Original paper

Control of the temperature rise in magnetic hyperthermia with use of an external static magnetic field

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ABSTRACT

Our purpose in this study was to investigate the usefulness of a method for controlling the temperature rise in magnetic hyperthermia (MH) using an external static magnetic field (SMF), and to derive an empirical equation for describing the energy dissipation of magnetic nanoparticles (MNPs) in the presence of both the alternating magnetic field (AMF) and SMF through phantom experiments.

We made a device that allows for MH in the presence of an SMF with a field-free point (FFP) using a Maxwell coil pair. We measured the temperature rise of MNPs under various conditions of AMF and SMF and various distances from the FFP (d), and calculated the specific absorption rate (SAR) from the initial slope of the temperature curve.

The SAR values decreased with increasing strength of SMF (H_s) and d . The extent of their decrease with d increased with an increase of the gradient of SMF (G_s). The relationships between SAR and H_s and between SAR and d could be well approximated by Rosensweig's equation in which the amplitude of AMF (H_{ac}) is replaced by $H_{ac}^2 / \sqrt{H_{ac}^2 + H_s^2}$, except for the case when G_s was small.

In conclusion, the use of an external SMF with an FFP will be effective for controlling the temperature rise in MH in order to reduce the risk of heating surrounding healthy tissues, and our empirical equation will be useful for estimating SAR in the presence of both the AMF and SMF and for designing an effective local heating system for MH.

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Introduction

Hyperthermia is one of the most promising approaches in cancer therapy. The most commonly used heating method in the clinical setting is capacitive heating that uses a radiofrequency (RF) electric field [1]. However, a major technical problem with hyperthermia is the difficulty of heating the targeted tumor to the desired temperature without damaging the surrounding tissues, as the electromagnetic energy must be directed from an external source and penetrate normal tissue. Other hyperthermia modalities, including RF ablation and ultrasound hyperthermia, have been reported [2,3], but the efficacies of these modalities depend on the size and depth of the tumor, and disadvantages include the ability to target the tumor and control the exposure.

Hyperthermia with use of magnetic nanoparticles (MNPs) (magnetic hyperthermia) was developed in the 1950s [4] and is still

under development in an effort to overcome the above disadvantages [5]. MNPs generate heat in an alternating magnetic field (AMF) as a result of hysteresis and relaxational losses, which results in heating of the tissue in which MNPs accumulate [6]. The degree to which magnetic hyperthermia can be applied to cancer therapy depends on the ability to deliver MNPs systematically to tumor cells in sufficient concentrations. If MNPs were adsorbed only to tumor cells, the MNPs could be administered intravenously. This feature would be of great advantage in terms of the quality of life of patients. However, because the administered MNPs migrate passively to a reticuloendothelial system such as the Kupffer cells of the liver and spleen, the passive targeting of MNPs for cancer is a very important issue for the establishment of cancer therapy with use of magnetic hyperthermia.

With regard to the delivery of MNPs, magnetoliposomes (MNPs encapsulated within liposomes) may be a promising tool for passive targeting. Shinkai et al. [7] developed magnetite cationic liposomes (MCLs) with improved absorption and accumulation properties within tumors. Administration of the MCLs, however, is limited to direct injection into the tumor tissue [8].

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The conjugation of antibodies to MNPs is a possible approach to achieving the passive targeting of MNPs for cancer. Le et al. [9] and Shinkai et al. [10] have developed MNPs conjugated to the Fab' fragments of anti-human MN antigen-specific antibody. DeNardo et al. [11] developed ^{111}In -chimeric L6 monoclonal antibody-linked MNPs for magnetic hyperthermia. However, because the target concentration is very low in antibody targeting tumors and particle penetration to the surrounding healthy tissues still has not been significantly prevented, producing considerable adverse effects [12], this approach cannot yet be translated successfully from research to the clinical stage. In contrast, the combination of thermosensitive liposomes and local heating has been shown to improve anticancer drug delivery in both animal and human patients [13]. Thermosensitive magnetoliposomes (MNPs encapsulated within thermosensitive liposomes) appear to be a versatile delivery system due to their biocompatibility, chemical functionality, and potential for use in a combination of drug delivery and hyperthermia treatment of cancers [13]. To establish this approach and to minimize the side effects, it will be necessary to focus the heat deposition into the targeted tissue or organ.

