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Benchtop magnetic particle relaxometer for detection, characterization and analysis of magnetic nanoparticles

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Abstract

This paper presents the design, construction, and testing of a magnetic particle relaxometer (MPR) to assess magnetic nanoparticle response to dynamic magnetic fields while subjected to a bias field. The designed MPR can characterize magnetic particles for use as tracers in magnetic particle imaging (MPI), with the variation of an applied bias field emulating the scan of the MPI field free point. The system applies a high-frequency time-varying excitation field (up to 45 mT at 30 kHz), while slowly ramping a bias field (± 100 mT in 1 s). The time-resolved response of the sample is measured using an inductive sensing coil system, made of a pick-up coil and a rotating and translating balancing coil to finely cancel the induction feed-through from the excitation field. A post-processing algorithm is presented to extract the tracer response related to the point spread function for MPI applications, and the performance of the MPR is demonstrated using superparamagnetic iron oxide particles (ferucarbotran).

1. Introduction

Over the last decade, progress in magnetic nanoparticle synthesis and functionalization, along with the emergence of innovative applications in biology and medicine, have motivated theoretical modeling and experimental measurement of the dynamic response of magnetic nanoparticles in suspension. These emerging application areas have also catalyzed the development of new actuation and sensing equipment for the characterization of magnetic nanoparticle suspensions. The dynamic response of magnetic nanoparticles depends on their properties, the environment in which they are suspended, and the applied magnetic field. Current research is focused on understanding and optimizing these variables for biomedical imaging, diagnostic, and therapeutic applications.

The dynamic response of magnetic particles in suspension can be probed by a variety of instruments, differing mainly in the strength, the offset, and the frequency of the applied

magnetic field. AC susceptometers probe the linear response of a magnetic suspension at low applied field amplitude in frequency (Nikolo 1995, Fannin 2003), with commercial systems being available (e.g. Dynomag, Acreo). Magnetic particle spectrometers (MPS) probe the nonlinear behavior of the suspension by applying larger magnetic field amplitudes (Weaver *et al* 2008, Biederer *et al* 2009, Garraud *et al* 2017). In magnetic particle relaxometers (MPR), as presented in this paper, a bias field offsets the time-varying excitation field, and the suspension behavior is probed asymmetrically (Goodwill *et al* 2011, Tay *et al* 2016).

The MPR described herein was primarily developed to assess the performance of magnetic tracer suspensions being developed for magnetic particle imaging (MPI) by emulating the dynamic magnetic fields created by a scanning MPI system (Gleich and Weizenecker 2005, Goodwill *et al* 2012). MPI is a promising biomedical imaging technique that addresses drawbacks of nuclear imaging by using non-radioactive magnetic nanoparticle tracers, with theoretically higher resolution and faster scan times. MPI functions by magnetically stimulating the nanoparticles and then probing their dynamic magnetization response. Spatial selectivity is achieved by creating, via a non-uniform field, a “field free point” (FFP) that is scanned in three-dimensional space over the field of view (FOV). MPI has application in real-time cardiovascular imaging (Weizenecker *et al* 2009), probing blood clot formation (Murase *et al* 2014, Khurshid *et al* 2017) and stem cell tracking (Zheng *et al* 2016, Tay *et al* 2016), as well as therapeutic applications such as magnetic hyperthermia (Dhavalikar and Rinaldi 2016, Hensley *et al* 2017, Murase *et al* 2015, Tay *et al* 2018).

The MPR is a more compact, cheaper, and faster alternative to assess tracer performance, compared to using a full MPI system. The MPR design allows for a large range of magnetic fields (amplitudes, offsets, frequencies, and excitation waveforms) and the system has high sensitivity for measuring the response of small volumes of nanoparticles in suspension. Furthermore, since the entire suspension volume is subjected to a spatially uniform magnetic field, the MPR facilitates detailed analysis of the particle response at different bias field amplitudes along the magnetization curve. In contrast, the full MPI system measures the superposition of all particles within the FOV, i.e. the cumulative response of particles that range from fully saturated (outside the FFP) to unsaturated (fully within the FFP). Consequently, obtaining the intrinsic behavior of the tracers using a MPR can be beneficial to interpret MPI signals.

The tracer performance for MPI application can also arguably be assessed by instruments with no bias field capability, as in Tomitaka *et al* (2015) and Bauer *et al* (2016). The first drawback of using an instrument with no bias field is the difficulty to design a system applying excitation magnetic fields that are high enough to saturate the particles at high frequency. For example, the system designed by Bauer *et al* (2016) applies a moderate field of 20 mT, arguably too small to effectively saturate small particles like ferucarbotran. In comparison, the maximum field applied by a MPR with a bias field is the sum of the excitation field amplitude and the bias field, and can easily exceed 100 mT, which is high enough to saturate 5-nm magnetic particles. The second drawback of not using a bias field is that the nanoparticles are not subjected to a magnetic field representative of the field in a MPI scanner (high ac magnetic field compared to a smaller biased ac field). This difference

can cause discrepancies in the suspension dynamic response, especially for relaxing particles with a non-negligible lag between the magnetization and the excitation field, undermining the accurate emulation of the behavior of these particles in a MPI.

