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RESEARCH

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Special report: magnetic nanoparticles

The magnetic properties of nano-sized particles are attracting increasing attention in biomedical research. Greater knowledge of how magnetic nanoparticles behave - and why - is furthering a raft of investigations into promising diagnostic and therapeutic applications.

One thing is clear: the development and study of magnetic nanoparticles has evolved into a truly multidisciplinary, global endeavour. Nowhere was this more evident than at the Sixth International Conference on the Scientific and Clinical Applications of Magnetic Carriers, held earlier this year in Krems, Austria, and attended by more than 300 physicists, chemists, materials scientists, engineers, clinicians and biologists from 43 countries.

Key to their work is the ability to tailor the magnetic properties of materials by simply reducing the lengthscale of certain critical dimensions. Smaller particle, fibre or grain diameters, separation distances, aspect ratios and thicknesses can all influence behaviour, says Robert Shull, leader of the magnetic materials group at the US National Institute of Standards and Technology, Gaithersburg, MD. "If you nanostructure a material in some way, you can change the importance of magnetic interactions between neighbouring entities, or the ability to retain this magnetization over time," he explained.

Switching states

Considerable interest has been generated by materials that exhibit superparamagnetic behaviour when produced with nanoscale dimensions. Like ferromagnetic materials, these nanoparticles can magnetize strongly under the influence of an applied magnetic field. But once the applied field is removed from superparamagnetic materials, their magnetic field returns to zero.

Such on/off magnetic switching can be seen at room temperature in nanoparticles made from magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3). These materials are essentially biocompatible, since any iron left when the particles break down can be recycled naturally by the human body. Consequently, this has led to the development of superparamagnetic iron oxide (SPIO) particles (≥50 nm) and ultrasmall superparamagnetic iron oxide (USPIO) particles (<50 nm) specifically for clinical applications.

For example, MRI contrast agents based on SPIO and USPIO particles have already been approved for clinical use. These agents work by altering the transverse relaxation times (T2 decay) of water protons as they realign with the scanner's static magnetic field following the application of RF pulses. This leads to dark spots, or "negative contrast", on T2-weighted MRI scans. Longitudinal (T1) decay is generally unaffected by this class of agents.

SPIO- and USPIO-based contrast agents are attracting particular interest as a means of detecting individual cancer cells on MRI scans. The superparamagnetic particles are first coated with agents that will bind selectively to certain cells. On injection into the body, the loaded particles accumulate round their quarry. An MRI scan can then show exactly where the malignant cells are and provide some estimation of their quantity. Applications under investigation include *in vivo* monitoring of transplanted pancreatic islet cells to treat diabetes patients, bone-marrow stem cells administered to improve impaired cardiac function, and dendritic cells being trialled as potential "cancer vaccines".

Size matters

Neuromagnetism pioneer Ed Flynn, formerly of Los Alamos National Laboratory, NM, US, believes that nanoparticles' superparamagnetic properties could also be exploited in an ultrasensitive cell-detection system based on SQUID technology (i.e. superconducting quantum-interference devices). Now president of the start-up Senior Scientific, based in Albuquerque, NM, Flynn has demonstrated the potential of such a set-up to improve the early detection of breast cancer.

The system works by measuring the decaying, remanent field produced by clusters of superparamagnetic nanoparticles when an external, magnetizing field is switched off. Flynn has trialled this method using a seven-channel SQUID and breast phantoms impregnated with various iron oxide nanoparticles. The set-up enabled the detection of clusters with at least 10^4 cells when 2 cm away, and clusters of 10^5 cells or more from a distance of 5 cm.

Central to the system's success is control of the nanoparticles' size distribution. "We need particles of around 20-25 nm in diameter," Flynn said. "Any smaller, we don't see them. Any larger, the remanence field decays too slowly for us."

An added advantage is that the SQUID system only detects nanoparticles that attach to cancer cells; the magnetization of free nanoparticles decays far too quickly to be picked up. MRI, on the other hand, will generate signals from iron oxide nanoparticles whether they have reached their target or not. "We have demonstrated this again and again," Flynn said. "When we look at live cells, we get a beautiful signal. We put the same number of nanoparticles into a solution without live cells and we don't get any signal at all."

