Hyperthermic effects of dissipative structures of magnetic nanoparticles in large alternating magnetic fields

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Targeted hyperthermia treatment using magnetic nanoparticles is a promising cancer therapy. However, the mechanisms of heat dissipation in the large alternating magnetic field used during such treatment have not been clarified. In this study, we numerically compared the magnetic loss in rotatable nanoparticles in aqueous media with that of non-rotatable nanoparticles anchored to localised structures. In the former, the relaxation loss in superparamagnetic nanoparticles has a secondary maximum because of slow rotation of the magnetic easy axis of each nanoparticle in the large field in addition to the known primary maximum caused by rapid Néel relaxation. Irradiation of rotatable ferromagnetic nanoparticles with a high-frequency axial field generates structures oriented in a longitudinal or planar direction irrespective of the free energy. Consequently, these dissipative structures significantly affect the conditions for maximum hysteresis loss. These findings shed new light on the design of targeted magnetic hyperthermia treatments.

\[ \chi'' = \chi''_0 \left( 2\pi f \tau \right) \div \left[ 1 + \left( 2\pi f \tau \right)^2 \right], \]

where \( \chi''_0 \) is the initial susceptibility per unit mass of SPIONs. When reversal and rotation occur in a nanoparticle in parallel, the characteristic time \( \tau \) is given by the following equation:

\[ \tau^{-1} = \tau_N^{-1} + \tau_B^{-1}, \]

where \( \tau_N \) is the Néel relaxation time for reversal, and \( \tau_B \) is the Brownian relaxation time for rotation. Consequently, the heating efficiency \( P_{\text{th}} / (H_{\text{ac}} f) \) for individual monodisperse nanoparticles has a single maximum at the peak frequency \( 2\pi f_p \), where \( f_p = \tau^{-1} \). For a sufficiently small SPION, \( \tau \) is determined only by \( \tau_N \) because \( \tau_N \) is much shorter than \( \tau_B \). In this case, it has been assumed that the conditions for maximising the efficiency are unaffected by uncontrolled rotation of the nanoparticles.

However, in some experiments, dual peaks have been observed for the frequency dependence of \( \chi'' \propto P_{\text{th}} / (H_{\text{ac}} f)^{\gamma} \) despite the prediction of a single peak at a \( 2\pi f_p \) value of \( \tau^{-1} = \tau_N^{-1} + \tau_B^{-1} \). For this reason, size
distribution" or aggregation of the nanoparticles was considered based on the linear response theory. In an earlier study, the low-frequency peak observed for the susceptibility was attributed to Brownian relaxation of larger nanoparticles, while the high-frequency peak was attributed to Néel relaxation of smaller nanoparticles. In another study, the low- and high-frequency peaks were attributed to individual and agglomerated nanoparticles, respectively. Thus the observed dual peaks have been theoretically explained by the coexistence of two kinds of nanoparticles. In other words, these explanations are based on the assumption that a single kind of nanoparticle will produce only a single peak at $\tau^{-1} (=\tau_N^{-1} + \tau_B^{-1})$. However, this assumption has never been theoretically verified under a large AC magnetic field, where the linear response theory does not hold.

The second guiding principle is to use hysteresis loss in ferromagnetic nanoparticles. In mechanical models such as the Stoner–Wohlfarth model for single domain particles, $\mu$ is reversed in the time scale of Larmor precession (picoseconds) when $\Delta \mu$ disappears at the switching field $H_{sw}$ because thermal fluctuations are not considered. Such fast reversals are considered to dominate the response to high frequency AC magnetic field because the Brownian relaxations of large ferromagnetic nanoparticles are generally slow compared with the oscillation of the field. In this case, the work done in one cycle is given by the area inside the hysteresis loop, $\mu H_{sw} M_s$, where $M_s$ is the spontaneous magnetisation and $\mu$ is a coefficient related to the rectangularity of the loop. In the simple case of a rectangular hysteresis loops, $\mu = 0$ for $H_{ac} < H_{sw}$ and $4$ for $H_{ac} \geq H_{sw}$. Consequently, the maximum efficiency, $P_{bl}/(H_{ac}^2) = \mu H_{sw} / (H_{ac}/H_{sw}) / \rho$, where $\rho$ is the density of magnetite, is achieved when $H_{ac}$ is adjusted to $H_{sw}$. Because $H_{sw}$ depends on the magnetic anisotropy field $H_K$ specific to each nanoparticle, it has been assumed that, in cases where reversal is much faster than rotation, the amount of hysteresis loss is unaffected by the inhomogeneous rotations of nanoparticles in cancer cells.

