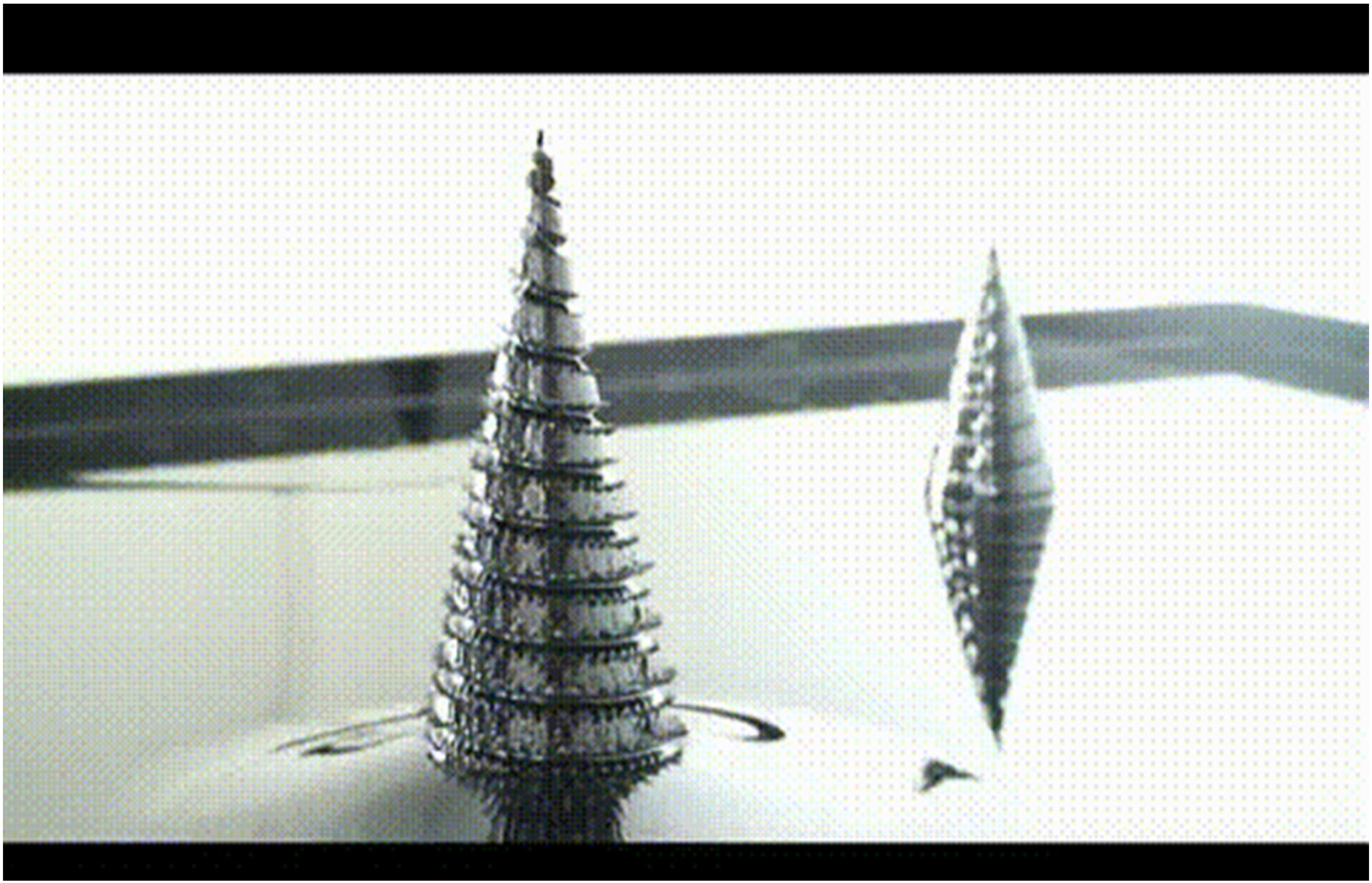
Biosensors based on magnetic nanoparticles.



Biosensors based on magnetic nanoparticles.

"There's Plenty of Room at the Bottom" was a lecture given by physicist Richard Feynman at an American Physical Society meeting at Caltech on December 29, 1959. Feynman considered the possibility of direct manipulation of individual atoms as a more powerful form of synthetic chemistry than those used at the time. The talk is considered to be a seminal event in the history of nanotechnology, as it inspired the conceptual beginnings of the field decades later.

Magnetic nanoparticles

Magnetic nanoparticles are a class of nanoparticle which can be manipulated using magnetic field. Such particles commonly consist of magnetic elements such as iron, nickel and cobalt and their chemical compounds. While nanoparticles are smaller than 1 micrometer in diameter (typically 5–500 nanometers), the larger microbeads are 0.5–500 micrometer in diameter. The magnetic nanoparticles have been the focus of much research recently because they possess attractive properties which could see potential use in catalysis including nanomaterial-based catalysts, biomedicine, magnetic resonance imaging, magnetic particle imaging, data storage, etc……

Magnetic nanoparticles

Currently, three different kinds of magnetic nanoparticles are being produced and used

1. **Ferrite nanoparticles** are the most explored magnetic nanoparticles up to date. Once the ferrite particles become smaller than 128 nm they become superparamagnetic which prevents self agglomeration since they exhibit their magnetic behavior only when an external magnetic field is applied. With the external magnetic field switched off, the remanence falls back to zero. Just like non-magnetic oxide nanoparticles, the surface of ferrite nanoparticles is often modified by surfactants, silicones or phosphoric acid derivatives to increase their stability in solution

Magnetic nanoparticles

2. **Metallic nanoparticles** have the great disadvantage of being pyrophoric and reactive to oxidizing agents to various degrees. This makes their handling difficult and enables unwanted side reactions.
3. **The metallic core** of magnetic nanoparticles **may be passivated** by gentle oxidation, surfactants, polymers and precious metals. In an oxygen environment, Co nanoparticles form an anti-ferromagnetic CoO layer on the surface of the Co nanoparticle. Recently, work has explored the synthesis and exchange bias effect in these Co core CoO shell nanoparticles with a gold outer shell.

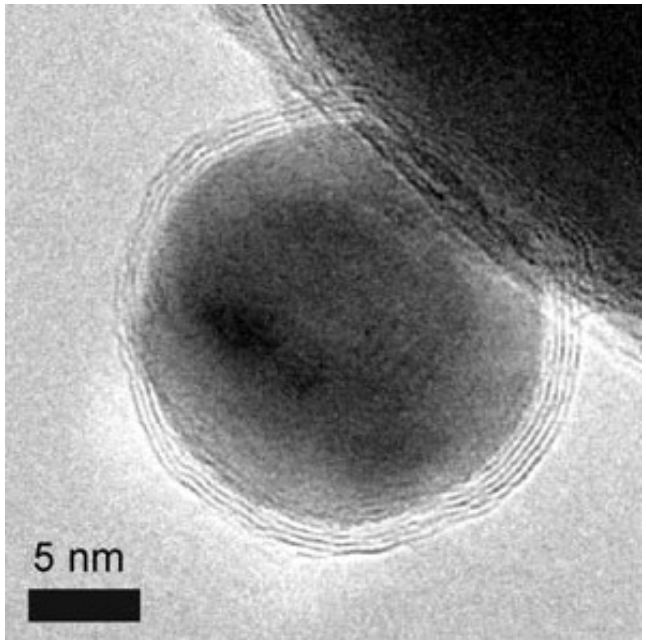
Magnetic nanoparticles

Nanoparticles with a magnetic core consisting either of elementary Iron or Cobalt with a nonreactive shell made of graphene have been synthesized recently. The advantages compared to ferrite or elemental nanoparticles are:

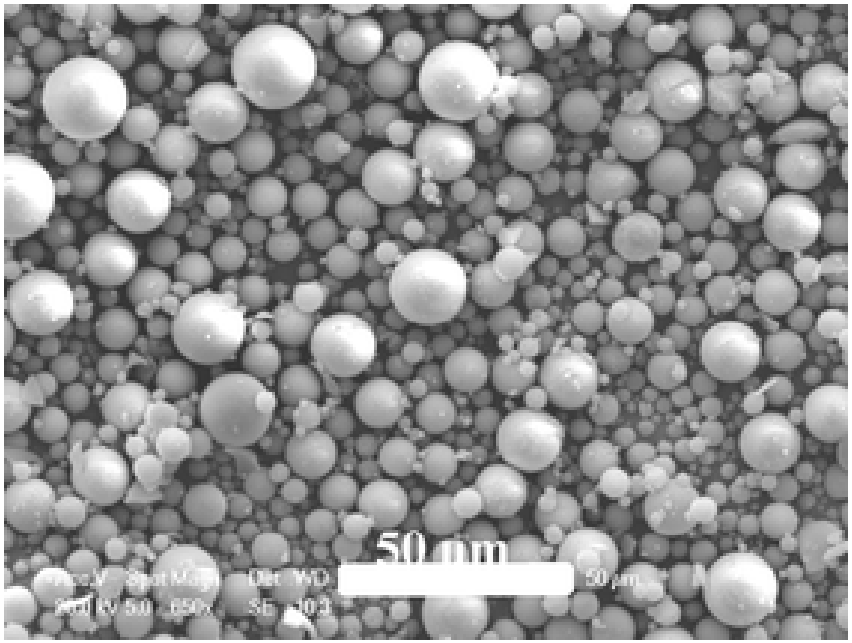
- **Higher magnetization**
- **Higher stability in acidic and basic solution as well as organic solvents**
- **Chemistry on the graphene surface via methods already known for carbon nanotubes**

Magnetic nanoparticles

The physical and chemical properties of magnetic nanoparticles largely depend on the synthesis method and chemical structure. In most cases, the particles range from 1 to 100 nm in size and may display **superparamagnetism.**



Cobalt nanoparticle with graphene shell (note: The individual graphene layers are visible)



Ferrite (Fe_3O_4) nanoparticles

Superparamagnetism

Superparamagnetism is a form of magnetism, which appears in small ferromagnetic or ferrimagnetic nanoparticles. In sufficiently small nanoparticles, magnetization can randomly flip direction under the influence of temperature. The typical time between two flips is called the Néel relaxation time. In the absence of external magnetic field, when the time used to measure the magnetization of the nanoparticles is much longer than the *Néel relaxation time*, their magnetization appears to be in average zero: they are said to be in the superparamagnetic state. In this state, an external magnetic field is able to magnetize the nanoparticles, similarly to a paramagnet. However, their magnetic susceptibility is much larger than the one of paramagnets.

Superparamagnetism

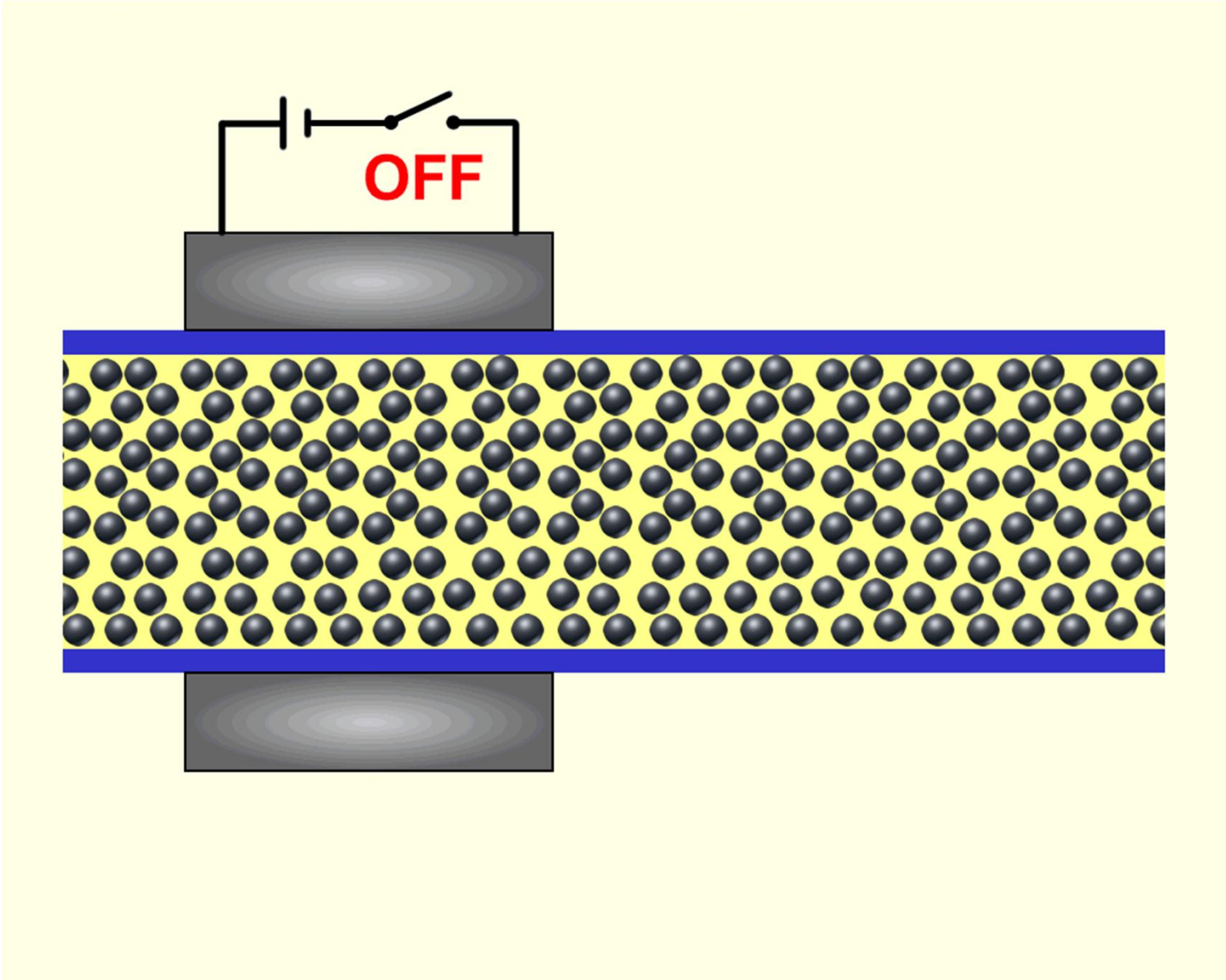
Normally, any ferromagnetic or ferrimagnetic material undergoes a transition to a paramagnetic state above its Curie temperature. Superparamagnetism is different from this standard transition since it occurs below the Curie temperature of the material.

Superparamagnetism occurs in nanoparticles which are single-domain, i.e. composed of a single magnetic domain. This is possible when their diameter is below 3–50 nm, depending on the materials. In this condition, it is considered that the magnetization of the nanoparticles is a single giant magnetic moment, sum of all the individual magnetic moments carried by the atoms of the nanoparticle. Those in the field of superparamagnetism call this “macro-spin approximation”.

Superparamagnetism

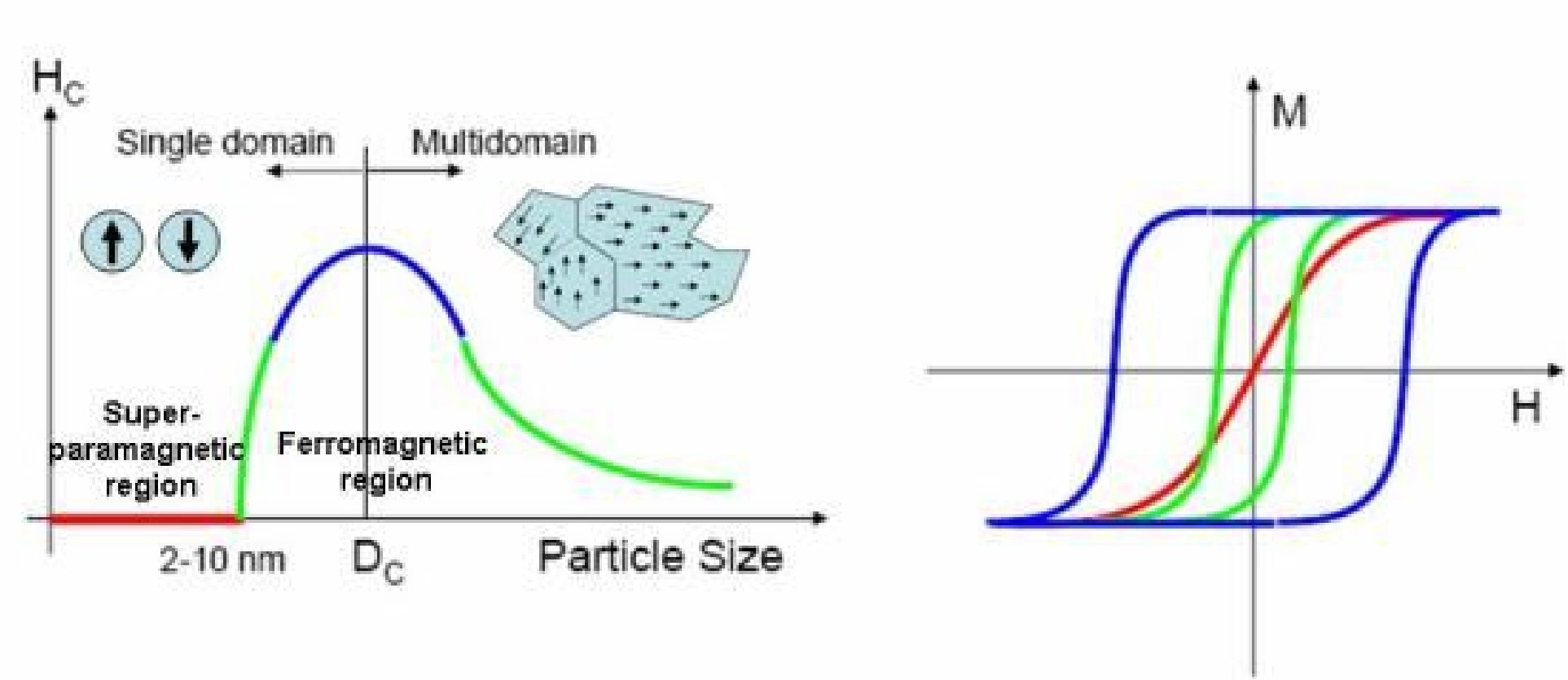
Because of the nanoparticle's magnetic anisotropy, the magnetic moment has usually only two stable orientations antiparallel to each other, separated by an energy barrier. The stable orientations define the nanoparticle's so called "easy axis". At finite temperature, there is a finite probability for the magnetization to flip and reverse its direction. When an external magnetic field is applied to an assembly of superparamagnetic nanoparticles, their magnetic moments tend to align along the applied field, leading to a net magnetization.

Behavior of magnetic nanoparticles in solution



Superparamagnetism

The magnetization curve of the assembly, i.e. the magnetization as a function of the applied field, is a reversible S-shaped increasing function.



