Nanomagnets-From Fundamental Physics to Biomedicine

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Abstract: Nanomagnets are expected to expand the capabilities of widely established technologies such as data recording and to implement new functionalities of applicability in biosciences. The basis for these potential benefits of nanomagnets is their intrinsic small size and their outstanding properties derived from finite-size and surface effects as well as collective phenomena and unusual transport properties. This review aims to describe recent developments on the potential use of nanomagnets in data recording, which rest in three fundamental approaches and their combinations (composition, shape and exchange interactions). Aside from data recording, we also describe recent advances on the use of nanomagnets in biosciences from analytical (biosensors, magnetic resonance imaging, separation) to therapeutic applications (drug delivery, hyperthermia eradication of malignancy). Special emphasis has been set in understanding the physics behind the benefits of using nanomagnets of different characteristics. Finally, we have addressed some of the perspectives and challenges for the potential future development of nanomagnets and applications based on these systems.

Keywords: Nanomagnets, Data Recording, Biomedicine, Nanoneedles, Nanowires, Nanorings, High Anisotropy, Exchange Bias, Biosensors, MRI, Drug-targetting, Hyperthermia.

1. INTRODUCTION

Magnetic materials are in the heart of numerous appliances and devices used in everyday life. From macroscopic magnetism (e.g. compass needle) to atomic-scale magnetic phenomena (e.g. crystal-field interaction, relativistic spin-orbit coupling) their importance has led to intensive research for a long time [1]. Nowadays, it becomes clear that the future development in magnetism rests upon recent developments in the nanoworld [2]. Magnetic materials containing nanomagnets are expected to enhance the efficiency of widely established technologies such as data recording and to implement new functionalities of applicability in biosciences. The key for this expected improvement in technological capabilities is the unique combination of small size, exotic properties and processability of nanomagnets.

Real and potential technological applications of nanomagnets are countless. Ferrofluids (magnetic liquids) are suspensions of nanomagnets, bearing a giant magnetic moment in a liquid carrier [3]. The magnetic control of ferrofluids opens the possibility to position the fluid inside a technical device allowing their use in a broad range of technological applications [4]. Soft ferromagnetic materials are those magnetic materials with high permeability, low coercivity and low hysteresis loss, which can be used to amplify the flux density generated by a magnetic field. In recent years the range of available soft magnetic materials has been significantly increased by the development of nanoparticulate magnetic materials [5]. Magneto-optical properties of nanomagnets have attracted also considerable attention in the last years due to their potential use as magneto-optical storage materials, magneto-optical switches, modulators or sensors based on the Faraday effect [6]. Aside from these applications it seems clear that nowadays the applications of nanomagnets, which are attracting more attention, are those in the data recording and bioscience fields.

Magnetic recording, invented over 100 years ago, has played a key role in the development of non-volatile information storage technologies, including audio, video and data [7]. It seems clear that one of the keys to improve magnetic storage is the increase in the areal density achieved by scaling down the particle size [8]. In the past few years, nanomagnets have become increasingly important for applications in biomedicine [9-15]. Superparamagnetic composites containing nanomagnets are ideal candidates for applications in biosensing, biological separation and purification, magnetic resonance imaging (MRI), hyperthermia eradication of malignancy and magnetically controlled drug and gene delivery.

When the sample dimensions become comparable to length scales, such as the domain-wall width, exchange length, or grain size, the magnetic properties differ significantly from the bulk behavior [16]. Thus, understanding the magnetic properties of nanoparticles is a central issue to implement applicability to nanomagnets. For example, in data recording the continued areal density growth by scaling current hard disk drive designs is limited by enhanced thermal effects, or superparamagnetism, which leads to loss of information [17]. The superparamagnetic effect occurs when the grain volume is too small to prevent thermal fluctuations from spontaneously reversing the grain magnetization direction. Also, this increase in the areal density of magnetic storage devices and the attempt to fabricate magnetic dynamic random access computer memories whose performance exceeds that of standard
semiconductor technology have fueled the need for progressively more refined understanding of the thermal magnetization reversal, or switching, of small magnetic systems [18].

The properties of materials composed of nanomagnets are a result of both the intrinsic properties of the particles and the interactions between particles [19]. For example, near surfaces the magnitude of the magnetic moment per atom in ferromagnetic metals can change drastically as a result of reduced coordination at the surface [20]. In contrast, in ionic compounds the moment of each ion is less sensitive to the proximity of a surface because the distribution of valence electrons is highly localized. However, the orientation of each moment can be altered, due to competing exchange interactions in an incomplete coordination shell for surface ions. This can result in a disordered spin configuration near the surface and a reduced average net moment as compared to bulk materials [21].

