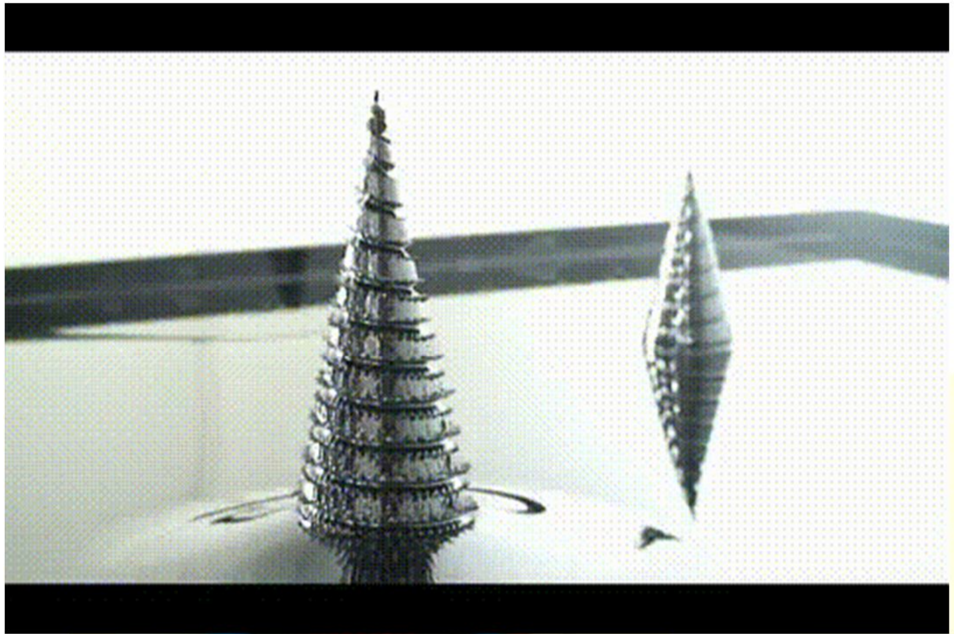
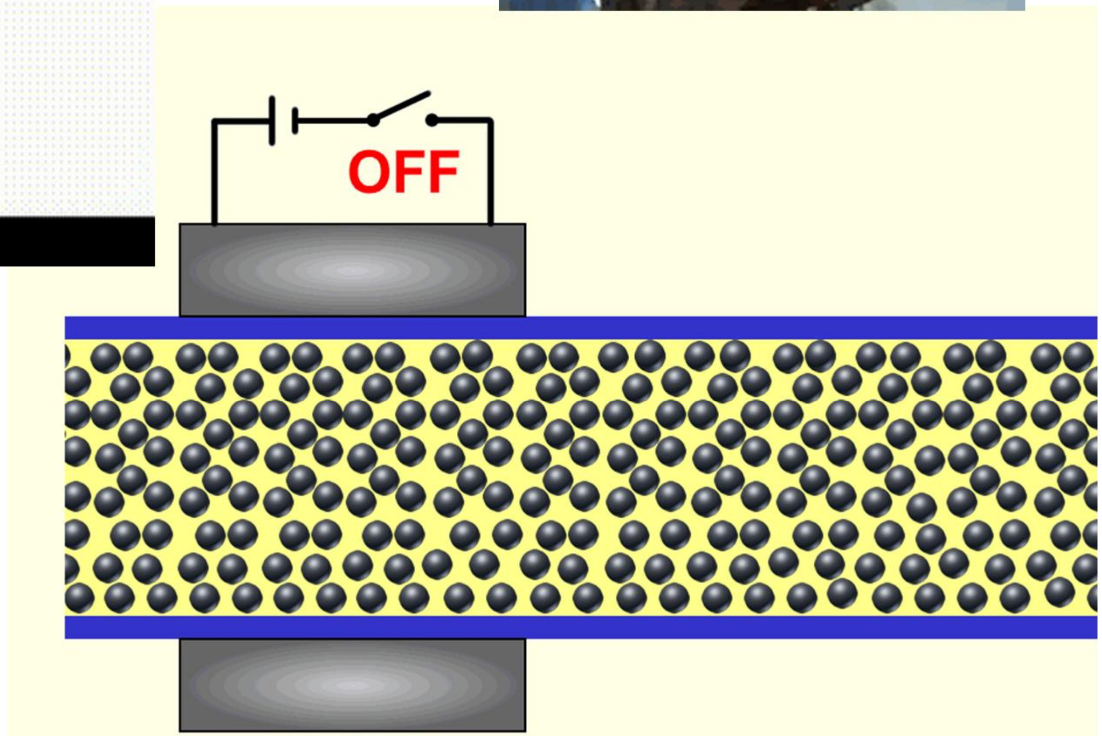
Magnetic biosensors and impact of neutron scattering for their development.





Baldin ISHEPP XXII, September 15-20, 2014, JINR, Dubna

В начале было Слово

Св. Евангелие от Иоанна, глава 1

In the beginning was the Word

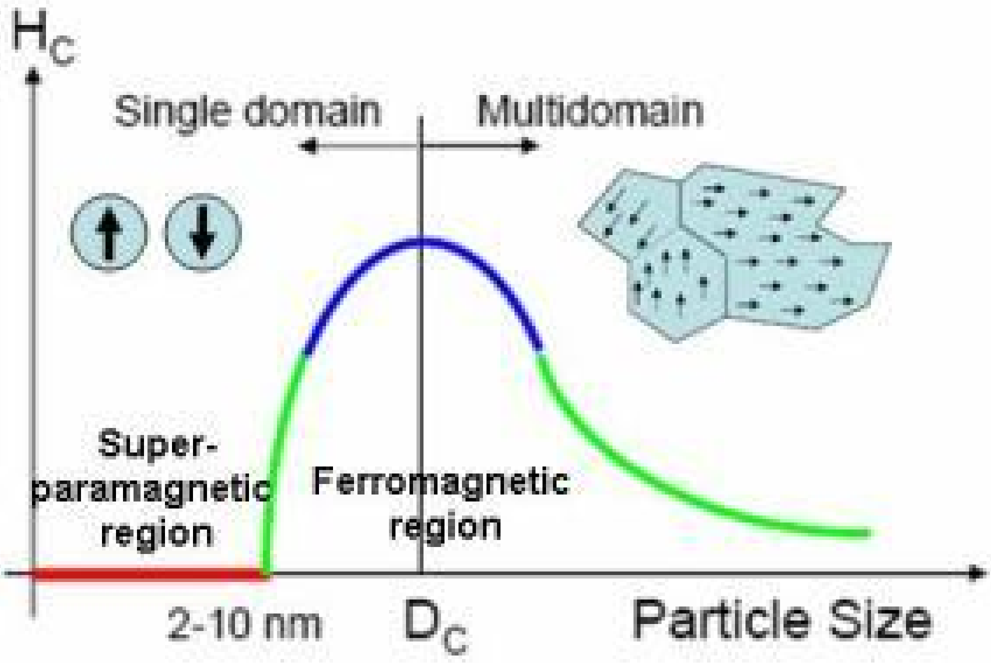
The Gospel of John, 1

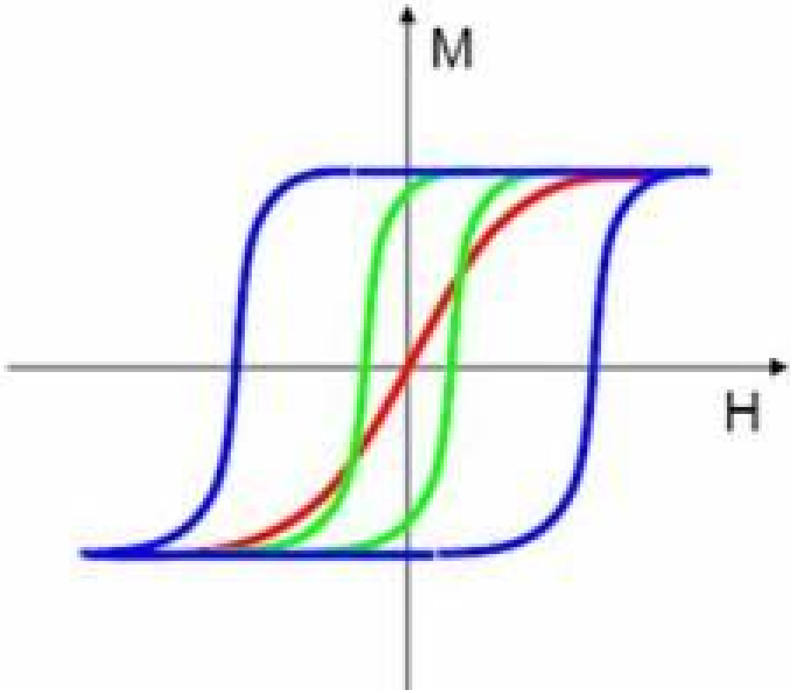
Biosensors based on magnetic nanoparticles.

"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

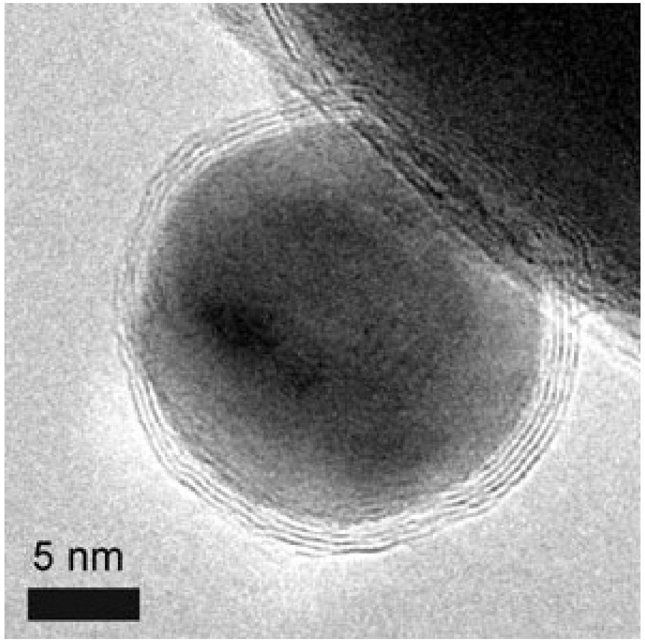
Magnetic nanoparticles are a class of nanoparticle which can be manipulated using magnetic field. Such particles commonly consist of magnetic elements such as iron, nickel and cobalt and their chemical compounds. Nanoparticles are smaller than 1 micrometer in diameter (typically 5–500 nanometers.



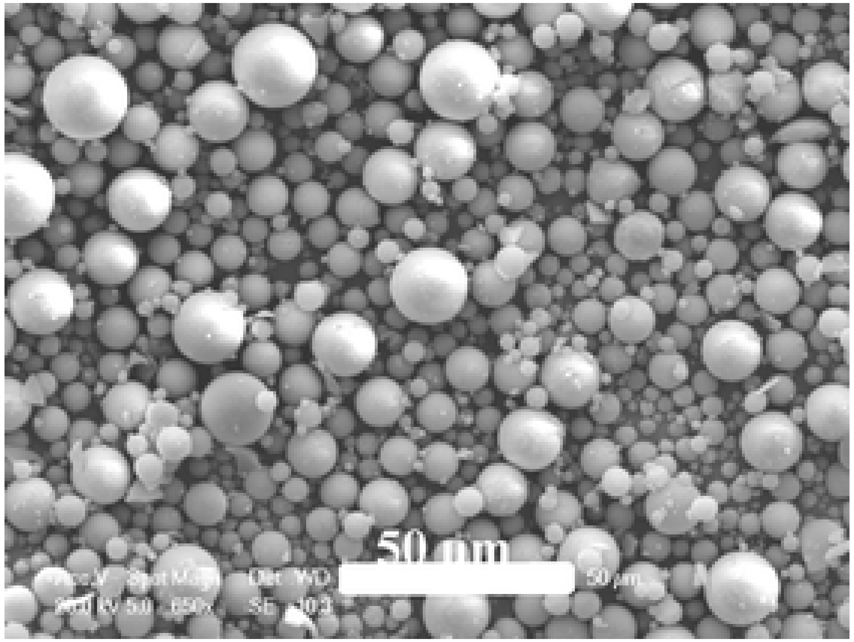


Magnetic nanoparticles

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.**



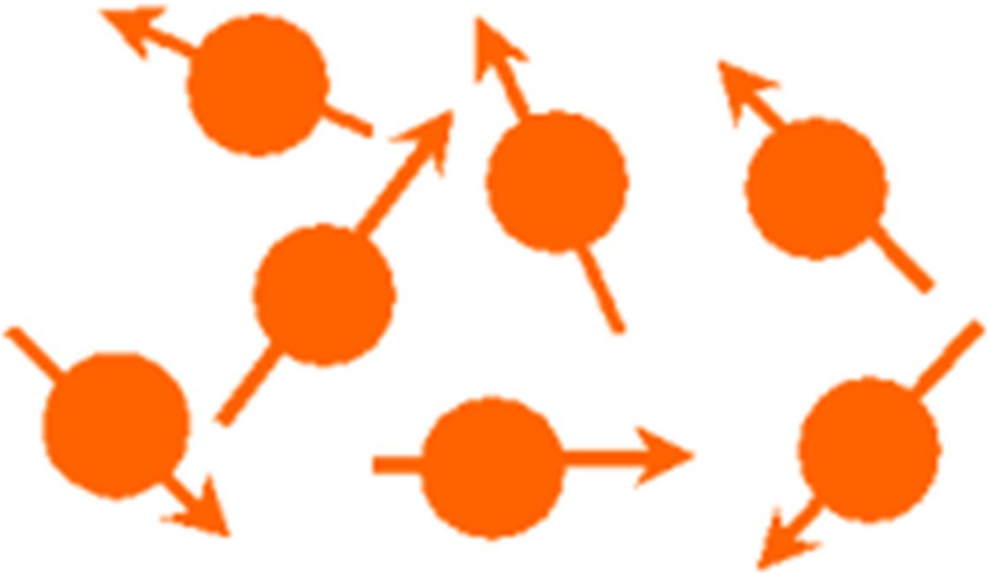
Cobalt nanoparticle with graphene shell (note: The individual graphene layers are visible)



