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Review

Heating efficiency in magnetic nanoparticle hyperthermia

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ABSTRACT

Magnetic nanoparticles for hyperthermic treatment of cancers have gained significant attention in recent years. In magnetic hyperthermia, three independent mechanisms result in thermal energy upon stimulation: Néel relaxation, Brownian relaxation, and hysteresis loss. The relative contribution of each is strongly dependent on size, shape, crystalline anisotropy, and degree of aggregation or agglomeration of the nanoparticles. We review the effects of each of these physical mechanisms in light of recent experimental studies and suggest routes for progress in the field.

Particular attention is given to the influence of the collective behaviors of nanoparticles in suspension. A number of recent studies have probed the effect of nanoparticle concentration on heating efficiency and have reported superficially contradictory results. We contextualize these studies and show that they consistently indicate a decrease in magnetic relaxation time with increasing nanoparticle concentration, in both Brownian- and Néel-dominated regimes. This leads to a predictable effect on heating efficiency and alleviates a significant source of confusion within the field.

1. Introduction

It its most general clinical sense, hyperthermia is a therapeutic procedure in which tissues are heated above normal physiological ranges. It is most often considered as an alternative therapy for cancer treatment, where a notable lack of side effects makes it an attractive substitute for chemotherapy and radiation. Hyperthermia therapeutics is generally considered in two distinct temperature ranges, in which increasing temperature results in varying degrees of cellular upset. Moderate increases in temperature (41–46 °C) may alter the functionality of intercellular proteins, leading to cellular degradation and ultimately inducing apoptosis [1–3]. However, in moderate hyperthermia longer treatments on the order of hours are generally required for effective treatment, often in combination with additional treatment modalities such as radiation or chemotherapy [4–6]. By contrast, hyperthermia treatment at temperatures above 46 °C may result directly in cell death even in acute treatments lasting only minutes. Hyperthermia at these temperatures is generally referred to as thermoablation, and is characterized by tissue necrosis, coagulation or carbonization [7].

Many distinct modes of hyperthermia are available for anticancer therapeutics today, but most suffer from significant limitations in tumor targeting or precise localization of thermal energy. In whole-body hyperthermia, the entire body is heated above normal physiological temperatures. Techniques employing the remote application of electromagnetic radiation, such as radiofrequency capacitance hyperthermia or phased-array microwave hyperthermia are more finely targeted than whole-body hyperthermia, but are still tissue non-specific. In addition, their precision is limited by their wavelength, leading to significant heating of surrounding tissues or insufficient heating of targeted tumors. Percutaneous treatments with radiofrequency and microwave probes and laser-mediated photocoagulation techniques enable more precise spatial localization, but require physical access to the tumor and *a priori* tumor localization. Other modalities such as ultrasound suffer from similar limitations.

The ideal delivery mechanism for hyperthermia would be non-invasive, tissue-specific, and capable of precisely localized, high-intensity heating in deep tissues. Gilchrist et al. first proposed magnetic materials for hyperthermia in the 1950s, and in the intervening years magnetic nanoparticles have been shown to be capable of meeting each of these requirements [8]. Magnetic nanoparticles in stable colloidal suspensions can be delivered non-invasively via a variety of drug delivery routes. Upon delivery, they may be heated remotely with alternating magnetic fields at frequencies which pass unaffected through healthy tissues. This enables efficient heating in deep tissues with negligible energy delivery en route. In addition, magnetic nanoparticles may be directed to some degree with external magnetic fields, enabling a tissue non-specific remote localization. Tissue-*specific* localization can also be achieved with an appropriate chemical functionalization, and furthermore, magnetic nanoparticles have been shown to selectively aggregate within certain types of tumors. Finally,

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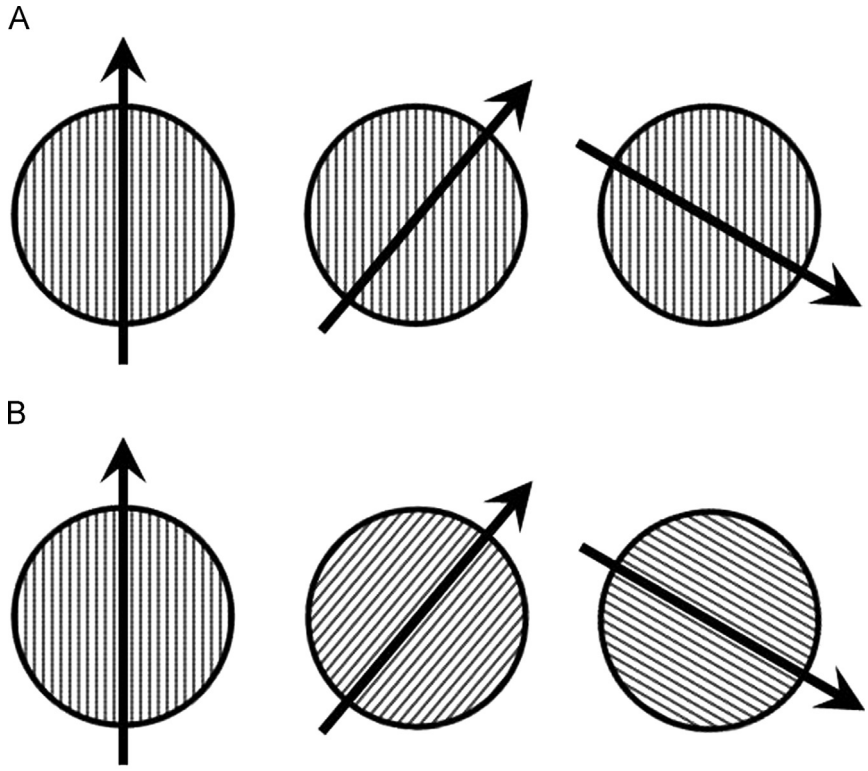

