# Comparison of positive contrast MRI methods for depiction of field disturbing objects/paramagnetic contrast agents

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## Abstract

Local field inhomogeneities, that extend over areas larger than one voxel size, change the applied imaging gradient and result in an echo shift in the readout direction and phase encoding direction. In this article, the field inhomogeneities that are caused by the presence of (super)paramagnetic (SPIO) particles in the human body are discussed. The presence of these particles eventually causes signal loss. Positive contrast methods are an attempt to invert the dark contrast of the field perturbing structures. Two categories of positive contrast techniques are presented: preprocessing and postprocessing methods. Among the acquisition methods the white marker techniques and the inversion recovery with on-resonance water suppression (IRON) techniques will be treated. White marker conserves signal from regions with field inhomogeneities while the background is cancelled. IRON method suppresses the water protons which frequency is in the range of the saturation radio frequency (RF) pulse. On the other hand, susceptibility gradient mapping (SGM) is a postprocessing technique in which the positions of the echo shifts in k-space are calculated to determine the susceptibility induced gradient. For comparison the white marker and IRON technique can be simulated by postprocessing. The choice for a positive contrast technique depends on the application. It is a trade-off between the advantages and disadvantages of each technique. However, postprocessing techniques are more promising for future research.

## 1 Introduction

Today, MRI is an important imaging modality. However, it still has several limitations. One of these limitations is its sensitivity to (local) field inhomogeneities. These field inhomogeneities will eventually cause signal loss [10]. The main goal of this article is to review different positive contrast methods: methods that obtain signal from regions where local field inhomogeneities occur, while suppressing the background. Here, the background is defined as the regions with no (super)paramagnetic particles that surround the region that contains these particles. The focus of this article will be on field inhomogeneities caused by the presence of (super)paramagnetic particles.

First, the effects of field inhomogeneities and sources of (super)paramagnetic particles will be considered. Second, the positive contrast methods will be treated. The acquisition methods will be discussed first: White marker/gradient echo acquisition for superparamagnetic particles (GRASP) ([1]-[4]) and the inversion recovery with on-resonance water suppression (IRON) ([5]-[8]). Next are the postprocessing methods: Susceptibility gradient mapping (SGM) ([9]-[15]) and simulated white marker and IRON [16]. In the last two chapters, these techniques will be compared and discussed to finally draw a conclusion.

## 2 Field inhomogeneities in MRI

### 2.1 Effects of field inhomogeneities

A difference in the magnetic susceptibility between two substances will result in local field inhomogeneities [1]. These inhomogeneities, that extend over areas larger than the voxel size, change the applied imaging gradient and cause spin dephasing, due to the increased $T_2^*$ decay, and thus signal loss [9]. The influence of these field inhomogeneities depends on the direction in which the field inho-

mogeneities occur. Inhomogeneities in the read direction lead to image distortion and echo shift effects [10]. The first effect is caused by the incorrect frequency encoding which leads to an error in the positioning of a spin subset and so a local image distortion ([10], [13]). The echo shift effect happens because the occurred echo time (TE) is shifted away from the designed TE [9]. This will induce a phase shift of

$$\Delta\phi = 2\pi\frac{\Delta TE}{TS} \tag{1}$$

where TS is the total sampling time. This phase shift will accumulate and eventually result in a severe signal loss [10]. This echo shift also occurs in the phase encoding direction when applying a phase encoding gradient ([10], [13]). Another problem in phase encoding direction is the shearing effect; the shift of information from one voxel to the next ([10], [13]). Similar effects are observed in the slice selection direction, where slice dephasing and local slice distortion occur [10]. The dephasing will result in signal loss.

### 2.2 (Super)paramagnetic particles

Today, superparamagnetic iron oxide (SPIO) particles are used as a contrast agent for different purposes ([6], [7], [17]). Imaging with a contrast agent is preferred and often performed because of the ability of this contrast agent to reduce $T_1$ and $T_2$ ([3], [7]). The difference between paramagnetic and superparamagnetic particles is that, when applying an external magnetic field, a superparamagnetic substance will lead to a higher magnetic moment and susceptibility than a paramagnetic substance [7]. In [6], Bulte and Kraitchman reviewed the use of SPIO for molecular and cellular imaging. The molecular and cellular imaging is possible because of the fact that SPIO particles are able to attach to specific cells. Labelling these cells or molecules allows visualization and tracking of the cells. [3]. This could help in early detection of different diseases or for organ specific imaging [3]. The choice for SPIO based contrast agents is based on different properties. For example, a SPIO contrast agent provides a significant change in the signal; is composed of biodegradable iron and therefore biocompatible (unlike the contrast agent gadolinium chelates); and can be magnetically manipulated ([6], [18]). SPIO particles bind straightforward to functional groups and ligands [6] and causes local field disturbances that extend 10-100 times their diameter causing the spins to dephase ([12], [18]). The amount of dephasing depends on different factors, e.g. particle size, the concentration of the particles in the tissue and particle composition [7].

