Selective positive contrast of subvoxel field-disturbers using off-resonance excitation

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Introduction: Positive contrast by means of selective excitation is a helpful way of visualizing objects of clinical interest, like iron-labeled cells, paramagnetic agents or labeled therapeutics. In regular gradient echo imaging, these entities cause negative contrast due to intra voxel dephasing effects which cannot be distinguished from signal voids caused by other effects, and is subjected to partial volume effects. Positive contrast can be generated by selectively exciting the off-resonance protons surrounding the paramagnetic material while suppressing the on-resonance background. This mechanism has been shown to be effective for e.g. iron-labeled cells [1] and gadolinium containing structures [2,3]. However, in these cases, contrast was based on macroscopic effects from relatively large clusters of paramagnetic particles occupying several voxels. In this work we will show that the same mechanism is also effective on a microscopic scale, i.e. we will show that it is feasible to selectively obtain signal from protons that reside in the vicinity of Holmium-166 loaded microspheres, used for internal radiation therapy [4].

Theory: The presence of HoMS gives rises to a distribution of dipole fields inside a homogeneous object. For an individual sphere, the field is given by $B_{dipole}=\chi\cdot(R/r)^3\cdot(3\cos^2\theta-1)\cdot B_0/3$. Here, χ is the volume susceptibility of the HoMS material, R is the radius of the microsphere, and r and θ are spherical coordinates. As a result, protons surrounding the microspheres will have a Larmor frequency that depends on their position with respect to the microsphere: $f(r,\theta)=\gamma/(B_0+B_{dip}(r,\theta))/2\pi$. Applying an rf-excitation pulse with bandwidth bw and center frequency f_0 will selectively excite those protons that fulfill the criterion $f_0-bw/2 < f(r,\theta) < f_0+bw/2$. Since the number of protons in a voxel having a Larmor frequency $f(r,\theta)$ will be proportional to the number of microspheres, the excited proton fraction within a voxel will be dependent on the concentration of the microspheres in that voxel. This results in a voxel intensity that is related to the concentration HoMS. Shifting the center frequency f_0 to a positive or negative offset leads to excitation of protons in a certain shell enclosing the microspheres. In this way, by choosing the appropriate combination of bandwidth and frequency offset, positives contrast can be generated for voxels containing HoMS.

Materials and methods: Phantoms: An agarose gel series (1% by weight) containing HoMS concentrations ranging from 0 to 7.7mg/ml was made in plastic spheres (38mm diameter). $MnCl_2.4H_2O$ was added to the native gel to decrease the baseline T1. The Holmium content of the microspheres was 18.6% by weight resulting in a volume susceptibility of the microspheres of 880ppm (SI units) [5]. Experiments: 2D spin echo projection measurements were performed on a clinical 1.5 T clinical scanner (Phillips Healthcare, Best, The Netherlands) using an rf-excitation bandwidth of 1050Hz without slice selection gradients and various values of center frequency f_0 (TR=1.5s, TE=10ms, FOV=192x192mm^2, matrix=96x96, pixel size=2x2mm^2). The center frequency of the phantom, $f_{phantom}$, was determined by the full width at half maximum (FWHM) of spectrum. Taking the frequency $f_{phantom}$ as a starting point for f_0, the excitation pulse was manually shifted with respect to f_{sample} in steps of 100Hz covering a total range of -700Hz to +700Hz. From the images, signal intensities were measured for the various concentrations of HoMS using an ROI the size of the samples. Simulations: Simulations were carried out using Matlab 7 (The Mathworks, Natick, Massachusetts). Spherical objects with radius R=15µm were placed at equidistant locations in a homogeneous 3 T B_0-field. The inter particle distance was chosen in such a way that a certain concentration of objects was homogeneously distributed over the total volume. For a box with a lattice size equal to the distance between objects and a grid resolution of 2 µm, the frequency was determined for each grid element by calculating the total B-field induced by the objects plus the main field B_0. Elements that fulfilled the criterion $f_0+f_{0\text{-shift}}-bw/2 < f(r,\theta) < f_0+f_{0\text{-shift}}+bw/2$ were counted as excited fraction of the entire box. A bandwidth bw of 1050Hz was used and the center frequency f_0 was varied between -700 and +700Hz with respect to baseline frequency $\gamma B_0/2\pi$.