In recent experimental studies, the observed $P_{bl}$ of immobilised ferromagnetic nanoparticles was lower than that of the same nanoparticles dispersed in a fluid. Kim et al. attributed the difference to variation in the rates of convective heat transfer. Müller et al. suggested that the orientation or agglomeration of the nanoparticles, or interaction effects, may be responsible for the observed difference. The orientation of nanoparticles is important because it is related to the magnetic torque intrinsic in rotatable ferromagnetic nanoparticles. However, there has been no theoretical study on magnetic field-driven reversals of $\mu$ in ferromagnetic nanoparticles with easy axes that simultaneously rotate under the magnetic torque.

There are many reported inconsistencies between experimental results and predictions based on the above two guiding principles for optimising hyperthermia treatment. These guiding principles are based on the simple models established at the two limits: in zero magnetic field or at zero temperature. Under the conditions for hyperthermia ($H_{ac} \neq 0$, $T \neq 0$), where $T$ is temperature, the validity of the guiding principles has not been theoretically verified even for an ideal system of non-interacting monodisperse nanoparticles. Consequently, we attempted to simulate the thermally assisted magnetic response of individual superparamagnetic/ferromagnetic iron oxide nanoparticles exposed to a large AC magnetic field like that used in hyperthermia treatment. The simulation was performed in the following two extreme cases: non-rotatable nanoparticles strongly anchored to structures resembling organelles, and rotatable nanoparticles in an aqueous phase mimicking cytoplasm. In the simulations, the thermally activated reversals of $\mu$ were calculated between the meta-stable directions. Simultaneously, the rotations of the spheroidal nanoparticles were computed in the inertialless limit (Brownian dynamics simulation), where the frictional torque always balances with magnetic torque and with Brownian torque (details are reported in the Methods section). The results allow examination of whether the relaxation loss for $\tau_N < \tau_B$ and the hysteresis loss at $H_{ac} = H_{sw}$ are independent of the ability of the nanoparticles to rotate under the conditions for hyperthermia treatment.

### Results

The magnetic response to an AC magnetic field $H_{ac} \sin(2\pi f t)$ at $T = 310$ K was simulated for individual monodisperse spheroidal magnetite nanoparticles with non-magnetic surfactant layers in non-rotatable and rotatable situations (see the Methods section for details). Results are presented for the following representative nanoparticles: nearly spherical nanoparticles with an aspect ratio, $\kappa$, of 1.1 and an equatorial diameter, $2R_{eq}$, of 18 nm, and elongated spherical particles with $\kappa = 1.4$ and $2R_{eq} = 24$ nm. The parameters of these nanoparticles are summarised in Table 1. The former nanoparticles with $\tau_N (H_{ac} = 0)$ of 20 ns can be considered as typical SPIONs, while the latter with $\tau_N (H_{ac} = 0)$ of $2 \times 10^5$ s (1 year) can be regarded as typical ferromagnetic nanoparticles in the frequency range of hyperthermia treatment ($2\pi f \approx 10^7$ Hz). Results for nanoparticles with other sizes and shapes are shown in the Supplementary Information.

The magnetisation curves of the non-rotatable nearly spherical nanoparticles at low $H_{ac}$ (1 kA/m) are shown in Fig. 1. A linear response without hysteresis was observed at $f = 100$ kHz. Such superparamagnetic behaviour is reasonable because the estimated $\tau_N (H_{ac} = 0)$ for the nanoparticles is 20 ns. Hysteresis appeared in the curves at $f = 1,000$ kHz. As $f$ increased further, the area inside the hysteresis loop grew. This area corresponds to the work done in one cycle. Therefore, $P_{bl}/(H_{ac}^2)$ also increased with $f$, and a single maximum was observed at a peak frequency, $f_p$, of 10,000 kHz (Fig. 1 (b)). Figure 2(a) shows the $H_{ac}$ dependence using a contour plot of $P_{bl}/(H_{ac}^2)$. As $H_{ac}$ increased, $f_p$ shifted towards higher frequencies. As indicated by the dashed line in Fig. 2(a), this shift can be explained by the values of $\tau_N (H_{ac})$ calculated using the conventional Brown’s equation as follows:

