Volumetric reconstruction of targeted nanoparticles for superparamagnetic relaxometry

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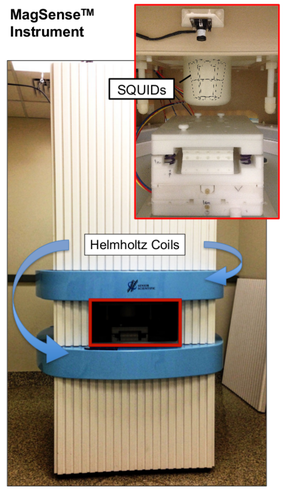
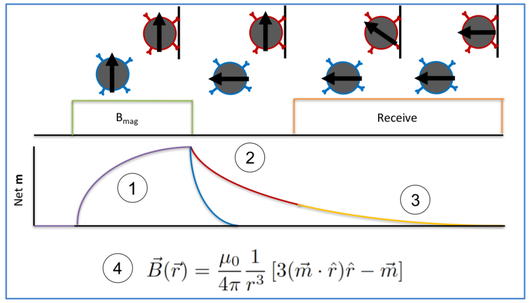
Introduction

Superparamagnetic relaxometry (SPMR) is an emerging technology that detects a signal only from immobilized superparamagnetic iron oxide (SPIO) nanoparticles. SPMR is currently being developed for the early detection of cancer using cancer specific antibody labeled particles. After intravenous injection, the particles only produce a signal once they are immobilized by antibody specific binding to cancer cells. This technique has high sensitivity and specificity because there is no background signal from normal tissue, or free floating SPIOs.

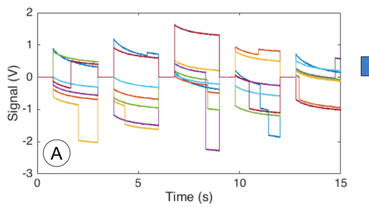
MagSense™ Instrument

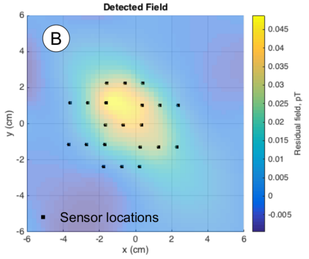


Superparamagnetic Relaxometry (SPMR)



1. The superparamagnetic relaxometry process starts when a pair of Helmholtz coils apply a uniform 0.6T magnetic field to the sample. The magnetic moment of each SPIO aligns with the applied field.
2. Shortly after the field is removed, unbound particles rotate back to a net zero field configuration via Brownian processes.
3. Unable to rotate, bound particles return to a net zero field configuration via Neel relaxation over the next few seconds. During this time, SQUID detectors measure the residual magnetization of the bound particles.
4. The spatial distribution of the bound particles can be reconstructed from the detected residual field according to the Biot Savart law.

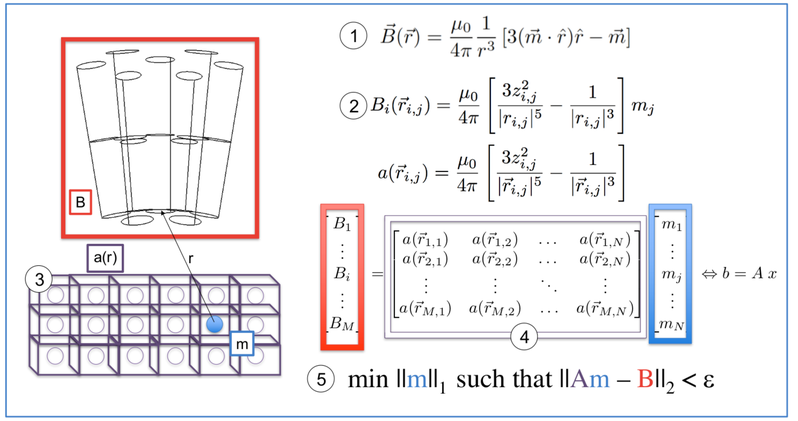




After the decay curves (A) are collected, they are pre-processed to remove spurious jumps and noise, then fit to determine the underlying magnetic field strength at each detector. Data can be acquired at multiple stage positions to increase the spatial sampling of the magnetic field (B).

The Reconstruction Algorithm

Reconstructing the location and quantity of cell-bound nanoparticles from the detected residual magnetic field requires solving the magnetic inverse problem. This problem is ill-posed, meaning there are many possible bound particle distributions that create the same residual magnetic field. For example, a large quantity of bound particles farther from the sensors could create the same magnetic field as a just a few bound particles closer to the detectors. In the current reconstruction algorithm, each cluster of bound nanoparticles is treated as a single dipole moment with a location equivalent to the centroid of the cluster and a moment equal to the total moment of the particles in the cluster. Due to the ill-posedness of the problem, the user must first define the number of clusters to solve for, then determine their strength and location. This approach is acceptable for cases in which the number of clusters and their approximate location is known *a priori*, such as *in vitro* or phantom studies. However, in clinical applications the location and number of tumors is not known. Therefore, we developed a sparse reconstruction algorithm which does not require prior information about the location of bound particles. Furthermore, this method provides a volumetric reconstruction of the bound particle distribution, rather than determining only the centroid of each cluster.