Ferrite (Fe_3O_4) nanoparticles

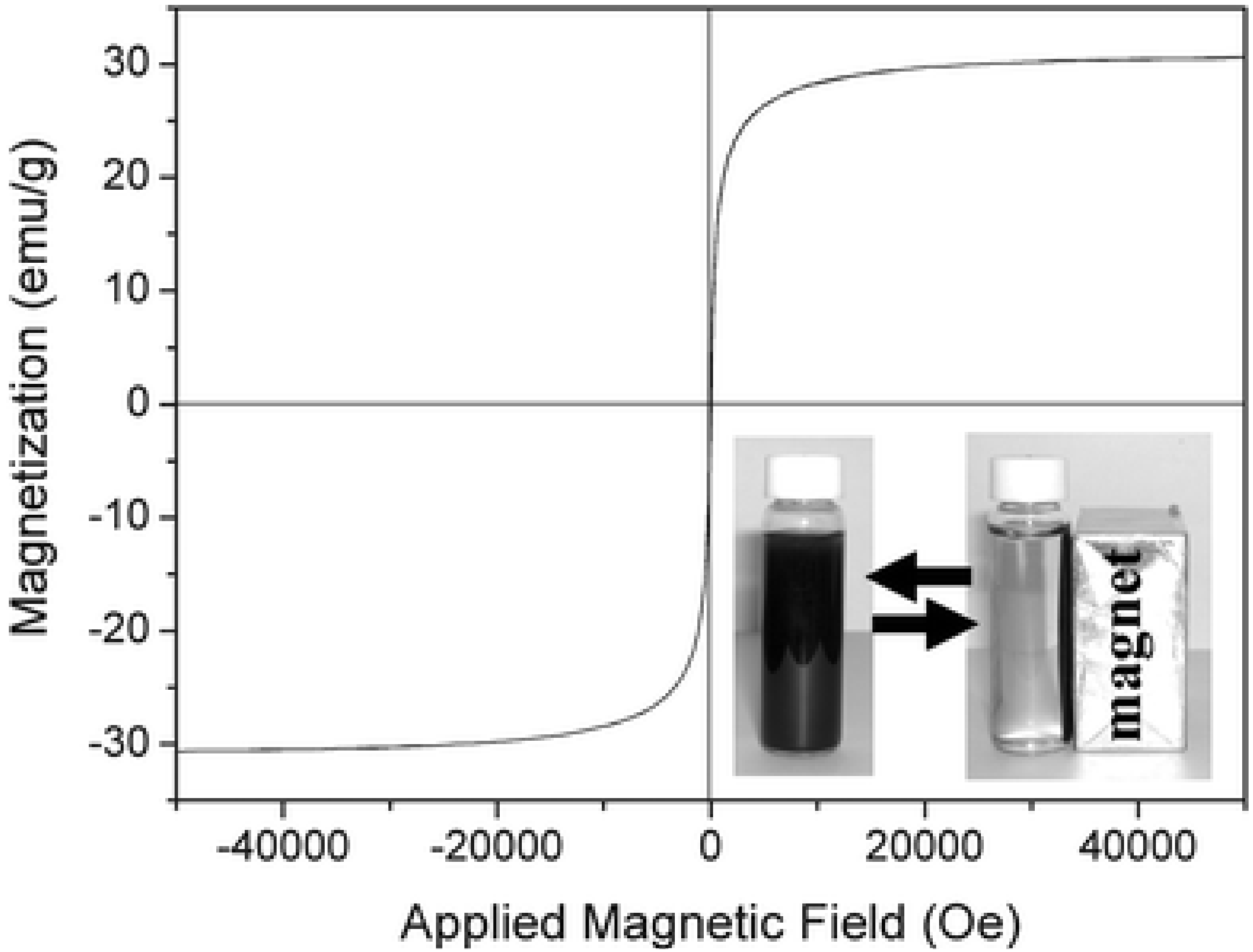
Superparamagnetism

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. 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.

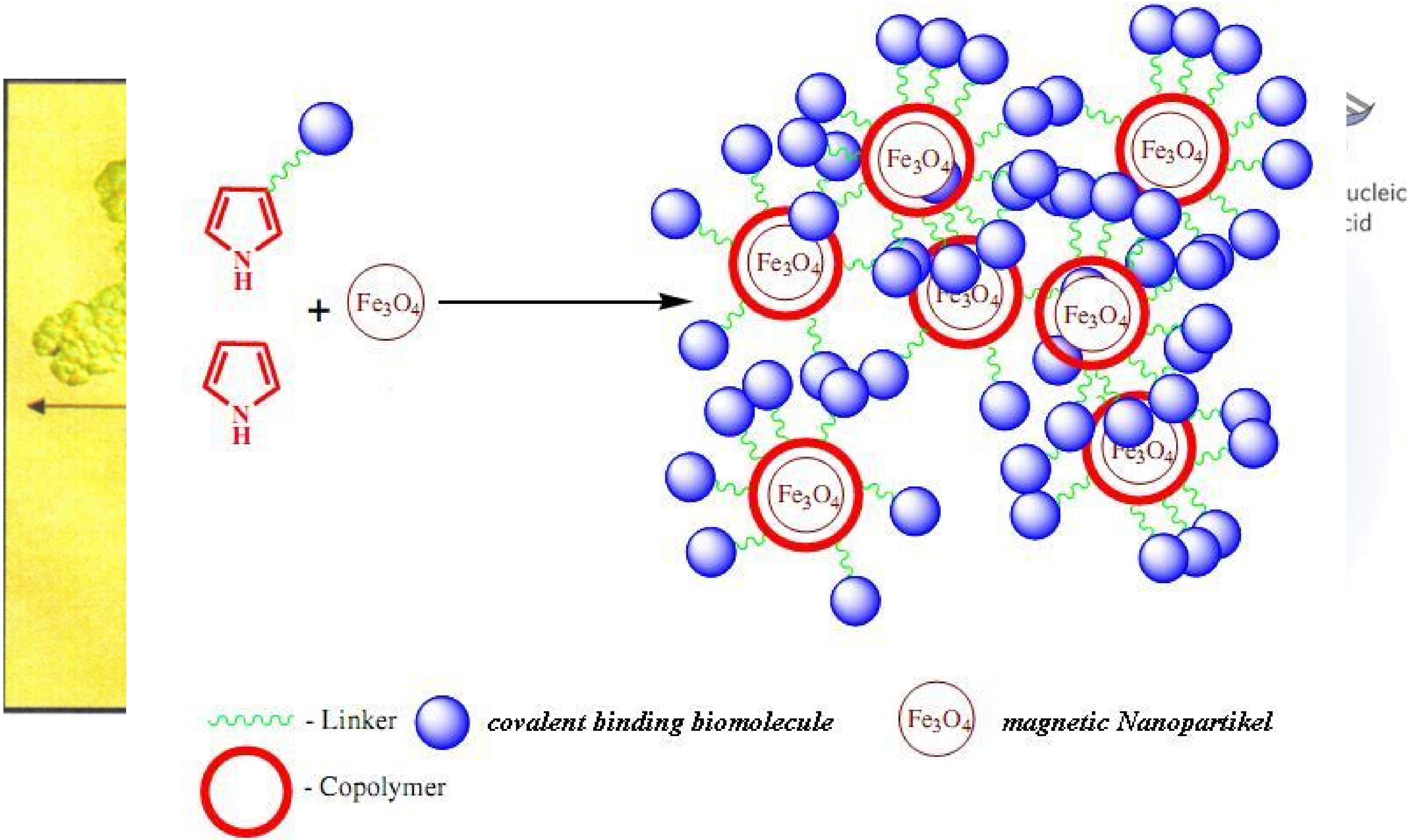


Superparamagnetism

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



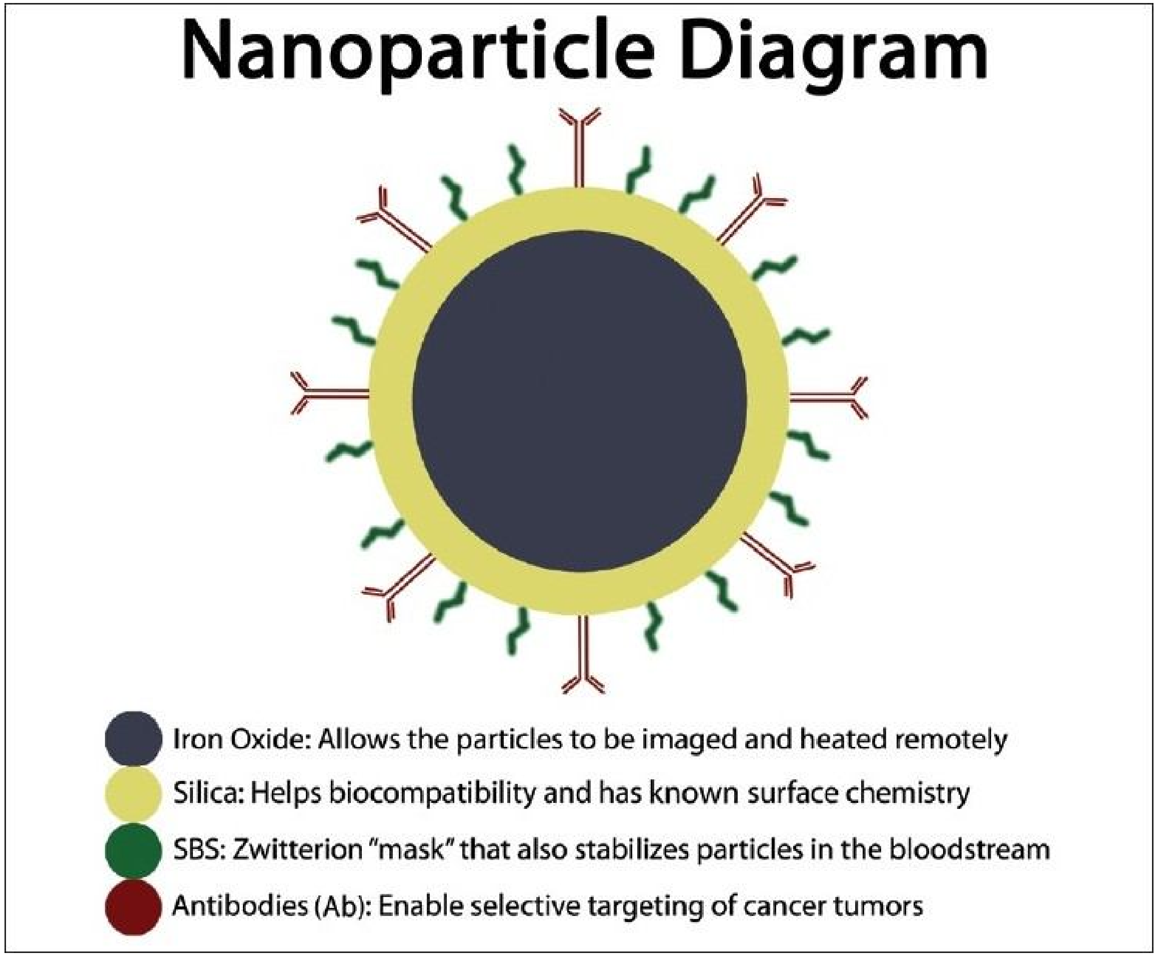
Nanoparticle’s preparation for biomedical use



Antibody-coated magnetic nanoparticles: Targeting and treating cancer

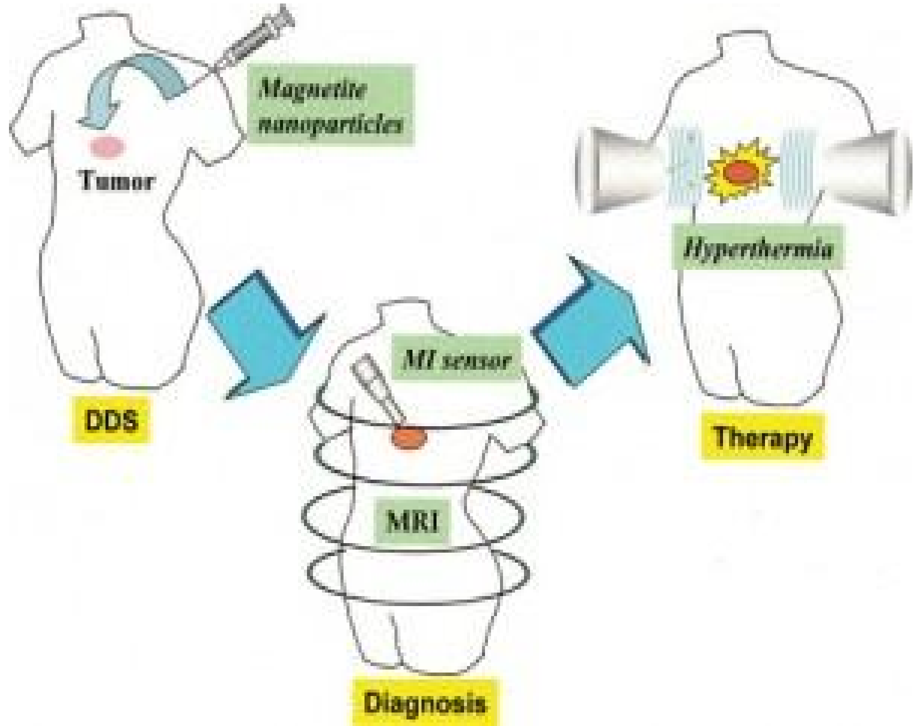
Philip Schlenoff Maclay School (Tallahassee, Florida)