$$
[H_{ac} (H_{ac})]^{-1} = f_p (1 - h) \left\{ (1 + h) \exp \left[ (-K_d V / K_b T) (1 + h)^2 \right] 
+ (1 - h) \exp \left[ (-K_d V / K_b T) (1 - h)^2 \right] \right\},
$$

where $h = \mu H/(2 K_d V)$, $K_d$ is the shape anisotropy constant, $V$ is the volume of the magnetic core, and $K_b$ is the Boltzmann constant. Therefore, the emergence of a single peak in $P_{bl}/(H_{ac}^2)$ can be attributed to Néel relaxation loss, as expected for SPIONs.

For the nearly spherical nanoparticles with a low $H_{ac}$ (1 kA/m), the magnetisation curves in the rotatable case were the same as those in the non-rotatable case (see Fig. 1). An equivalent maximum appeared in the $f$-dependence of $P_{bl}/(H_{ac}^2)$ in the linear response range.

### Table 1 | Parameters of the simulated nanoparticles: including the aspect ratio $\kappa$, equatorial diameter $2R_{eq}$, thickness of the surfactant layer $\delta R$, density of magnetite $\rho$, spontaneous magnetisation $M_s$, anisotropy field $H_K$, viscosity $\eta$, Néel relaxation time $\tau_N (H = 0)$, and Brownian relaxation time $\tau_B$.

| $\kappa$ | $2R_{eq}$ (nm) | $\delta R$ (nm) | $\rho$ (kg/m$^3$) | $M_s$ (kA/m) | $H_K$ (kA/m) | $\eta$ (mPa s) | $\tau_N (H = 0)$ (sec) | $\tau_B$ (sec) |
|---|---|---|---|---|---|---|---|---|
| Nearly spherical nanoparticle | 1.1 | 18 | 4.5 | 5200 | 450 | 17 | $1.0 / \infty$ | $2 \times 10^{-8}$ | $8 \times 10^{-6}$ |
| Elongated spheroidal nanoparticle | 1.4 | 24 | 6.0 | 5200 | 450 | 57 | $1.0 / \infty$ | $2 \times 10^7$ | $2 \times 10^{-6}$ |
The magnetisation curves at $f = 10\,000\,\text{kHz}$ for the elongated spheroidal nanoparticles, which are typical ferromagnetic nanoparticles, in the non-rotatable case are shown in Fig. 4(a). The curve was reversible at $H_{\text{ac}} = 20\,\text{kA/m}$, and hysteresis appeared in the curve at $H_{\text{ac}} = 26\,\text{kA/m}$. As $H_{\text{ac}}$ increased further, the area inside the hysteresis loop grew. When $H_{\text{ac}}$ became larger than $32\,\text{kA/m}$, the expansion of the area was saturated and the shape of the magnetisation curve approached that predicted by the Stoner–Wohlfarth model. $P_{\text{H}}(H_{\text{ac}}; f)$ was almost zero at low $H_{\text{ac}}$, then at approximately $30\,\text{kA/m}$ it began increasing rapidly with $H_{\text{ac}}$, followed by a gradual decrease with increases in $H_{\text{ac}}$ (Fig. 4(b)). This behaviour depends weakly on the frequency (Fig. 5(a)). In mechanical models that do not consider thermal fluctuation, a hysteresis loop appeared when $H_{\text{ac}}$ was higher than $H_{\text{sw}}$. Because $H_{\text{sw}}$ of ferromagnetic nanoparticles with randomly oriented easy axes ranges from $H_{\text{K}}/2 = 29\,\text{kA/m}$ to $H_{\text{K}} = 57\,\text{kA/m}$, and is often close to $0.5\,H_{\text{K}}$, that $P_{\text{H}}(H_{\text{ac}}; f)$ is almost independent of frequency at $H_{\text{ac}} > 30\,\text{kA/m}$ in the non-rotatable range ($H_{\text{ac}} = 1\,\text{kA/m}$) (Fig. 1(b)). This behaviour is consistent with the above assumption because the estimated $\tau_{\text{N}}(H_{\text{ac}} = 0)$ of $20\,\text{ns}$ is much shorter than $\tau_{\text{B}} = 8\,\mu\text{s}$ (Table 1). The shift of this peak with increasing $H_{\text{ac}}$ is analogous to that in the non-rotatable case (Fig. 2(b)). However, another maximum of $P_{\text{H}}(H_{\text{ac}}; f)$ was observed at $H_{\text{ac}} = 8 - 16\,\text{kA/m}$ and $f = 30\,\text{kHz}$ in the contour plot shown in Fig. 2(b). A secondary maximum like this has not previously been theoretically predicted for individual monodisperse nanoparticles. Figure 3(a) shows the magnetisation curves calculated under these conditions. Unlike the non-rotatable case, an S-shaped hysteresis loop without remanence existed. At the same time, the mean orientation of the long (easy) axes of the nanoparticles showed butterfly-shaped hysteresis, as shown Fig. 3(b). Because such behaviour cannot be explained using the present linear response theory, its origin is discussed in the next section from the viewpoint of the rotation of the long axis of SPION.

