Sparse reconstruction of molecular images: the MRFM challenge

Nicolas Dobigeon, Alfred O. Hero, Daniel Rugar and Jean-Yves Tourneret

***Abstract*—Recently, an emerging technology called magnetic resonance force microscopy (MRFM) has demonstrated the ability to detect and localize magnetic force signals originating from individual electron spins and from small ensembles of nuclear spins. By measuring weak magnetic forces from hydrogen nuclei, three dimensional (3D) magnetic resonance images with nanometer resolution have been successfully reconstructed. In the future, 3D imaging of individual molecules may become possible. In this paper, we propose to provide a brief review of the MRFM imaging technique and to highlight interesting challenges for the signal and image processing communities.**

***Index Terms*—Magnetic Resonance Force Microscopy, image reconstruction, sparse representation.**

I. Introduction

For more than 30 years, magnetic resonance imaging (MRI) has been widely used by the medical community to detect pathologic tissues in a patient body. It is fair to say that magnetic resonance imaging has revolutionized the imaging of soft tissues by providing excellent contrast while avoiding the use of ionizing radiation required by other standard medical imaging methods, such as computed tomography (CT) and positron emission tomography (PET). However, in spite of major technical improvements in MRI, fundamental sensitivity issues limit the resolution of clinical imaging systems to the millimeter or sub-millimeter range. Even the most specialized MRI microscopes face severe sensitivity constraints that limit resolution to a few micrometers.

In order to overcome the sensitivity and resolution limitations of MRI, Sidles in 1991 proposed that, by using sensitive mechanical detection of magnetic force, MRI resolution could be greatly extended, perhaps even down to the atomic scale [1]. The resulting technique, called magnetic resonance force microscopy (MRFM), essentially combines MRI with force detection technology originally developed for atomic force microscopy (AFM). A key goal of Sidles' proposal was to achieve sufficient resolution to perform three-dimensional imaging of individual protein molecules. In the early 1990's, Rugar *et al.* at IBM reported experiments that demonstrated the basic practicality of MRFM and produced the first micrometer-scale MRFM images [2], [3]. More recently, MRFM volumetric spatial resolutions of less than 10nm have been demonstrated for imaging individual virus particles [4]. The resulting improvement in sensitivity over the best conventional MRI detection is an impressive factor of 100 million.

As MRFM resolution and sensitivity continue to improve toward the molecular level, a number of interesting and challenging signal and image processing problems will be encountered. These challenges include: spatially sparse image reconstruction, molecular classification from MRFM data, incorporation of molecular priors and penalties, and uncertainty in the point spread function. The purpose of this paper will be to describe MRFM, review its signal and image processing aspects, explain some of the technical challenges, and suggest ways to meet these challenges.

II. The magnetic resonance force microscope

MRFM forms images of nanoscale objects by detecting minute magnetic forces exerted on a sensitive microfabricated cantilever by the atomic spins in the sample. Although electrons spins have been detected by MRFM and can be used in many applications, we will concentrate here on nuclear spin imaging (especially hydrogen nuclei) since nuclear spins are ubiquitous in biological materials and provide elemental selectivity.

The magnetic force signal is generated by positioning a small (sub-micron) magnetic tip near the sample while simultaneously manipulating the orientation of the nuclear spins in the sample. The magnetic tip generates a strong magnetic field gradient which acts to either attract or repel the sample spins depending on their orientation. To create a distinctive force signal, the

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spins are cyclically inverted at a rate that matches the mechanical resonance frequency of the cantilever. The resulting oscillating magnetic force causes a slight (sub-angstrom) cantilever vibration which is detected using a laser interferometer.

