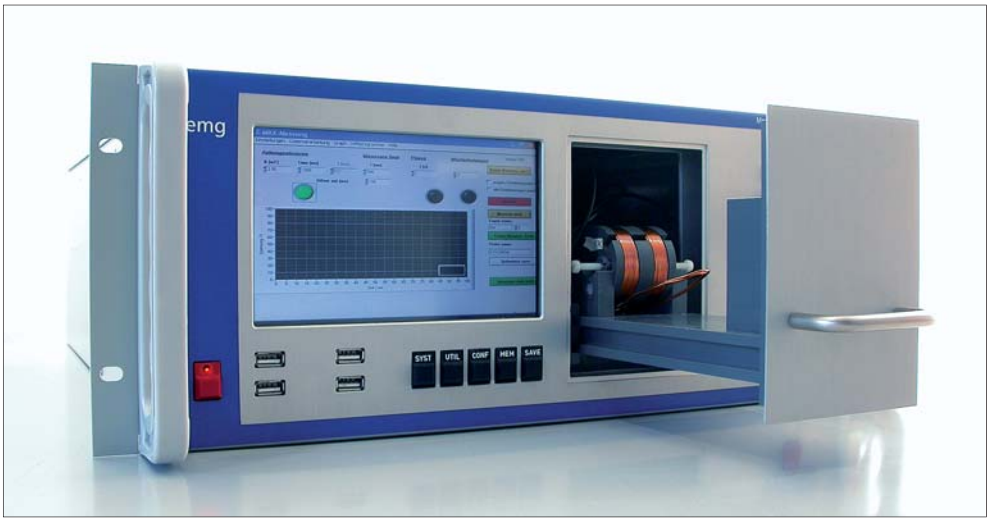
PRESS RELEASE

To find the invisible:
Magnetic Nanoparticles in Medicine und Bioanalysis

Magnetic nanoparticles become more and more important in medicine and bioanalysis. Well established is their use as contrast agents in magnetic resonance imaging and as markers in biotechnology and biochemistry. Very promising is their application in tumor therapy to guide drugs directly to the tumor or to locally heat up tumor cells in hyperthermia without damaging surrounding healthy cells.



The **Magnetic Nanoparticle Analyzer** provides characterization of magnetic nanoparticles and the analysis of biochemical test with magnetic nanoparticle markers.

The novel Magnetic Nanoparticle Analyzer provides manufacturers and users of magnetic nanoparticles a tool to characterize properties and quality state of their samples. These measurements can be done reproducibly, exactly and fast in a single laboratory instrument. This measurement technique is necessary for quality assurance for all who rely on magnetic nanoparticles in medicine and bioanalysis.

Based on our research in the Sonderforschungsbereich (SFB) 578 a novel instrument has been constructed which uses our low-noise fluxgate-magnetometers. It allows easy handling for biochemical assays, as well as complete and fast characterization of the magnetic nanoparticles. The measurement procedure employs the relaxation of the magnetic nanoparticles. Advanced algorithms for the analysis and the metrological background are enforced in a new BMBF-project under guidance of Dr. Frank Ludwig. Together with the Physikalisch-Technische Bundesanstalt PTB and the instrumentation company Magnicon GbR the **Magnetic Nanoparticle Analyzer** will be further completed and made commercially available. The instrument has been presented for the first time at Hannover-Messe 2007 in the research exhibition of Lower Saxony/Germany.

Contact

Prof. Dr. Meinhard Schilling

Telefon 0049.0531.391-3866
Telefax 0049.0531.391-5768

eMail
m.schilling@tu-braunschweig.de

Technische Universität Braunschweig
Fachbereich Elektrotechnik

Institut für Elektrische Messtechnik und Grundlagen der Elektrotechnik

Hans-Sommer-Straße 66
D-38106 Braunschweig

Postfach 3329
D-38023 Braunschweig
http//: www.emg.ing.tu-bs.de

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emg The "Institut für Elektrische Messtechnik und Grundlagen der Elektrotechnik"