Having so far briefly illustrated the importance of the nanomagnets in technological applications and how their unique properties are of relevance to implement improved capabilities in such technological applications, it is clear the need to present a clear and structured state-of-the-art description on some of the applications of nanomagnets. Particularly, this review focuses upon recent developments in the use of nanomagnets in data storage and biomedical application. On one hand, everybody recognizes the importance of magnetic storage on society. On the other hand, bioapplications of nanomagnets nowadays can be considered as a hot field. This seems not surprising since it is generally accepted in the scientific community the 21st century as the “biocentury” (see for example an essay of George M. Whitesides in Angewandte on some of the possible new directions in the chemistry field, Ref. 22). Throughout this review, special emphasis has been set in understanding the physics behind these recent developments in the use of nanomagnets.

2. NANOMAGNETS FOR DATA RECORDING

In data storage applications, the particles must have a stable, switchable magnetic state to represent bits of information, a state that cannot be affected by temperature fluctuations. Magnetic particles below a critical diameter cannot support more than one domain, and are thus described as single domain. This critical diameter is approximately, \(2A/M_S\) (\(A = \) exchange constant, \(M_S = \) moment per unit volume) [23], and for typical material parameters is 10-100 nm. Much of the behavior of single-domain particles can be described by assuming that all the atomic moments are rigidly aligned as a single giant spin.

The rotational barriers due to magnetocrystalline, magnetoelastic, and shape anisotropy can trap nanomagnets in two or more metastable orientations, giving rise to hysteresis in the moment versus applied field. However, for a single domain magnetic particle of volume \(V\) to hold its magnetic polarization in the face of thermal agitation (superparamagnetic limit) requires that its magnetic anisotropy energy \(K\) far exceed the characteristic thermal energy \(k_B T\), that is \(KV >> k_B T\). A typical criterion for the desired data storage lifetime is \(KV/k_B T > 50-80\) [17]. While \(V\) scales downward as the recorded bit area on the medium surface shrinks, anisotropy constant is a parameter determined by the storage medium material selection.

To push further out the confining limitations of media thermal instabilities, different paths involving departures from current technology may be followed which should allow for much higher areal densities before impinging on superparamagnetic limitations [24]. Current magnetic recording is based on longitudinal magnetic media, where the magnetic anisotropy axes of the grains can be considered as randomly oriented in the plane of the film, or in more recent longitudinal media with some degree of preferential circumferential alignment [25]. Since there are many grains per bit, the grain-to-grain dispersion in the in-plane angle of the anisotropy axes is averaged out. However, with a discrete bit medium there is only one grain (or magnetic switching volume) per bit, and thus there is no averaging by the read head. An alternative scheme is to orient the magnetic easy axis normal to the film surface, to form a perpendicular recording medium. It is likely that perpendicular media will be the choice for patterned bit media, and it has received the most attention [26]. An additional motivation for perpendicular discrete bit media is the likely change from longitudinal to perpendicular media in conventional magnetic recording. This shift is likely to occur due to the increased head write field and thus increased density potential of perpendicular recording.

Excluding the obvious advantage of using discrete bit or perpendicular recording media for the next generation recording media (which are out of the scope of this review), we can act to overcome the superparamagnetic limit by increasing the magnetic anisotropy constant.

2.1. Nanoneedles, Nanowires and Nanorings

One approach to overcome the superparamagnetic limit is to compensate the decrease of grain size by increasing the shape anisotropy. In fact, needle-like FeCo metallic nanomagnets coated with an oxide-protecting layer, which are deposited longitudinally on a film, are routinely used for the storage of digital and analogue signals in the area of advanced flexible media [27]. The main reason for using Fe metals and Fe-based alloys, rather than iron oxide, for recording applications is that they have higher values of saturation magnetization and coercivity. The main disadvantage of these media is the intrinsic chemical instability of finely divided metal, which requires after reduction a controlled oxidation of particles surfaces.

The only commercially significant process for the production of iron metallic elongated particles is the thermal reduction of \(\alpha\)-FeOOH (goethite) particles [28]. This thermal treatment can promote interparticle sintering and therefore the loss of the elongated shape. Both silica and alumina are common elements added to the system to prevent sintering of the particles during the required heat treatment [29]. Ultimately, the recording density achievable with these magnetic particles is limited by the coercivity and also the distribution of coercivities or switching fields within the material, which are closely associated with the crystallochemical characteristics of the particles. Therefore, it seems necessary to create new synthetic routes or to
develop the existing ones to produce highly uniaxial and uniform metallic particles in a rather simple way and with the adequate particle size and microstructure [30].