Superparamagnetism

This function is quite complicated but for some simple cases: If all the particles are identical (same energy barrier and same magnetic moment), their easy axes are all oriented parallel to the applied field and the temperature is low enough, then the magnetization of the assembly is

$$M(H) \approx n\mu \tanh\left(\frac{\mu_0 H \mu}{k_B T}\right)$$

If all the particles are identical and the temperature is high enough, then, irrespective of the orientations of the easy axes:

$$M(H) \approx n\mu L\left(\frac{\mu_0 H \mu}{k_B T}\right)$$

in the above equations:

n in the density of nanoparticles in the sample

μ_0 is the magnetic permeability of vacuum

μ is the magnetic moment of a nanoparticle

$L(x) = 1/\tanh(x) - 1/x$ is the Langevin function

Superparamagnetism

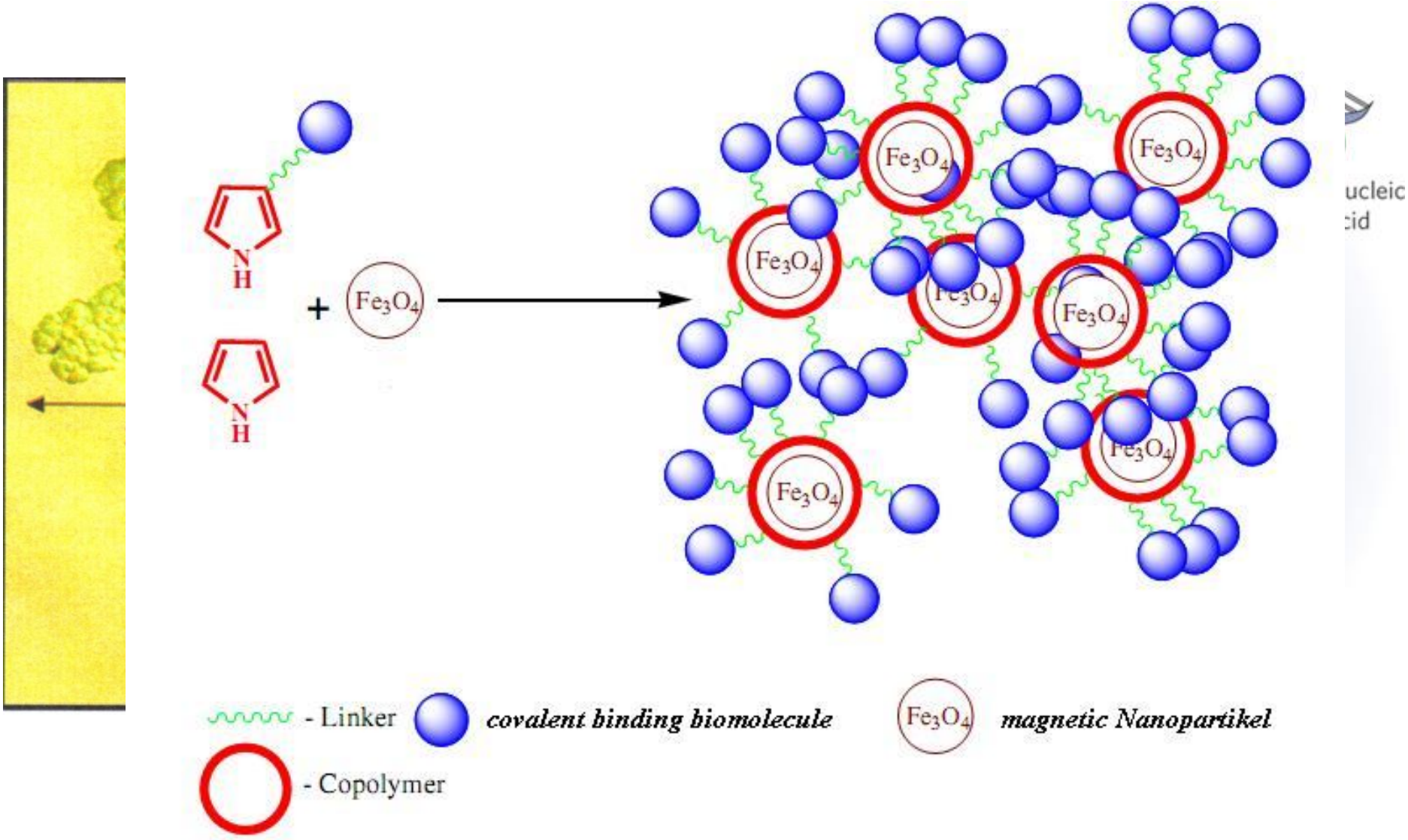
The initial slope of the M(H) function is the magnetic susceptibility of the sample χ:

$$\chi = \frac{n\mu_0\mu^2}{k_B T}$$ in the first case

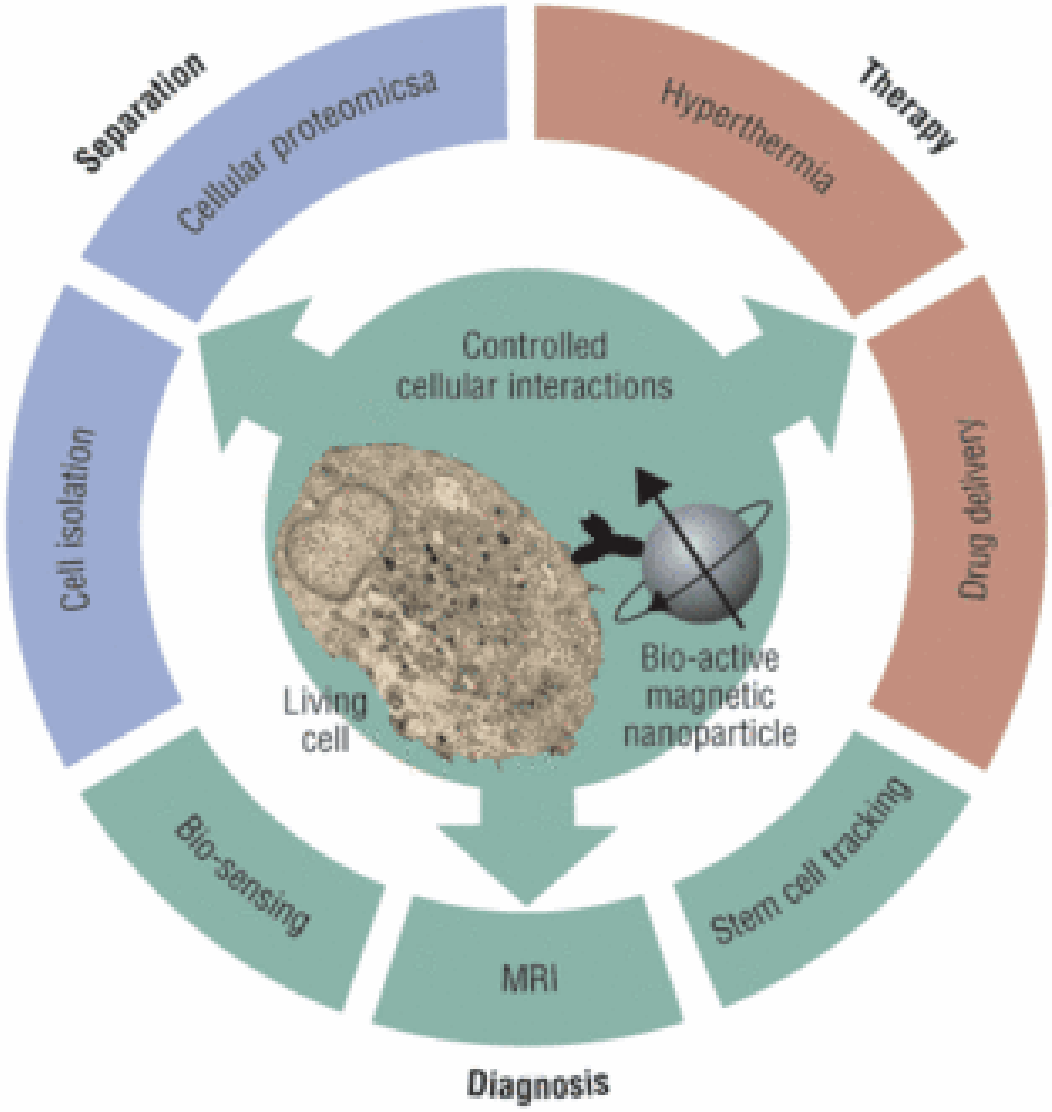
$$\chi = \frac{n\mu_0\mu^2}{3k_B T}$$ in the second case.

It can be seen from these equations that large nanoparticles have a larger μ and so a larger susceptibility. This explains why superparamagnetic nanoparticles have a much larger susceptibility than standard paramagnets: they behave exactly as a paramagnet with a huge magnetic moment.

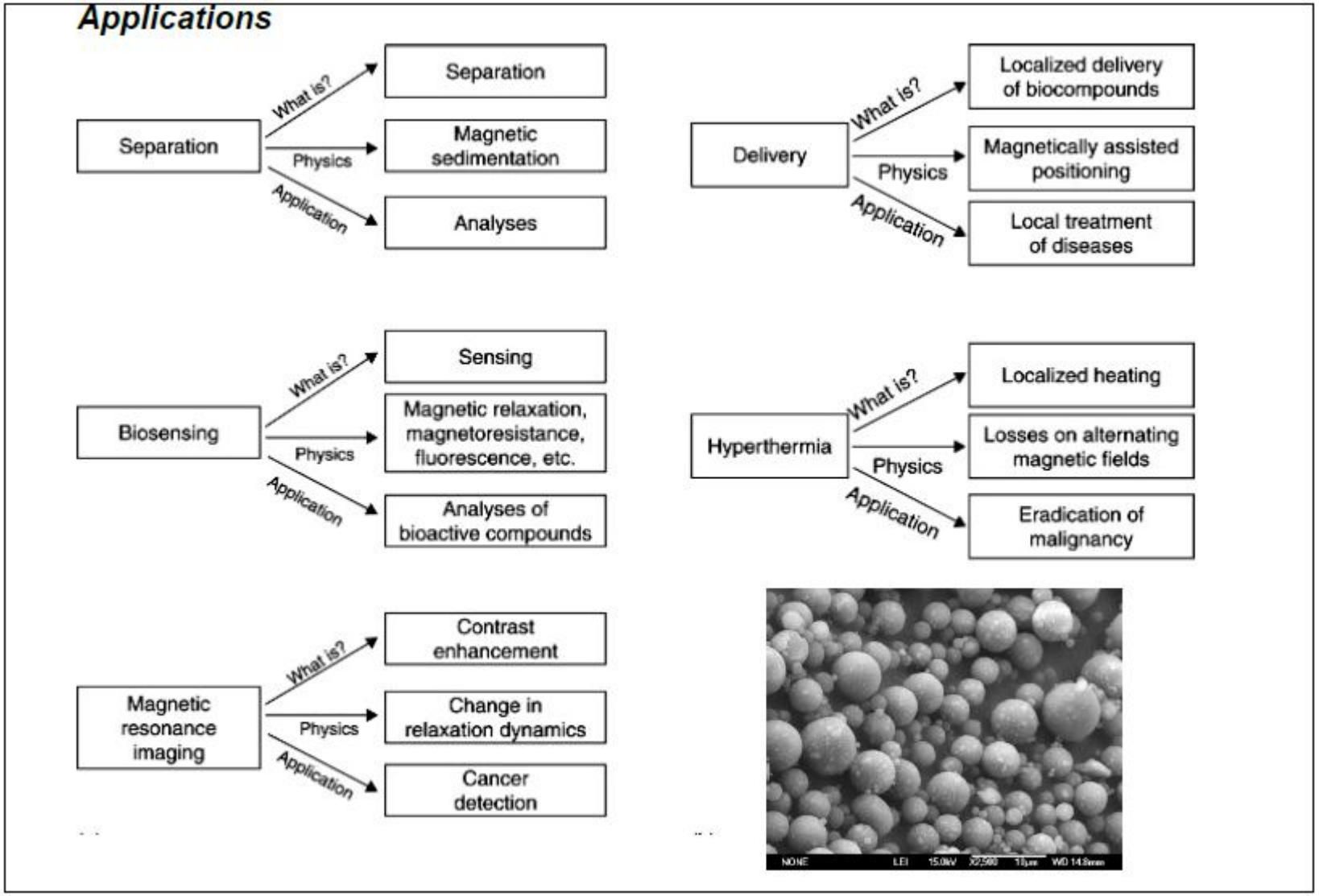
Nanoparticle's preparation for biomedical use



Areas for magnetic nanoparticles applications in biology and medicine



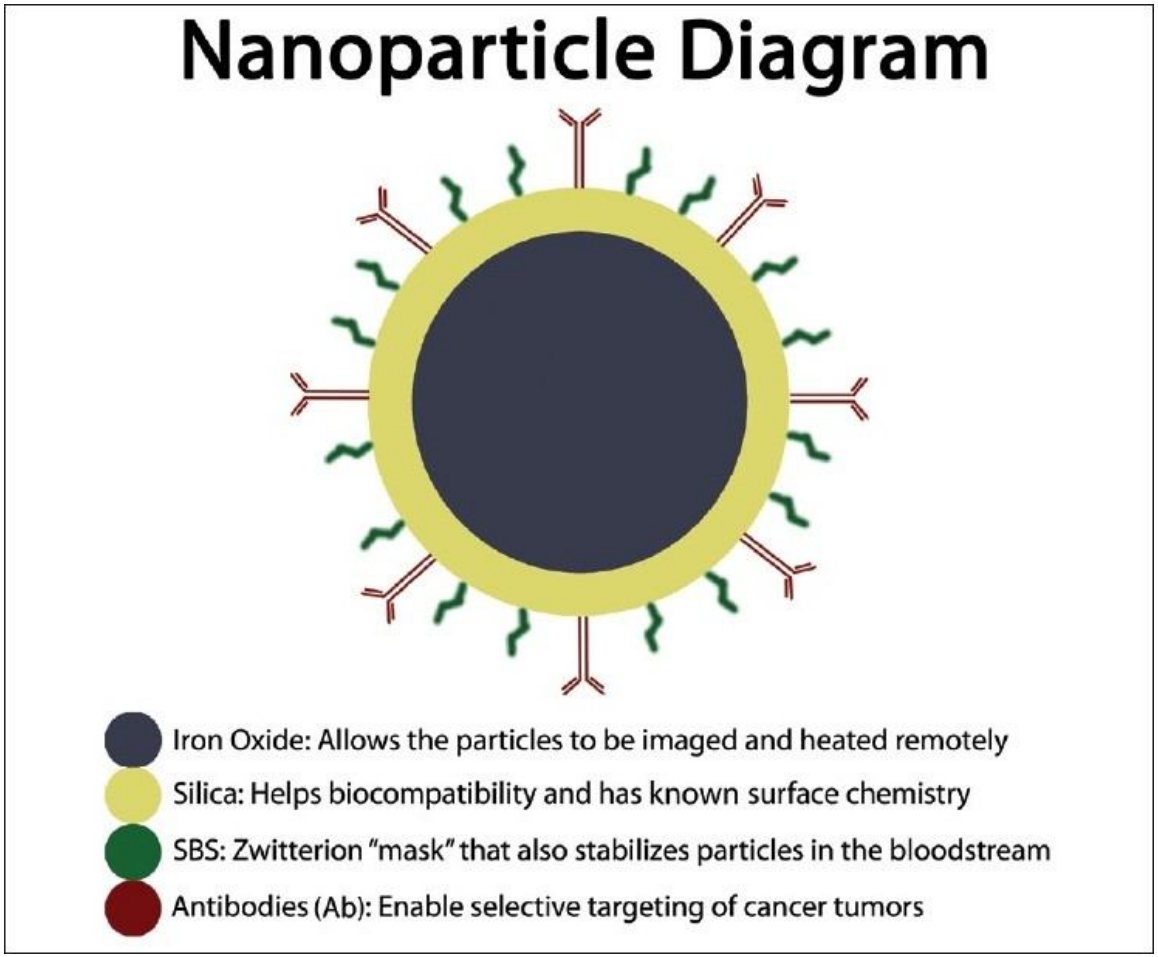
Physical phenomena behind different applications



Antibody-coated magnetic nanoparticles: Targeting and treating cancer

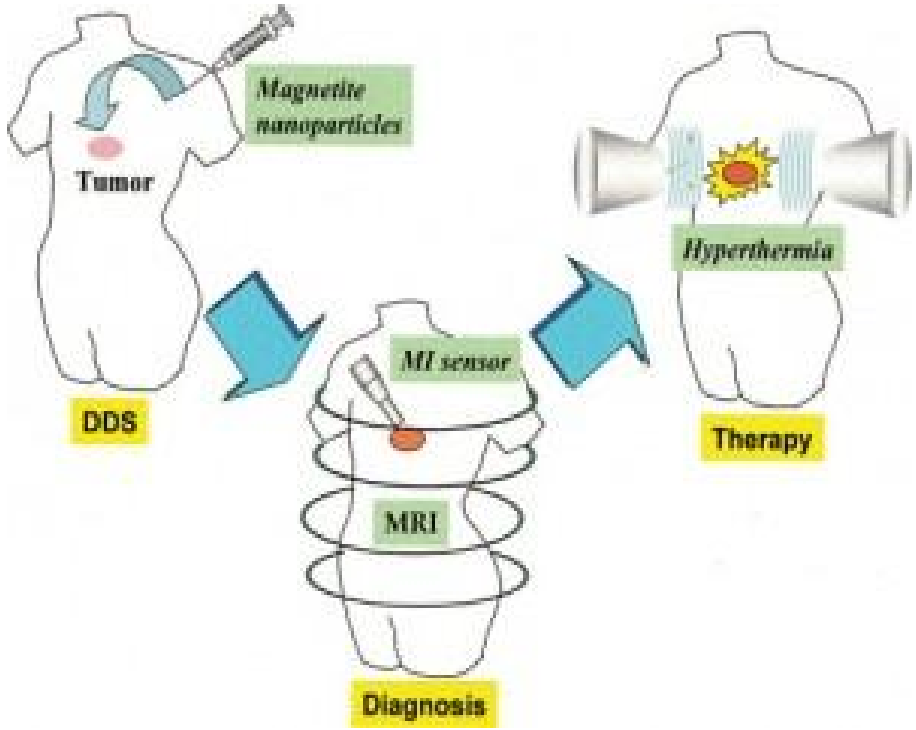
Philip Schlenoff Maclay School (Tallahassee, Florida)

NANOTECHNOLOGY 3(8) 33 (2010)



The nanoparticles are composed of Iron Oxide, Silica, Antibodies, and a Zwitterion molecule

Cancer Treatment: Multifunctional Magnetic Nanoparticles for Molecular Imaging and Hyperthermia

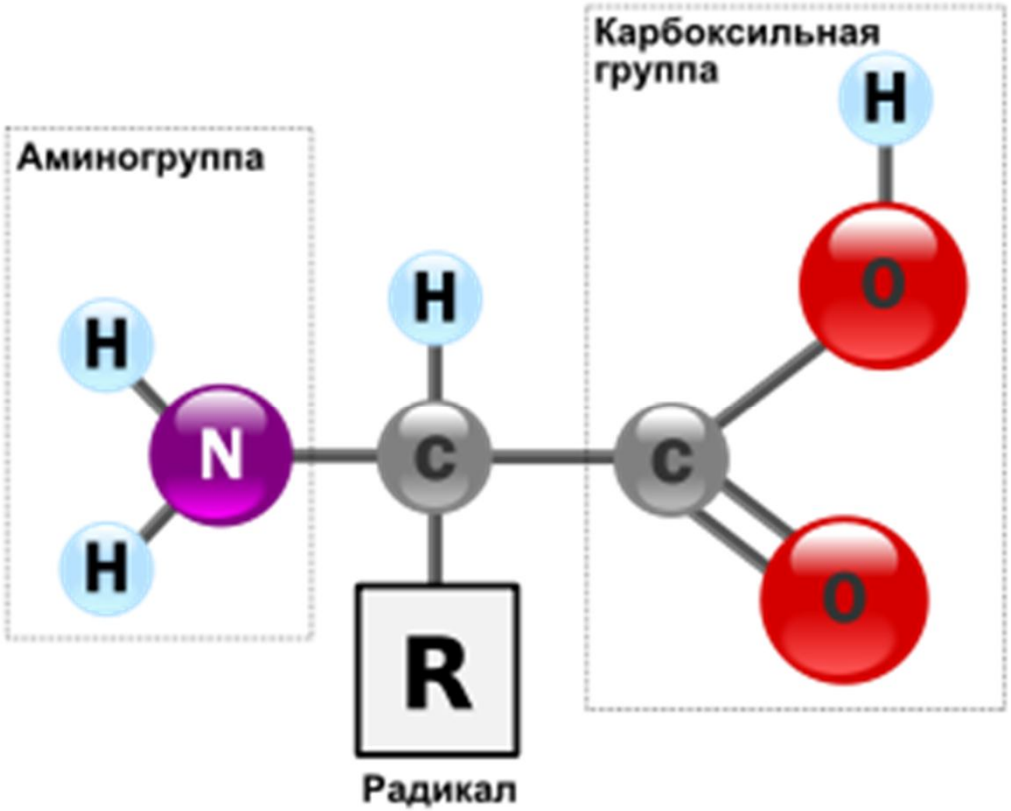


Hyperthermia involves heating up of local environment of a tumor resulting in cell damage and death. Tumor cells are more sensitive to high temperature than normal cells, hence hyperthermia doesn't affect normal cells. It is an adjuvant cancer therapy used to enhance the efficacy of traditional therapies such as radiotherapy and chemotherapy, surgery, gene therapy, and immunotherapy for cancer.

