Journal of Magnetism and Magnetic Materials 326 (2013) 14–21

Contents lists available at SciVerse ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

Simple models for the heating curve in magnetic hyperthermia experiments

G.T. Landi *

Instituto de Física da Universidade de São Paulo, 05314-970 São Paulo, Brazil

ARTICLE INFO

Article history:
Received 27 April 2012
Received in revised form
24 July 2012
Available online 31 August 2012

Keywords:
Magnetic hyperthermia
Single-domain particles
Dynamic hysteresis

ABSTRACT

The use of magnetic nanoparticles for magnetic hyperthermia cancer treatment is a rapidly developing field of multidisciplinary research. From the material's standpoint, the main challenge is to optimize the heating properties of the material while maintaining the frequency of the exciting field as low as possible to avoid biological side effects. The figure of merit in this context is the specific absorption rate (SAR), which is usually measured from calorimetric experiments. Such measurements, which we refer to as heating curves, contain a substantial amount of information regarding the energy barrier distribution of the sample. This follows because the SAR itself is a function of temperature, and reflect the underlying magneto-thermal properties of the system. Unfortunately, however, this aspect of the problem is seldom explored and, commonly, only the SAR at ambient temperature is extracted from the heating curve. In this paper we introduce a simple model capable of describing the entire heating curve via a single differential equation. The SAR enters as a forcing term, thus facilitating the use of different models for it. We discuss in detail the heating in the context of Néel relaxation and show that high anisotropy samples may present an inflection point related to the reduction of the energy barrier caused by the increase in temperature. Mono-disperse and poli-disperse systems are discussed in detail and a new alternative to compute the temperature dependence of the SAR from the heating curve is presented.

1. Introduction

The basic idea behind magnetic hyperthermia is to explore the energy dissipated as heat when magnetic nanoparticles are excited by an external high frequency magnetic field [1–8]. On the one hand this process is of substantial academic interest in light of the intricate relation between the heating power and the magnetic properties of the material [9–14]. On the other hand, several applications based on this technique have also been proposed [15,16], the most notable of which is in oncology, where the nanoparticles are used as local heating centers to eliminate tumorous cells [8,17,18].

Magnetic hyperthermia experiments usually measure the temperature variation of the sample under the application of a time varying magnetic field, commonly approximated by a harmonic wave of the form $H(t) = H_0 \cos \omega t$. The specific absorption rate (SAR) — a figure of merit of the experiment — is usually the only extracted parameter, computed from the initial slope of the measured data. Such procedure clearly squanders valuable information. For, embedded in the heating curve are details concerning the entire temperature dependence of the SAR. To illustrate the importance of such knowledge, note that in practically all dynamical models describing the magnetic properties of nanoparticles [11], the temperature (T) always appears in ratios of the form E/kT, where E is some effective barrier which, more often than not, is the fundamental quantity dictating the magnetic properties of the system. Whence, from knowledge of the temperature dependence of the SAR, one may extract information (qualitative at least) about the distribution of energy barriers in the system.

Several authors have also reported the existence of heating curves with an inflection point at small times (being initially convex instead of concave) [2,7,19,20]. One may argue that these initial points reflect an intrinsic response time of the experimental setup and should thence be discarded (e.g., transients in the coil which produce the magnetic field). Even though this is in fact true, it has also been reported that the response time may actually vary from one sample to another, an effect whose physical interpretation is not immediately obvious. Indeed, as we show in this paper, samples with high magnetic anisotropy may present an inflection point that is entirely unrelated to any response times. As we discuss, this is a direct consequence of the fact that the SAR is itself a function of temperature which, for some systems, may vary significantly over the temperature ranges involved in the experiment. Clearly, such property may incite altercations as to what value best represents the SAR and,

* Tel.: +55 113 091 7081.
E-mail address: gtlandi@gmail.com

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http://dx.doi.org/10.1016/j.jmmm.2012.08.034

more importantly, what impact this may have on actual oncological treatments.

In this paper we discuss a simple model to describe the heating curve in magnetic hyperthermia experiments. Besides its simplicity, this model also provides a direct link between the calorimetric and magnetic properties of the nanoparticles. Albeit not our primary goal, we also propose a new method of data analysis that, with sufficient care, may be successfully employed to extract information from real systems. More importantly, however, it is our hope that the present discussion may provide additional insight into the physical processes taking place in this important experiment.

The vast range of experimental systems (including *in vivo* experiments) clearly inhibits a general treatment of the problem. Thus, our focus is on a framework that is simple enough to represent at least a broad range of conditions. In this sense, it is interesting to avoid model containing spatial variables, as e.g., temperature gradients. For these would result in partial differential equations that are strongly dependent on the boundary conditions of the experiment. We thus approach the problem from the viewpoint of lumped element models; that is, we replace spatially distributed systems with discrete entities that approximate the real system under certain conditions. This allows us to describe the heating curve via a simple ordinary differential equation (DE), which is not only more easily tractable, but also more general: all properties of a given system are entirely represented by parameters appearing in the DE and may, therefore, be fitted from experiment.