Besides the above-mentioned approaches, gene-based therapies are promising tools with which to treat a wide range of diseases. However, the efficient and specific delivery of a therapeutic gene to an identified tissue or organ and its controlled activation remain important challenges [14]. Spatial and temporal control of gene expression is made possible through the use of local heat deposition coupled with the use of a thermosensitive promoter [14]. Thus, to focus the heat deposition into the targeted tissue or organ will also be essential for establishing a gene-based therapeutic approach with use of a thermosensitive promoter.

Recently, Tasci et al. [15] proposed and designed a system that focuses the heat into very small regions using a static magnetic field (SMF) with a field-free point (FFP) generated by two solenoid coils, and reported that this method will be useful for making magnetic hyperthermia a more effective approach to cancer therapy with a decreased risk of heating surrounding healthy tissues. Although this approach appears to be useful for focusing the heat deposition into the targeted tissue or organ, it would be necessary to investigate the effectiveness of this approach under various conditions of AMF and SMF. Furthermore, it would be desirable to derive an equation describing the energy dissipation of MNPs in the presence of both the AMF and SMF for estimating and controlling the heat deposition into the targeted tissue or organ and for designing an effective local heating system.

Our purpose in this study was to investigate the usefulness of a method for controlling the temperature rise in magnetic hyperthermia with use of an external SMF under various conditions of AMF and SMF through phantom experiments. We also attempted to derive an empirical equation for describing the energy dissipation of MNPs in the presence of both the AMF and SMF, and validated this equation by comparing the energy dissipation estimated by this equation with the specific absorption rate measured experimentally under various conditions of AMF and SMF.

Materials and methods

Theory

Rosensweig [6] developed analytical relationships and computations of the energy dissipation of MNPs subjected to an AMF in the case when an SMF is not applied. From this theory, the energy dissipation (P) can be given by [6]

$$P = \pi\mu_0\chi_0 H_{ac}^2 f \frac{2\pi f \tau}{1 + (2\pi f \tau)^2}, \quad (1)$$

where μ_0 is the permeability of free space, χ_0 is the equilibrium susceptibility, and H_{ac} and f are the amplitude and frequency of the AMF, respectively. τ is the effective relaxation time given by $1/\tau = 1/\tau_N + 1/\tau_B$, where τ_N and τ_B are the Neel relaxation time and Brownian relaxation time, respectively [6]. τ_N and τ_B are given by $\tau_N = \tau_0 \sqrt{\pi e^I / 2\sqrt{T}}$ and $\tau_B = 3\eta V_H / k_B T$, respectively [6], where τ_0 is the average relaxation time in response to a thermal fluctuation, η is the viscosity of the medium, k_B is the Boltzmann constant, T is the absolute temperature, and $I = KV_M / k_B T$ with K being the anisotropy constant of MNP. V_H is taken as the hydrodynamic volume of MNP that is larger than the magnetic volume $V_M = \pi D^3 / 6$ for MNP of diameter D . As a model for V_H , it is assumed that $V_H = (1 + 2\delta/D)^3 V_M$, where δ is the thickness of a sorbed surfactant layer. Since the actual equilibrium susceptibility χ_0 is dependent on the magnetic field, χ_0 is assumed to be the chord susceptibility corresponding to the Langevin equation given by $\chi_0 = \chi_{i\xi} \left(\coth \xi - \frac{1}{\xi} \right)$, where

$\chi_i = \mu_0 \phi M_d^2 V_M / 3k_B T$, $\xi = \mu_0 M_d H_{ac} V_M / k_B T$, M_d is the domain magnetization of a suspended particle, and ϕ is the volume fraction of MNPs. In this study, we assumed M_d , K , and η as 414 kA/m, 4.7 kJ/m³, and 0.00235 kg/m/s, respectively, for Resovist® (magnetite, $\gamma\text{-Fe}_2\text{O}_3$) [16], and T as a room temperature (20 °C = 293.15 K).