Contact

Prof. Dr. Meinhard Schilling

Telefon 0049.0531.391-3866
Telefax 0049.0531.391-5768

eMail m.schilling@tu-braunschweig.de

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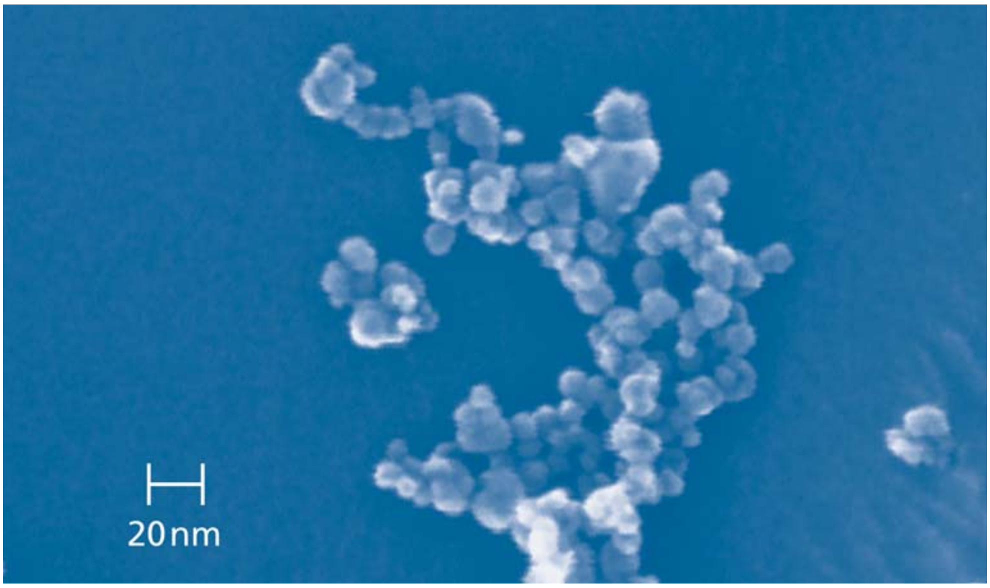
What are Magnetic Nanopaticles?

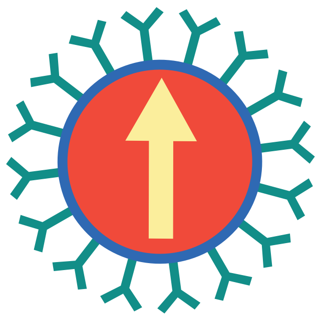
BACKGROUND INFORMATION



Magnetische Nanoteilchen bestehen aus magnetischem Material und haben Durchmesser von weniger als 50 nm. Erst zweitausend Nanoteilchen nebeneinander ergeben die Breite Magnetic nanoparticles consist of magnetic material and have diameters of less than 50 nm. About 2000 nanoparticles side by side correspond to the width of a human hair. Nanoparticles have approximately the size of large biochemical molecules (i.e. large protein complexes). Thus, they can reach many places, where larger instruments fail.

Due to their small diameter, all atoms in a magnetic nanoparticle contribute equally to their magnetic properties, these are called **monodomain particles**. For even smaller nanoparticles with a diameter below about 20 nm, without external magnetic field no permanent magnetism can be observed, since the magnetic direction of the atoms becomes independent of the crystalline structure of the nanoparticle. This property is called **superparamagnetism**. In an external magnetic field even the smallest magnetic nanoparticles show the expected strong magnetic properties, which we analyze.

In the mentioned exciting applications in medicine and bioanalysis the magnetic nanoparticles are used in solution and have to be protected against corrosion. Therefore, the nanoparticles are enclosed in a non-magnetic layer, shown blue in the figure. This layer ensures a minimum distance between the nanoparticles and prevents their aggregation. Precise control of this protection layer of only a few atomic monolayers thickness as well as of the diameter of the magnetic core of the nanoparticle (shown in red in the figure) is desirable. Both can be characterized precisely and fast by our new **Magnetic Nanoparticle Analyzer**.



eines menschlichen Haares. Nanoteilchen sind etwa so groß wie große biochemische Moleküle (z.B. große Protein-komplexe). Dadurch können sie an viele Stellen vordringen, die für größere Partikel unerreichbar sind.

