A highly accurate determination of absorbed power during magnetic hyperthermia

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Abstract

Absorbed power of nanoparticles during magnetic hyperthermia can be well determined from changes in the quality factor (Q factor) of a resonator in which the radiofrequency absorbent is placed. We present an order of magnitude improvement in the Q factor measurement accuracy over conventional methods by studying the switch-on and off transient signals of the resonators. A nuclear magnetic resonance console is ideally suited to acquire the transient signals and it also allows to employ the so-called pulse phase-cycling to remove transient artifacts. The improved determination of the absorbed power is demonstrated on various resonators in the 1–30 MHz range, including standard solenoids and also a birdcage resonator. This leads to the possibility to detect minute amounts of ferrite nanoparticles which are embedded in the body and also the amount of the absorbed power. We demonstrate this capability on a phantom study, where the exact location of an embedded ferrite is clearly detected.

Keywords: hyperthermia, pulses, quality factor, resonance, time domain techniques, Fourier transform

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(Some figures may appear in colour only in the online journal)
accurate determination of $Q$. A highly sensitive measurement could lead to e.g. the localization of minute amounts of ferrite and to study its diffusion under in vivo conditions, a better assessment of specific absorbed power in the NMH materials or to study non-linear absorption effects in the ferrites.

Conventional measurement of a resonator $Q$ factor is performed by sweeping the excitation frequency and studying the reflected signal [24–26]. Albeit readily implemented, the frequency swept method is known to have a low accuracy for $Q$ and it is limited in measurement time to a few 100 ms thus this method does not enable the study of dynamic absorption effects ([24, 25, 27]). Rather than measuring in the frequency domain, resonator parameters can be determined in time-domain measurements [28–31]; then the resonator is excited with a pulsed carrier signal, whose frequency is close to the resonator eigen-frequency, $f_0$. Importantly, during both the switch-on and off, the resonator oscillates at its eigen-frequency, $f_0$, and the transient decay envelope has a time constant of $\tau = Q/2nf_0$. The transient signal can be Fourier transformed following a superheterodyne detection, which yields directly the resonance profile. This scheme is widely used in the study of high-$Q$ optical resonators [32–35] and it was also implemented to measure the properties of microwave resonators [36, 37].

In general, the time-domain measurements (like Fourier-transform NMR [38] and Fourier transform infrared spectroscopy) have two advantages: improved accuracy (or Connes advantage [39]) since the measurement is traced back to a stable clock-frequency and simultaneous measurement (the Fellgett or multiplex advantage [40]) of the resonance curve is attained. In fact, the resonator transient (also known as resonator ring-down) is usually an unwanted side effect and a well-known hindrance in low-frequency NMR [41]. It results in a ‘dead-time’ in pulsed magnetic resonance and various schemes have been devised to reduce it [41, 42]. However, the very same instrumentation of a standard pulsed NMR instrument, known as an NMR console, allows a direct measurement of the resonator transients.

The present study is motivated by the quest for improved $Q$ determination accuracy with the goal to improve the absorbed power measurement during hyperthermia. We present that the switch-on and off transients yield a Lorentzian function when $f \neq f_0$ and decay with a delay of a few ms.

For both switch on and off, the resonators reflects a transient signal, which differ only in their phase [31, 36], and has a frequency $f_0$ and decay with $\tau$. Note that the NMR console detects in (or Re) and out-of-phase (or Im) signal (also known as quadrature detection) but only one component is shown in the figure to retain clarity. The meaningful spectral data is obtained from the power spectrum of the FT data, i.e. $Re^2 + Im^2$ and is shown in the figure.

In the superheterodyne detection scheme of the NMR console, the time-dependent signal is downconverted with $f$, it thus appears as an exponential function when $f \approx f_0$ or an oscillating function when $f \neq f_0$. When Fourier transformed, both the switch on and off transients yield a Lorentzian function with respect to the intermediate frequency (IF), $f = f_0$.