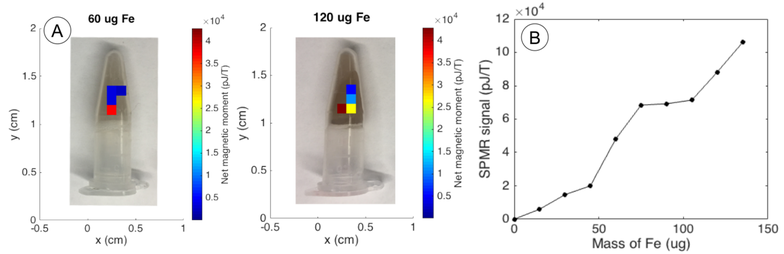


1. Each bound nanoparticle can be modeled as a magnetic dipole with a moment *m*. The magnetic field detected at a location *r* from a dipole moment *m* is described by the Biot Savart law.
2. The net residual magnetization left in the bound nanoparticles is parallel to the applied field. Given that the only non-zero component of the moment is in the *z* direction, the Biot Savart law can be simplified into a linear combination of the magnetic moment and a function of the vector between the magnetic moment in voxel j and the measured field at detector location j, $a(r_{i,j})$.
3. In order to solve the inverse problem without defining a number of dipole moments *a priori*, the field of view is divided into voxels. The magnetic field detected at each SQUID is then a sum of the contributions from each voxel.
4. This allows the definition of a linear system, B=Am, where the vector B is the magnetic field measured at each detector location, the vector m is the moment in each voxel, and the matrix A is the spatial relationship between each detector and each voxel.
5. Because the number of voxels is much larger than the number of magnetic field measurements, the problem is under-determined. This means that there are multiple possible solutions. For the application of cancer detection, we can assume that only a few of the voxels, those containing cancer-bound nanoparticles, will have a non-zero magnetic moment. We use a sparse optimization to determine which of the possible solutions has the fewest non-zero voxels, and therefore is the closest approximation of the true nanoparticle distribution.

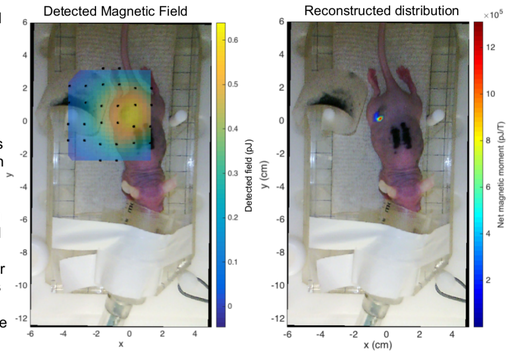
Experimental Validation

In phantom studies, we have demonstrated that immobilized nanoparticles produce a SPMR signal that is approximately linear with SPIO concentration. We also demonstrated that we are able to reconstruct tumor bound nanoparticles *in vivo*.

In the study shown here, a range of nanoparticle quantities were distributed in melted glycerin soap. The samples were then allowed to cool to room temperature at which point the glycerin becomes solid, immobilizing the nanoparticles, as shown in A. SPMR was conducted on the samples using the MagSense™ instrument. The magnetic moment per voxel, was reconstructed from the magnetic field data using in house software based on a sparse reconstruction algorithm using a 1mm³ voxel size. The total SPMR signal plotted in B as a function of mass of iron is the sum of the voxel values within a ROI around the sample location.



To validate the algorithm for use in preclinical settings, SPMR was performed on SKOV3 ovarian tumor bearing mice (n = 3) with the MRX device over time following an intratumoral injection of anti-Her2 antibody-conjugated 25nm SPIONs (Imagion Biosystems). The SMPR data was reconstructed with our sparse solver and was found to be highly correlated (r = 0.9978) with the results generated by the commercial software that accompanies the MagSense™ instrument (MSA). Additionally, segmentation of the reconstruction revealed a strong signal ($2.0 \cdot 10^6$ pJ/T) in the area of the tumor and almost no signal in areas outside of the tumor (0.077 pJ/T) at four hours after injection. This result was consistent with our prior observations which have revealed that a large fraction of intratumorally-injected nanoparticles remain localized within the tumor for several hours after injection. Furthermore, these results were consistent with SPMR data collected by measuring excised tissue samples, of which the tumor had the highest signal. Thus, our sparse reconstruction algorithm was able to return the expected results without prior information regarding the location of nanoparticles.



References

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