Another source of SPIO particles is the use of paramagnetic rings to visualize endovascular devices. Visualising and tracking these devices is achieved by using the contrast between the endovascular device and blood by locally attenuate or enhance the signal [2]. A signal enhancement can be reached by coating the device with paramagnetic rings that serve as markers [1]. These paramagnetic markers will affect the imaging.

### 2.3 Other sources of field inhomogeneities

There are other causes for field inhomogeneities in addition to the presence of iron particles. For example, there are field inhomogeneities that are caused by the difference in the susceptibility between two tissues (for example tissue-air interface), pathologically misplaced hemoglobin concentration [10] or by deoxyhemoglobin blood in small vessels [18]. The amount of these inhomogeneities depends on the field strength ([10], [13]). The ability to distinguish between the different sources of signal voids is a major challenge for positive contrast techniques. This will be discussed in more details in the next chapters.

## 3 Acquisition techniques to generate positive contrast

The loss of signal due to dephasing results in black spots which lead to the loss of the anatomical information in the image [18]. Furthermore, it is not a trivial problem to discriminate between the targeted cells and regions that are affected by other field inhomogeneities ([5], [6]). Developing an imaging sequence that deals with these problems will make it possible to benefit from this artifact. It will be possible to trace and map different cell movements into and out of tissue and to study different inflammatory processes [9]. It is also a non-invasive and repeatable imaging method. SPIO contrast agents were employed as negative contrast agent. However, this results in poor contrast between the target region and the background [3], in addition to the fact that is not possible to distinguish between this regions from other signal voids in the image. An alternative method is to

implement positive contrast techniques to visualise SPIO labeled cells.

### 3.1 White marker phenomenon and GRASP

The presence of SPIO particles will produce local field inhomogeneities within voxels, as was mentioned above. Outside these voxels, these inhomogeneities, $B_{sus}$, are described in terms of the magnetic field strength, the difference in magnetic susceptibility and position [1]. The derivative of $B_{sus}$ is the local susceptibility gradient: a gradient that is created by the local field inhomogeneities which are induced by the paramagnetic particles [1]

$$G_{sus,x}(x,y,z) = -3\frac{B_0 \Delta\chi V}{4\pi} x \frac{x^2+y^2-4z^2}{(x^2+y^2+z^2)^{7/2}} \quad (2)$$

where $B_0$ is the magnetic field strength, $\Delta\chi$ is the susceptibility difference, V is the volume while x, y and z are the spatial positions. Equation (2) presents an expression for the susceptibility induced gradient in the x direction [1]. It is possible to derive these gradients in the other directions.

The new approach, *White marker phenomenon*, that is proposed by Seppenwoolde et al., is based on the idea that suppressing the background, by adding a background gradient, will invert the contrast [1]. It is called the white marker phenomenon because this method succeeds in visualising the paramagnetic markers of endovascular devices, using a gradient echo (GRE) imaging sequence. The signal from the background will be cancelled while the signal from the (super)paramagnetic particles is maintained. The background gradient will create a gradient imbalance, thereby the accumulated phase is changed and the spins will not be fully rephased at TE ([1], [3], [17]). In other words, these spins will have a non-zero phase at TE. This non-zero phase leads to a decreased signal from the background. Adding a positive background gradient in the slice selection direction is eventually similar to reducing the negative rephasing lobe in this direction [1]. In this way, it will not cost extra scan time. The reduction of the slice selection gradient will be cancelled (at a certain point TE') in the regions with the markers by the extra local susceptibility gradient due to the field disturbers. This gradient will compensate for the reduction of the slice selection gradient ([1], [3], [17]). The gradient balance is restored in this region and the spins are fully rephased at TE' [1]. Figure 1 illustrates this sequence.