Ferromagnetic nanowires and their arrays are also attracting a great deal of interest for magnetic storage. The magnetic nanowire arrays have high-density recording ability in excess of 100 Gb in\(^2\) [31]. In particular, Fe-rich nanowire alloys with high coercivity are widely used to control the magnetic properties of recording media by varying the concentration [32]. Moreover, ferromagnetic nanowires and their arrays are also attracting interest because of their potential applications in magnetic sensors, memory devices, spintronic nanodevices, and energy storage [33]. They are also good candidates for giant magnetoresistance (GMR) materials without the occurrence of structural defects in multilayers.

By electrodeposition into porous anodic alumina it is now possible to produce Fe, Co and Ni wires with diameters ranging from 4 to 200 nm, depending on the anodization conditions, and lengths of up to about 1 \(\mu\)m [1,34]. Typically, the nanowires form nearly hexagonal columnar arrays with variable centre-to-centre spacings of the order of 50 nm. Much of the early work on magnetic nanowire arrays was concerned with exploratory issues, such as establishing an easy axis for typical preparation conditions, the essential involvement of shape anisotropy, as opposed to magnetocrystalline anisotropy, and the description of magnetostatic interactions between wires [1,34]. More recently, attention has shifted towards the understanding of magnetization processes [1,34]. On a nanometre scale, interatomic exchange is no longer negligible compared to magnetostatic interactions. This leads to a transition from curling-type to quasi-coherent nucleation [1,34]. For Fe, Co and Ni, the corresponding diameters are about 11, 15 and 25 nm, respectively, irrespective of the critical single-domain radius [1].

Magnetic nanorings are also excellent candidates for high-density storage devices, in this case, because of the existence of vortex or flux-closed states in which the magnetization is oriented circularly and for which stray magnetic fields are essentially absent [35]. In a nanoring made of a vortex, magnetic structures are highly stabilized without forming multidomain structures [36]. Since the vortex structures generate the smallest stray field and have two-fold degeneracy with respect to the magneto chirality, that is, clockwise or counter-clockwise magnetic moment circulation, the ring is promising as a device element in high density data storage technologies such as magnetic record media or magnetic random access memories [36]. Aside from theoretical considerations on the magnetic behavior of nanorings, recent advances are in the direction of improving the reliability and microstructural control of the resulting nanorings. For example, the application of shadow nanosphere lithography for the preparation of Fe nanorings has been recently reported [37]. Through changing the mask morphology by temperature processing and varying the evaporation conditions, particles with ring morphologies can be produced (Fig. 1). This process allows outstanding control of the size and morphology of the particles. The efficient technique is shown to scale down the size of metallic nanoparticles from 200 to 30 nm, while preserving the original nanosphere spacing and order. The 150-nm-diameter Fe rings produced by this method show ferromagnetic behavior.

2.2. High Anisotropy Media

Another approach to overcome the superparamagnetic limit is to compensate the decrease of grain size by increasing the magneto-crystalline anisotropy [38]. High anisotropy L1\(_0\) type nanoparticles, such as FePt and CoPt, have attracted much attention due to their potential for the development of ultrahigh-density magnetic recording media [39]. The chemically ordered L1\(_0\) phase of the FePt system is of particular interest, because of its high bulk magneto-crystalline anisotropy energy density (\(K_u \approx 6.6 \times 10^7\) ergs cm\(^{-3}\)) at the equiaxial composition that should allow the use of smaller, thermally stable magnetic grains than being used in today's

Fig. (1). Scanning electron microscopy picture of ordered Fe nanorings evaporated over an annealed 540-nm polystyrene latex mask. The outer diameter of the single ring is 150 nm and the width of the ring is 20-30 nm. Reproduced with permission from _Small_, 2005, 1, 439. Copyright 2005 Wiley-VCH Verlag.
media. One of the key questions is whether these favorable bulk magnetic properties can be preserved in small, nanometer-sized particles, where surface effects should play a dominant role [40].

It is clear that any application of these nanomagnets demands their arrangement in order arrays [41]. Methods used to generate nanoscale structures and nanostructured materials are commonly characterized as “top-down” and “bottom-up”. The top-down approach uses various methods of lithography to pattern nanoscale structures. This approach includes serial and parallel techniques for patterning features typically in two-dimensions (2D)-over length scales approximately 4 orders of magnitude larger (in linear dimension) than an individual structure. The bottom-up approach uses interactions between molecules or colloidal particles to assemble discrete nanoscale structures in two and three dimensions [25,42]. Nanoparticle superlattices can be obtained by slowly evaporating the solvent in which the monodisperse nanoparticles are dispersed and the spacing between nanoparticles in the solids can be tuned with the modification of the capping materials. Ordered arrays of FePt nanoparticles (Fig. 2) with potential application on ultrahigh density magnetic recording media have been recently reported [25,43].

