Nanomagnets in Medicine

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Each Quarterly includes a list of publications relating to rock magnetism. We compile the list from several weekly literature searches. The searches produce scores of biomedical engineering articles, because these articles contain “magnetite” or “maghemite” search terms. “Nano” search terms are also returning an ever-increasing number of biomedical engineering articles. So, in honor of these articles, which inevitably fall prey to the Quarterly’s procrustean editing, we have this issue’s cover article: nanomagnets and medicine. This article discusses four medical applications using magnetic materials: drug delivery, hyperthermia, magnetic separation, and magnetic-resonance image enhancement.

Note that this article is largely based on an excellent review: Pankhurst, et al., [2003].

Forces on Magnetic Particles

Before discussing medical applications, it is useful to consider first some basic physics. The physics that underpins medical applications of nanomagnets is familiar to rock magnetists: basic material magnetism. However, one particularly important topic, forces on magnetic particles, is somewhat foreign to rock magnetism. The force is produced by the magnetic field gradient; a uniform field, no matter what its strength, exerts no force on a magnetic dipole. The force is:

\[ F_m = (\vec{m} \cdot \nabla) \vec{B} \]

\[ \vec{m} \] is the magnetic moment of the particle, and \( \vec{B} \) is the magnetic field. \( \vec{m} \) is the grain volume multiplied with magnetization: \( VM \); for the special case of non-remanence carrying particles, \( M \) is the applied field multiplied by susceptibility: \( \chi H \); and \( H \) is, of course, \( \vec{B} / \mu_0 \). So,

\[ F_m = \frac{V \chi}{\mu_0} (\vec{B} \cdot \nabla) \vec{B} \]

And if \( \nabla \times \vec{B} = 0 \) (i.e., no current or time-varying electric fields) then

\[ (\vec{B} \cdot \nabla) \vec{B} = \frac{\nabla (B^2)}{2} \]

So,

\[ F_m = V \chi \nabla \left( \frac{B^2}{2 \mu_0} \right) = V \chi \nabla \left( \frac{1}{2} (\vec{B} \cdot \nabla - \vec{H}) \right) \]

The magnetic force on a magnetic particle is proportional to the gradient of the magnetostatic field energy density. The force acts along the direction of steepest ascent of the energy density. Iron filings near a bar magnet illustrate this relationship. The energy density gradient is greatest at the magnet’s poles, and is, thus, where iron filings collect in the familiar demonstration. (Astute Quarterly readers will note that this force is what controls the “dry-Bitter” depositions discussed in the Quarterly vol. 16.1, and also forms the basis for magnetic force microscopy.)

Targeted Drug Delivery

Many therapeutic drugs cause collateral damage, so to speak. Chemotherapy is a particularly well-known example; the same drug that kills a malignant medical nanomagnets, continued on page 4
Visiting Fellows’ Reports

Magnetic properties of greigite (Fe₃S₄)

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Greigite (Fe₃S₄) is a strongly ferrimagnetic iron sulfide mineral, which is inferred to have the same inverse spinel crystal structure as magnetite (Fe₃O₄) [1]. During recent years, greigite has been recognized as a widespread mineral that forms under anoxic, sulfate-reducing conditions in a range of sedimentary environments. The discovery of magnetotactic bacteria that produce greigite magnetosomes provides further evidence for a potentially widespread source of sedimentary greigite [2]. The presence of greigite has significant implications for palaeomagnetic, tectonic, biomagnetic and environmental magnetic studies. In order to interpret the complex magnetic signals carried by greigite in such settings, and to model the composite magnetizations that often occur, it is necessary to know the fundamental magnetic properties of greigite.

Despite its importance and widespread occurrence, the magnetic characteristics of greigite are relatively poorly known [3]. This is partially because it is difficult to synthesize pure greigite samples and because greigite can be metastable with time and temperature. I have obtained a unique collection of almost pure synthetic and natural greigite samples and aim to determine fundamental parameters, such as the spontaneous magnetization, the anisotropy constant and exchange energy of greigite using these samples. These analyses have commenced in a range of laboratories, but it was necessary to perform a detailed magnetic characterisation of these samples during my visit to the IRM. The synthetic samples include one stoichiometric Multi-domain greigite samples produced using a hydrothermal method and one superparamagnetic sample with ~20 nm particles [4]. Natural greigite samples were collected from world-wide locations, e.g., Taiwan, Italy, New Zealand and the Czech Republic. Greigite nodules from Valle Ricca in Italy [5] and from Southwestern Taiwan [6] have typical single-domain (SD) behaviour. Samples from Neogene marine sediment in New Zealand were demonstrated to be a mixture of superparamagnetic (SP) and SD greigite [7], while greigite samples from the Czech Republic provided a mixture of SD and MD grains [8].

