Quantification of Labeled Cell Clusters in a Rat Brain In Vivo Using MRI

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Purpose: (1) To demonstrate the use of a complex summation based magnetic moment quantification method for estimating the numbers of *in vivo* stem cells labeling by iron-based nanoparticles, which appear in local clusters. (2) To analyze the effect of high pass filters on this quantitative method.

Introduction: Tracking cells tagged by nanoparticles and imaged by MRI has been well demonstrated. However, this tracking is only a qualitative process. Quantitatively, it is more useful to obtain the number of cells from MR images. In this abstract, we show how to quantify the magnetic moment of nanoparticles in a local cluster from MRI and in turn how to estimate the number of cells. Previously, Del Gratta et al. [1] had estimated the number of cells using an SQUID magnetometer *ex vivo*. On the other hand, using MRI, it is possible to perform a least squares fit to MR phase images and obtain the magnetic moment of an object of interest through susceptibility mapping techniques [2]. However, both of these methods have high uncertainties for small objects. Quantifying the magnetic moment from the complex signal around the object of interest can provide a higher degree of accuracy. Such a method has been proposed for cylindrical and spherical objects [3], and it is used here. Magnetostatics governs that small magnetized objects such as the clusters analyzed here, regardless of geometry, can be modeled as perfect spheres. The magnetic moment of an object can be expressed as the product of its mass magnetization and mass. Thus, given the mass magnetization of the iron nanoparticles and the quantified magnetic moment of the nanoparticle cluster, the mass of iron can be calculated. Further, if the cellular iron uptake is known, the mass of iron can be used to derive the number of cells. In this abstract, we first use simulations to study the effect of high-pass (HP) filters on magnetic moment quantification as HP filtering is a standard method of eliminating background fields from phase images. Next, our quantitative method is applied to six clusters of cells from several *in vivo* rat brain images.

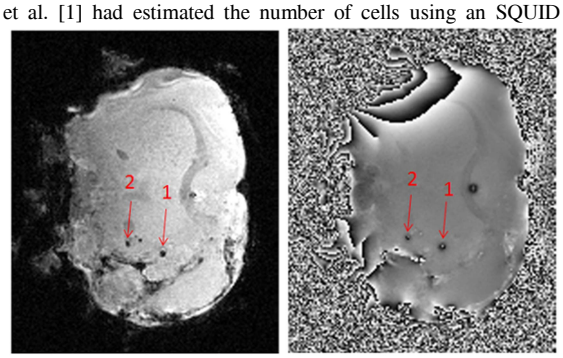

Figure 1: (A) Magnitude and (B) Phase image of 2 cell clusters quantified from *in vivo* rat brain data

Methods: *Simulations*: A total of 15 spheres were simulated with effective magnetic moments of 8, 15, 20, 30, and 100 radian*pixel^3 and targeted radii of 1, 2, and 3 pixels. The definition of the effective magnetic moment here is p' = $0.5\gamma\Delta\chi B_0 TE*V$, where $\gamma = 42.58$ MHz/T, B_0 is the main field, TE is the echo time, and V is the volume of the sphere. The word effective is dropped hereafter. Each simulation was created on a 1024^3 matrix (with a much larger radius of each sphere) and cropped down to 32^3 in the spatial frequency domain, in order to include the partial volume and Gibbs ringing effects. Each sphere was assumed to have zero signal inside. Each of the 32 slices was zero-filled in image space to 256^2. Hanning HP filter of size 32^2 were then applied to each simulation.

p'	R	error (%)	p'	R	error (%)
8	1	-8.1	30	1	-6.9
	2	-7.4		2	-7.8
	3	-20.4		3	-10.7
15	1	-5.9	100	1	-13.7
	2	-5.9		2	-13.7
	3	-10.8		3	-14

Table 1: Percentage errors of quantified magnetic moments (p' in units of radian*pixel^3) of 15 different simulated spheres.

In vivo data: Pre-existing *in vivo* 3D gradient echo k-space data sets of a stroke induced rat brain that was injected with ferumoxide (Feridex) labeled neural progenitor cells were obtained from Henry Ford Hospital [4]. The sequence parameters were $B_0 = 7$T, TR = 200ms, TE = 8ms, Flip Angle = 20°, FOV = 24 x 24 x 12mm, and a matrix size of 256 x 256 x 128. Six separated cell clusters were chosen for analyses (two shown in Fig. 1). As our current quantification method requires isotropic resolutions, the data were zero-filled in k-space along the slice select direction. A 32^2 homodyne HP filter was applied to remove the background phase and MATLAB was used for image reconstructions.

Cluster	p'_HP	dp'/p' (%)	p'	cells
1	7.66	8.78	8.34	48
2	21.71	0.76	23.1	133
3	11.47	3.14	12.2	70
4	28.8	1.17	31.3	180
5	12.17	3.61	12.95	74
6	5.38	2.37	5.72	33

Table 2: Quantified results of the six cell clusters. p'_HP represents the magnetic moment prior to adjusting for the effects of HP filtering.

Quantification: All quantifications were performed using an internally developed program written in C++. First, the object is interpolated by a factor of 10 in each direction. The center of the interpolated object is determined as described in [5]. The magnetic moment is then quantified. Parameters in our method were chosen to minimize the effect of Gaussian noise. Systematic errors in addition to those from HP filtering (Gibbs ringing and intravoxel dephasing) were estimated by quantifying simulated spheres with the same magnetic moment as of each cluster. These errors were included in the presented uncertainties. The values of Feridex mass magnetization and neural progenitor cellular uptake are found in literature to be 96.3emu/g Fe [6] and 14.5pg Fe/cell [7], respectively.

Results: *Simulations*: Table 1 summarizes the results from the HP filtered simulated data in terms of errors estimated from the true (listed) magnetic moment values. It is seen that, in general, underestimation of the true magnetic moment becomes significant when the radius (R) of the object is greater than 2. In addition, a high magnetic moment value is also shown to lead to more severe underestimation.

In Vivo: Table 2 summarizes the quantification results from six stem cell clusters that were analyzed. Each result was adjusted based on findings from the simulated HP-filter results. All quantifications resulted in less than 10% uncertainty. The number of cells was rounded to the nearest integer. It was found with this particular data that 1 cell (or 14.5 pg Fe) corresponds to a magnetic moment of 0.17 radian*pixel^3. Heyn et al. [8] had a required cellular uptake of 43.3pg/cell for the visual detection of one of their cells. This 43.3 pg Fe translates to a magnetic moment of roughly 0.5 radian*pixel^3 which is about the lower limit that our method can quantify.

Conclusion: The effect of HP-filter and the feasibility of the complex sum magnetic moment quantification method for estimating the numbers of labeled cells in clusters have been demonstrated.

References: [1] Del Gratta. C., et al. Phys. Med. Biol. 1995; 40: 671. [2] Liu, S., et al. MRM. 2013 ; 69 : 716-723. [3] Hsieh, C., et al. Medical Physics. 2008; 35: 2906. [4] Athiraman, H., et al. MRM. 2009; 61: 587-594. [5] Cheng, Y.C.N., et al. Phys. Med. Biol. 2009; 54: 7025-7044. [6] Jung, C.W. MRI. 1995; 13: 675-691. [7] Panizzo, R.A., et al. F1000Research. 2013; 2: 252. [8] Heyn, C., et al. MRM. 2005; 53: 312-320.