2.3. Exchange Interactions

When a ferromagnetic-antiferromagnetic (FM-AFM) system is cooled down in an external magnetic field through the Néel temperature of the antiferromagnet, the magnetic hysteresis loop is shifted along the field axis, a phenomenon known as exchange bias (EB) [44]. A simple model for EB was proposed by Meiklejohn and Bean [45]. Before cooling down, the AFM part is in a paramagnetic state and its magnetic moments can be aligned by an external field. When cooling down through the Néel temperature, the AFM structure is established with AFM spins parallel to FM spins. The interfacial AFM spins tend to align collinearly with the FM spins. Since the AFM structure does not rotate in a magnetic field, this collinear interfacial spin alignment creates a unidirectional anisotropy, such that it is harder to rotate FM spins in one direction than in the opposite one. Although knowledge on the FM-AFM interface structure is crucial for the understanding of EB in particular systems, all present approaches assume that only interfacial exchange interactions cause the EB [46]. Therefore, in practice, one can consider an empirical interfacial exchange energy directly proportional to the FM-AFM interface area.

Hybrid FM-AFM nanoparticles are important for applications such as asymmetric exchange-biased loops used in spin valves. Our interest, however, on these systems are based upon recent experimental studies that have indicated that exchange coupled ferromagnetic (FM) and antiferromagnetic (AFM) nanostructures experience an improved thermal stability, that is, it helps to overcome the superparamagnetic limit [47]. Aside from theoretical models that could help to understand this behavior and provided that as aforementioned already exist many experimental reports that confirm this behavior, one of the crucial issues in these systems, is the size dependence for exchange bias and their possible disappearance at a critical size. In this direction, Dobrynin et al. [44] have recently presented a study of the magnetic properties of oxidized Co nanoparticles with an average grain size of 3 nm, embedded in an amorphous Al2O3 matrix. These nanoparticles can be considered as imperfect Co-core CoO-shell systems. Magnetization measurements after magnetic field cooling show a vertical shift of the hysteresis loop, while no exchange bias is observed. With a simple model, these authors show that there is a critical grain size for hybrid ferromagnetic-antiferromagnetic particles, below which exchange bias is absent for any ratio of ferromagnetic and antiferromagnetic constituents. The reason, these authors give, is that the interfacial exchange energy dominates over other energies in the system due to a large surface-to-volume ratio in the nanoparticles.

3. BIOMEDICAL APPLICATIONS

Particularly with biomedicine, there exists a need for enhanced speed, throughput and sensitivity, since many effects in biology are nonlinear, transient, complex and very faint [48]. A gene may be expressed for a very short time, and in a specific location within a specific type of cell. Discerning this event within a large population of cells can be very difficult. Furthermore, many DNA analyses are limited by the scant amount of starting material, which in the

Fig. (2). (A) Transmission electron microscopy (TEM) picture of a 3D assembly of 6-nm as-synthesized Fe80Pt20 nanoparticles deposited from a hexane/ octane (v/v 1/1) dispersion onto a SiO-coated copper grid. (B) TEM micrograph of a 3D assembly of 6-nm Fe80Pt20 sample after replacing oleic acid/octyl amine with hexanoic acid/hexylamine. (C) High-resolution Scanning electron microscopy image of a 180-nm-thick, 4-nm Fe80Pt20 nanomagnet assembly annealed at 560 °C for 30 min under 1 atm of N2 gas. (D) High-resolution TEM image of 4-nm Fe80Pt18 nanomagnets annealed at 560 °C for 30 min on a SiO-coated copper grid. Reproduced with permission from Science, 2000, 287, 1989. Copyright 2000 Science Magazine.
case of forensics or epidemiology may be severely degraded. As an example, the concentration of a single gene (one DNA strand) within the volume of a typical mammalian cell is of the order of $10^{-12}$ M. If this one DNA strand is then diluted into a more conventional analysis volume of 100 μl, the concentration drops to $10^{-18}$ M. The most sensitive systems for nucleic acid analysis can detect concentrations in the femtomolar–picomolar range. Therefore, reduction in assay volume is critical for the reliable detection of scarce biological analytes. As we describe below the use in nanomagnets as analytical probes can lead to improve efficiency with respect to already established technologies.

