) was computed by fixing the lung volume and susceptibility of all patients to 4000 cc and 4000 mg Fe/g respectively and then taking the relative ratios of the lung source strength to the known (SQUID-generated) liver source strength.

**VIII.4 Results and Discussion**

**VIII.4.A In Vivo Magnitude, Phase Maps, and Segmentation**

The magnitude reconstruction of the transverse slice at mid-liver is shown for a normal and 10-fold elevated iron patient in figure 8-2(a) and 8-2(b) for a normal and an abnormal patient. Note the 'black-liver' phenomenon seen in the overload patient of figure 8-2(b). The phase reconstructions for the same patients are seen in figure
8-2(c) and 8-2(d). While a qualitative difference of the reference baths is observable between patients, without background correction, it is not quantitative. The phase across the liver of the normal patient is relatively homogeneous (predicted by equation 3.2(b)). The phase is somewhat distorted across the liver of the overload patient. This phase distortion may also be contributed to by to the low SNR in the iron laden liver, which, in turn, is caused by reduced T2 (Stark). The compartment segmentation for these representative normal and abnormal patient slices are shown in figures 8-2(e) and 8-2(f), and are derived as described from the magnitude images.

VIII.4.8 Field Noise

The effect of increased field noise is shown in figure 8-3. Normal MRI operating parameters for the sequence used provide S/N > 30:1, for which all estimations are within 5% of the noise-free estimations. The effect of noise in the in vivo cases is similar to the analytical simulations. Although the geometry of the human subject is more tortuous than the perfect spheres, the human subjects used had differential susceptibilities that are on the same order as those of the analytical simulations. The liver volume of each patient was on the order of 1/8 of the torso volume, as were the simulations. The liver depth of each patient was 23 mm and 25 mm, which are roughly greater than 1/2 eccentric (where eccentricity of the human subject was determined as the mean radius shift of center of mass). As seen in figure 8-3, the noise influenced error of the estimation is equivalent to that of a 1/2 eccentric spheres model. This behavior would be expected as the source signal strength for the in vivo cases is similar in magnitude to to the analytical models (after appropriate normaliza-
Figure 8-2. Transverse slices at mid-liver for a-c) Normal patient, d-f) Iron overload patient, iron level = 1876 ug Fe/ml. a,d) magnitude reconstructions, b,e) phase reconstructions and c,f) operator segmented into water bath, torso and liver compartments.
tion). The maximum estimate errors at expected MRI operational levels of noise (S/N = 30:1) were less than 1.5%.

**VIII.4.C Object Inhomogeneity**

The effect of disturbing the compartment homogeneity for the same model is shown in figure 8-4, for the same patients, and the same analytical simulations as in figure 8-3. Inhomogeneity S/N is calculated as the square of the mean of the compartment value over the variation of compartment (equation [7-7]). Therefore, a compartment with +/- 10% variation across would have an inhomogeneity S/N of 100. The minimum amount of S/N would be 1 or a variation of +/- 100%. The analytical simulations are much more susceptible to object homogeneity than are the in vivo simulations as seen in figure 8-4. The estimation of susceptibility of inhomogeneity S/N = 100 is within 5% of the expected (normalized) estimate.

**VIII.4.D Origin Shift Error**

The effect of spatial translation of a compartment was shown in chapter VII to have a large effect on the LSE fit of concentric spheres, and less and less on eccentric spheres. As above, the in vivo geometry was investigated for its sensitivity to compartment shift by artificially shifting the segmented object before calculating the DFC field model. For reference, the maximum shift of 50% of the mean radius of the liver compartment for the in vivo model was 16 and 17 pixels respectively.

The effect of in vivo compartment shift is shown in figure 8-5 along with the
Figure 8-3. Estimates of liver susceptibility for simulated field noise of in vivo measurements compared to similar in vitro field noise simulations. Normal patient iron level = 200 ug Fe/ml, overload patient iron level = 6000 ug Fe/ml.

Figure 8-4. Same as figure 8-3, but for inhomogeneity simulations.
data for the same set of analytically simulated eccentric spheres with shifted origin. The in vivo cases both lie somewhere in between the eccentric and 1/2 eccentric analytical cases. Both analytical and in vivo cases show little sensitivity to iron levels. The mean center of mass shift for a experienced operator performing repetitive outlining, was less than 2% of the radius of the object (Appendix C), which would result in less than 2 pixels of an outline shift.

**VIII.4.E.1 In Vivo Measurements**

In normal, or near normal, patients the lung, comprised mostly of air, has a differential susceptibility which is equivalent to liver iron levels of the order of 4000 µg Fe/cc, while the susceptibility of the heart is more nearly the level of the rest of the torso, equivalent to 25-50 µg Fe/cc. The range of liver iron can be from 125-250 µg Fe/cc in normal patients to 12000 µg Fe/cc in the most extreme overload cases.

It is expected, from the unmodeled sources analysis, that the effect of the unmodeled source will diminish as the susceptibility of the liver is increased. This effect can be seen in the 2-D mesh plot of normal and iron-overload patients with respective liver iron levels of about 200 µg Fe/cc and 4100 µg Fe/cc, shown at mid-liver slice in figure 8-6(a). The modeled field includes only the liver-torso compartments, which is sufficient to model the bulk of the field variation. The axial data directly below the center of mass of the liver are compared with the modeled data for two patients, one normal (hepatic iron assumed to be 125 µg Fe/cc), and one abnormal (hepatic iron = 4100 µg Fe/cc), as shown in figure 8-6(b). Only the liver and torso compartments are used in these fits.
Figure 8-5. Figure 8-4. Same as figure 8-3, but for simulated origin shift.
Comparison of Fields for Mid-Liver Slice for an Iron Elevated Patient (4100 ug Fe/cc)

Figure 8-6. 2-D meshes of mid-liver slice of iron elevated patient (iron level = 4100 ug Fe/ml) 
(a) Measured field (unwrapped MRI phase reconstruction data corrected for background variation) 
(b) DFC modeled field based on liver and torso compartments. Field distortion levels are normalized to maximum.
VIII.4.E.2 Field Model Strength Based Data Restriction

The region of fit restriction based on the liver field model (equation [4.1]), was applied to MRI data and field models from 19 chronic liver iron overload patients and 3 normal patients using liver and torso compartments only. The correlation values for all threshold levels are shown in figure 8-7, and is never seen to rise above 0.495 when the entire data set is examined, peaking over \( 0.70 < \eta < 0.90 \). In figure 8-8(a), the in vivo liver iron estimates are shown versus the SQUID measurements for \( \eta = 0.75 \). As seen, the correlation is \( r = 0.492 \) for all patients. In figure 8-8(b), for the data subset examining only the patients with Liver Iron < 2000 mg Fe/g tissue, the correlation value was \( r = 0.540 \).

VIII.4.E.3 Data Pre-Filtration Correlation, Confidence Interval and Fits

The method of field-based data restriction, and pre-filtered with an \( L \times M \times 1 \) (\( L = M = 5, 9, 13 \) and 19) over the same 22 patients is shown in figure 8-9. The correlation values are much higher than in figure 8-7, peaking at up to \( r = 0.985 \) over the ranges of \( 0.93 < \eta < 0.97 \). Pre-filtering with at least \( 9 \times 9 \times 1 \) filter was shown in chapter VII to be necessary for estimation in vitro. In vivo pre-filtering with a \( 19 \times 19 \times 1 \) averaging filter provided the highest level of correlation, \( r = 0.985 \) at \( \eta = 0.94 \). Examination of this data using the CI analysis method shows that the number of points which the error lies within the CI is also low, and in some cases below \( n=1 \) (equivalent to \( \eta = 0 \)) as shown in figure 8-10(a-e) for increasing filter size.
Figure 8-7. Correlation of MRI to SQUID estimates as a function of liver model field strength. Maximum correlation = 0.495 at $H/H_{\text{max}} = 0.72$. 
Liver Iron Estimates for all Patients
Fit from top 10% of Liver Model

Liver Iron Estimates for X(liver) < 2000 mg/g
Fit from top 10% of Liver Model

Figure 8-8. Linear regression comparison MRI Susceptometry and SQUID Susceptometry estimates of liver iron over 22 patients at \( H/H_{\text{max}} = 0.90 \). a) all patients b) regression for patients with liver iron < 2000 ug Fe/ml.
Correlation of MRI to SQUID Iron restricted by Field Model Strength Estimates with NxNx1 Prefiltering

Figure 8-9. Same as for figure 8-7, but with prefiltration of 5x5x1, 9x9x1, 13x13x1, and 19x19x1 filters.
90% CI Efficacy of In Vivo Liver Iron Estimation with prefiltering

Maximum Number of Points such that Estimated X(Liver) error lies in 90% Confidence Interval

![Graphs showing the number of points in the fit varying with unmodeled source strength for different levels of prefiltering: No Prefiltering, 5x5x1 Prefiltering, 9x9x1 Prefiltering, 13x13x1 Prefiltering, and 19x19x1 Prefiltering.]

Figure 8-10. Maximum number of points such that the estimated susceptibility lies within the 90% confidence interval as the unmodeled source strength increases, with different levels of prefiltering.
In figure 8-11(a, b) regression curves are shown for the 19x19x1 pre-filtered data. Similar to figure 8-8, the correlations are shown for all patients (figure 8-11(a), $r = 0.889$), and for only those patients with SQUID measurements below 2000 mg Fe/g (figure 8-11(b), $r = 0.662$). The CI analysis predicted that more error would appear in the estimates of normal to low-level iron overload which is validated by the fits over patients below 2000 mg Fe/g. As stated above, the susceptibility estimates were made for some region of fit which encompasses all patients (in this case for $\eta = 0.90$), as the goal was to find a generalized protocol which does not require a priori information about the iron overload.