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

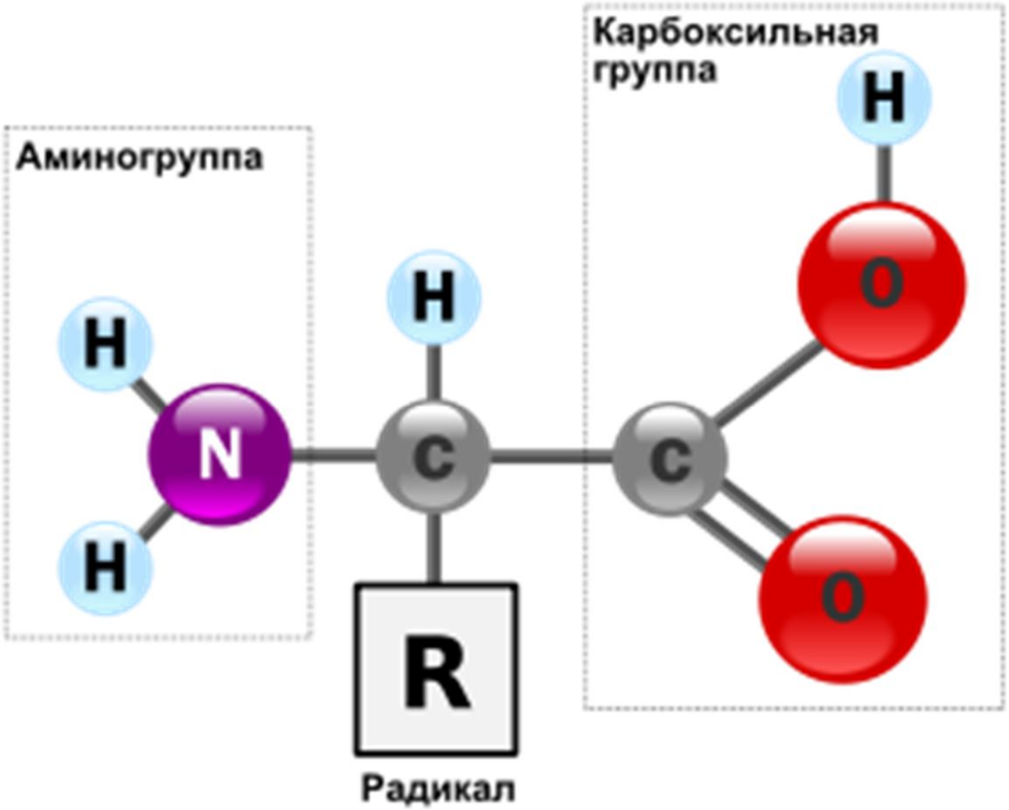


Hyperthermia involves heating up of local environment of a tumor resulting in cell damage and death. Tumor cells are more sensitive to high temperature than normal cells, hence hyperthermia doesn't affect normal cells. It is an adjuvant cancer therapy used to enhance the efficacy of traditional therapies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

Proteins

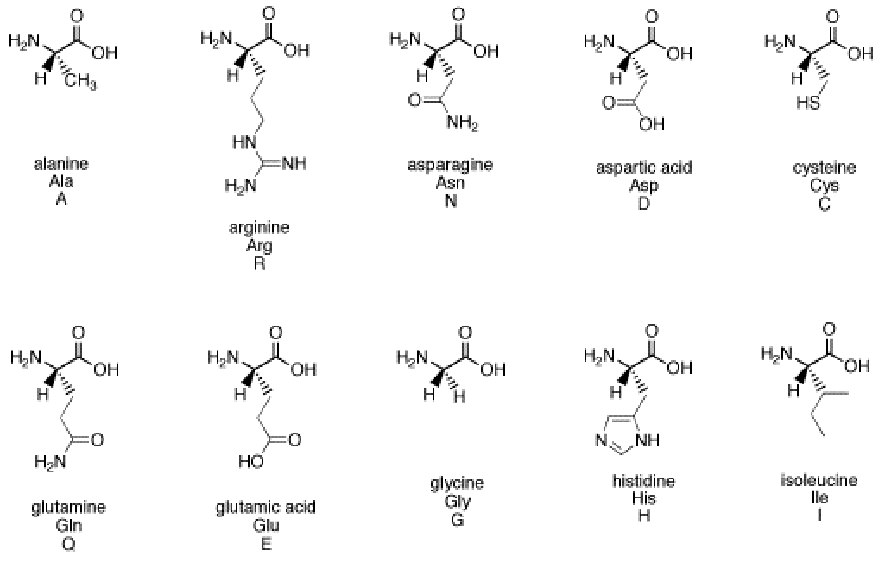
Proteins are large biological molecules, or macromolecules, consisting of one or more chains of amino acid residues. Proteins perform a vast array of functions within living organisms, including catalyzing metabolic reactions, replicating DNA, responding to stimuli, and transporting molecules from one 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.

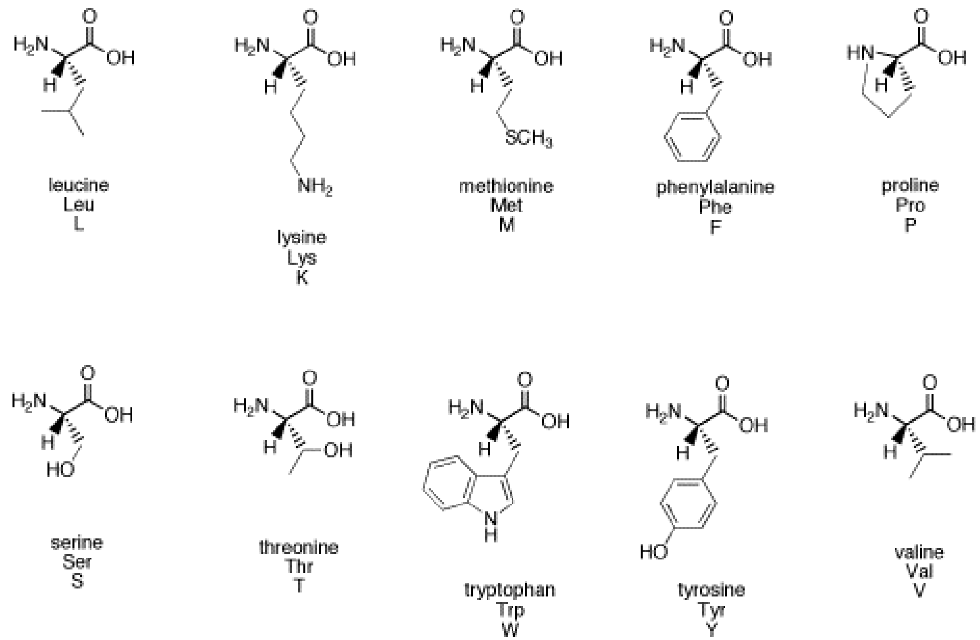
Amino acids



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



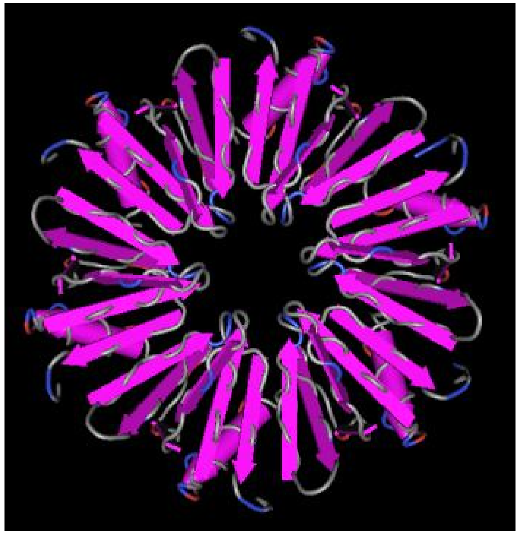


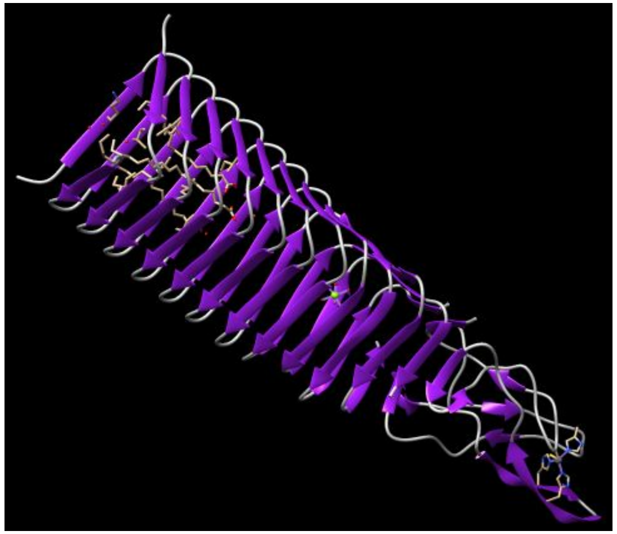
In protein biosynthesis coded by genes 20 α-amino acids are involved. The question why these 20 particular amino acids are so special is still waiting to be resolved.

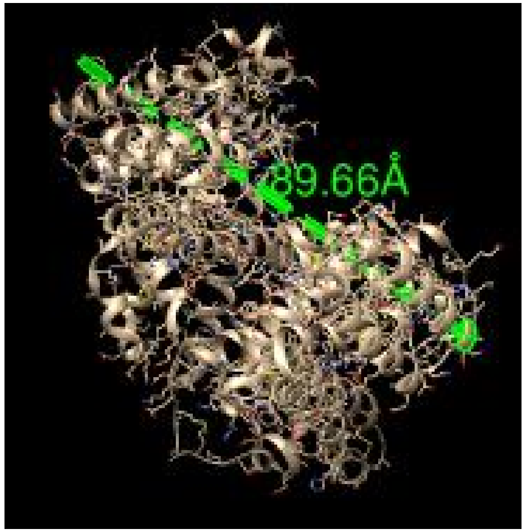
"It's amazing what they can do with amino acids these days."

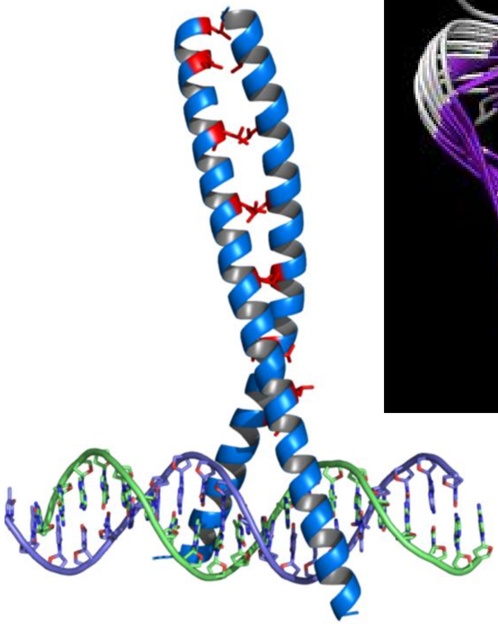
The smallest protein called Trp-cage consists of just 20 amino acids while the largest protein called titin which plays an important role in muscle contraction consists of 27000 to 33000 amino acids. Modern protein crystallography station at synchrotron facility is capable to solve several protein structures per day.

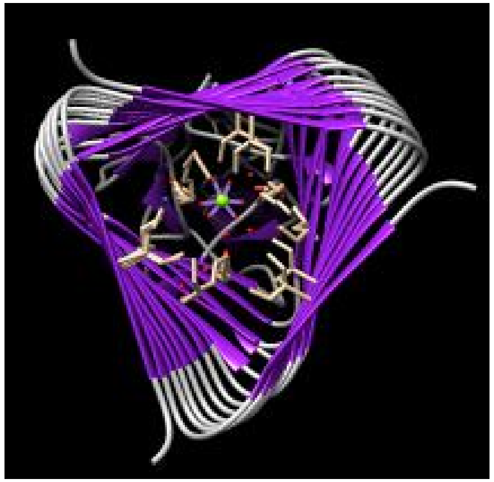
Examples of protein molecules

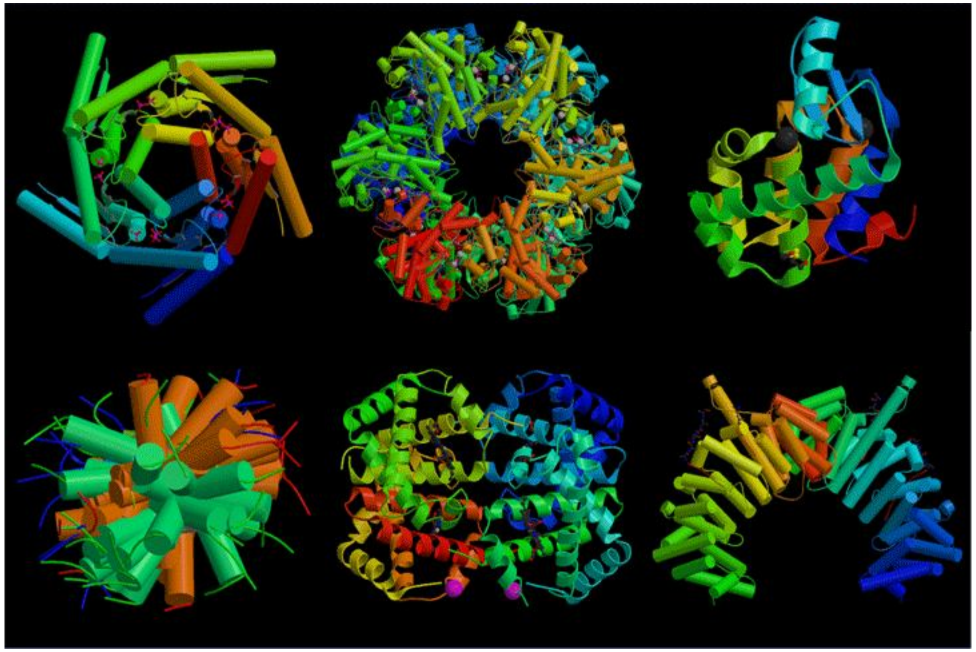






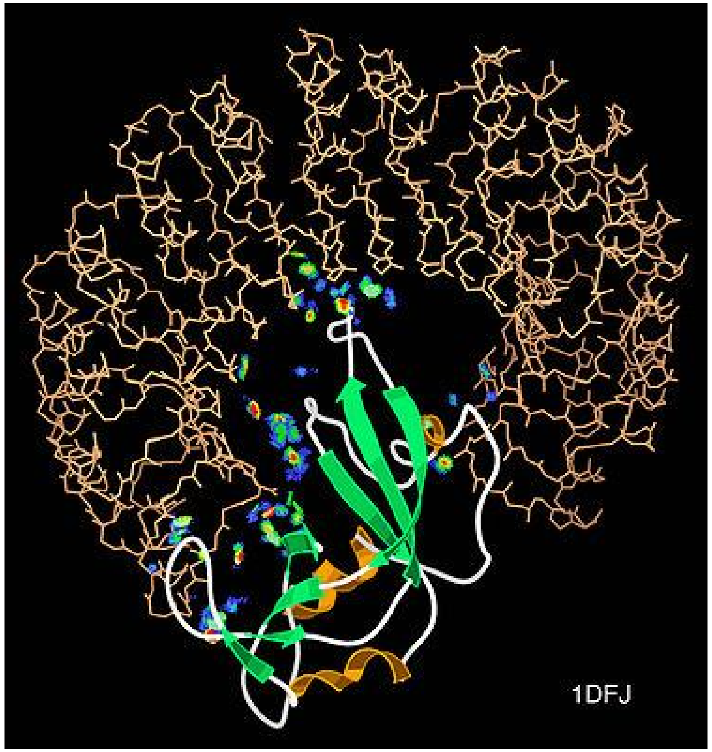






Protein–protein interactions (PPIs)