Other than MPI-based applications, an MPR could be used to measure changes in the magnetic nanoparticle's local environment, for example in changes in fluid viscosity as in Utkur *et al* (2017) and Rauwerdink and Weaver (2010), changes in temperature as in Perreard *et al* (2014), adsorption of disease specific biomarkers as in Gandhi *et al* (2016), or changes in particle-particle interaction (colloidal stability, particle aggregation state), as has been done with MPS. In these applications, changes in the particle's environment induce a change in their relaxation time. Another method used to assess relaxation effects on magnetic nanoparticle suspension is called magnetorelaxometry (Matz *et al* 1998, Kötitz *et al* 1999). In this method, the magnetic particles are oriented by a pulse of magnetic field and their relaxation time is characterized by recording the change of magnetization in time. This method is well suited to determine the magnetic or the hydrodynamic diameters of the particles, or the conditions of the medium surrounding the particle (e.g., viscosity). However, this method is limited to the characterization of relaxation times higher than 0.1 ms due to instrumentation limitations, limiting the minimum particle size that can be assessed (Kötitz *et al* 1999).

The MPR reported here features measurements of full time-series data and a unique method to attenuate the feed-through from the excitation signal, which otherwise would limit the measurement range of the DAQ and the sensitivity of the instrument. One method, used by Biederer *et al* (2009) for example, is to filter out the fundamental of the signal and analyze its other harmonics. However, in order to fully characterize the dynamic behavior of the magnetic nanoparticles, it is crucial to measure the first harmonic by eliminating the feedthrough. Additionally, the equipment is calibrated to obtain the instantaneous suspension magnetic moment per weight per magnetic field in $1/(\text{mg}_{\text{Fe}}/\text{mL})$ (i.e. in $(\text{emu}/\text{g}_{\text{Fe}})/(\text{A}/\text{m})$) from the induced voltage. Consequently, the measured signal depends only on the magnetic suspension response and not the instrument, which allows instrument and post-processing algorithms comparison across different research groups. Furthermore, the proposed postprocessing allows one to retrieve the tracer response and estimate the performance of the magnetic suspension quickly.

2. MPR explained

An MPI system detects the local response of nanoparticles excited by an alternating magnetic field (typically ~25 kHz sinusoid) (Gleich and Weizenecker 2005). The system is composed of three magnetic sources: the excitation field (time-varying field for particle excitation), the gradient field (established by permanent magnets as in Goodwill *et al* (2012) or a set of coils as in Franke *et al* (2016)), and the bias fields (electronically controllable field offsets for scanning the FFP) (Goodwill *et al* 2012). A pick-up coil system is commonly used to measure the magnetic response within the FOV. Due to the excitation field variation, the nanoparticle magnetic moments rotate, inducing a measurable signal in a pick-up coil by induction. The MPI spatial resolution relies on using a high magnetic field gradient source to saturate most particles in the FOV. The signal measured in the pick-up

coil is predominantly from the nanoparticles located at the FFP, since their magnetic moments rotate in response to the excitation field, while all of the particles outside of the FFP are saturated, and thus do not change in magnetization direction. By scanning the FFP over a region of space with the bias coils, an image of the magnetic particle density can be obtained (Goodwill *et al* 2012a).

The MPR emulates the fields of an MPI system, but without any spatial scanning capability. The MPR subjects the sample to an ac excitation field $H_{exc} = H_{exc}^0 \sin(2\pi f_0 t)$ and a slow-ramping bias field H_{bias} (figure 1a). The bias field emulates the scanning of a virtual FFP through the sample, as if the sample were in an MPI system. At large negative bias field, the particles are saturated due to the virtual FFP being away from the particles and respond weakly to the ac field. As the bias field ramps up, the virtual FFP approaches the particles. At zero bias field, one could imagine the sample to be located at the center of the virtual FFP and thus produce the largest signal. At high positive bias field, the particles are again saturated due to the movement of the virtual FFP further away from the particles, resulting in a small signal.

While varying the bias field with time, the FFP position depends on both the bias and excitation fields, as depicted in figure 1b. While unnoticeable for very low excitation field amplitudes, for higher excitation fields, the FFP position change must be accounted for in the signal post-processing. Indeed, the position of the FFP moves during one cycle of the excitation field, making the FFP position dependent on the total applied field amplitude (excitation and bias) instead of solely the bias field amplitude (Goodwill and Conolly 2010, Goodwill *et al* 2012).

