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Geometry and extension of signal voids in MR images induced by aggregations of magnetically labelled cells

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Abstract

The ability of magnetic resonance imaging (MRI) to visualize magnetically labelled cells has attracted much attention for revealing cellular events. The present study addressed the geometry and the extension of signal voids in static signal dephasing MRI induced by aggregations of magnetically labelled cells by means of a three-dimensional numerical model. The magnetic field distortions around spherical cell aggregations were treated as equivalent to those of a magnetic dipole. Intravoxel signal dephasing and respective signal voids attributed to these field inhomogeneities were computed. Effects of cell concentration on the signal void in the plane of view were evaluated in terms of dipole magnetization. Signal void characteristics were scrutinized systematically for fundamental sequence parameters including echo time, voxel size and plane-of-view orientation. For all variables examined, significant changes in geometry as well as extension of signal voids were demonstrated. The results are of crucial importance to optimize and interpret MR images with regard to spatial accuracy as well as sensitivity to detect aggregations of labelled cells in vitro or even in vivo. It is anticipated that the dependence of the extension of signal voids on the local magnetization may be valuable for quantifying labelled cells.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Cellular imaging by means of magnetic resonance imaging (MRI) has become very attractive since it provides anatomical, functional and biochemical information as well as excellent image quality (Arai et al 2006, Bulte and Kraitchman 2004, Cherry 2004, Xu et al 2006). Due to its limited spatial resolution, MRI is in fact not capable of visualizing single cells. However, cells labelled with superparamagnetic iron oxide (SPIO) particles cause intense magnetic field...
distortions over fairly large distances. Thus, SPIO-labelled cells become detectable due to their significant effects on MRI signal dephasing induced in water molecules near the cells (Yablonskiy and Haacke 1994, Ziener et al 2005). The in vitro (Foster-Gareau et al 2003, Zhang et al 2005) and even the in vivo (Heyn et al 2006, Shapiro et al 2006) detection of single labelled cells by means of MRI have already been accomplished.

The ability of MRI to visualize aggregations of thousands to millions of SPIO-labelled cells has attracted much attention in the past few years (Bos et al 2004, Daldrup-Link et al 2005, Himes et al 2004, Hoehn et al 2002, Jendelova et al 2003). Aggregations of labelled cells are reflected either as low-intensity signal spots or signal voids, particularly in $T_2^*$-weighted gradient echo MRI (De Vries et al 2005, Hauger et al 2006, Pintaske et al 2005, Zhang et al 2004). It is important to know that localized MR signal loss can be caused by tissue-specific magnetic field inhomogeneities, which mimic the appearance of labelled cells under in vivo conditions. In order to separate both effects, it is of critical importance to understand the physical basis as well as the effect of sequence parameters on the SPIO-induced signal voids in MRI.

The aim of the current work was to achieve a profound understanding of signal voids in static signal dephasing MRI caused by spherical aggregations of SPIO-loaded cells. The effects of fundamental variables on the intravoxel signal dephasing close to those cell clusters were investigated systematically by means of a static three-dimensional (3D) numerical model. First, variables attributed to the aggregation of SPIO-labelled cells including their spatial distribution and the concentration of labelled cells as well as the iron label per cell were studied. Second, geometry and extension of the image signal voids were examined in dependence on elementary sequence parameters including echo time, voxel size and orientation of the plane of view with respect to the main field $\mathbf{B}_0$. The first parameters are relevant for the SPIO-induced magnetic field inhomogeneities, whereas the latter parameters define how these field inhomogeneities affect the MR image.

2. Materials and methods

2.1. General considerations

MRI signal voids can be caused by both signal dephasing in voxels containing labelled cells (i.e., microscopic effects) and signal dephasing near cell aggregations (i.e., macroscopic effects). Studying the geometry and extension of signal voids with respect to magnetization and sequence parameters demanded the modelling of the magnetic field inhomogeneities within these signal dephasing volumes around cell clusters.

In the current study, clusters of labelled cells were considered as homogeneous magnetic spheres, and the field distortion was assumed to be equivalent to that caused by a magnetic dipole with the same total magnetic moment (Cunningham et al 2005, Ziener et al 2005). The physical size of the cell aggregation was presumed to extend over several imaging voxels. Recent studies have shown that labelled cells can aggregate in spherical cluster (Daldrup-Link et al 2003, Jendelova et al 2003, Pintaske et al 2005). Consequently, the present restriction to spherical geometries is no major limitation. A homogeneous distribution of labelled cells throughout the spherical volume was assumed.