Proteins

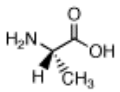
Proteins are large biological molecules, or macromolecules, consisting of one or more chains of amino acid residues. Proteins perform a vast array of functions within living organisms, including catalyzing metabolic reactions, replicating DNA, responding to stimuli, and transporting molecules from one location to another. Proteins differ from one another primarily in their sequence of amino acids, which is dictated by the sequence of a gene, which is encoded in the genetic code, and which usually results in folding of the protein into a specific three-dimensional structure that determines its activity. Proteins are essential parts of organisms and participate in virtually every process within cells.

Amino acids

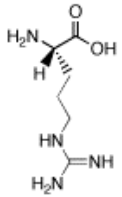


General structure α-amino acids, which are the building blocks of the proteins. Molecule consists of amine group NH_2, carboxyl group COOH, and a radical (differs from one acid to the other) α-atom is carbon (in the center).

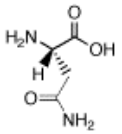
20 “magic” amino acids involved in protein biosynthesis



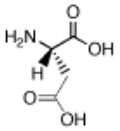
alanine
Ala
A



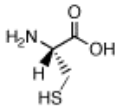
arginine
Arg
R



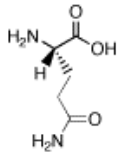
asparagine
Asn
N



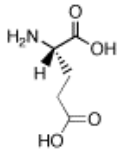
aspartic acid
Asp
D



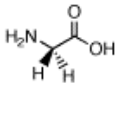
cysteine
Cys
C



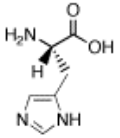
glutamine
Gln
Q



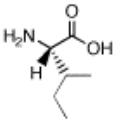
glutamic acid
Glu
E



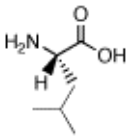
glycine
Gly
G



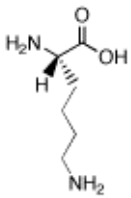
histidine
His
H



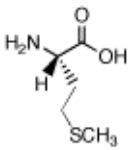
isoleucine
Ile
I



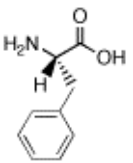
leucine
Leu
L



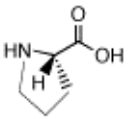
lysine
Lys
K



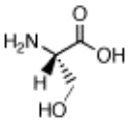
methionine
Met
M



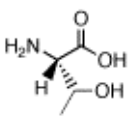
phenylalanine
Phe
F



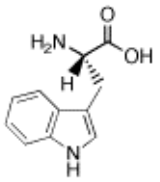
proline
Pro
P



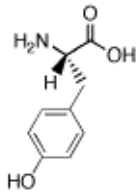
serine
Ser
S



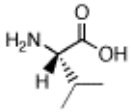
threonine
Thr
T



tryptophan
Trp
W



tyrosine
Tyr
Y

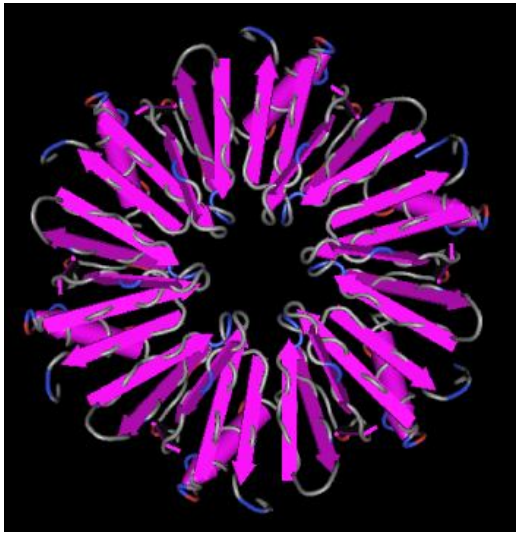


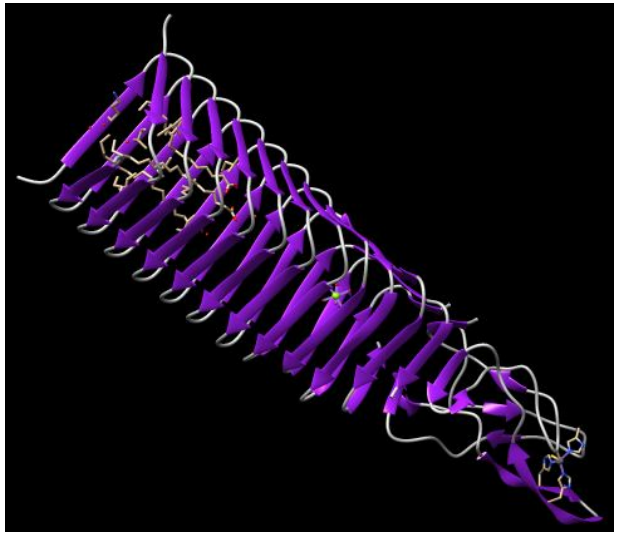
valine
Val
V

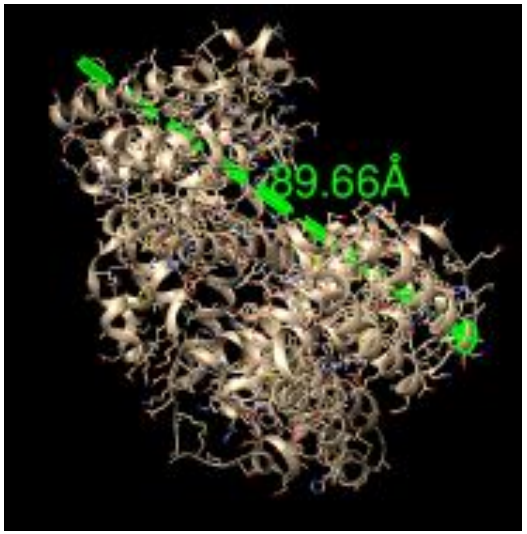
In protein biosynthesis coded by genes 20 α-amino acids are involved. The question why these 20 particular amino acids are so special is still waiting to be resolved.

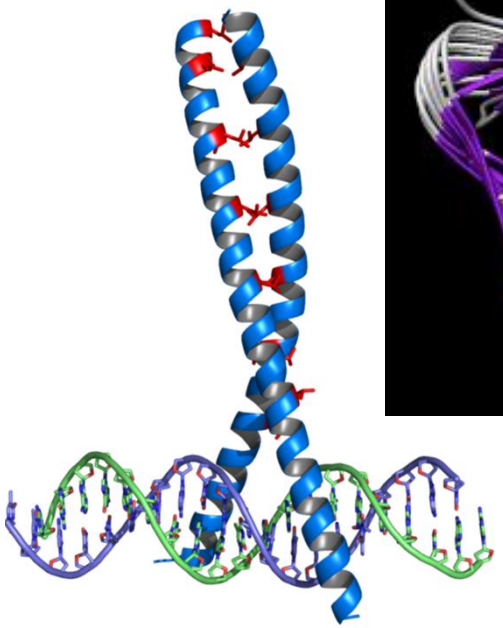
"It's amazing what they can do with amino acids these days."

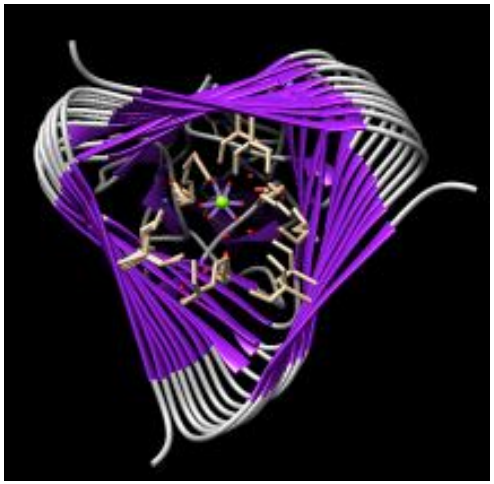
Examples of protein molecules

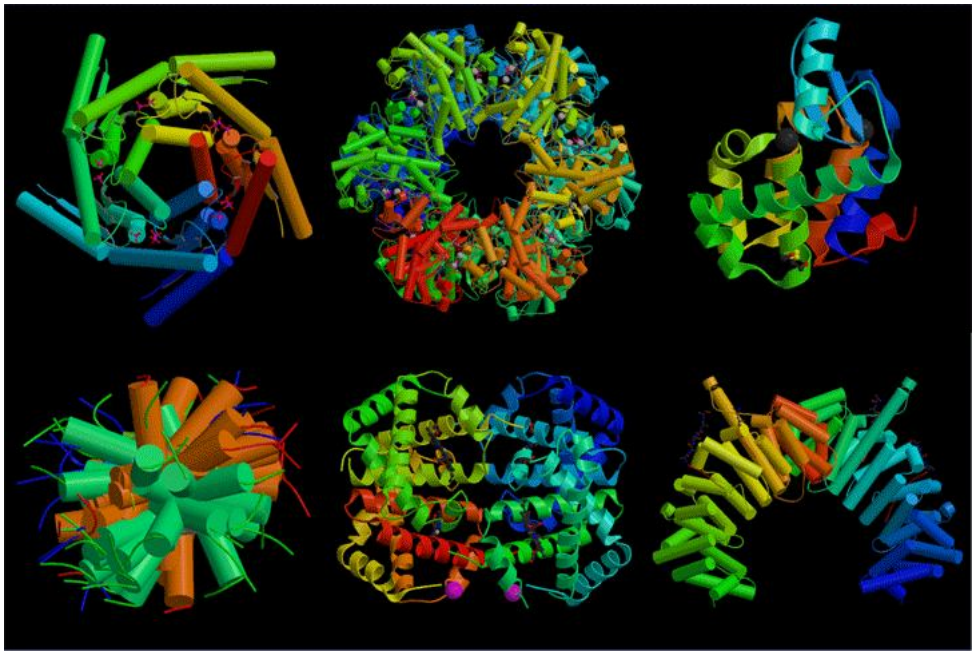






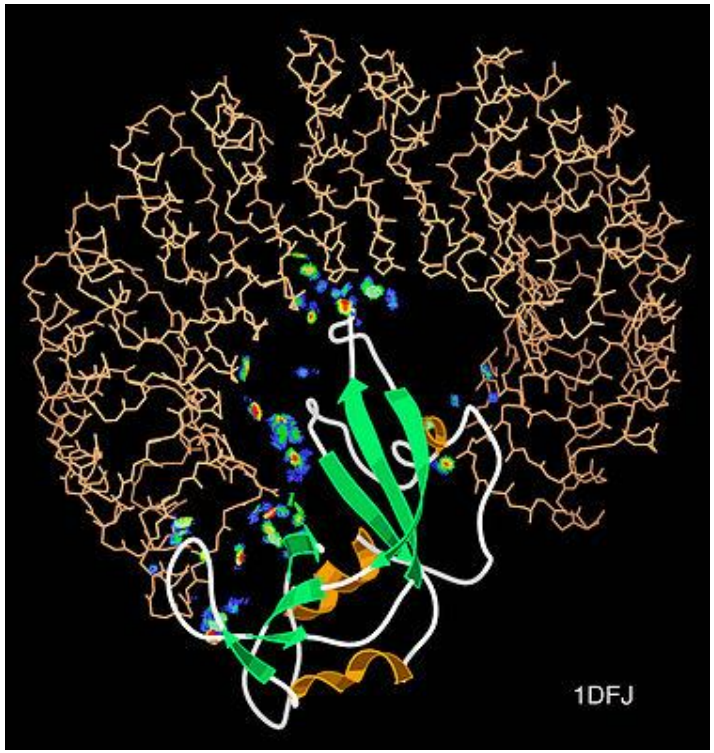






Protein–protein interactions (PPIs)

Proteins are vital macromolecules, at both cellular and systemic levels, but they rarely act alone. Diverse essential molecular processes within a cell are carried out by molecular machines that are built from a large number of protein components organized by their PPIs. Indeed, these interactions are at the core of the entire interactomics system of any living cell and so, un-surprisingly, **aberrant PPIs are on the basis of multiple diseases, such as Creutzfeld-Jacob, Alzheimer's disease and cancer**.



The horseshoe shaped ribonuclease inhibitor (shown as wireframe) forms a protein–protein interaction with the ribonuclease protein. The contacts between the two proteins are shown as coloured patches.

Examples of protein-protein interactions

Signal transduction

The activity of the cell is regulated by extracellular signals. Signals propagation to inside and/or along the interior of cells depends on PPIs between the various signaling molecules. This process, called signal transduction, plays a fundamental role in many biological processes and in many diseases (e.g. Parkinson's disease and cancer).

Transport across membranes

A protein may be carrying another protein (for example, from cytoplasm to nucleus or vice versa in the case of the nuclear pore importins).

Cell metabolism

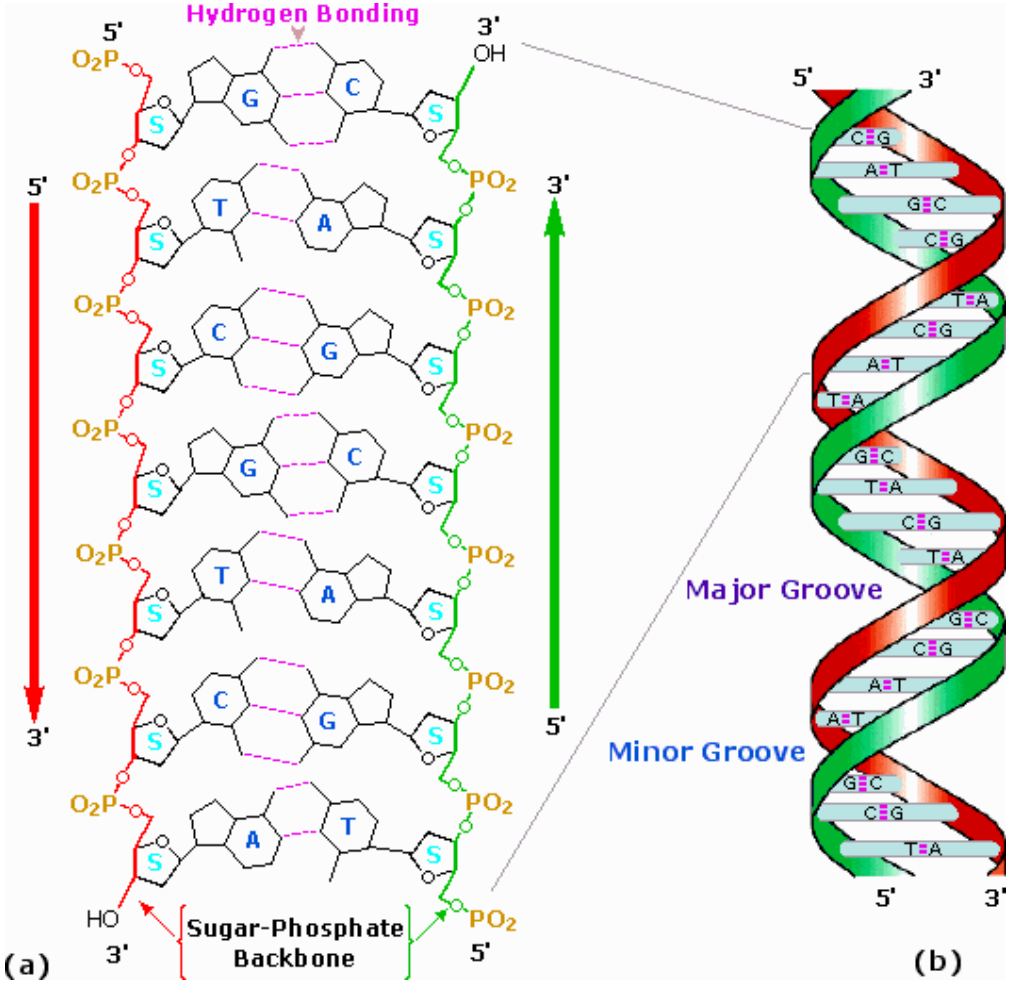
In many biosynthetic processes enzymes interact with each other to produce small compounds or other macromolecules.

Muscle contraction

Physiology of muscle contraction involves several interactions. Myosin filaments act as molecular motors and by binding to actin enables filament sliding.

Therefore, the study which proteins are interacting with each other and which are not is one of the current issues for modern biology!

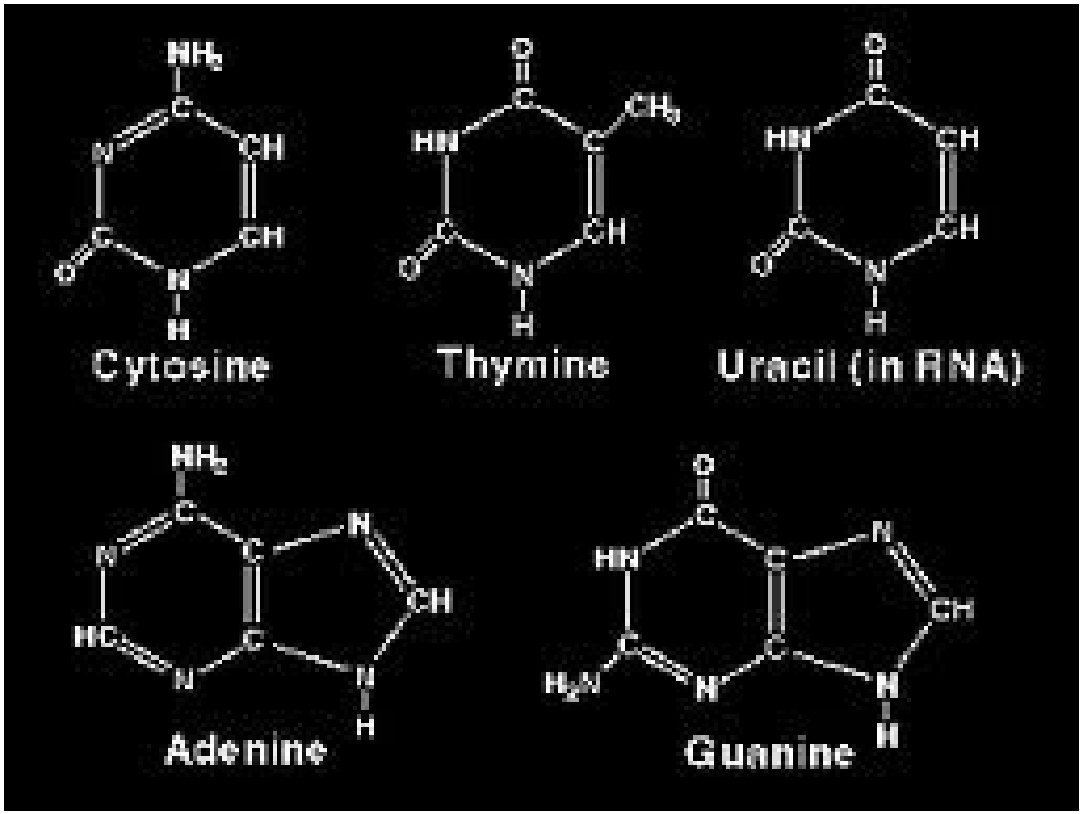
Deoxyribonucleic acid (DNA)

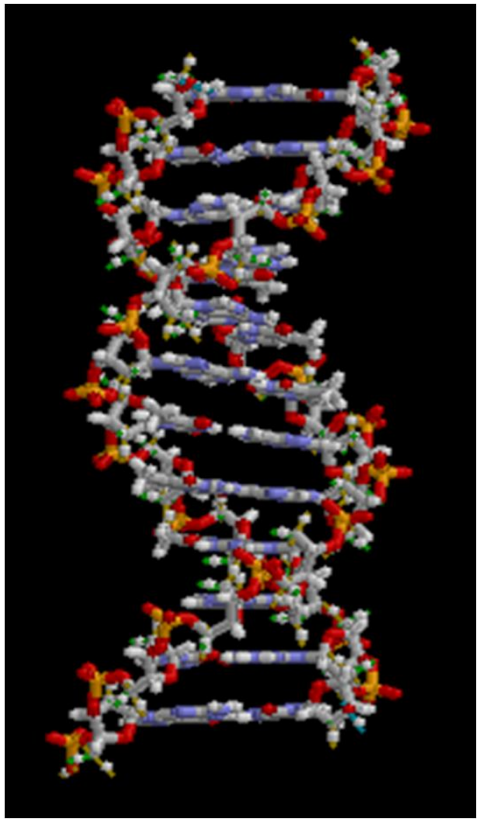


DNA is a molecule that encodes the genetic instructions used in the development and functioning of all known living organisms and many viruses. DNA is a nucleic acid; alongside proteins and carbohydrates, nucleic acids compose the three major macromolecules essential for all known forms of life.