The MPR infers the response strength and the resolution that magnetic tracers would exhibit in a MPI scanner. The actual resolution of the MPI image is highly impacted by how fast the particles saturate as a function of applied field amplitude and by how fast they respond in time to a change of magnetic field. The particle response time, called relaxation time, depends on which relaxation mechanism (Brownian or Néel) governs the particle rotational dynamics (Rosensweig 1997, Dhavalikar *et al* 2015 2016a). In Brownian relaxation, the magnetic moment is blocked within the particle, and their rotation is hindered by hydrodynamic drag due to the surrounding medium. In Néel relaxation, the magnetic moment rotates within the particle with characteristic time that depends on thermal energy and crystalline anisotropy. In practice, the relaxation time is a combination of these two mechanisms and the faster of the two dominates. A finite relaxation time causes a delay between the excitation and the particle response, causing a blur in MPI images and lowering MPI resolution.

3. MPR setup design

The MPR reported here was designed to provide a spatially uniform field (excitation and bias) to a nanoparticle suspension in a 200 μL cylindrical vial (VWR, catalogue no. 66065–666, 8 mm diameter, 40 mm long). The sinusoidal excitation field was generated by a gapped solenoid (excitation coil), and the dc bias field was generated by a solenoid coil (bias coil) (figure 2). The nanoparticles react in response to the total applied magnetic field,

inducing a change in magnetic flux, which is detected by a sensing coil system. The measured signal strength depends on the particle dynamic behavior (magnetization, relaxation), the particle density, and the system sensitivity.

3.1. Bias and excitation fields

The bias and excitation coils, whose characteristics are reported in table 1, are optimized to provide a large-amplitude and homogeneous magnetic field over the sample. Alternating and direct currents, respectively, are supplied by two power amplifiers (AE Techron 7224, voltage gain of 20) fed by a computer-controlled data acquisition (DAQ) system (National Instruments PCI-6115, 12-Bit, 4 MS/s for multi-channel I/O) that supplies the synchronized signal waveforms. The excitation coil is designed to have low resistance and inductance, allowing a larger current, and therefore a larger magnetic field at high frequency. In direct connection mode, where the excitation coil is directly connected to the power amplifier, the system can supply excitation fields up to 40 mT for frequencies up to 5 kHz, 8 mT up to 30 kHz, and 1 mT up to 120 kHz. In order to obtain higher fields at higher frequencies, the excitation coil can also be connected to the power amplifier via resonant matching circuits implemented using pairs of high-voltage capacitors (Cornell-Dubilier). With the matching circuits, the system can supply 45 mT at discrete frequencies (3.6, 13.2, 19.5, 24 and 29.3 kHz). The bias coil design is simpler, since only slowly varying currents (ramp rate of 30 A/s) need to be supplied by the power amplifier.

A 1.6-mm-thick, 60-mm-diameter, 135-mm-long cylindrical copper shield is inserted between the excitation coil and bias coil to reduce the unwanted induction from the excitation coil to the bias coil. At 29.3 kHz, the induced voltage on the bias coil terminals decreases from 2350 V/A without shield, to 0.63 V/A with shield (3730× reduction). The inductive coupling coefficient between the coils decreases from ~0.39 to ~0.006. Note that the slow-ramping field from the bias coil is not affected by the copper shield.

3.2. Signal measurement and feed-through cancellation strategy

The DAQ records the induced voltage from the sensing system through a low-noise pre-amplifier (Stanford Research Systems, SR560). Depending on the nanoparticle concentration in the sample, the preamplifier gain is adjusted from 1 to 100 in order to maximize utilization of the DAQ dynamic range. The measured signal is then divided by the gain to recover the induced voltage. The DAQ also simultaneously records both currents feeding the bias and the excitation coils via one current probe (Tektronix, TCP305A probe with TCPA300 amplifier). The measured signal from the current probe is decoupled by a linear fit and thereby separated into the linear ramping bias field and the sinusoidal excitation field. The sinusoidal excitation current signal is used as phase reference.

The main challenge in the sensing coil system is to negate the direct induction from the excitation coil on the pick-up coil (called “feed-through”), so as to measure only the magnetic moment change of the sample through Faraday’s law of induction. The sensing coil system is composed of two coils: a pick-up coil, surrounding the sample and sensing its magnetic moment change, and a balancing coil to counteract the inductive feedthrough. The pick-up and balancing coil characteristics are reported in table 2.

The pick-up coil is wound within an epoxy support, in order to minimize its distance to the sample so as to increase sensitivity and minimize feed-through. The balancing coil is mounted in series with the pick-up coil, but wound in opposite direction to negate the inductive feed-through from the pick-up coil. The balancing coil is located 15 mm below the sample and is manually adjustable in both axial position (d) and tilt (θ), as shown in figure 3. These adjustments vary the magnetic flux through the balancing coil via spatial variations of the field near the end of the excitation coil, and via change in the projected area, respectively.