The results of the double blind study are shown in figure 8-12(a, b), with a regression curve shown for the 19x19x1 pre-filtered data as compared to the liver biopsy measurements. Similar to figure 8-8, the correlations are shown for all patients (figure 8-12(a), $r = 0.622$), and for only those patients with SQUID measurements below 2000 mg Fe/g (figure 8-12(b), $r = 0.17$). In figure 8-13, the relative error is displayed (computed as the difference between MRI-susceptibility liver iron levels and liver biopsy iron levels relative to expected, or liver biopsy, liver iron levels), and it can be seen that the relative error reduces with increasing levels of known iron.
Liver Iron Estimates for all Patients
Fit from top 10% of Liver Model
with 19x19x1 Pre-Averaging Filter

Liver Iron Estimates for X(liver) < 2000 mg/g
Fit from top 10% of Liver Model
with 19x19x1 Pre-Averaging Filter

Figure 8-11. Same as for figure 8-8, but following 19x19x1 pre-filtration.
Figure 8-12. Linear regression comparison of MRI Susceptometry and hepatic biopsy estimates of liver iron over 29 beta thalassemia major patients at $H/H_{\text{max}} = 0.90$ with 19x19x1 pre-filtration. a) all patients b) patients < 2000 ug Fe/ml.
Relative Error in MRI Susceptometry Estimates Compared to Liver Biopsy Iron Measurements

Figure 8-13. Error of MRI susceptometry to regression curve with biopsy, error is absolute distance of MRI susceptibility estimate from regression curve.
VIII.5 Discussion

In vivo MRI noise and methodological error sources do not interfere with the robustness of the method as shown in figures 8-3, 8-4 and 8-5. MRI phase/field noise is well above the minimum levels for a less than 5% error. Compartment outline error has been shown to be well within tolerance. The effect of perturbing the assumption of compartment homogeneity has also been shown to be within biological limits. As these forms of error are not correlated to each other, the effect of a combination of all forms of error should not be greater than the addition of the worst cases of each. Although the estimation method is sensitive to spatial translation, the expected error should not effect the sensitivity of the model, provided that the operator is cautious during the outlining stages.

Initial estimates based on the whole data space fits (i.e. unrestricted data sets) were in error, as predicted by the Cl method in chapter VII, where no reasonable fit was expected without pre-averaging. The threshold affects the fit such that the lower the value of \( \eta \), the larger the number of points included in the average, and the further from the patient the data set encompasses. The degradation of fit at lower values of \( \eta \) can be attributed to the increased dominance of unmodeled sources, which are largely the effect of the lungs in the magnetic field. At very high values of \( \eta \), the number of points averaged are few, and the field noise is seen to influence the fit. Therefore, the efficacy of the MRI method is limited at normal to low iron levels.

Pre-filtering this data increases the number of points which can be used in the susceptibility estimate. Similar to the in vitro studies in chapter VII, the number of
points allowed reflects the amount of spatially correlated noise, as well as the confidence of the fit. For low levels of relative unmodeled source strength (i.e. high levels of iron-overload), all of the points measured in the water bath can be used. However, when making overall correlations, as in figure 8-10(a), some choice must be made for the number of points fit, which can apply to all patients, as the degree of unmodeled source strength cannot be determined a priori. This also points out a constraint of the use of the CI analysis, as the desired susceptibility values must be known a priori in order to determine the error. Therefore, the CI cannot be used for measuring patients for which no data exists, but must only be used to analyze the efficacy of a particular model (in much the same way as the regression curves and correlation fits are). The conclusions to be drawn from figure 8-11, are that normal-level patients will have large unmodeled source strength levels which are associated with small regions of fit, and that pre-filtering the data will increase the number of data points which can be used in the fit.

The final, double blind, comparison of the MRI-susceptometry method to liver biopsy results is less conclusive than the retrospective study ($r = 0.622$ vs. $r = 0.889$). Some differences in experimental methods and patient set may be accountable, such as; differences in disease (retrospective - mixed hemochromatosis and betathalassemia, prospective - beta thalassemia only) median patient age (retrospective - 25, prospective - 17), median patient weight (retrospective - 148 lbs, prospective - 134 lbs.) and the comparison of SQUID-derived iron levels versus liver biopsy derived iron levels. According to the theory behind MRI susceptometry, these differences should not be a factor; etiology of liver iron levels is not important, age is immaterial, the weight of the patient should be accounted for in the geometrical
modeling, and biopsied liver iron correlates well with SQUID measurement of liver iron. One possible explanation (based on anecdotal evidence) could be that the younger subjects did not maintain absolute motionlessness during the MRI scans, the effects of which were not completely analyzed in this study.

**VIII.6 Conclusions**

The most important results of the region of fit section are that the number of compartments may be limited to the liver and the torso, provided the data is fit according to the restricted data set, pre-filtering method. The robustness of this approach was predicted by in vitro models in the previous chapter and has held for the in vivo measurements. As stated in chapter VI, the exact nature of the pre-filter averaging are not explained by linear estimation techniques. The spatially distributed noise due to the lung or intestinal contents invalidate the standard linear fit approach. For a known form of non-random noise, non-linear estimation techniques can be found to reduce the effect of the noise, as has been done here by restricting the region of fit (Ljung, 1987). This restriction takes advantage of the expected inverse-cubed effect of the field distortion (chapter III). End effect of each compartment is also a minor concern, but, data space restriction minimizes this also. Finally, the correlation of region-limited, pre-filtered MRI-susceptometry measurements to both SQUID-susceptometry measurements and liver biopsy measurements shows that this method has some promise.
CHAPTER IX - Discussion and Conclusions

IX.1 Introduction

This thesis commenced by recognizing that there is a clinical need for non-invasive iron measurement and proposed that MRI susceptometry could satisfy the need. This chapter error sources and the advantages and limitations of MRI susceptometry in fulfilling this clinical need. The efficacy of the method, as it has been developed to date, is compared with the required accuracy for a clinical procedure while suggesting methods and needs for improvement. Also, the likelihood that these requirements could be met based on available information are analyzed.

IX.2 Error Analyses

The efficacy of MRI Susceptometry was postulated in chapter I, when the hypothesis was stated:

"Liver susceptibility can be estimated from MRI GFE phase information when appropriately fit to a field model based on two compartments consisting of the liver and torso."

The accuracy of the MRI susceptometry method in comparison to the liver biopsy was reflected in the correlation of $r < 0.622$ in the prospective (double blind) study and of $r < 0.884$ in the retrospective study shown in chapter VIII. These correlations values indicate that most of the variation in the data is explained by the theory, but that some improvements can be made in the overall method.
The difference between retrospective and prospective studies may reflect the
groups examined and the differences between them, such as disease types, patient
weight and patient age. Not enough data points exist between the two sets to statistically determine if any of these would cause the disparity in correlation. For both studies, the relative error in the MRI measurements was found to decrease with larger amounts of iron, suggesting that the amount of certainty in the measurement correlates slightly with the level of iron in the liver. This result is consistent with the expectation from in vitro simulations, where higher iron levels produced lower errors for all types of simulated methodological error. In general, the error behavior for the in vivo studies compared well with the predicted error behavior in the studies in vitro and in vivo. Therefore, correcting the identifiable sources of error from the in vitro analyses should improve the MRI susceptrometry measurement in vivo.

For the initial series of in vitro experiments (chapters II-V) good correlation of data was obtained between MRI susceptrometry measurements and known reference values. This was anticipated since each of the six fundamental assumptions of the method were confirmed experimentally. The inherent assumptions (or conditions) were: (1) direct correlation of FE phase to magnetic field, (2) superposition, (3) DFC accuracy, (4) non-contribution of higher order magnetic field terms, (5) use of the reference bath, and (6) compartment homogeneity.

For example, the phase reconstruction of MRI FE data of in vitro spheres was shown to correlate with the field model predicted field distortions ($r > 0.989$, $p < 0.0001$) showing that the field distortion data can be well predicted by analytical solutions of perfect spheres phantoms (chapter III). The high correlation of the superposi-
tion test ($r > 0.995, p < 0.0001$) indicates that superposition held, and that the background field can be corrected for (chapter IV). Therefore, the validity of either the superposition assumption and the assumption of FE phase to field distortion proportionality are not expected to contribute to the methods overall error. It is not believed that further work in these areas will improve either correlation or error in the future.

The third and fourth assumptions were verified by comparison of analytically derived field solutions to DFC derived field solutions (chapter V). Testing of these assumptions was important to insure that the field modeling method was sound. Field generation of modeled spheres using the DFC method correlated well with analytical simulations ($r > 0.995$). The higher orders of field were shown to be non-contributory for the DFC method as well. This was demonstrated by estimating them iteratively and showing that they contribute less than 0.01% of the total field for biological levels of differential susceptibility. Therefore, the DFC method provides an adequate field model for use in susceptibility estimation. A small improvement in the field model accuracy would be generated by the use of finite or boundary elements methods at the expense of computation time and effort. Based on the minimal amount of error in the field modeling step, correction of this source of error should receive a very low priority.

The fifth item in the list of assumptions, the reference bath, is actually an experimental protocol which, based on the principle of superposition, is primarily responsible for the feasibility of the method. The advantages gained in using the external reference bath are: (1) it provides a method for correcting background field
inhomogeneities, (2) it is uniform and hence unaffected by local proton density varia-
tions, (3) relaxation parameters can be adjusted to provide a strong MRI signal, (4) it
can be made non-conductive to prevent or reduce "tissue" eddy currents, and (5) it
allows measurement of liver iron susceptibility even when the source signal is unav-
ailable as would occur in cases where iron overload levels cause liver $T_2$ to be so short
as to appear black in most sequences (Stark, 1985).

It is possible that the sixth assumption, compartment homogeneity, will intro-
duce errors that prevent accurate susceptibility estimation. Despite evidence of tissue
homogeneity in liver biopsies by Overmoyer et. al., there is no independent means to
confirm that the extent of in vivo homogeneity is equivalent to the compartment
homogeneity assumed in the model. Homogeneity is inherently valid for iron loaded
phantom constructs in vitro, but not for measurements in vivo, and, while the first
five assumptions could be tested experimentally, compartment homogeneity had to be
tested with simulations. For analytical simulations in chapter VI and on in vivo
graphology in chapter VIII, where it was shown that, for expected amounts of random
inhomogeneity across a compartment, the estimates of iron content would not vary by
more than 5% in the worst cases. However, only a simple form of randomly distrib-
uted homogeneity error was examined, and, it is possible that non-random distrib-
utions of inhomogeneity error would contribute larger than two percent error in
susceptibility estimation. Clearly, future work must establish the implications of this
assumption for error contents when the inhomogeneity is not randomly distributed.
Along these lines, some suggestions are made in the future works discussion in chap-
ter X.
In practice, some simple cautionary measures should be taken in order to reproduce the results derived in this thesis. When comparing field data to analytically derived models, care must be taken to minimize water bath motion, and to specify the spatial position in the static field of the objects exactly when generating the analytical solutions. Duplication of the reference bath phantom position with the field when processing the spherical iron loaded phantom measurements with the background correction measurement is also critical. Phantom construction must also be carefully followed in order to avoid contamination of the solutions. The breath-hold method which was used is preferable to other longer duration imaging methods with higher SNR since respiratory movement and ghosting artifacts from the liver (which impinges on the diaphragm) can be minimized. For patients not able to breath-hold for 32 seconds, a large number of signal averages will improve the phase and magnitude reconstruction SNR to within usable range, but the bulk patient motion offers an additional modeling error which has not been considered in this thesis. Also, echo time (TE) should be minimized as much as possible; although phase signal strength increases linearly with TE (chapter III), the magnitude signal decreases exponentially. As phase SNR is proportional to magnitude SNR, the loss of signal will not be offset by the associated increase in phase/field SNR.