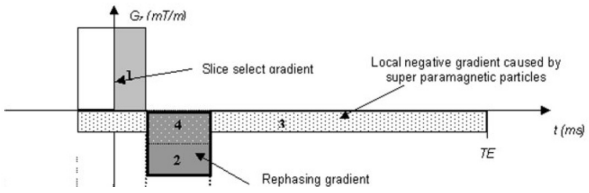


Figure 1: Slice selection gradient (area 2) is responsible for rephasing the spins at TE. Reducing this gradient to area 4 will result in non-fully rephasing of these spins. Susceptibility induced gradient (area 3) will compensate for this reduction in regions where field inhomogeneities occur

In other words: cancelling the dephasing of the regions with paramagnetic particles will result in a positive signal while the background is suppressed. Therefore, factors that generally affect the dephasing process are important for this technique. The most relevant factors are the slice selection thickness (d), TE and the background gradient ($G_{BG,z}$) [1]:

$$S(x,y) = \frac{1}{d}\int_{-d/2}^{d/2} \rho(x,\, y,\, z) \times exp(-i\,\phi)\, dz \quad (3)$$

where $S(x,y)$ is the signal and:

$$\phi = \gamma(B_{sus,\,z}\, TE + G_{BG,\,z}\, \tau_{BG}\, z) \quad (4)$$

where $\tau_{BG}$ is the duration of the background gradient in de z direction ($G_{BG,z}$) and $B_{sus,z}$ is the field inhomogeneities in the z direction.

Similar to White Marker is GRASP for imaging SPIO labeled cells instead of paramagnetic markers ([3], [18], [19]). GRASP verified the results of applying white marker approach for SPIO labeled cells in [3]. Furthermore, this study confirms the dependence of the results on the mentioned factors earlier in addition to the iron oxide concentration. The optimal settings are low field strength (1.5T) [3], small background gradient strength ([1], [3]) and low iron oxide concentration that is localized, e.g. relatively small tumours ([3], [17], [18]). GRASP could be used for tumour screening and cell tracking, for example.

*Advantages and limitations* The white marker phenomenon succeeds in localizing the paramagnetic markers and GRASP in visualising the iron labeled cells, without a dramatic adaptation of the acquisition sequence ([1], [3], [17]). These techniques are robust, intuitive, fast and could be applied for different settings and with different imaging sequences ([1], [3], [19]). In addition to these

advantages, white marker and GRASP are highly sensitive to the presence of SPIO particles, even to low iron concentration ([17], [19]).

However, there are many limitations for this approach. First, white marker would only be useful for cases where the iron oxide uptake was limited, due to the $R_2^*$ effects ([3], [17]). The approach doesn't correct for signal loss caused by motion and is not applicable for thick slices ([3], [1]). A simple solution will be to use thinner slices [1]. The price for this solution is longer scan time and decreased SNR.

Secondly, there are many parameters involved which determines the results of this approach. The most important factors for this approach are TE, $R_2^*$ effects, slice thickness, background gradient strength, iron oxide concentration, voxel size, field strength and SNR ([1], [3], [18]). Generally, CNR decreases for higher field strength, large $R_2^*$ values and long TE [3]. To optimize TE, it is important to consider the SPIO concentration. For example, short TE results in the highest CNR if the iron concentration is high. On the other hand, long TE provides the highest signal if the iron concentration is low [3]. This dependency on the SPIO concentration is related to the $R_2^*$ effects, which increases for higher SPIO concentrations. Furthermore, small voxels provide the highest CNR values for low SPIO concentration, while the highest CNR is provided by large voxels if the iron concentration is high [3]. Finally, applying small background gradients results in the best performance of white marker/GRASP ([1], [3]).

There is no linear relationship between CNR and field inhomogeneities or background gradient at higher field strength [3]. Simultaneously, all these factors are affected by the TE value [3]. The sensitivity of this approach decreases for higher field strength while the effect of $R_2^*$ on the signal increases [3]. In addition to that, all the limitations of GRE sequence play also a role for this approach, since this approach is based on a modified GRE sequence, e.g. the increase of amount of field inhomogeneities for higher field strength which leads to decreased CNR [3]. Another problem with this approach is that cancelling the background signal also means cancelling the anatomical information from the image ([1], [18]). Overlay techniques, with conventional GRE or spin echo (SE) MRI, could solve this problem ([1], [18]). Besides, this method merely corrects for susceptibility induced field inhomogeneities along slice selection direction ([9], [17], [18]), which is only one of the directions in which field inhomogeneities occur. Furthermore, this approach requires special pulse sequence: a modified GRE sequence that does not result in conventional MRI images [18].