The feed-through minimization with the displacement of a straight balancing coil has been already reported by Weaver *et al* (2008) or Tay *et al* (2016), for example. The ability to tilt the balancing coil reduces even more the feed-through. Figure 4 presents measurements of the feed-through in the sensing coil system for an excitation current of 140 mA at 29.3 kHz (black curve), for different configurations. When there is no balancing coil (figure 4a blue curve), the feed-through is about $54.8 \text{ mV} \cdot \text{Hz}^{-1} \cdot \text{A}^{-1}$. Note the $-\pi/2$ phase-shift between the signal and the reference current, explained by the induction. The feed-through is reduced by a factor of 466 (-53 dB) by translating the straight balancing coil, and further reduced by a total factor of 45800 (-93 dB) by rotating the tilted balancing coil (figure 4b). Extrapolating from these results, and assuming feed-through is linear with both excitation field amplitude and frequency, for a 50 mT excitation (i.e. 16.4 A) at 29.3 kHz, the maximum feed-through is reduced from 27.9 V to 0.6 mV. A zero phase-shift between the induced signal and the current indicates that the adjustment in position reached the minimum achievable feed-through for a given tilt, minimum showed for both configurations (straight and tilted balancing coil) on figure 4b.

3.3. Raw signal analysis

Figure 5 presents an example of a typical raw signal obtained for ferucarbotran (58.6 mg_{Fe}/mL stock solution) at 40 mT and 29.3 kHz after feed-through subtraction. At high bias field (region 1), the particles are almost saturated and respond slightly. At zero bias field (region 3), the voltage signal exhibits very sharp symmetrical changes, since 40 mT pushes deep into the non-linear magnetization response of the suspension. The observed signals are similar to measurements done with a magnetic particle spectrometer, which has no bias field capability (Garraud *et al* 2017). When the excitation field is offset with a small bias field (region 2 and 4), the overall signal strength decreases, and the response is non-symmetric. The non-symmetry comes from the magnetic moment rotational dynamics being influenced by the small bias field direction. Indeed, the magnetic moments stay aligned longer with the bias field when the excitation field increases in the opposite direction, resulting in a slower changing signal than when the excitation field realigns itself with the bias field. In this case, the magnetic moments rotate faster, resulting in a sharper signal. This asymmetry can be seen for a MPI system as the virtual FFP oscillation not being centered on the particle location.

4. Post-processing method and algorithm

The first following section describes the link between the measured signal, the physical behavior of the magnetic suspension, and the tracer response TR , which is the output of the post-processing in our MPR. The second section describes the post-processing algorithm to obtain the tracer response TR from the measured signal. The tracer response TR , as introduced and defined in this paper, is the signal from the MPR that is normalized to obtain a quantity intrinsic to the tracer behavior. It should be noted that the derivation of TR avoids assumptions on the behavior of the particles (*e.g.* non-linearity or relaxation phenomena). Eventually, the Langevin approach is introduced to describe the behavior of particles with very small relaxation time.

4.1. Expression of the tracer response from the measured signal

The suspension's magnetization M along the sensing coil system axis is described as a function of time by $M(t) = \sigma_{Fe} C_{Fe} \mathcal{F}(H_{app}(t))$ with σ_{Fe} the specific magnetization (i.e magnetic moment per weight of iron) in $\text{A}\cdot\text{m}^2/\text{kg}_{Fe}$, C_{Fe} the iron concentration in mg_{Fe}/mL . $\mathcal{F}$ is a function that describes the unitless magnetic behavior of the suspension as a function of H_{app} saturating at ± 1 for high fields. In the MPR system presented here, a harmonic excitation is coupled with a slow ramping bias field such as $H_{app} = H_{bias} + H_{exc}^0 \sin(2\pi f_0 t)$. By neglecting the small dynamic effects due to the bias field variation, $\mathcal{F}$ is a function of the field bias H_{bias} , the excitation field amplitude H_{exc}^0 , and frequency f_0 . The change of the suspension magnetization induces a voltage at the sensing coil system terminals, such as:

$$V_{ind}(t) = -\frac{Vol}{2\pi K_{pickup}} \dot{M}(t) = -\frac{Vol \sigma_{Fe} C_{Fe}}{2\pi K_{pickup}} \dot{\mathcal{F}}(H_{app}) \dot{H}_{app}(t),$$

with K_{pickup} the sensing system calibration coefficient in $\text{A}\cdot\text{m}^2/\text{V}\cdot\text{s}$ (as in Garraud *et al* 2017), Vol the sample volume, and $\dot{y}(x)$ the partial derivative of y by x . The tracer response TR is defined by:

$$TR(H_{app}) = -\frac{2\pi K_{pickup}}{Vol C_{Fe}} \frac{V_{ind}(t)}{\dot{H}_{app}(t)} = \sigma_{Fe} \dot{\mathcal{F}}(H_{app}).$$

This tracer response is the signal induced by the particles after

- normalization by the sample concentration of iron and its volume, and the sensing system calibration coefficient, and therefore is independent from the instrument and the sample characteristics;
- normalization by the rate of change of the applied field, which would correspond to a FFP velocity compensation in the case of MPI;
- being expressed as a function of the applied magnetic field instead of time, which would correspond to the FFP position compensation discussed in Section 2.