In figure 2, we show the time-dependent resonator transients as detected with the NMR console. The detection was performed in quadrature which allows a Fourier transformation of the signal, which yields directly the resonator curve around the intermediate frequency, IF. This is also shown on the lower panel in figure 2. The LO frequency is added to obtain the resonance curve on an absolute frequency scale. We performed measurements with a conventional, frequency swept method, in order to validate the present measurements. The two curves match well as demonstrated in figure 2. This means that the transient detection methods also yield the same kind of data such as the conventional measurement technique.

The use of the NMR console allows to implement the so-called phase cycling experiments, which is customary in NMR to get rid of the instrumental artifacts. Such artifacts include a DC offset of the digitizer or an imbalanced amplification in the two quadrature channels. As an example, the DC offset is tackled by exciting the NMR nuclei with pulses in...
Gresits et al. (2019) showed that the opposite RF phase and subtracting the signals after digitization. Imbalances in the quadrature detection are tackled by exciting the nuclei by cycling the RF phase by 90 degrees in consecutive excitation phases and cycling the phase of the digital downconversion by the same value. This scheme leads to the generic name, phase cycling, of the method.

In our case, the dominant artifact is a peak followed by some parasitic "ringing" which appears when the pulses are either switched on or off. This can be tackled by alternating the RF phase of the exciting pulse by 180 degrees: the parasitic signal is not sensitive to the RF phase, whereas the resonator transient is also rotated by 180 degrees as it is shown in figure 3(a). When the resulting transients are subtracted accordingly only the desired transient is observed and the parasitic signal is eliminated. The effect of this phase cycling scheme is demonstrated in figure 3(b): the measured transient signal is free from any parasitic signal and its Fourier transform is a regular Lorentzian curve. In contrast, the unwanted signal appears without phase cycling and the corresponding Fourier transformed signal is also distorted.

Application to detect a minute amount of buried ferrite

The ultra-high sensitivity of the present method opens the way for a number of applications in ferrite based hyperthermia of which we envisage a few. First, it allows to detect minute amounts of ferrite with high accuracy. The setup used to determine the resonator Q and $f_0$ from the switch on/off transients (upper panel). The NMR console outputs the exciting pulse sequences and also detects them. A hybrid junction acts as duplexer to separate the excitation and the signal reflected from the resonator which is referenced with respect to 50 Ω. The transient scheme is also shown: for both switch on and off, a transient signal is observed (lower panel, left). It is a single exponential, when $f = f_0$, but it oscillates when $f \neq f_0$ the corresponding Fourier transform signals are also shown as a function of the intermediate frequency $f - f_0$ (lower panel right).

It was established earlier [36, 37] that the appropriate errors of the $f_0$ and $Q$ determination accuracies are the following quantities:

$$\delta(Q) : = \frac{\sigma(Q)}{Q}; \delta(f_0) : = \frac{\sigma(f_0)}{\Delta f},$$

where $Q$ and $\Delta f$ are the mean values of $Q$ and the resonator bandwidth $\Delta f$, respectively. $Q = f_0/\Delta f$, where $f_0$ is the resonator frequency [36]. We note that the error of $f_0$ is not $\sigma(f_0)/f_0$ as it would be intuitive at first sight. This quantity would overestimate the accuracy for an ultra-high frequency resonator with a moderate $Q$ factor.

When comparing different measurement methods, a normalization with the measurement time is also important and we present data which is normalized to 1 second, thus the data is given in units of $1/\sqrt{\text{Hz}}$. We found that the conventional frequency swept power detector results in about $\delta(Q) \approx \delta(f_0) \approx 2 \cdot 10^{-3} \cdot 1/\sqrt{\text{Hz}}$. In contrast, under the most optimal settings, the transient detection method results in about 20 times smaller $Q$ and $f_0$ determination errors, as small as $\delta(Q) \approx \delta(f_0) \approx 10^{-4} \cdot 1/\sqrt{\text{Hz}}$. The details of the most optimal transient acquisition settings, as well as a discussion of the error sources in terms of stochastic and drift-like errors, is presented in the supplementary material (stacks.iop.org/JPhysD/52/375401/mmedia).