When the SMF is applied, we hypothesized that the energy dissipation (P_s) is given by

$$P_s = \pi\mu_0\chi_0 \tilde{H}_{ac}^2 f \frac{2\pi f \tau}{1 + (2\pi f \tau)^2}, \quad (2)$$

where $\tilde{H}_{ac}$ is the amplitude of AMF corrected for the effect of SMF and is assumed to be given by $\tilde{H}_{ac} = CF \cdot H_{ac}$, with CF being a correction factor. In this study, CF was empirically assumed to be $CF = H_{ac} / \sqrt{H_{ac}^2 + H_s^2}$. It should be noted that when H_s is equal to 0, CF becomes unity. The validity of this assumption will be investigated by comparing the energy dissipation estimated by Eq. (2) with the experimental data of the specific absorption rate.

Because not all particles in a certain volume have the same diameter D , the energy dissipation P_s given by Eq. (2) should be averaged based on the particle size distribution as

$$\langle P_s(x) \rangle = \int_0^\infty P_s(D, x) \rho(D) dD, \quad (3)$$

where $P_s(D, x)$ denotes the energy dissipation of an MNP having a diameter D and located at x , and $\rho(D)$ denotes the probability density function of the particle size distribution. The result of a natural growth process during particle synthesis yields particles that do not have a single diameter D , but a polydisperse particle size distribution [17]. A reasonable and commonly used approach for modeling is the log-normal distribution [17]. Thus, $\rho(D)$ is given by [17]

$$\rho(D) = \frac{1}{\sqrt{2\pi}\sigma D} \cdot \exp \left[-\frac{1}{2} \left(\frac{\ln(D) - \mu}{\sigma} \right)^2 \right], \quad (4)$$

where μ and σ are given by $\mu = \ln[E(D)] - \frac{1}{2} \ln \left[\frac{\text{Var}(D)}{E^2(D)} + 1 \right]$ and $\sigma = \sqrt{\ln \left[\frac{\text{Var}(D)}{E^2(D)} + 1 \right]}$, respectively. $E(D)$ and $\sqrt{\text{Var}(D)}$ denote the mean and standard deviation (SD) of D , respectively. The integration in Eq. (3) was performed by use of the trapezoidal rule [19].

Furthermore, when the spatial distribution of MNPs is not infinitely narrow unlike Dirac's δ -function, it is necessary to consider the spatial distribution of MNPs. For the sake of simplicity, we consider the case when the MNPs distribute in one dimension from $-a$ to a , where a denotes the distance between the edge and the center of the distributed space, i.e., a half width of the source of MNPs. When the gradient of SMF along the x axis is denoted by G_s , H_s at a position of x is given by

$$H_s(x) = G_s(x - x_0), \quad (5)$$

where x_0 denotes the position of an FFP. When considering the variation of SMF in the targeted region, the energy dissipation can be obtained by averaging the energy dissipation within the distributed region as follows:

$$\langle P_s \rangle = \frac{\int_{-a}^a \langle P_s(x) \rangle dx}{2a}. \quad (6)$$

In this study, G_s was obtained by averaging the actual measured gradient of the magnetic field. Also, a was taken as 4 mm, because the diameter of the experimental tube filled with samples was 8 mm. As in Eq. (3), the integration in Eq. (6) was also performed by use of the trapezoidal rule [19].

Experimental studies

Figure 1 shows our experimental apparatus for magnetic hyperthermia. An AMF was generated with use of an external coil (3 cm in diameter and 10 cm in length) comprising 19-turned loops of copper pipe (3 mm in diameter) and was cooled by water to ensure a constant temperature and impedance. The coil was connected to a power supply (T162-5723BHE, Thamway, Shizuoka, Japan) through an impedance tuner (T020-5723AHE, Thamway, Shizuoka, Japan). The coil was placed in a Maxwell coil pair that allows for generating the SMF and FFP (Fig. 1). The DC electric power was supplied to the individual Maxwell coils by two programmable power supplies (EC1000S, NF Co., Kanagawa, Japan). The position of FFP was moved by applying different amounts of electric currents to the individual Maxwell coils. The experimental tube (8 mm in diameter) filled with samples was placed inside the coil generating the AMF, and the temperature of samples was measured with a fluorescence-type optical-fiber thermometer (FL-2000, Anritsu Meter Co., Ltd., Tokyo, Japan).