On the other hand, nanomagnets can be used in therapeutic applications. Engineering delivery systems of therapeutic agents has grown into an independent field, transcending the scope of traditional disciplines and capturing the interest of both academic and industrial research. At the same time, the acceleration in the discovery of new therapeutic moieties (chemical, biological, genetic and radiological) has led to an increasing demand for delivery systems capable of protecting, transporting, and selectively depositing those therapeutic agents to desired sites [49]. The use of an appropriate targeted drug delivery system can promote the ability of an active compound because aims to target drug to specific sites without the possible marked side effects associated with abundant concentration. The obvious advantage of using nanomagnets for the delivery of biocompounds is that the system can be easily localized using an external magnetic field [11-12,13-15,50]. Aside from drug-targeting and gene delivery, nanomagnets can be used for cancer therapy based upon the heating (hyperthermia) that magnetic materials with low electrical conductivity generate when placed in an external alternating magnetic field [14,51].

3.1. Analytical Applications

Development of a new generation of biosensors has been the subject of much research [52]. The idea of using a magnetic field sensor in combination with magnetic particles working as magnetic labels for detecting molecular recognition events (antigen—antibody interaction, ligand—receptor binding) was first reported a few years ago [53]. Such a biosensor was based on magnetoresistance technology, and used magnetic microbeads for simultaneous characterization of many biomolecular interactions. An alternative geometry was proposed for a magnetoresistive prototype of biosensor to detect a single micron-sized magnetic sphere by a ring element based on anisotropic magnetoresistance [54]. In any case, it is clear that the next generation of magnetic biosensors must be based upon new physical properties that could allow high sensitivity, small size, low power consumption, stability of operation parameters, quick response, resistance to aggressive medium, and low price. In this direction, Kuryandskaya and Levit have recently developed a biosensor prototype based in giant magnetoresistance (Fig. 3) [55]. These authors detect a

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**Fig. (3).** Possible processing for detection of biocompatible magnetic particles by magnetoeimpance based sensor. Top line: magnetic particles with attached specific antibody are mixing with test solution; the particles which did not participate in the molecular recognition events removed somehow; the voltage $U_0$ induced in a sensitive element of a biosensor with a complementary to testing solution compared with the voltage $U_1$ induced when the solution contains the magnetic marker-biocompound of the interest complex. Bottom line: surface modified magnetic nanoparticles are mixing with test cell sample; the particles which did not participate in the intracellular uptake events removed; $U_0$ induced in a sensitive element of a biosensor with a complementary to testing solution compared with the voltage $U_1$ induced when the solution contains the magnetic nanoparticles inside the cells. Reproduced with permission from Biosens. Bioel., 2005, 20, 1611. Copyright 2005 Elsevier B.V.
change in giant magnetoimpedance when using superparamagnetic Dynabeads® particles coated with an antibody. Grancharov et al. have developed a novel method of detecting either protein binding or DNA hybridization at room temperature using 12-nm manganese ferrite nanoparticles and a magnetic tunnel-junction-based biosensor situated in orthogonal magnetic fields [56].

An entirely different approach based upon the combination of fluorescence and magnetic properties has been developed by Kopelman and co-workers [57]. These authors have synthesized magnetically modulated optical nanoprobes (Mag-MOONS). These nanoprobes can be considered as the next generation of photonic explorers for bioanalysis (PEEBLEs). PEEBLEs consist of fluorescent dyes entrapped in a matrix composed of silica, polyacrylamide or methyl methacrylate. MagMOONs, on the other hand, are novel nanosensors designed to emit a fluorescence signal and to blink in response to a rotating magnetic field. MagMOONs are generated by vapor depositing a layer of aluminum over one hemisphere of a silica nanoparticle in which is entrapped magnetic material and fluorescent dye. When a rotating magnetic field is applied to MagMOONs in solution, the microspheres rotate, seemingly passing through the phases of the moon (Fig. 4). Thus, the MagMOONs appear to blink as the light emitting side comes in and out of view. The aluminum coating prevents excitation light from entering and fluorescence from leaving the coated side of the MagMOON (Fig. 5). Subtracting unmodulated background fluorescence from the modulated MagMOON signal greatly increases the single-to-background ratio, thus enhancing sensitivity and lowering detection limits. In addition, the blinking capabilities of the magnetic nanosensors allow for the detection of analytes in the presence of naturally occurring autofluorescence of biological samples as well as fluorescently stained cells.