Fig. 1. Néel rotation vs. Brownian rotation. (A) Néel rotation: the magnetic moment rotates while the particle remains fixed. (B) Brownian rotation: the magnetic moment remains fixed with respect to the crystalline axes while the particle rotates.

magnetic nanoparticles have been used as drug delivery vehicles as well as for hyperthermia, and therefore raise possibilities for multi-modal therapeutic agents.

Magnetic particles which have been studied for use in hyperthermia studies consist almost entirely of magnetite (Fe_3O_4) and related spinels with cobalt, nickel, or other substitutions [7] and range in size from several nanometers to a few tenths of a micron. In recent years, much of the focus has been on smaller paramagnetic particles, since single-domain nanoparticles have been shown to absorb much more power at physiologically relevant magnetic fields and frequencies than multi-domain particles [9]. Given the clinical importance, there is a strong need for nanoparticles which are optimized for magnetic hyperthermia. However, optimization is not yet well-understood, and experimental results from nanoparticle systems vary widely.

In this work, we review the state-of-the-art in magnetic nanoparticles for hyperthermia therapeutics. We begin with a discussion of theoretical models which predict the specific absorption rate (SAR) at which magnetic energy is absorbed and converted into thermal energy. Experimental studies have shown varying degrees of consensus with respect to these models, and so we discuss current candidate materials and explore in detail the wide range of physical parameters which affect SAR in nanoparticle systems. Finally, a key challenge in the field stems from the unpredictable influence of aggregation and agglomeration of nanoparticles in high-concentration solutions. Collective behavior of this sort is neither well-described by theory nor well-controlled in most experiments. We therefore give a great deal of attention to the complex role of collective behavior in nanoparticle ensembles and highlight some emerging trends.

2. Models of loss mechanisms

In general, high-frequency magnetic fields may cause heating in magnetic materials by any one of the four independent mechanisms: eddy currents, hysteresis loss, and Brownian and Néel relaxation. In bulk materials, eddy currents induced by rapidly changing magnetic flux may produce significant resistive heating, and the shifting of magnetic domain walls in multi-domain materials (i.e. hysteresis loss) may also produce thermal energy. Eddy currents are only significant in materials at the centimeter scale or larger and are therefore clearly inconsequential for magnetic nanoparticle hyperthermia. However, there is some debate as to the significance of hysteresis loss in hyperthermia applications. It is certainly true that heating attributable to shifting domain walls occurs in magnetic particles on the order of 100 nm or larger [10]. Hysteresis remains significant in larger single-domain particles as well; however, both coercivity and remanence depend strongly on particle volume and both vanish abruptly for smaller particles [11]. In particular, coercivity is given by $H_C = (2K/M_S)[1-(V_C/V)^{1/2}]$ for $V > V_C$, where V_C is the critical volume of the particle, below which relaxation effects dominate [12]. This dominance occurs when the relaxation time of the particle is equal to the field frequency ($\omega\tau = 1$). As we will discuss below, the relaxation time τ depends strongly on particle volume, thus for typical parameters ($f = 200$ kHz and anisotropy energy density of 25 kJ/m^3) the critical size is about 15 nm in diameter.

In such particles heating is accomplished by rotating the magnetic moment of each particle against an energy barrier. If conditions are such that this rotation results in the wholesale rotation of the particle itself, then the particle has undergone Brownian relaxation and thermal energy is delivered through shear stress in the surrounding fluid. If, however, the moment rotates while the particle itself remains fixed, then the particle has undergone Néel relaxation and thermal energy is dissipated by the rearrangement of atomic dipole moments within the crystal (Fig. 1). In practice, both mechanisms may occur simultaneously and the relative contributions are determined by the time scales at which each mechanism occurs.