But SQUIDs should not be viewed as a rival to MRI, says Flynn, who prefers to view the biomagnetic approach as a complementary diagnostic tool. He now aims to improve the system's accuracy by moving to a 32-channel device. Additional clinical applications could include the non-invasive detection of cells responsible for organ rejection in transplant patients, early detection of ovarian and prostate cancers, and accurate diagnosis of Alzheimer’s disease.

Feel the heat

In addition to their emerging role in diagnosis and disease monitoring, superparamagnetic nanoparticles are also being considered as possible drug-delivery "vehicles". Researchers are investigating ways of coating SPIO and USPIO particles with chemotherapy agents as well as with antibodies that home in on cancer cells. Such schemes envisage that the loaded nanoparticles could then be drawn towards a target tumour under the influence of an externally applied magnetic field. This should improve the efficacy of chemotherapy by ensuring that a far higher percentage of drug molecules actually reach their intended target. Side-effects caused by the highly toxic anti-cancer agents attacking healthy tissue should also be reduced.

Another option under investigation is the use of SPIO and USPIO particles to deliver heat to the site of cancerous tumours (i.e. hyperthermia). Raising the temperature of cancers to 41-46 °C has been shown to induce apoptosis (cell death). This method of cancer treatment has fewer side-effects than chemotherapy. Pretreatment of cancers with hyperthermia has also been shown to improve the efficacy of radiotherapy.

The use of nanoparticles as agents of hyperthermia rests with their ability to generate heat under an applied AC magnetic field. Heating in multidomain ferromagnetic materials can be explained from hysteresis losses. Heating from apparently superparamagnetic materials, such as SPIO and USPIO particles, is less easily explained and remains a subject for considerable debate.

Researchers have pointed to energy dissipated from Néel relaxation, when particle moments relax to their equilibrium orientation, and during Brownian motion, as the particles rotate under the applied AC field. It is also possible that the magnetic properties of SPIO and USPIO particles change under higher-frequency applied magnetic fields.

Sara Majetich, a physics professor at Carnegie Mellon University, Pittsburgh, PA, explained: "These particles may be perfectly superparamagnetic when you are measuring their properties with a vibrating sample magnetometer under fields that are essentially DC. But hyperthermia is performed at hundreds of kilohertz, and at that point the magnetization can't necessarily keep up with the driving AC field. So by the time you get to 500 kHz, you have got an open loop with a finite area, and that contributes to the heating."

Magnetic moments

Whatever the reasons behind the observed heating, not all researchers are convinced that SPIO and USPIO nanoparticles are the best candidates for magnetic hyperthermia applications. Switching to out-and-out ferromagnetic nanoparticles could improve the heating efficiency, they claim. Ferromagnetic nanoparticles also tend to have a higher saturation magnetization, and hence a greater magnetic moment. The particles should consequently be easier to move round the body under magnetic force for drug-delivery applications, and to visualize on MRI scans. Achieving comparable effects with iron oxide would mean increasing the size of particles or using higher doses of material.

"We need to use materials with a high saturation magnetization so we can have a high magnetic moment per unit volume," explained Jian-Ping Wang, associate professor at the Center for Micromagnetics and Information Technologies at the University of Minnesota, Minneapolis, MN. "In this way, we can have high heating, tracking and imaging efficiency by using the same amount or smaller quantities of nanoparticles."

Wang's group is one of many investigating ferromagnetic alternatives to SPIO and USPIO. They are especially interested in pure cobalt and iron cobalt nanoparticles. The toxicity of cobalt means that the ferromagnetic core must be encased in a shell to which therapeutic agents could also be attached. Favoured options for the shell include gold and silicon dioxide. "It is very important to have a biocompatible shell for these high-moment particles [as] this will remove concerns about toxicity," Wang concluded.

About the author

Paula Gould is a contributing editor on *medicalphysicsweb*. Background research for this report was carried out at the Sixth International Conference on the Scientific and Clinical Applications of Magnetic Carriers in Krems, Austria.

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