Effects of cell concentration and iron load per cell were studied in terms of magnetization (i.e., the density of magnetic moments). To account for the huge spread in cell concentration (up to $10^6$ cells $\mu l^{-1}$) as well as in cell iron label (1–100 pg Fe/cell; Bulte and Kraitchman 2004, Heyn et al 2006), the signal voids, due to aggregations of labelled cells, were studied in an appropriately wide range of magnetization.
For each imaging voxel within the signal dephasing volume, the respective phase gradient $\delta \phi$ depends linearly on both the intravoxel magnetic field gradient $\delta B_z$ and the echo time $TE$ according to $\delta \phi \propto TE \cdot \delta B_z$. The considerations were limited to linear field gradients and linear phase gradients over the voxel. This was no major restriction since for aggregations of labelled cells the voxel size is small compared to the extension of the magnetic field perturbation.

Signal dephasing is associated with geometry and size of the imaging voxel. For the sake of simplicity, isotropic volume elements were assumed. Although the magnetic dipole field is symmetric with respect to rotation about the $z$-axis (i.e., the axis of the main magnetic field $\vec{B}_0$), the magnetic field distribution in the plane of view depends on the angle of this plane relative to $\vec{B}_0$ (figure 1). This implies that the slice orientation also affects the observable signal void in the plane of view.

### 2.2. Magnetic dipole field

The magnetic field distortions around spherical cell aggregations were treated as equivalent to those of a magnetic dipole. SPIO particles lack remnant magnetization when the external magnetic field is terminated since they can be regarded as thermodynamically independent, single-domain particles (Wang et al. 2001). Thus, the field components induced by cells loaded with SPIO particles are mainly governed by the vector properties of the external magnetic field $\vec{B}_0$.

The field perturbation $\delta B_z$ of a magnetic dipole with respect to the $z$-axis is given by the dipole formula (Hardy and Henkelman 1989, Cunningham et al. 2005)

$$\delta B_z(r, \Phi) = \frac{p_m}{4\pi r^3} (3 \cos^2 \Phi - 1).$$

(1)

In this equation, $p_m$ is the magnetic moment, $r$ is the distance from the dipole centre and $\Phi$ is the angle with respect to the main field $\vec{B}_0 = B_0 \cdot \vec{z}$. In order to model different concentrations of labelled cells as well as different iron loads per cell, the magnetic moment $p_m$ was varied and the respective dipole field was computed. The computed 3D magnetic field distribution around a magnetic dipole ($p_m > 0$) is represented in figure 1.
2.3. Numerical model

By means of a 3D numerical model, geometry and extension of the MRI signal void were studied in dependence on magnetization, echo time TE, voxel size and slice orientation with respect to the main field $\vec{B}_0$. The program was written in C++ (Microsoft Visual C++) and has already been described in previous publications (Müller-Bierl et al 2004, 2005, Pintaske et al 2006). Briefly, the field distortion of a magnetic dipole in a homogeneous main magnetic field $\vec{B}_0$ was computed. The magnetic dipole was placed at the centre of the simulation universe, which was discretized to identical computational units. To reproduce isotropic voxel sizes commonly selected for MR cellular imaging, the size of the computational units was varied from 0.1 $\mu$m to 0.4 $\mu$m. The magnetic moment of the dipole was varied. The field perturbation $\delta B_z$ induced by the magnetic dipole was computed for each computational unit within the simulation universe.

Signal dephasing due to magnetically labelled cells is attributed to the intensity of the magnetic field inhomogeneities and the strength of diffusion of water molecules through these field inhomogeneities. As pointed out by Yablonskiy and Haacke (1994), diffusion effects become negligible in the case of intense magnetic field distortions and large magnetic perturbers (i.e., diffusion correlation frequency $\ll$ frequency dispersion due to magnetic field inhomogeneities). As confirmed by Bowen et al (2002), these static dephasing conditions are well satisfied for aggregations of magnetically labelled cells, thus enabling to be found a relationship between field distortions and static signal dephasing in gradient echo MRI. The simulations were performed under static conditions where the position of each computational unit was fixed with respect to the 3D volume grid. The program code permits choosing the plane of view (as a cross section through the 3D volume grid) arbitrarily. The orientation of the plane of view was varied with respect to the $xz$-plane by rotating the plane around the $x$-axis with the angle $\Phi$ (figure 2).