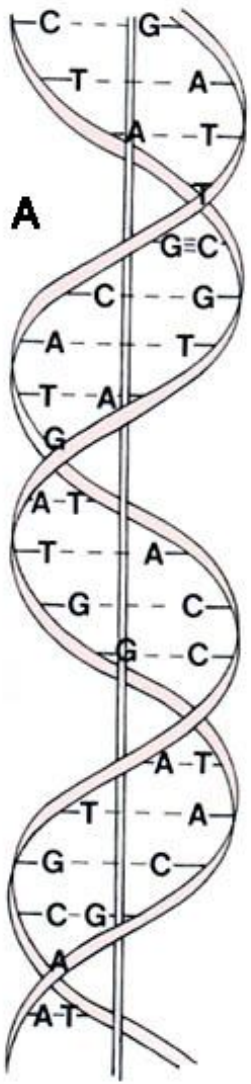
Deoxyribonucleic acid (DNA)

Most DNA molecules are double-stranded helices, consisting of two long biopolymers made of simpler units called nucleotides—each nucleotide is composed of a nucleobase (guanine, adenine, thymine, and cytosine), recorded using the letters G, A, T, and C, as well as a backbone made of alternating sugars (deoxyribose) and phosphate groups (related to phosphoric acid), with the nucleobases (G, A, T, C) attached to the sugars.

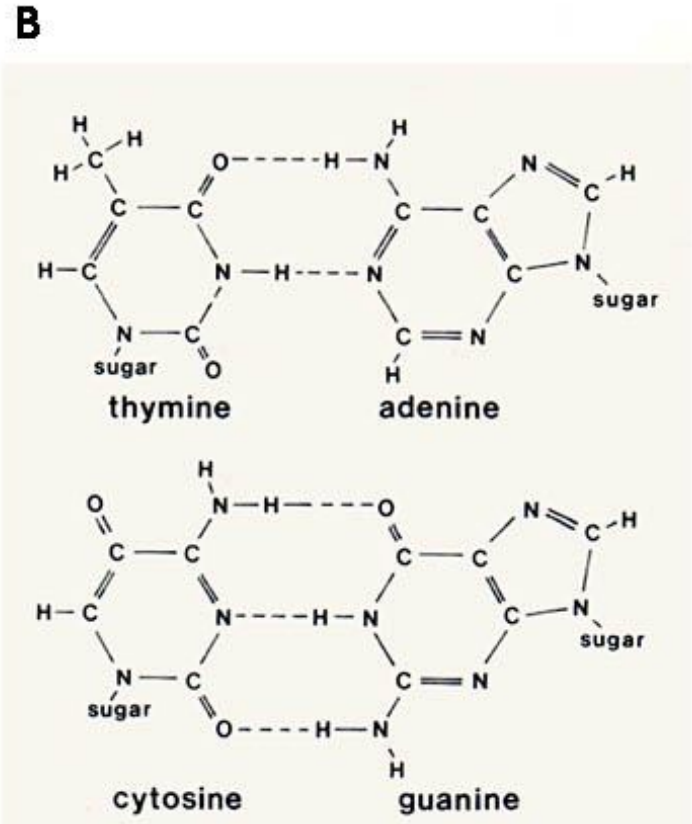


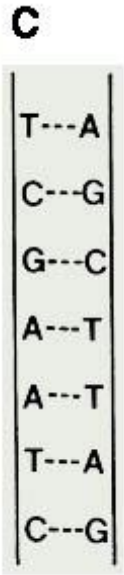


Deoxyribonucleic acid (DNA)



The nucleobases are classified into two types: the purines, A and G, being fused five- and six-membered heterocyclic compounds, and the pyrimidines, the six-membered rings C and T. A fifth pyrimidine nucleobase, uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring.



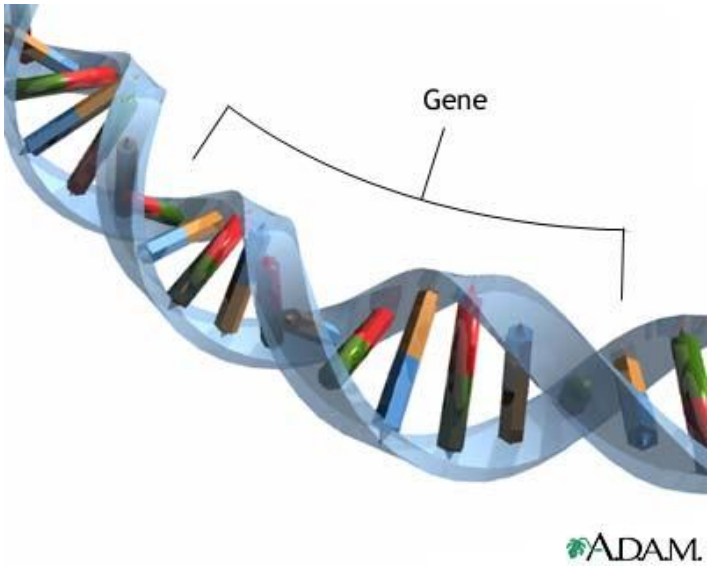


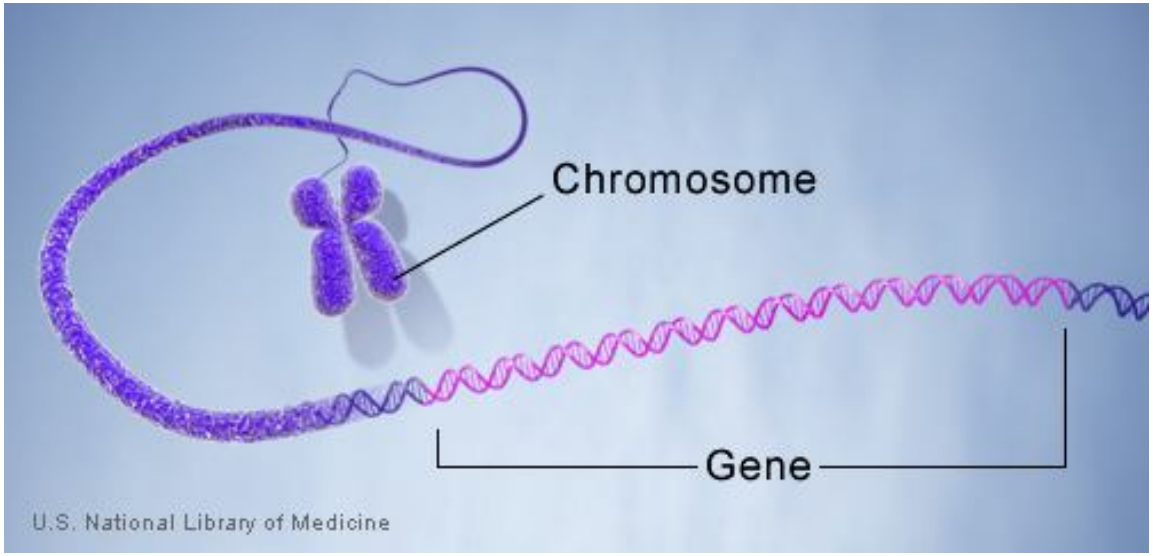
The DNA double helix is stabilized primarily by two forces: hydrogen bonds between nucleotides and base-stacking interactions among aromatic nucleobases.

What is a gene?

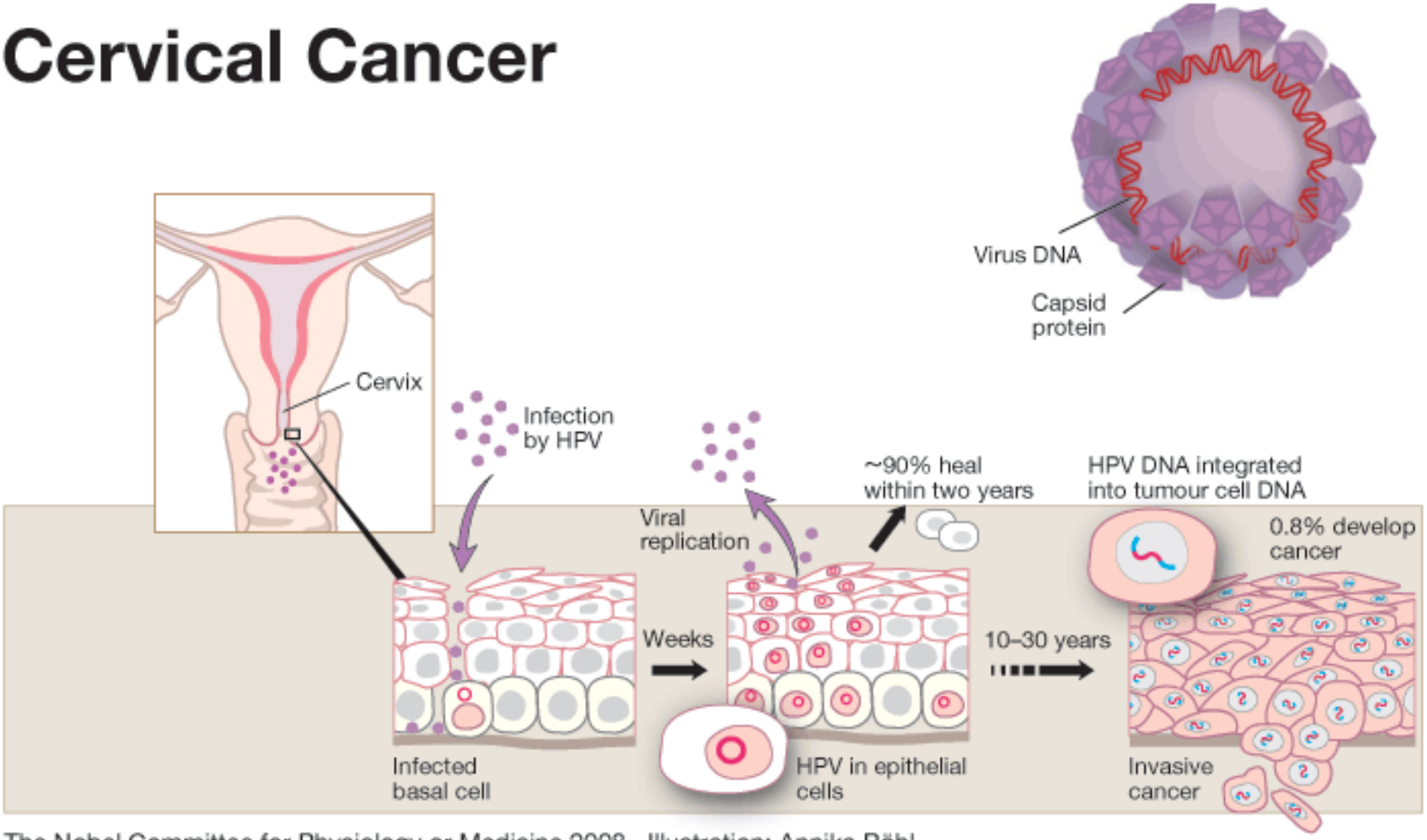
A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 20,000 and 25,000 genes.

DNA can be damaged by many sorts of mutagens, which change the DNA sequence. These mutations can cause cancer.





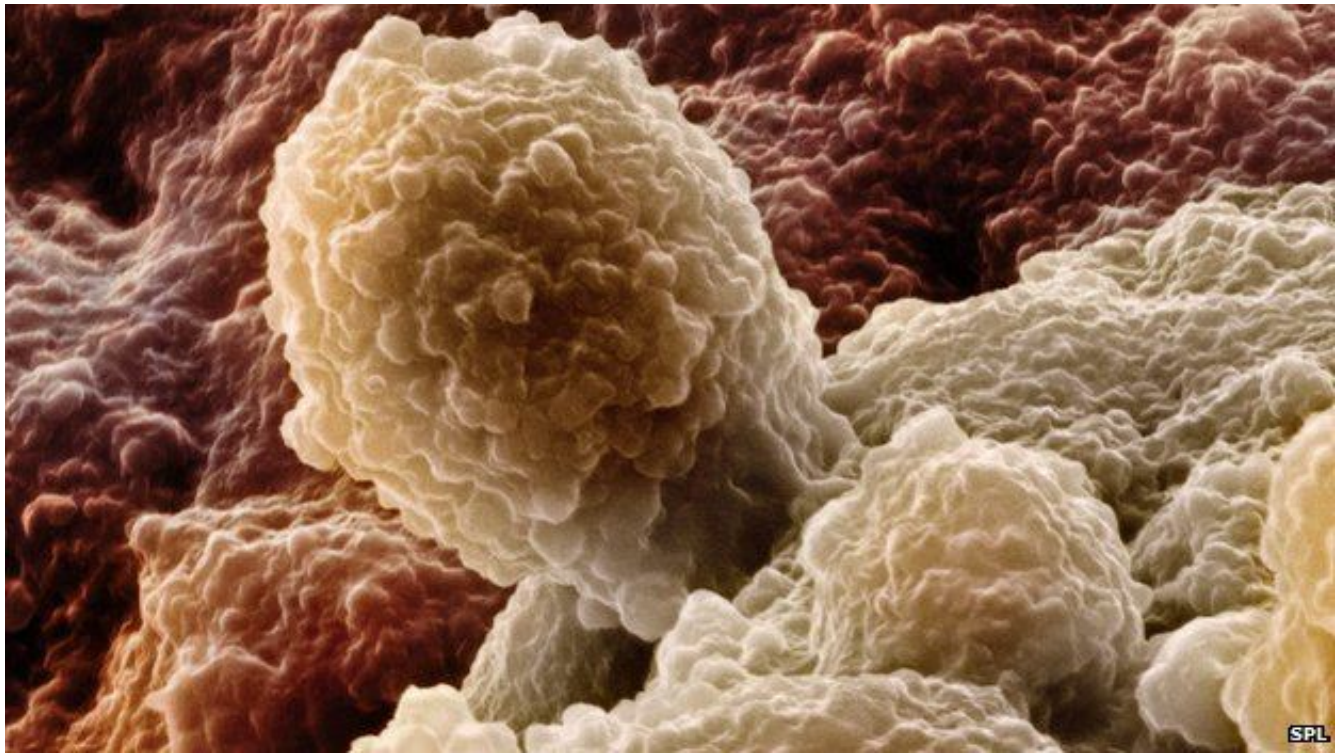
Cervical Cancer



The Nobel Committee for Physiology or Medicine 2008 Illustration: Annika Röhl

DNA testing can predict which men face the highest risk of deadly prostate cancer, scientists say.

By James Gallagher Health and science reporter, BBC News



Prostate cancer is the commonest cancer in men in many countries, including the UK - where more than 40,000 people are diagnosed each year. But not every patient has, or needs, invasive therapy that results in severe side-effects.

Danger genes

Identifying which men will need treatment - those who are likely to develop the most aggressive and deadly form of the cancer - is a huge challenge. The researchers took blood samples from 191 men with prostate cancer and at least three close family members with the same condition. Each was tested for risky mutations - this included the BRCA genes that are involved in repairing DNA and already linked to breast and ovarian cancers.

"Genetic testing to predict risk could revolutionise how we treat the 40,000 men diagnosed with the disease every year in the UK.

Therefore, methods and tools for diagnostic of DNA damages and mutations are of vital importance for modern medicine!

Applications of biosensors

There are many potential applications of biosensors of various types. The main requirements for a biosensor approach to be valuable in terms of research and commercial applications are the identification of a target molecule, availability of a suitable biological recognition element, and the potential for disposable portable detection systems to be preferred to sensitive laboratory-based techniques in some situations. Some examples are given below:

- Glucose monitoring in diabetes patients ←**historical market driver**
- Other medical health related targets
- Environmental applications e.g. the detection of pesticides and river water contaminants such as heavy metal ions

Applications of biosensors

- Remote sensing of airborne bacteria e.g. in counter-bioterrorist activities
- Detection of pathogens
- Determining levels of toxic substances before and after bioremediation
- Detection and determining of organophosphate
- Routine analytical measurement of folic acid, biotin, vitamin B12 and pantothenic acid as an alternative to microbiological assay
- Determination of drug residues in food, such as antibiotics and growth promoters, particularly meat and honey.
- **Drug discovery and evaluation of biological activity of new compounds**.
- **Protein engineering in biosensors**
- Detection of toxic metabolites such as mycotoxins
- **DNA biosensors**

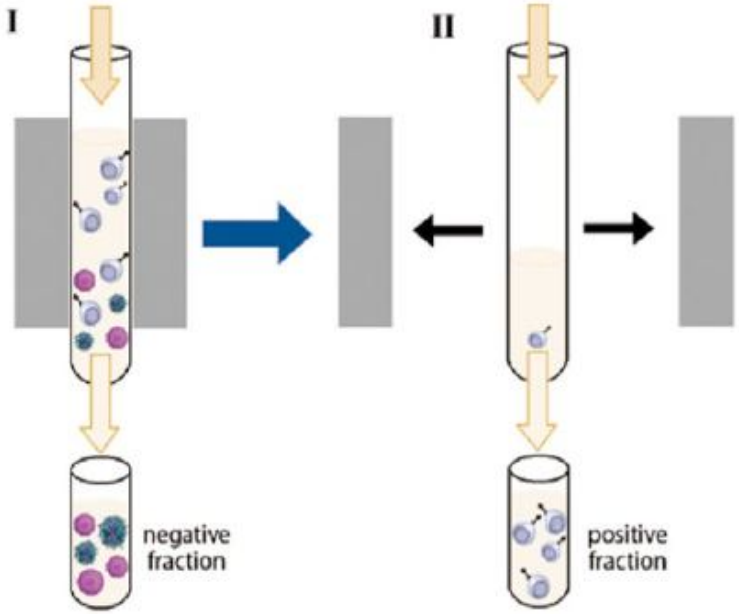
How magnetic nanoparticles can help biomedical research?

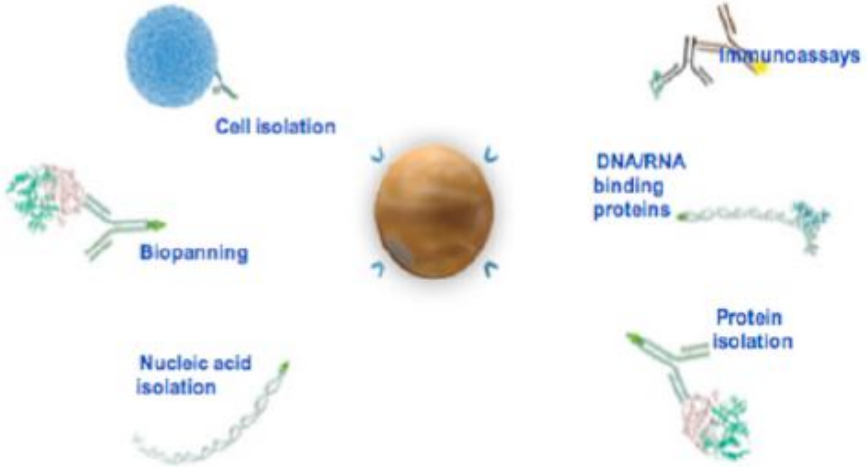
Despite the success of fluorescence-based microarrays in biomedical research, the investigation of novel biochip platforms continues to be driven by the huge market potential for bio-detection systems offering unique advantages or reduced cost.