The major disadvantage of this technique is that it is necessary to have prior knowledge about the local field inhomogeneities caused by the (super)paramagnetic particles [9]. Otherwise it is not possible to determine the background gradient strength. Finally, it has been shown in [17] that the white marker phenomenon technique performs less efficient and provides less positive contrast than other positive contrast methods that will be discussed later. Finally, the major challenge of positive contrast techniques (inability to distinguish between the different signal voids) is still not solved by this approach [17].

## 3.2 Saturation/excitation of the on/off-resonance water protons

Stuber and his colleagues in [5] introduced another approach to obtain positive contrast of SPIO labeled cells to the background, the so called *inversion recovery with ON-resonant water suppression* (IRON) methodology. This approach allows imaging of the regions with SPIO particles. This is achieved by adding a spectrally selective on-resonance radio frequency (RF) saturation prepulse with a limited bandwidth [5]. This pulse contains a specific range of frequencies (see figure 2). The protons from the background, where no field inhomogeneities are present, oscillate on-resonance with the Larmor frequency $\omega_0$: the on-resonance protons. While the protons from regions where field inhomogeneities occur will have a different frequency, which means that they will oscillate at a different frequency: the off-resonance protons. The off-resonance frequency $\Delta\omega$ depends on the amount of field inhomogeneities $\Delta$B:

$$\Delta\omega = \gamma \Delta B \tag{5}$$

The saturation prepulse saturates the on-resonance water protons [5]. The off-resonance protons (see figure 2) are not affected by this pulse [5], which means that these protons will provide the signal, while the on-resonance spins are suppressed.

The off-resonance protons are not affected by the saturation pulse because their frequency does not match the pulse bandwidth (see figure 3).

The off-resonance protons are from regions where field inhomogeneities occur. The bandwidth of the pulse will determine the size of area to which this pulse will be applied and the flip angle $\alpha$ of this

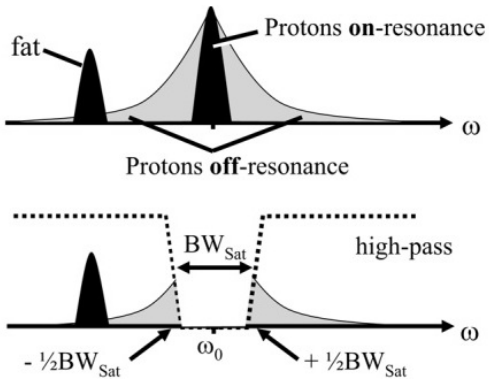


Figure 2: A selective RF pulse will eliminate the on-resonance protons.

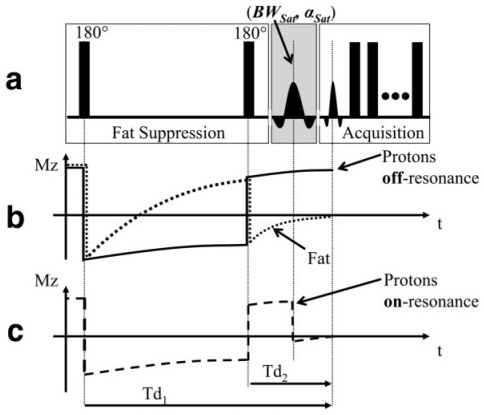


Figure 3: The principle of IRON. a: the acquisition sequence with the suppression pulse. b: the longitudinal magnetization of fat and off-resonance protons. The fat is nulled due to the dual 180 RF pulse, while off-resonance protons are not affected by the suppression pulse. c: the longitudinal magnetization of on-resonance protons. After the application of the suppression pulse, the longitudinal magnetization of these protons is zero.

pulse will determine the amount of background suppression [5]. This is comparable with slice-selective excitation [8], where the bandwidth of the RF pulse determines the slice/set of spins that will be excited. This approach is applicable for both GRE and fast SE imaging sequences. It is also possible to combine this with a fat suppression prepulse [5] (see figure 3).