The strength of SMF (H_s) was measured as a function of the position from the center of the Maxwell coil pair by use of a gauss meter (GM-301, Denshijiki Industry Co., Ltd., Tokyo, Japan). Figure 2 shows an example of the measured H_s values as a function of the position from the center. The DC electric currents applied to the left and right coils (Fig. 1) are also shown in the caption of Fig. 2. The position of FFP was determined by finding the position at which the H_s value was zero from the interpolated data of H_s .

In this study, we used Resovist® as MNPs. Resovist® is an organ-specific contrast agent for magnetization resonance imaging (MRI), used for the detection and characterization especially of small focal liver lesions. Resovist® consists of superparamagnetic iron oxide (SPIO) (maghemite, γ - Fe_2O_3) coated with carboxydextran. We purchased Resovist® from Bayer HealthCare (Osaka, Japan) and adjusted the concentration of Resovist® to 100 mM Fe by diluting Resovist® with saline (total volume: 0.8 ml), which corresponds to $\phi = 0.0035$. When doing experiments, the sample including Resovist® was put into an experimental tube with an inner diameter of 8 mm. The height of the sample was approximately 16 mm. Biederer et al. [18] reported that the mean and SD of the particle

Figure 1. (a) Illustration of our experimental apparatus that allows for magnetic hyperthermia in the presence of the static magnetic field generated by use of a Maxwell coil pair. (b) Photograph of our experimental apparatus.

size of Resovist® were 15.2 nm and 3.21 nm, respectively, resulting

in $\sigma = \sqrt{\ln \left[\frac{3.21^2}{15.2^2} + 1 \right]} = 0.209$ in Eq. (4). In this study, we calculated $\langle P_s(x) \rangle$ given by Eq. (3) based on these data.

First, in order to investigate the effect of SMF on the temperature rise, we measured the temperature of samples from the start of heating to 10 min for a Resovist® concentration of 100 mM Fe with varying of the H_s value from 0 to 14 mT with a step of 2 mT for H_{ac} of 1.1, 1.5, and 1.9 kA/m, while f was fixed at 600 kHz. Second, in order to investigate the relationship between the position of FFP and the temperature rise, we measured the temperature from the start of heating to 10 min at various positions of FFP by varying the DC electric currents applied to the Maxwell coils for H_{ac} of 1.1, 1.5, and 1.9 kA/m, while f and G_s were fixed at 600 kHz and 0.9 T/m,

Figure 2. Strength of static magnetic field (H_s) measured by use of a gauss meter as a function of the position from the center of the Maxwell coil pair. The numbers denote cases with different DC electric currents applied to the left (I_L) and right coils (I_R). 1: $I_L = 6.4$ A and $I_R = -1.6$ A; 2: $I_L = 6.0$ A and $I_R = -2.6$ A; 3: $I_L = 5.7$ A and $I_R = -3.3$ A; 4: $I_L = 5.4$ A and $I_R = -4.1$ A; 5: $I_L = 5.0$ A and $I_R = -5.0$ A; 6: $I_L = 4.4$ A and $I_R = -5.6$ A; 7: $I_L = 4.2$ A and $I_R = -6.3$ A; 8: $I_L = 3.8$ A and $I_R = -7.0$ A; 9: $I_L = 3.5$ A and $I_R = -7.8$ A; 10: $I_L = 3.1$ A and $I_R = -8.6$ A.

respectively. Third, we measured the temperature from the start of heating to 10 min at various positions of FFP for f of 400, 500, and 600 kHz, while H_{ac} and G_s were fixed at 1.5 kA/m and 0.9 T/m, respectively. Finally, in order to investigate the relationship between G_s and the temperature rise, we measured the temperature from the start of heating to 10 min with varying of the G_s value as 0.4, 0.9, and 1.2 T/m, while H_{ac} and f were fixed at 1.5 kA/m and 600 kHz, respectively.