The cyclic spin inversion is accomplished using a radiofrequency (rf) magnetic field that is frequency modulated about the precession frequency of the spins. Because of the field gradient from the magnetic tip, the spin precession frequency is a strong function of position and matches the rf field frequency only within a narrow "resonant slice". The confinement of the spin response to the resonant slice is the basis of MRFM spatial resolution and determines the point spread function (psf) of the imaging system. Only spins that are within the resonant slice will generating a significant cantilever vibration signal. The resonant slice is essentially an isosurface defined by the surface of constant tip magnetic field and typically has the form of a thin paraboloidal bowl. Figures illustrating the MRFM point spread function have been published in [5] and [4].

Given the point spread function $\boldsymbol{\kappa}(x,y,z)$ over (x,y,z) in 3D space, the spin density image $\mathbf{N}(x,y,z)$ can be related to the positionally-dependent forces exerted on the cantilever $\mathbf{F}(x,y,z)$ through the following 3D convolution integral [6] [7]

$$\mathbf{F}(x,y,z) = \int\int\int \mathbf{N}(u,v,w) \times \boldsymbol{\kappa}(x-u, y-v, z-w)\, dudvdw \quad (1)$$

Image reconstruction consists of estimating the spin density $\mathbf{N}$ from the measured force map $\mathbf{F}$ by numerically inverting the convolution integral (1).

A mathematical model for the psf has been derived under some simplifying assumptions in [8], and successfully used to reconstruct 3D spin images [4], [9], [10]. The mathematical model depends on physical parameters such as: amplitude of external magnetic field, tip dimensions, distance from tip to sample, cantilever tip moment etc. Uncertainty in the psf $\boldsymbol{\kappa}(x,y,z)$ will lead to mismodeling errors that negatively affect image reconstruction. Strategies for controlling the effect of mismodeling errors are described below.

III. Sparse reconstruction of MRFM

As highlighted above, the signal provided by the MRFM imager is a so-called force map that is the 3D convolution of the atomic spin distribution and the point spread function [7]. The observation of the spin distribution through this force map can be approximated as the following linear model

$$\mathbf{F} = T(\boldsymbol{\kappa}, \mathbf{N}) + \mathbf{E} \quad (2)$$

where $\mathbf{F}$ is an $l_x \times l_y \times l_z$ matrix that stands for the sensed force map, $\mathbf{N}$ is the $m_x \times m_y \times m_z$ matrix of the spin distribution to be recovered, $T(\cdot,\cdot)$ is a bilinear function and $\mathbf{E}$ is an additive term modeling the error measurements (e.g., noise). In (2), κ is the 3D convolution kernel that characterizes the point spread function of the device. This formulation casts the estimation of the spin density from the force map as a standard inverse problem. Several approaches have been proposed to solve this problem, i.e., to reconstruct the unobserved matrix $\mathbf{N}$ from the data $\mathbf{F}$. In early MRFM experiments conducted by Züger *et al.* [3], [6], [11], a Wiener filter was implemented to recover the spin density. In [12], several techniques based on linear filtering and maximum-likelihood principles were proposed. More recently, an iterative least squares reconstruction approach was adopted [4], [7], [9] using Landweber iterations [13].

However, while previously proposed Wiener filtering, maximum likelihood, and Landweber are well established methods they do not take advantage of the natural sparsity of molecular images. Indeed, since molecules and groups of molecules are sensed at a nanoscale resolution, most of the image pixels are identically zero. This sparsity is a strong property which can be exploited to improve the image reconstruction. Ting [5] introduced sparse reconstruction techniques for MRFM images. In this work the MRFM reconstruction was decomposed into a deconvolution step and a denoising step, resulting in an iterative thresholding framework. Within a Bayesian formulation, a penalized criterion rule was used to favor the sparsest solutions of (2). More precisely, the image pixels $n_{i,j,k}$ ($i = 1,\ldots,m_x$, $j = 1,\ldots,m_y$, $k = 1,\ldots,m_z$,) were assigned priors composed of a weighted mixture of a Laplacian distribution and an atom at zero (LAZE), whose probability density function (pdf) is defined as

$$f(n_{i,j,k}|w,a) = (1-w)\delta(n_{i,j,k}) + w g(n_{i,j,k}|a) \quad (3)$$

where $g(\cdot|a)$ is the pdf of the Laplacian distribution with parameter a.