Figure 2 | Efficiency of heat dissipation in the nearly spherical nanoparticles (typical SPIONs) that are (a) non-rotatable and (b) rotatable, where $P_{\text{H}}$ is the specific energy dissipation rate. Dashed lines represent the Néel relaxation time $(2\pi\tau_{\text{N}})^{-1}$, dotted lines show the Brownian relaxation time $(2\pi\tau_{\text{B}})^{-1}$, and solid lines indicate typical angular velocity, $\omega_{\text{d}}(H = H_{\text{ac}}, \psi = \pi/4)/2\pi$, of the rotation caused by magnetic torque. White lines show the thresholds for biomedical safety. Diamonds A and B on the white lines denote the conditions for maximum $P_{\text{H}}(H_{\text{ac}}; f)$ in the rotatable nanoparticles.

Figure 3 | Magnetic response of nearly spherical nanoparticles (typical SPIONs) with an applied AC field with $H_{\text{ac}} = 8\,\text{kA/m}$ and $f = 30\,\text{kHz}$. (a) Steady magnetisation curves, (b) mean orientation of the long (easy) axis of the nanoparticles, $<\cos\theta>$. Orientations are indicated in the inset images.

Figure 4 | Magnetic response of elongated spheroidal nanoparticles (typical ferromagnetic nanoparticles) in high-frequency AC fields with $f = 10\,000\,\text{kHz}$ and various values of $H_{\text{ac}}$. (a) Steady magnetisation curves in the non-rotatable case; the corresponding curves for rotatable nanoparticles are presented in Fig. 6(a) and (b). Solid lines indicate Stoner–Wohlfarth model curves. (b) $H_{\text{ac}}$-dependence of the efficiency of heat dissipation. The open and solid symbols show the values of the non-rotatable and rotatable nanoparticles, respectively. The arrows indicate the peak maxima of $P_{\text{H}}(H_{\text{ac}}; f)$ in both cases, and the broken line shows half of the anisotropic field, $H_{\text{K}}/2$. The inset shows an enlarged view.
ferromagnetic nanoparticles is consistent with the properties expected for the hysteresis loss.

Figure 5 shows the magnetisation curves for rotatable elongated spherical nanoparticles at $f = 10,000$ kHz. Because the magnetic response slowly changed after the AC magnetic field was applied at $t = 0$, transient variations of the hysteresis loops are observed. The shape of the major hysteresis loop at $H_{ac} = 60$ kA/m was initially consistent with that predicted by the Stoner–Wohlfarth model with randomly oriented easy axes. However, the remanence of the major loop gradually increased from 0.5 $M_t$ to $M_r$. In other words, the major loop became squarer, and the area inside the loop increased with time. In comparison, the remanence of the minor loop at $H_{ac} = 26$ kA/m gradually decreased and the area became smaller over time. As shown in Fig. 6(c) and (d), the long (easy) axes of the nanoparticles gradually turned when the variations of the loops proceeded (see the next section for details). Consequently, the increased area of the major hysteresis loops and decreased area of the minor loops caused the maximum of $P_{th}(H_{ac}, f)$ to shift towards higher $H_{ac}$ compared with the non-rotatable case (see arrows in Fig. 4(b)). Note that reversals occurred every hundred nanoseconds (~1/11), while rotations took several microseconds (Fig. 6(c)). Thus, the assumption that the amount of hysteresis loss is unaffected by the rotation of nanoparticles when reversal is significantly faster is invalid for ferromagnetic nanoparticles in large AC magnetic fields at high frequencies.

