Phase-Based Imaging of Magnetically Tagged Cells

T. L. Chenevert[1], V. Schepkin[1], G. D. Luker[1], B. A. Moffat[1], B. D. Ross[1]
[1]Radiology, University of Michigan, Ann Arbor, MI, United States

Background and Purpose

Cell tracking offers several potentially powerful applications such as migration and distribution of immune, stem, inflammatory and disease cells. To date, the majority of cell tracking MRI methodologies have utilized superparamagnetic iron oxide (SPIO) particles incorporated within labeled cells, with their presence depicted as signal void on gradient echo sequences [1-3]. The purpose of this work is to investigate an alternative mechanism to detect the presence of magnetically-labeled cells.

Introduction

Means to detect migration, proliferation and distribution of living cells within normal and diseased tissues has inherent appeal for basic studies in model systems as well as clinical applications. Cells labeled with SPIO particles have been detected as a signal void on gradient echo MRI sequences. Susceptibility-induced signal attenuation is accentuated by increasing echo time, magnetic field strength, and concentration of magnetic particulates. The conspicuity of these regions depends on the size and depth of the signal attenuation relative to background features and overall SNR of the imaged object. For optimal foci detection, signal loss should be complete and observed within a uniform high signal background. Obviously, the uniformity of background tissues depends on a variety of tissue-based factors and systematic effects (eg. coil uniformity and quality). In this work we propose a phase-based approach that is complimentary to the conventional magnitude-based method and offers improved sensitivity to the presence of small magnetic disturbances imbedded in tissues, thus is well suited for cell tracking applications. This approach substantially reduces background image features which otherwise obscure magnetic foci detection. In addition, complete signal loss due to T2* is not required thus may further raise sensitivity to weak magnetic disturbances.

Materials and Methods

Gradient echo imaging was used as in standard cell tracking techniques. Since our proposed method measures local field-induced phase shift, the sequence also included first-order motion compensation on all three axes to minimize motion-related phase shift. Other aspects of data acquisition performed in these experiments were: 9.4T Varian system; TR = 50ms; TE = 20ms; flip = 30degrees; acq matrix = 256x256; recon matrix = 512x512; FOV = 30x30mm; slice thk=1mm; Nave = 32; Tacq=6.8min. Magnitude and phase-based images were then derived from each acquisition as follows. Phase mapping requires correction to removed background and systematic phase shifts, although this information can be extracted from each dataset without additional scans. A highly filtered version of each dataset served its own phase reference. The premise of this correction scheme is that the spatial extent of desired phase shifts is small relative to undesired background phase patterns which are characterized by low spatial frequencies. Thus the central k-space data (radius = 25 points) were retained, zero-filled to 512x512 then 2DFT'd to yield complex data, REF(x,y). Similarly, unfiltered k-space data were zerofilled and 2DFT'd to yield the D(x,y) complex image. Phase-corrected images, C(x,y), were generated by,

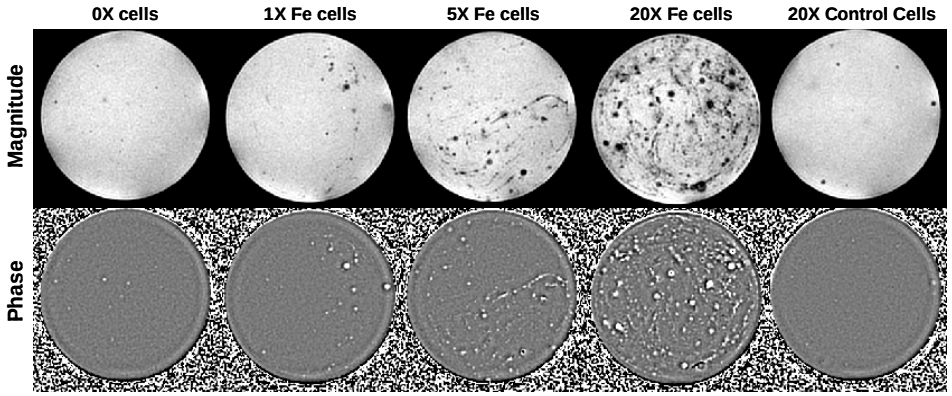
$$C(x,y) = \frac{D(x,y)\cdot conj\left[REF(x,y)\right]}{\left|REF(x,y)\right| + \varepsilon}.$$

The magnitude of C contains conventional anatomic contrast and, ideally, signal voids at SPIO sites as desired in conventional T2* weighted imaging. The T2*wt image also exhibits anatomic and systematic signal intensity modulations which can impede confident identification of subtle/small signal voids. The phase of C, however, has a relatively featureless background phase near zero upon which phase deviations are superimposed at small magnetic foci sites.

This approach was applied to gel-based phantoms containing variable quantities of SPIO-labeled and control (ie unlabeled) cells. The cells were splenocytes harvested from a SV129 mouse and labeled with complexes of ferumoxides and protamine sulfate in a ratio of 50:3 µg/ml [4]. Labeling was overnight in standard culture medium. Splenocytes were washed three times with phosphate buffered saline, and the labeled splenocytes then were fixed with 4% paraformaldehyde. Control splenocytes were cultured under identical conditions, except that ferumoxides were not added in the culture medium. Various numbers of splenocytes were mixed with 2% agarose in phosphate buffered saline, and 8 ml aliquots were prepared in 15 ml conical tubes. Dilutions were made to create "1X" (estimated 96 cells in the imaged slice) "5X" and "20X" concentrations of SPIO-labeled cells and unlabeled (control) cells. A tube with agarose alone was a negative control ("0X").

Results

The conventional T2* wt magnitude images are shown along the top row of the figure. These images depict a quantity of magnetic foci that scales with the known quantity of SPIO-labeled cells. The magnitude images were window-leveled individually in an attempt to reasonably show most signal voids regardless of their location. Background signal in these phantoms was relatively uniform, however detection of signal voids amidst an inhomogeneous background in real anatomy may be more difficult. The bottom row illustrates the phase maps derived from the same datasets. The phase correction by this method produces a flat background which aids detection of Fe-induced phase shifts. By inspection, there are several instances of new foci detected, or more clearly depicted on the phase-based image. The converse is also true, although keep in mind that one does not forfeit magnitude-based information for phase.



Conclusion

The proposed approach to detect magnetic foci for applications such as cell tracking is straightforward; requires no additional scan data; is complimentary and additive to standard T2* signal void methods; and in many instances substantially enhances foci detectability.

References

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