Following satisfaction of the assumed conditions, the overall method was tested on phantoms in vitro (chapter IV) where it was found that an unknown susceptibility parameter could be resolved to within 3% using the MRI susceptibility method (p > 0.9975). These experiments confirmed the fundamental validity of the method for MRI susceptibility. This suggests that the overall algorithm is sound, at least for simple spherical phantoms. But, as in any LSE fit, noise and error may corrupt the
estimations of susceptibility in this method. A number of these potentially important error sources were found, including methodological error, field noise and unmodeled source error.

Methodological errors such as outline jitter and volume error have little effect for the analytical simulations, while the sensitivity to outline shift is more noticeable. For example, outline jitter was simulated in vitro (chapter VII) and introduced less than 0.04% error in the estimation of susceptibility. As such, devoting effort to reducing jitter is not worthwhile. Also in chapter VII, error in estimated susceptibility was seen to be linear with volume error. That is, the expected levels of error in volume (about 2%) resulted in equivalent errors in the susceptibility estimates. Although volume error does systematically under- or over- estimate susceptibility, the expected levels of volume error are not large. Nonetheless, the volume outline has already been improved by use of the Fourier descriptors, and as further improvement in the outlining steps are not readily available, correction of volume induced error should also have a low priority.

Outline shift error may be an important source of error, and may be of interest in future refinements of the method. While the expected degree of outline shift error was small (less than 0.5 % for a one pixel shift), it could rapidly translate into large amounts of error in susceptibility estimation (up to 10 % for a 5 pixel shift) as seen in the simulations of outline shift error both in vitro (chapter VII) and in vivo (chapter VIII). The simulation of these outline errors on geometry in vivo (in chapter VIII) indicated that 1/2 to full eccentricity is a reasonable description of the geometry in vivo. In practice, the expected level of outline shift error was shown to be less than
one pixel (Appendix C). Reduction of outline shift error should not be a high priority for improving the MRI susceptometry method. However, the rapid increase in estimate error with small increases in outline shift error indicate that the outlining method is an important aspect of the method and increasing the outlining skills of the interactive operator may be important. It is implied in this analysis that the tissue geometry is accurately reflected by the image, and therefore the outline. However, geometric distortions in the image due to gradient non-linearity, gradient scaling, partial voluming, etc. will produce errors equivalent to outline error. As such, all steps should be taken to reasonably ensure minimized geometric distortion in the aquisition of the tissue geometry.

Another form of error which could disturb the estimation of susceptibility, random noise in the MRI phase reconstruction, was found to present little difficulty as less than 1.5 % error in the estimates was seen for in vivo geometries (chapter VIII). These were similar to the results from the in vitro studies in chapter VII (also less than 1.5 % error) and were predicted by the theoretical noise analysis in chapter VI. However, later analysis of unmodeled source error showed that presence of noise could increase susceptibility estimate error by as much as 50% when the number of data points were reduced in order to decrease the influence of unmodeled sources. This was predicted by the theory in chapter VI, as the goodness-of-fit was shown to be proportional to the number of field data points used in the fit. This suggests that some improvement in the estimation method would be achieved by increasing the SNR in the water bath. Given the restriction of finite-length breath hold times, improving SNR is not a straight-forward problem; some suggestions are made in chapter X.
The presence of unmodeled source noise turned out to be the principal source of error in MRI susceptometry. The overall error levels of susceptibility estimations in the presence of unmodeled sources were as much as 100-fold that of any other error source (chapter VII), suggesting that the highest priority be directed toward correction of unmodeled sources. Base on size and susceptibility, adding the lung compartments to the model will have the largest impact on improving susceptibility estimation of iron stores in the liver, followed by adding a cardiac compartment, and then a bowel compartment. Another method for reducing unmodeled sources - the predictor error method - is introduced and briefly examined in chapter X.

Admittedly, not all organs or unmodeled source error may be correctable. In chapter VI, it was suggested that all forms of non-random methodological error could be combined into the category of unmodeled source error. Without filtering or data set restriction, the MRI susceptibility estimates for in vivo data (chapter VIII) had low correlation to the SQUID susceptibility estimates ($r < 0.492$), which was increased following filtering and data set restriction ($r > 0.884$). Therefore, techniques such as data restriction and error filtering should be used in practice and investigated for possible improvement.

For example, data restriction had been predicted to be useful in reducing the influence of unmodeled source error in the analysis in chapter VI, where it was found that for LSE fits in the presence of spatially biased error, the region of fit should be chosen to maximize the strength of the field model of the liver. Similarly, fits in vitro over a physiologically relevant range of unmodeled sources in chapter VII were examined by CI analysis (which providentially, is also a useful method for specifying
the number of points to be chosen in the region of fit restriction). The CI analysis indicated that data restriction and error model filtration were necessary to obtain a good fit, but were not sufficient for all levels of unmodeled source error. For instance, while the correlation of MRI estimates to SQUID estimates following filtering and data set restriction was high over the entire range of patients observed (r > 0.884), it remained below r < 0.492 for the patient set under 2000 µg Fe/ml. This discrepancy over the range of patient data agrees with the CI analysis in chapter VII on in vitro and analytically simulated spheres as the results for the low-level iron patients were not expected to be as accurate. Additionally, all of the previous noise and methodological error results in vitro in chapter VII suggested that higher iron concentrations would provide better estimates of susceptibility. This was originally predicted in chapter VI; the larger the source of susceptibility, the larger the degree of field distortion produced, and the better the goodness-of-fit. While data restriction improves overall correlation, it is not sufficiently accurate at low levels of iron overload to indicate the use of MRI susceptometry in routine clinical practice.

The theory behind an additional method for reducing unmodeled source error, data filtration, was introduced in chapter VI. Pre-filtering of data in vivo increases the toleration of unmodeled source noise by as much as a factor of 10 as determined by CI analysis in chapter VIII. Error filtering was noted in chapter VII to be of use by altering the spatially varying error model. The asymmetric shape of the field distribution of the unmodeled source was taken advantage of by using a LxMx1 filter. Other filtration methods, like radial, cubic or otherwise geometrically shaped and frequency-response designed filters, may be able to more fully take advantage of this
asymmetric field distribution due to unmodeled sources, thereby improving the susceptibility estimates. The CI method of analysis also provided a clear and condensed interpretation of the efficacy of filtered and unfiltered results and should prove useful in future enhancements to the method. Similar to the results for data restriction, data filtration did not improve the susceptibility measurements at low levels of iron overload. Although improvement is noted, use of the combined data restriction/filtration corrections were not sufficient to allow clinical use of the procedure.

To summarize the results of the application of MRI susceptometry in vivo in this thesis, some improvements are required for this method in order to meet the requirements of accuracy for all patient levels. These enhancements will be necessary to correct the low correlation of the method for low-level and normal patients. Although only a two compartment model was investigated in human subjects in this thesis, the close comparison between in vivo results and the predicted in vitro results suggest that reducing the unmodeled source error should be sufficient to allow measurement over all ranges. Based on the in vitro results, methodological improvements should be attempted (in order of likelihood of improvement) along these directions; (1) enlarge the number of model compartments - first lungs, then heart, then bowel, (2) reduce random noise - possibly by filtering or increasing water bath SNR, and (3) reduce secondary points of unmodeled source error - by improving patient geometry outline error. As a clear clinical need exists, and especially as no reason exists to believe that these problems can not be overcome, it seems worthwhile to pursue these improvements in the MRI susceptometry method.

 IX.3 Comparison of MRI Susceptometry to Other Methods
In table 1-1, several liver iron measurement methods were presented with the advantages and disadvantages listed. Because of the presence of risk associated with liver biopsy, and the inherent limitations associated with serum tests to assess iron stores, an accurate non-invasive method would improve clinical diagnosis assessment. Since other methods do not provide information on the extent of damage in liver tissue, they are not likely to replace biopsy for final diagnosis. Intermediate methods currently under study suffer from either inaccuracy or inaccessibility. As MRI Susceptometry would be accessible, only the issue of accuracy is of concern.

The overall method for MRI liver susceptometry described in this thesis does not differ in principle from a similar method used in SQUID liver susceptometry. The specific differences are the use of an MRI GFE scan to obtain the field data, and the modeling procedure used to predict the field and fit them. The SQUID method uses a high-order magnetic gradient field to induce field distortions (Farrell, 1980). This gradient field can be focused on a small region, and neighboring sources of differential susceptibility do not contribute to the measured signal. Therefore, the signal measured is largely based on liver iron, and contributions from other tissues do not significantly interfere with the measurement. The use of high order gradients, and the lack of detailed individual anatomy prevent the use of geometry-based field models. Instead, a two or three term exponential fit is made to the SQUID field data, and the parameters are then back-fit to calibration tables. The calibration tables are based on a large, statistically significant patient population. In practice, the SQUID method is simpler, and faster than the MRI method. The largest advantage that MRI has over SQUID is wider availability. Clinical and experimental SQUID systems are rare, while MRI systems are located in virtually every major population center in the U.S.
While SQUID susceptometry measurements are accurate over all ranges of iron overload, MRI susceptometry measurements are, to date, unable to estimate low and normal level tissue iron reliably. The overall accuracy can be filled in on table 1-1 as +/- 20% for 2000-10000 ug Fe/ml and +/- 100% for 200-2000 ug Fe/ml. An important limitation of both MRI susceptometry and SQUID susceptometry is that differentiation between parenchymal and reticuloendothelial iron loading and damage is not possible with either method.

In practice, iron quantitation using MRI $T_2^*$ measurement shows high correlation ($r > 0.94$) with biopsy determined iron levels when measured on patients with normal to very low levels (200 to 800 ug Fe/ml) of liver iron (Gottshalk, 1991). However, this correlation is much lower ($r < 0.50$) for concentrations over all physiological ranges (Gottshalk, 1991; Hernandez, 1988; Stark, 1985; Murphy, 1986). It is possible that advancements in MRI technology (via TE reduction) will make accurate measurements at all ranges.