Before discussing this novel phenomenon observed at high frequencies, the other important variation in the contour plot of $P_{th}(H_{ac}, f)$ (Fig. 5) that occurred because of the ability of the ferromagnetic nanoparticles to rotate at lower frequencies shall be examined. The maximum of $P_{th}(H_{ac}, f)$ shifted toward lower $H_{ac}$ below 100 kHz for the rotatable elongated spherical nanoparticles, while it stayed between $H_{K2}$ and $H_K$ in the non-rotatable case. Figure 7(a) shows the magnetisation curve obtained when $H_{ac} = 16$ kA/m and $f = 30$ kHz. The curve in the rotatable case had an obvious hysteresis loop with a large remanence in the steady state, but there was no hysteresis observed for the non-rotatable situation. Because $H_{ac} = 16$ kA/m is much smaller than $H_{K2}/2$, no reversals of $\mathbf{M}$ occur at any orientation of the easy axis so hysteresis is not observed for the latter case. Figure 7(b) shows the variation of $<\cos\theta>$ in the rotatable case, where $<\cos\theta> (0 < \theta < \pi/2)$ is the mean angle between the magnetic field and the long axes of the spherical nanoparticles. Note that $<\cos\theta>$ is synchronised with $|M/M_r| = |\cos\psi|$, where $\psi$ is the angle between $\mathbf{M}$ and $\mathbf{H}$. This fact indicates that the hysteresis in the rotatable case (Fig 7(a)) is mainly caused by the rotation of the easy axis where the direction of $\mathbf{M}$ is fixed. Consequently, heat equivalent to the hysteresis loss dissipates even at $H_{ac} < H_{K2}/2$.

For Brownian relaxation, $\tau_B$ can be expressed as follows:

$$\tau_B = \left(\frac{3\eta V_{hi}(0.8 + 0.2c)}{|k_B T|}\right),$$

where $\eta$ is the viscosity of the surrounding medium, and $V_{hi}$ is the hydrodynamic volume. In equation (4), the frictional torque for spheroids, described in the Methods section, is considered. For the elongated spheroidal nanoparticle, $(2\pi\tau_B)^{-1}$ is calculated to be 8 kHz. This value is too low to cause the nanoparticle to rotate at 30 kHz. Therefore, Yoshida et al.\(^{33}\) also took into account the rotation caused by magnetic torque, $\mathbf{M}(t) \times \mathbf{H}(t)$. They concluded that the area of the hysteresis loop was maximised as follows:

$$2\pi f_t = \tau_B^{-1} \left[1 + 0.07(\mu H_{ac}/k_B T)^2\right]^{0.5}.$$  

The location of the peak in $P_{th}(H_{ac}, f)$ below 100 kHz can be explained by this equation, as shown in Fig. 5(b). An expression that describes all of the variation in the position of the primary peak of
conditions, occurs for ferromagnetic nanoparticles of any size, as long as the magnetic field to rotate. This expression is for the primary maximum; the secondary maximum is discussed later. The second loop at \( H = H_{ac} \) shows butterfly-shaped hysteresis under these conditions. This behaviour explains the atypical magnetic response in the period \( f^{-1} \) (33 ms) (Fig. 3(b)). Initially (at \( t = 0 \)), no magnetisation exists because the occupation probability of \( \mu \) in the two stable directions parallel to the low (easy) axis are equalised in a zero magnetic field. As \( H \) increases, the occupation probability in the more stabilised direction immediately increases because of reversals on a time scale of \( \tau_{m} \) (\( \approx 20 \) ns). The reversed \( \mu \) in the stabilised direction is not completely parallel to \( H \), \( \psi \neq 0 \), and the magnetic torque \( \mu H \sin \psi \) turns the long (easy) axis towards the direction of the field. If we neglect Brownian torque \( \mathcal{A}(t) \) (see equation (11) in the Methods section), the angular velocity of the rotation due to magnetic torque can be expressed as

\[
\omega_{1}(H(t), \psi(t)) = \left[ \mu H(t) \sin \psi(t) / [6\eta V_{VH}(0.8 + 0.2k)] \right].
\]