The technical challenges that still face fluorescence-based biological microarray systems include a lack of quantitative analysis, the difficulty encountered in comparing data collected from different microarray platforms and the often prohibitively high cost of associated equipment such as array scanners. The detection platform suffers from high background-fluorescence from microarray substrates and would also benefit from the use of more stable biological labels – fluorescent labels are photo-sensitive and, hence, samples bleach when exposed to light.

Since the late 1990s, magnetoelectronics has emerged as one of several new platform technologies for biosensor and biochip development.

Magnetic filtration



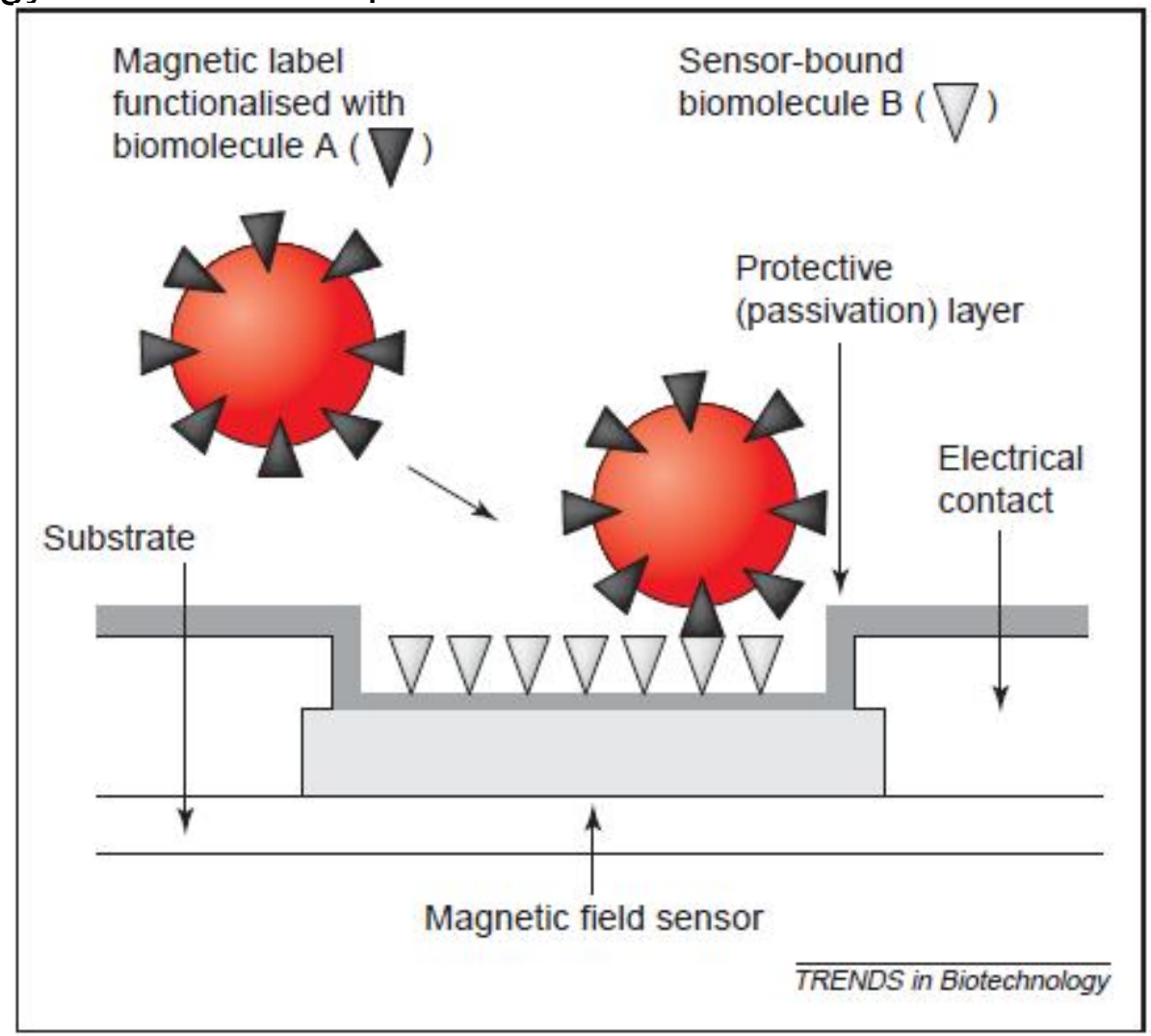


http://www.miltenyibiotec.com

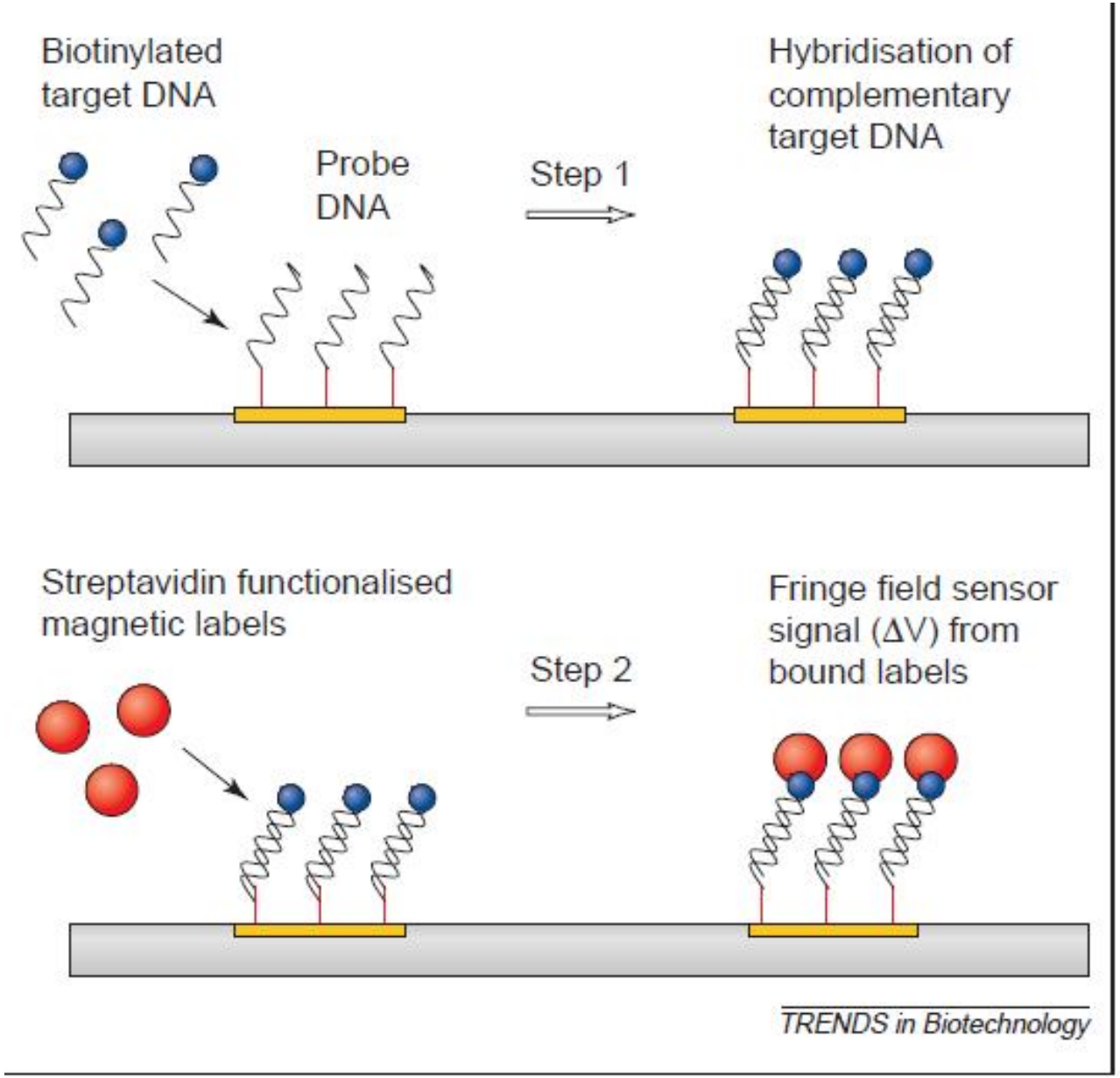
http://luminexcorp.de/Products/Instruments/MAGPIX/

Magnetic assisted biosensors

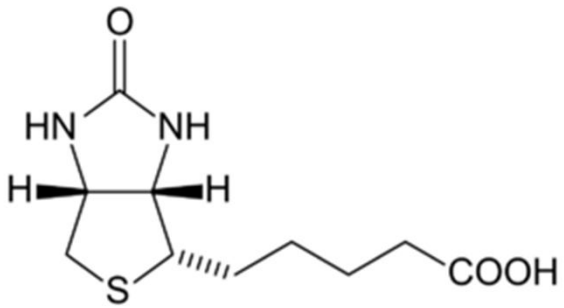
Daniel L. Graham, Hugo A. Ferreira and Paulo P. Freitas TRENDS in Biotechnology Vol.22 No.9 September 2004

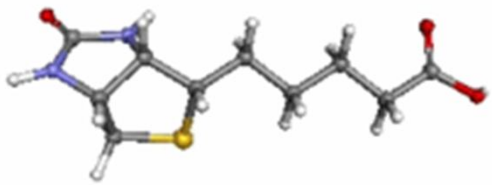


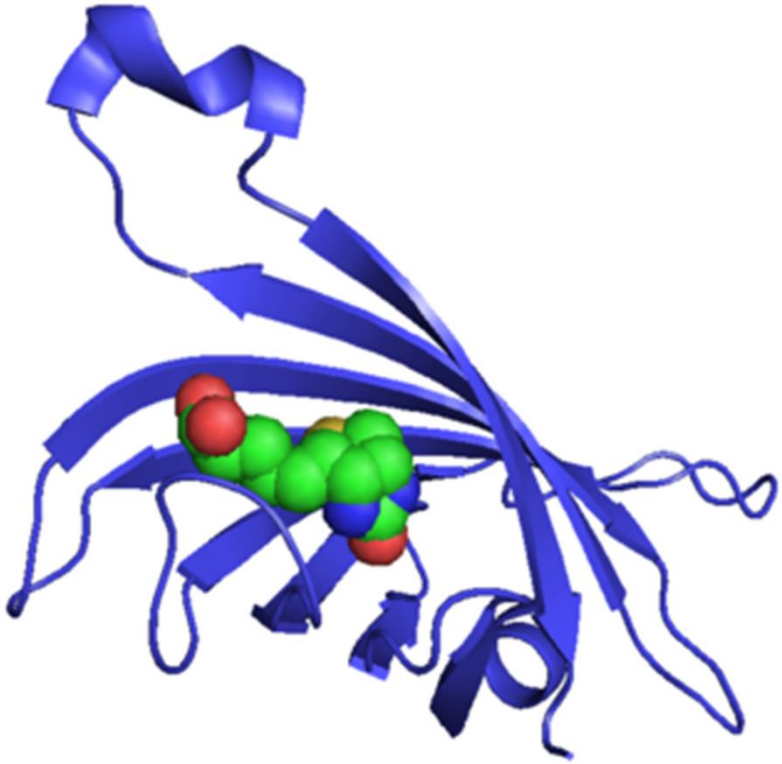
Magnetic assisted biosensors



Biotin and streptavidin



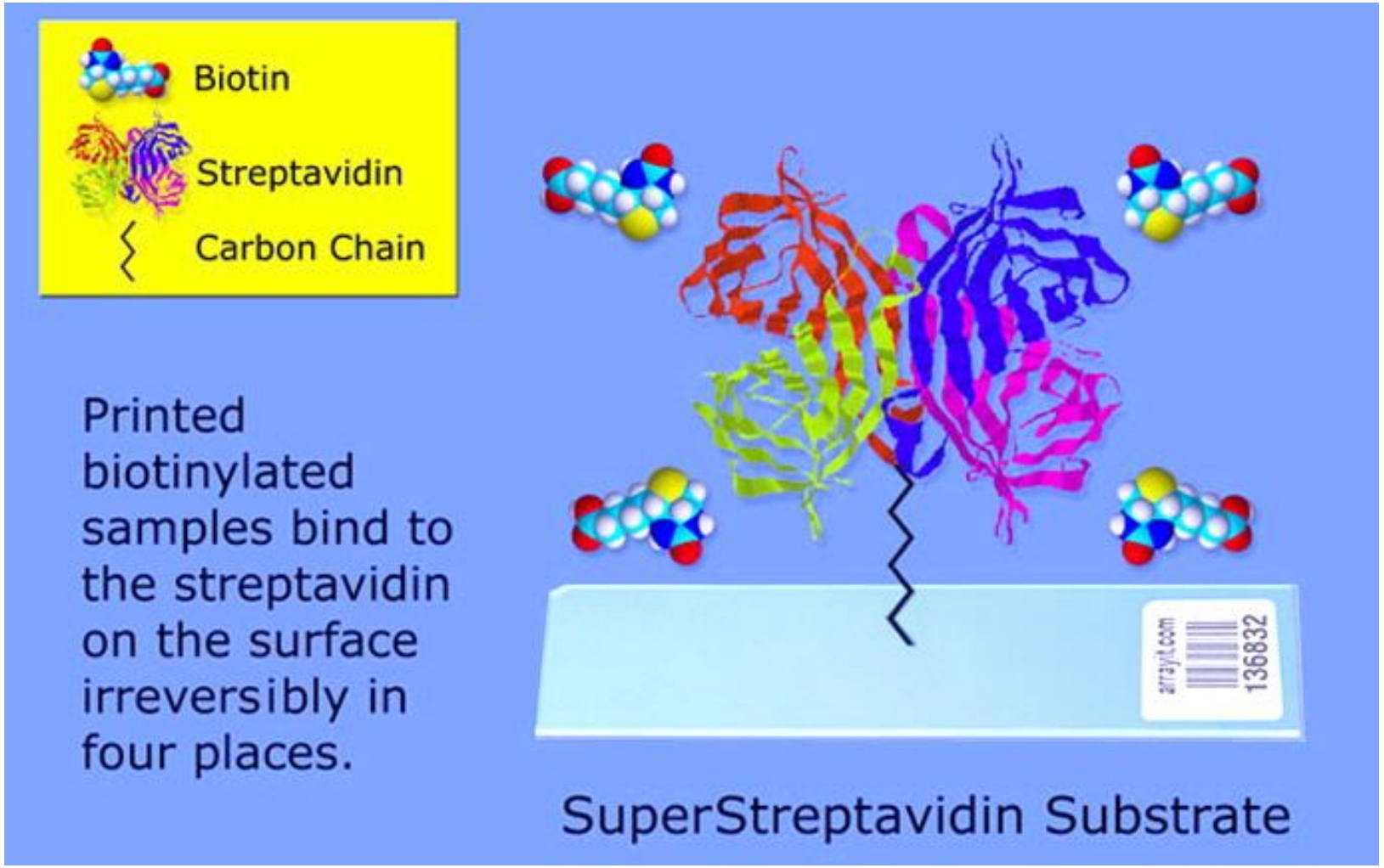




Biotin, also known as **vitamin H** or **coenzyme R**, is a water-soluble B-vitamin (**vitamin B_7**). Biotin is found in many cosmetics and health products for the hair and skin.

Monomeric streptavidin (ribbon diagram) with bound biotin (spheres). **Streptavidin** is a 52.8 kDa protein purified from the bacterium *Streptomyces avidinii*. Streptavidin homo-tetramers have an extraordinarily high affinity for biotin.

A highly uniform streptavidin covalently bound to an atomically flat glass substrate, provides a universal high-capacity biotin-binding surface for DNA and protein microarray applications and many other life sciences applications that require a biotin binding surface



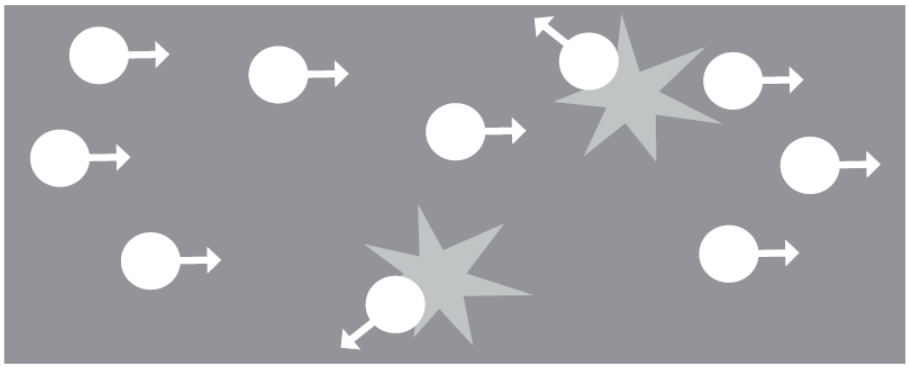
Magnetoresistive-based biosensors and biochips

The Nobel Prize in Physics 2007 was awarded jointly to Albert Fert and Peter Grünberg *"for the discovery of Giant Magnetoresistance"*

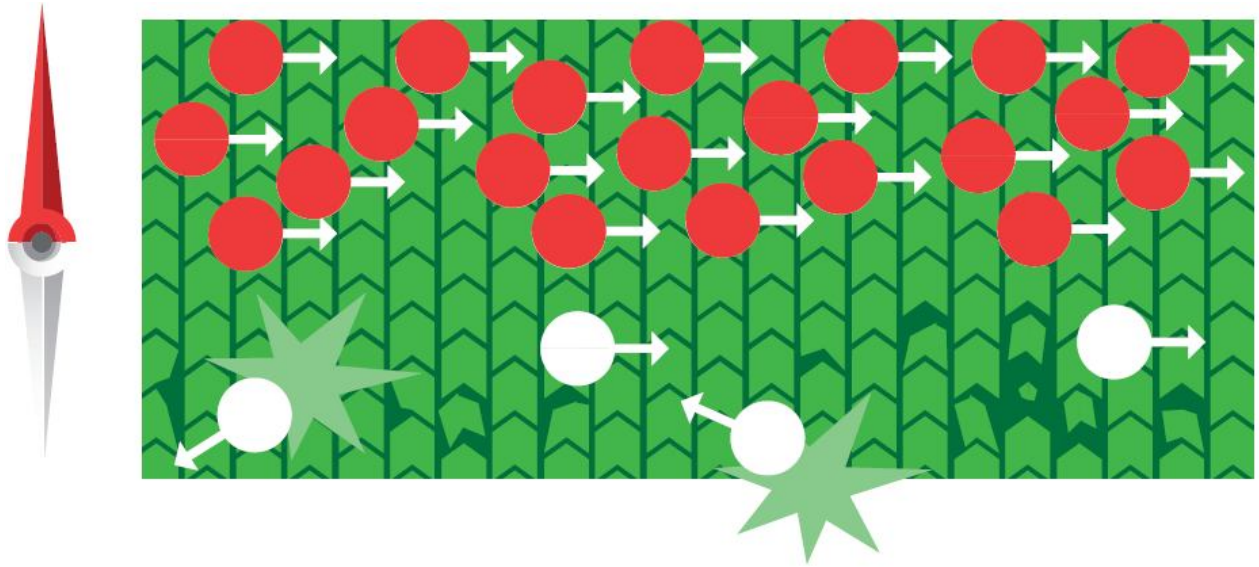
Peter Andreas Grünberg (born 18 May 1939) is a German physicist.