There is a definite need for a clinically useful non-invasive method for iron stores measurement. As mentioned, all methods other than biopsy suffer from lack of cellular differentiation, a key element in iron overload diagnosis and treatment. SQUID systems are not readily available, and MRI $T_2$ requires technology advances to become viable. MRI susceptometry, theoretically, has the sensitivity required to make these measurements, although some improvements could be made to the models before the required accuracy might be observed. No theoretical limitations were noted in the application of the general algorithm to in vitro and analytical measurements which would invalidate MRI susceptometry.
IX.4 Conclusion

This thesis introduced a completely novel method for MRI Susceptometry. The external phantom method as described here provides a new approach for estimating in vivo susceptibility, particularly as applied to the assessment of liver iron burden. This model based approach is non-invasive, utilizing the inherent magnetic properties of the iron-laden liver and the latent field mapping abilities of the MRI system. The major advantages in the MRI Susceptometry method are: (1) availability of magnet devices, (2) similarity to SQUID methodology (a proven method), (3) the specific use of the external reference bath which alleviates numerous problems, and (4) the ability of this method to make repetitive non-invasive measurements. As shown in this thesis, this method is able to accurately measure the liver iron in high-level patients, but is less accurate in low or normal level patients, provided appropriate steps to maximize the strength of the liver-induced field distortion and minimize methodological error are taken. The sources of noise or error have been isolated and all forms of error have been minimized with the exception of the unmodeled sources. Initial improvements should be directed towards enlarging the number of model compartments, followed by reduction of random noise, and then reduction of patient model error. If these improvements prove fruitful, MRI susceptometry will become a valuable tool in iron overload diagnosis over a broad enough range to be clinically useful.
Chapter X Limitations, Advantages and Future Directions of MRI Susceptometry

X.1 Introduction

There are many possibilities for expansion of this work. These extensions and improvements can be found in the hardware and software of the field acquisition, the modeling method and the type of problem to which the method is applied. Many aspects of this method may warrant future investigation, may blossom into fruitful technique, or may prove to limit the use of the MRI susceptometry method.

In the previous chapter, altering the model complexity and accuracy by increasing compartment number and phase reconstruction SNR were discussed as the most likely solutions to the observed error, and should be attempted first, possibly by examining improvements in magnetostatic modeling, additional organ measurements, filter applications and reference bath improvements. A few other issues are addressed; application of this method to susceptibility artifact correction, and expansion of this method to other MRI centers. Finally, experimental procedures and possible uses of MRI susceptometry are introduced. In particular, initial results from a predictor-corrector error method are reported.

X.2 Magnet-to-Magnet Variability

Other problems may be of concern when using the external phantom method. For instance, equation [3.1] states that the total distortion is directly proportional to the field strength. Magnetic field strength in clinical facilities typically varies from
0.15 T to 2.0 T. The experiments we have conducted have been at 1.5 T. If performed at 0.15 T, the same experiments would be expected to be 1/10 as sensitive to the susceptibility of the liver, and could be compensated by lengthening the echo time, but would still suffer from phase reconstruction SNR. Even at low field levels, the field distortion due to normal or abnormal liver iron levels would theoretically lie within the range of the measurement technique, as in equation [3.2(b)]. Therefore, any magnet currently being used for clinical measurements (0.15 T to 2.0 T) may be used for this method; however, the reduction in field SNR would reduce the effective sensitivity below 1/10 that due to field consideratons alone. The gradient amplification in the system is of consideration for the breath-hold method, where as short a scan time as possible is required. This limitation can be adjusted for in the same manner as breath-hold inability as explained above, by resorting to very long scan times with many averages. As the convolution method of the calculating the field model shows, the field distortion results from the DFC filtering of a volumetric step function. The effect of signal averaging would be to increase this filter effect by additional smoothing, and will also increase the MRI SNR.

X.3 Field Inhomogeneity

Most commercial magnets have isocenter homogeneity of less than 5 ppm over 30 cm. This background homogeneity is corrected for by the subtraction of the background phase of the bucket alone. The DFC method is actually a zero-order approximation of the field as shown in equation [5.12]. The actual field imposed on the object is not \( \overline{H}(\vec{r}) = \overline{H}_o \), but \( \overline{H}(\vec{r}) = \overline{H}_o + \Delta \overline{H}(\vec{r}) \), and can be converged to with recursive application of the DFC algorithm. As \( \Delta \overline{H}(\vec{r}) \) is on the order of \( 10^{-6} \), the
accuracy achieved by the single pass method is within $10^{-4}$ for the liver and torso. This is within tolerances of the LSE method to fit the liver iron data as shown in chapter IV. The recursive DFC approach is not the most efficient algorithm when a high level of accuracy is required. Finite element or boundary element methods are far more computationally expedient when high accuracy is desired (Borup, 1987), but are only needed for magnetodynamic problems or when a high degree of accuracy at the edges of the modeled compartments is required. However, these elemental solutions require prohibitively large amounts of computer memory and time to solve 3-D fields, and, until computer time and memory become cost-effective, the DFC approach will suffice.

X.4 Field Model Generation

High degrees of field distortion, time dependent fields, eddy current, biological current and ferromagnetic sources will all have the effect of changing the Laplacian solution into a Poisson Partial Differential Equation (Jackson, 1961)

$$\nabla^2 \mathbf{H}(\mathbf{r}) - \mathbf{M}(\mathbf{r}) = \frac{\delta \mathbf{H}(\mathbf{r})}{\delta t}$$  \[10.1\]

This type of problem can be solved by the DFC method, but for accurate solutions, requiring multiple iterations, the DFC method is much less computationally efficient than FEM or BEM methods (Borup, 1987), as discussed above. For the problem of liver iron, the time dependent field has been neglected. Until the more pressing problem of unmodeled source error is corrected, it cannot be determined whether or not a time-varying solution is required.
X.5 Improved Field Measurement Sequences

Alternative methods for obtaining field maps, such as the modified Dixon Point techniques, have the advantage of providing a map of the field differences along with an absolute reference point (Gomori, 1988). This method requires a secondary, simultaneous field measurement, much like a multiple echo sequence. Our method does not require absolute knowledge (i.e. constant offset) of the field, as the background subtraction step alleviates this necessity. Other methods of map measurement include partial flip angle techniques that induce stimulated echoes, giving a final field distribution that is due to $H_x$, $H_y$, and $H_z$ (Shinnar, 1989). Addition of $H_x$ and $H_z$, vector components as Shinnar describes would effectively triple the number of data points in the final estimation, thereby improving the fit.

X.6 Model Enlargement

The model is robust for the liver iron overload problem for patients with more than 10 times the normal levels of iron. It is clear from chapters VII and VIII, that field distortions arising from nearby sources, such as the lungs, heart, liver and bowel need to be accounted for in order to measure low, normal, and sub-normal liver iron levels. This is mostly a matter of acquiring the geometrical proportions and applying the model for the additional compartments. The model method itself can be extended to include other types of magnetic distortion.

The difficulty in using increased number of compartments is not just a matter of increased computation and operator segmentation, but is mostly due to the difficulty
of accurately segmenting the lungs and the heart. Nonetheless, it is an effort that may prove worthwhile, for as the accuracy of the estimation method increases, the wider the range of measurements that can be made. It may be possible to measure iron deficiencies as well, with accurate models, although the eccentric spheres field noise studies indicate that limits exist on the identification of the susceptibility of the central sphere.

**X.7 Additional Organ Measurements**

Besides the liver, the heart, gonads and skin will load iron preferentially in iron overload cases. Cardiac measurements would require gating methods, as the physical displacement of the heart will shift the field distortion due to cardiac susceptibility and add another form of unmodeled source noise. Gating to a repetitive component of the cardiac cycle would allow the measurement of the cardiac susceptibility for the geometry associated with that moment of the cycle. It has been shown that heart position is relatively unchanged from beat to beat at any point in the cardiac cycle (Paschal, )

Other forms of iron overload exist, such as the inhalation of iron particles by iron workers (Varpula, 1983). This contamination of the lungs causes progressive parenchymal fibrosis (pneumoconiosis), and has been successfully quantitated via magnetic susceptibility measurements using magnetometers. Direct lung measurements using MRI are very difficult due to the low signal and fast $T_1^*$. This external, indirect method may be applicable. Lung measurements would also have to be made using cardiac gating because of the close proximity of the heart to the lungs.
Trabeculae consist of large arrays of trabecular bone mixed with marrow. The large number of bone/marrow interfaces would theoretically induce large field distortions that would be measurable at large distances (Chapter III). It would be possible to make a few simple MRI-susceptometry field map measurements of trabeculae of known geometry in order to verify this. This experiment would be of more interest for pure science, than of clinical interest, except to indicate the reason for the observations of extremely short $T_2$ in bone (Wehrli, 1992).

X.8 Susceptibility Artifact Correction

Bone and joint implants distort images, as do surgical implant artifact and foreign object artifacts. It has been suggested that these artifacts could be determined from scans if the field distortions could be predicted and corrected. For the field distortions to be predicted, either the geometry or the susceptibility must be known. If susceptibility is known, or just as well, is homogeneous, the geometry can be uniquely determined if at least as many field points as unknown geometrical points are acquired. This is an inverse problem and is the opposite of the forward problem dervied in this thesis (susceptibility derived from geometry). Some caveats must be added to this broad statement. The solution to the field vector must be made by a complete magneto-dynamic field model with current sources such as eddy-current and ferromagnetic objects included. In addition, a large number of scans must be acquired with different fields of view to enable gradient distortion correction, as explained below.

In examining the problem of back-correction of field distortion artifacts, Ludeke
noted that the field distortions will cause frequency additions to the complex FID which will spatially shift some magnitude values into other spaces. If the other spaces are not also shifted elsewhere, then the net result will be to have magnitude addition at some voxel values. This is a sort of field-aliasing. Even if the field distortions which induce the spatial shift are known, they cannot be uniquely undistorted. It is essentially the non-distinctness of multiple variables in a single equation.