Contact

Prof. Dr. Meinhard Schilling

Telefon 0049.0531.391-3866
Telefax 0049.0531.391-5768

eMail m.schilling@tu-braunschweig.de

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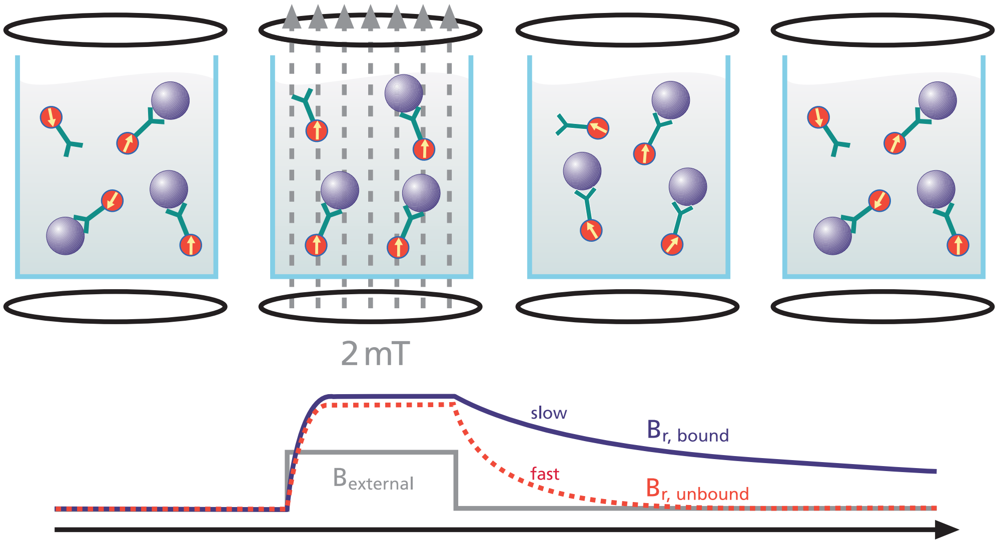
Magnetorelaxation

BACKGROUND INFORMATION



The measurement principle of the Magnetic Nanoparticle Analyzer is based on the magnetorelaxation of magnetic nanoparticles. The basic measurement cycle is depicted in the figure below. Without an external magnetic field, the superparamagnetic nanoparticles exhibit no measurable magnetic signal. If one applies a magnetic field Bextern, the magnetic nanoparticles are aligned and the sample shows a measurable magnetic signal. If the magnetic field is turned off again, the magnetic signal of the nanoparticles decays to zero. This so called relaxation of the magnetic signal depends on the size of the nanoparticles. If a nanoparticle is located in a liquid it can rotate as a whole. This mechanism is called Brownian relaxation. Large particles rotate slowly, small ones fast. Thus, in a magnetorelaxometry experiment, very small particles do not contribute to the relaxation signal.
Since the size of the nanoparticle depends on whether the chemical substance which is to be detected is bound to its shell, these substances can specifically be detected by means of magnetorelaxometry. The nanoparticles act as markers. The figure above depicts the situation for a so called **liquid-phase immunoassay**. Here the unbound magnetic nanoparticles relax faster than those bound to the biological target molecules to be detected. Due to the different relaxation behavior, bound and unbound markers can be distinguished without the need to wash out the unbound ones (Ludwig, Technisches Messen **4**, 217 (2006)).

Besides the measurement of liquid-phase immunoassays, the **aggregation behavior** of magnetic markers in solution can be quantified prior to their clinical use. In addition, from the size-dependent relaxation time, the **size distribution** of the nanoparticles can be determined and used for quality assurance in medicine and biochemistry.