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

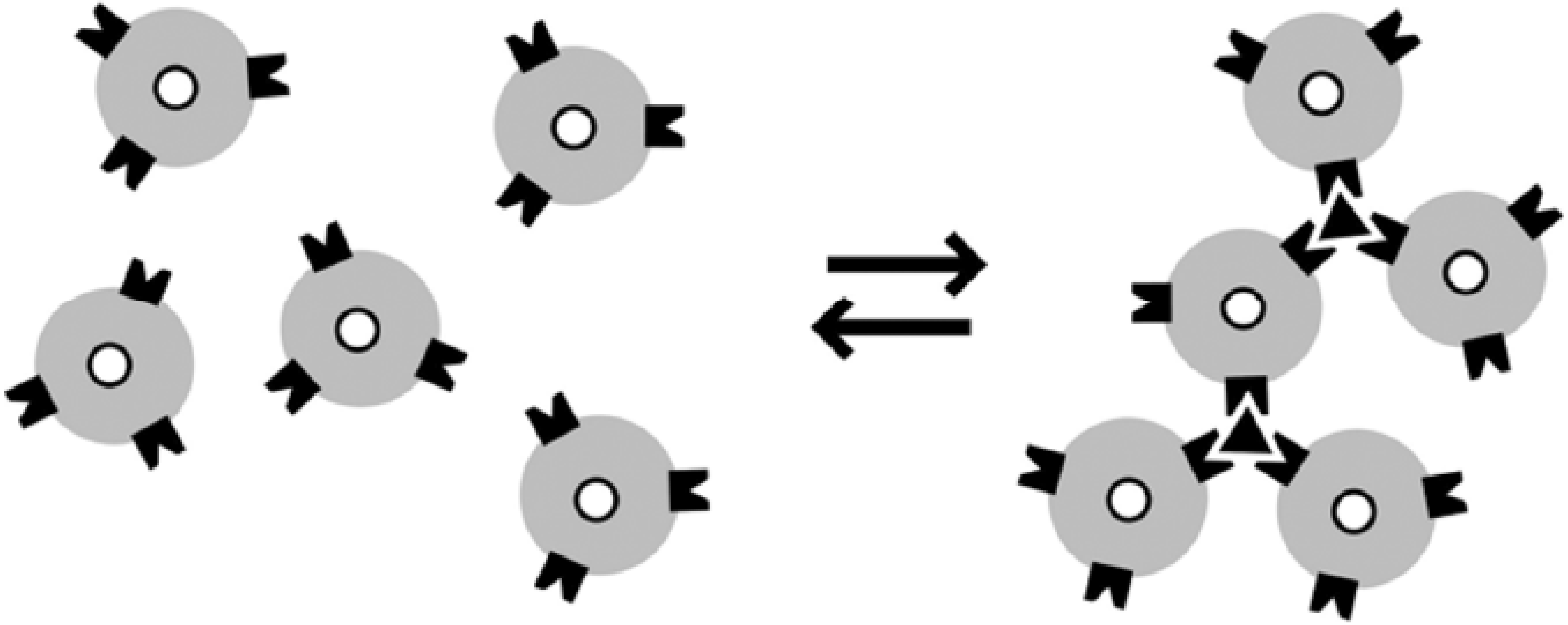
In many biosynthetic processes enzymes interact with each other to produce small compounds or other macromolecules.

Muscle contraction

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

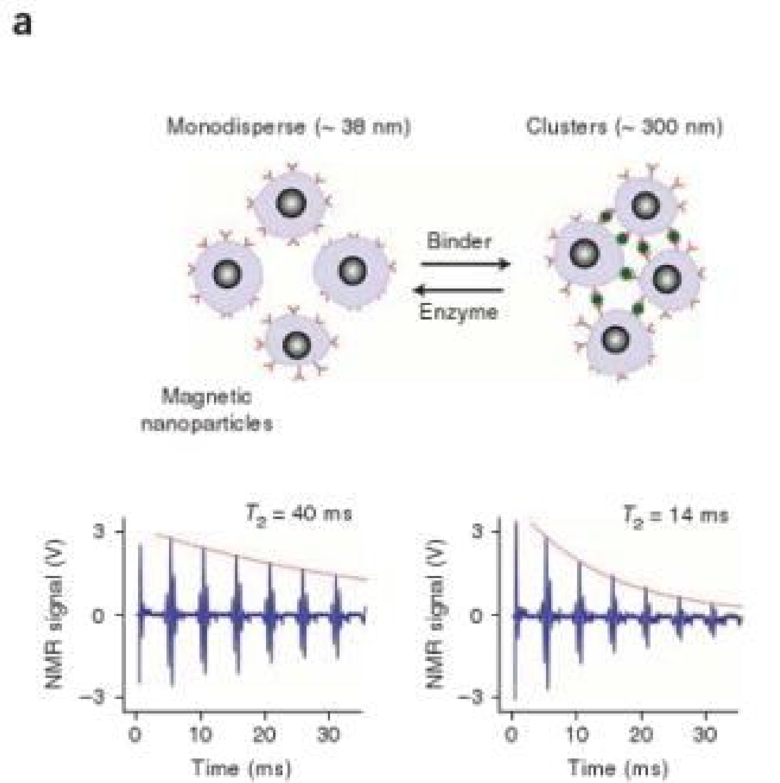
Therefore, the study which proteins are interacting with each other and which are not is one of the current issues for modern biology!

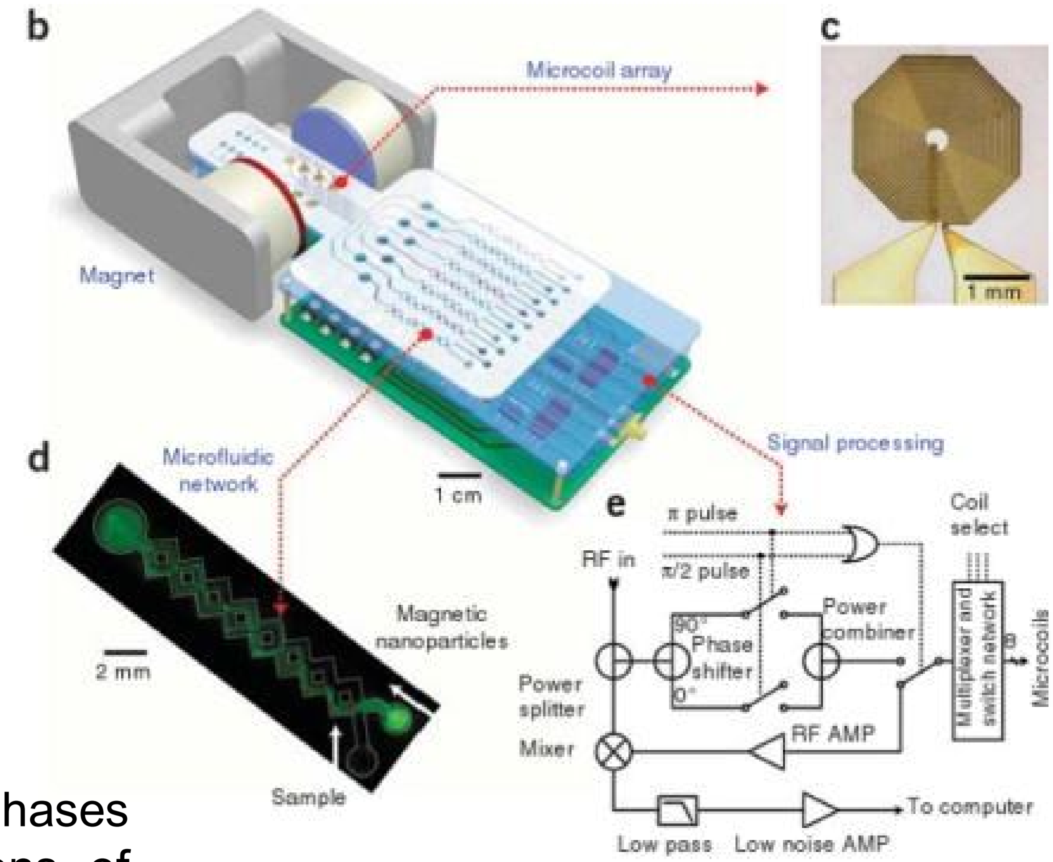
NMR biosensors



Dispersed magnetic nanoparticles (NPs) are coated with one type of protein molecules The particles are dispersed in water and then another protein molecules added (triangles). If two proteins interact then NPs start to aggregate (forming clusters).

NMR biosensors



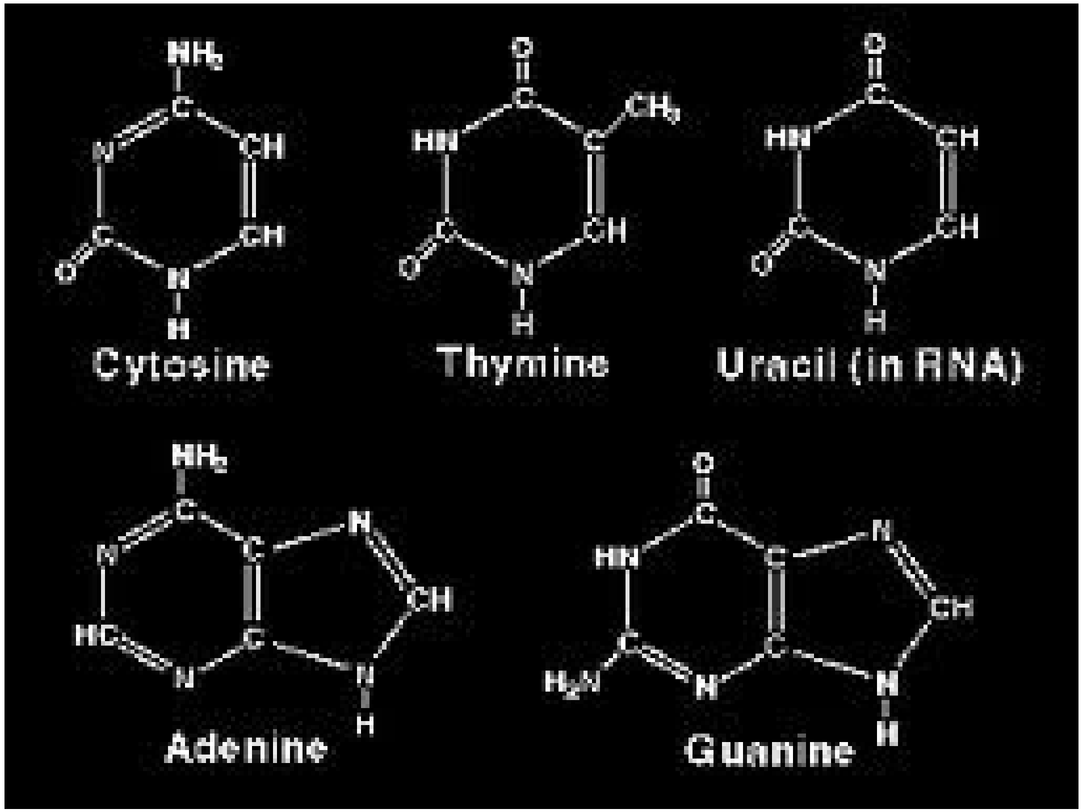


The aggregated form of the NPs dephases the spins of the surrounding protons of water molecules more efficiently than NPs present as the dispersed state. The effect is observed as a decrease in spin-spin relaxation time, T_2

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

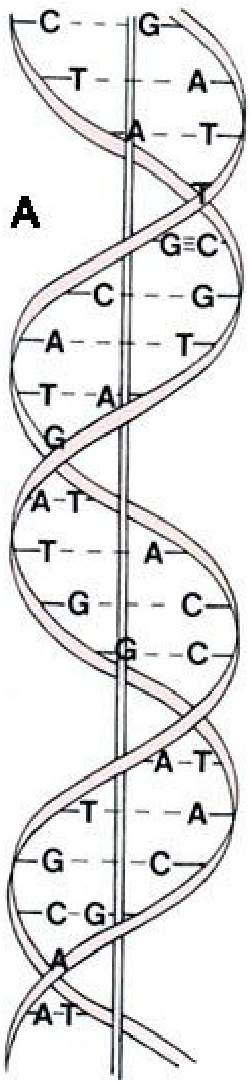
Deoxyribonucleic acid (DNA)

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.