Inspection, however of the amount of shift and the induction of the shift, a la Ludeke, shows that,

\[ H(x, y', z) + y' G_y = H_0 + y G_y \tag{10.2} \]

which gives a shift based on the field distortions,

\[ \Delta y = y' - y = \frac{\Delta H(x, y', z)}{G_y} \tag{10.3} \]

This implies that with smaller field of view, as \( G_y \) increases, the spatial shift will decrease. The inverse is also true. Then, multiple measurements at varying FOV, each causing different amounts of spatial shift, will give multiple equation sets with which the overlapping magnitude can be resolved.

Other susceptibility artifacts arise from bone/tissue/air interfacia in the *crysta gallis* superior to the nasal passages. This artifact prevents longer TE times in FE images of the pituitary. As in the proposed implant measurements, the possibility of field correction is possible to reduce the error in the neurology scans. With back-correction, close inspection can then be made of the areas concerned. Currently, the radiologist either accepts that no information is available about these regions, or alters the scan protocol so that some information might be obtained. If the field distortion could be corrected, no such stopgap procedures need be made.
X.9 External Reference Bath Improvements

An interesting hardware modification would increase field map SNR by the use of a surface coil located as near the reference bucket as possible. The most likely methods would be either to immerse a coil into the reference bucket or wrap a coil around the bucket. Surface coil images have spatially varying SNR, and as shown in chapter VI, any increase in signal is eventually beneficial in the LSE fit, although the statistics and predictability of goodness-of-fit would be affected. More importantly, the magnitude image, which provides the patient geometry would suffer, but may still retain sufficient information to generate a the geometry of the compartments. This method would lend itself to problems that require very high levels of field SNR, such as the normal, low-level or even iron deficient patient.

X.10 Pre-Filtering and the Choice of the Filter

The use of the pre-filter significantly improved the results of the estimation. In the in vitro section, several sizes (i.e. frequencies) of averaging filter were examined, with no clear direction as to which filter behaves best. Many other filter choices could be made. Ljung proposes that, if the model error is understood, any filter which reduces the error is valid. The ideal filter would reduce unmodeled source error, possibly taking advantage of the inverse $r$-cubed nature of the error, and are worth exploring.

X.11 Predictor Error Corrector Method
MRI External Reference Method for Susceptibility Estimation

Field Echo Scan of Patient  Background Scan

MRI Magnitude Reconstruction  MRI Phase Reconstruction

Geometry Segmentation

Field Model Calculation

Field Corrector

Known Susceptibility  Susceptibility Parameters

Field Data  Analytical Simulation

Least Squares Fit

Figure 10-1. General Algorithm with Predictor Corrector Step
The Predictor Error Method (PEM) is a means of adaptively correcting errors in modeled systems (Ljung, 1987). While the preferred method is to improve the model, such as adding a lung compartment for this study, PEM protocol admits that model improvement is not always practical. If so, then an adaptive filter may be introduced into the model to correct, alter or eliminate model error. In the case of MRI liver susceptometry, lung and heart modeling may not always be practical or accurate, due to motion artifacts, and the PEM may be necessary to improve the behavior of the system. This chapter concludes with the presentation of the first stages of the PEM which is used to reduce the non-stationary model error due to unmodeled sources.

The overall algorithm used to estimate liver iron is shown again in figure 10-1. The algorithm is unchanged, except for an additional step where a predictor-error correction can be made at the LSE step.

X.11 A Non-stationary Noise Reduction with Simulated Lung Model

The least squares estimation section introduced several methods for correcting or minimizing model error. In chapter VII, the examinations of the unmodeled source lead to a conclusion that, given proper restriction of data, a reasonable fit can be achieved in the case where it is not possible to model the lungs. Another approach to this situation would be to simulate the lung model as a simple sphere located above the liver (figure 10-2). The sphere would have a fixed location and source strength, which need not be solved for in each patient. This is a very simple form of the PEM (Ljung, 1987). The corrector term varies spatially, but is made identical for all patients, a sort of average lung model.
The final field model would be,

$$H_{\text{model}}(r) = H_0 + \chi_{\text{torso}} \cdot V_{\text{torso}}(r) + \chi_{\text{liver}} \cdot V_{\text{liver}}(r) + H_{\text{nuts}}(r)$$  \[10.4\]

which is then LSE fit to the field data. The simulated lung field is given by,

$$H_{\text{lung}} = -H_0 \frac{\Delta \chi \cdot V_{\text{lung}}}{3} \frac{2(z - z_o)^2 - (x - x_o)^2 - (y - y_o)^2}{[(z - z_o)^2 + (x - x_o)^2 + (y - y_o)^2]^{3/2}}$$  \[10.5\]

Rather than include the parameters governing this equation as additional unknowns in the estimation, a global series of susceptibility estimations were made over a large range of scalar field strength, $\langle \Delta \chi \cdot V_{\text{lung}} \rangle$, and distance of the sphere center from the top of the patient liver $(z_o, y_o$ and $x_o)$. The best choice of average lung was then used for subsequent fits.

If the lung compartment is not included in the model, it will act as an unmodeled source, the effects of which were described on in vitro and analytical models in chapter VII. From the analysis on unmodeled sources it was concluded that a reasonable fit could be made in the presence of unmodeled sources, provided the region of fit is restricted to the strongest 10% of the liver field model and pre-filtered with a 19x19x1 averaging filter.

X.11.B Materials and Methods

The data from the in vivo measurements in chapter VIII were used in this experiment. The source strength of the simulated lungs ranged over $dX = \Delta \chi \cdot V_{\text{lung}} = 10^3, 10^4, 10^5,$ and $10^6$, while the distance of the lung source from the top of the liver ranged over $dr = 2, 6, 8$ and $10$ cm. Initially, all of the 16 possible combinations of $dX$ and $dr$ were added into the field model, followed by the LSE
In Vivo Liver Iron Fits - with simulated Lung

The lung is positioned superior to the liver, where the z-axial distance of the center of the lung to the top of the liver (dr) is allowed to vary, as is the strength of the lung source (Sc = dX * Volume).

Transversely, the lung source is centered in the torso.

Figure 10-2. Simulated Lung for predictor error step.
step. For each simulated lung, the threshold of liver field strength used to restrict the data was then varied $0 < H/H_{\text{max}}$. The liver iron estimates were then correlated with the known SQUID estimates as in chapter VIII.

The optimal lung simulation would be that which corrects for the unmodeled source error, essentially making the correlation uniformly high, for any data restriction set. To this end, the liver iron estimates along the entire range of data restriction were condensed into the mean and variance, where high mean and low variance would indicate the optimally simulated lung. CI analysis was made for varying levels of pre-filtering with the optimal lung. The correlation of the liver iron estimates at the optimally simulated lung and pre-filter are then shown.

X.11.C Results

The correlation with thresholded field for all 22 patients is shown for varying source strength ($dX = 10^3, 10^4, 10^5$, and $10^6$) in figure 10-3(a) for all levels of distance from the top of the liver. The same results are rearranged for varying distances from the top of the liver ($dr = 2, 6, 10, \text{and } 14 \text{ cm}$) in figure 10-3(b) for all levels of source strength. The expected source strength of an average lung would be at about 20000, equivalent to normal lung tissue of two thirds the susceptibility difference between air and water (which measures at 4000 ug/ml of iron on the SQUID). The expected distance from the top of the liver to the center of the lungs would be between 4 and 10 cm. As compared to the unfiltered fits in chapter VII, the correlation in this experiment has a high, uniform value over all threshold levels, indicating that spatially varying noise has been reduced.
Figure 10-3. Correlation vs. threshold for varying lung distance and strength
a) each group of $d_r = 2, 6, 10, 14$ varies over $\log_{10}(dX) = 3, 4, 5, 6$. b) rearranged from above, now, each
group of $\log_{10}(dX) = 3, 4, 5, 6$ varies over $d_r = 2, 6, 10, 14$. 
In figure 10-4(a), the variance of the correlation with thresholded field (from figure 10-3) is seen to minimize when \( dr = 6 \) cm and \( dX \) is between 3000 and 30000 (i.e. \( 10^{3.5} \) to \( 10^{4.5} \)). In figure 10-4(b), the mean of the correlation is highest at \( dr = 2 \) cm and \( dX = 10000 \), but is not significantly different (0.96 vs. 0.95) at the minimized variance values (\( dX = 10000, dr = 6 \)). These lung parameters are consistent with expected values for normal lungs.

The CI analysis is shown in figure 10-5 is shown for the lung parameter set, \( dX = 10000, dr = 6 \), when pre-filtered with an \( L \times M \times 1 \) (\( L = M = 5, 9, 13 \) and 19) for the same 22 patients. The number of points which the error lies within the CI is from 10 to 100 times higher than for the CIs without the lung. The 19x19x1 pre-filtered results could use the largest number of points, indicating that the fit will be best at this filter level.

Finally, the linear regression for the SQUID and MRI estimates are shown in figure 10-6 for the best correlation fit, for number of points in the fit \( n = 100 \), of the simulated lung model with a 19x19x1 pre-filter applied. The correlation when all patients are included (figure 10-6(a)) is \( r = 0.962 \), and equally important, the regression runs through the origin, as expected by the model. The low end patient set (figure 10-6(b)), is not as successful, with \( r = 0.592 \), and a non-optimal regression line, and is, in fact, lower than the observed correlation value without the lung fit in chapter VIII (\( r = 0.662 \)).
Figure 10-4. a) variance and b) mean of thresholded correlation values of figure 10-3. The best lung parameters are $dr = 6$ cm and $dX = 10000-20000$. 
90% CI Efficacy of In Vivo Liver Iron Estimation with prefiltering and Simulated Lung Compartment

Maximum Number of Points such that Estimated X(Liver) error lies in 90% Confidence Interval

Figure 10-5. Confidence interval of 22 patients for a) 1x1x1, b) 5x5x1, c) 9x9x1, d) 13x13x1, and e) 19x19x1 prefiltering with simulated lung set at $dr = 6$ cm and $dx' = 20000$. 
Liver Iron Estimates for all Patients
Fit from top 10% of Liver Model
with 19x19x1 Filter and Simulated Lung

Liver Iron Estimates for X(liver) < 2000 mg/g
Fit from top 10% of Liver Model
with 19x19x1 Filter and Simulated Lung

Figure 10-6. Correlated fits from figure 10-5(e) at n=100 points in the fit. a) all patients and b) patients under 2000 ug Fe/mg.
X.11.D Discussion

Preferably, the lung would be accurately modeled, rather than simulated. Currently, not enough data exists with slices completely covering the lung volume to analyze this. Also, lung outlines in the MR data tend to be somewhat blurred, and a simulation may be no better or worse. It may also be possible to better simulate the lung with two prolate spheroids. But, it appears that even a simulated lung is better than no lung. This follows from the unmodeled sources investigation, as the addition of the lung term will reduce the overall unmodeled source error. This would be similar to reducing the relative source strength of the unmodeled compartment vs. liver from 32/1 to 4/1 or better.