Recently, magnetorelaxometry was introduced as a method for the evaluation of immunoassays [58]. Magnetorelaxometry measures the magnetic viscosity, i.e. the relaxation of the net magnetic moment of nanomagnets after removal of a magnetic field. The fact that magnetorelaxometry depends on the anisotropy and the core and hydrodynamic sizes, allows this technique to distinguish

![Fig. (4).](image-url) (a) Graphic of rotating magnet used for rotating MagMOONs in aqueous suspension. (b) MagMOONs appearing to blink as they rotate through the phases of the moon. Reproduced with permission from J. Magn. Magn. Mater., 2005, 293, 715. Copyright 2005 Elsevier B.V.

![Fig. (5).](image-url) MagMOONs are ON when the non-coated hemisphere is facing the detector. In this orientation fluorescent dyes are exposed to light of the appropriate excitation wavelength. The resulting fluorescent emission is allowed to reach the detector. MagMOONs are OFF when the coated hemisphere is facing the detector. In this orientation, the fluorescent dyes are protected from excitation energy and no emission signal reaches the detector. Reproduced with permission from J. Magn. Magn. Mater., 2005, 293, 715. Copyright 2005 Elsevier B.V.
between free and bound conjugates by their different magnetic behavior, and therefore can be used as an analytical tool for the detection of biocompounds [59] and even for *in vivo* diagnostics [60].

Separation is the most documented and currently the most useful application of nanomagnets [61]. Many composites containing nanomagnets have been developed as magnetic carriers in separation processes including proteins, DNA, cells and bacteria [62]. The combination of magnetic separation with sensing seems one of the most promising approaches in which future developments of analytical tools should be based on. In this direction, the so-called bio-bar code method recently developed by Mirkin and co-workers is worth noting. This group has used magnetic composites in combination with Au nanoparticles for the ultrasensitivity detection of biocompounds (Fig. 6) [63].

Superparamagnetic composites containing nanomagnets are routinely used as contrast agents in nuclear magnetic resonance imaging [11, 12a,14]. First introduced as contrast agents in the mid-1980s [64] these composites have been in NMR imaging for location and diagnosis of brain and cardiac infarcts, liver lesions or tumors, where the composites tend to accumulate at higher levels due to the differences in tissue composition and/or endocytotic uptake processes [65]. Lumirem® (silica-coated iron oxide particles with a diameter of 300 nm) and Endorem® (magnetite nanoparticles of 150 nm in diameter, coated with dextran) are commercial names of superparamagnetic iron oxides (SPIOs) available on the market. SPIO contrast agents are used for gastro-intestinal tract imaging and for liver and spleen diseases detection because of their relative large hydrodynamic size. Sinerem® (magnetite nanoparticles of 30 nm in diameter, coated with dextran) is an example of USPIO (ultrasmall superparamagnetic iron oxide) on the market. Due to their long-circulating properties, USPIOs can be used for blood pool and tumor imaging (experimental imaging), based upon the detection and characterization of the lesion by their vascular appearance.

The physical principle for which nanomagnets are used as contrast agents in nuclear magnetic resonance imaging is the change in relaxation time produced by magnetic particles. The nanomagnets possess very large magnetic moments in the presence of a static magnetic field, and dipolar interactions between the superparamagnetic cores and surrounding solvent protons result in decreasing both longitudinal and transverse relaxation times [66]. This change is a contribution of several complex mechanisms, the size and the composition represent the essential parameters [67].

One area of growing interest in the use of nanomagnets in medical imaging is specific cell tracking [68]. The ability to load enough nanomagnets in cell culture has provided a useful technique to label and track nonphagocytic cells *in vivo* using magnetic resonance imaging [69]. This method has allowed researchers to study the distribution of stem cells [70]. One of the major challenges in extending this cell-labeling is to probe the inerterness of the magnetic probes. Another area of growing interest is the development of synthetic routes able to produce biocompatible nanomagnets of smaller hydrodynamic size [71].

### 3.2. Therapeutic Applications

Almost 50 years ago, Gilchrist *et al.* (1957) reported on localized magnetic hyperthermia using fine magnetic particles exposed to an alternating magnetic field [72]. The heating of oxide magnetic materials with low electrical conductivity in an external alternating magnetic field is due to loss processes during the reorientation of the magnetization [73]. If thermal energy $K_BT$ is too low to facilitate reorientation, hysteresis losses dominate which depend on the type of remagnetization process (wall displacement or several types of rotational processes). With decreasing particle size thermal activation of reorientation processes lead to superparamagnetic behavior and the occurrence of the so-called Néel-losses [74]. In the case of dispersions of nanomagnets in liquid media losses related to the rotational Brownian motion of magnetic nanoparticles also act [75]. In principle, the heating power associated with hysteresis losses is higher than that based on the Brown and Néel relaxation mechanisms, however, experimentally it is necessary to apply high magnetic field amplitudes (at least above the effective anisotropy field). Unfortunately, the field amplitudes can rarely be used because of physiological and technological restrictions, and superparamagnetic particles (nanometer in size) absorb much more power at tolerable AC...
magnetic fields than the obtain by well known hysteresis heating of multidomain (microns in size) particles [14].