During my visit, I made a range of measurements on greigite in relation to: 1) the electronic structure using Mössbauer spectroscopy; 2) estimation of the exchange energy from low temperature magnetization measurements; 3) magnetic properties of MD greigite; 4) super-paramagnetism of greigite in Neogene marine sediments from New Zealand; and 5) low- and high-temperature magnetic characteristics of SP, SD and MD greigite. Some of the results are presented below.

A new hydrothermal synthesis method has enabled the production of highly crystalline multi-domain greigite. I have carried out magnetic measurements coupled with Mössbauer spectroscopy and later neutron diffraction work at the Institut Laue-Langevin (ILL) to confirm the purity. Neutron powder diffraction and polarization analysis enabled unambiguous determination of the magnetic structure of greigite. Detailed magnetic measurements including FORC diagrams, hysteresis loops, low temperature demagnetization (LTD) and low temperature cycling (LTC) of remanence confirm the MD behavior. I attempted to make domain observations during my visit, but these were unsuccessful because fine polishing is required for such work. I also measured the low temperature saturation magnetization for pure samples. Based on a spin wave model [9], these data have enabled an estimation of the exchange energy of greigite. Direct measurement of the exchange energy is difficult without neutron inelastic scattering on single crystals. The presented estimate is therefore be important. We also propose to carry out small-angle neutron scattering and low temperature heat capacity measurements in the future to compare with this estimate.

Rowan and Roberts [2006] demonstrated the widespread occurrence of SP greigite in sediments. I carried out low temperature magnetic measurements to understand these SP signals in Neogene marine sediments from New Zealand. Low-temperature FORC diagrams and hysteresis of these samples and the synthetic SP greigite samples also indicate an increasing SD contribution due to magnetic blocking at low temperature. This confirms the interpretation that SP greigite is important in many settings [7].

Detailed low- and high-temperature measurements were conducted using a wide range of samples with vary-
domain states (see Fig. 1, Fig. 2). These results will constrain the critical SP/SD/MD grain-size thresholds for greigite, which be significant for understanding the mechanisms of remanence carried by greigite. The purity of the studied samples is finally enabling determination of some of the key magnetic parameters for greigite. The results of this work will be prepared for publication in the near future as additional measurements of physical properties become available to constrain the results.

I would like to take this opportunity to thank Mike, Brian, Peat and Amy for their great help and suggestions during the measurements. I also thank Subir, Bruce and the IRM crew for their helpful discussions.

References

**Visiting Fellows Program**

**CALL FOR VISITING FELLOW APPLICATIONS:**

Due April 30, 2007; see www.irm.umn.edu for details; or email irm@umn.edu.

**Fellows from the Second Half of 2006.**

Liao Chang; Nat’l Oceanography Centre, Southampton; **Quantifying the magnetic properties of greigite (Fe3S4).**

Christoph Geiss; Trinity College; **Reconstructing Secular Variation and Environmental Change From two Lake Records in the Southern Wind River Range, WY.**

Gerardo Goya; Univ. of Zaragoza; **Determination of magnetic anisotropy’s origin in Ferrihydrite nanoparticles.**

Tomas Kohout; Univ. of Helsinki; **Low temperature magnetic properties of Neuschwanstein EL6 meteorite.**

David Krása; Univ. of Edinburgh; **Low-temperature magnetometry of nanopatterned magnetite thin films.**

**Fellows from the First Half of 2007.**

Alexandra Abrajevitch; Univ. of Michigan; **Indian monsoon and pedogenesis in the Himalayan foreland basin from the Bengal Fan sediments perspective.**

Julie Bowles; Univ. of Hawaii; **Magnetic characterization of synthetic Martian basalts.**

Maxwell Brown; Univ. of Liverpool; **Using FORC measurements to link rock magnetic properties and in-flow variability in paleointensity in lavas from the last geomagnetic field reversal.**

Sarah Brownlee; Univ. of California, Berkeley; **Characterizing the formation of magnetic microstructures in hematite-ilmenite intergrowths on a transect towards a thermal boundary.**