Albert Fert (born 7 March 1938) is a French physicist

Principle of the GMR effect

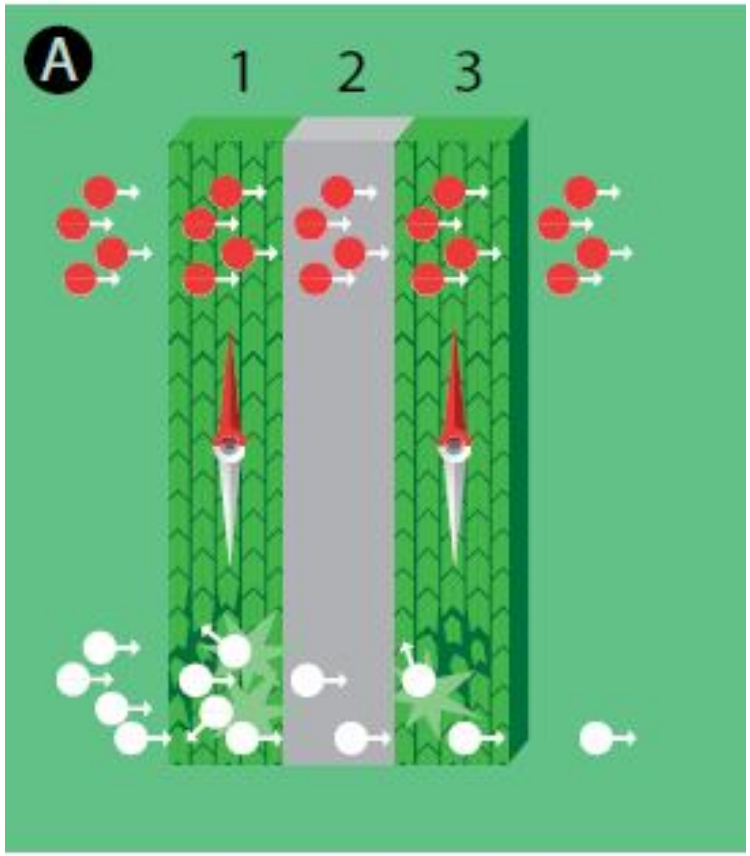


The electrical resistance in a conductor arises when electrons scatter against irregularities in the material so that their forward movement is obstructed.

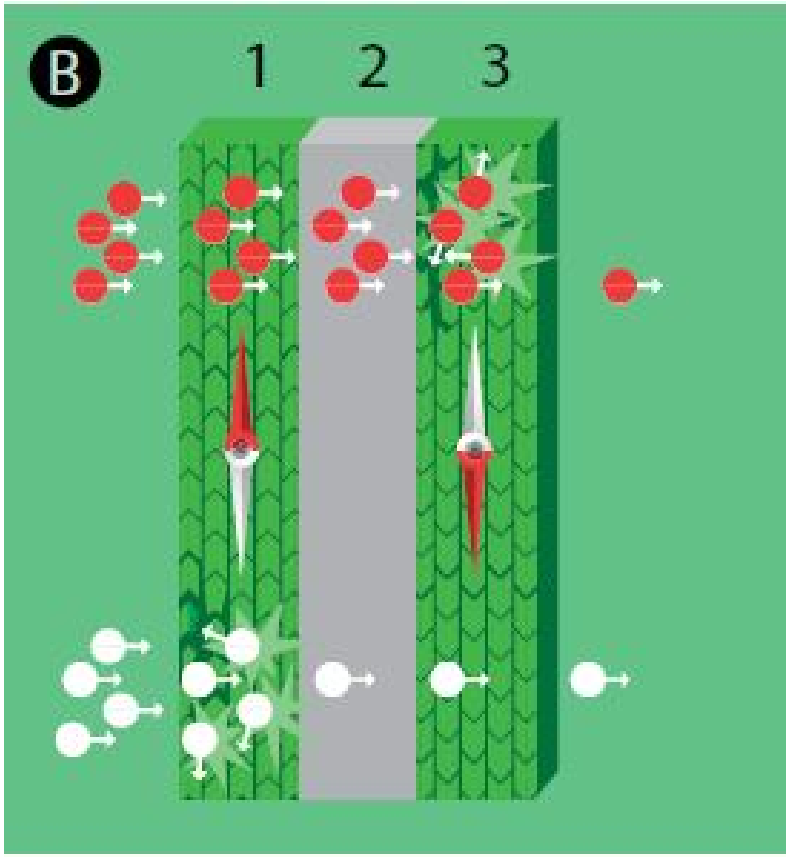


In a magnetic conductor the direction of spin of most electrons is parallel with the magnetization (red). A minority of electrons have spin in the opposite direction (white). In this example electrons with antiparallel spin are scattered more.

Principle of the GMR effect

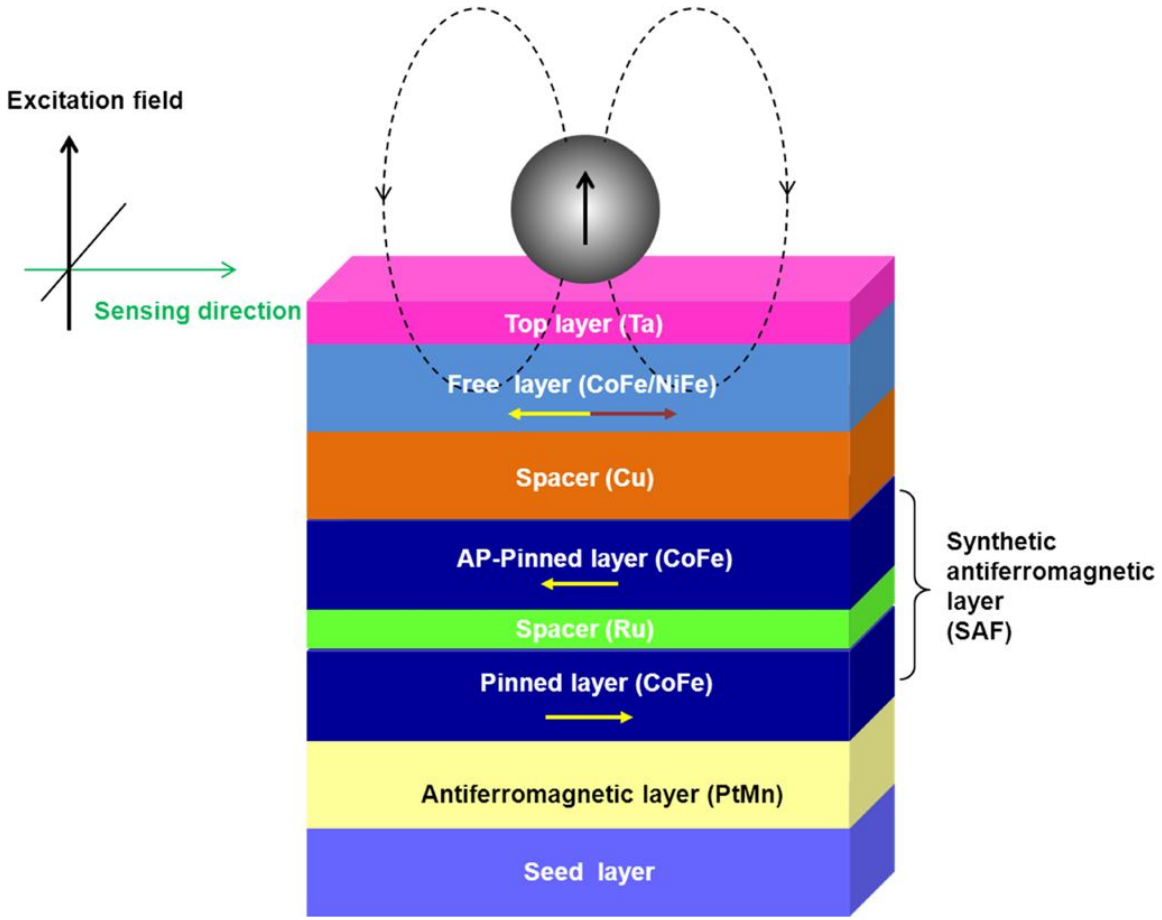


If the direction of the magnetization is the same in both magnetic layers the electrons with parallel spin (red) can pass through the entire system without scattering to any great extent. The total resistance of the system will therefore be small.



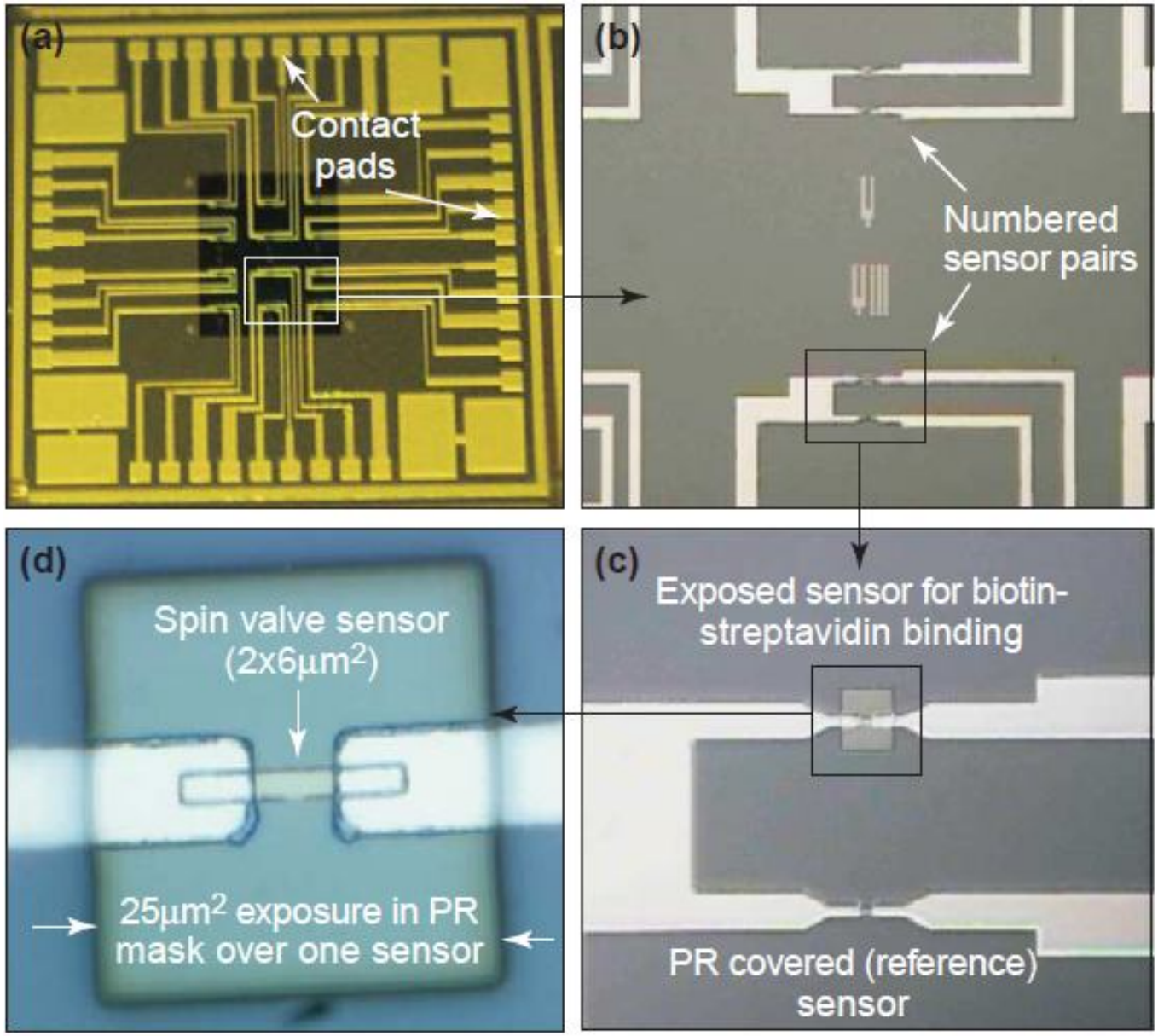
If the direction of magnetization in the two magnetic layers is opposed, all the electrons will have anti-parallel spin in one of the layers and will therefore scatter a great deal. As a result the total resistance is high.

Magnetic assisted biosensors

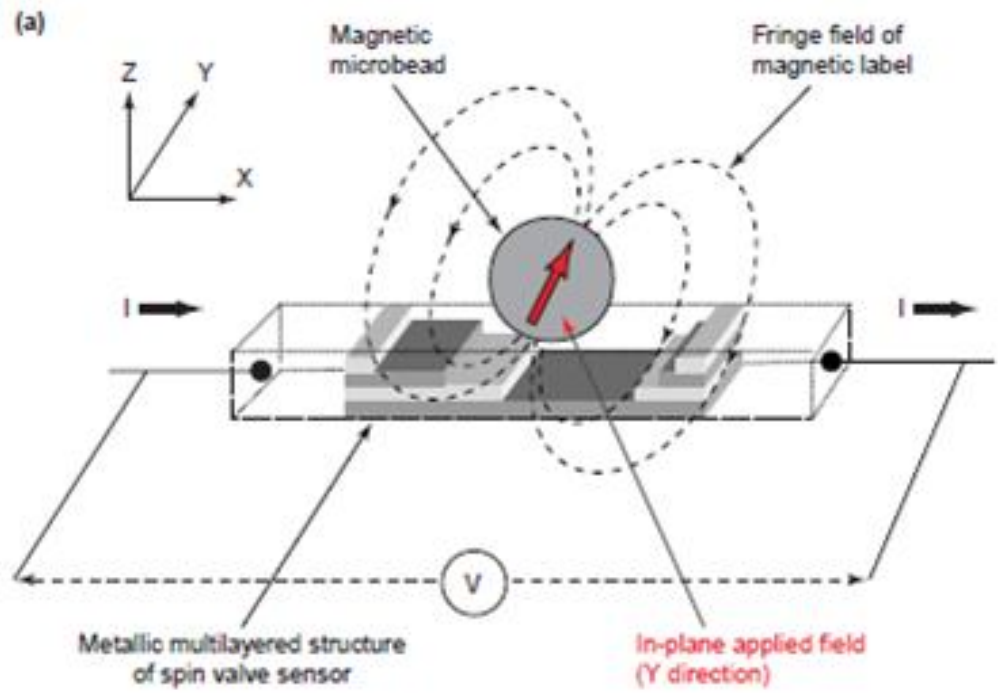


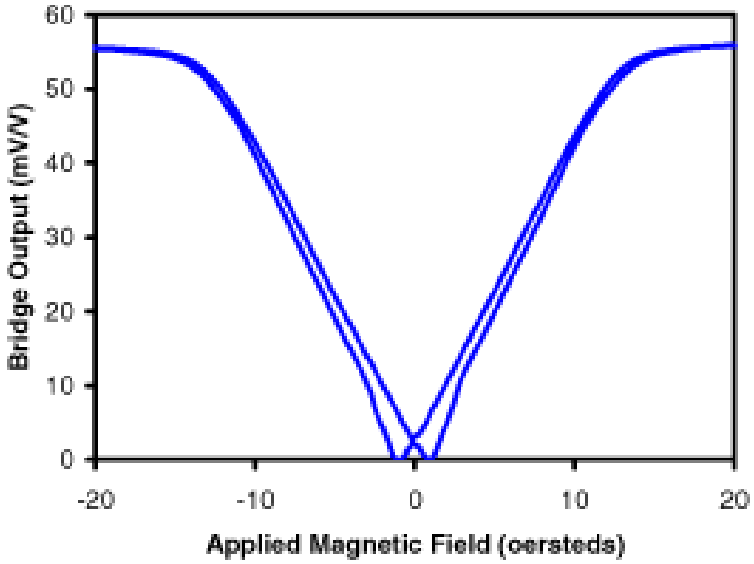
Schematic structure of the exchange-biased GMR spin valve. It is composed of seed/PtMn/CoFe/Ru/CoFe/Cu/ CoFe/NiFe/Ta. The antiparallel-pinned (AP-pinned) structure provides an alternative pinning mechanism in place of a conventional single antiferro-magnet. The arrows indicate the possible magnetization directions. The superpara-magnetic iron oxide nano-particles (SPIONs) are magnetized out-of-plane while the sensors are sensitive to the in-plane component of the stray field emanated from the SPIONs.

Magnetic assisted biosensors



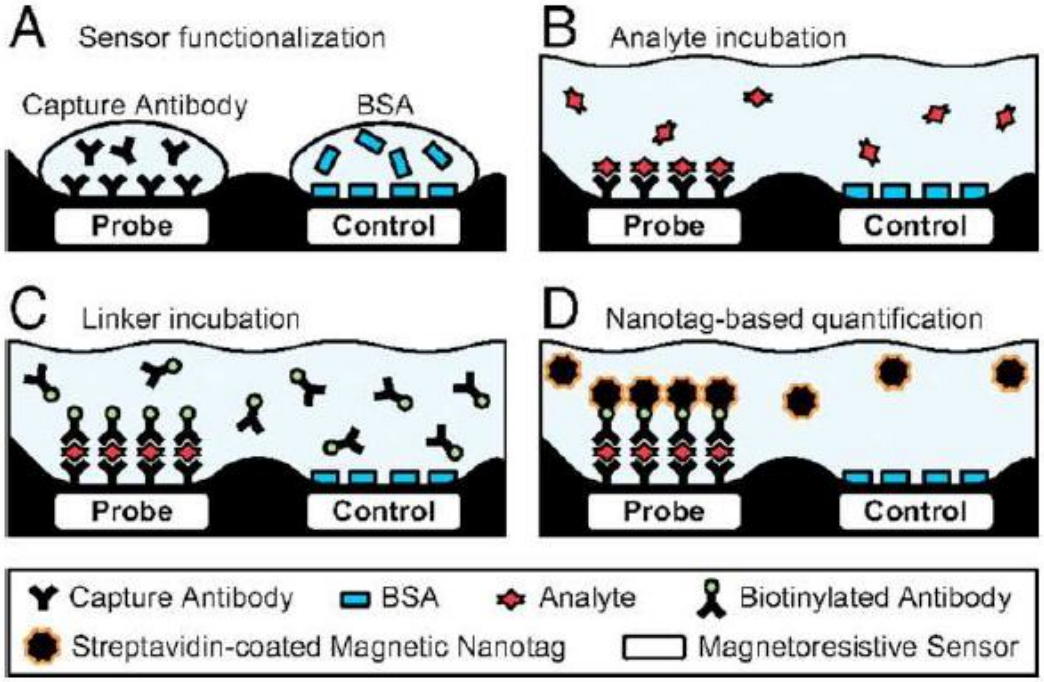
Magnetic assisted biosensors





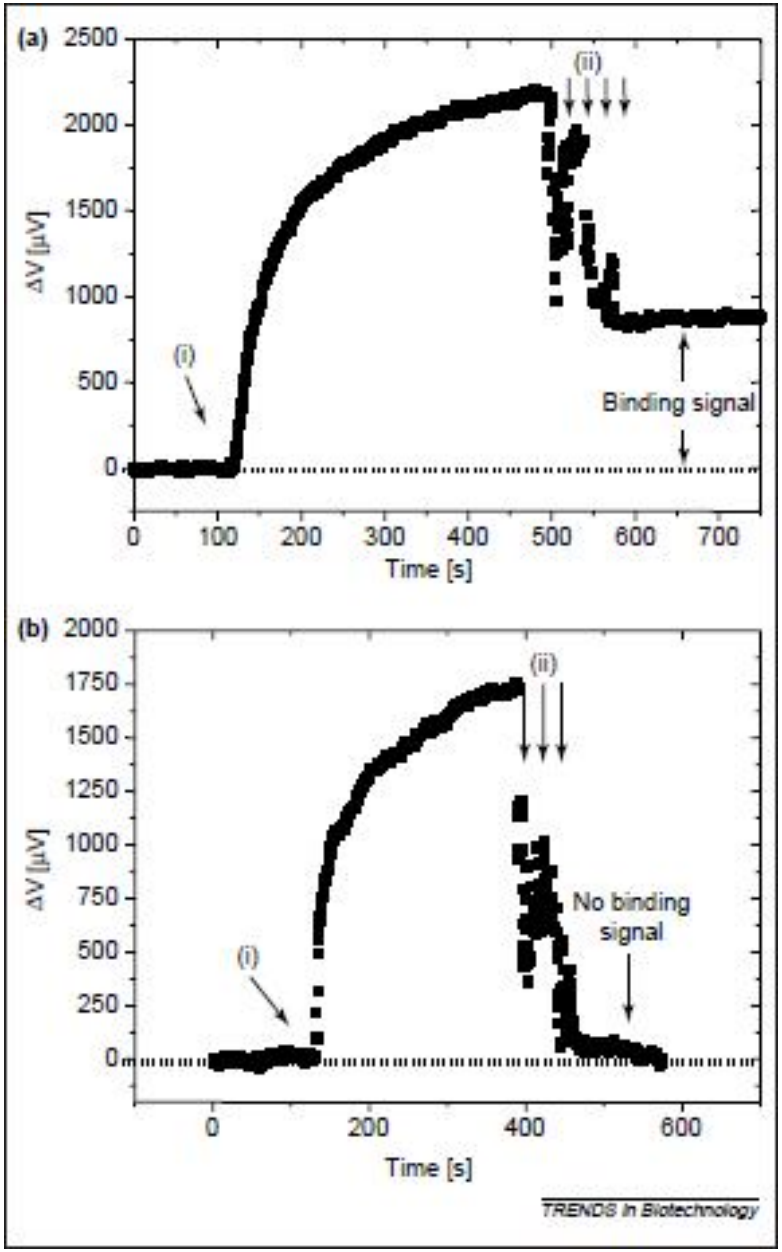
The GMR effect is based on the spin dependent interfacial and bulk scattering asymmetry that is found for spin-up and spin-down conduction electrons crossing ferromagnetic–nonmagnetic–ferromagnetic multilayer structures, where the parallel or antiparallel alignment of the ferromagnetic layers can be engineered. An applied magnetic field is used to change the relative orientation of the magnetisations of the two magnetic layers. When they are aligned, the electrical resistance of the structure is low. When the magnetisations are antiparallel aligned, the resistance is high.