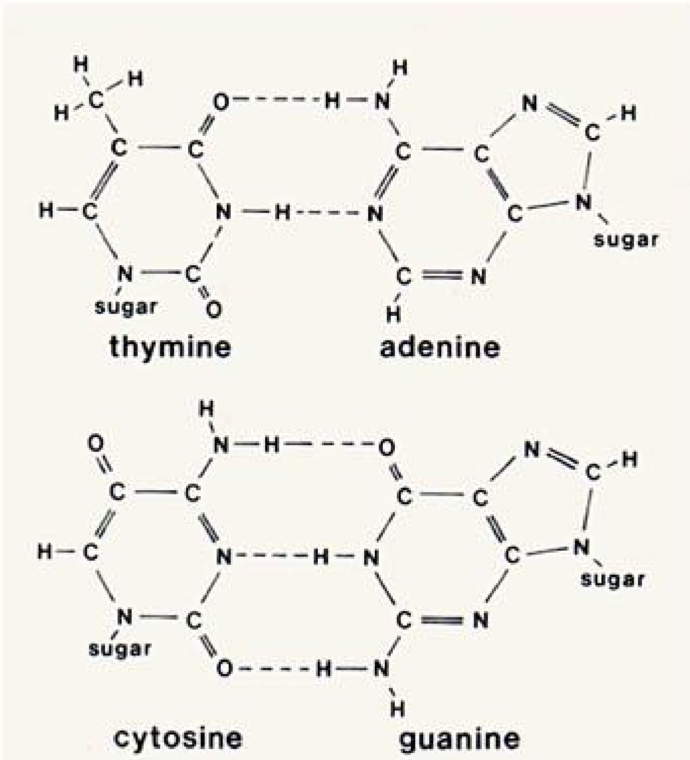
Deoxyribonucleic acid (DNA)

A

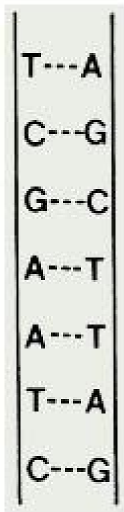


The nucleobases are classified into two types: the purines, A and G, being fused five- and six-membered heterocyclic compounds, and the pyrimidines, the six-membered rings C and T. A fifth pyrimidine nucleobase, uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking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

B



C

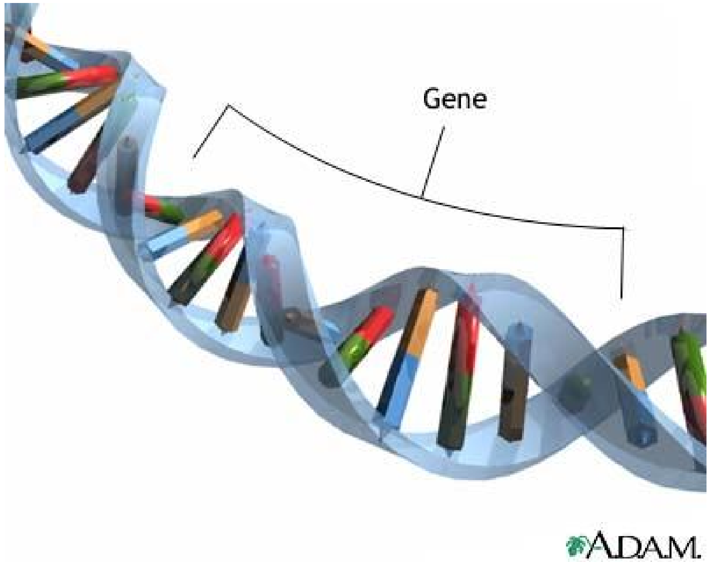


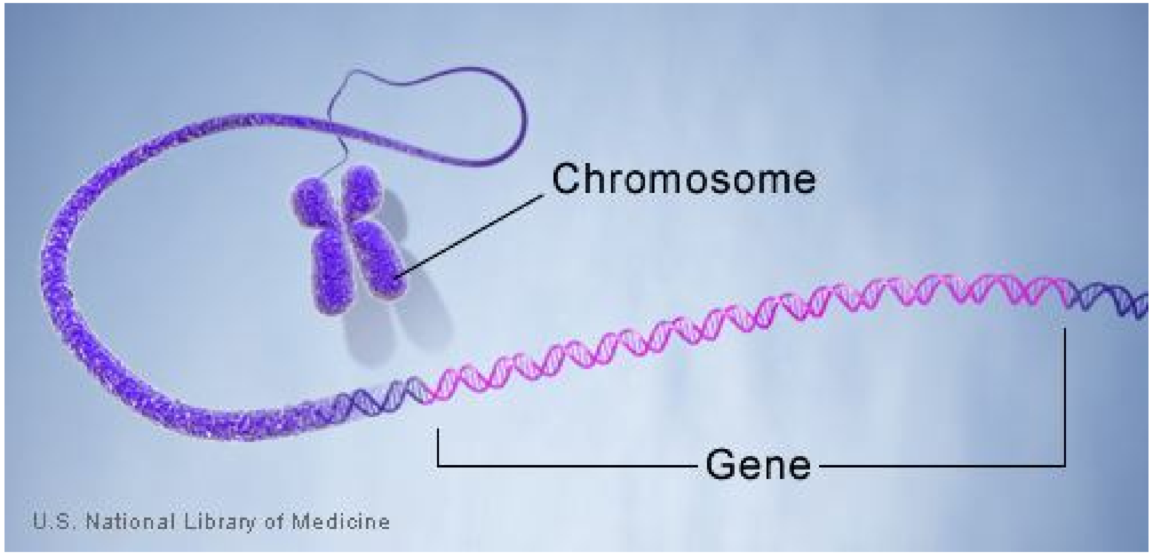
The DNA double helix is stabilized primarily by two forces: hydrogen bonds between nucleotides and base-stacking interactions among aromatic nucleobases.

What is a gene?

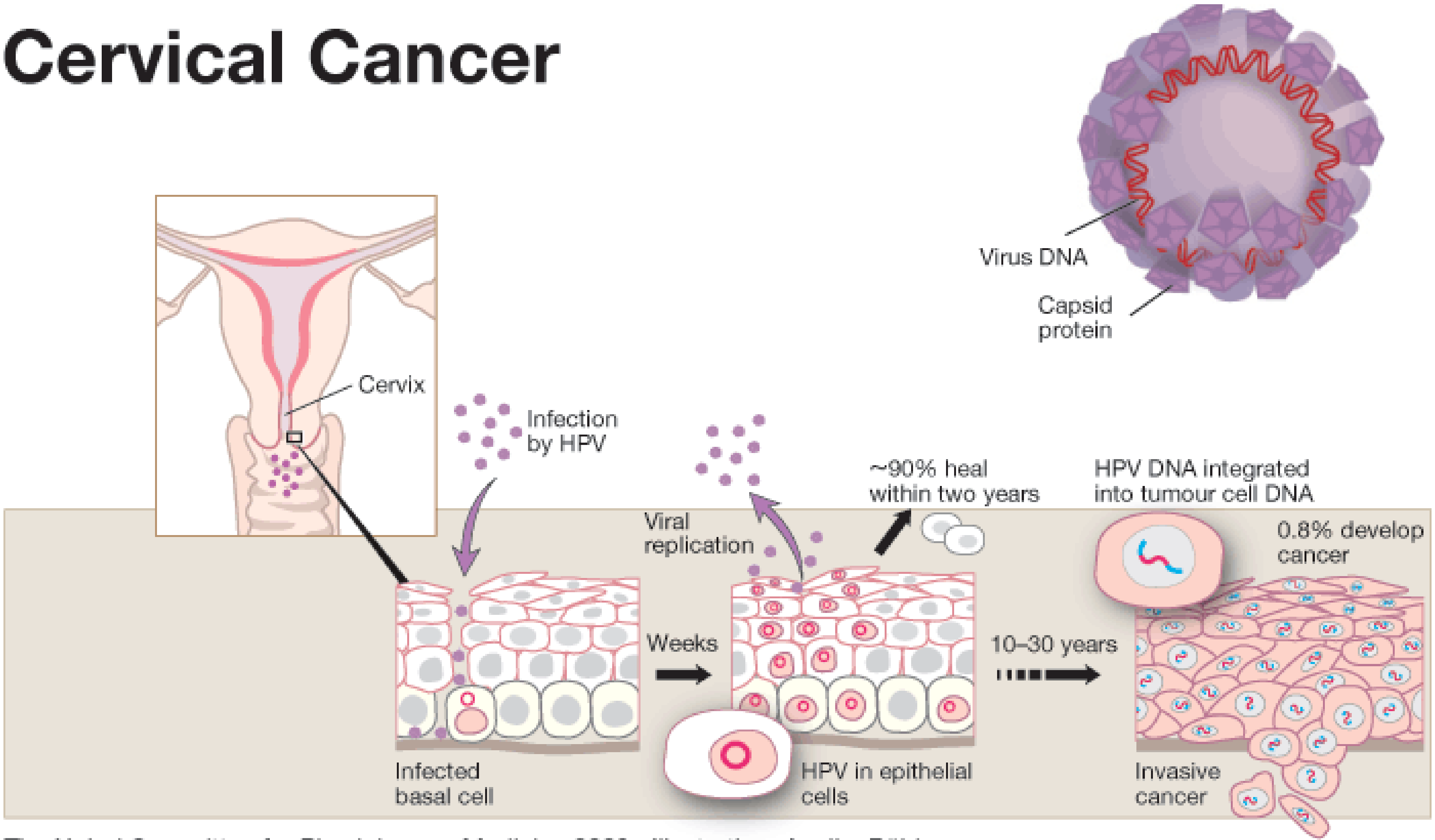
A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes, which are made up of DNA, act as instructions to make molecules called proteins. In humans, genes vary in size from a few hundred DNA bases to more than 2 million bases. The Human Genome Project has estimated that humans have between 20,000 and 25,000 genes (and this is just 3% of total DNA. What for is the rest 97% is not known clear yet!).

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





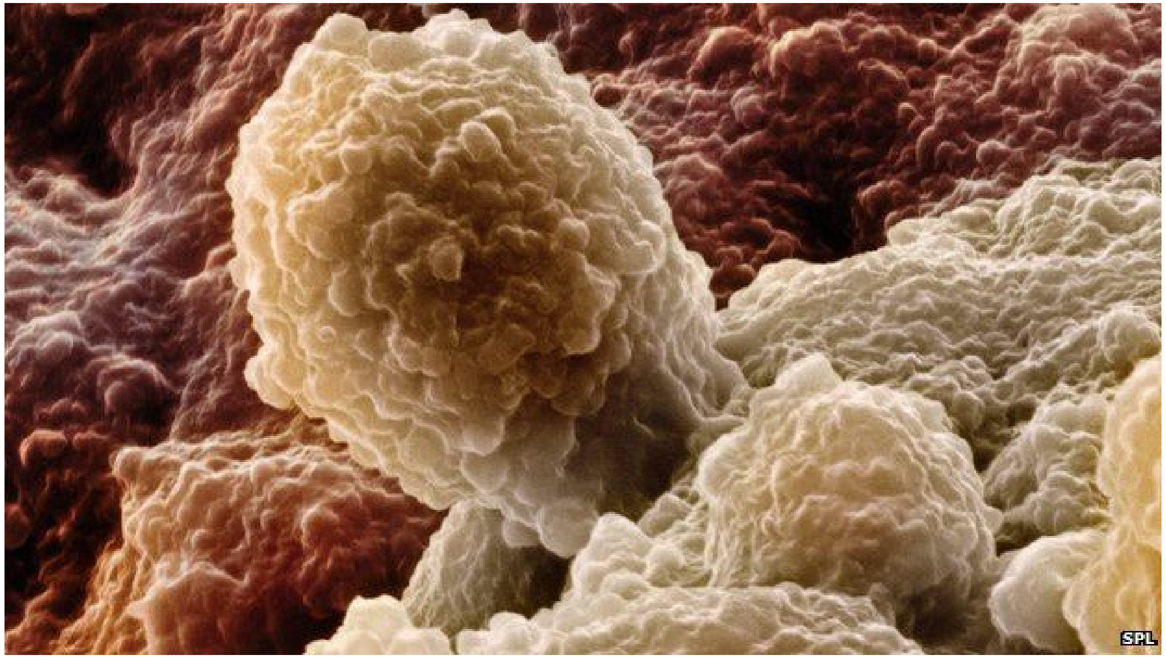
Cervical Cancer



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

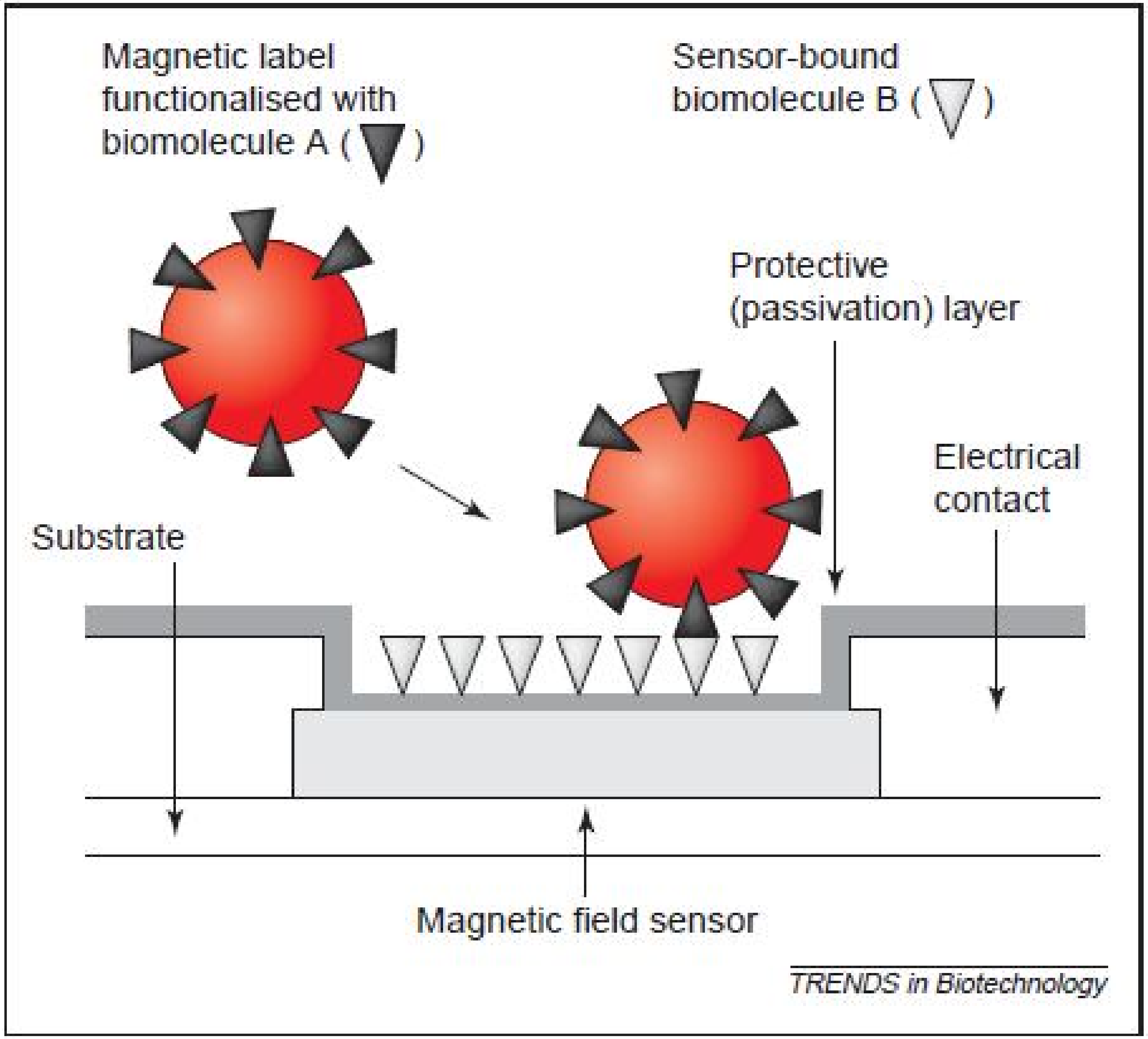


“Prostate cancer is the commonest cancer in men in many countries, including the UK - where more than 40,000 people are diagnosed each year. But not every patient has, or needs, invasive therapy that results in severe side-effects.
Genetic testing to predict risk could revolutionise how we treat the 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!