In general, the specific absorption rate (SAR) is used for characterizing the heating property of MNPs, which can be estimated by the formula [20]

$$\text{SAR} = \left(\frac{\Delta T}{\Delta t} \right)_0 \frac{C_w m_w + C_{Fe} m_{Fe}}{m_{Fe}}, \quad (7)$$

where $(\Delta T/\Delta t)_0$ is the initial slope of the time-dependent temperature curve, C_w is the specific heat capacity of water, C_{Fe} is the specific heat capacity of iron oxide, m_w is the mass of water in the fluid per unit mass of fluid, and m_{Fe} is the mass of iron oxide in the fluid per unit mass of fluid. The time-dependent temperature curve was fitted by use of the phenomenological Box–Lucas equation given by $T(t) = A(1 - e^{-Bt})$. This equation is often used to describe the AMF heating of MNPs [20]. The product of the fitting parameters, $A \times B$, is equivalent to the initial temperature rise $(\Delta T/\Delta t)_0$, and the SAR value was calculated from $(\Delta T/\Delta t)_0$ using Eq. (7). In this study, we assumed C_w and C_{Fe} as 4190 J/kg/K and 746 J/kg/K, respectively [16].

Results

Figure 3 shows an example of the temperature rise as a function of time for various values of H_s (0, 2, 4, 6, and 8 mT). In these cases, f and H_{ac} were fixed at 600 kHz and 1.5 kA/m, respectively. The solid lines represent the fitted curves using the phenomenological Box–Lucas equation given by $T(t) = A(1 - e^{-Bt})$. As shown in Fig. 3, the temperature rise decreased as H_s increased.

Figure 3. Temperature rise as a function of time for various values of H_s . The solid lines represent the fitted curves using the phenomenological Box–Lucas equation given by $T(t) = A(1 - e^{-Bt})$.

Figure 4 shows the SAR values as a function of H_s for H_{ac} of 1.1, 1.5, and 1.9 kA/m. For comparison, the $\langle P_s \rangle$ values calculated from Eq. (6) are also shown by solid, dashed, and dotted lines for H_{ac} of 1.1, 1.5, and 1.9 kA/m, respectively. It should be noted that the $\langle P_s \rangle$ values were normalized so that they agreed with the corresponding SAR values in the case when the H_s value was taken as zero. As shown in Fig. 4, the SAR values decreased with increasing H_s .

Figure 4. Specific absorption rate (SAR) values as a function of H_s for amplitudes of alternating magnetic field (AMF) (H_{ac}) of 1.1, 1.5, and 1.9 kA/m, with the frequency of AMF (f) being fixed at 600 kHz. The solid, dashed, and dotted lines represent the energy dissipation ($\langle P_s \rangle$) values calculated from Eq. (6). Note that the $\langle P_s \rangle$ values were normalized so that they agreed with the corresponding SAR values in the case when H_s was taken as zero. When calculating the $\langle P_s \rangle$ values, the mean and standard deviation (SD) of the diameter of Resovist® (D) were assumed to be 15.2 nm and 3.21 nm, respectively.

There was good agreement between the SAR values and the normalized $\langle P_s \rangle$ values calculated from Eq. (6).

Figure 5 shows the SAR values as a function of the position of samples from that of FFP for various values of H_{ac} (1.1, 1.5, and 1.9 kA/m). In these cases, f and G_s were fixed at 600 kHz and 0.9 T/m, respectively. The solid, dashed, and dotted lines represent the normalized $\langle P_s \rangle$ values calculated from Eq. (6) for H_{ac} of 1.1, 1.5, and 1.9 kA/m, respectively. It should be noted that the position of samples was fixed at the center of the system, and the position of FFP was moved. For example, -5 mm in the graph corresponds to the case when the sample was located at the center of the system, whereas the FFP was located at 5 mm to the right of the center. The strength of the SMF at the center of the sample is also shown on the upper axis in the graph. As shown in Fig. 5, the SAR values decreased with increasing distance from the FFP and increased with increasing H_{ac} . There was good agreement between the SAR values and the normalized $\langle P_s \rangle$ values calculated from Eq. (6).