Magnetoresistive biosensing



A schematic representation of a giant magnetoresistive (GMR) sensor for an ELISA-type protein assay. A. The probe surface was functionalized with a specific antibody, while the control surface was passivated with BSA. B. A sample solution was added for a specific binding of analyte proteins to the probe surface. C. A biotinylated antibody bound to the surface-immobilized analytes. D. Finally streptavidin-coated NPs were added for tagging the probe surface by biotin-streptavidin interaction. GMR signals were detected for sensing the presence of analytes on the surface. (D.Graham, e.a. Trends in biotechnology, 22 (9) 2004 p. 455-462)

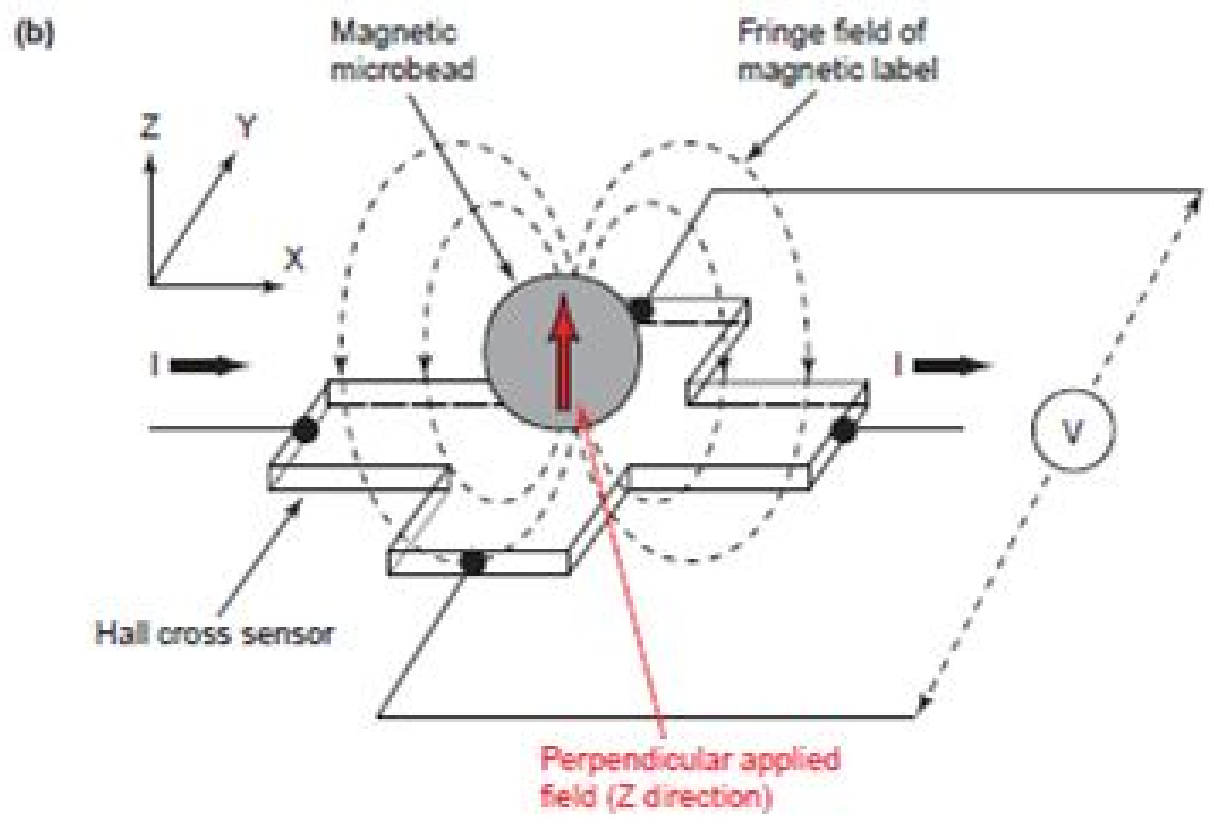
Magnetoresistive biosensing



Real-time magnetoresistive detection of a cystic fibrosis-related DNA target. (a) biotinylated complementary target DNA and (b) biotinylated non-complimentary DNA. Hybridised DNA was then detected via the introduction of 250 nm streptavidin functionalised magnetic nanoparticles toward sensor saturation (i), followed by washing of the sensors (ii). The resulting hybridisation signal of 0.9–1.0 mV for sensor-bound probe hybridised complementary target DNA (a) corresponds to 90–100 nanoparticles or, 50% sensor coverage with labels. Sensor-bound probe hybridised with non-complimentary target DNA gave no hybridisation signal.
(D.Graham, e.a. Trends in biotechnology, 22 (9) 2004 p. 455-462)

Micro-Hall biosensors

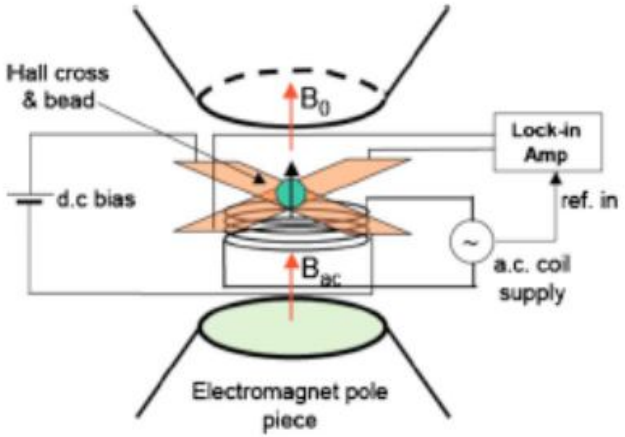
Micro-Hall sensors are sensitive tools to examine magnetization patterns on a nanoscale. These Hall sensors can either be used as non-invasive ‘tips’ which are scanned across a magnetic surface and deliver spatially resolved information on sub-micron magnetic stray field distributions or, alternatively, as miniaturized magnetometers to study the magnetization reversal of individual nanomagnets.

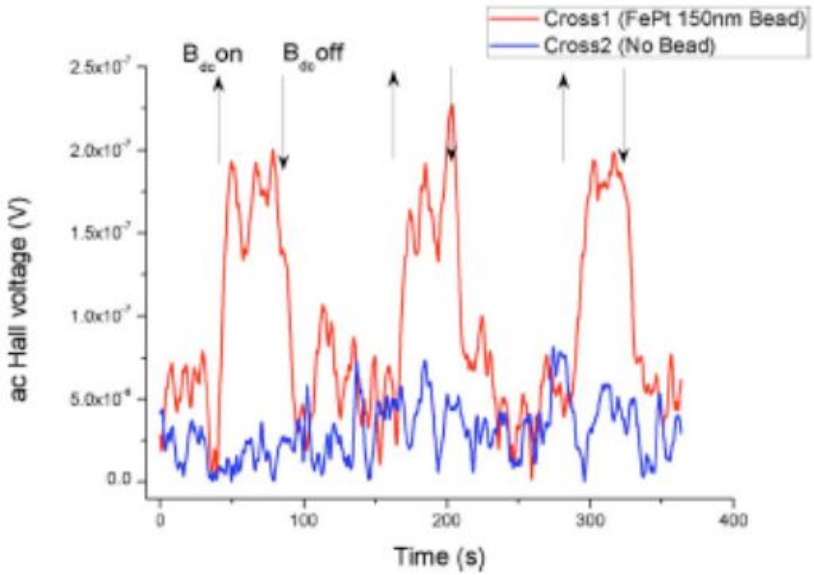


Micro-Hall biosensors

O.Kazakova, e.a., J. Appl. Phys. 107, 09E708 (2010)

Schematic of the detection experiment.



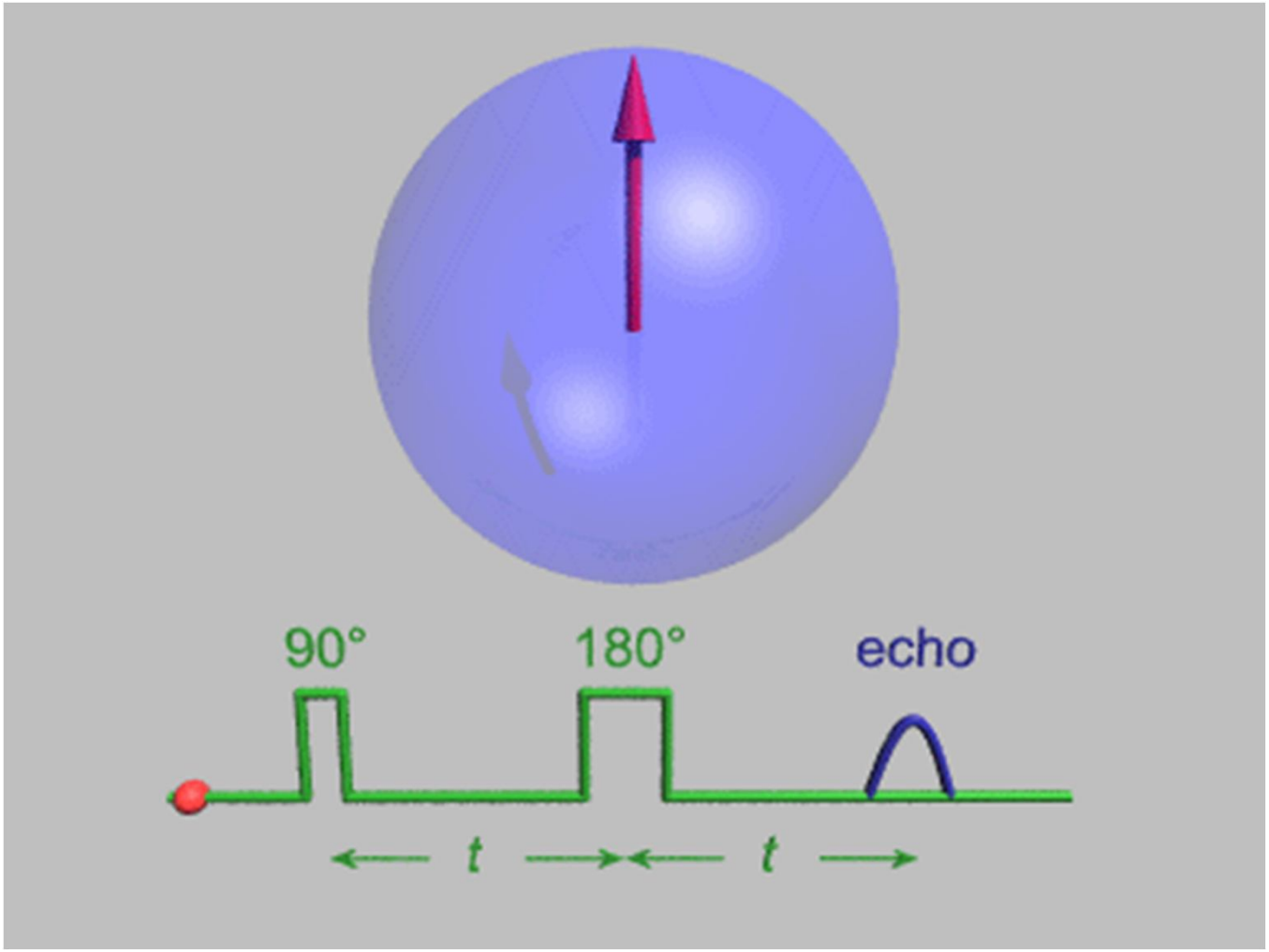


The technique developed here is based on measurements of the nonlinear susceptibility change in a bead exposed to an ac magnetic field B_{ac}=1.1 mT, f =491 Hz applied perpendicular to the plane of the Hall sensor, as a function of an external dc magnetic field B_{dc}=340mT, applied parallel to the ac field.

Detection of an FePt bead, based on the ac-dc measurement technique. Arrows indicate switching of the dc magnetic field on and off, each pulse having a duration of 40 s. The cross with a magnetic bead shows a clear step-wise increase in the ac Hall voltage, V_H=150 nV. No signal is measured on the empty cross no. 2.

Diagnostic magnetic resonance – miniaturized chip-based NMR system

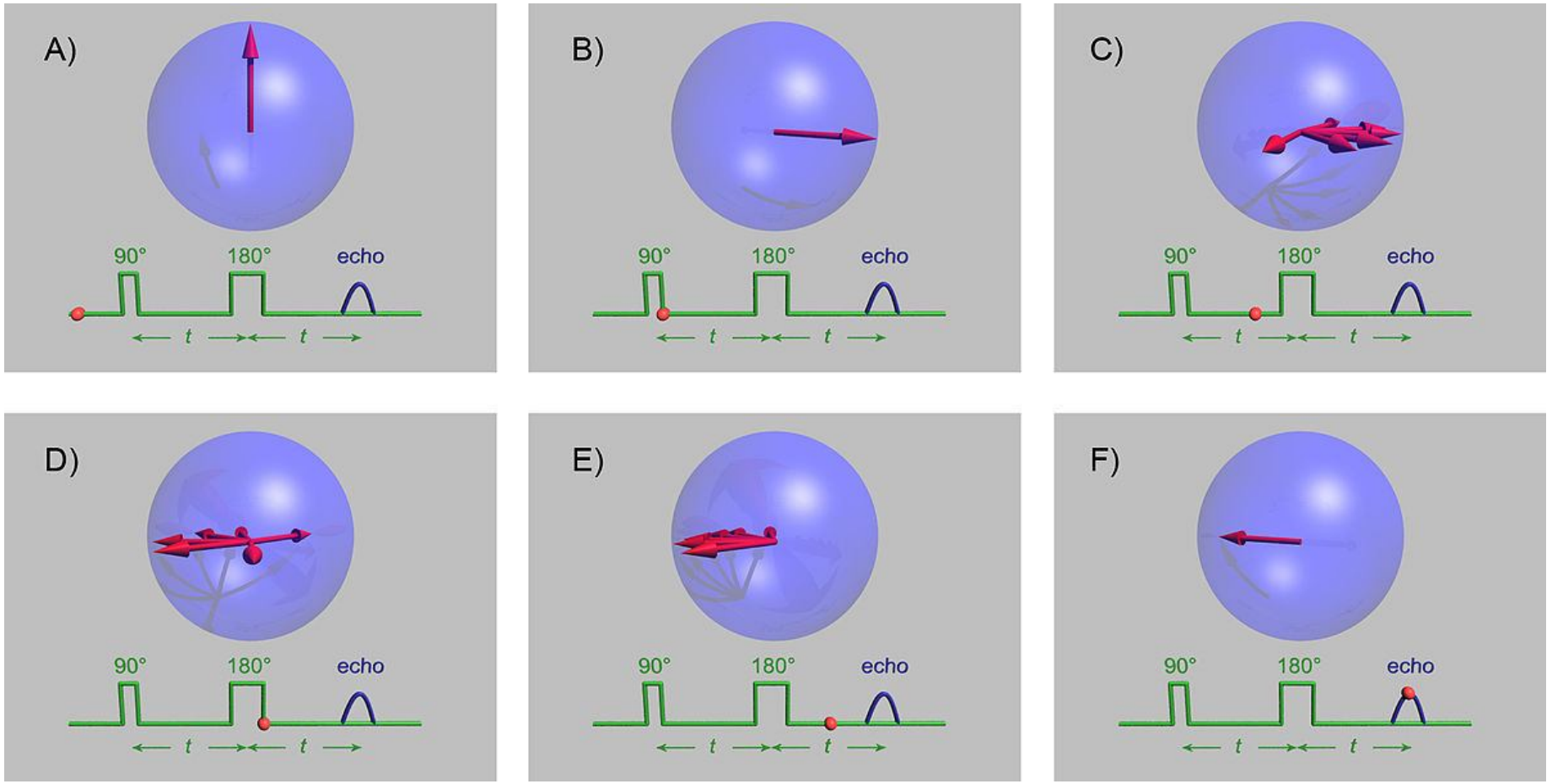
NMR spin-echo



In magnetic resonance, a **spin echo** is the refocusing of spin magnetisation by a pulse of resonant electromagnetic radiation. Modern nuclear magnetic resonance and magnetic resonance imaging make use of this effect.