The starting point for our analysis is based on the following very important argument. During the heating experiment the particle ensemble continually undergoes dynamic hysteresis loops with a period of $\sim 10^{-5}$ s. Energy is thus being continually dissipated, with a rate that depends not only on the external field and the magnetic properties of the sample, but also on the temperature, which itself changes during the experiment. In this sense, the system should never reach a *steady state*. However, the time scales of heat conduction are much larger than the average hysteresis cycle (heating experiments extend well beyond hundreds of seconds). Thus, at every instant, the average power dissipated by the nanoparticles in the form of heat (S), may be taken to a very good approximation as an average over a large number of steady state hysteresis cycles; that is, we write $S=S(T)$.

In Section 2 we define the proposed model and discuss some of its basic properties. In order to provide a definite example to illustrate its applicability, we briefly discuss the linear response Néel relaxation in Section 3. Then, in Section 4, the heating curves simulated using Néel relaxation within the developed model are analyzed in detail for mono-disperse systems. The subject of polidispersivity, of fundamental importance in real systems, is discussed in Section 5. In Section 6 we present a method to extract the temperature dependence of the SAR from the experimental data. In Section 7 we briefly discuss a model of two temperatures, whose intent is to describe the difference between the temperature of the particles and that of the fluid. Finally, Section 8 provides an additional discussion and summarizes the most relevant conclusions.

2. Single temperature model

To study the heating curve, the simplest approach is to assume that the temperature is homogenous throughout the sample, being only a function time. This is motivated by the random spatial arrangement of the nanoparticles within it, which entail a somewhat uniform heating. Let us first consider the system in the absence of an external field. Then, according to Le Chatelier's principle, any changes in the equilibrium between the sample and the environment should prompt an opposing reaction to counteract this change. For the present case — where these arguments are also sometimes referred to as Newton's law of cooling — this implies that the rate of heat loss ($\dot{Q}$) is proportional to the difference in temperature between the sample (T) and the medium (T_e), viz.,

$$\dot{Q} = a_1(T_e - T), \tag{1}$$

where a_1 is a constant whose order of magnitude is that of the thermal conductivity of the magnetic fluid times the characteristic length of the sample. If we assume a constant specific heat (C), we may write $\dot{Q} = C\dot{T}$. Then, defining $a = a_1/C$ and changing variables to $\Gamma = T - T_e$ we arrive at

$$\dot{\Gamma} = -a\Gamma, \tag{2}$$

whose solution is $\Gamma(t) = \Gamma(0)\exp(-at)$. Whence, Eq. (1) states that when the system is momentarily disturbed from equilibrium with the thermal bath, its tendency will be to return exponentially to the original state with characteristic time, a^{-1}. We refer to this as the *cooling curve*. It may be computed as an extension of the heating curve, continuing the data acquisition after the external field has been shut off. A graph of $\log(\Gamma)$ vs. t should yield a straight line with slope $-a$, as illustrated by the solid curve in Fig. 1(a). Henceforth, in numerical calculations, we shall usually take $a=1$ to simplify the discussion, given that its effect is simply to change the time scale. For reference, in real systems $a \sim 10^{-2}\ \mathrm{s}^{-1}$.

It is possible that the cooling curve takes the form shown in dashed lines in Fig. 1(a), represented instead by a sum of decaying exponentials. Quite likely, the main reason for this lies in the heat dissipated by the coil itself. This can be unambiguously verified by heating the sample with an external heat source and measuring the corresponding cooling curve.

The heating curve is obtained from Eq. (2) by introducing the dissipated power as a forcing term

$$\dot{\Gamma} = -a\Gamma + S(\Gamma). \tag{3}$$

The main goal of hyperthermia experiments is to extract $S(\Gamma)$ from $\Gamma(t)$. In our notation, S is given in units of degree per unit time. The SAR, on the other hand, is usually expressed in units of power per unit mass of magnetic material. Whence, it may be computed from S by multiplying by C and dividing by the mass.

At ambient temperature, $\Gamma = 0$, and from the DE (2) we immediately see that

$$S(\Gamma = 0) = \lim_{t \to 0} \dot{\Gamma}(t), \tag{4}$$

which is the usual method of computing the SAR. Within the scope of the current model, this procedure is quite satisfactory

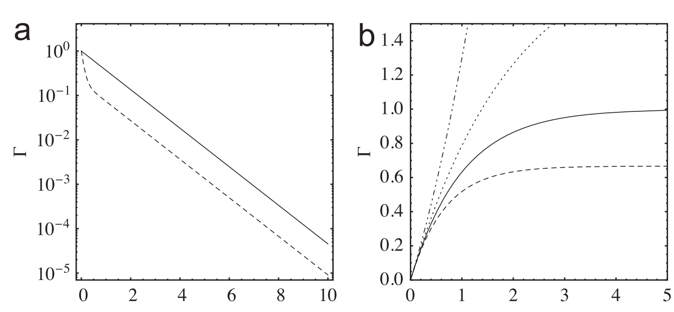

Fig. 1. (a) Example cooling curves. (solid) $\Gamma = e^{-t}$, corresponding to the model in Eq. (2); (dashed) $\Gamma = 0.3e^{-t} + 0.7e^{-5t}$, illustrating the possibility of additional sources of heat (e.g., from the coil). (b) Example heating curves [Eq. (3)] with $a=1$. (solid) Eq. (5), with $S_0 = 1$. Others are for Eq. (10) with $S_0 = 1$: (dashed) $\alpha = -1/2$, (dotted) $\alpha = 1/2$ and (dot-dashed) $\alpha = 3/2$.