The opposite technique, but similar idea, is to excite and refocus the off-resonance water protons at a specific frequency using a spectrally selective RF pulse (EROR) [8]. For this method to succeed it is important to apply an RF pulse with the right bandwidth and center-frequency to minimize the off-resonance frequency shift [8], so that the protons will oscillate on-resonance. Minimizing the off-resonance frequency shift will excite the largest volume of off-resonance protons. Therefore, the bandwidth, the center-frequency shift and TE are the most important parameters that affect the results for IRON and EROR [8].

*Advantages and limitations* The IRON and EROR methods succeed in visualising the SPIO labeled cells while background (and fat) is (are) highly suppressed ([5], [19]). The amount of this signal is determined by the bandwidth of the spectrally selective RF pulse ([5], [8]). This technique can be employed for different efficient imaging sequences, without modifying the imaging part of the sequence [5]. This makes this technique applicable for 2D and 3D fast imaging [5]. Furthermore, IRON/EROR allows flexible selection of the area that has to be suppressed/excited [19].

The first obvious disadvantage of this approach is that determining the bandwidth and the flip angle of the saturation/excitation pulse is not straightforward. Similar to the white marker phenomenon, these approaches require prior knowledge about the amount of the field inhomogeneities in order to determine the frequency shifts and the bandwidth of the pulse [9]. It will require additional steps in advance to adjust these parameters. This will be more complicated if the region is also affected by other sources of susceptibility induced gradients or by chemical shift [19].

Another drawback of IRON/EROR is that it is sensitive to other sources of field inhomogeneities ([5], [9], [18]). Furthermore, the signal and amount of background suppression depend on the imaging sequence and on the bandwidth of the suppression/excitation pulse [5]. Increasing the bandwidth of the saturation pulse results in higher signal from these regions, but also in a worse background suppression ([8], [17]). In addition to that, the techniques provide an insufficient amount of anatomical information ([17], [18]). IRON and EROR perform less efficient than other positive contrast methods, including the white marker method ([17], [18]). This is the case for detection of high concentration SPIO labeled cells, where the off resonance frequency is large due to the large amount of field inhomogeneties that are caused by the large $R_2^*$ value ([17], [18]). Finally, the volume of the positive signal from the off-resonance protons correlates with the concentration of SPIO labeled cells which means that the amount of labeled-cells is derivable from the results. However, this signal also depends

on the spatial distribution and the local concentration of these cells ([5], [8]). These two factors are difficult to determine, which means that it is still difficult to quantify the volume of these cells ([5], [8]).

# 4 post-processing techniques to generate positive contrast

## 4.1 Susceptibility gradient mapping (SGM)

This method addresses the same problem as the previous section. Instead of creating a special imaging sequence, this approach is a postprocessing step that only requires the complex image data from a GRE imaging sequence ([9], [18]). As discussed in section 2.1, each field inhomogeneity results in a echo shift in k-space. Earlier the capability of highlighting parts of the image that are affected by the echo shifts by using a reconstruction window that is applied on the full k-space, was also shown [9]. The problem with this approach, is that it requires a larger k-space and heuristic determination for this reconstruction function to perform well [9].

Another method to avoid signal loss along slice selection direction that is caused by the field inhomogeneities, is to apply higher resolution and 3D imaging sequence with thinner slices [10]. However, this leads to longer scan time and decreased SNR. Signal loss could be reduced by using a low pass filter [10]. This means that the filtering is local, in contrast to the previous approach [9].

The signal of a $T_2^*$ weighted image along the readout direction depends on $B_0$ inhomogeneities and susceptibility induced gradients [9]. An additional position-dependent phase will be induced in regions that are affected by the susceptibility gradients [9] (see equation (1)). The echo will then occur at a specific moment TE', as was explained in section 2.1. TE' will depend on the susceptibility induced gradients and on the original TE [9]:

$$TE' = \frac{G_{sus,x} \cdot TE}{G_{imaging,x} + G_{sus,x}} \tag{6}$$

where $G_{imaging,x}$ is the imaging gradient in the x direction and TE' the shifted echo time. The echo shift $\delta$ is then:

$$\delta = \frac{TE'}{\tau_x} \tag{7}$$

where $\tau_x$ is sampling time. It was mentioned that it is possible to highlight the parts of the image that are affected by the echo shift, by using a reconstruction window. For this purpose, a 1D short-term Fourier transform (STFT) (see figure 4) is used ([9], [13]).