Claire Carvallo; Université Pierre et Marie Curie; **Magnetic characterization of cultured magnetotactic bacteria using FORC diagrams.**

Karl Fabian; NGU; **Magnetic ordering in hematite-ilmenite compounds.**

Jennifer L. Kelley; Southern Illinois Univ. at Carbondale; **Magnetic properties of young volcanic tuffs and implications for devitrification processes.**
medical nanomagnets, continued from page 1

tumor damages healthy cells and tissues. The side effects can be debilitating. The drugs are typically administered intravenously, leading to indiscriminate delivery and, largely, indiscriminate damage. Targeted drug delivery allows two major improvements: 1. it limits the drug to specific locations in the body; and 2. it lowers the required dosage.

Using magnetic nanoparticles as drug delivery agents was suggested nearly three decades ago: “[t]his system [of microspheres filled with drug and magnetite] permits extracorporeal control over the distribution of intravascular soluble chemotherapeutic agents and allows their concentration at specific body sites” [Senyei et al., 1978]. Notwithstanding the aforementioned obfuscation, the idea is simple: attach a drug to a nanomagnet; inject it into the patient; and move it to a specific location with an externally applied magnetic field. To define the problem rigorously, however, we need to add another force term, the fluid’s hydrodynamic drag on the magnetic particle. Note that this force balance is also important to rock magnetism; it describes how magnetic separators work. At IRM, for example, our “Cow” magnetic separator works by pumping a sediment slurry past a magnet. The drag force is given by:

\[ F_d = 6\pi \eta R_m \Delta v, \]

where \( R_m \) is the magnetic particle’s radius, \( \eta \) is the liquid’s viscosity, and \( \Delta v \) is the particle’s velocity less the fluid’s. We can solve for \( \Delta v \) by equating the magnetic and hydrodynamic forces, yielding:

\[ \Delta v = \frac{R_m^2 \chi}{9 \mu \eta} \nabla \left( B^2 \right). \]

It is convenient to define epsilon as \( \frac{R_m^2 \chi}{9 \mu \eta} \). This term, the magnetophoretic mobility, describes how easily the particle is manipulated by a magnetic field. Note that we have neglected some potentially important terms, such as gravitational and electrostatic forces. Interestingly, larger grains have a higher mobility than smaller ones. (Magnetic force increases as \( R_m^3 \) and drag increases as \( R_m^5 \).) Moreover, it is obvious that drug-delivery efficacy depends on a variety of factors, including field gradient, blood-flow rate, distance from the magnet to the target site, and the drug-carrier’s grain size.

So, a cytotoxic drug is attached to biocompatible magnetic nanoparticles (such as magnetite) and the complex is injected and manipulated with a high gradient magnetic field. Once the complex reaches the desired location, the drug is released. Researchers have developed a number of drug-release mechanisms, e.g., enzymatic reactions or changes in physiological condition, such as pH or temperature. Typically, two types of carriers are used: 1. a ferrite core coated with a biocompatible polymer; or 2. a porous biocompatible polymer in which nanophase magnetic material is precipitated. The polymer shields the magnetic material from the environment and is also functionalized by attaching various molecules. One researcher has developed mesoporous silica that acts as a sponge, soaking up a liquid drug. Magnetite “corks” are then precipitated to cap the pores. After the material is manipulated to the target site, the drug is released by “popping” the “corks” with an AF field. In designing the carrier, researchers have managed to have their cake and eat it too. Micron-sized agglomerations of SP particles have a large particle’s stability against fluid flow; and a nanomagnet’s high susceptibility. Since fluid flow is so critical, targeting effectiveness varies depending on blood flow and the type of arteries involved: low-flow femoral arteries require much lower field gradients than high-flow carotid arteries. Specifically, fields of ~0.2 T are needed at the delivery site with gradients between 8 and 100 T/m [Voltairas et al., 2002]. Producing strong enough fields with high enough gradients at targeted location is probably the most difficult aspect of magnetic drug delivery.