Hence, \( \omega_{1}(H(t), \psi(t)) \) increases in proportion to the field amplitude \( H = H_{ac}\sin(2\pi f\tau) \). For example, \( \omega_{1}(H, \psi = \pi/4) = 0.15 \times 10^{6} \) rad/s when \( H = 5 \text{ kA/m} \). Subsequently, \( H \) decreases to zero at \( t = 1/2f = 17 \) ms, and the occupation probabilities are again equalised because reversal is rapid, so the magnetic torque disappears. Alternatively, the Brownian torque randomises the orientation of the long axis on a time scale of \( \tau_{m} = 8 \mu s \). Therefore, competition between the magnetic and Brownian torques can cause the butterfly-shaped hysteresis of \( \langle \cos \theta \rangle \). Because the equilibrium magnetisation of SPIONS with easy axes parallel to \( H \) is higher than that of randomly oriented SPIONS\(^{13,14} \), the magnetisation curve shows hysteresis without remanence. Consequently, a secondary maximum appears for the rotatable SPIONS even though \( \tau_{m} \propto H \).

Next, we investigate the influence of the ability of elongated spheroidal nanoparticles to rotate under a high-frequency AC magnetic field on the shift of the maximum \( P_{16}/(H_{ac} f) \). As shown in Fig. 6(a) and (b), the magnetisation curves varied after an AC magnetic field was applied at \( t = 0 \). At the same time, transient variations also occurred in \( \langle \cos \theta \rangle \), as shown in Fig. 6(c). In the case of the major loop at \( H_{ac} = 60 \text{ kA/m}, \langle \cos \theta \rangle \) gradually increased from 0.5 to 0.95. In other words, the long (easy) axis became oriented towards the direction parallel to \( H \). The characteristic time, \( \tau_{rot} \), was estimated to be 1.3 \( \mu \)s using the approximation of exponential decay. Note that the direction of \( \mu \) is not completely parallel to \( H \) even for \( H \approx H_{K} \); even \( \mu \) is already reversed for all of the nanoparticles. Because \( \psi \) is 0.43 when \( \cos \psi = 0.9 \), a large magnetic torque can turn the long axis even if the magnetisation is almost saturated after reversals at \( H \approx H_{K} \). Indeed, \( \tau_{rot} \) at \( H_{ac} \approx H_{K} \) is comparable to the reciprocal of typical values of \( \omega_{1}(H = H_{ac}, \sin \psi = 0.43) \) (Fig. 6(d)). Therefore, these transient variations can be attributed to the longitudinal orientation being adopted preferentially because of the magnetic torque.

In the minor loops at \( H_{ac} = 26 \text{ kA/m}, \) the remanence of the rotatable nanoparticles decreased gradually with time (Fig. 6(b)) and \( \langle \cos \theta \rangle \) simultaneously decreased from 0.5 (Fig. 6(c)). The long axis was oriented perpendicular to \( H \) during this period, although the longitudinal orientation is preferred when the Zeeman energy is considered. It should be noted that the angle \( \psi \) for \( \mu \) in a stable direction more parallel to \( H \) is smaller than that in a metastable direction less parallel to \( H \) (Fig. 6(d)). In other words, the magnitude of the magnetic torque toward the longitudinal orientation in the former is weaker than that toward the perpendicular orientation in the latter. This difference makes the orientation of the long axis planar on average, because the stable and metastable states alternate every half period when the reversal of \( \mu \) is blocked in the minor loop. These arguments suggest that the slowing of the rotation for

\[
\tau_{s} = [\tau_{N}^{-1} + \tau_{B}^{-1}]^{-1} + 0.07(\mu H_{ac}/k_{B}T)^{0.5}.
\]
0.5 $H_K \leq H_{ac} \leq H_K$ (Fig. 6(d)) can be attributed to compensation between two magnetic torques in the intermediate range. Briefly, in ferromagnetic nanoparticles in the aqueous phase, longitudinal or planar orientations are adopted, irrespective of the free energy, as dissipative structures under a high-frequency AC magnetic field. Consequently, $P_{2f}(H_{ac})$ increases gradually in major hysteresis loops and decreases in minor loops. These variations cause the maximum of $P_{2f}(H_{ac})$ to shift towards higher $H_{ac}$.