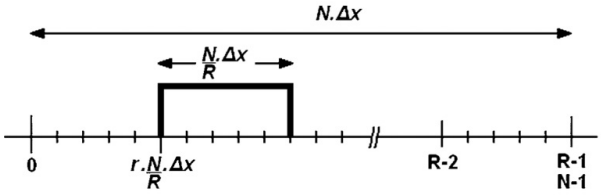


Figure 4: N is the number of pixels of the Fourier component and R is the number of regions for STFT. $N/R \cdot \Delta x$ is the size of the window function ($\zeta$) while $r \cdot \zeta$ is the selected position in the region [9].

This 1D STFT can be applied to the data in x, y and z-direction [9]. The k-space could be considered as a sum over locally shifted STFT [9]. Fortunately, this convolution will not affect the position of the maximum of the echo shift in k-space [9]. This position allows determining the echo shift ([9], [16]). This means that it is possible to calculate the direction and the absolute magnitude of the susceptibility induced gradient for each position in the image, since the echo shifts are caused by these gradients ([9], [13], [17]). The data of magnitude of the susceptibility induced gradient represents the positive contrast image ([9], [16], [17]). This method is called susceptibility gradient mapping (SGM). In this image, the background is suppressed, because this part doesn't contain echo shift information. No echo shift corresponds to a maximum [13]. The upper limit of this approach is obviously when the echo shift is larger than the k-space itself [9].

Crucial parameters for this technique are TE, SPIO concentration and the size or length of the window function (STFT) ([13], [16]). For low SPIO concentration, long TE is required to obtain optimal CNR values, however, large TE is not realistic for in vivo imaging [16]. While short TE is optimal for high PSIO concentrations to obtain high CNR values [16]. Therefore, it is necessary to consider the SPIO concentration to obtain the optimal TE. Another important parameter is the number of voxels, N, of each STFT window component ([9], [16]). Increasing N results in better accuracy to calculate the echo shifts, however, CNR drops due to averaging effects and the influence of the partial volume effects ([9], [16]). These partial volume effects arise

if the susceptibility induced gradient extends over less voxels than N [16]. The partial volume effects have to be minimized to obtain an optimal fit of the echo shift [9].

*Advantages and limitations* Regions with SPIO-labeled cells were well visualised using SGM [9]. An advantage of this approach is that a positive contrast image can be calculated without a special imaging sequence and without extra scan time. Simultaneously, the anatomical information is provided with the same sequence [17]. Two studies showed that the results from SGM are often better than the results obtained with the preprocessing techniques ([16] - [17]). Finally, SGM can be applied in any direction, which means that it is possible to calculate 2D and 3D SGM images [9].

SGM has a few drawbacks too. First, the resolution of an SGM image is lower than the resolution of the original conventional MRI image [9]. Second, two important assumptions are made that could be not true and affect the results. The first important assumption is that the susceptibility induced gradients will contribute linearly to field inhomogeneities. The shifts that occur due to non-linear contribution of these gradients are not taken into account in this approach [9]. This could result in an underestimation of the magnitude of these gradients. The other assumption is that the field inhomogeneities are large enough to be observed with STFT [9]. Otherwise, it would be difficult to derive the echo shift from the k-space: the main echo, which is not shifted, will overlap the small one [9]. This means that SGM is only sensitive to strong field inhomogeneities. At the same time, the shift may not be too large, because the position of the maximum still has to be near $k_0$ [9]. Furthermore, a gradient should be spread over several voxels to be detectable by SGM [9].

Finally, this technique should allow to distinguish between the different sources of signal voids in all spatial directions [9]. However, this has not been confirmed in other studies. In fact, the high sensitivity of SGM to other sources of field inhomogeneities has been reported in several studies ([16], [17]). These different field inhomogeneities could be displayed by applying 1D SGM, if these inhomogeneities occur in different directions [17]. This approach will fail for field inhomogeneities that have the same direction, even if they have different causes.

### 4.2 White marker

White marker technique displays the field inhomogeneities in the slice selection direction. Therefore, applying 1D STFT over small slices in the slice selection direction can simulate this technique in postprocessing ([13], [16]). The difference with SGM is that SGM is about determining the positions of the echo shifts in k-space, while white marker postprocessing technique only highlights the response of the STFT to the field inhomogeneities [16]. The results from [16] shows that this technique has a low sensitivity rate and performs worse than SGM but it succeeds better than the preprocessing white marker in cancelling out other sources of field inhomogeneities. However, this is a strange result given that SGM and simulated white marker are similar: they are both based on their response to STFT.