2.4. Computation of signal void

The computed 3D magnetic field distributions were post-processed by a home-built code written in MatLab® (version 6.5, The Mathworks, Natick, MA). The computational units were treated as imaging voxels in this regard. At a given intensity of the magnetic field gradient per imaging voxel, the respective phase gradient is

$$\delta \phi = \gamma \cdot TE \cdot \delta B_z,$$

with $\gamma = 2\pi \times 42.58$ MHz T$^{-1}$ the proton gyromagnetic ratio and TE the echo time.

Kingsley (1995) recognized that a complete intravoxel signal dephasing requires at least a linear phase gradient $\delta \phi \geq 2\pi$ parallel to one side of an isotropic imaging voxel. In the present model, the area of the signal void in the plane of view included all computational units for which the dephasing condition $\delta \phi - 2\pi \geq 0$ was satisfied.

The plane of view was rotated stepwise about the $x$-axis within an angular range of $0^\circ \leq \Phi \leq 90^\circ$. For each orientation, the phase gradient was calculated on a voxel-by-voxel basis and was evaluated for orthogonal directions denoted by $a_{yz}$ and $a_x$ as specified in the plane of view. The dashed vertical line in figure 2, labelled as the plane of view, corresponds to the $y$-$z$ axis denoted by $a_{yz}$ in figure 3. The direction $a_{yz}$ accounts for the extension of the computed signal void in the $yz$-plane, whereas the $a_x$ direction specifies the extension of the signal void along the $x$-axis.
MRI signal voids caused by magnetically labelled cells

Figure 2. By rotating the plane of view with respect to the external $\vec{B}_0$ field, the geometry and the extension of the signal voids in this plane of view were studied. The normal vector of the plane of view points parallel to the image plane. The dashed vertical line, labelled as the plane of view, corresponds to the $y$–$z$ axis denoted by $a_{yz}$ in figure 3.

Figure 3. The magnetic field distribution and the signal void geometries in the plane of view depend on the angle $\Phi$ of the plane of view with respect to the main field $B_0$. Cross sections through the computed 3D magnetic dipole field (colour encoded) and the respective signal voids (black) in the plane of view are depicted.
2.5. Dependence of signal void on magnetization

The extension of the signal void was determined in dependence on the magnetization $M$ and hence on the magnetic moment $p_m$ of the dipole, which is the product of the dipole’s magnetization and volume:

$$p_m = M \cdot \frac{4}{3} \cdot \pi \cdot a_d^3.$$  \hspace{1cm} (3)

All simulations considered spherical cell aggregations with constant radius $a_d = 500 \, \mu m$ and diameter $D_0 = 1.0 \, mm$. This physical extension reflected experimental conditions adequately (Hoehn et al 2002, Himes et al 2004, Pintaske et al 2005, Ahrens et al 2003).

To account for the spread in both the local cell concentration and the average iron label per cell, the value of $M$ was varied logarithmically in a domain ranging from $5 \, \mu T$ to $20 \, 480 \, \mu T$. The extension of the signal void was evaluated for an isotropic voxel size of $100 \, \mu m$, an echo time $TE = 20 \, ms$ and plane-of-view orientations within the angular range of $0^\circ \leq \Phi \leq 90^\circ$.

2.6. Dependence of signal void on plane-of-view orientation

The magnetic field in the plane of view depends on the angle $\Phi$ of this particular plane relative to the main field $\mathbf{B}_0$. Thus, the respective signal voids were expected to also depend on this orientation. The magnetic field distribution was computed for various plane-of-view orientations (i.e., $\Phi = 0^\circ$, $15^\circ$, $30^\circ$, $45^\circ$, $54.74^\circ$, $60^\circ$, $75^\circ$ and $90^\circ$) as illustrated in figure 2. Due to the symmetry of the dipole field with respect to rotation about the $z$-axis as well as mirroring with respect to the $xy$-plane, the investigation of these orientation effects was confined to $0^\circ \leq \Phi \leq 90^\circ$. For these simulations, an isotropic voxel size of $100 \, \mu m$ and $TE = 20 \, ms$ were selected, and all strengths of the magnetic moment were considered.