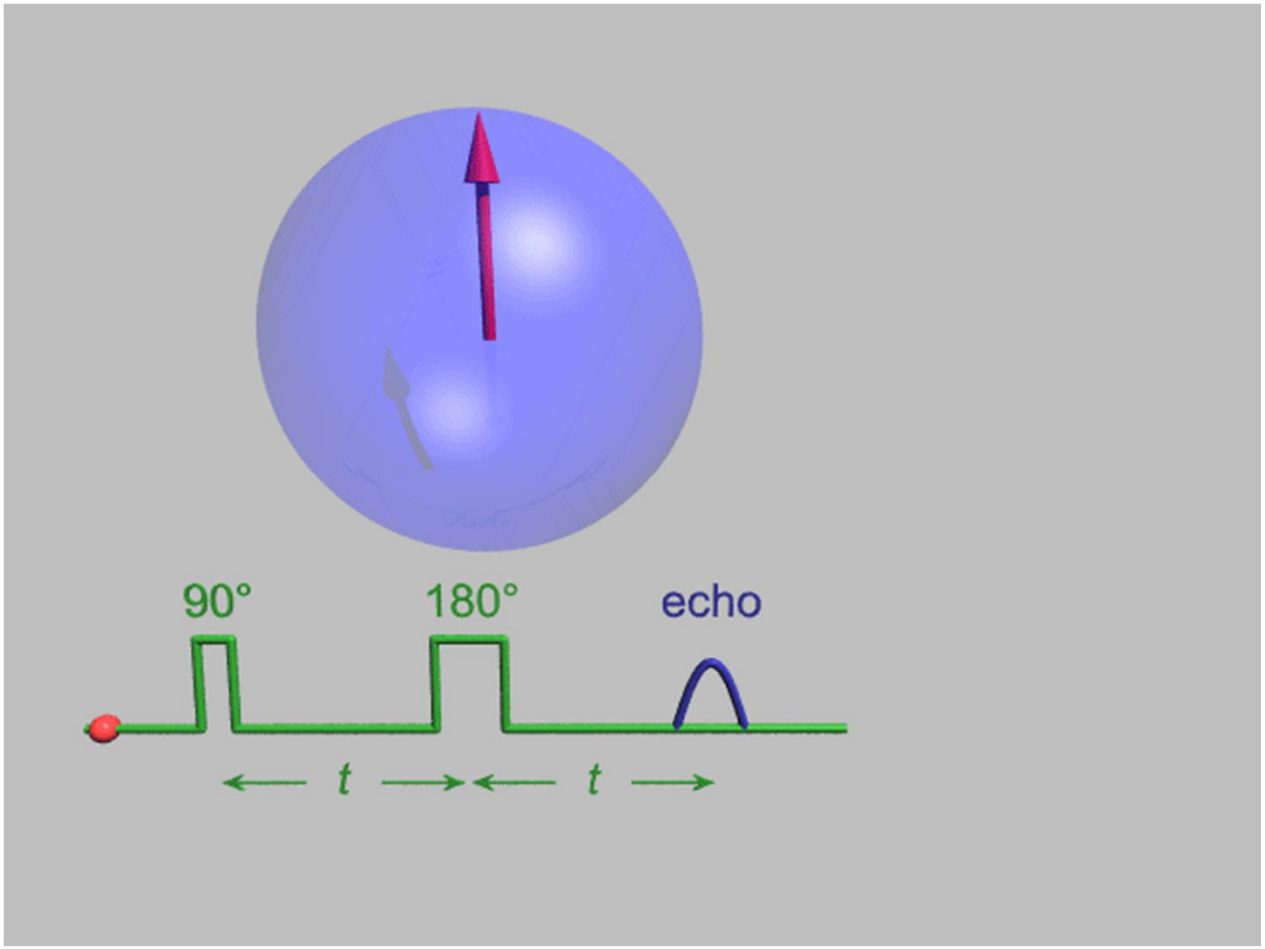
NMR spin-echo

The spin echo effect was explained by Erwin Hahn, and further developed by Carr and Purcell who pointed out the advantages of using a 180° refocusing pulse for the second pulse. The pulse sequence may be better understood by breaking it down into the following steps:

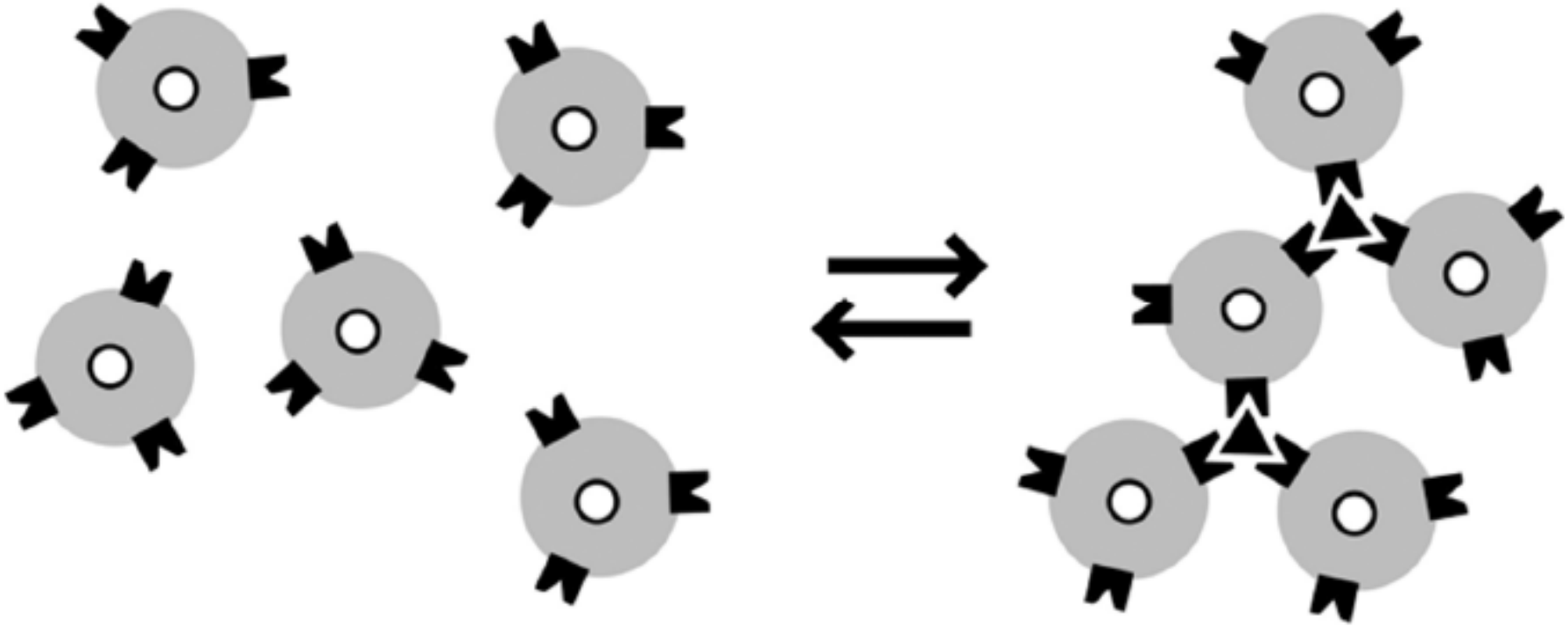


Spin-echo decay

A Hahn echo decay experiment can be used to measure the spin–spin relaxation time, as shown in the animation below. The size of the echo is recorded for different spacings of the two pulses. This reveals the decoherence which is not refocused by the π pulse. In simple cases, an exponential decay is measured which is described by the T_2 time.

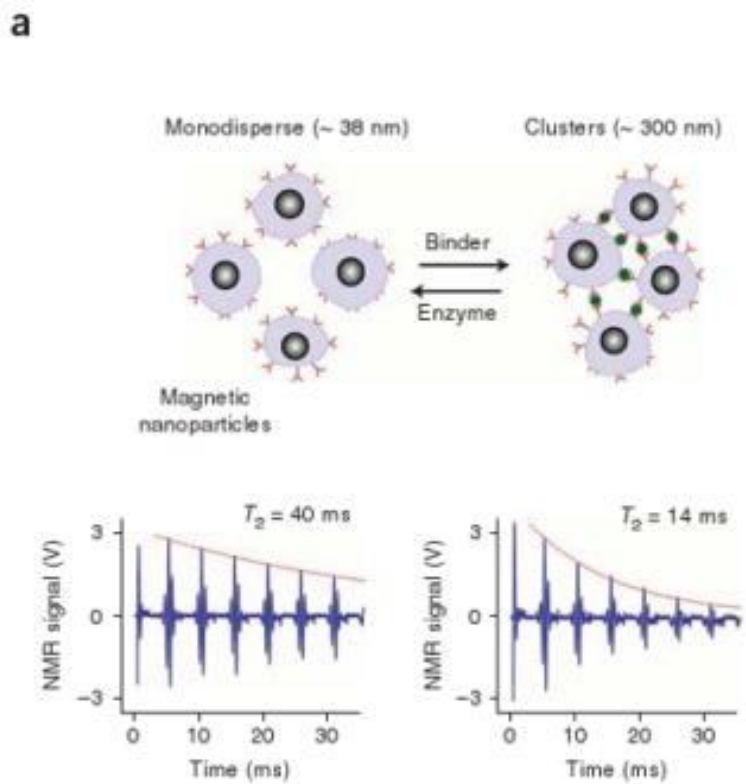


NMR biosensors

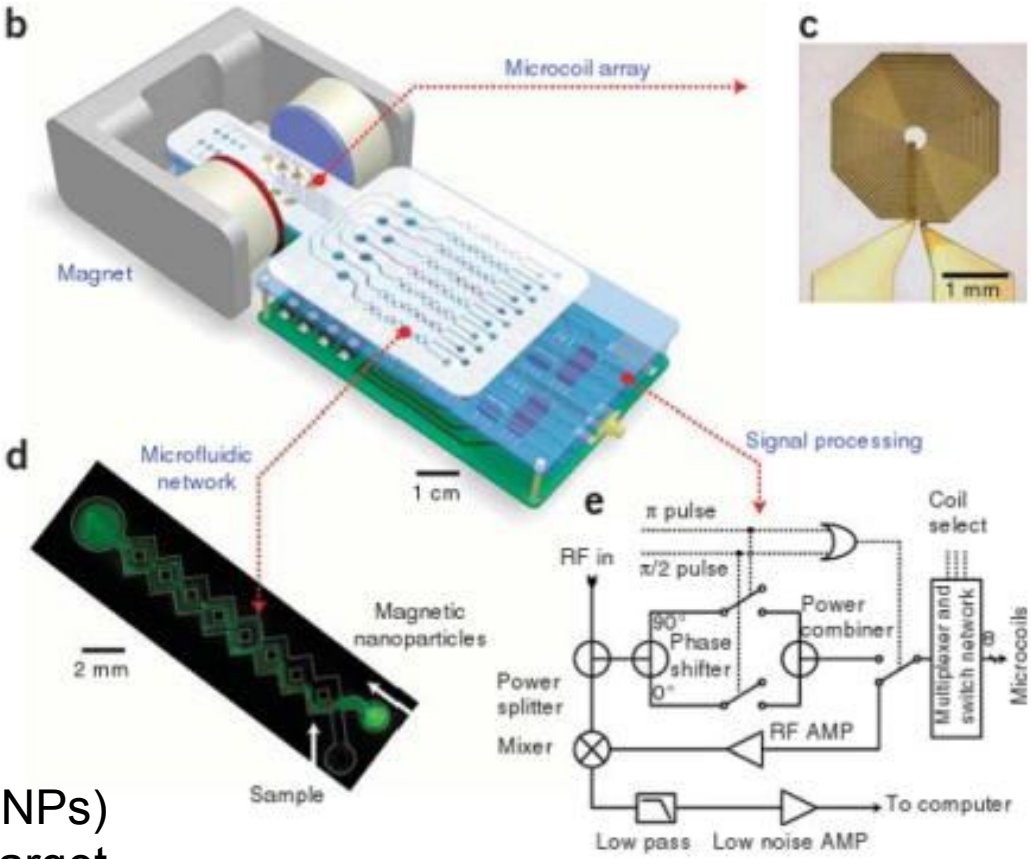


Principle of Type I MRSws. Dispersed magnetic nanoparticles (NPs) form an aggregate upon binding with target analytes (triangle). The aggregated form of the NPs dephases the spins of the surrounding protons of water molecules more efficiently than NPs present as the dispersed state. The effect is observed as a decrease in spin-spin relaxation time, T2

NMR biosensors

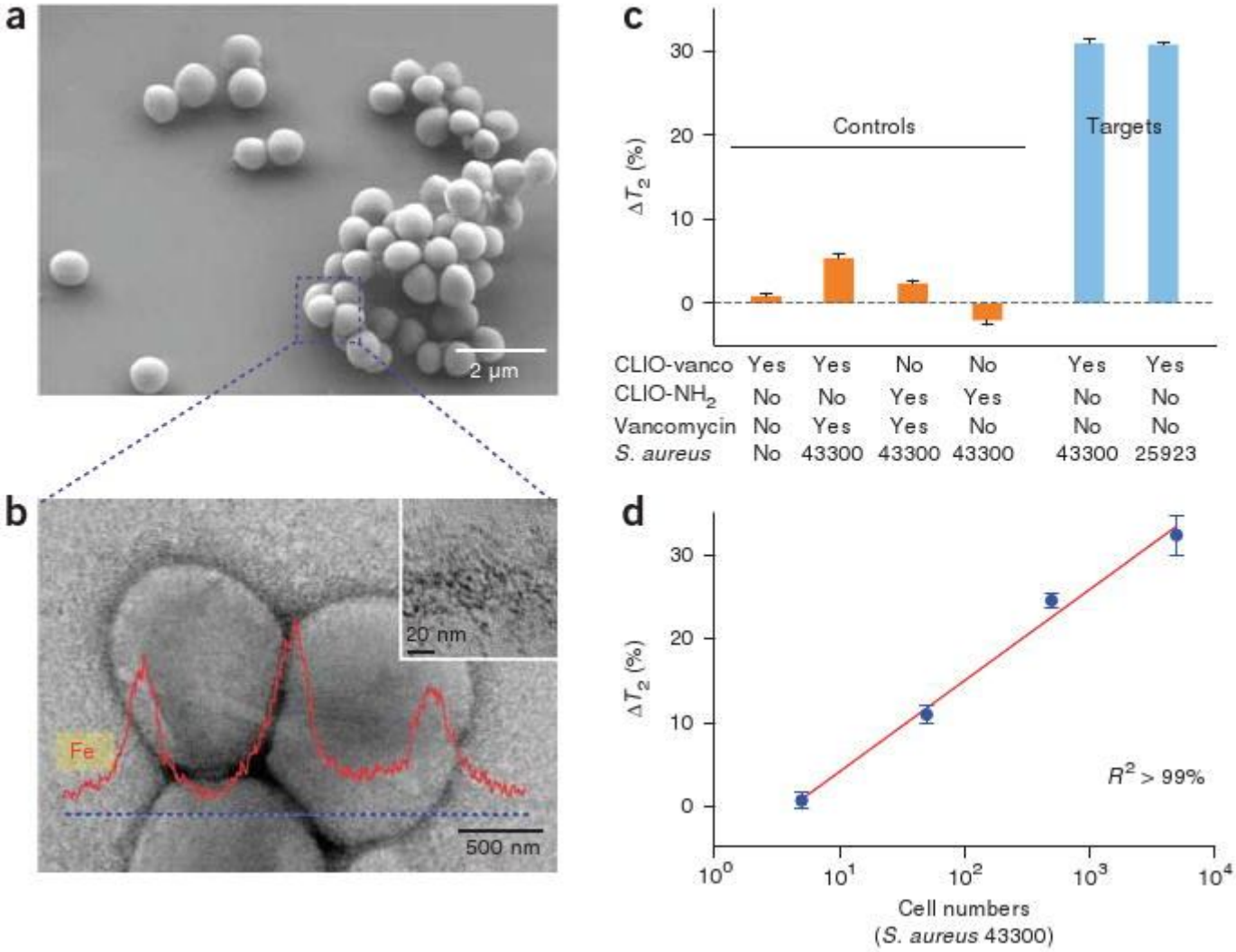


Dispersed magnetic nanoparticles (NPs) form an aggregate upon binding with target analytes (triangle). The aggregated form of the NPs dephases the spins of the surrounding protons of water molecules more efficiently than NPs present as the dispersed state. The effect is observed as a decrease in spin-spin relaxation time, T_2



Schematic representation of a miniaturized chip-based NMR system, diagnostic magnetic resonance (DMR).

Sensitive detection of bacteria.



The larger labels (~1–3 μm diameter) have been the most widely studied in preliminary detection experiments using different types of MR sensor.

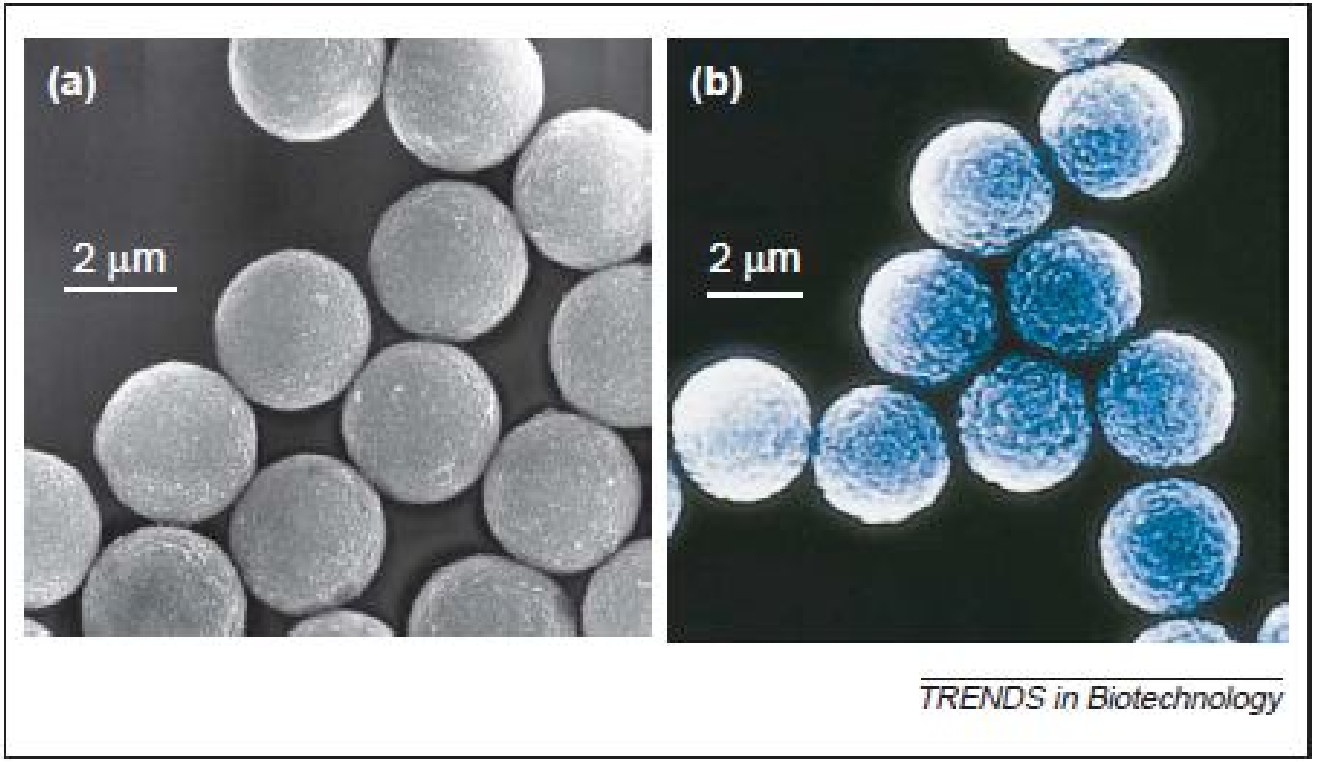


Figure 3. SEM images of magnetic microspheres. Scanning Electron Microscope (SEM) images of magnetic microspheres showing uniform size and shape: **(a)** 3 μm Micromer®-M, image courtesy of Micromod and **(b)** 2.8 μm M280 Dynabeads, image courtesy of Dynal Biotech.

Magnetic microspheres

Micron sized microspheres are easily observed and, hence, enumerable using non-specialized light microscopy techniques. They may also be manufactured in a uniform size and shape using preparative methodologies such as cone-filling (Micromerw-M, Micromod; http://www.micromod.de) or core-shell techniques (Dynabeadsw M280, Dynal; http://www.dynal.no). Furthermore, despite the fact they have a lower percentage magnetic composition (~15%) in comparison to magnetic nanoparticles, their increased volume results in a higher magnetic moment per label in an applied magnetic field, allowing distinct detection signals at the single-label level. Their uniform size and shape also allows for quantitative signal data with linearity between the signal and the number of labels detected for a defined sensing area.

Magnetic nanoparticles

The disadvantages of micron-sized labels are the high mass of the label in relation to the biomolecules tethering the label to the sensor surface and the large diameter of the label, hindering high-density label binding across the sensor surface.

Smaller nanometer-sized labels with a high magnetic (iron-oxide) content (70–85%) offer a solution to these problems; the smaller size allows for increased density of label binding across the sensor surface. Unfortunately, at present, most commercially available magnetic nanoparticle product samples contain particles with heterogeneous size (for example. 200–400 nm) and shape (non-spherical), thus hindering quantification.

Magnetic nanoparticles

In addition, their high resultant magnetisation and anisotropy for their volume in an applied magnetic field may lead to rapid clustering (single particles aggregating to form groups). Permanent clustering of labels, which cannot be remedied using a discriminatory magnetic force applied to the chip or on-chip washing cycles, can lead to exaggerated positive signals because non-biologically bound labels may remain attached to biologically bound labels. Finally, despite their higher magnetic percentage composition, magnetic nanoparticles as detectable labels acquire a smaller magnetic moment than a magnetic microsphere in an equivalent applied field (e.g. ~10^{-13} and ~10^{-12} emu, respectively, at 15–20 Oe. Consequently, smaller labels require progressively more sensitive sensors and measurement systems.

Conclusions

Magnertic nanoparticles offer a great promise for the miniaturized chip-based biosensors. However, the problems mentioned above, like

- heterogeneous size (for example. 200–400 nm) and shape (non-spherical)
- rapid clustering (single particles aggregating to form groups)
- a smaller magnetic moment than a magnetic microsphere in an equivalent applied field

require reliable methods for their characterization, as well as progressively more sensitive sensors.

And neutron scattering methods provide a possibility to address these issues.