### 4.3 IRON

The IRON technique is about the saturation of the on-resonance protons by applying a specific frequency range to detect (super)paramagnetic particles. This technique can also be simulated in postprocessing by calculating the response of the protons to a (virtual) RF prepulse [16]. This is achieved by first applying the fast FT to the complex data (with different TEs), which will result in a frequency map with information about the frequency distribution [16]. From this frequency map, it is possible to determine the amplitude, the phase and afterwards the frequency of the virtual echo [16]. Then, it is possible to simulate the response of the data to a saturation RF prepulse [16]. The bandwidth and the center-frequency have to be optimized. Postprocessing IRON method provides better results than the preprocessing IRON technique for small SPIO concentrations but have similar results for larger concentrations [16]. The background is better suppressed, which results in better CNR [16]. However, there is still room for improvement for the filter that is used to simulate the frequency response to the RF pulse and the technique is still sensitive to other sources of signal voids [16].

## 5 Discussion

Previous work comparing the positive contrast methods showed that the best performance is obtained with the SGM method. In this section, sev-

eral aspects of these techniques: CNR, speed, resolution and sensitivity will be discussed.

## 5.1 CNR and sensitivity

White marker phenomenon/GRASP have the advantage of being highly sensitive, even to low iron concentration, if this concentration is localized; e.g. small tumours. These techniques could be used to localize the position of iron labeled cells or a device, but not to quantify the cell population. Higher field strength are not desirable for this technique.

IRON has comparable results with the white marker for small and medium SPIO concentrations if the background tissue is homogeneous [17]. This provides images with high CNR. In the case of an inhomogeneous background, IRON performs worse than white marker [17]. It even fails for large SPIO concentrations. Another important difference between IRON and white marker method is that white marker only highlights the susceptibility induced gradients in the slice selection direction, while IRON works in different directions. This also means that it is not possible to create 3D images with white marker, unlike IRON and SGM. A way to deal with this problem, is to apply the white marker technique three times while changing the orientations of the image each time. The results can then be combined.

Another advantage of IRON is that IRON could be applied with all kind of acquisition sequences, even with a fat nulling prepulse. While the white marker technique is only usable for an GRE imaging sequences. IRON could be used to derive the SPIO concentration, but this is not easy because of the complex relationships between the different parameters. The sensitivity of IRON to field strength is not reported in the literature. However, it is known that SE sequences are less sensitive to $B_0$ inhomogeneities than GRE for higher field strength. This means that IRON performs well at higher field strength.

SGM generate more positive voxels than white marker and IRON and thereby better CNR [17]. However, it is not verified that this positive signal is caused by the presence of the SPIO particles and not by other effects, especially because SGM is more sensitive to other sources of signal voids than white marker. This claimed advantage of SGM vanishes for larger tumours: white marker performs then as well as SGM. Quantification with SGM will be more difficult than with white marker for large and medium SPIO concentrations, due to its high sensitivity to the different field inhomogeneities. Furthermore, SGM is insensitive to small field inhomogeneities, which limits the detection range of this technique. Due to its high sensitivity, white marker might be expected to show positive signal for the small field inhomogeneities.

The disability of SGM to distinguish between the different sources of field inhomogeneities, could be solved by considering the direction of the susceptibility induced gradients. It is possible that considering the vector of this gradient instead of only its magnitude, will result in discriminating regions with similar properties: these regions would be the regions that are affected by the same field inhomogeneities. This is due to the fact that a subset of spins that is affected by the same cause of field inhomogeneity, will dephase (almost) similarly. This approach is expected to fail for regions that contain different sources of field inhomogeneities. This disability is (partly) shared by the white marker and IRON techniques. The white marker is more insensitive, compared to SGM, to the field inhomogeneities that are larger or smaller than the field inhomogeneities caused by the SPIO particles, because a smaller or larger susceptibility induced gradient will not compensate for the background gradient in the same way as the susceptibility induced gradient that is caused by the SPIO particles. IRON saturates the on-resonance protons, which means that all the off-resonance protons contribute to the signal. IRON is not able to distinguish between the different off-resonance protons. Its opposite technique, EROR, will succeed better in eliminating other field inhomogeneities, because this method refocuses off-resonance protons with a specific off-resonance frequency. Only protons with frequency in that range, will provide the signal. This will be often protons that are affected by the same field inhomogeneities.