Figure 6 shows the SAR values as a function of the position of samples from that of FFP for various values of f (400, 500, and 600 kHz). In these cases, H_{ac} and G_s were fixed at 1.5 kA/m and 0.9 T/m, respectively. The solid, dashed, and dotted lines represent the normalized $\langle P_s \rangle$ values calculated from Eq. (6) for f of 400, 500, and 600 kHz, respectively. As in Fig. 5, for example, -5 mm in the graph corresponds to the case when the sample was located at the center of the system, whereas the FFP was located at 5 mm to the right of the center. The strength of the SMF at the center of the sample is also shown on the upper axis in the graph. As shown in Fig. 6, the SAR values decreased with increasing distance from the FFP and increased with increasing f . As in Fig. 5, there was good agreement between the SAR values and the normalized $\langle P_s \rangle$ values calculated from Eq. (6).

Figure 5. SAR values as a function of the position of samples from that of FFP (x) for H_{ac} of 1.1, 1.5, and 1.9 kA/m, with f and the gradient of static magnetic field (G_s) being fixed at 600 kHz and 0.9 T/m, respectively. The solid, dashed, and dotted lines represent the $\langle P_s \rangle$ values calculated from Eq. (6) for H_{ac} of 1.1, 1.5, and 1.9 kA/m, respectively. Note that the $\langle P_s \rangle$ values calculated from Eq. (6) were normalized so that they agreed with the corresponding SAR values at $x = 0$ mm. When calculating the $\langle P_s \rangle$ values, the mean and SD of D were assumed to be 15.2 nm and 3.21 nm, respectively.

Figure 6. SAR values as a function of the position of samples from that of FFP (x) for f of 400, 500, and 600 kHz, with H_{ac} and G_s being fixed at 1.5 kA/m and 0.9 T/m, respectively. The solid, dashed, and dotted lines represent the $\langle P_s \rangle$ values calculated from Eq. (6) for f of 400, 500, and 600 kHz, respectively. Note that the $\langle P_s \rangle$ values calculated from Eq. (6) were normalized so that they agreed with the corresponding SAR values at $x = 0$ mm. When calculating the $\langle P_s \rangle$ values, the mean and SD of D were assumed to be 15.2 nm and 3.21 nm, respectively.

Figure 7. SAR values as a function of the position of samples from that of FFP (x) for G_s of 0.4, 0.9, and 1.2 T/m, with H_{ac} and f being fixed at 1.5 kA/m and 600 kHz, respectively. The solid, dashed, and dotted lines represent the $\langle P_s \rangle$ values calculated from Eq. (6) for G_s of 0.4, 0.9, and 1.2 T/m, respectively. Note that the $\langle P_s \rangle$ values calculated from Eq. (6) were normalized so that they agreed with the corresponding SAR values at $x = 0$ mm. When calculating the $\langle P_s \rangle$ values, the mean and SD of D were assumed to be 15.2 nm and 3.21 nm, respectively.

Figure 7 shows the SAR values as a function of the position of samples from that of FFP for various values of G_s (0.4, 0.9, and 1.2 T/m). In these cases, f and H_{ac} were fixed at 600 kHz and 1.5 kA/m, respectively. The solid, dashed, and dotted lines represent the normalized $\langle P_s \rangle$ values calculated from Eq. (6) for G_s of 0.4, 0.9, and 1.2 T/m, respectively. As in Figs. 5 and 6, for example, -5 mm in the graph corresponds to the case when the sample was located at the center of the system, whereas the FFP was located at 5 mm to the right of the center. As shown in Fig. 7, the SAR values decreased with increasing distance from the FFP, and the plot of the SAR values against the position from the FFP became broad as G_s decreased. There was good agreement between the SAR values and the normalized $\langle P_s \rangle$ values calculated from Eq. (6) except for the case when G_s was taken as 0.4 T/m.

Discussion

In this study, we made an experimental device that allows for magnetic hyperthermia in the presence of the SMF generated using a Maxwell coil pair (Fig. 1). This device can also generate an FFP and move it by varying the DC electric currents applied to the individual Maxwell coils (Fig. 2). We investigated the effect of SMF on the temperature rise in magnetic hyperthermia using this device and then evaluated the feasibility of controlling the temperature rise using an SMF with an FFP under various conditions of AMF and SMF. Our results (Figs. 4–7) demonstrated that it is possible to control the temperature rise in magnetic hyperthermia using the present method. Although the temperature rise can also be controlled by varying the duration of an AMF exposure, it would be difficult for this approach to control local heating, unlike the present method.