Nevertheless, magnetic drug delivery has shown some success. One of the first studies involved magnetic drug delivery to tumors in rat tails. The (un)lucky rodents experienced total remission. One author succinctly summarized the major hurdle facing magnetic drug delivery while discussing this study: “[I]t has to be considered that this tumor is located in a thin[,] long extremity. It is much more difficult to focus the particles by a magnetic field deeper inside the body. For this reason, magnetic targeting has not so-far found broad application” [Kreuter, 2007]. Other studies document the successful magnetic-delivery of cytotoxic drugs and tumor remission in swine (e.g., Gloucester Old Spot), rabbits, and still more rats. (Note the conspicuous absence of guinea pigs.) The results show that magnetic drug delivery can result in a fourfold increase in delivered-drug at the target site compared with indiscriminate intravenous drug delivery. Drug delivery to brain tumors is especially difficult because of the blood-brain barrier. (Capillaries are lined with endothelial cells: in the brain these cells are packed more closely together than in other locations within the body. This barrier restricts the movement of chemicals between the blood and the brain. Ethanol, luckily, has no problem crossing the blood-brain barrier.) Due to their size, 10-20 nm magnetic carriers have shown promise in targeting brain tumors.

Though still at an early stage, researchers have begun clinical studies on human patients. One study found that “ferrofluids [were] well tolerated in most of the 14 patients” [Pankhurst et al., 2003]. On a more negative note, one company halted magnetic drug delivery clinical trials for liver cancer after two years: the benefit to patients was not statistically significant. Summarizing, the problems facing magnetic drug-delivery include: 1. achieving high enough fields and field gradients at the target site; 2. magnetic carriers might cause embolisms; 3. once the drug is released it is unaffected by the magnetic

“[T]he idea is simple: attach a drug to a nanomagnet; inject it into the patient; and move it to a specific location with an externally applied magnetic field.”
Hyperthermia

One possible treatment of cancerous tumors is to heat the tumor cells. Ideally, the surrounding healthy cells would not be heated. Researchers have designed numerous devices to do this, including systems that exploit magnetic particles. More or less, the idea is to deliver magnetic particles to the tumor and apply AC fields of sufficient strength and frequency to heat up the magnetic particles; the heat then conducts to adjacent cells. If a temperature of 42 °C is maintained for 30 minutes, the cells are destroyed. Magnetic-particle hyperthermia is appealing because it allows targeted heating.

The main difficulty with magnetic-particle hyperthermia is obtaining and maintaining enough heat using an AC field while not damaging healthy tissue. High-frequency magnetic fields can cause a number of deleterious responses in the body, including nonspecific heating; skeletal-muscle stimulation; cardiac stimulation and arrhythmia. The usable field range is thought to be 0.05 < f < 1.2 MHz and H < 15 kA/m (19 mT). One researcher concluded that fields with H · f < 4.85 × 10⁶ A/(ms) are acceptable [Atkinson et al., 1984]. Of course, a sufficient amount of magnetic material is also needed. ~5 mg per cc of tissue is thought to be appropriate [Pankhurst et al., 2003].

Next, consider what makes one magnetic material more appropriate than another for hyperthermia applications. Ignoring ferromagnetic resonance, and eddy-currents, the rate of heat generation by a magnetic particle is simply the area of its hysteresis loop multiplied by the frequency of the applied field:

\[ P = \mu_0 f \oint H dM. \]

Given the acceptable field range for humans, this is not magnetotactic’s breakthrough application. The ultimate material would be aligned single-domain grains that saturate below 15 kA/m. Since most stable ferromagnetic materials do not saturate at such low fields, researchers have turned to superparamagnetic material. The heat generated by SP particles can be defined using a simple Debye model. The heat is proportional to the out-of-phase susceptibility:

\[ P = \mu_0 \pi f \chi'' H^2. \]

The best SP samples can generate 209 W/g in a 14 kA/m field with f=300 kHz [Hergt et al., 1998]. The current thinking is that SP particles are the most promising agents of hyperthermia.

Magnetic-particle hyperthermia has been successfully tested in a few animal models [Pankhurst et al., 2003]. It has also been used to treat prostate cancer in a human patient [Johannsen et al., 2005].

Cell Labeling and Separation

In medicine, it is often necessary to separate certain cells from their environment. Magnetic particles have been successfully employed to do this. The technique is a two step process: 1. the cells are tagged with magnetic particles; and 2. the cells are separated using a magnet. Most often, iron oxide particles are coated with a biocompatible substance, like dextran; a “binding site” is then attached, such as an antibody or hormone. Antibodies, for example, can be very efficient at attaching to the matching antigen. The technique has been used to successfully tag red-blood cells, lung cancer cells, and bacteria [Pankhurst et al., 2003].