Addition of the simulated lung to the model is similar to reducing the strength of the unmodeled source, and of the spatially colored noise. In figure 10-5(a), the number of points allowed in the fit increase by nearly a factor of 100 for the unfiltered case when compared to the simulated lung-free estimates. The number of points allowed pre-filtered fits also increase by one to two orders of magnitude after including the simulated lung. If the simulated lung were exactly the size and strength of the patients lung, then it would be expected that the number of points fit would increase to cover the entire water bath space (about $64 \times 16 \times 192 = 192K$ points), which appears to occur for one or two patients. As discussed when modeling the simulated lung, the purpose was to provide a reduction of the spatially distributed noise, not to eliminate the unmodeled source entirely. Complete elimination would require inclusion of a patient-specific lung model, and possibly intestines, rather than the gross attempt to reduce the error.
In general, the lung simulation does reduce the error attributed to the unmodeled sources. This implies that, as predicted, the unmodeled sources do exist, and can be attributed to the lung susceptibility. It also implies that it should be possible to measure not only higher end iron patients with more accuracy, but also to measure normal iron and mid-range iron patients. Optimally, the lung would be included in the model, but one of the purposes of this analysis was to indicate at what levels the susceptibility could be measured with as minimal of a model as possible.

X.12 Summary

The advantages of MRI susceptometry are attractive enough that effort should be made to reduce the overriding limitation, that of poor performance at low iron levels. The simulated lung results shown in this chapter show that any form of reduction of unmodeled sources is beneficial to the estimation. After all, the simulated lung is merely a lung which is an average for all patients - not the best method, but the best for the available data. If a gross correction of the unmodeled sources is that noticeable, then fine-tuned corrections, such as adding the lungs and heart into the original geometry may increase the accuracy of the method.

X.13 Conclusion

MRI can measure and quantify a large number of tissue parameters such as molecular density, transverse and longitudinal relaxation, diffusion, magnetization transfer rates and motion. The combination of these parameters provide the clinician
with a detailed portrait of the internal structure and function of the living human subject. The external phantom technique extends the number of quantifiable tissue parameters by one - MRI Susceptometry.
APPENDIX A - Derivation of Phase Signal in GFE Scan

A.1 Magnetization Vector Calculation

The phase relationship in the Gradient Field Echo experiment can be analyzed by observing the rotational matrix method of spin mechanics (Mansfield, 1980). Using the rotational matrix method, the time varying nature of each component of magnetization is,

\[
\vec{M}(TE) = \vec{R}_z(TE) \cdot \vec{P}_x(\alpha)\vec{M}(0) + M_0(1 - E1(TE))\hat{k}
\]

\[
= \vec{R}_z \cdot \vec{M}_+ + M_0(1 - E1(TE))\hat{k} \tag{A.1}
\]

where, \(\vec{M}(TE)\), is the magnetization vector at echo time TE, \(\vec{M}(0)\) is the initial magnetization, \(\vec{M}_+\) is the magnetization vector following the RF pulse applied at time zero, and \(M_0(1 - E1(TE))\hat{k}\) is the return to maximum Zeeman alignment of the longitudinal magnetization. The rotational vector due to the RF pulse \(\alpha\) is

\[
\vec{P}_x(\alpha) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\alpha & \sin\alpha \\ 0 & -\sin\alpha & \cos\alpha \end{bmatrix} \tag{A.2}
\]

for a rotation about \(x\). The field echo decay matrix for a field along \(z\) is the combination of precessional spin decay and transverse relaxation,

\[
\vec{R}_z(t) = \begin{bmatrix} E2 & 0 & 0 \\ 0 & E2 & 0 \\ 0 & 0 & E1 \end{bmatrix} \begin{bmatrix} \cos(\Delta wt) & \sin(\Delta wt) & 0 \\ -\sin(\Delta wt) & \cos(\Delta wt) & 0 \\ 0 & 0 & 1 \end{bmatrix}
\]

\[
= \begin{bmatrix} E2 \cos(\Delta wt) & E2 \sin(\Delta wt) & 0 \\ -E2 \sin(\Delta wt) & E2 \cos(\Delta wt) & 0 \\ 0 & 0 & E1 \end{bmatrix} \tag{A.3}
\]

where,

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\[ E_1 = e^{\frac{i}{\tau_1}}, \quad E_2 = e^{\frac{i}{\tau_2}} \]  

[A.4]

The effective frequency of precession is,

\[ \Delta \omega = \gamma H_{\text{eff}} = \gamma \overline{H}(\vec{r}) - \gamma H_0 \hat{\kappa} + \gamma \overline{G} \cdot \vec{r} \]  

[A.5]

for the true field \( \overline{H}(\vec{r}) \) in the presence of the imposed Zeeman field, \( H_0 \hat{\kappa} \), and for imposed linear field gradients \( \overline{G} \), at a point in space, \( \vec{r} \). The linear gradient term encodes dimensional information with frequency and phase. When the inverse two-dimensional Fourier transform is applied, these linear terms will be translated into two-dimensional spatial shifts, and are not retained in the signal of the phase map (except as spatial position).

A.2 Phase Vector Calculation

For an arbitrary initial pulse (i.e. an imperfect \( \pi/2 \) pulse), the rotated magnetization becomes,

\[ \overline{M}_* = \overline{P}_4(\alpha) \overline{M}_0(0) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos \alpha & \sin \alpha \\ 0 & -\sin \alpha & \cos \alpha \end{bmatrix} \begin{bmatrix} 0 \\ M_0 \sin \alpha \\ \cos \alpha \end{bmatrix} = \begin{bmatrix} 0 \\ M_0 \sin \alpha \\ \cos \alpha \end{bmatrix} \]  

[A.6]

The precession and decay term of [A.1] is then,

\[ \overline{R}_4(t_\omega) \overline{M}_* = M_0 \begin{bmatrix} E_2 \cos(\Delta \omega t_\omega) & E_2 \sin(\Delta \omega t_\omega) & 0 \\ -E_2 \sin(\Delta \omega t_\omega) & E_2 \cos(\Delta \omega t_\omega) & 0 \\ 0 & 0 & E_1 \end{bmatrix} \begin{bmatrix} 0 \\ \sin \alpha \\ \cos \alpha \end{bmatrix} \]  

[A.7]

The components of each magnetization vector including longitudinal decay are,

\[ \overline{M}(t_\omega) = \begin{bmatrix} M_x(t_\omega) \\ M_y(t_\omega) \\ M_z(t_\omega) \end{bmatrix} = M_0 \begin{bmatrix} E_2 \sin(\Delta \omega t_\omega) \sin \alpha \\ E_2 \cos(\Delta \omega t_\omega) \sin \alpha \\ E_1 \cos \alpha \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ M_0(1 - E_1) \end{bmatrix} \]  

[A.8]
and the arctangent of the ratio of the transverse \((x\text{ and } y)\) magnetization is,

\[ \phi = \tan^{-1} \left( \frac{M_z}{M_x} \right) = \tan^{-1} \left( \frac{M_0 E 2(t_E) \sin(\Delta \omega t_E) \sin \alpha}{M_0 E 2(t_E) \cos(\Delta \omega t_E) \sin \alpha} \right) = \Delta \omega t_E \quad [A.9] \]

It is of interest to note that the phase of the signal is independent of the actual RF tip angle \(\alpha\), relaxation, \(E2\) or \(E1\), and strength of magnetization, \(M_0\).

**A.3 Longitudinal Field Vector Dominance of Phase Signal**

The average effective frequency of precession over the voxel is actually the phase angle that is measured in equation \([A.9]\). This angle depends on the imposed background field and the actual field, as well as the imposed gradients (equation \([A.5]\)). The imposed gradient term will be demodulated from the term as a function of the two or three dimensional Fourier Transform that translates k-space free-induction decay into spatially separated intensity signals (Mansfield, 1980). However, the true field will have components in each vector,

\[ H(\vec{r}) = H_x(\vec{r}) \hat{i} + H_y(\vec{r}) \hat{j} + H_z(\vec{r}) \hat{k} \quad [A.10] \]

The background field in \(H_x(\vec{r}) = H_0 + H'_z(\vec{r})\) will dominate the other two vector terms, \(H_x\) and \(H_y\), by a factor of \(10^5\) and can be neglected (Mansfield; 1980).

An alternative approach which demonstrates the dominance of the \(H_z\) term in the phase angle examines the precessing signal being emitted by the proton and received by the RF coil. Although the signal has real angular frequencies due to \(H_x(\vec{r}) \hat{i}\) and \(H_y(\vec{r}) \hat{j}\), they will be demodulated out to the megahertz range and not observed. Only the signal precessing about the \(z\)-axis will be observed by the RF coils aligned along the \(x\) and \(y\) axes.
APPENDIX B - Phase Unwrapping of MR Images

B.1 Introduction

The purpose of this appendix section is to provide the reader with a description or understanding of the methods and limitations in the recovery of true spatial variation of phase information for a phase-wrapped signal. The GFE method measures a two-dimensional phase map which relates to the field distortions in the MRI magnet. A 'zebra-stripe' effect results from the inherent arc-tangent calculation of the phase when values exceed $+\pi$ (as in equation [A.9]), resulting in values from $-\pi$ to $\pi$ (as seen in figure 8-4 of the text). This phase-wrapped field map must be unwrapped in order to compare it to the generated field model. The following is a discussion on methods of phase unwrapping.

B.2 Phase Wrapping

Phase wrapping occurs in many disciplines, such as interferometry, MRI phase analysis, solid-state physics, and adaptive optics. Tribolet introduced an algorithm which is suitable for most instances of unwrapping (Tribolet, 1977). Ghiglia derived a method based on cellular automata, which works well in many cases where the more straightforward, and much less computationally intense, Tribolet method fails (Ghiglia, 1987).

Linear homomorphic filter theory describes the processes of wrapping and unwrapping of phases (Oppenheim, 1975), but a simple example is adequate to
understand the problem. Beginning with an arbitrary signal, \( x(k) \), as in figure B-1.A, phase wrapping occurs when a tangent function followed by an arc-tangent function is applied,

\[
x_{\text{Wrap}}(k) = \tan^{-1}\{\tan x(k)\}
\]  
[B.1]

By transforming the arbitrary function by equation [B.1], a series of discrete jumps (or phase wraps) are seen when the function exceeds \(+/-\pi\), as in figure B-1.B. The recovery of \( x(k) \) from \( x_{\text{Wrap}}(k) \), is the process known as phase unwrapping.