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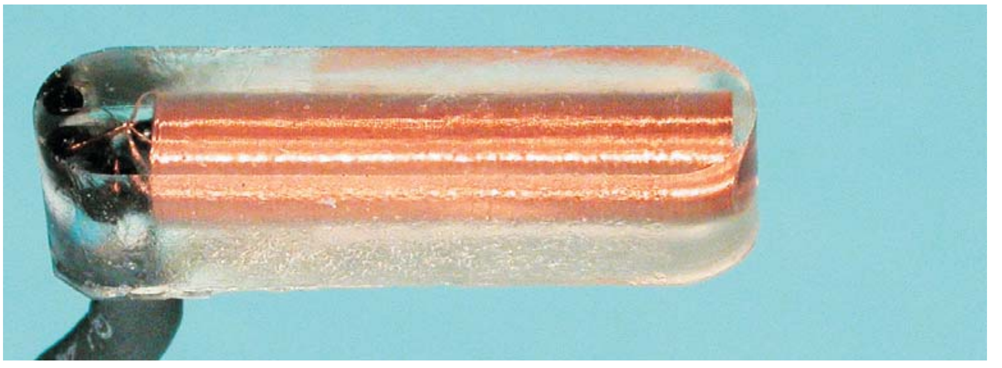
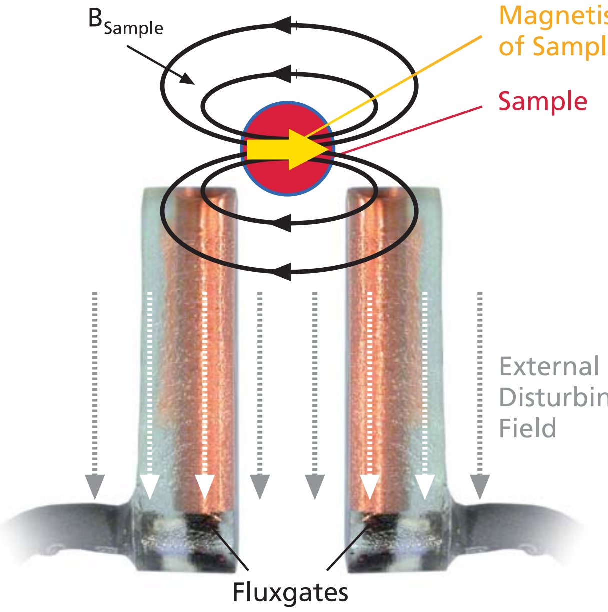
Fast Fluxgate-Magnetometers

BACKGROUND INFORMATION



Fluxgate magnetometers are sensors for the simple and precise measurement of magnetic fields. These sensors can also follow fast changes of magnetic fields. The fluxgate magnetometers that are used in the **Magnetic Nanoparticle Analyzer** are developed at our institute. We also investigate how sensors of even smaller size and with lower noise can be built.

In the **Magnetic Nanoparticle Analyzer** the magnetic field of the nanoparticles is measured with these fluxgate sensors outside the sample container. In order to eliminate magnetic disturbances from power lines or other devices, two fluxgate magnetometers are used in the **Magnetic Nanoparticle Analyzer**. Taking the difference of the two fluxgate magnetometers, signals from distant sources of magnetic disturbances cancel each other. Thus, both sensors see the same field and the difference of the signals is zero. The nanoparticle sample is positioned such that its magnetic field is sensed by the two magnetometers with opposite signs. This causes the nanoparticle difference signal to be twice that of the individual fluxgate sensors (Ludwig et al., Review of Scientific Instruments **76**, 106102-1 (2005)).



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Magnetic Nanoparticles as Bioanalytical Markers

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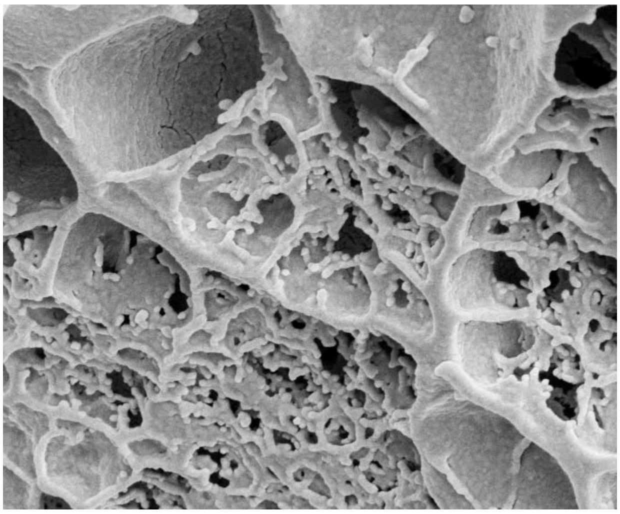