Figure 1. The setup used to determine the resonator $Q$ and $f_0$ from the switch on/off transients (upper panel). The NMR console outputs the exciting pulse sequences and also detects them. A hybrid junction acts as duplexer to separate the excitation and the signal reflected from the resonator which is referenced with respect to 50 Ω. The transient scheme is also shown: for both switch on and off, a transient signal is observed (lower panel, left). It is a single exponential, when $f = f_0$, but it oscillates when $f \neq f_0$ the corresponding Fourier transform signals are also shown as a function of the intermediate frequency $f - f_0$ (lower panel right).

Figure 2. Comparison of the $Q$-factor measurement using the conventional frequency swept power detector detection and the Fourier transformed transient signal. Note the larger noise for the power detector measurement, this includes the digitalization noise of the oscilloscope.
amounts of ferrite and the small amount of absorbed power in a realistic in vivo animal model study. We previously calculated [23] that the smallest amount of detectable magnetite is 6 mg which is too much for hyperthermia therapy even in small laboratory animal models. However, as the sensitivity of our method is about 20 times better than our previous one, thus the lowest detectable ferrite amount is about 0.3–0.5 mg, which is typically employed in mice animal model studies [21, 43, 44].

In addition, our method could be further exploited in the study of novel, non-magnetite based nanoparticles with possibly improved magnetic hyperthermia properties such as those reported in [45].

The high sensitivity of the present method makes it suitable to detect non-linear (e.g. saturation) effects or the change of the absorbed power due to the change of sample parameters e.g. the sample temperature. We demonstrate its utility to detect the position of a small amount of ferrite whose location is otherwise unknown. Locating the ferrite in hyperthermia is of great importance in medical applications; it could assess the success of drug delivery targeting and it could also allow to better focus the heating RF irradiation.

We show in figure 4, the variation of $Q$ and $f_0$ when a small amount of magnetite (about 4 mm long, containing 1 mg of magnetite) is moved across the solenoid (with 14 mm length) of an RF circuit. We used two manual linear translation stages...
the so-called smart phase cycling schemes, which allows the etic resonance console. The latter technique allows the use of frequency resonant circuit using a conventional nuclear magn-

riffication irradiation. The method is based on monitoring the transient response of an impedance matched radiofre-

cine the power absorbed in nanomagnetic particles during (BME FIKP-NAT), are acknowledged.

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Summary

In summary, we presented a highly sensitive method to determine the power absorbed in nanomagnetic particles during radiofrequency irradiation. The method is based on monitoring the transient response of an impedance matched radiofrequency resonant circuit using a conventional nuclear magnetic resonance console. The latter technique allows the use of the so-called smart phase cycling schemes, which allows the artifact-free detection of the short transients. The method yields an unprecedented accuracy of the resonator quality factor and resonance frequency which reduces the amount of detectable ferrite during nanomagnetic hyperthermia. We demonstrated the utility of the method by sensitively detecting the location of a small amount of ferrite in a test tube.

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Figure 4. Variation of $f_0$ and $Q$ when a small ferrite sample (containing about 1 mg of magnetite in solution) is moved across a solenoid. Each data point was recorded for 1 s. Arrows indicate the length of the solenoid and that of the sample. Note that both $f_0$ and $Q$ differ slightly on the two sides of the lateral movement due to an asymmetry in the sample holder.

(Thorlabs GmbH) to achieve a lateral movement of 50 mm. Clearly, both circuit parameters are affected by the presence of the ferrite. Therefore locating an otherwise invisible ferrite with a good accuracy is made possible with the present technique.

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