Recent developments in the use of nanomagnets in hyperthermia are based upon the development of theoretical predictions on relaxation mechanisms and the combination of hyperthermia with some other tumors treatment. For example, taking into account the frequency range of the used magnetic field (100-1000 KHz), Rosensweig has estimated that to achieve high heating rates, Brownian relaxation must be allowed to dominate against Néel relaxation [76]. On the other hand, Ito et al. have combined gene therapy with hyperthermia using magnetite cationic liposomes [77].

The use of magnetic targeted carriers containing nanomagnets for drug delivery aims to target drug to specific sites through the selective application of a magnetic field, and to achieve prolonged release of high, localized concentrations of drug by retention of the carriers in the region of interest [78]. The first clinical trial in humans, using magnetic-drug targeting therapy, was reported by Lübbe et al. [79]. These authors used magnetic nanoparticles to which the drug epirubicin was chemically bound.

The process of drug localization using magnetic delivery systems is based on the competition between forces exerted on the particles by blood compartment, and magnetic forces generated from the applied magnet. When the magnetic forces exceed the linear blood flow rates in arteries (10 cm·s⁻¹) or capillaries (0.05 cm·s⁻¹), the magnetic particles are retained at the target site and maybe internalized by the endothelial cells of the target tissue [80]. Thus, for drug delivery applications, an important parameter is the magnetophoretic mobility in a liquid (μₘ), which is the measure of the mobility of a magnetic carrier in a liquid medium under the influence of an applied inhomogeneous magnetic field [81]. This parameter depends on the viscosity of the liquid medium, the carrier diameter and the effective susceptibility given by the difference in magnetic susceptibility between the carrier and the suspending medium. Susceptibility of the carrier depends on the size and the saturation magnetization of the magnetic carrier material. Thus, the highest magnetophoretic mobility should be achieved by using a carrier material with a large saturation magnetization.

A nice an illustrative example of the advantages and new trends in the use of magnetic carriers for the treatment of diseases was recently reported by Tanaka et al. [82]. These authors have tested magnetoliposomes containing the transforming growth factor (TGF)-β₁ for the treatment of articular cartilage defects in a rabbit model. TGF-β₁ is a cytokine that can increase bone formation and subsequent cartilage formation. However, cytokines show marked side effects when administrated in abundant concentrations so, in this particular case, selective drug delivery is essential for the use of these compounds for the treatment of this disease.

A further research interest in the use of targeted magnetic nanoparticles is in the field of gene therapy [13]. Gene therapy represents an exciting development in medical treatment [83]. The theory is that by insertion of plasmid DNA into target cells, it may be possible to rectify genetic disorders, and to produce therapeutic agents in the form of peptides and proteins to stimulate the immune system. Magnetofection is a method in which magnetic nanoparticles associated with vector DNA are transfected into cells by the influence of an external magnetic field [15].

4. PERSPECTIVES AND CHALLENGES FOR THE FUTURE

The search for new synthetic routes or the improvement of established ones, which are able to produce reliable nanomagnets with the correct characteristics, is an area in continuous development whatever the application we use the nanomagnets for. In this direction, we can emphasize recent developments in the synthesis of nanomagnets by using methods based on precipitation from organic solutions [84]. The unique microstructural control achieved by this method is a contribution of several factors such as temperature of synthesis, concentration, nature of the solvent and precursors, complexing strength, addition of seeds and even the speed at which the reactants are added over the seeds.

If we can gain sufficient understanding of the individual properties of nanomagnets, their further applicability is guaranteed. A clear example is the recent reported development of ferromagnetism in Pd and Au nanoparticles. Pd metal exhibits enhanced Pauli paramagnetism with large susceptibility. However, in bulk Pd no spontaneous ferromagnetic order has been observed. Although the density of states shows a sharp peak just below the Fermi level, the Stoner criterion for ferromagnetism is not satisfied. Nevertheless, Pd lies close to a ferromagnetic instability. The factors that can affect the onset of ferromagnetism are those increasing the density of states at the Fermi level (confinement effects associated with a reduced coordination number, local symmetry changes and lattice expansion that induces a narrowing of the d band) [85]. Even more exotic is the ferromagnetism observed in Au nanoparticles [86]. Because Au metal is a typical diamagnetic material, its ferromagnetic polarization mechanism is thought to be quite different from the ferromagnetism observed in transition metals.