The sparsity properties of the LAZE prior were established by Johnstone [14] for problems of pure denoising (without deconvolution). When using LAZE as prior distribution, the main issue is to accurately estimate the hyperparameters defining the mixture: the prior probability w of having non-zero pixels and the average amplitude a of these non-zero pixels. In [15], Ting *et al.* used empirical Bayes and Stein unbiased risk (SURE) solutions to deal with this problem. Unfortunately, although the proposed iterative algorithm performs well at low signal-to-noise ratio (SNR), the reconstruction

performance significantly decreases at higher SNR. This loss of performance was mainly due to poor estimation of hyperparameters associated to the LAZE prior.

To cope with the deficiencies of the LAZE prior, Dobigeon *et al.* proposed to address this as a hyperparameter estimation problem under a hierarchical Bayesian model [10], [16]. By assigning non-informative (i.e., vague) priors to the unknown hyperparameters, they introduced a second level of hierarchy within the Bayes' framework. The hyperparameters w and a, as well as the spin density of interest $\mathbf{N}$, were then inferred via Markov chain Monte Carlo (MCMC) sampling, providing Bayes-optimal estimates of all the unknown image parameters. More detailed descriptions of the techniques introduced in [15] and [10], with a particular interest on the algorithm performance, will be provided in the final version of the paper. However, these promising results encounter some limitations. In particular, all these previous methods require an exact *a priori* knowledge of the MRFM imager response, i.e., the psf.

IV. Towards myopic and semi-blind MRF estimation strategies

In all the above cited works, the response of the imaging device is assumed to be *a priori* known and fully described by the psf derivation introduced in Section II. As shown in [8], the shape of this convolution kernel is based on several physical parameters fixed by the operator during the conducted experiment: tip magnetization, external field, field at resonance... However, in some practical situations, the physical parameters that tune the response of the MRFM tip are only partially known, even totally unknown. In such circumstances, prior knowledge of the psf is unreliable and image quality will suffer if one does not account for this uncertainty.

Two main approaches for reconstructing MRFM images with unknown psf can be considered. They will be more extensively presented in the full paper and are summarized in what follows. The first is a parametric approach consisting of assuming a model for the psf and estimating the most uncertain parameters in the model. This approach is referred to as semi-blind [17] [18] or myopic [19] [20] deconvolution. Within the fully Bayesian framework proposed in [10], a simple additional step in the initial MCMC algorithm allows one to estimate the parametric convolution kernel, resulting in a Metropolis-within-Gibbs algorithm.

The second approach for MRFM reconstruction under uncertain psf is non-parametric and relies on decomposition of the convolution matrix $\mathbf{H}$ that represents the operator $T(\boldsymbol{\kappa}, \cdot)$ in (2) [21]–[23]

$$\mathbf{H} = \mathbf{H}_0 + \epsilon \boldsymbol{\Delta}. \tag{4}$$

In (4), $\mathbf{H}_0$ is the approximated forward operator coming from available prior knowledge and $\boldsymbol{\Delta}$ is an additive perturbation term reflecting possible model errors. The joint estimation of the unknown spin density and the convolution kernel is conducted in [21], [24], [25] by using a minimax criterion coupled with the optimization transfer concept.

V. Conclusion

We propose to write an overview of MRFM from a signal and image processing perspective. This technology is emerging as one of the most promising 3D imaging modalities capable of atomic level sensitivity on the order of a single spin of an electron or nucleus. While there are a considerable number of signal and image processing challenges, there have been recent advances in spin detection and sparse Bayesian reconstruction that can lead to significant gains in imaging performance. Several of these challenges and recent advances will be discussed in the full paper.

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