The tracer response TR is expressed in $(\text{emu/g}_{\text{Fe}})/(\text{A/m})$ or $(\text{A}\cdot\text{m}^2/\text{kg}_{\text{Fe}})/(\text{A/m})$, representing the local variation of instantaneous magnetization per magnetic field normalized by the amount of iron. It is also expressed in $\text{m}^3/\text{kg}_{\text{Fe}}$ or in $1/(\text{mg}_{\text{Fe}}/\text{mL})$ as used in this paper, highlighting its link to the dynamic susceptibility normalized by the iron content.

TR is a good metric to assess the magnetic suspension performance, especially for MPI applications, because it provides a method to compare different batches or between different research groups, since it does not depend on the instrument, the sample characteristics (volume, concentration in iron), or the experimental conditions for a suspension of particles with very short relaxation time relative to the excitation field frequency. The tracer response depends only on the unknown tracer characteristics: its specific magnetization σ_{Fe} and in the case of fast-relaxing particles, in the derivative of its behavior $\dot{\mathcal{F}}(H_{\text{app}})$. Once H_{app} is expressed in terms of the FFP position x and the field gradient G in A/m/m , $\dot{\mathcal{F}}(xG)$ represents the point spread function (PSF) of the suspension in a MPI system (Goodwill and Conolly 2010). The convolution of this PSF with the spatial distribution of the nanoparticles contributes to the final MPI image. As such, the signal strength and expected MPI resolution of the assessed suspension can be inferred from TR .

The tracer response TR can be derived further in the case of the quasi-static behavior of superparamagnetic suspensions that are usually well described by the Langevin function $\mathcal{F}(H_{\text{app}}) = \mathcal{L}(\alpha) = \coth(\alpha) - 1/\alpha$, with $\alpha = \mu_0 m H_{\text{app}} / (k_B T)$, where m is the magnetic moment of one nanoparticle, T is the temperature, μ_0 the vacuum permeability, and k_B the Boltzmann constant. This is the case of magnetic suspension exhibiting negligible relaxation time, i.e. relaxation time much shorter than any other phenomena involved. In this case, the magnetization follows the Langevin function using the instantaneous magnetic field, and the parameter TR is not time-dependent and follows the curve:

$$TR(H_{\text{app}}) = 3\sigma_{\text{Fe}} \dot{\mathcal{F}}(0) \left(\frac{1}{\alpha^2} - \frac{1}{\sinh^2(\alpha)} \right)$$

with $\dot{\mathcal{F}}(0) = \mu_0 m (3k_B T)^{-1}$. One can note that the maximum value of the tracer response, which is $TR(0) = \sigma_{\text{Fe}} \dot{\mathcal{F}}(0)$ corresponds to the maximum slope F occurring for $H_{\text{app}}=0$, and is linked to the initial susceptibility normalized by the iron concentration $TR(0) = \chi_0 / C_{\text{Fe}}$.

More importantly, $TR(0)$ is independent of the frequency and the amplitude of the excitation field. This counter-intuitive result concerning the evolution of TR with the field amplitude is explained by higher harmonic terms weighting more in the induced voltage than in the magnetization. Indeed, although the magnetization saturates and is non-linear with increasing field, the maximum induced voltage happens to evolve linearly with the field as harmonic terms at higher frequencies induce relatively more voltage than the ones at lower frequencies. Considering the harmonic decomposition of the magnetization M , and the fact that the voltage V_{ind} is linked to its derivative, one can notice that the k^{th} term of V_{ind} is multiplied by k , while this is not the case for the k^{th} term of M . This phenomenon is

experimentally observed later in the paper, although the characterized magnetic suspension presents relaxation.

For measurements with real samples, the tracer response is highly distorted by any modification of the induced voltage near the lowest rate of change of the applied field, corresponding to a near zero FFP velocity. Indeed, around these points the small induced voltage is divided by a small rate of change of the applied field, and the tracer response is highly influenced for example by the signal noise, and by relaxation phenomena inducing phase-shift between the induced voltage and the applied magnetic field. The first solution we implement to lower these distortions is to trim parts of the signal around the zero rate of change of the applied field and consider only the signal corresponding to significant rate of change (Croft *et al* 2016). The second solution we employ is to extract the envelope (i.e. the local maximum values) of the obtained response as there are multiple values of TR for a given applied field H_{app} . Indeed, in the ideal case, all values of TR would fall on a smooth curve. However, because of the noise and the phase-shift introducing uncertainties, the values of TR obtained are spread over a wide range.