More rigorously, the phase unwrapping problem is equivalent to computing the argument, B, of a complex function, \( x(t) = Ce^{(A + jB)t} \). It will be noted, that the addition of \( n \) \( 2\pi \) to the argument B, will not effect the result of the function. If the function is expressed as its real and imaginary sinusoids,

\[
x(t) = x_r(t) + jx_i(t), \quad x_r(t) = Ce^{At}\cos(Bt), \quad x_i(t) = Ce^{At}\sin(Bt) \quad [B.2]
\]

then the magnitude and phase of the signal are,

\[
|x(t)| = |x_r(t) + jx_i(t)| = \sqrt{x_r^2 + x_i^2} = Ce^{At} \quad [B.3(a)]
\]

\[
\phi[x(t)] = \phi[x_r(t) + jx_i(t)] = \tan^{-1}\left(\frac{x_i}{x_r}\right) = \tan^{-1}\left(\frac{\sin(Bt)}{\cos(Bt)}\right) = Bt \quad [B.3(b)]
\]

Because the arctangent function determines phase from the real and imaginary signals of the function, only the phase principal values can be recovered. The principal value (PV) of phase is the \( 2\pi \) modulo of the phase, an inherent property of the arctangent function. When the function crosses a \(+/-\pi\) boundary, a discontinuity from \(+/-\pi\) to \(-/+\pi\) appears in recovered phase, which is known as a phase wrapping (as in figure B-1.B).
In PV operator form, the phase wrapping is,

\[ W_l[\phi(n)] = \phi_{pv}(n) \quad n = 0, 1, 2, \ldots, N \]  \[B.4\]

where, \( \phi_{pv}(n) \) are samples of PVs, and \( l \) is an identifier for use in separating different wrapping operators. This is equivalent to,

\[ W_l[\phi(n)] = \phi(n) + 2\pi k_l(n) \quad n = 0, 1, 2, \ldots, N \]  \[B.5\]

where \( k_l(n) \) is a sequence of integers chosen to force,

\[ -\pi \leq W_l[\phi(n)] \leq \pi \]  \[B.6\]

A differencing operator is defined such that,

\[ \Delta \phi(n) = \phi(n) - \phi(n - 1) \quad n = 1, 2, \ldots, N \]  \[B.7\]

Computing the difference of PVs from [B.5] using [B.7] yields,

\[ \Delta W_l[\phi(n)] = \Delta \phi(n) + 2\pi \Delta k_l(n) \]  \[B.8\]

The PV of this result, obtained by applying the wrapping operator again, is,

\[ W_2[\Delta W_l[\phi(n)]] = \Delta \phi(n) + 2\pi [\Delta k_l(n) + k_2(n)] \]  \[B.9\]

which gives the wrapped difference of wrapped phases. Since the wrapping operator \( W_2 \) produces values between \( \pm \pi \), then, if,

\[ -\pi \leq \Delta \phi(n) \leq \pi \]  \[B.10\]

the term \( 2\pi [\Delta k_l(n) + k_2(n)] \) in equation [B.9] must always equal zero (i.e. \( W_2 \) adds back the signal lost in the wrapping step). Thus,

\[ \Delta \phi(n) = W_2[\Delta W_l[\phi(n)]] \]  \[B.11\]

which can be rearranged to show,

\[ \phi(n) = \phi(0) + \sum_{n=1}^{N} W_2[\Delta W_l[\phi(n)]] \]  \[B.12\]
Equation [B.12] implies that the phase can be unwrapped by integrating the wrapped differences of principal values, but only if equation [B.10] is satisfied can the phase be completely and correctly recovered. This implies that the function must be adequately sampled such that the phase may not change by more than \( \pi \) radians per sample (i.e., the sampling frequency must be greater than twice the wrapping frequency) to avoid inconsistencies. If not, the unwrapped phase will be incorrect, but smooth in the sense that phase differences will be lower than \( \pi \) radians as equation [B.12] demands.

**B.3 Phase Unwrapping - Trbolec Method**

This formalized unwrapping operator (equation [B.12]) can be reduced to the following algorithm for unwrapping the arbitrary 1-D discrete signal \( x_{\text{WRAP}}(k) \) (which would be the MRI phase signal for this thesis) in figure B-1.B;

1. Take the backward point derivative of the signal (figure B-1.C.1),

\[
p(k) = x_{\text{WRAP}}(k) - x_{\text{WRAP}}(k - 1)
\]

2. Threshold the derivative at a given value \( 0 \leq \eta \leq 1 \) (figure B-1.C.2),

if \( p(k) > \eta \pi \) then \( \rho(k) = 1 \),

if \( p(k) < -\eta \pi \) then \( \rho(k) = -1 \),

otherwise \( \rho(k) = 0 \).

3. Integrate \( \rho(k) \) along the k-axis (figure B-1.C.3),

\[
q(k_m) = \rho(k_m) + \rho(k_{m-1}) \text{ with } q(0) = 0 \text{ and } m = 1, 2, \ldots, N
\]

4. The unwrapped signal is the wrapped signal plus the integrated, thresholded, difference function (figure B-1.C.4),

\[
x(k) = x_{\text{WRAP}}(k) + q(k)
\]
This algorithm works well, in either one or more dimensions, except for the case when a large amount of noise is added, or else when the sampling rate is less than half of the wrapping rate. If the noise introduced at a point where the signal would wrap, then the signal can bounce from \(-\pi\) to \(\pi\). This will be perceived by the algorithm as an inconsistent derivative, and false thresholded discontinuity points will appear. In such cases, streaking is seen. Experience suggests a normal choice of threshold to be \(\eta = 1/2\), but in cases of high noise, it is better to raise the threshold value.

One method for reducing the bounce effect that noise introduces, is to first filter the signal with a median filter (Oppenheim, 1975). The median filter will remove any noise points which don’t belong. That is, it will remove any outlying points in the signal, and force them to be equivalent to the median value of the surrounding values. The drawback of this approach is that median filters will reduce the amount of true edge signal as the phase wraps, and subsequent unwrapping will show discontinuous rounding at the wrap edges. A method which eliminates the rounding error, but reduces noise, is performed by median filtering the phase wrapped signal used in generating the integrated, discontinuity threshold function (prior to step 1), which is then added to the unfiltered phase wrap function in step 4.

### B.4 Phase Unwrapping in Field Distortion Studies

A Tribolet-style unwrapping method works well for GFE phase signals inside the external phantom (figures 4-3, 4-4, 8-2) as the phase wrapping is minimal (usually less than 4 or five wrappings over 100 points) and relatively noise free. For a 2-D data set, the phase map is first unwrapped along a single line parallel to the y-axis,
which will serve as a reference line (figure B-1.D). Beginning from the y-axis reference, each of the lines along the x-dimension are now unwrapped, resulting in a 2-D phase image. This method can be extended to 3-D by first unwrapping a reference line along the z-axis, which is used to unwrapping a reference zy-plane. Finally, starting from the zy-plane of reference, each x-axial line is unwrapped.
Figure B-1. Tribolet phase unwrapping. The a) original arbitrary function, is b) phase-wrapped to lie within +/- \( \pi \) by first taking the tangent, then the arctangent. The phase unwrapping begins with c.1) differentiating the warpped function, and then c.2) thresholding by accepting only values greater than \( 2\pi \) or less than \(-2\pi\). c.3) Integration of the thresholded, differentiated function returns the values lost when phase wrapping occurs. c.4) The unwrapped phase is the sum of the wrapped phase and the recovered (integrated) function. d) 2-D unwrapping proceeds by first unwrapping along one axis, then using that axis as a reference point to unwrap along the other axis.
APPENDIX C - Segmentation of Torso Compartment Geometry

C.1 Segmentation

A brief overview of automatic, or semi-automatic segmentation methods are given below. Well-researched texts on this area exist, to which the reader is directed for additional detail (Lim, 1990; Oppenheim, 1975).

C.1.A Compartment Segmentation Methods

Segmentation of an image into separate components usually begins with the identification of the edges of the image. Several edge detection methods have been introduced into the literature, based on gradient, Laplacian or frequency information. All of these edge detectors rely on the quality of the images, and well-defined edges are usually required. However, when high levels of image noise are present, edges can be over-defined, and produce spurious edges appearing where none were intended.

Gradient-based edge detection expects the spatial derivative of an image to reach a maximum or minimum at the object edge. Laplacian based detection is an improvement which includes multiple-dimensionality into the edge maxima/minima identification. Sharp edges have more high-frequency content than gradual edges, which forms the basis for frequency based edge detectors.

Segmentation then proceeds by edge-connection and iterative isolation of object
from an image, until no objects are left to be defined. Over-detection of edges complicates the segmentation process, with as many as 65536 separate objects defined in a 256x256 image. Low-pass filtering occasionally improves the segmentation process, by reducing the noise levels, usually at the expense of high-frequency information (Lim, 1990).

Morphological segmentation is another method which uses the low and high frequency information (Haralick, 1987). It is initiated with a seed inside the object, usually placed by the operator, which enlarges until a boundary is found. The boundary is usually defined by image contour specifics, such as threshold levels or image texture statistics. Morphological segmentation is more successful than straight edge detection, but still suffers from noise. Again, low pass filtering can aid the process.

C.1.B Operator Interactive Segmentation

Operator interactive methods are the fail-safe segmentation procedure. Hand drawing (or rather trackball/mouse/tablet identification) is tedious, but the human visual system is well-adapted to object segmentation (Lim, 1990). The number of points required for an object outline can be reduced by either parametric fitting or data interpolation methods. However, operator interactive segmentation can be subjective, as well as labor intensive.

C.1.C Parametric Segmentation
The measurements and representations of the human torso are attempts to reduce the number of parameters needed to adequately describe the major (and minor) anatomical landmarks or represent the torso as a set of continuous functions (Keeling, 1981; Messinger-Rapport, 1987). The functions described by Keeling are mathematically described as a sum of ellipses and rosettes, and connected longitudinally (along the length of the patient) by piecewise continuous polynomials. Five simple measurements taken on the pronate patient at four transverse location, shoulder, chest, waist and hips, provide all the data necessary to reconstruct a low error model of the torso. The measurements needed are 1) the anterior-posterior distance, 2) the lateral distance, 3) the distance from the axillary line and the table, 4) the anterior hemi-circumference and 5) the posterior hemi-circumference. These measurements provide a believable human torso which has been used in surface potential mapping studies (Messinger-Rapport, 1987).