In data recording applications the development of new crystalline phases with the adequate morphology that present large coercivity is an area of continuous interest. In this direction, Jin et al. [87] have recently reported that a nanocrystals of iron oxide in a silica matrix exhibited a giant coercivity of 2.0 T at room temperature. These nanomagnets were composed of a particular phase of iron oxide, e-Fe₃O₅, with a rod-like shape.

The potential use of self-assembled arrays of high anisotropy magnetic nanoparticles as both patterned bit media and as a substitute for thin film media will continue to attract interest in data recording during the next years. Understanding the principles that rules organization during evaporation is a complex problem that it is starting to be faced [88]. Systems far from equilibrium can exhibit complex transitory structures. The relatively weak attractions between nanocrystals, which are efficiently screened in solution, become manifest as the solvent evaporates, initiating assembly of intricate, slowly evolving structures. Although certain aspects of this aggregation process can be explained using thermodynamic arguments alone, it is in
principle a non-equilibrium process [88]. Ultimately, the study of ordered arrays could lead to the emerging concept of metamaterials—materials with properties arise from the controlled interaction of the different entities in an assembly [89]. For example, Redl et al. [90] have reported the self-assembly of PbSe semiconductor quantum dots and Fe₂O₃ nanomagnets into precisely ordered three-dimensional superlattices. The use of specific size ratios directs the assembly of the magnetic and semiconductor nanomaterials into AB₁₃ or AB₂ superlattices with potentially tunable optical and magnetic properties. These arrays could ultimately enable the fine-tuning of magnetic responses to magnetic, electrical, optical and mechanical stimuli.

The understanding of the collective behavior of nanomagnets also reaches real interest. For sufficiently diluted systems, interparticle interactions are negligible and the magnetic properties depend only on physical properties of the individual particles. When the interparticle interactions become significant the behavior of a magnetic moment is not only governed by its own intrinsic anisotropy energy but also by the coupling with its neighborhoods. Although it has been studied very intensively, it remains unclear how the magnetic interactions affect the magnetic behavior of nanoscale systems [91].

In the biomedical field, one area of special interest is the development of strategies able to increase the circulation time of nanomagnets in the blood. Integration of such nanomagnets in stealth liposomes [92], artificial hollow capsules [93], dendrimers [70,94] or bioreactors such as ferritin [95] or magnetotactic bacteria [96] seems a promising approach to solve this problem. Another area of significant importance is to evaluate the cytotoxicity of the nanomagnets or composites they are integrated with [97]. We have to be sure that this parameter remains low for practical applications.

The search for new techniques or the refinement of already established techniques represents another challenge in expanding the capabilities of nanomagnets for biomedical applications. In this direction, we can highlight a recent work carried out by Gleich and Weizeneker, which have developed a new technique of tomographic imaging using the nonlinear response of magnetic particles [98]. The object to be imaged is immersed in an external field whose strength varies with location. In most regions the magnetization of a magnetic particle sitting inside the object is saturated. An additional weak radio-frequency field—oscillating between a minimum and a maximum value—cannot change this state. However, in regions where the external field has a value close to zero, the additional field is able to alter the magnetization, which will start to oscillate and therefore induce a signal in a detection circuit. This signal can be unambiguously assigned to the narrow field-free region. By systematically varying the position of the field-free area in the object, a map can be created that gives the spatial distribution of the magnetic particles.

Modern medicine faces the challenge of developing safer and more effective therapies. Bioactive natural products are an important source of drug leads, but their modes of action are usually unknown. Elucidation of their physiological targets is essential for understanding their therapeutic and adverse effects. Moreover, the discovery of novel targets of clinically proven compounds may suggest new therapeutic applications. Target identification is also important in chemical biology. In this direction, we can highlight a recent work of Won et al. [99] which have developed a technology called magnetism-based interaction capture that identifies molecular targets upon the basis of induced movement of superparamagnetic nanomagnets inside living cells. Efficient intracellular uptake of superparamagnetic nanoparticles (coated with a small molecule of interest) was mediated by a transducible fusogenic peptide. These nanoparticles captured the small molecule’s labeled target protein and were translocated in a direction specified by the magnetic field.

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