Magnetic separation varies considerably in complexity. At the low-tech extreme, a permanent magnet is held to the side of a test tube and the supernatant is removed. Complicated systems can involve fluid flow fractionation. If different tagged cells have different magnetophoretic mobility, progressively stronger magnetic fields and gradients can be applied to remove cells with higher mobility first. Alternatively, the magnetic field is held constant and the fluid flow is manipulated. It is easy to imagine using such a system to physically unmix the magnetic components in natural sediment. The medical community has found several applications for magnetic separation of cells: the selection of rare tumor cells from blood; separation of malarial parasites; and pre-processing samples for DNA analysis [Pankhurst et al., 2003].

Magnetic Resonance Imaging Contrast Agents

Magnetic resonance imaging (MRI) essentially measures the response of protons to an applied field. Though the response of a single proton is vanishingly small, the large number of protons in water yield a measurable response. (Proton-precession magnetometers work on this...
principle as well.) A DC magnetic field is applied, typically of order 1 T; protons align slightly with the applied field and precess around the field with a frequency of $\gamma B_0$, the Larmor frequency. $B_0$ is the DC field and $\gamma$ is 2.67 x 10^6 rad/(sT) for $^1$H protons. (The human body is ~60% H atoms.) A small AC field orthogonal to $B_0$ is applied and tuned to the Larmor frequency. The magnetic response is measured as a function of time after the radio-frequency AC field is turned off. The magnetization in the plane parallel to the RF field and perpendicular to the DC field decays quickly with time, following $m_{+2} = m \sin (\omega t + \phi) (e^{-t/\tau_2})$.

And the magnetization parallel to the DC fields increases with time, following:

$$m_{+1} = m (1 - e^{-t/\tau_1}).$$

$\tau_1$ and $\tau_2$ are relaxation times. $\tau_1$ is related to the energy loss due to heat; and $\tau_2$ is related to dipole interactions between protons, resulting in a rapid loss of magnetization as the protons' phase coherence is lost when the RF field vanishes. Dephasing is also a function of inhomogeneities in the total field. The total field is a function of the applied field gradient and local variations of magnetic susceptibility. So, we replace $\tau_2$ with $\tau_2'$.

$$\frac{1}{\tau_2'} = \frac{1}{\tau_2} + \frac{\gamma \Delta B}{2},$$

where $\Delta B$ is the inhomogeneity in the total field. For MRI the important point is that different tissues have different $\tau_1$ and $\tau_2'$ constants.

Ferromagnetic contrast agents work by locally distorting $B$. Typically, SP particles that are saturated by the DC field are used. If the SP particles are present in different concentrations in different tissues, then the SP particles locally distort $B$ and affect $\tau_2'$. In this manner SP iron oxide is employed to image liver lesions; other examples include, imaging of bone marrow and lymph node tumors [Pankhurst et al., 2003].

References


Current Articles

A list of current research articles dealing with various topics in the physics and chemistry of magnetism is a regular feature of the IRM Quarterly. Articles published in familiar geology and geophysics journals are included; special emphasis is given to current articles from physics, chemistry, and materials-science journals. Most abstracts are taken from INSPEC (© Institution of Electrical Engineers), Geophysical Abstracts in Press (© American Geophysical Union), and The Earth and Planetary Express (© Elsevier Science Publishers, B.V.), after which they are subjected to Procrustean culling for this newsletter. An extensive reference list of articles (primarily about rock magnetism, the physics and chemistry of magnetism, and some paleomagnetism) is continually updated at the IRM. This list, with more than 10,000 references, is available free of charge. Your contributions both to the list and to the Abstracts section of the IRM Quarterly are always welcome.

Note that this issue’s selection of articles highlights a special issue of the Journal of Geophysics. An excellent selection of other current articles may be found on IRM’s website: the articles have been added to the posted EndNote file.

The Dunlop Volume, JGR Solid Earth: Fundamental and Frontier Research in Rock Magnetism


Dunlop, D. J., and B. Carter-Stiglitz (2006), Day plots of mix-
Early medical applications of magnetism were of questionable benefit to patients. Above, is a patient using a “theronoid,” essentially a current loop worn as a belt that was supposed to be of therapeutic benefit to the patient.

...
The Institute for Rock Magnetism is dedicated to providing state-of-the-art facilities and technical expertise free of charge to any interested researcher who applies and is accepted as a Visiting Fellow. Short proposals are accepted semi-annually in spring and fall for work to be done in a 10-day period during the following half year. Shorter, less formal visits are arranged on an individual basis through the Facilities Manager.

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