2.7. Dependence of signal void on echo time

In an MRI experiment, the phase distribution is directly associated with the fundamental sequence parameter $TE$. The value of $TE$ was varied from $5 \, ms$ up to and including $80 \, ms$ in steps of $5 \, ms$, and the geometry as well as the extension of the respective signal voids was scrutinized. Within the numerical simulations performed, isotropic voxel sizes of $100 \, \mu m$, magnetizations $M = 160 \, \mu T$, $640 \, \mu T$ and $2560 \, \mu T$ as well as plane-of-view orientations parallel ($\Phi = 0^\circ$) and perpendicular ($\Phi = 90^\circ$) to the $\mathbf{B}_0$ field were considered. In order to assess the relative changes in the diameter $D$ of signal voids for echo times $TE > 5 \, ms$, the ratio between $D(TE)$ and $D(TE = 5 \, ms)$ was calculated for each TE data point.

2.8. Dependence of signal void on voxel size

The signal void characteristics were assessed in dependence on the voxel size. Utilizing dedicated small-animal MRI scanners operating at high magnetic field strength facilitates high-resolution MR cellular imaging with 3D isotropic spatial resolutions up to $100 \, \mu m$ (Heyn et al 2006, Shapiro et al 2006, Stroh et al 2005). For numerical simulations, isotropic voxel sizes of $R = 100 \, \mu m$, $200 \, \mu m$ and $400 \, \mu m$ were evaluated. The simulation parameters included magnetizations $M = 160 \, \mu T$, $640 \, \mu T$ and $2560 \, \mu T$, $TE = 20 \, ms$ and plane-of-view orientations $\Phi = 0^\circ$ and $\Phi = 90^\circ$ with respect to $\mathbf{B}_0$. 
MRI signal voids caused by magnetically labelled cells

Figure 4. Effects of cell concentration on the signal void in the plane of view were studied in terms of dipole magnetization. For both directions evaluated (\(a_x, a_y\)), the diameter of the image signal void \(D(M)\), as compared to the physical diameter \(D_0\) of the spherical aggregation, increased with magnetization \(M\). A nonlinear dependency \(D(M)\) on \(M\) was demonstrated.

3. Results

3.1. Dependence of signal void on magnetization

The dependence of the diameter of the signal void \(D(M)\) on the magnetization \(M\) is displayed in figure 4. For both directions evaluated (\(a_x, a_y\)), the diameter of the signal void rises with increasing magnetization. Relative enhancements in \(D(M)\) up to a factor of 9 as compared to the physical diameter \(D_0\) of the spherical aggregation were found. A nonlinear dependency of \(D(M)\) on \(M\) was revealed: the higher the magnetization, the smaller the slope \(d(D(M))/dM\).

3.2. Dependence of signal void on plane-of-view orientation

The orientation of the plane of view was varied with respect to \(\vec{B}_0\), and the effects on geometry and extension of the signal void were studied. Representative geometries of the plane-of-view-dependent magnetic field distributions as well as respective signal voids are shown in figure 3. The signal void geometries as well as extensions (figure 4) exhibited a significant dependence on the orientation of the plane of view. Since the plane of view was rotated around the \(x\)-axis, the diameter of the signal void along the \(a_x\) direction was independent of their orientation. In contrast, the diameter of the signal void along the \(a_y\) direction was a function of the orientation of the plane of view with respect to the external \(B_0\) field. At
the ‘magic angle’ of $\Phi = 54.74^\circ$, the signal void in the $\alpha_z$ direction was found to be $D_0 = 1.0$ mm.

3.3. Dependence of signal void on echo time

The diameter $D(TE)$ of the signal void in the $\alpha_z$ direction was evaluated for echo times in the interval $5 \text{ ms} \leq TE \leq 80 \text{ ms}$. As depicted in figure 5, the extension of the signal void increased significantly with progressing TE. Furthermore, a nonlinear dependency of $D(TE)$ on TE was demonstrated. The slope of the simulated data (i.e., $d(D(TE))/d(TE)$) decreased at higher TE. The ratio $D(TE)/D(TE = 5 \text{ ms})$ increased with TE. This ratio was found to be independent of dipole magnetization.