4.2. Signal processing for determination of expected MPI performance of the magnetic suspension

The signal-processing algorithm to obtain the tracer response from the raw signals is illustrated in figure 6 (29.3 kHz and 41 mT). The raw voltages recorded by the DAQ are divided by the preamplifier gain to obtain the voltage induced by the sample. After trimming the signal to obtain a symmetrical span ($\sim \pm 85$ mT), the time signal is partitioned into ~ 250 snapshots, each containing a fixed number of cycles, ranging anywhere from 10 to 100 cycles. In each snapshot, the bias field varies slowly compared to the particle relaxation characteristic time, and is considered constant over several excitation cycles. Signal filtering is achieved by performing a FFT on each partition, followed by feed-through subtraction and time signal reconstruction using only the signal harmonics. Then the reconstructed (filtered) signal is compensated by the rate of change of the applied field (velocity compensation) by keeping only 50 % of the signal, and eliminating the signal corresponding to the 50 % lowest applied field rate of change. Then, the signal is rearranged according to its corresponding applied field (sum of bias and excitation fields) instead of bias field only (position compensation) as described in Section 2 and figure 1b. Another ± 85 mT symmetrical span trimming and partitioning in ~ 250 snapshots are performed, and the maximum and minimum values for each snapshot are extracted to obtain the negative and positive scan envelopes. The obtained envelopes are then normalized and converted to magnetization per weight of iron to obtain the tracer response TR (with the instrument calibration coefficient K_{pickup} estimated at $21.6 \text{ A}\cdot\text{m}^2/\text{V}\cdot\text{s}$). From the tracer response TR , the full width at half maximum (FWHM), the envelope peak deviation from the center, and the overall magnetization per weight of iron are extracted. Finally, the projected resolution r , in m, of $FWHM$ a MPI system with constant field gradient G is inferred from $r = \frac{FWHM}{G}$.

5. Experimental results and discussion

The MPR system was tested by performing measurements on a ferucarbotran nanoparticle suspension (also known as Resovist[®] and FeraSpin[®]). In clinical applications, ferucarbotran (Reimer and Balzer 2003) has been widely studied as an MRI contrast agent (Wang 2015). Ferucarbotran has also been commonly employed in MPI (Ishihara *et al* 2013, Kaul *et al* 2017, Kuhlmann *et al* 2015, Yoshida *et al* 2013, Keselman *et al* 2017, Dieckhoff *et al* 2017) and, being commercially available, was chosen as the standard to test the MPR. The first section describes the magnetic and physical characterization of the ferucarbotran batch used here, while the second and third sections describe tests of the performance of the MPR.

5.1. Ferucarbotran characterization

Ferucarbotran was obtained from Meito Sangyo Co. Inc. and consists of carbodextran-coated iron oxide particles suspended in deionized water. Figure 7 presents the characterization of the magnetic suspension diluted from the stock solution to contain 1.09 mg_{Fe}/mL (verified by o-phenanthroline assay). Figure 7a shows a histogram of the physical size distribution of the inorganic cores. The physical diameter of the particles was found to be 5.43 nm (geometric deviation of $\ln \sigma = 0.42$) as determined from images obtained from a Hitachi H-7000 transmission electron microscope (TEM) (inset in figure 7a). The hydrodynamic diameter was obtained from dynamic light scattering (DLS) measurements in a Brookhaven Instruments ZetaPALS/BI-MAS. As seen in figure 7b, a bimodal size distribution in hydrodynamic diameter was observed, which is similar to the results described by Eberbeck *et al* (2011). Approximately 75 % of total particle volume had a volume-weighted hydrodynamic diameter of 26 nm (geometric deviation of $\ln \sigma = 0.065$) while the rest were 79 nm (geometric deviation of $\ln \sigma = 0.067$). Dynamic magnetic susceptibility measurements were conducted in a commercial susceptometer (DynoMag) to evaluate the magnetic relaxation mechanism of the particles (figure 7c). The absence of a prominent out-of-phase susceptibility (χ'') peak around 1.67×10^5 rad/s, which corresponds to the peak frequency for Brownian-relaxing particles as determined by the Debye model (Calero-Ddelc *et al* 2011), suggests that the particles relax primarily by the Néel mechanism. A Quantum Design SQUID MPMS3 magnetometer was used to obtain the equilibrium magnetization curve of the particles per weight of iron at 300 K (figure 7d). From this measurement, the saturation magnetization was found to be around 99 A·m²/kg_{Fe}, or 69 A·m²/kg_{magnetite}. The magnetic diameter was evaluated to be 9.24 nm (geometric deviation of $\ln \sigma = 0.553$) by fitting the equilibrium curve to the Langevin function (Maldonado-Camargo *et al* 2017). Surprisingly, the magnetic diameter was found to be larger than the physical diameter, contrary to the usual observation of iron oxide nanoparticles. The configuration of the iron oxide nanoparticles in clusters and their polydispersity in size could contribute to an effective magnetic diameter that is larger than the physical diameter, as suggested by Eberbeck *et al* (2011) and Bauer *et al* (2015).