C.2 Fourier Descriptors

The Fourier descriptor (FD) method takes data points of non-uniform sampling on the surface of any torso and transforms them into a two dimensional Fourier series (Van Oostrom, 1978; Park, 1987). These FDs can be manipulated in Fourier space to determine such things as cross-sectional area, centroid, and other geometrical or shape descriptive parameters.

The FD smoothing method, as shown in figure C-1, is a vector of sampled contour information,

\[ f_i = x_i + j \cdot y_i \quad i = 1, \ldots, N \quad \text{[C.1(a)]} \]
which is then Fourier transformed to provide the FD,

\[ F = \mathcal{F}(f), \quad F_i = \Re_i + j \Im_i \quad i = 1, \ldots, N \quad [C.1(b)] \]

Following Fourier transformation, the spectral information can be filtered using standard digital filters. After filtering with a low pass filter, the inverse transformed contour will have less high frequency variation. Smoothing of a liver outline is shown in figure C.2. An added benefit of FDs are that FD smoothing also improves the calculated volume of a discretely sampled object (Park, 1987).

### C.3 Application to GFE Liver Images

For most segmentation procedures, the object edges must be well defined about the entire contour. Automatic segmentation of liver, torso and water bath are not possible due to the large amount of noise in the magnitude reconstruction image which disrupts edge continuity. Cardiac motion and field inhomogeneity are significant factors in the GFE scans required by the MR susceptibility measurement protocol. The patient-to-patient variability of the liver signal intensity precludes the use of segmentation routines for the liver. Although some algorithms are able to segment healthy liver, torso and water bucket, an iron-loaded liver is not readily distinguishable from other tissues such as lung or bowel or spleen. Even with operator positioned seed values in morphological segmentation routines, the intensity variation across the image is too large to overcome. The edges of the liver are generally not of the same intensity as the central portion, due to inherent MRI signal variance.

The remaining options are to segment each object by hand, or to reduce manual segmentation by offering parametric fits of regularizable shapes. These fits lend
themselves well to torso and bucket segmentation, but the liver must still be manually separated from each of the 16 slices, using FDs to improve the fit of a non-uniformly sampled hand-drawn outline to the liver.

C.4 Human Variation in Hand Drawn Outlines

C.4.A Potential Errors

Poor operator technique or systematic error in outlining will result in several types of outline error. Random error about the outline will manifest as a jittery outline. Non-random error can result in a mean shift of the center of mass, as well as a bulge or depression in an outline at one specific point. The volume of the object may also be changed with error. Each of these errors will influence the calculation of a magnetic field and the robustness of the susceptibility estimation, as discussed in chapter VII. The amount of expected error for a population of operator needed to be investigated.

C.4.B Methods

Random outlines can be given liver-like contours by appropriate low pass filtering. Outlines were generated in FD space using a normally white random, zero-mean sequence of 15 complex numbers, and then filtered by the heuristically chosen sequence; [1, 1/3, 1/9, 1/27, 1/81, 1/343, 1/1029, 1/1029, 1/343, 1/81, 1/9, 1/3, 1]. The filtered random sequence was zero-padded from 15 to 1024 points (Oppenheim, 1975), which were then inverse Fourier transformed, resulting in the desired
arbitrary, closed, non-overlapping contours shaped similar to liver outlines.

Untrained volunteers were requested to manually outline the contours using a mouse-driven tracking device of objects displayed on a 640x480 VGA screen. The outlining proceeded by choosing a starting point, with the mouse-pointer, and pressing a button, then moving the mouse-pointer to a new point along the contour and pressing the mouse button. This is continued until, in the opinion of the operator, the object had been circumscribed, at which point a second button was depressed. The choice of segment length was left up to the operator, but it was suggested that approximately 20-30 points be marked over the object.

Following outlining, the sampled contour point data were interpolated to remove the sampling non-uniformity, so that comparisons between 'true' object outlines and operator segmented outlines could be made. Interpolations were also made to raise the sampling to 1024 points around the segment. Calculations of jitter, cross-sectional error and shift error between study object and operator outline were made from the FID data. Jitter, or outline error is expressed as the ratio of the power of the noisy outline to the expected outline,

\[
\text{Outline Jitter } S/N = \sum_{i=1}^{N} \left( x_{i,\text{outline}}^2 + y_{i,\text{outline}}^2 \right) / \sum_{i=1}^{N} \left( x_{i,\text{object}}^2 + y_{i,\text{object}}^2 \right) \quad [C.2]
\]

Park and Lee showed that cross sectional area is equivalent, by way of Parseval's Theorem, to

\[
V = \frac{1}{N^2} \sum_{i=1}^{N/2} i \cdot (R_i^2 + S_i^2) + \left( \frac{N}{2} - i \right) \cdot (R_{i+N/2}^2 + S_{i+N/2}^2) \quad [C.3]
\]

Cross-sectional error (or volume error for a series of slices) would be described as
\[ V_{\text{err}} = 1 - \frac{V_{\text{object}}}{V_{\text{outline}}} \]  [C.4]

The center of mass of an object is simply the second harmonic value of the FD of each outline (Park, 1987). Shift error is the difference between the centers of mass of real \(F_{\text{object}(1)}\) and measured \(F_{\text{sampled}(1)}\) outlines,

\[
\text{shift error} = -\frac{F_{\text{object}(1)} - F_{\text{sampled}(1)}}{\frac{1}{N} \sum_{i=1}^{N} \sqrt{\{x_i - \Re[F_{\text{object}(1)}]\}^2 + \{y_i - \Im[F_{\text{object}(1)}]\}^2}}  \]  [C.5]

normalized by the mean radius of each object, and is a complex number corresponding to the x and y axial shifts. The mean radius of an object (the denominator of equation [C.5]) is the variance of each uniformly sampled outline about its center of mass.

Each outline-patient test was regarded as a single unbiased data point, with no patient/group statistics computed. Average aggregate values of mean and variance were computed after 6 subjects each drew 6 outlines.

C.4.C Results

The results are summarized in table C-1. Overall, jitter error (Jitter S/N) averaged at 0.0333 +/- 0.0163 pixels in the x-direction, relative volume error (Verr) averaged at 0.0038 +/- 0.0123, and shift error averaged at 0.0119 +/- 0.0380 in the x-direction (dXo) and -0.0034 +/- 0.0328 in the y-direction (dYo). In these calculations, the units are inherently normalized. The degree of shift error on a 640x480 screen amounted to from 1/2 to 2 pixels in an object of about 200 pixels in radius.
These values aid in determining the extent of expected error of hand drawn outlines for the examination of the robustness of the susceptibility method as discussed in chapter VII.

C.5 Application to Liver Iron Quantification

MR liver iron quantification, as proposed in this project, requires multiple image components to be segmented from the GFE magnitude images. What follows is a description of segmentation methods used to define operator points on the contour of the bucket phantom, the patient torso and liver.

C.5.A Bucket Segmentation

Segmentation of the bucket is a simple matter of picking out the upper and lower corners of three slices. The water bucket need only be specified on three slices in order to uniquely identify the position of the bucket in space.

C.5.B Torso Segmentation

The two approaches for stylized torso representation outlined above each have their relative advantages. The FD approach very accurately describes the torso, and can be truncated to the 15th harmonic for any torso representation (Park, 1987). This means that only 15 points must be sampled per slice in order to avoid aliasing and accurately represent the geometry, for a total of 240 samples for a 16 slice torso. In the other method, the parametric torso requires only 12 data-point measurements,
which are numerically fit to the summed ellipses formulation to provide an accurate representation of the torso (Keeling, 1981). Because of the requirement of fewer points for accurate representation, the parametric torso representation was chosen for the model of the torso.

The segmentations of two magnitude reconstruction slices were shown in figures 8-2(c) and 8-2(f) (shown along with the phase reconstructions in figures 8-2(a) and 8-2(d)). The operator must point out the extents of the torso, the left and right axillary points, and the medial dorsal and medial ventral points of the torso surface. This need only be done on three slices (4th, 8th and 12th of 16) as extrapolation and interpolation can be used to calculate the torso compartment of the other slices from the parameterized torso model (Keeling, 1981).

C.3.C Liver Segmentation

The high accuracy of the FD technique for volume matching and high frequency error smoothing indicates that it will be the best method for actual patient liver sampling. An outline of the liver can be reduced to 15 harmonics, for which only 15 points need be specified by the operator in order to avoid aliasing (note that each contour-point contains two data points - x and y, thus satisfying the Nyquist requirement of 2x sampling for non-aliasing) (Oppenheim, 1975).

The segmentation of the liver is carried out point by point on each slice acquired in the scan in the same manner described above for mouse-pointer outlining. The segmented version of the magnitude slice was shown in figure 4-2(c,f). Although,
only 15 points are needed for adequate resolution, the operator is encouraged to oversample. The liver data is smoothed (or low pass filtered) by eliminating all but the lowest 15 spectral coefficients.

Each compartment (lung or torso) is made solid by a boundary-search method filling algorithm. It should be noted that no hole is left behind, when the liver is segmented out of the torso, as in figure 4-2(a). Instead, the liver compartment is modeled with a differential susceptibility of the liver less the torso, as shown in figure 4-2(b). Each segmented solid object is then submitted to the Field Model algorithm.
Figure C-1. Fourier Descriptor smoothing begin with a) sampled contour points, b) Fourier transform into FDs, c) low pass filter, and d) inverse transform into a smoothed contour.
Liver Outlining with FD Smoothing

Original Liver Outline

Operator chosen Outline Points

FD Interpolated and Smoothed Liver Outline

Figure C-2. Liver outline smoothing via FDs. 21 sampled points are FD-smoothed with by retaining the 15 harmonics of lowest frequency (i.e. low pass filtered).
### Table C.1

**Operator Error in Matching Random Outlines**

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Errors evaluated are:

- Volume Error - Verr
- Shift of Center of Mass in x - dXo
- Shift of Center of Mass in y - dYo
- Outline Jitter Error - Jitter S/N

The mean and standard deviations of each class of error are also computed. Units are implied as:

- Verr = cubic pixels
- dXo, dYo = pixels
- Jitter S/N = unitless ratio
References