3.4. Dependence of signal void on voxel size

Finally, geometry and extension of signal voids were computed for isotropic computational units scaled to $R = 100 \mu \text{m}$, $200 \mu \text{m}$ and $400 \mu \text{m}$, respectively, in order to account for effects due to voxel size. The calculated values of $D(R)$ in the $\alpha_z$ direction are plotted against $R$ in figure 6. For each dipole magnetization examined, the bigger the voxel size the larger the extension of the signal void. In general, $D(R)$ was found to be several times larger than the physical diameter $D_0$ of the underlying magnetic sphere. In the case of the plane-of-view orientation $\Phi = 90^\circ$ with respect to $B_0$, these enhancement effects were less pronounced as compared to an orientation of $\Phi = 0^\circ$.

4. Discussion

4.1. Relevance for spatial accuracy in MR cellular imaging

MRI-based cellular imaging of certain biological processes including stem cell homing and cancer cell migration requires tracking aggregations of magnetically labelled cells with high
MRI signal voids caused by magnetically labelled cells

The diameter $D(R)$ of the signal void in the plane of view in dependence on the voxel size $R$.

Figure 6. The diameter $D(R)$ of the signal void in the plane of view in dependence on the voxel size $R$.

In the present study, MRI signal voids were anticipated to comprise the aggregation of labelled cells as well as the signal dephasing region around those aggregations. The effects of sequence parameters including echo time, voxel size and plane-of-view orientation on the geometry and the extension of this dephasing region were verified quantitatively. Based on numerical simulations, it is anticipated that longer TE might prevent a clear localization of labelled cells in the MR image. The results imply that in static signal dephasing MRI at TE > 20 ms a particular cell aggregation may be visible in the MR image as an image signal void enlarged by a factor of approximately 1.5 compared to the real size of the cell cluster.

In order to benefit from high spatial accuracy to detect aggregations of labelled cells, TE as short as possible and high spatial resolution (i.e., small voxel size) are preferable. Very short TE can be achieved using advanced MR scanners, which usually offer fast 3D gradient echo sequences with TE of less than 2–3 ms (Schick 2005). Limitations in minimizing the voxel size definitely arise from the respective reduction in signal-to-noise ratio (SNR). However, gradient coil inserts (Graf et al 2003, Heyn et al 2006) or dedicated animal scanners that are operated at high magnetic field strengths (Stroh et al 2005) allow us to achieve spatial resolutions of less than 100 $\mu$m combined with excellent SNR.

A plane of view with an angle around 54° (the ‘magic angle’) to the external $B_0$ field has no additional magnetic field inhomogeneity and signal dephasing effects along one direction. This property is advantageous for the detection of cell clusters with high spatial accuracy, since the image signal void directly reflects the size of the cellular aggregation in that case. The physical diameter of the cell cluster was denoted by $D_0$ in the present paper.

4.2. Relevance for sensitivity in MR cellular imaging

The increase in the image signal void with echo time and voxel size may allow the detection of even lower concentrations of labelled cells. In order to benefit from high MR sensitivity to detect aggregations of labelled cells, appropriate $T_2^*$-weighted pulse sequences with sufficiently long TE should be applied. Gradient echo sequences provide superior sensitivity to the SPIO-induced magnetic field perturbations as compared to spin echo approaches (Yablonskiy and Haacke 1994, Bowen et al 2002). Results of the present numerical simulations show that the diameter of the signal void approximately doubles if TE increases from 5 ms to 60 ms. It is of crucial importance that the relative enhancement of the signal void with TE is independent of magnetization. It is anticipated that this effect is even independent of the cell concentration under experimental conditions.
Furthermore, extension and geometry of the image signal void were found to depend on the orientation of the plane of view with respect to $\vec{B}_0$. Applying sagittal or coronal slice orientations containing the axis of the $\vec{B}_0$ field, the observable signal void should resemble the characteristic magnetic dipole field pattern. It is anticipated that for transverse slices perpendicular to $\vec{B}_0$ the induced signal void will show circular geometries as depicted in figure 3.

4.3. Relevance for cell quantification

As has been discussed above, the signal void increases with local magnetization, which was considered the physical quantity of choice to study concentration effects of magnetically labelled cells. Evaluating experimental data, this dependency has been reported to obey an empirical logarithmic function (Pintaske et al. 2005). In the current study, this concept could be confirmed numerically.