5.2. MPR minimum detectable signal

Ferucarbotran stock solution was serially diluted with deionized water to create samples with varying concentrations. The concentration of the samples was confirmed using the o-phenanthroline assay (Unni *et al* 2017). A deionized water sample was used to evaluate the

noise floor. The deionized water sample and the diluted ferucarbotran samples were tested in the MPR at 24 kHz, 26 mT amplitude excitation field and ± 80 mT bias field to determine the minimum detectable concentration of iron. The signal was reconstructed from the acquired raw signal and the gain normalized maximum signal intensities from the reconstructed response for various preamplifier gains were compared at different concentrations, as shown in figure 8. The minimum detectable concentration of ferucarbotran above the deionized water reference signal was found to be $7.4 \mu\text{g}_{\text{Fe}}/\text{mL}$. This concentration corresponds to $1.48 \mu\text{g}$ of iron when using a $200 \mu\text{L}$ sample volume. Discrepancies occur below this concentration due to noise and inaccuracies in the feedthrough cancellation. The signal strength was observed to change linearly with concentration over three orders of magnitude, ranging from 7.4 to $12800 \mu\text{g}_{\text{Fe}}/\text{mL}$. Note that at pre-amplifier gain of 100, the signal shows a plateau at higher concentrations due to voltage saturation of the DAQ.

5.3. MPR measurements of ferucarbotran

Figure 9 shows examples of positive and negative tracer response envelopes for various excitation field amplitudes (4 to 41 mT) at various excitation frequencies (3.6 to 29.3 kHz) for $1.09 \text{ mg}_{\text{Fe}}/\text{mL}$ ferucarbotran. The bias field varies from -80 mT to 80 mT in 1 s, and the preamplifier gain was set to 10. The tracer response peak $TR(0)$ (maximum magnetic moment per weight over field amplitude) is seen to be almost constant around $6.1 \times 10^{-3} \text{ 1}/(\text{mg}_{\text{Fe}}/\text{mL})$ for all excitation field conditions and close to the susceptibility normalized by the iron concentration (figure 9). This shows that the measured signals vary linearly with the excitation frequency and field amplitude within the tested ranges. This demonstrates that the dynamic behavior of the nanoparticles operates similarly as the quasi-static behavior following the Langevin function in which the nonlinearity is compensated by higher contribution of higher harmonics to the signal as discussed in Section 4.1. For each envelope for excitation field higher than 23 mT, a second peak near $H_{\text{app}}=0$ appears. This bump is due to relaxation effects inducing a phase-shift between the measured signal and the applied field rate of change distorting the tracer response for higher fields. Finally, the signal to noise ratio becomes poor at low field and frequency, so unwanted noise is observed for all envelopes at 3.6 kHz.

Extracted parameter evolutions with the excitation field characteristics are summarized in figure 10, which also includes measurements at higher frequencies ranging from 41 kHz to 113 kHz at 0.8 mT field amplitude (the envelopes, identical to those at low fields, are not shown in figure 9). The expected MPI resolution is reported in figure 10a, assuming a 5 T/m gradient MPI (± 160 mT bias field corresponding to 64 mm FOV). The minimum FWHM obtained is about 6 mT at low field, corresponding to a 1.2-mm resolution. For comparison with an actual MPI scanner, the FWHM at 19.5 kHz and 13-mT excitation is about 9.5 mT, which is similar to the 9.6-mT FWHM of the MPI proposed by Goodwill *et al* (2012) operating almost at the same field conditions. Interestingly, the FWHM increases with the field amplitude but depends only slightly on the excitation frequency (figure 9 and 10a). Indeed, the FWHM depends on how fast the particles saturate (which is linked to their diameter), and how large the excitation field is (the larger it is, the longer the virtual FFP will have an effect on the particles during the scan). The tracer response peak corresponding

to the maximum of the sample magnetic moment per weight is almost constant, although showing a slight decrease with the excitation field amplitude. This modest drop of the signal is explained mainly by the post-processing algorithm and depends for example on how much signal is cut off during the velocity compensation step. The peak deviation from the center increases linearly with excitation field amplitude and the frequency. Indeed, the deviation of the peak from the center is due to particle response lagging behind the excitation field due to relaxation effects as observed by Goodwill *et al* (2011) and Croft *et al* (2012).

The desired behavior for MPI application requires both high signal strength and high spatial resolution. Therefore, these results show that a trade-off is needed. One solution, suggested by Croft *et al* (2016) and Kuhlmann *et al* (2015), is to operate at high frequency and low amplitude (113 kHz and 10 mT for example), to combine good resolution and sufficient signal strength. Indeed, because ferucarbotran mainly relaxes through Néel relaxation as shown in figure 7, the signal strength remains strong even at high frequency. Moreover, in a full MPI system, the advantage of such excitation field characteristics would be to have a faster FOV scan, at the expense of a more expensive measurement (higher measurement rate) and excitation system (harder to supply more current at high frequency).