Since Resovist® has already been used as a contrast agent for MRI in the clinical setting and is commercially available [21], we used Resovist® as the MNPs in this study. As we reported in our previous paper [21], the energy dissipation and temperature rise in magnetic hyperthermia largely depend on the particle size of MNPs. Biederer et al. [18] reported that the mean and SD values of the diameter of Resovist® were 15.2 nm and 3.21 nm, respectively. Thus, we used these values when calculating the $\langle P_s(x) \rangle$ values from Eq. (3). As previously described, the result of a natural growth process during particle synthesis yields particles with a poly-disperse particle size distribution [17]. Thus, we took this feature into account by use of the probability density function of the particle size distribution based on a log-normal distribution [Eq. (4)]. Since the SD value of the diameter of Resovist® is relatively large, the use of Eq. (4) appears to be essential for analyzing the temperature rise in magnetic hyperthermia. Although we focused on Resovist® as MNPs in this study, it might be necessary to perform similar further studies with MNPs of different sizes and/or other MNPs in order to confirm the validity of our results.

We hypothesized that H_{ac} in Rosensweig's equation [Eq. (1)] is decreased by a factor of CF for magnetic hyperthermia in the presence of SMF. Since CF should be unity in the case when H_s is zero, we empirically assumed that CF is given by $H_{ac}/\sqrt{H_{ac}^2 + H_s^2}$ [Eq. (2)]. As shown in Figs. 4–7, the relationships between the SAR value and H_s and between the SAR value and the distance from FFP could be well approximated by the Rosensweig's equation in which H_{ac} is replaced by $H_{ac}/\sqrt{H_{ac}^2 + H_s^2}$ [Eq. (2)], except for the case when G_s was taken as 0.4 T/m (Fig. 7). These results appear to suggest that our empirical equation given by Eq. (2) is valid. Recently, Cantillon–Murphy et al. [22] investigated the effect of a large DC magnetic field on the magnetic fluid temperature rise in the MRI environment theoretically and by use of simulation, and reported that significant heating can take place even in low-field MRI systems where the magnetic

fluid saturation is not significant. Although it will be necessary to perform more detailed analysis by extending Rosensweig's approach and solving Shliomis' relaxation equation as done by Cantillon–Murphy et al. [22], we believe that our empirical equation obtained in this study will be useful for estimating the SAR value in the presence of SMF. However, it will be necessary to perform further studies under various conditions in order to establish the usefulness and effectiveness of our empirical equation.

As mentioned above, when G_s was taken as 0.4 T/m (Fig. 7), there was some difference between the SAR values actually measured and the normalized $\langle P_s \rangle$ values calculated from Eq. (6). As previously described, when calculating the energy dissipation using Eq. (6), we assumed that the magnetic field changes linearly with distance with a constant gradient (G_s). Actually, the magnetic field change with distance is not linear as shown in Fig. 2. Thus, the above finding shown in Fig. 7 may be due to this nonlinearity of SMF and/or the error caused in estimating G_s . Furthermore, we used a simple calculation model of one dimension when deriving Eq. (6). Ideally we would use a more realistic calculation model. However, our results suggest that the simple model used here is appropriate for the purpose of this study.

When SMF was not applied, i.e., at $H_s = 0$ mT in Fig. 4, the SAR value was proportional to H_{ac} raised to a power of approximately 2.3 (plot not shown). This result agreed with our previous report [21]. On the other hand, as can be seen from the comparison of Figs. 4 and 5, the SAR value at the FFP (Fig. 5) was smaller than the SAR value in the absence of SMF (Fig. 4) and this underestimation increased with decreasing H_{ac} (Fig. 5). This appears to be due to the fact that the spatial distribution of samples is not point-like but has a certain volume. When G_s was varied, with H_{ac} and f being constant, the SAR value at the FFP changed depending on the value of G_s (Fig. 7). However, Tasci et al. [15] reported that the SAR value at the FFP was unchanged in the case when only the value of G_s was varied. This may be due to the fact that Tasci et al. used spherical plastic cups with a diameter of 0.4 cm filled with a magnetic fluid [15], which were much smaller than our samples.