Results: 2D coronal spin echo projection images of the phantoms are shown in figure 1 for three different center frequency offsets a) $f_0=f_{phantom}$, b) f_0=+700Hz, c) f_0= -700Hz). Concentrations of HoMS are indicated by the numbers near the samples. In the left image, the sample without HoMS shows the maximum signal intensity, followed by respectively 2.0, 3.9, 5.8 and 7.6 mg/ml. In the middle image, where the center frequency f_0 was shifted by +700Hz, the samples with the relatively high concentrations 5.8 and 7.6 mg/ml show high signal intensities and the sphere with 2mg/ml shows a bright area. This bright spot is likely caused by clustering of microspheres resulting in a locally high concentration. In the right image where f_0 was shifted by -700Hz, the samples containing concentrations of 2.0 and 3.9 mg/ml, show high signal intensities whereas the other spheres display a very low signal. In figure 2, the measured intensities for f_0 between -700Hz and +700Hz are plotted for each concentration HoMS. Figure 3 shows a close-up of the large f_0-shifts to show that the signal intensities for the various concentrations intersect each other, reversing the contrast between concentrations. In figure 4, results of the simulations are shown. Excited proton fractions S_0 calculated for the various concentrations are plotted as a function of frequency shift f_0. The resultant signal intensity profiles are similar to the experimental results, including asymmetric signal behavior around $f_0=f_{phantom}$. A difference is visible between simulation and experiments for the intersection point of the profiles. For the simulations, the profiles intersect one another at the same f_0-shift, while this is not the case for the experimental results.

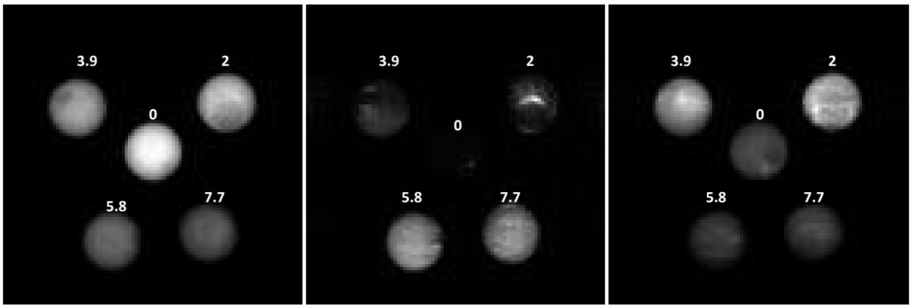

Fig 1. 2D coronal spin echo projection images (TE=10ms) of plastic spheres filled with various concentrations of HoMS. a) $f_0=f_{sample}$, b) f_0= +700Hz, c) f_0= -700Hz. Concentrations of HoMS are indicated by the numbers near the samples. 0.0mg/ml, 2.0mg/ml, 3.9mg/ml, 5.8mg/ml and 7.6mg/ml

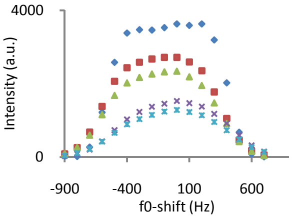

Fig 2. Intensities of the spin echo images for various concentrations of HoMS as a function of f0-shift: ◆0.0, ■2.0, ▲3.9, x5.8, ✱7.6 mg/ml

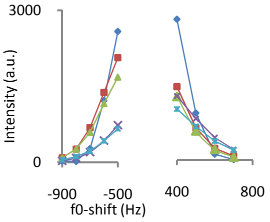

Fig 3. Intensities of the spin echo images for various concentration of HoMS for large f0-shifts: ◆0.0, ■2.0, ▲3.9, x5.8, ✱7.6 mg/ml

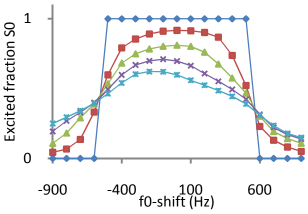

Fig 4. Excited protons fraction S_0, simulated for various concentrations of HoMS as a function of f_0-shift: ◆0, ■2, ▲4, x6, ✱8 mg/ml

Discussion and Conclusions: It was shown that is feasible to excite protons that reside in the vicinity of HoMS inside a voxel by shifting the center frequency f_0 of the rf-excitation pulse. Due to this frequency shift, on-resonance protons having a Larmor frequency close to $\gamma\cdot B_0/2\pi$ are not excited and signal is only generated by protons strongly influenced by the dipole fields invoked by the microspheres. The total signal intensity of a voxel is related to the concentration HoMS in that voxel. The asymmetric behavior for positive and negative shift can be explained by the asymmetric frequency distribution in the vicinity of a magnetic dipole [7]. The resulting positive contrast can be manipulated by the user since the number of excited protons will depend on the excitation bandwidth and profile and on the f_0 frequency shift. In addition, the measured signal will be weighted by concentration a dependent T2 decay. These aspects lead to image contrast that is not straightforward to predict as illustrated by the images in figure 1 where a f_0-shift of +700 and -700Hz do not provide the same contrast. We therefore believe that the method is proficient for qualitative purposes like depiction of the distribution of HoMS but more research needs to be done to elucidate the observations and investigate the potential of quantitative analysis.

References [1] CH Cunningham et al. *Magn Res Med* 2005; 53:999 [2] RR Edelman et al. *Magn Res Med* 2007;57:475 [3] E Vonken et al. *Magn Res Med* 2009;62:314 [4] JF Nijsen et al. *Radiology* 2004; 231:491 [5] PR Seevinck et al. *Magn Res Med* 2008;60:1466 [6] JH Seppenwoolde et al. *Phys Med Biol*;50:361