6. Conclusion

This paper presents the design, construction, and testing of a magnetic particle relaxometer to infer magnetic nanoparticle suitability for MPI application. Post-processing of the data is described to obtain the tracer response TR and infer nanoparticle performance for MPI. Tests from 3.6 kHz to 29.3 kHz at 41 mT excitation field and up to 113 kHz at 0.8 mT excitation were conducted on 1.09 mg_{Fe}/mL ferucarbotran. The envelope FWHM, and thus the projected MPI resolution, is shown to depend mainly on the excitation field strength. The envelope peak deviation, due to relaxation effects, depends on both the field strength and frequency. Finally, the signal strength, depending on the magnetic induction, depends linearly on the frequency and the field strength in the tested field range. The minimum FWHM obtained in the tested conditions is about 6 mT for ferucarbotran, which corresponds to a 1.2-mm resolution for an MPI system with a 5 T/m gradient field.

The designed MPR is shown to characterize magnetic suspension and in future work will be used to improve the nanoparticle synthesis, experiment new excitation methods, improve the image reconstruction algorithm, and validate rotational dynamic simulations.

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Figure 1.

(a) In a MPR, the sample is subjected to an ac excitation field and a slow ramping bias field to emulate the MPI field-free-point (FFP) scan. (b) Dependence of FFP position on the total applied field. Note that the figures display a low-frequency excitation field for illustrative purposes.

Figure 2.

(a) MPR setup diagram. The concentric excitation and bias coils subject the nanoparticle suspension to an ac excitation field superimposed by a slow ramping bias field. The sample magnetization change induces a voltage in a sensing coil system, which is recorded by a DAQ. (b) Exploded view of the bias and the excitation coils, along with copper shield and the sensing coil system comprising the pick-up coil and the balancing coil.

Figure 3.

Induction feed-through balancing via balancing coil displacement (a) and rotation (b) in an inhomogeneous field. By displacing the balancing coil towards lower field or by tilting it, the balancing induced voltage decreases, allowing for fine feed-through balancing.

Figure 4.

Comparison of the minimum feed-through from excitation coil on the sensing system without balancing coil, with straight balancing coil, and with tilted balancing coil: (a) full scale, and (b) zoom of the y-axis showing the fine-tuning effect of the balancing coil tilt.

Figure 5.

Example of raw signal measured by the sensing system for 58.6 mg_{Fe}/mL ferucarbotran at 40 mT and 29.3 kHz: (a) full timeseries data, and (b) signal zooms (in time) show evolution of the time signal for (1) saturated particles, (2) small negative field, (3) zero bias field, and (4) small positive bias fields.

Figure 6. Signal post-processing to obtain the tracer response envelopes and the projected MPI performances of the magnetic suspension from the raw signal.

Figure 7.

Ferucarbotran properties: (a) core diameter using transmission electron microscopy, (b) hydrodynamic diameter through dynamic light scattering measurements, (c) AC susceptibility curve showing particles relaxing by the Néel mechanism, and (d) magnetic diameter determined from magnetization curve obtained with a SQUID.

Figure 8. Dilution series of ferucarbotran suspension to characterize the minimum detectable concentration shows signal linearity with the sample concentration in iron.

Figure 9.

Positive (blue) and negative (red) scan tracer responses extracted from ferucarbotran MPR measurements for various excitation field conditions.

Figure 10.

Summary of ferucarbotran (1.09 mg_{Fe}/ml) performances for excitation fields varying from 0.8 to 41 mT from 3.6 to 113 kHz: full width at half maximum (FWHM) and expected resolution for a 5 T/m gradient MPI (a), signal strength (b), and peak deviation from the center (c).

Table 1.

Excitation and bias coil characteristics.

	Excitation coil	Bias coil
Type	Multi-layer gapped solenoid	Multi-layer solenoid
Internal diameter (mm)	30	60
Length (mm)	73	120
Gap size (mm)	3.3	n/a
Number of turns	206	1220
Number of layers	3	8
AWG gauge	19	19
Resistance (Ω)	0.615	6.8
Inductance (μH)	400	37400
Field (mT/A)	2.38	10.7
Field homogeneity (%)	< 1	1.5
Inductive coupling coefficient	0.006	

Table 2.

Pick-up and balancing coil characteristics.

	Pick-up Coil	Balancing Coil
Type	Multi-layer solenoid	Single-layer solenoid
Internal diameter (mm)	8.5	8.1
Length (mm)	6.9	16
Number of turns	64	80
Number of layers	2	1
AWG gauge	34	34
Resistance (Ω)	2.16	2.5
Inductance (μH)	29.1	24.5
Inductive coupling coefficient	0.012	