Magnetic assisted biosensors

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

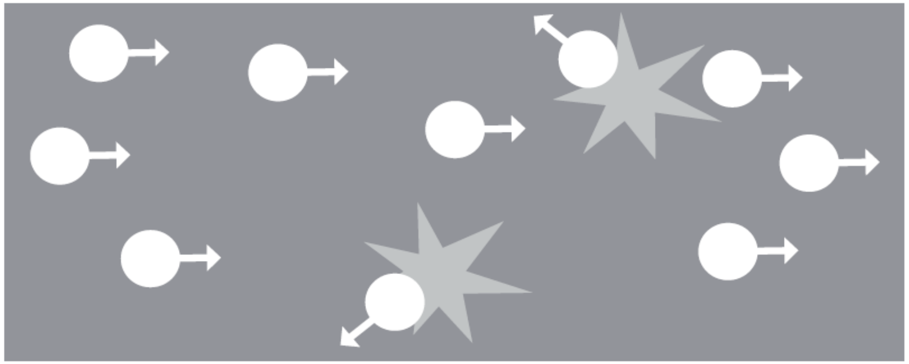


The Nobel Prize in Physics 2007 was awarded jointly to Albert Fert and Peter Grünberg *"for the discovery of Giant Magnetoresistance"*

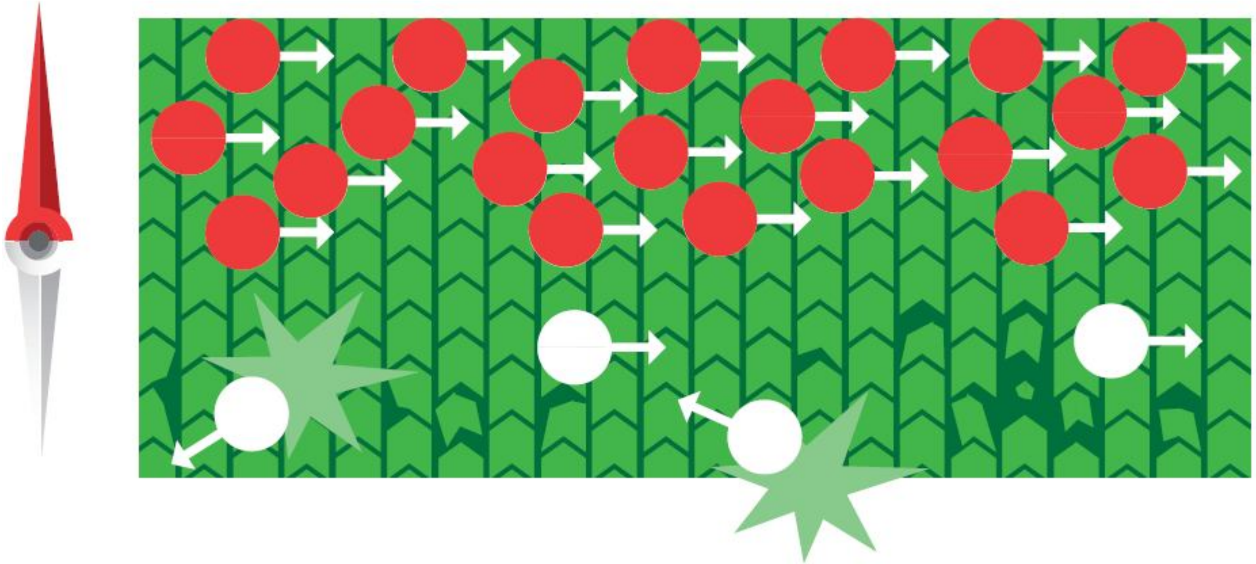
Peter Andreas Grünberg (born 18 May 1939) is a German physicist.

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

Principle of the GMR effect

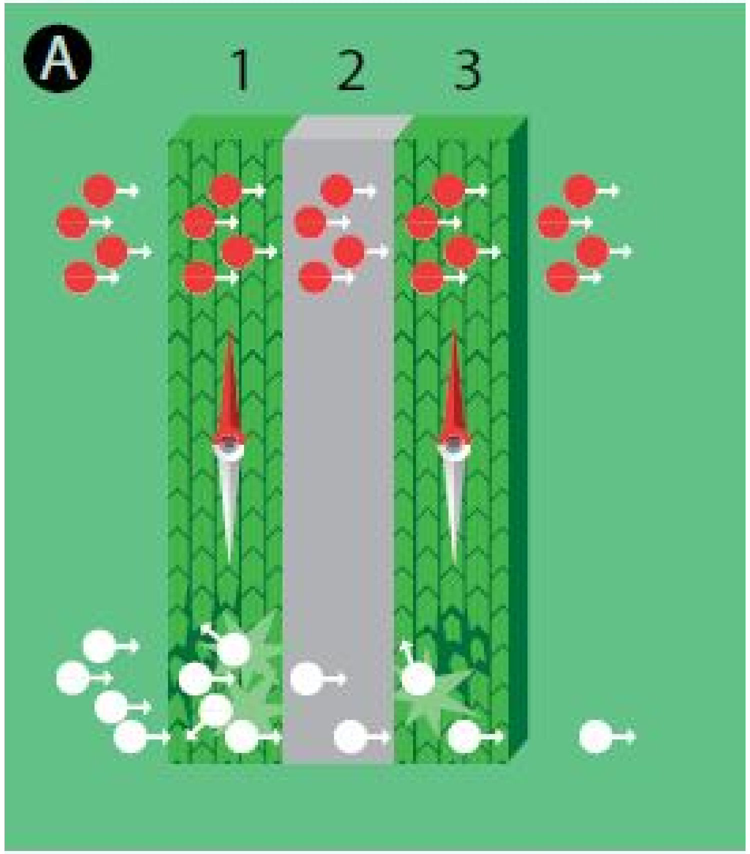


The electrical resistance in a conductor arises when electrons scatter against irregularities in the material so that their forward movement is obstructed.

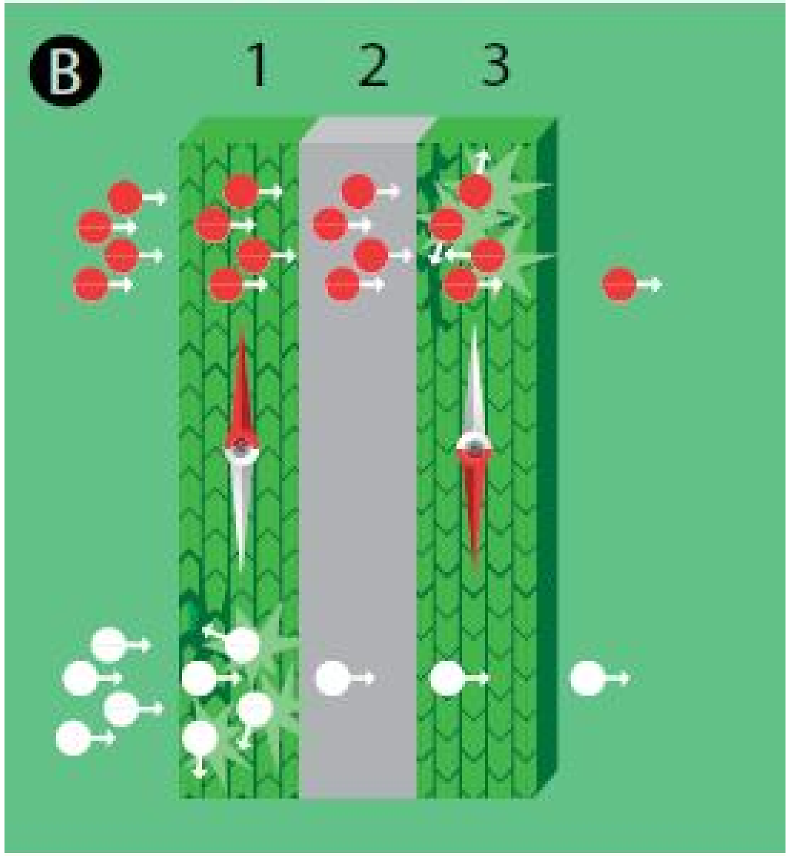


In a magnetic conductor the direction of spin of most electrons is parallel with the magnetization (red). A minority of electrons have spin in the opposite direction (white). In this example electrons with antiparallel spin are scattered more.

Principle of the GMR effect

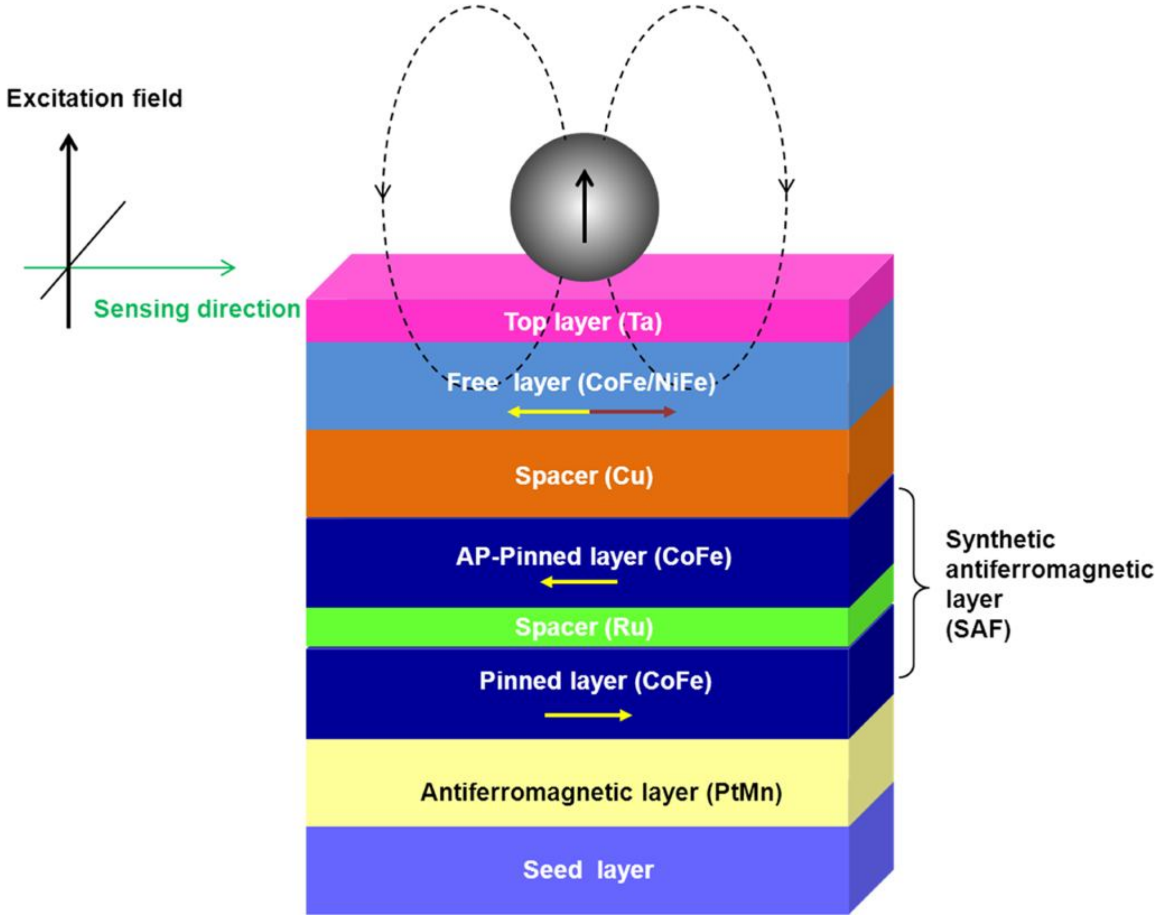


If the direction of the magnetization is the same in both magnetic layers the electrons with parallel spin (red) can pass through the entire system without scattering to any great extent. The total resistance of the system will therefore be small.