SGM has been considered to provide more positive voxels than white marker and IRON [17]. This, however, was determined by considering the voxels with intensities higher than three times the standard deviation, positive. This will influence the results of the techniques in different ways. The background of an SGM image is more suppressed than the background of a white marker image. The background of a white marker or an IRON image mostly provides a signal, because the suppression is never perfect. While the background of an SGM image is zero if no echo shift occurs. It is possible that due to this choice, white marker and IRON perform worse in this study.

### 5.2 Speed and resolution

White Marker and GRASP are modified GRE sequences. While IRON can be applied with GRE or with fast SE. However, GRE performs worse at higher field strength due to the increased amount of $B_0$ inhomogeneities. These both sequences guarantee fast imaging. Postprocessing techniques should be applicable for fast imaging. Therefore it is important to have fast SGM implementation. However, in the literature it was not mentioned what the computation time was of SGM. Vonken et al. mentioned in [13] that the computation complexity was reduced, but no actual numbers were reported. So it's not possible to evaluate this aspect. However, due to the complexity of this approach, it is possible that the method needs powerful hardware and long calculation time.

In addition to the long calculation time, SGM images have lower resolution than conventional MRI images [9]. Comments on the resolution of White Marker and IRON were not reported, however they uses adapted conventional imaging sequences. This will not result in a change in the resolution, which means that IRON and white marker provide images with better resolution compared to SGM.

### 5.3 Other artifacts

Two of the most important artifacts in MRI are the partial volume effects and motion artifacts. The White marker phenomenon solves the partial volume effects by subtracting two images with opposite echo shifts [4]. Due to the symmetrical nature of the partial volume effects, these effects could be easily eliminated by this subtraction. However, this is not priceless: two images means twice the acquisition time. SGM is more sensitive to partial volume effects, because they have to be minimized to be able to fit the echo shifts. Partial volume effects depend on the size of the STFT component and on the voxel size, as was mentioned in section 4.1. It is not reported in the literature how this problem is solved, neither for IRON.

The other artifact is motion. It is possible that signal loss will occur due to motion. SGM is less sensitive to motion because motion does not affect the position of the echo shift. IRON is also not sensitive to motion. However, white marker is more sensitive to motion, because it affects the readout. The approach does not correct for this artifact.

## 6 Conclusion

In general we can conclude that it is easier to differentiate field inhomogeneities with the positive contrast techniques than studying the signal voids in conventional $T_2^*$ weighted MRI ([17], [18]). Furthermore, CNR depends in particular on TE and on SPIO concentration [16]. So, in order to determine the optimal settings for each technique, it is important to experiment with these two parameters first. The drawbacks of positive contrast methods is that each technique depends on different complex parameters. Until now, they are not suitable for quantitative imaging and can't discriminate between the sources of the different signal voids. The main differences between the pre- and postprocessing methods is that preprocessing methods require prior knowledge about the field inhomogeneities and cannot provide anatomical information from a single imaging sequences, while postprocessing techniques doesn't have these disadvantages.

White marker technique is fast, simple and provides images with better resolution and its high sensitivity to the presence of iron is also advantageous. However, it is not applicable at higher field strength. SGM results in better CNR for smaller tumours and can be combined with different imaging sequences or with other detection techniques. But it has lower resolution, similar sensitivity to white marker for larger tumours and is slower than white marker. The detection range is also limited to only high field inhomogeneities, while its sensitivity to other sources of field inhomogeneities is higher than that of white marker, for example. IRON is beneficial because of its ability to be combined with other fast imaging sequences and fat nutting pulses. IRON cannot be used for larger SPIO concentrations or for high field strength, but can be used to quantify cell population if the relationship between the different parameters is known. So each technique has its advantages and drawbacks. To choose a technique, you first should know for which application it is required and what is the purpose of this application: localization, visualisation or quantification.

Nevertheless, I think that postprocessing techniques are more promising than the preprocessing methods. This is due to the fact that is possible to perform more experiments on the same data to obtain the best parameter settings, while this is not possible with the preprocessing methods. Furthermore, there are more possibilities to improve postprocessing methods than the preprocessing ones. Finally, postprocessing techniques are more flexi-

ble in their interpretations: it would be possible to explore phase information and use that instead of echo shift information, for example.

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