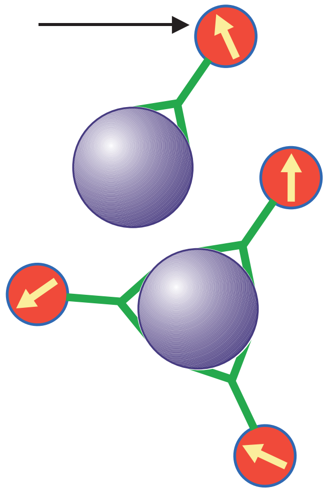

Magnetic nanoparticles (red) mark via antibodies (green) the wanted chemical substance (blue). In the left figure nanoparticles are bound to the surface of pores of a substance which – as a spongy gel – is used for the release of drugs (Heim et al., Journal of Magnetism and Magnetic Materials **311**, 150 (2006)).

An important and frequent task in biochemistry and molecular biology is the search of molecules of only one specific chemical substance in a mixture of numerous, different molecules. This is the proverbial search of a needle in a haystack. This hopelessly appearing task is, however, extremely simplified by using magnetic nanoparticles as markers. First, the magnetic nanoparticles are equipped with antibody molecules so that they can specifically bind to the wanted molecules. Next, the nanoparticles marked with antibodies are added to the mixture and they autonomously go on search for target molecules to which they bind after a short time. If one now applies an external magnetic field, all magnetic nanoparticles including the bound target molecules can be collected. Often it is sufficient to measure the number of magnetic nanoparticles to which the target molecules are bound in order to estimate the number of wanted molecules. This measurement is significantly simplified by our novel **Magnetic Nanoparticle Analyzer** for magnetic nanoparticles.

Another useful property of magnetic nanoparticles is that they can be manipulated in a magnetic gradient field. This property is utilized in the so called **magnetic drug targeting**. Here magnetic fields from outside the body direct the nanoparticles including the attached drugs to the desired location. Thus, for example in chemotherapy against cancer, the required dose can be reduced significantly.

Contact

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The “Institut für Elektrische Messtechnik und Grundlagen der Elektrotechnik”

BACKGROUND INFORMATION

At home and in cars, as well as in industry and economy: Everywhere electrical sensors are at work for many kinds of instruments. The “Institut für Elektrische Messtechnik und Grundlagen der Elektrotechnik” der TU Braunschweig headed by Prof. Dr. rer. nat. Meinhard Schilling investigates how sensors can be manufactured smaller, more precise and more reliable. Also new metrological concepts are developed. The sensors are produced in a modern cleanroom by means of nanotechnology and are attached to analog and digital measurement systems. These systems are employed for magnetic field measurements, biochemical/medical applications and for the analysis of microchips working at the highest frequencies up to more than 1000 GHz. In all these areas close cooperations with industry and international research institutes are maintained and extended.

The **magnetic sensors and systems** are tested in a magnetically shielded room. There also is a SQUID magnetometer system for biomagnetical measurements of the heart and the brain located.

For the development and testing of **biochemical sensors** a bioreactor is placed in a S1-laboratory, which guarantees the secure handling of microorganisms.

For analysis of microchips at **ultrahigh frequencies** a microwave laboratory is maintained with a far infrared laser-system, where also the novel terahertz-microscope has been developed.

Contact

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D-38023 Braunschweig
http//: www.emg.ing.tu-bs.de

Prof. Dr. Meinhard Schilling

Head of the “Institut für Elektrische Messtechnik und Grundlagen der Elektrotechnik” der Technischen Universität Braunschweig