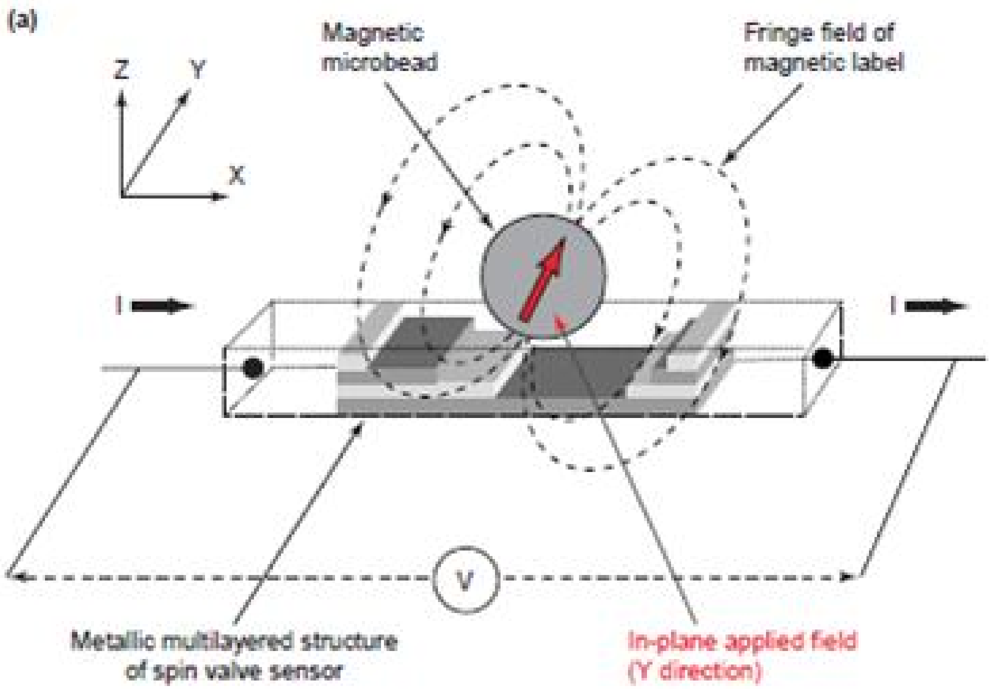
If the direction of magnetization in the two magnetic layers is opposed, all the electrons will have anti-parallel spin in one of the layers and will therefore scatter a great deal. As a result the total resistance is high.

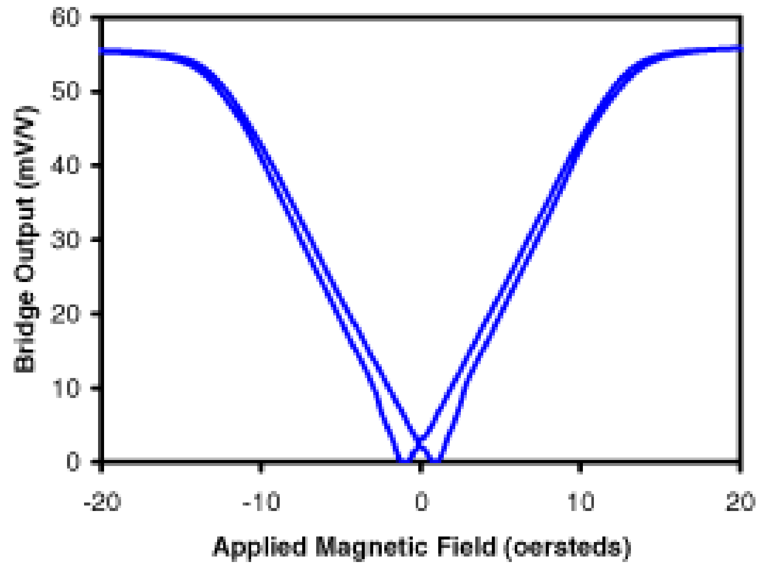
Magnetic assisted biosensors



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.

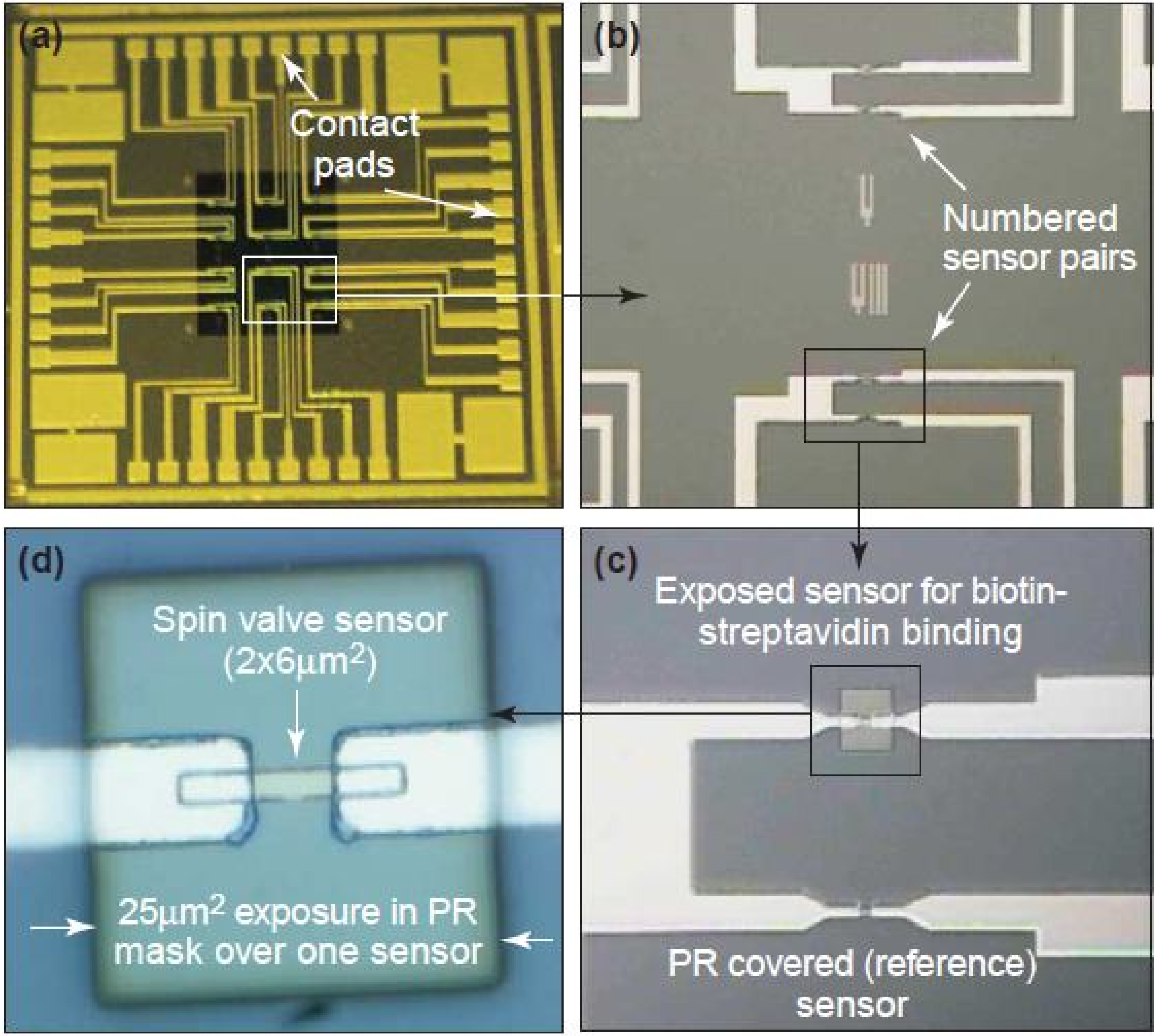
Magnetic assisted biosensors



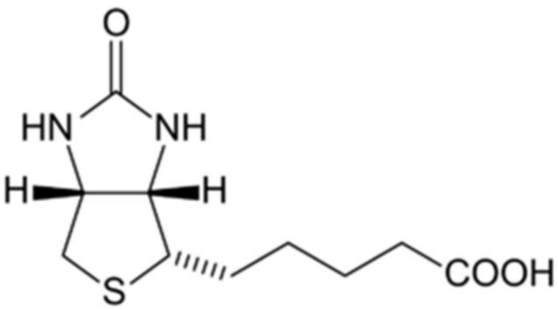


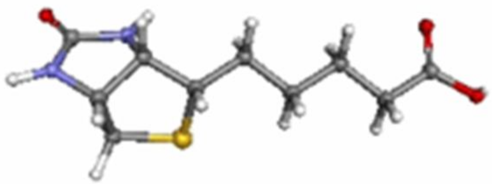
The GMR effect is based on the spin dependent interfacial and bulk scattering asymmetry that is found for spin-up and spin-down conduction electrons crossing ferromagnetic–nonmagnetic–ferromagnetic multilayer structures, where the parallel or antiparallel alignment of the ferromagnetic layers can be 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.