The effectiveness of stem cell migration can be assessed by quantifying labelled cells. The demonstrated concentration dependency of the diameter of signal void represents a potential calibration standard for the quantitative assessment of labelled cells and possibly the iron load per cell in vitro and even in vivo. In order to optimize pulse sequences as well as sequence parameters appropriate tissue models might be derived, on the basis of the proposed quantification. It is anticipated that a certain concentration of labelled cells causes comparable signal voids under both in vitro and in vivo conditions, since the physical principles describing signal dephasing are identical. Thus, investigating the dependency of the signal void on cell concentration in vitro may allow quantification of aggregations of labelled cells in vivo. It should be stressed that those calibrations must be separately performed for each sequence and each set of sequence parameters that are being used for the measurement of the SPIO-induced signal void.

4.4. Limitations of the numerical model

It is worthwhile reviewing the limitations resulting from the assumptions and approximations upon which the numerical model is based. First, signal dephasing in the vicinity of spherical aggregations of SPIO-labelled cells was studied. For the calculation of the magnetic field inhomogeneities, the magnetic dipole approach was used. For spherical or spherical-like aggregations of magnetically labelled cells, this assumption should be valid. For arbitrarily shaped cell aggregations, however, the validity of this assumption is less certain because the actual magnetic field distribution close to the cell cluster depends on its shape and the distribution of SPIO-loaded cells.

In addition to spherical aggregations of labelled cells, cells can aggregate arbitrarily. Several studies have shown that cells loaded with SPIO compared to unlabelled cells had similar viability and proliferation profiles and also maintained their differentiation capacity (Himes et al. 2004). One may suppose that the in vivo distribution of labelled cells is determined by the tissue structure, in which cells have been transplanted or to which cells have migrated. In contrast to spherical cell aggregations, no analytical description of the magnetic field perturbation is available in the case of arbitrarily shaped cell cluster. Studying those geometries was beyond the scope of the present study.

Second, aggregations of labelled cells induce intense magnetic field gradients over fairly large distances. A linear field gradient over the imaging voxel was assumed since the voxel size is usually small as compared to the extension of the field distortion. Third, the MR imaging voxels were approximated to be isotropic.
Fourth, a phase dispersion criterion \( \delta \phi \geq 2\pi \) parallel to one side of an isotropic imaging voxel was used as the criterion to compute the image signal void. Under experimental conditions, however, considerable signal loss may occur before this numerical criterion is fulfilled. This introduces measurement uncertainties in the experimental determination of the extension and in the delineation of the signal voids, and thus represents another limitation in the comparison of numerical results and MR measurements.

Finally, water diffusion effects were neglected in the numerical model. Given the size of the aggregation and the intense magnetic field inhomogeneities caused by thousands to millions of labelled cells, solvent spins move so slowly that they appear to be stationary, meaning that diffusion has practically no effect on signal dephasing. Thus, considering this static dephasing regime a relationship between field distortion and MRI signal dephasing could be found.

Studies indicated that for magnetic objects above some critical size, diffusion effects quickly become less important. In those cases, signal dephasing and relaxation is dominated by the magnetic field inhomogeneity effects. In fact, in microscopic MR images of magnetite particles (average size 3.5 \( \mu m \)), Lauterbur et al (1986) observed the characteristic dipole field. The magnetic dipole pattern was also observed for aggregations of cells labelled with SPIO nanoparticles (Cunningham et al 2005, Pintaske et al 2005), indicating that the criterion of motion averaging, due to diffusion, fails. Thus, for magnetically labelled cells considered in this work, signal dephasing is dominated by their magnetic field inhomogeneity effects and for aggregations of labelled cells it is reasonable to neglect spin diffusion in the numerical simulations (Bowen et al 2002).

5. Conclusions

The present study contributes to the understanding of the geometry as well as the extension of signal voids in static signal dephasing MRI induced by spherical aggregations of magnetically labelled cells. In order to study the physical characteristics of these signal voids, basic sequence parameters such as echo time, voxel size and plane-of-view orientation have been varied over a wide range. The results are considered to be of paramount importance in optimizing MR sequence parameters with regard to spatial accuracy and sensitivity to detect clusters of labelled cells in vitro or even in vivo. Knowing the effect of the local magnetization on the extension of signal voids will be crucial in assessing numbers of labelled cells experimentally. The findings reported herein are anticipated to be transferable to each type of cell, since the physical principles describing signal dephasing are indifferent to cell type as long as the cell label is superparamagnetic.

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