As previously described, we studied three cases with G_s of 0.4, 0.9, and 1.2 T/m. These values appear to be much higher than the gradient strength of the magnetic field used in MRI (10–50 mT/m [23]). Thus, when considering the clinical application of the present method, it might be necessary to take into account the issues such as the large inductance of gradient coils and the induction of eddy currents. Recently, a new imaging method called magnetic particle imaging (MPI) has been introduced that allows for imaging the spatial distribution of MNPs [24]. MPI uses the nonlinear response of MNPs to detect their presence in an AMF and performs spatial encoding by moving an FFP as done in our device. The gradient strength of the SMF used in MPI is also much higher than that for MRI [23,24]. However, Borgert et al. [25] reported that a gradient strength of 2.5 T/m could be achieved in a clinical scanner with reasonable effort. Thus, we expect that the gradient of the SMF for controlling the temperature rise in magnetic hyperthermia can also be achieved in the clinical setting. We also studied three cases with f of 400, 500, and 600 kHz. Atsumi et al. [26] used 600 kHz for f in consideration of the safety and the capacity of their power supply. Thus, we also selected the above values for f in consideration of the safety, the capacity of our power supply, and the heating efficiency [21].

In this study, we treated the case in which the FFP is moved in one dimension by use of a single Maxwell coil pair. However, it would be possible to extend this to two or three dimensions by the use of multiple Maxwell coil pairs. Furthermore, the position of the FFP was determined from the magnetic field strength actually measured at various positions by use of a gauss meter (Fig. 2). Theoretically, the magnetic field strength generated by a Maxwell coil pair can be calculated from the Biot–Savart law [27].

Thus, when the electric currents applied to the coils are known, the position of the FFP can be determined by solving the equations describing the magnetic field strength based on the Biot–Savart law [27]. Conversely, when the position of the FFP is given, the electric currents applied to the coils can be determined by a similar procedure. If this could be realized, it would become easy to control the position of the FFP, i.e., the position of local heating. As shown in Fig. 7, the plot of the SAR values against the position from the FFP became broad as G_s decreased. These results suggest that the area of local heating can be controlled by varying the value of G_s . The G_s value can also be calculated from the Biot–Savart law [27]. Thus, it would become possible to control not only the position but also the area of local heating by controlling the electric currents applied to the coils based on the Biot–Savart law [27]. This will further enhance the feasibility and effectiveness of magnetic hyperthermia, with the temperature rise being controlled and thereby reducing the risk of heating surrounding healthy tissues.

When application of the present method in the clinical setting is considered, the influence of blood flow on the temperature rise in living tissue should also be taken into account. Thus, for simulating the temperature rise behavior in vivo more accurately, it will be necessary to consider the bioheat transport via blood perfusion. Temperature response and blood perfusion have been studied by several investigators [28,29]. Bioheat transfer analysis often needs to deal simultaneously with transient and spatial heating inside living tissues. The Pennes bioheat transfer equation [30], which describes the exchange magnitude of the heat transfer between tissue and blood, has been used widely for solving the temperature distribution for thermal therapy [31]. We will perform a more detailed analysis by solving the Pennes bioheat transfer equation [30]. As previously described, the concentration of Resovist® was fixed at 100 mM in this study. As we reported in our previous paper [21], however, the temperature rise largely depends on the concentration of MNPs accumulated in the targeted region. Thus, for determining the concentration of MNPs suitable for achieving the effective temperature rise and for establishing the usefulness and effectiveness of the present method in cancer therapy, it will be necessary to perform in vivo experiments on tumor-bearing small animals injected with various concentrations of MNPs. We will perform these studies in the near future.

In conclusion, we made a device for generating an AMF and placed it in the SMF generated by a Maxwell coil pair that allows for generating and moving an FFP, and investigated the usefulness of a method for controlling the temperature rise in magnetic hyperthermia with use of the FFP. We verified that this method will be useful for controlling the temperature rise in magnetic hyperthermia in order to reduce the damage to surrounding healthy tissues. We also derived an empirical equation for describing the energy dissipation of MNPs in the presence of both the AMF and SMF, which will be useful for estimating the temperature rise in the presence of both the AMF and SMF, for controlling the temperature rise, and for designing an effective local heating system for magnetic hyperthermia.

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