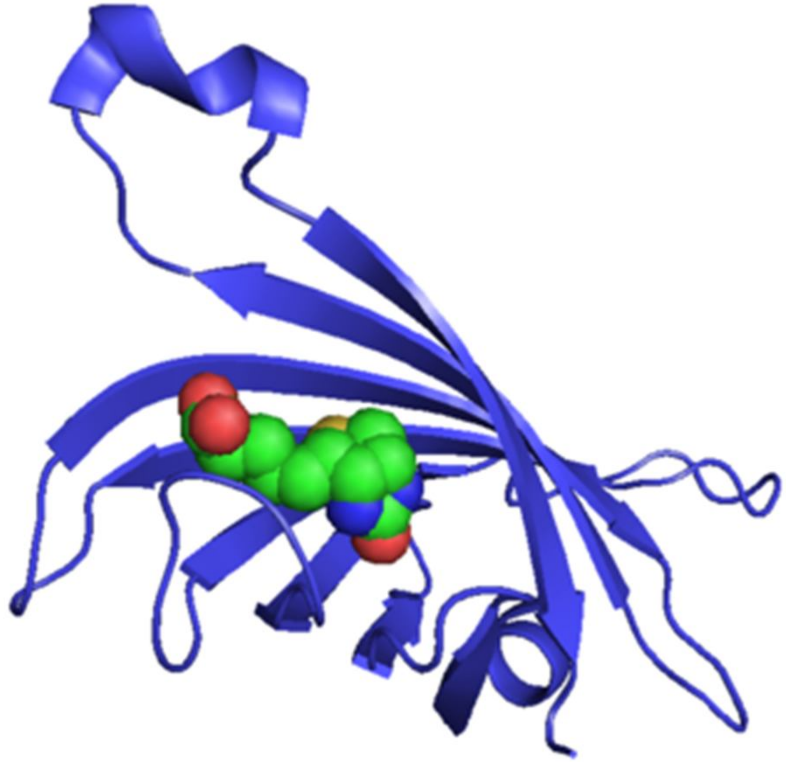
Magnetic assisted biosensors



Biotin and streptavidin



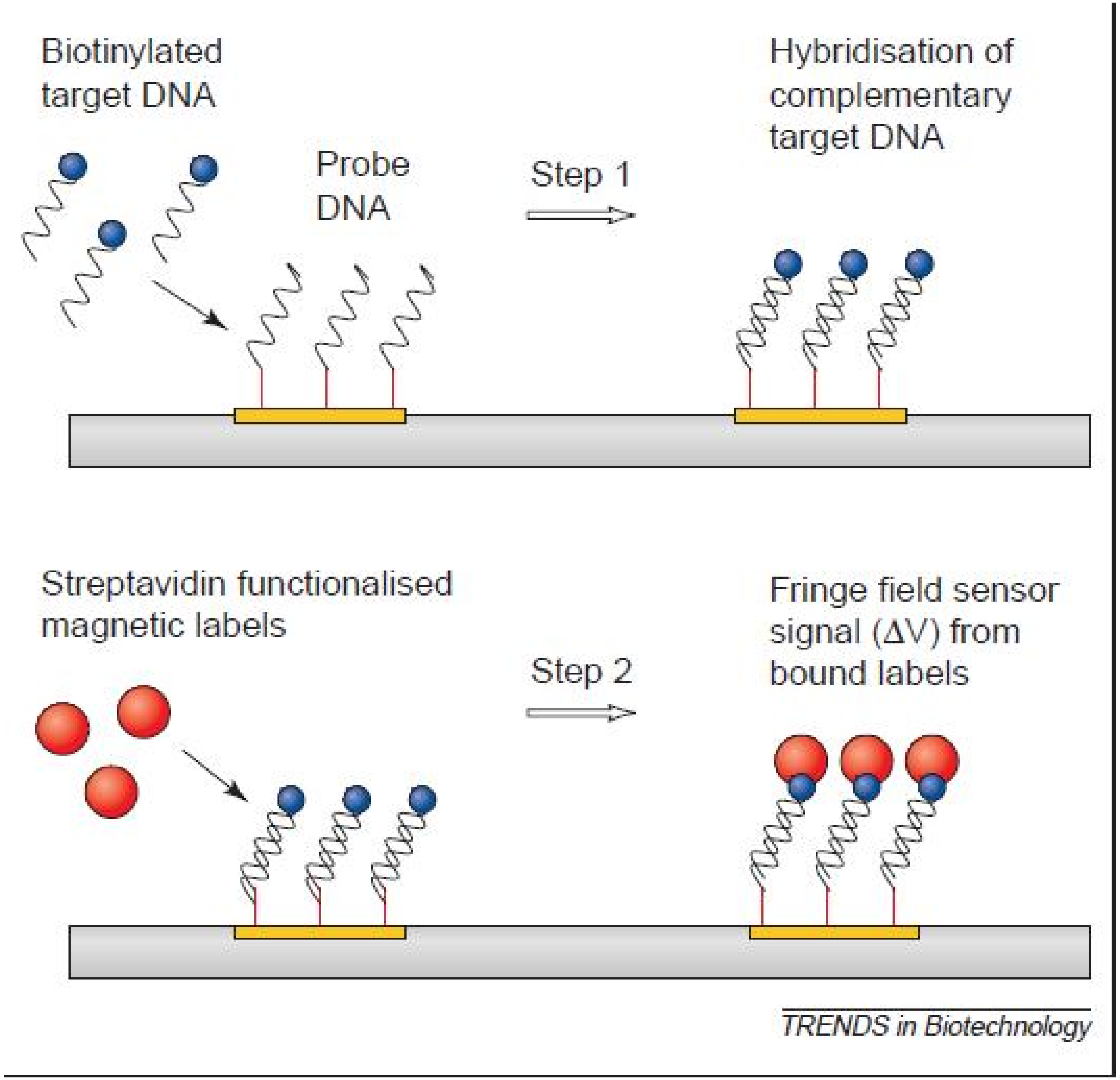




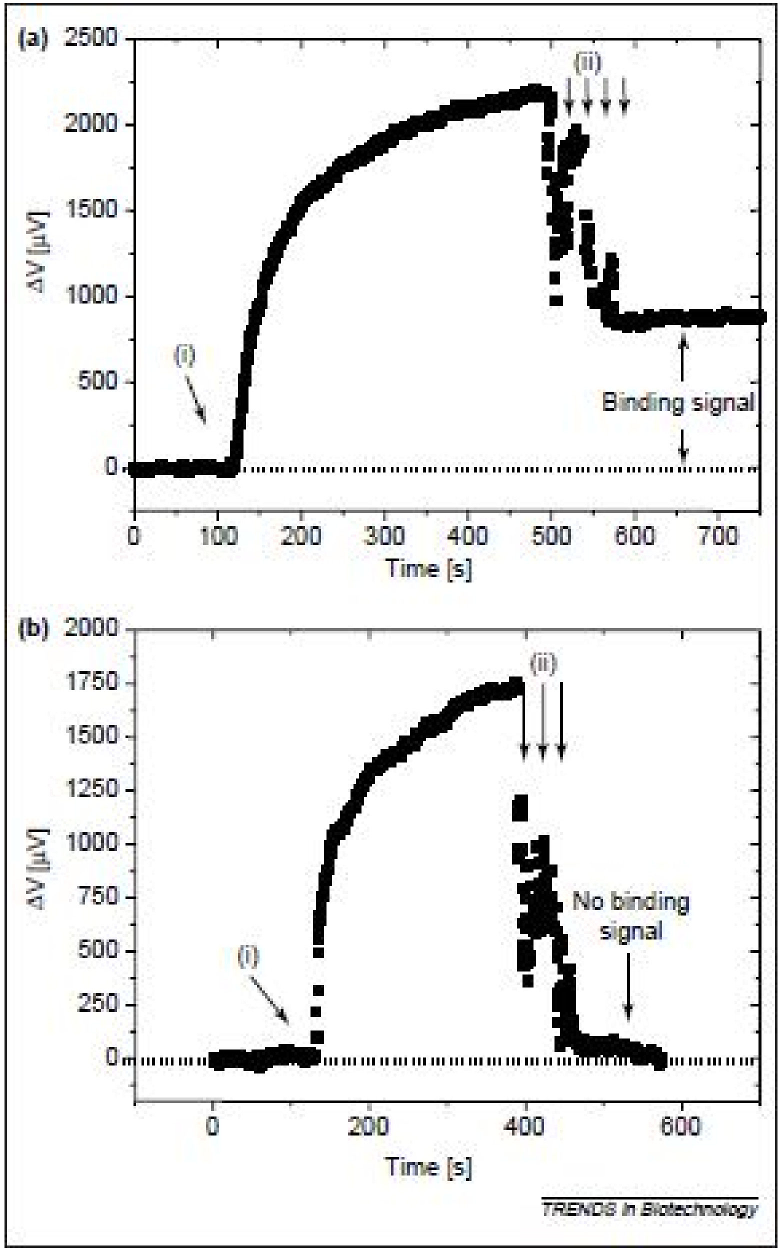
Biotin, also known as **vitamin H** or **coenzyme R**, is a water-soluble B-vitamin (**vitamin B_7**). Biotin is found in many cosmetics and health products for the hair and skin.

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.

Magnetic assisted biosensors



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)

Can neutrons help?

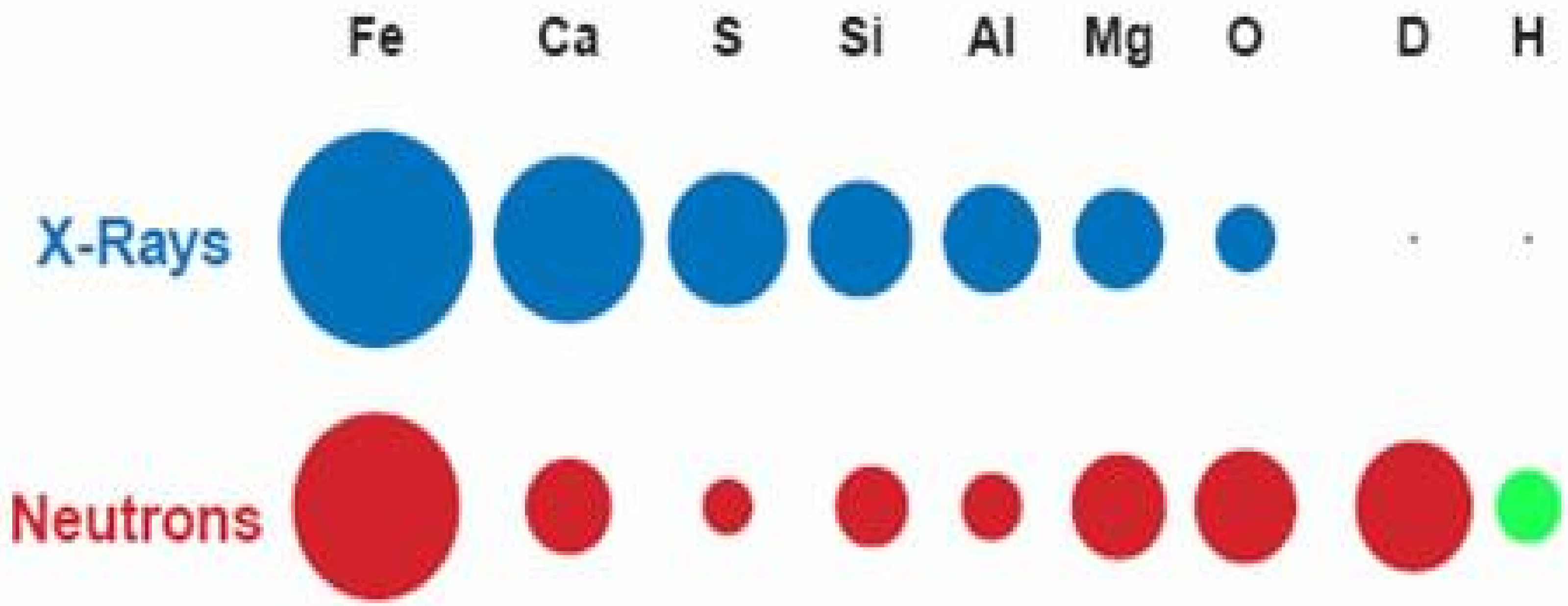
Magnetic nanoparticles offer a great promise for the miniaturized chip-based biosensors. However, their

- heterogeneous size (for example. 200–400 nm) and shape (non-spherical)
- rapid clustering (single particles aggregating to form groups)
- a small magnetic moment

require reliable methods for their characterization.

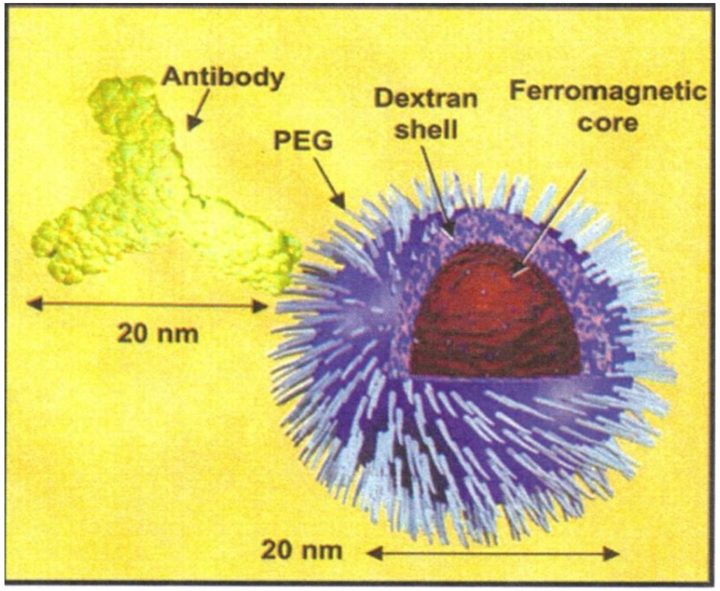
And neutron scattering methods provide a possibility to address these issues.

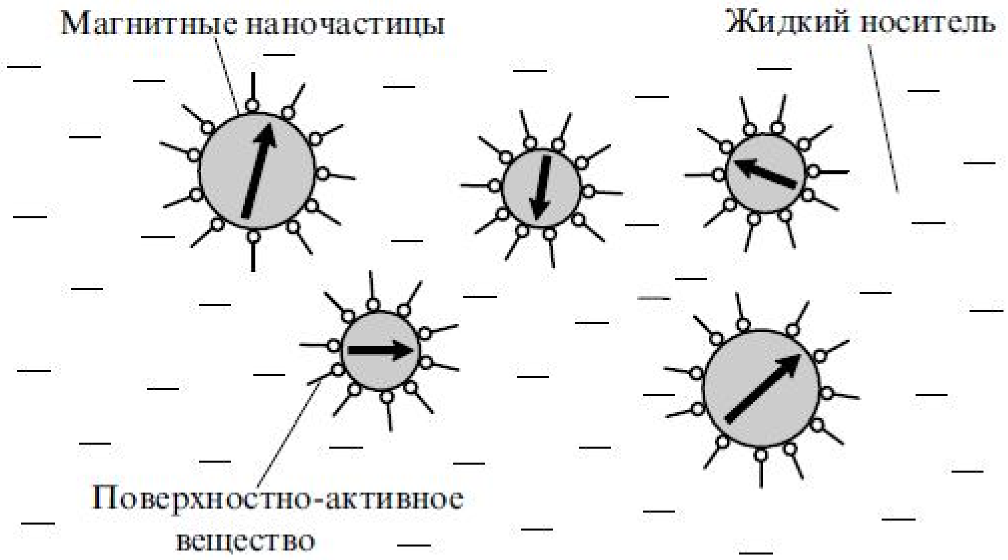
With neutrons the strength of scattering is different for different isotopes so that isotopic substitution can be used



Neutrons have a magnetic moment and their scattering is sensitive to the magnetic moment of atoms making neutron scattering the ideal means to study magnetic materials.

Small Angle Neutron Scattering (SANS) from magnetic nanoparticles in solution

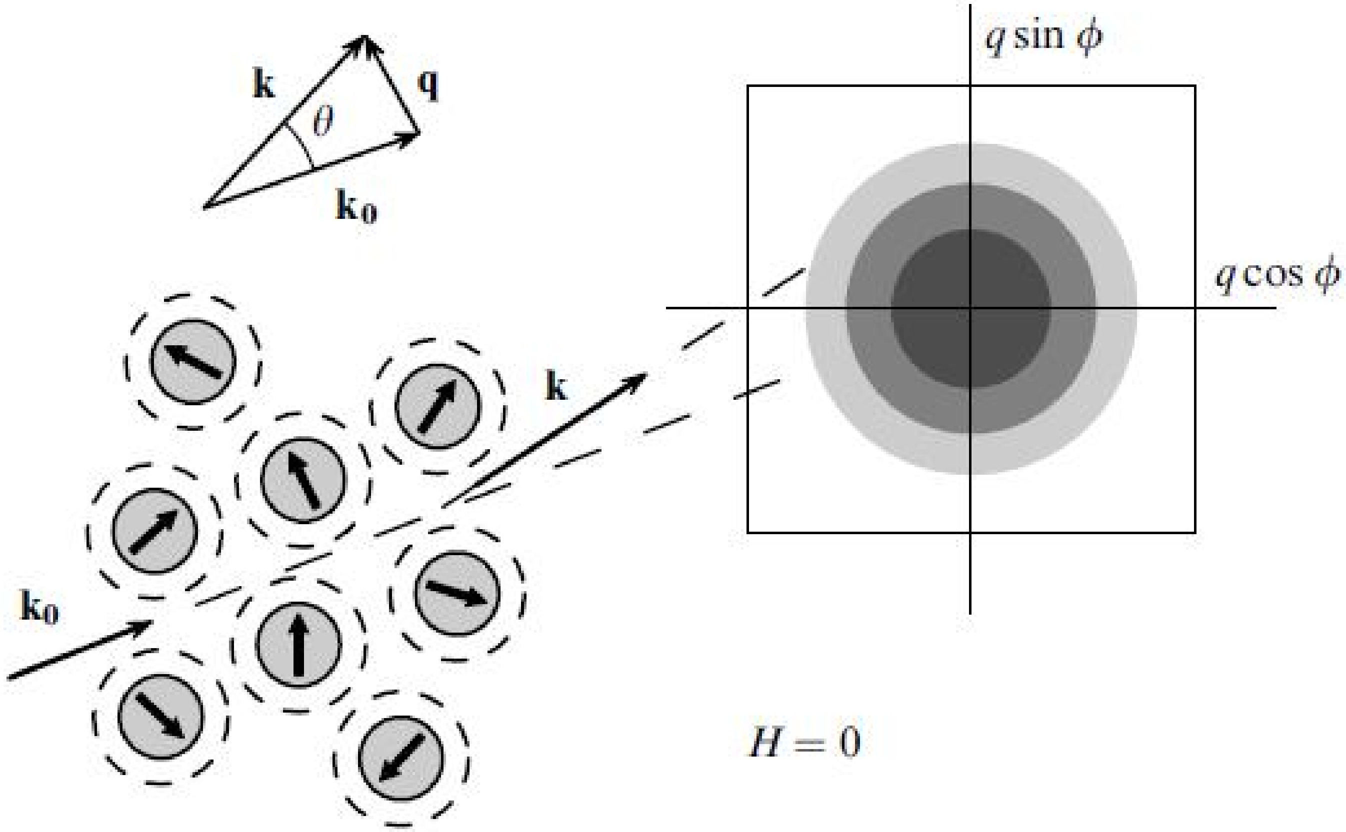




Scattering from a single nanoparticle:

- Nuclear scattering from magnetic core
- Nuclear scattering from hydrogen containing shell
- Magnetic scattering from magnetic core
- Nuclear scattering from the solvent

SANS from magnetic nanoparticles in solution



Principal scheme of SANS on magnetic nanoparticles in solution. In the absence of external magnetic field magnetic moments of nanoparticles are randomly oriented in space.