Finally, we return to the contour plots of $P_{2f}(H_{ac})$ in Figs. 2 and 5, and discuss the effect of rotation on the design for maximising $P_{2f}(H_{ac})$. If a safety limit of $H_{ac} < 4.85 \times 10^4$ Am s$^{-1}$ is applied, then maximum values of $P_{2f}(H_{ac})$ for rotatable SPIONs and ferromagnetic nanoparticles are obtained at the conditions shown by diamonds A and C in Figs. 2(b) and 5(b), respectively. However, no heat dissipation occurs under the same conditions (A and C) if the rotation of these nanoparticles is blocked (Figs. 2(a) and 5(a)). If a highly amplified AC magnetic field $H_{ac} < 1.74 \times 10^5$ Am s$^{-1}$ is allowed$^{40}$, a maximum $P_{2f}(H_{ac})$ of $3.0 \times 10^4$ m$^3$ s$^{-1}$ for the rotatable ferromagnetic nanoparticles can be obtained (diamond D in Fig. 5(b)). However, $P_{2f}(H_{ac})$ halves when the rotation of these nanoparticles is blocked (Fig. 5(a)) because oriented structures are not formed. In contrast, condition B for the primary maximum of $P_{2f}(H_{ac})$ in the rotatable SPIONs remains the optimum condition when these nanoparticles cannot rotate (Fig. 2(a) and (b)). This is because the long (easy) axis of SPIONs are randomly oriented in rotatable SPIONs as Brownian torque has more effect than magnetic torque in a weak magnetic field. As demonstrated here, rotation generated by the magnetic torque caused by a large alternating magnetic field greatly affects the conditions for maximising heat dissipation in magnetic nanoparticles.

In this study, we simulated the magnetic responses of superparamagnetic and ferromagnetic magnetite nanoparticles in a large alternating magnetic field. The results show that both the relaxation loss of SPIONs in a low frequency AC magnetic field and the secondary relaxation loss in SPIONs in a high frequency AC magnetic field demonstrate here, rotation generated by the magnetic torque in an AC magnetic field. These rotations lead to dissipative structures under a high-frequency AC magnetic field. Consequently, the secondary loss peak becomes less diffuse compared with the primary relaxation loss peak. For ferromagnetic nanoparticles, the shift of the hysteresis loss at high frequencies should still be significant even if the size of nanoparticles is not uniform, because the anisotropy field is independent of nanoparticle size. Finally, the effect of dipole–dipole interactions is considered, because the density of nanoparticles accumulated in cancer cells might be inhomogeneous if they are trapped at specific sites. In such a case, chain structures of longitudinally aligned nanoparticles have been conventionally discussed in a magnetic field, although their details are still controversial$^{48}$. Our findings illuminate this conventional view, because in some cases, formation of structures with a planar orientation is predicted even for individual ferromagnetic nanoparticles. In future studies, we will clarify a variety of dissipative structures, which are different from ordinary chains, for interacting nanoparticles. As discussed here, knowledge of the heat dissipation in the non-equilibrium steady states of rotatable nanoparticles is essential for the design of targeted magnetic hyperthermia treatments using large AC magnetic fields.

**Methods**

**Model for the simulation.** The magnetic response to an AC magnetic field applied at an oblique angle to the long easy axis of a spherical particle can be precisely simulated by solving the stochastic Landau–Lifshitz–Gilbert equations. However, we are only interested in the reversal of $\theta$ once every microsecond because the frequency used for hyperthermia is limited. Therefore, we can use a well-known coarse-grained approach, or “two-level approximations”$^{44}$, that considers the totally activated reversals between the meta-stable directions, $(\phi_1, \psi_1)$ and $(\phi_2, \psi_2)$, via the mid-way saddle point at $(\phi_3, \psi_3) = U(\phi, \psi)$.

**Simulation of the reversal.** The detailed trajectories of $\theta$ in a magnetic field applied at an oblique angle $\theta$ to the long easy axis of a spherical particle can be precisely simulated by solving the stochastic Landau–Lifshitz–Gilbert equations. However, we are only interested in the reversal of $\theta$ once every microsecond because the frequency used for hyperthermia is limited. Therefore, we can use a well-known coarse-grained approach, or “two-level approximations”$^{44}$, that considers the totally activated reversals between the meta-stable directions, $(\phi_1, \psi_1)$ and $(\phi_2, \psi_2)$, via the mid-way saddle point at $(\phi_3, \psi_3)$. The reversal probability from $(\phi_1, \psi_1)$ to $(\phi_2, \psi_2)$, $v_{12}$, is given by $v_{12} = \exp(U(\phi_2, \psi_2) − U(\phi_1, \psi_1))/k_B T$, while the backward reversal...
In the simulation, the time evolution of the occupation probabilities, \( p_1(0), p_2(0) = 1 - p_2(0) \), at the two stable directions of a nanoparticle tilted at \( \theta \) was computed using the following relationship:

\[
\tilde{c}_1(\tilde{t}) = \sum \frac{\langle \hat{r}_1(\tilde{t} \mid \hat{r}_1(0)) \rangle}{\phi_2(\hat{r}_1(0))},
\]

where \( \phi_2(\hat{r}_1(0)) \) is the attempt frequency of \( 10^5 \) s\(^{-1}\).

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Simulation of reversal and rotation. The rotation of spheroidal nanoparticles was simulated in synchronisation with the reversal of \( \mu \). In Newtonian fluids, the frictional torque for rotation can be expressed as \( 6\eta V_T (0.8 + 0.2\varepsilon) v_{cT} \), where \( V_T = \mu/\pi R^3 + \partial R^3 \) is the hydrodynamic volume and \( \varepsilon \) is the angular velocity of rotation; \( \eta \) is the unit vector along the long axis of the spheroid; and \( \mu(t) \) is the effective magnetic moment. Under typical conditions, where \( \eta = 1 \) mPa\( \cdot \)s, \( V_T = 10^{-12} \) m\(^3\), \( \mu(t) = 1 \times 10^{-9} \) emu, and \( \eta/\mu(t) < 10^{-2} \), the inertia of the nanoparticle can be neglected. (Brownian dynamics simulation). In this inertialess limit, the frictional torque balances with magnetic torque \( \mu(t) \times H(0) \) and Brownian torque \( \partial \eta(t) \) as follows:

\[
6\eta V_T (0.8 + 0.2\varepsilon) v_{cT} = \mu(t) \times H(0) + 2\eta \partial \eta(t)
\]

where \( \tilde{t} = \tilde{t} - t \) is the Dizel delta function.

At the beginning of the simulation for the rotatable nanoparticles, an assembly of randomly oriented nanoparticles was generated, where their number ensures an optimum compromise between calculation time and precision. Then, the time evolution of the direction of \( \mu \) and the orientation of the long easy axis were computed by the following steps. (i) Using equation (9), reversible variations of the meta-stable field directions \( (\phi_1(t), \phi_2(t)) \) were realised by a pseudorandom number generated by the Xorshift algorithm. The backward reversal was computed in a similar manner. (ii) Substituting the reversed (or held) \( \mu(t) \) into equation (11), \( \phi_1(t) \) was calculated. (v) The change of \( \phi_1(t) \) was finally computed using the relationship \( \varepsilon \) was sufficiently small compared to one. Magnetisation was obtained using the relationship \( \mu = \mu(T) \times H(0) + 2\eta \partial \eta(t) \) at each step. Test simulations were performed to check the validity of this method. There have been no prior theoretical studies on systems where both reversal and rotation occur simultaneously in large AC magnetic fields. Consequently, comparisons with prior studies were performed under two extreme conditions. In the first case, high viscosities were assumed. Because reversal dominates rotation under these conditions, the results were compared with those reported by Carrey et al. In the second case, a high anisotropic field was assumed. Because rotation dominates reversal in this situation, the results were compared with the numerical simulations of Yoshida et al., where nonlinear Brownian rotational relaxation of magnetic fluids with a large excitation field was studied using the Fokker–Planck equation. The results obtained from our simulation of reversal and rotation were consistent with those of earlier studies (Supplementary Figs. S1–S4).

Therefore, we can now take a first step toward understanding the roles that rotation of a nanoparticle and reversal of its magnetic moment play together in large AC magnetic fields.

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Author contributions
H. M. performed the simulation. H. M. and B. J. wrote the manuscript.

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